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SCIENTIFIC PRINCIPLES & PRACTICE

SEVENTH EDITION

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Gilbert R. Upchurch, Jr
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SURGERY

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Preface

The editors are pleased to present the seventh edition of *Mulholland and Greenfield's Surgery: Scientific Principles & Practice*. The field of surgery has changed fundamentally in the years since the first edition of this text. Growth in the knowledge base of clinical surgery continues exponentially. Surgical practice has been transformed through scientific advancements and the introduction of new technology. The accelerating pace of scientific progress demands rapid adoption of new ideas into surgical therapy and a commitment to lifelong learning. Accordingly, the new edition of *Mulholland and Greenfield's Surgery* seeks to integrate new scientific knowledge with evolving changes in surgical care.

The seventh edition brings many changes and updates. First, there is a change in editorial leadership. Dr. Michael Mulholland, who has been integral to the success of this text since its inception, has stepped down. It is my great honor to be selected by our publisher to succeed Dr. Mulholland as the editor in chief. To recognize Dr. Mulholland's contributions, we have added his name to the title of the book to be recognized with Dr. Greenfield.

Second, the composition of the editorial team has also changed. Drs. Keith Lillemoe and Gerard Doherty have also stepped down after making great contributions to their sections during their long tenure as editors. We are grateful for their service and excited to build on their work as a new editorial team. Drs. Hasan Alam, Tim Pawlik, and Gilbert Upchurch, have agreed to continue to serve on the editorial team; and I am excited to add Dr. Mary Hawn and Dr. Julie Ann Sosa to our team of editors. The expertise, energy, and vision of this great team of editors has invigorated this edition.

With new leadership and editorial team, we have made many changes to the style, content, and authors. We have kept the vision of the text by integrating science and practice, but have shortened the book by eliminating some chapters that can be accessed elsewhere and are less relevant to current practice. We also instructed authors to shorten chapters and consolidate information into easy to read tables, rather than long blocks of text. This edition has many new authors and represents perhaps the greatest turnover in authorship since the book was launched.

On behalf of the editorial team, we hope that you find the seventh edition of *Mulholland and Greenfield's Surgery: Scientific Principles & Practice* to be an important part of your surgical library. We have carefully curated the content to serve your lifelong education goals and, ultimately, to improve the care of your patients.

Justin B. Dimick, MD, MPH

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Part One Scientific Principles

1

Lifelong Learning

Laura Mazer, Rebecca M. Minter, and Gurjit Sandhu

Key Points

1. Surgery is an ever-evolving field, and residency programs must provide trainees with the skills necessary to continuously evaluate and integrate new knowledge.
2. Many high performing students arrive in advanced training programs without explicit understanding of the *process* of learning.
3. Self-regulated learners are metacognitively, motivationally, and behaviorally active participants in the learning process: they set learning goals; they perceive themselves as capable of learning; and they structure their environment to optimize learning.
4. Lifelong learning depends on teaching students how to *self-regulate* their learning.
5. A number of evidence-based tools exist to help trainees explicitly identify and develop self-regulatory processes, including assessment tools, self-regulated reading strategies, and coaching.

"We can say that he learned rapidly because his first training was in how to learn. And the first lesson of all was the basic trust that he could learn. It is shocking to find how many people do not believe they can learn, and how many more believe learning to be difficult."

—Frank Herbert

1 THE IMPORTANCE OF LIFELONG LEARNING

Today more than ever, surgical practice is evolving quickly. Beyond any specific curricular objective, medical education needs to focus on creating lifelong learners: Physicians who will continue to acquire, retain, and integrate new knowledge from the first day of medical school through the last day of their careers. The Accreditation Council for Graduate Medical Education (ACGME) draws a clear and explicit connection between professionalism, safe patient care, and lifelong learning: "The ACGME Core Competencies aim to spur a lifelong-learning pattern for physicians and continuous improvement for medical schools."[1] Similarly, the Global Commission on Education for Health Professionals asks medical schools to create graduates "educated to mobilize knowledge and to engage in critical reasoning and ethical conduct."[2]

In a field that is changing faster than ever, how can surgical educators create this kind of lifelong learner and how can surgical trainees develop the skills necessary to become intentional, independent, and self-directed scholars? This is especially important because there is evidence that students frequently arrive in graduate education without these requisite skills. A 2009 study asked veterinary students to identify the factors considered most important in their learning. Overwhelmingly, they cited the quality of the instruction, workload, and curriculum, but almost never their own effort or study skills.[3] Learning is considered something that happens *to the learner*, rather than something the learner can control. This feeling is reinforced by a primary and secondary educational system that decouples effort from reward.[4] Similarly, undergraduate students asked to explain the reason for academic failures mostly describe either inadequate instruction, or an innate lack of ability—both things that are out of their control, rather than attributing failure to a volitional process or effort.[5] Overall, many students—even very high performers—come to professional education lacking essential self-regulation skills.[5] Even those students who have been very academically successful may have only a subconscious understanding of the traits leading

to that success. Understandably, medical training focuses on knowledge, technical skills, and professionalism: 2 the *end products* of learning. To create lifelong learners who can continue to expand their knowledge and skills beyond the confines of a training program, dedicated attention is needed to the metacognitive traits that enable the *process* of learning.

WHAT IS SELF-REGULATED LEARNING?

Self-regulated learning refers to a constellation of skills, traits, and habits that promote and sustain learning. It is the *volitional process* by which learners transform mental abilities into academic skills.[5] The volitional component explains why a very talented trainee can fail to achieve what a motivated but less gifted student can accomplish. The ability to self-regulate is consistently the strongest independent predictor of educational and workplace success, outperforming IQ, parental education level, or economic status.[5–7] In surgical training, these character traits, like self-control, discipline, perseverance, and determination, are a major predictor of successful completion of residency.[8,9]

Self-regulated learning is a total engagement activity, regardless of whether the learner is sitting in a class, reading a textbook, or learning in the workplace. Such learners are "metacognitively, motivationally, and behaviorally active participants in their own learning process."[10]

1. 3 **Metacognitively active learners** plan, organize, self-instruct, self-monitor, and self-evaluate. Crucially, such learners have the ability to set their own goals, and can determine when and if those goals are being met.
2. **Motivationally active learners** perceive themselves as competent, self-efficacious, and autonomous. Originating from Albert Bandura's work in clinical psychology, there is a strong correlation between perceived self-efficacy and performance.[11] When trainees are estimating their ability to perform a future task, they base the evaluation on past performance. An estimation of high ability exerts a strong positive effect on goal setting, effort, and persistence. It then becomes a virtuous cycle: perceived self-efficacy improves effort, effort improves performance, and good performance positively reinforces the sense of efficacy. In short: they think they can, so they do. Of note, this does not imply that learners will benefit

from an inflated sense of their own abilities. Studies of medical students on the wards show that inaccurate self-assessment results in worse performance.[12] It is *earned* self-efficacy and the ability to accurately self-evaluate—neither under- nor overestimating one's abilities—that is the key to self-regulation.

3. **Behaviorally active learners** select, structure, and create environments that optimize learning.

4 Because self-regulated learning takes place over time, several theorists have developed a three-stage model of the process. In this model, learners progress through a cycle of planning or forethought, through performance of the task, and then into a self-reflection or evaluation phase (**Fig. 1.1**).[5,13] Sitzmann et al. performed a meta-analysis of the theories of self-regulation in multiple fields, and developed a heuristic framework of the elements of self-regulatory learning as they fall into those three components.[6] In the planning phase, learners chose a *regulatory agent*—the specific goal to be achieved. The goal is accomplished by utilizing *regulatory mechanisms*—a broad list of skills and traits including learning strategies, persistence, help-seeking, emotion control, and more. Finally, *regulatory appraisals* allow the learner to self-evaluate and reassess self-efficacy. This stage is crucial for determining if the goal is achieved, and for connecting success or failure to their legitimate cause. Attributing failure to an innate lack of ability or an external process beyond the learner's control, usually results in a loss of motivation and reduced effort. A learner who emphasizes the success or failure of the regulatory mechanisms they employed toward the chosen goal is much more likely to continue learning. Some specific regulatory mechanisms are described in **Table 1.1**.[6,14] Three processes salient to self-regulatory learning—use of assessment tools, coaching, reading strategies—are explored in further detail.

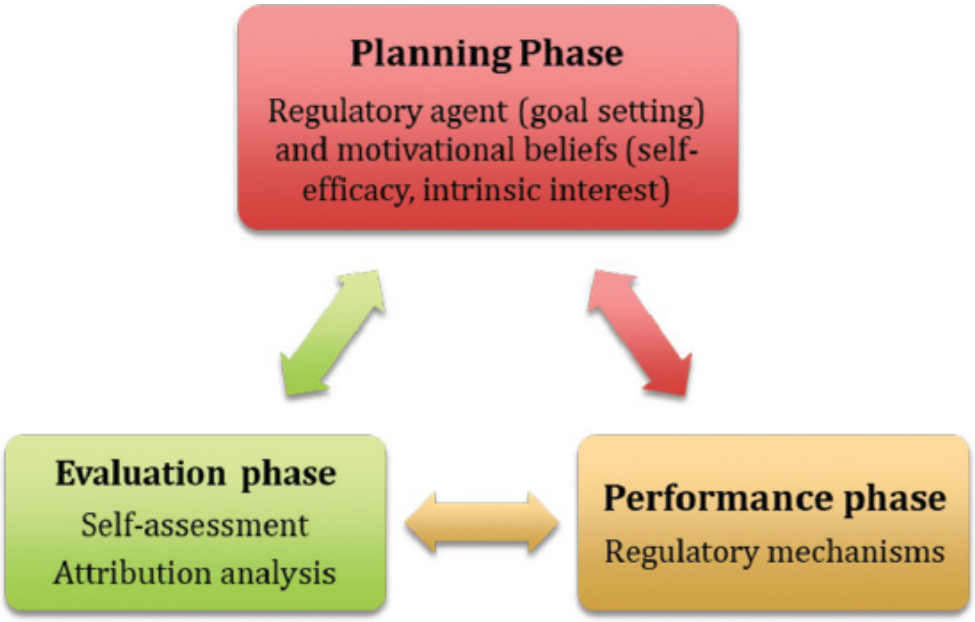

Figure 1.1 Model of self-regulated learning. The cycle of self-regulated learning, beginning with a planning, or forethought, phase where learners set a regulatory agent (learning goal), and decide on the amount of time and other resources to dedicate to the task. This continues through the performance phase, where regulatory mechanisms are employed, and is reinforced by an ongoing process of self-assessment. (Adapted in part from Zimmerman BJ. Becoming a self-regulated learner: an overview. *Theor Pract* 2002;41:64–70; Schraw G. Promoting general metacognitive awareness. *Instr Sci* 1998;26:113–125.)

Table 1.1 Personal and Social–Environmental Factors Contributing to Self-Regulated Learning

Personal Factors	
Goal setting	Standards trainees aim to achieve during training
Planning	Setting task-specific goals and deciding on strategies to achieve them
Monitoring	Paying attention to one's performance and understanding
Learning strategies	Techniques employed to integrate components of the material with existing knowledge
Persistence	Continuing to allocate effort and attention in the face of boredom or failure
Help seeking	Asking for help when one has difficulty understanding the material
Motivation	Willingness to engage in learning, desire to learn
Emotion control	Keeping anxiety, stress, or fear at bay while learning
Effort	Amount of time trainees' devote to learning
Attributions	Trainee beliefs about the causes of outcomes, e.g., attributing failure to external forces vs. one's own effort and work
Self-efficacy	Belief in one's ability to achieve goals or succeed in training
Social–Environmental Factors	
Cultural norms	Higher group standards encourage individuals to set higher personal goals
Role modeling	Positive role modeling of self-regulated

	behavior, including goal setting, help seeking, and attribution
Feedback	Feedback that stresses self-improvement and achievement toward the goal, emphasizing personal agency
Prepared environment	An environment that is optimized for educational goals as much as possible within the demands of the workplace

5 FOSTERING SELF-REGULATED LEARNING: ASSESSMENT TOOLS

The first step toward developing self-regulated learners is to explicitly value the *process* of learning, not just the end results. This requires a shift from evaluating students based on ability or achievements, toward focusing on how they activate and sustain learning processes.[10] Many learners have never consciously thought about the nature of learning; indeed, many educators do not think about how students learn, and these skills are rarely explicitly taught or evaluated.[4] One tool that can help both learners and educators is a structured self-assessment of regulatory behaviors. This type of assessment can provide a model for the evaluation stage of learning, helping trainees to identify potential areas for improvement in regulatory mechanisms. Additionally, a self-assessment can allow learner evaluations to reflect more than just current ability level or achievement, rewarding the traits known to predict long-term success. This can help improve perceived self-efficacy and autonomy, and empower the trainee to take control of their own learning process. Finally, the assessments serve as an indicator of learners who need help developing metacognitive skills, and can be the basis of early interventions and support systems.

Table 1.2 Sample Items from the Metacognitive Awareness Inventory (MAI)

Statement	Category[a]
I consider several alternatives to a problem before I answer	M
I try to use strategies that have worked in the past	PK
I learn best when I know something about the topic	CK
I pace myself while learning in order to have enough time	P
I understand my intellectual strengths and weaknesses	DK
I think about what I really need to learn before I begin a task	P
I know how well I did once I finish a test	E
I slow down when I encounter important information	IMS
I summarize what I've learned after I finish	E
I change strategies when I fail to understand	DS
I find myself pausing regularly to check my comprehension	M
I can motivate myself to learn when I need to	CK

[a]The MAI asks learners to rate their agreement with 52 items classified by either type of knowledge (declarative knowledge [DK], procedural knowledge [PK], or conditional knowledge [CK]) or type of metacognitive process (planning [P], information management strategies [IMS], monitoring [M], debugging strategies [DS], and evaluation [E]).

There are several available self-assessment tools for measuring metacognitive skills. In general, these scales ask learners to rate their agreement with statements like "I try to relate unfamiliar problems with

previous situations or problems solved,"[15] or "I ask myself periodically if I am meeting my goals."[16] The statements provide both an assessment and a model of self-regulated behaviors. A sample of the Metacognitive Awareness Inventory, developed by Schraw and Dennison in 1994, is seen in **Table 1.2**.[16] These assessments of learning skills are different than a self-assessment of technical skills or knowledge base, for example, asking a resident to rate their performance in the operating room. An operative performance self-assessment can identify strengths and weaknesses, and help the learner align performance expectations with external standards: the end products of learning. The self-regulation assessments help the learner identify aspects of the learning *process* that can be improved, providing tools that will help them succeed in any future learning goal.

FOSTERING SELF-REGULATED LEARNING: COACHING

Self-regulatory behaviors stress individual (and independent) identification of learning goals, strengths, and challenges. Putting aside the hurdle of an objective assessment of your own abilities, trainees face the additional difficulty of "not knowing what they don't know." As residents progress through the stages of learning, they may not have enough knowledge to evaluate their own strengths and challenges. In this setting, coaching can be a powerful tool that creates access to both the content and the process of learning.

While all of medical education can be defined as helping the trainee to expand upon knowledge, skills, and attitudes, coaching has a distinctive focus on empowering the coachee to become their own agent of change.[17] In other words, coaching is a tool for creating the skills of self-regulation. The Wisconsin Surgical Coaching Framework has been proposed as a systematic approach to surgical coaching interventions, and mirrors the essential elements of self-regulation: (1) Setting goals (metacognitively active learners), (2) encouraging and motivating (creating motivationally active learners), and (3) developing and guiding (behaviorally active).[17,18]

Lifelong learning can be set in motion during training, but requires a consistent and career-long effort to retain. Coaching can occur at any stage, and is as effective for practicing surgeons as it is for residents.[19–21] Video-based coaching in particular has been utilized in a variety of graduate and continuing medical education spheres. In this model, a surgeon or resident works with a trained colleague to evaluate their performance and identify areas for improvement.[22] By adding the wisdom and accountability of a supportive coach, participants improve both the development and the application of self-regulatory mechanisms.

FOSTERING SELF-REGULATED LEARNING: SELF-REGULATED READING

One of the primary means of acquiring knowledge independently remains the written word: journal articles, textbooks, even blog posts. The surgical textbook remains the mainstay of education for most students, residents, and fellows, yet many learners struggle to retain and integrate knowledge from reading. There are numerous strategies to improve reading comprehension, efficiency, and retention, and applying such a strategy ensures that trainees can continue to learn long after leaving the formal educational system.

Reflective writing: For learners who are reading an assigned chapter, comprehension questions can serve as both a knowledge test and a prompt to deepen the level of understanding.[4] The goal of such questions is to provide readers with a framework with which to evaluate similar readings in the future. These reflection exercises also model the process of *attentive reading* and *integration of knowledge*. Sample questions include the following: What was the most important point from this chapter? What was the most confusing point, and why? How will this chapter change your practice? Can you apply anything in this chapter to a patient you've seen recently?

Recall self-testing: There are multiple proposed methods by which readers can create their own reflective exercises, to improve independent reading comprehension and retention. One of the most popular methods for textbook reading is the SQ3R (**Table 1.3**).[4] In this method, students progress

through the stages of survey → question → read → recall → and review. First, they survey the chapter, paying attention to the headings, subheadings, tables, and any highlighted terms. This survey helps the reader assign a purpose or goal for the reading by developing questions to answer for each heading or subheading. The chapter is then read, with an eye toward answering the self-assigned questions. Next, the reader performs a verbal or written recall exercise, jotting down the essential points. Finally, the recall is reviewed against the text to check for omissions or mistakes. While this method has been criticized for being time-intensive, it is also ten times more effective for long-term retention compared with re-reading the material multiple times.[4,23] A modification of the SQ3R has also been proposed for journal articles, where the survey stage involves reading the abstract, and the questioning stage is a list of standardized questions, such as "what was the rationale for conducting the study?" and "what type of research methodology was used?"[24]

Table 1.3 SQ3R Method of Textbook Reading: Survey, Question, Read, Recall, Review

S	Q	3 R
1. Survey Skim the text first, paying attention to headings, subheadings, and any bold or highlighted words	**2. Question** Assign a purpose or goal to the reading by developing questions to answer from the headings and subheadings	**3. Read** Read the chapter with the goal of answering the self-assigned questions **4. Recall** Put away the book, and either verbally or in writing jot down the key points from memory **5. Review** Check your recall against the text, looking for omissions or mistakes

THE CHALLENGE OF SELF-REGULATED LEARNING DURING SURGICAL TRAINING

Self-regulated learning is both particularly vital and uniquely challenging in clinical education. The majority of training occurs on the wards, in the clinic, or in the operating room, rather than the organized and controllable environment of the classroom. In this context, trainees cannot focus entirely on their own learning goals, and they have much less ability to control their environment.[25] Even students who have developed good self-regulation skills in the academic setting may struggle to apply them in the world of clinical medicine. Surgical educators must acknowledge this challenge, and help

trainees develop self-regulation skills that can meet the demands of a chaotic setting and busy schedule.

The first strategy for surgical educators is to optimize those elements of training that are amenable to control. This includes providing strategies to increase the effectiveness of independent study, like using the SQ3R method described above for textbook reading, or integrating coaching behaviors into routine clinical interactions. This also includes training outside the wards, in simulation centers. Simulation-based curricula designed around principles of self-regulated learning, where each trainee is provided with materials and allowed to progress at their own pace, have led to increased long-term skill acquisition when compared with instructor-led sessions.[26] Similarly, providing clear learning plans, level-specific milestones, and dedicated feedback can help trainees integrate self-regulated learning into the activities of clinical care.

In the operating room and on the wards, the cultural norms of the training program are essential for encouraging or discouraging self-regulated behavior (**Table 1.1**).[14] Attending physicians can role model specific behaviors: for example, help seeking in the operating room, or openly discussing their own errors or mistakes to model self-reflection and attribution. In morbidity and mortality conferences, a culture of blame will teach residents to avoid self-reflection; a just culture of honest inquiry will encourage trainees to seek out a more genuine self-assessment and attribution of responsibility.

Ultimately, the goal of surgical training is to produce surgeons who can treat the problems of today, and help solve the problems of tomorrow. Surgery is not static, and surgeons cannot afford to be static either. Our field continues to change and grow, and we cannot expect residents to graduate with a mastery of every problem they will face in their career. For residents to be truly capable of independent practice, more than any specific surgical skill, they must have the ability to continually seek out new information, continually revising, reviewing, and questioning their knowledge base. By explicitly valuing and encouraging the elements of self-regulated learning, training programs can create surgeons who are prepared for the problems of today, and can face the challenges of tomorrow.

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2

Substrate Metabolism in Surgery

Carrie Sims

Key Points

1. Despite wide fluctuations in dietary carbohydrate intake, blood glucose levels are tightly regulated through the balance of glycogenesis, glycogenolysis, and gluconeogenesis.
2. The hepatic Cori cycle is highly efficient at converting serum lactate, a byproduct of anaerobic metabolism, into pyruvate. As such, even patients with advanced liver disease do not exhibit elevated lactate levels at baseline although the rate at which lactate is cleared does correlate with liver function.
3. The pentose phosphate pathway (PPP) is an anabolic pathway that uses excess glucose to generate 5-carbon sugars known as pentoses, ribose-5-phosphate, a necessary component of nucleotides and nucleic acids, and NADPH, a critical bioreductive agent needed to detoxify intracellular reactive oxygen species.
4. Fat is a highly energetic fuel source with triglycerides yielding more than twice the energy per unit mass when compared to proteins or carbohydrates. The glycerol backbone undergoes glycolysis, whereas the fatty acid undergoes beta oxidation in the mitochondria to generate acetyl CoA molecules.
5. Excessive lipolysis during periods of starvation or with uncontrolled diabetes leads to an overall abundance of acetyl CoA and the creation of ketone bodies that can be sued for fuel.
6. Increased dietary intake of cholesterol suppresses endogenous synthesis by inhibiting the rate-limiting enzyme, 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase. This key enzyme can also be pharmacologically inhibited by statins which act as competitive antagonists and effectively lower plasma cholesterol by blocking cholesterol synthesis.
7. Essential amino acids include histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Arginine is conditionally essential amino depending on the developmental stage of the individual. All other amino acids are synthesized by the Krebs cycle or PPP.

8 The Krebs cycle includes a series of mitochondrial enzymes that transform acetyl CoA into water, carbon dioxide, or reducing equivalents (NADH and $FADH_2$) that drive the electron transport chain.

9 Biotransformation of potentially toxic, often hydrophobic compounds, into hydrophilic and excretable compounds occurs mainly in the liver by cytochromes P-450, the uridine diphosphate (UDP)-glucuronyl transferases, the glutathione (GSH)-transferases, and the sulfotransferases.

Substrate metabolism predominantly refers to the cellular fate of dietary carbohydrate, fat, and protein as they undergo a series of chemical reactions. Although admittedly intricate, all surgeons should be familiar with the biochemistry by which nutrients are converted to energy. This chapter will provide an overview of these biochemical pathways and delineate how cellular metabolism is impacted by surgical stress, critical illness, and trauma.

CARBOHYDRATE METABOLISM

Despite wide fluctuations in dietary carbohydrate intake, blood glucose levels are tightly regulated. Carbohydrates are initially broken down by salivary and pancreatic amylase. Additional enzymes secreted by the intestinal villi further facilitate absorption by converting sucrose into glucose and fructose, maltose into two glucose molecules, and lactose into galactose and glucose. After facilitated diffusion (fructose) or active transport (galactose and glucose), absorbed sugars are then transported to the liver via the portal system where galactose and fructose 1 are converted to glucose. The liver can store up to 100 g of glucose a day by converting it into glycogen (i.e., glycogenesis). It can also release glucose into the circulation by breaking down glycogen (i.e., glycogenolysis) or by creating new glucose from metabolic substrates (i.e., gluconeogenesis). Whether glucose is stored as glycogen or exported back into the systemic circulation is under tight

neurohormonal control. In times of ample glucose, insulin stimulates glycogenesis and glycolysis. In contrast, in times of fasting, glucagon stimulates glycogenolysis and gluconeogenesis.[1] Catecholamines can also influence the availability of glucose with epinephrine inhibiting glycogenesis and promoting glycogenolysis.[2]

Glycogenesis and Glycogenolysis

The first step in glycogen storage is the creation of glucose-6-phosphate (G6P) from glucose and G6P is then converted to glucose-1-phosphate followed by the creation of uridine diphosphate (UDP)-glucose. Glycogen synthase then anchors UDP-glucose to growing glycogen chains, creating a final molecule that can reach 107 daltons. Because complete oxidation of one molecule of G6P generates 37 molecules of ATP, and its creation only uses one molecule of ATP, the overall efficiency of glucose storage as glycogen is a remarkable 97%.

The release of glucose from glycogen, or glycogenolysis, however does not occur by simple reversal of glycogenesis. Following a series of cyclic AMP and kinase-mediated activations, each molecule of glucose on the glycogen chain is eventually released by glycogen phosphorylase which leads to the formation of G6P (**Fig. 2.1**). The conversion of G6P to glucose is catalyzed by glucose-6-phosphatase, an enzyme that exists only in hepatocytes, kidney, and intestinal epithelial cells. As such, once glucose is absorbed it is directly utilized by the majority of cells and not re-released into circulation.

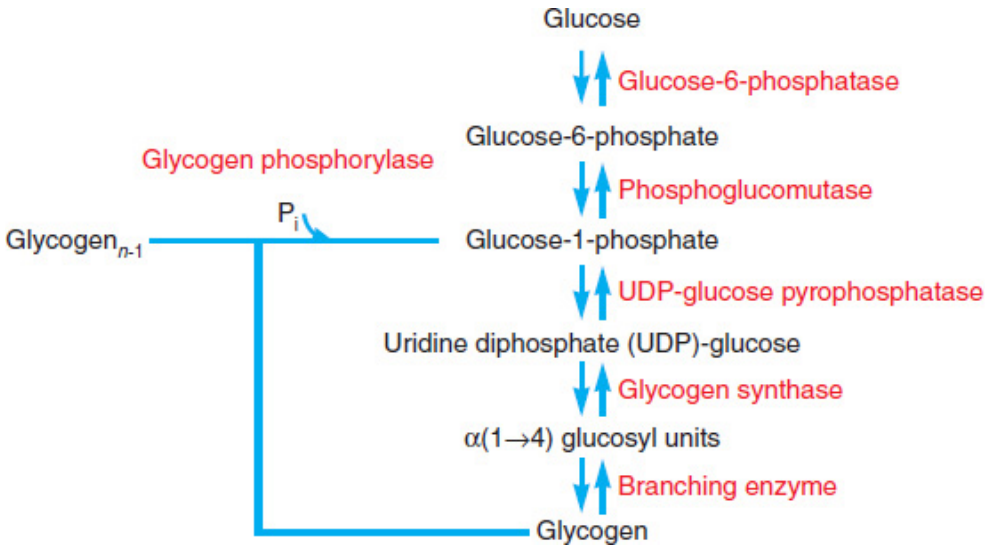

Figure 2.1 The chemical reactions of glycogenesis and glycogenolysis. Glucose-6-phosphatase allows hepatic glucose to be transported out of the hepatocyte for use in other tissues. Glucose-6-phosphate plays a central role in carbohydrate metabolism.

Glycolysis

Glycolysis is an oxygen-independent pathway by which glucose is converted to pyruvate in the cytoplasm. Although the process requires 10 enzymatic reactions, 3 are rate limiting and include hexokinase (or glucokinase in the liver), phosphofructokinase, and pyruvate kinase. As a result, a number of metabolic intermediates can either enter the glycolytic pathway at these various steps or they can exit to join other metabolic pathways depending on the needs of the organism (**Fig. 2.2**). During times of glucose excess, hepatic glycolysis can generate energy in the form of ATP, but the oxidation of ketoacids is a preferred energy source in liver. Overall, glycolysis results in the following biochemical equation:

$$\text{Glucose} + 2\ NAD^+ + 2\ ADP + 2P_i = 2\ \text{Pyruvate} + 2\ NADH + 2\ H^+ + 2\ ATP$$

While energetically favorable, this equation is not perpetual and cytosolic NAD^+ must be rejuvenated for this reaction to continue. In the absence of oxygen, NAD^+ is recovered when NADH is used to convert pyruvate to lactate in a process known as lactic acid fermentation. Because lactate levels

are proportional to ongoing tissue oxygen deficits, serum values can be used to gauge the degree of tissue perfusion during shock and the success of resuscitative therapies.[3]

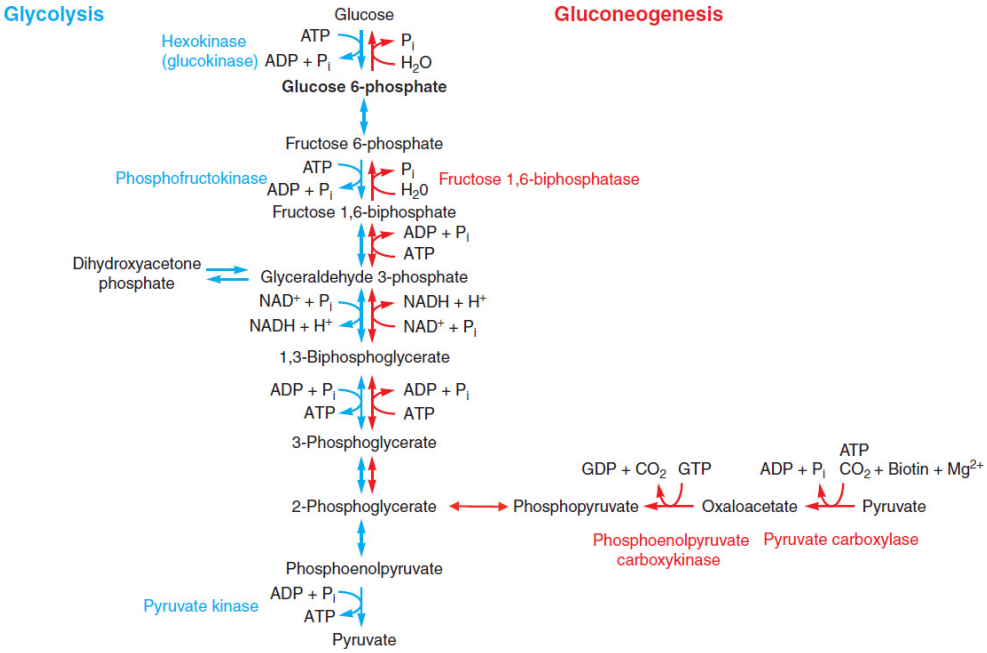

Figure 2.2 The glycolytic and gluconeogenesis pathways. Phosphofructokinase is the key regulatory enzyme in this glycolytic pathway. The irreversible nature of the glycolytic pathway means that a different sequence of biosyntheses is required for glucose production, or gluconeogenesis. In mammals, glucose can only be synthesized from cytosolic pyruvate. All the enzymes in *red* catalyze irreversible reactions.

In the presence of oxygen, however, NAD+ is recouped when electrons from NADH are "shuttled" across the impermeable inner mitochondrial membrane using the malate–aspartate or the glycerol phosphate shuttles. Simultaneously, pyruvate is transformed into acetyl CoA, CO_2 and NADH + H^+ within the mitochondria. Acetyl CoA then enters the Krebs cycle where additional intramitochondrial NADH is created (**Fig. 2.3**). In a process known as oxidative phosphorylation, electrons from intramitochondrial NADH (or $FADH_2$) are transferred through the electron transport chain and ultimately transferred to oxygen to form water. The energy released during this process creates a hydrogen ion gradient across the inner mitochondrial membrane that drives the formation of 2.5 ATP for every NADH oxidized.

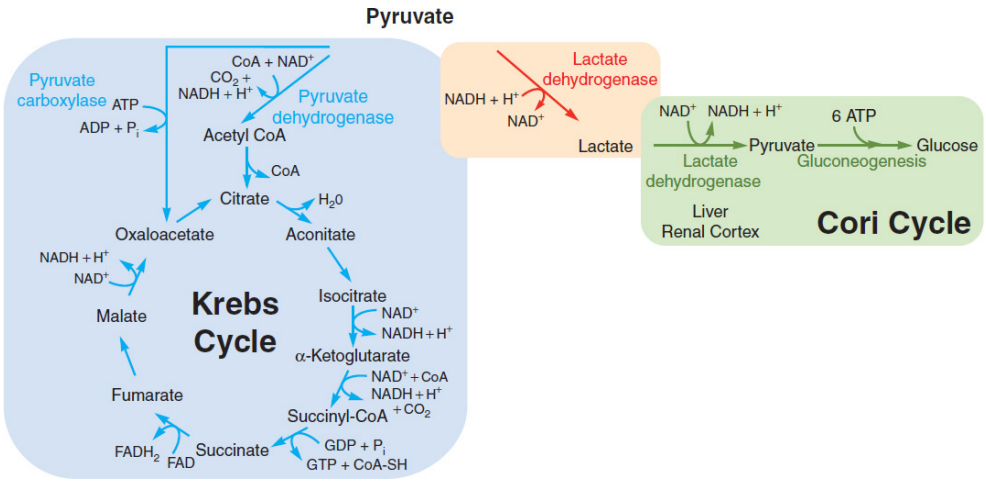

Figure 2.3 Pyruvate plays a key role in cellular metabolism. During hypoxic conditions (*red* box), pyruvate undergoes lactic acid fermentation. The Cori cycle (*green* box) is an elegant mechanism for the liver to convert systemic lactate into new glucose. In the presence of oxygen (*blue* box), pyruvate is converted to Acetyl CoA, or oxaloacetate, and enters the Krebs cycle to produce NADH and $FADH_2$ which will then drive the generation of ATP through oxidative phosphorylation.

The Cori Cycle

Under normal conditions, large quantities of lactate are made from active skeletal muscles and erythrocytes. Lactate can also be made during seizures, in the setting of shock, and in patients 2 with large wounds or burns. Thankfully, in the presence of oxygen, the liver is exceptionally efficient at converting lactate to pyruvate through the Cori cycle (**Fig. 2.3**). As such, even patients with cirrhosis do not exhibit elevated lactate levels at baseline although the rate at which a lactate load is cleared does correlate with liver function.[4] The kidneys also play a key role in lactate clearance with up to 20% to 30% of serum loads being metabolized and/or actively excreted. Thus, significant renal dysfunction will impair lactate clearance.

Gluconeogenesis

Glucose is absolutely required for cellular function and levels are tightly regulated in order to prevent brain dysfunction, coma, and death. When blood glucose levels fall, glucagon is secreted by the pancreas and there is a concomitant decrease in insulin secretion. Glucagon stimulates both

glycogenolysis (see above) as well as gluconeogenesis. Although the majority of gluconeogenesis occurs in the liver, the kidney becomes a key site in diabetics, during critical illness and with prolonged fasting.[5]

Gluconeogenesis creates new glucose from a variety of sources that primarily enter via the creation of pyruvate or oxaloacetate. Gluconeogenic precursors include glucogenic amino acids from the metabolism of proteins, glycerol and odd-chain fatty acids from the breakdown of lipids, and pyruvate and lactate from the glycolysis of carbohydrates. In humans, however, over 90% of new glucose is derived from lactate, glycerol, alanine and glutamine.

Gluconeogenesis is not a simple reversal of the glycolytic pathway and requires four separate, functionally irreversible enzymatic reactions to convert pyruvate into glucose (**Fig. 2.2**). Gluconeogenesis begins in the mitochondria where pyruvate carboxylase converts pyruvate into oxaloacetate. This reaction is stimulated by high levels of acetyl CoA and inhibited by high levels of ADP and glucose. Oxaloacetate is then reduced to malate using NADH and exported out of the mitochondria where it is reoxidized to oxaloacetate in the cytosol. Oxaloacetate is irreversibly transformed into phosphoenolpyruvate by phosphoenolpyruvate carboxykinase. The next reactions are the same as glycolysis but in reverse. Fructose-1,6-bisphosphatase, however, converts fructose-1,6-biphosphate into fructose-6-phosphate which is subsequently converted to glucose-6-phosphate. Glucose-6-phosphate can either feed into other metabolic pathways (e.g., pentose phosphate pathway [PPP]) or it can be hydrolyzed by glucose-6-phosphatase in the endoplasmic reticulum to produce free glucose that can easily diffuse out of the cell.

Pentose Phosphate Pathway

3 The PPP is an anabolic pathway that uses excess glucose to generate NADPH, 5-carbon sugars known as pentoses, and ribose-5-phosphate, a necessary component of nucleotides and nucleic acids (**Fig. 2.4**). These cytosolic reactions take place in two distinct phases. The first is an oxidative phase in which NADPH is generated utilizing the energy released when glucose-6-phosphate is converted to ribulose 5-phophate by the rate-limiting enzyme glucose-6-phosphate dehydrogenase (G6PD). NADPH is an essential

bioreductive molecule that is required for fatty acid, cholesterol, and steroid biosynthesis. It also plays a key role in preventing oxidative stress by generating reduced glutathione, a major scavenger of reactive oxygen species. NADPH is particularly important in maintaining red blood cell integrity because these cells lack mitochondria. As such, these cells have no alternative means of generating reducing power and no other way of mitigating oxidative damage. Indeed, patient with G6PD deficiency are at increased risk of hemolysis when exposed to fava beans, infections, aspirin, and other medications that increase oxidative stress and promote the formation of methemoglobin. In contrast, neutrophils and macrophages use NADPH to generate bacteria-killing superoxide radicals. Thus, patients with G6PD are also at increased risk of severe infections and sepsis.[6]

The second phase of the PPP is a series of nonoxidative reactions that converts ribulose 5-phophate into ribose 5-phosphate in order to synthesize RNA, DNA, ATP, NAD, FAD, or coenzyme A. Intermediates of the glycolytic pathway can enter and exit the PPP at various points with 5-phophate and other three-, four-, five-, six-, and seven-carbon sugars undergoing a series of nonoxidative interconversions (**Fig. 2.4**). Thus, the nonoxidative branch of the PPP can not only replenish the metabolites of the oxidative branch, it can regulate the flux of glycolysis or gluconeogenesis.

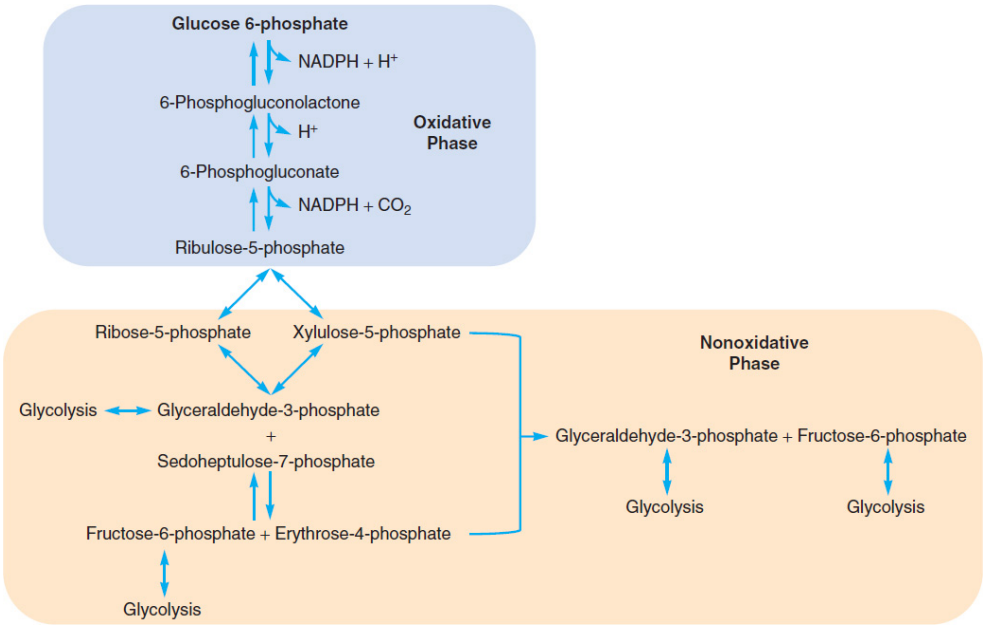

Figure 2.4 The Pentose Phosphate Pathway is divided into an oxidative phase (*blue* box) and a nonoxidative phase (*orange* box). One of the major purposes of this pathway is to generate reduced nicotinamide adenine dinucleotide, which can serve as an electron donor and allow the liver to perform reductive biosynthesis. Glucose-6-phosphate plays a central role and can be generated either through glycolysis or gluconeogenesis.

LIPID METABOLISM

Although fats are digested to a minimal degree by lingual and gastric lipases, the majority of lipid digestion occurs in the small intestine. When chyme reaches the duodenum, it stimulates the release of cholecystokinin (CCK) from the intestinal epithelial cells. CCK causes the gallbladder to contract releasing bile salts and stimulates the secretion of pancreatic lipase. Once emulsified by bile salts, pancreatic lipase breaks down each triglyceride into two free fatty acids (FFAs) and a monoglyceride. Short- and medium-chain FFAs (less than 10 to 12 carbons) are relatively water soluble and diffuse directly into the enterocyte where they enter the portal venous system. In contrast, long-chain fatty acids are hydrophobic and require encapsulation by micelles, or tiny spheres of bile salts and lecithin that create a hydrophobic core and hydrophilic exterior. The hydrophilic surface of the micelle enhances close contact with the enterocyte such that simple diffusion of the

fatty acid can then occur. Micelles also aid in the absorption cholesterol and fat soluable vitamins.

Given their relative hydrophobicity, triglycerides in circulation are carried by various lipoproteins of different densities and compositions. Once absorbed, FFAs and monoglycerides recombine within the enterocyte into triglycerides. Triglycerides are then packaged with phospholipids, cholesterol, and proteins into chylomicrons, a lipoprotein that enters the lymphatic circulation via exocytosis. After leaving the lymphatic system and entering the systemic circulation via the thoracic duct, chylomicrons can either go to the liver to be processed or they can be stored in adipocytes for later use. Once absorbed by the liver, triglycerides can either be converted into energy via lipolysis or they can be combined with proteins in the Golgi apparatus, processed in the endoplasmic reticulum, and exported to extrahepatic tissues as very–low-density lipoproteins (VLDLs). Low-density lipoproteins (LDLs) are subsequently formed when triglycerides are removed from VLDL by lipoprotein lipase thereby creating a smaller, denser, and more cholesterol-rich molecule. LDLs provide cholesterol to cells and may be oxidized in the vascular wall leading to atherosclerosis. In contrast, high-density lipoproteins (HDLs) are the smallest, most dense lipoprotein with the highest protein-to-lipid ratio. HDLs transport lipids out of tissues like the vasculature, decrease macrophage accumulation, and are associated with decreased atherosclerosis.[7]

Just like chylomicrons, VLDLs, HDLs, and LDLs have a nonpolar lipid core with a surface of phospholipids, cholesterol, and apolipoproteins. Different types apolipoproteins provide not only structure, but also serve as ligands, enzymatic cofactors, or inhibitors. For example, the apolipoprotein C-II serves as a cofactor for lipoprotein lipase and whereas the both apoliprotein B-100 and E serve as ligands for the LDL receptor.

Finally, fatty acids mobilized from adipocytes or liberated from plasma triglycerides can be “free” in the circulation. These FFAs are bound to serum albumin and can be taken up by target tissues such as the heart, skeletal muscle, and liver. FFAs are the main source of fuel during fasting or when glucose is not available. However, increased concentrations of FFAs correlate with higher rates of obesity and are associated with development of insulin resistance.[8]

Lipolysis

4 Fat is a highly energetic fuel source with triglycerides yielding more than twice the energy per unit mass when compared to proteins or carbohydrates. Lipolysis, or the hydrolysis of fat for energy, begins by breaking down each triglyceride molecule into one glycerol and three fatty acids. The glycerol enters glycolysis as dihydroxyacetone phosphate whereas the fatty acids undergo beta oxidation in the mitochondria. In order to cross the mitochondrial membrane, fatty acids in the cytosol must first be converted to fatty acyl CoA which then combines with carnitine via the rate-limiting enzyme carnitine palmitoyltransferase-1. Once in the mitochondrial matrix, the fatty acyl carnitine molecules are converted back to fatty acyl CoA. Beta oxidation occurs by cleaving two carbons from the fatty acyl CoA molecule in a four-step reaction to create acetyl CoA. This process continues until all the carbons of the fatty acyl CoA molecule are converted to acetyl CoA, or propionyl CoA in the case of odd-numbered fatty acids. Acetyl CoA can then take one of the following routes: (a) enter the Krebs cycle and be degraded to carbon dioxide, (b) enter the Krebs cycle and be converted to citrate for fatty acid synthesis, or (c) be converted into 3-hydroxy-3-methylglutaryl CoA (HMG-CoA), a precursor of cholesterol and ketone bodies (**Fig. 2.5**).[9]

Ketogenesis and Ketone Oxidation

5 Excessive lipolysis can result in the production of ketone bodies. During periods of starvation or with uncontrolled diabetes where there is insufficient insulin to utilize serum glucose, hepatic oxidation of fatty acids leads to an overall abundance of acetyl CoA. The excess acetyl CoA overwhelms the Krebs cycle and is subsequently diverted to create ketone bodies as an alternative fuel source. In the mitochondria, ketogenesis begins with two acetyl CoA–forming acetoacetyl CoA which is then transformed into hydroxymethylglutaryl CoA (HMG-CoA). HMG-CoA is then converted to the ketone body, acetoacetate. Although the majority of acetoacetate is reduced to beta-hydroxybutyrate, a small amount is converted to acetone. When ketones are produced faster than they can be used, the overall percentage of serum acetone increases. Acetone is removed by exhalation which gives the breath a fruity odor.

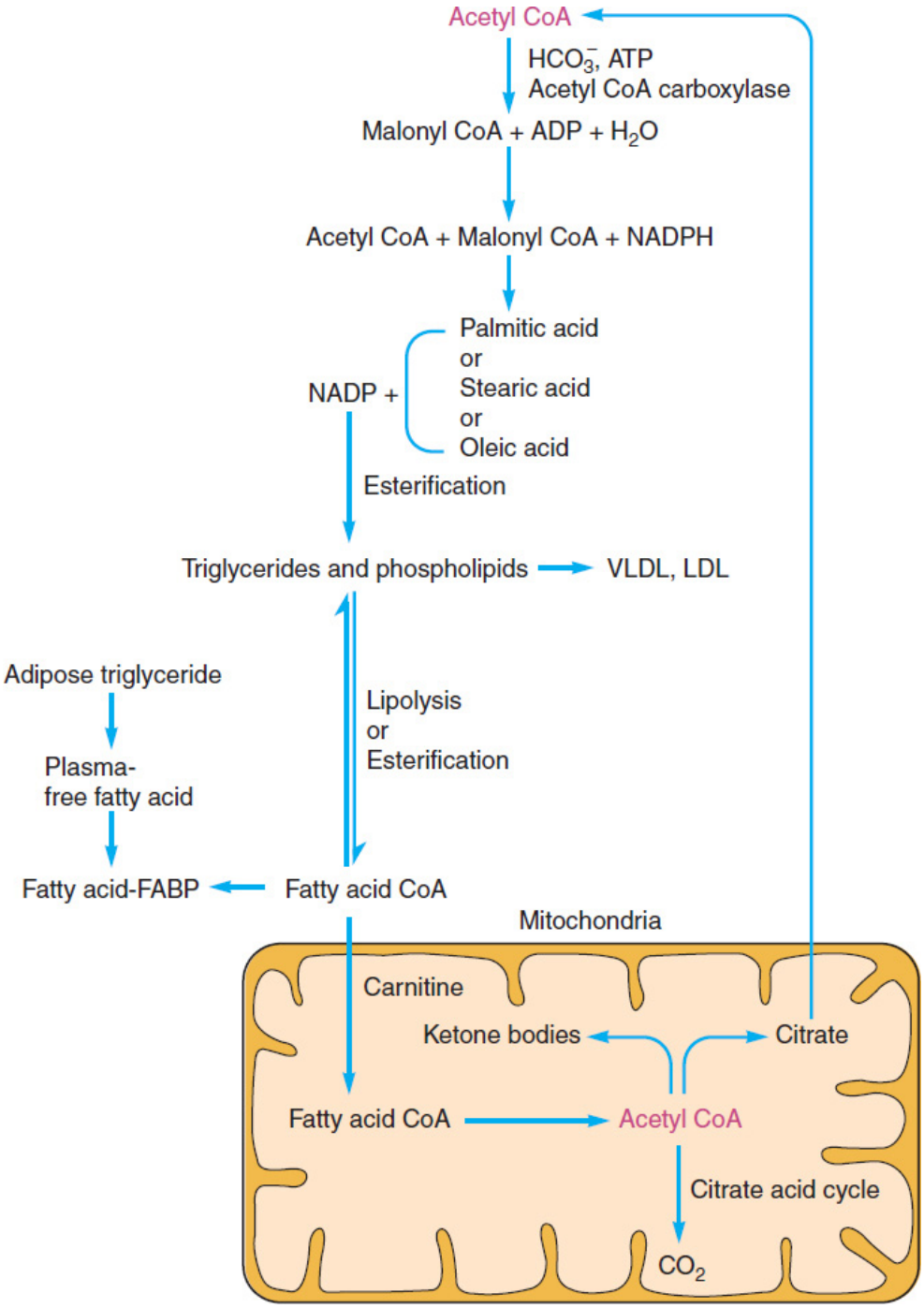

Figure 2.5 Diagram of hepatic fatty acid metabolism. Both dietary and newly synthesized fatty acids are esterified and subsequently degraded in the mitochondria for energy, first as reducing equivalents, then adenosine triphosphate via the electron transport chain. Acetyl CoA, in *red*, plays a central role in lipid metabolism.

Both acetoacetate and beta-hydroxybutyrate can pass easily through membranes and serve as key energy sources during fasting. This is particularly true for the brain which cannot directly metabolize fatty acids. Interestingly, although the liver produces ketone bodies, it lacks succinyl CoA transferase, the enzyme needed to use ketones for energy.

Lipogenesis

The intake of surplus glucose can stimulate lipogenesis, or the creation of triglycerides stored as fat in adipocytes and hepatocytes. In the cytoplasm, excess acetyl CoA is converted to malonyl CoA by acetyl CoA carboxylase in a rate-limiting step stimulated by insulin. Malonyl CoA, in turn, inhibits the mitochondrial uptake of fatty acid CoA in favor of triglyceride synthesis and serves as the building block for the creation of larger fatty acids. Fatty acids are then esterified to glycerol in the endoplasmic reticulum to create triglycerides, which can either be transported to extrahepatic tissues via VLDLs or stored in hepatocytes. Hepatic storage of triglyceride or fatty infiltration of the liver can be significant, leading to the development of nonalcoholic steatohepatitis (NASH). In many developed countries, NASH is the most common cause of liver disease and is rapidly becoming the number one indication for liver transplantation.[10]

Cholesterol Metabolism

Cholesterol is an important regulator of membrane fluidity and is a substrate for bile acid and steroid hormone synthesis. Most plasma cholesterol is esterified with oleic or palmitic acid. Cholesterol can be ingested or it can be created de novo 6 from its precursor, acetyl CoA. Increased dietary intake of cholesterol suppresses endogenous synthesis by inhibiting the rate-limiting enzyme, HMG-CoA reductase. This key enzyme can also be pharmacologically inhibited by statins which act as competitive antagonists and effectively lower plasma cholesterol by blocking cholesterol synthesis.[11] Perhaps more importantly, decreased levels of hepatic cholesterol stimulate the expression of LDL receptors on the liver leading to increased removal and metabolism of serum LDL lipoproteins.

Phospholipids

Phospholipid formation is controlled by the overall rate of fat metabolism and by the availability of choline and inositol. Phospholipids are amphiphilic and are essential for reducing surface tension between membranes and surrounding fluids. As such, the main role of phospholipids is to form plasma and organelle membranes. Although most cells in the body are capable of some phospholipid synthesis, the liver produces 90%. The three major classes of phospholipids synthesized by the liver are lecithins, cephalins, and sphingomyelins. Phosphatidylcholine, one of the lecithins, is the major biliary phospholipid and promotes the secretion of free cholesterol into bile. Thromboplastin, one of the cephalins, is needed to initiate the clotting cascade. The sphingomyelins are necessary for the formation of the myelin nerve sheath.

PROTEIN METABOLISM

Much of the body is made of protein and its metabolism includes both anabolism, or the synthesis of amino acids and proteins, and catabolism, or the breakdown of proteins. Although proteins can be synthesized from amino acids, humans cannot create nine amino acids which must come from 7 the diet. These "essential" amino acids include histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Arginine is a conditionally essential amino acid and depends on the developmental stage of the individual. For example, preterm infants are unable to synthesize arginine. The remaining 11 amino acids can be generated from intermediates of the Krebs cycle and the PPP (**Table 2.1**).

Protein metabolism begins with digestion in the stomach where hydrochloric acid denatures the proteins and pepsin breaks them into smaller polypeptides and amino acids. Once in the duodenum, pancreatic enzymes including trypsin, chymotrypsin, and elastase are activated by enterokinase in order to digest proteins into individual amino acids. Amino acids are subsequently absorbed using sodium–amino acid transporters. Free amino acids can then be used to make proteins. Although all tissues can make proteins, the liver is particularly prolific and can generate up to 50 g/d.

Hepatic protein synthesis includes albumin, fibrinogen, apolipoproteins, purines, heme proteins, and hormones. Of the total hepatic protein synthesized, 75% is destined for export. Unfortunately, excess amino acids cannot be stored for later use and must be converted to glucose or triglycerides. Excess amino acids can also be degraded resulting in nitrogenous waste that is cleared by the urea cycle (see below).

CLASSIFICATION

Table 2.1 Amino Acids Required by Adult Humans

Nutritionally Essential	Nutritionally Nonessential	
	Amino Acid	Precursor
Arginine	Alanine	Pyruvate
Histidine	Asparagine	Oxaloacetate
Isoleucine	Aspartate	Oxaloacetate
Leucine	Cysteine	Methionine
Lysine	Glutamate	α-Ketoglutarate
Methionine	Glutamine	α-Ketoglutarate
Phenylalanine	Glycine	3-Phosphoglycerate
Threonine	Hydroxyproline	α-Ketoglutarate
Tryptophan	Hydroxylysine	Lysine
Valine	Proline Serine Tyrosine	α-Ketoglutarate 3-Phosphoglycerate Phenylalanine

Proteins can also be catabolized, or broken down, into amino acids. Protein degradation occurs primarily by one of two routes. Proteins can be internalized into lysosomes via receptor-mediated endocytosis. The lysosomal enzymes do not require ATP and are nonselective in their

activities. A second pathway involves the covalent attachment of ubiquitin targeting proteins for destruction. This pathway is ATP dependent and generally is used for proteins with shorter half-lives. Liberated amino acids can then be used for new protein synthesis or they can be broken down into their carbon skeleton and amino groups by a transamination reaction. The carbon components are then converted to glucose, triglycerides, or Krebs cycle intermediates whereas the amino group is transferred to pyruvate, oxaloacetate, or α-Ketoglutarate converting it to alanine, aspartate, or glutamate respectively (**Fig. 2.6**).

THE UREA CYCLE

When amino acids are broken down for energy, the amino group is transferred to α-Ketoglutarate to form glutamate. Glutamate is then converted back to α-Ketoglutarate by glutamate dehydrogenase in reaction that generates both NADH and ammonium, a toxic metabolite. Ammonia is eliminated in the urea cycle, also known as the ornithine cycle. In the liver and kidney, ammonia combines with CO_2 in a series of five reactions of to create water and urea. The overall equation of the urea cycle is: $NH_3 + CO_2$ + aspartate + 3ATP + $2H_2O$ -> urea + fumarate + 2ADP + $2P_i$ + AMP + PP_i. The urea is then excreted in the urine.

CELLULAR ENERGY GENERATION

Overview

The fundamental mechanism by which mammalian cells generate energy is the aerobic conversion of sugars and fatty acids 8 into ATP. Stage I, glycolysis, occurs in the cytosol, and converts glucose into two molecules of pyruvate (see above). Cytosolic fatty acids are also converted to fatty acyl CoA. Pyruvate and fatty acyl CoA are then transported to the mitochondrial matrix where they are converted to acetyl CoA, a key metabolic intermediate, and in the process generates NADH, $FADH_2$, and CO_2. In stage II, mitochondrial acetyl CoA enters the Krebs cycle further generating NADH,

$FADH_2$, additional CO_2, and GTP. In stage III, oxygen is reduced to water via the electron transport chain using previously generated molecules of NADH and $FADH_2$ as electron donors. The electron transport chain causes hydrogen ions to move from the mitochondrial matrix to the intermembrane space generating a proton motive force. Lastly, in stage IV, ATP synthase uses energy generated by the proton motive force to generate large amounts of ATP.[12]

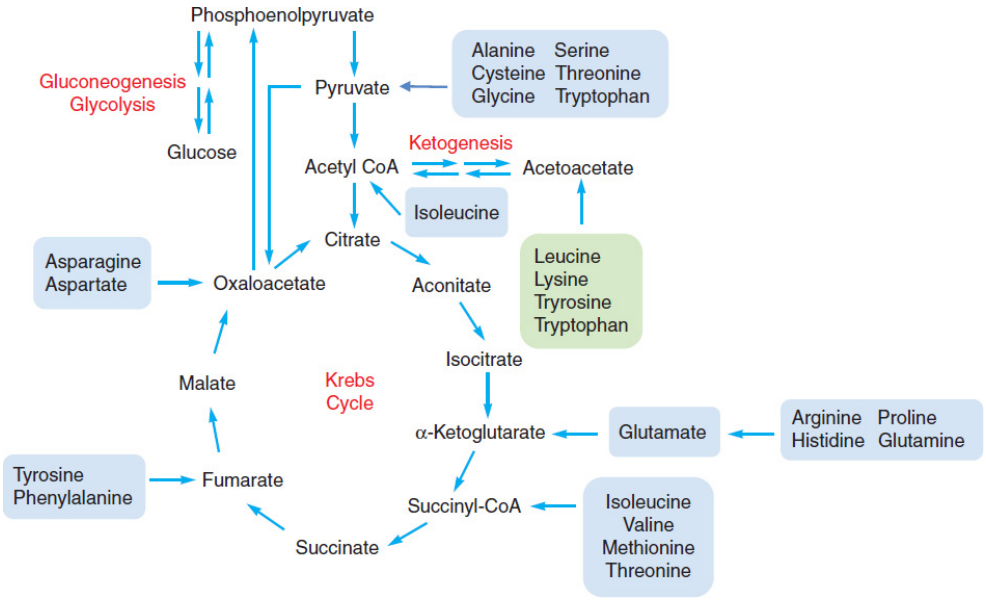

Figure 2.6 Amino acid degradation. Some amino acids such as glutamate can undergo direct deamination to their corresponding ketoacid (α-ketoglutarate). However, most amino acids undergo an initial transamination where the amino group is transferred to α-ketoglutarate, yielding glutamate and a ketoacid. The resulting glutamate is then deaminated to α-ketoglutarate and the ketoacids are converted to Krebs cycle metabolites. Some amino acids are glucogenic (*blue* boxes), while others are ketogenic (*green* boxes) and yield acetoacetyl CoA, and thus, ketone bodies. Note that some amino acids can be either glucogenic or ketogenic.

Stage II: The Krebs Cycle—Integration of Metabolic Pathways and Oxidation of Acetyl CoA

The Krebs cycle not only acts as a common pathway for the oxidation of carbohydrate, lipid, and protein, it also provides substrates for

gluconeogenesis, lipogenesis, and amino acid metabolism depending on the energy needs. As such, the metabolism of sugars, fats, and proteins changes can change rapidly based on conditions ranging from fed to fasting to starvation. Three key metabolites, G6P, pyruvate, and acetyl CoA orchestrate the fine balance between catabolism and anabolism (**Fig. 2.3**).

G6P can be stored as glycogen or converted into glucose, pyruvate, or ribose-5-phosphate (a nucleotide precursor). Pyruvate can be converted into lactate, alanine (and other amino acids), and acetyl CoA, or it can enter the Kreb cycle after conversion to oxaloacetate. Acetyl CoA that does not proceed through the whole Krebs cycle can be converted to HMG-CoA (a cholesterol and ketone body precursor depending on cellular location) or citrate for fatty acid and triglyceride synthesis. In humans, acetyl CoA cannot be converted into pyruvate due to the irreversible reaction of pyruvate dehydrogenase.

Probably the most important Krebs cycle function is to oxidize acetyl CoA into CO_2. The Krebs cycle is a series of enzymatic reactions that occur in the mitochondrial matrix and inner membrane. Here, acetyl CoA combines with oxaloacetate to form citrate. Through a series of subsequent enzymatic reactions involving both dehydrogenases and decarboxylases, each revolution of the Krebs cycle, generates three molecules of the reduced coenzyme NADH, one molecule of the reduced coenzyme $FADH_2$, and one molecule of GTP. The reduced coenzymes NADH and $FADH_2$ are charged with high-energy electrons that subsequently drive the electron transport chain (stage III) to generate a hydrogen ion gradient. Each molecule of NADH yields three molecules of ATP, and each molecule of $FADH_2$ generates two molecules of ATP. One molecule of ATP is created at the substrate level when succinyl CoA is converted to succinate; thus, a total of 12 molecules of ATP are generated per molecule of acetyl CoA.

Stages III and IV: Oxidative Phosphorylation

Oxidative phosphorylation uses the energy from NADH and $FADH_2$ to generate ATP. Electrons donated from NADH and $FADH_2$ are transferred down the proteins of the electron transport chain in a series of redox

reactions that ultimately create water from O_2. Electrons from NADH are transferred through complex I (NADH-CoQ reductase) to coenzyme Q (CoQ) whereas those from $FADH_2$ enter the electron transport chain via complex II (succinate-Q dehydrogenase). Complex II is also part of the Krebs cycle and the transfer of electrons from $FADH_2$ to CoQ is coupled with the oxidation of succinate to fumarate. Electrons then travel from CoQ to complex III (Q-cytochrome c oxoreductase) and finally to complex IV (cytochrome c oxidase). At complex IV, oxygen accepts the electron and is reduced to water. This final reaction releases half of all the energy in aerobic respiration. The energy transferred during the flow of electrons through the electron transport chain is used to pump protons across the mitochondrial inner membrane. This generates potential energy by creating both a pH gradient and a voltage gradient known as the proton motive force. ATP synthase uses the proton motive force to drive the conversion of ADP to ATP in a phosphorylation reaction. **Figure 2.7** is an admittedly simplified explication of a complex process.

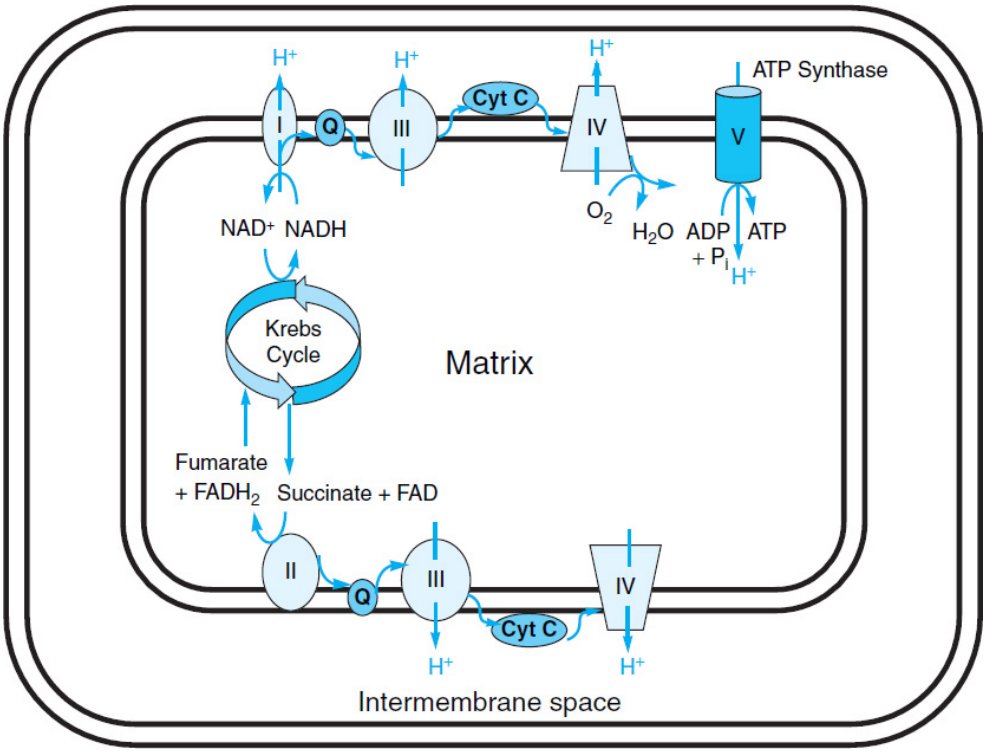

Figure 2.7 The electron transport chain. Electrons are donated from NADH and flow through complex I to complex III via the lipid-soluble molecule Coenzyme Q. From complex III, the electrons are transported through the intermembrane space by cytochrome *c* to complex IV. For every two electrons that flow from NADH to O_2, 10 protons are pumped to the intermembranous space creating a proton motive force. Electrons can also be donated during the conversion of succinate to fumarate via $FADH_2$. Electrons then flow from complex II from to complex III as previously described. For every two electrons that flow from $FADH_2$ and succinate to O_2, six protons are pumped to the intermembranous space. Complex V, or ATP synthase, then uses the proton motive force to drive the creation of ATP.

BIOTRANSFORMATION

Biotransformation is defined as the intracellular metabolism of endogenous organic compounds (e.g., heme proteins and steroid hormones) and exogenous compounds (e.g., drugs and environmental compounds). Most biotransformation occurs in the liver, which contains enzyme systems that can expose functional groups, such as hydroxyl ions (phase I reactions), or alter the size and solubility of a wide variety of organic and inorganic compounds by conjugation with small polar molecules (phase II reactions).[13] A general

strategy is to convert hydrophobic, potentially toxic compounds into hydrophilic conjugates that can then be excreted into bile or urine.

Biotransformation of compounds mainly occurs by the cytochromes P-450, the uridine diphosphate-glucuronyl (UDP-glucuronyl) transferases, the GSH S-transferases, and the sulfotransferases. 9 Biotransforming enzymes are not distributed uniformly within the cells of the hepatic lobule. This heterogeneity may account for the ability of some drugs to cause damage preferentially in zone 3 hepatocytes which are closest to the central venule.

Cytochromes P-450

The cytochromes P-450 are named for their ability to absorb light maximally at 450 nm in the presence of carbon monoxide. These enzymes are bound to the endoplasmic reticulum and collectively catalyze reactions by using NADPH and oxygen. P-450 isozymes catalyze a number of reactions including oxidation, hydroxylation, sulfoxide formation, oxidative deamination, dealkylation, and dehalogenation. Such reactions allow further phase II conjugation with polar groups such as glucuronate, GSH, and sulfate. The cytochromes P-450 can also create potentially toxic metabolites. Drugs such as acetaminophen, isoniazid, halothane, and phenothiazines can be converted into reactive forms that cause cellular injury and death. These cytochromes also are responsible for the formation of free radicals that can directly injure cells or act as haptens in the generation of an autoimmune response. In fact, cytochromes P-450s modify several of the most potent aromatic carcinogens.

Uridine Diphosphate-Glucuronyl Transferases

Glucuronidation is the conjugation of UDP-glucuronic acid to a wide variety of molecules by either ester (acyl) or ether linkages. The transferases catalyzing these reactions reside in the endoplasmic reticulum. Many common compounds are metabolized in this way, including bilirubin, testosterone, aspirin, indomethacin, acetaminophen, chloramphenicol, and oxazepam. Clinically significant loss of activity can occur with acute ethanol

exposure or acetaminophen overdose, when formation of UDP-glucuronic acid from UDP-glucose is outstripped by use. Some acyl linkages lead to the generation of electrophilic centers that can react with other proteins. The covalent linkage of conjugated bilirubin to albumin is believed to occur by this mechanism.

Glutathione S-transferases

The GSH transferases are more selective and GSH conjugation occurs only with compounds that have electrophilic and potentially reactive centers. The role of GSH conjugation is demonstrated by acetaminophen. In metabolism of this drug, cytochromes P-450 create an electrophilic center that reacts with protein thiol groups or GSH. The presence of GSH S-transferase allows the preferential detoxification of acetaminophen rather than its potentially injurious binding to thiol groups. A class of GSH S-transferases, known as *ligandins,* appears to facilitate the uptake and intracellular transport of bilirubin, heme, and bile acids from plasma to liver. In addition to the detoxification of potential toxins, GSH is a substrate for GSH peroxidase, an enzyme important in the metabolism of hydrogen peroxide.

Sulfotransferases

The sulfotransferases catalyze the transfer of sulfate groups from 3′-phosphoadenosine-5′-phosphosulfate (PAPS) to compounds such as thyroxine, bile acids, isoproterenol, methyldopa, and acetaminophen. They are located primarily in the cytosol. Although many P-450 derivatives can be further conjugated by either the sulfotransferases or the glucuronyl transferases, the limited ability of the liver to synthesize PAPS makes glucuronidation the predominant mechanism.

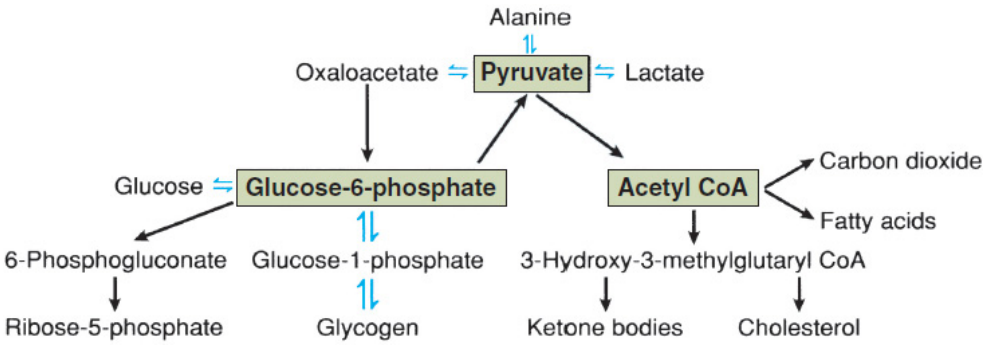

Figure 2.8 Summation of the key regulatory molecules used by the liver during diverse metabolic functions. Essentially, any compound found in the body can be synthesized in the liver from glucose-6-phosphate, acetyl coenzyme A, or pyruvate. As a consequence of the inability of mammalian liver to convert acetyl coenzyme A to pyruvate, fats cannot be converted to carbohydrates.

SUMMARY

Although the fundamentals of intermediary metabolism have been known for years, knowledge of how these details impact health and disease is continuously growing. A summary of the key regulatory molecules and their interconnected metabolic pathways can be found in **Figure 2.8**. A working understanding of the fundamental biochemical reactions by which substrates are metabolized is important for all surgical disciplines. Advanced knowledge of the genetics, cellular biology, bioenergetics, and molecular biology is being exploited to support and perhaps enhance general and specialized cellular function, combat disease, and improve health.

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3

Surgical Nutrition and Metabolism

Melissa H. Coleman and Deborah M. Stein

Key Points

1. In the absence of indirect calorimetry, critically ill patients should be provided nutritional support targeting 25 to 30 kcal/kg/day.
2. Assessment of nutritional status is key in the perioperative period. Malnutrition is associated with worse outcomes after injury or surgery.
3. There is no single laboratory biomarker that accurately reflects a patient's nutritional status.
4. While adequate caloric intake is necessary to maintain weight and promote health, overprovision of calories can lead to overfeeding and obesity.
5. A strong relation between protein depletion and postoperative complications has been demonstrated in nonseptic, nonimmunocompromised patients undergoing elective major gastrointestinal (GI) surgery.
6. Preoperative optimization with nutritional support may be indicated in patients who are malnourished or at high risk of delayed initiation of postoperative nutritional support.
7. Critically ill patients should receive early enteral nutrition within 48 hours of admission to the intensive care unit. Nutritional support should prioritize the provision of adequate protein.
8. Enteral nutrition is preferable to parenteral nutrition in the presence of a functioning GI tract. Recent studies of parenteral nutrition versus enteral nutrition have not demonstrated increased mortality with parenteral nutrition. Parenteral nutrition should be utilized when enteral nutrition cannot be administered.
9. The maintenance of an intact brush border and intercellular tight junctions prevents the movement of toxic substances into the intestinal circulation and minimizes bacterial translocation. These functions may be affected in critical illness. Enteral nutrition helps restore them.

10 Routine glutamine supplementation is not supported during critical illness.

11 Routine monitoring of gastric residual volumes is not recommended. Postpyloric feeding can be used for patients at high risk of regurgitation or for patients with gastric feeding intolerance.

12 In the setting of sepsis, the BMR increases. Total energy requirements need to be assessed, increasing energy requirements by 20% to 30% for mild or moderate infection and approximately 50% above basal levels in severe infection.

INTRODUCTION

Surgery has a significant impact on the body, causing the release of stress hormones and is associated with a considerable inflammatory response. Nutritional support is needed to prevent and treat the catabolic state induced by surgery. Patients undergoing gastrointestinal (GI) procedures with evidence of malnutrition at baseline are more likely to suffer postoperative morbidity and mortality and require longer hospital stays than their well-nourished counterparts.[1–3] It has been shown that poor nutritional status can detrimentally affect postoperative outcomes, and in a consensus review of Enhanced Recovery After Surgery (ERAS), it was recommended that patients receive carbohydrate loading 24 hours preoperatively and nutritional supplements, from the day of surgery, until oral intake is achieved.[4]

In addition to patients undergoing elective surgery, severe injury and critical illness are associated with a hypermetabolic state that can increase energy expenditure dramatically and complicate the resuscitation and recovery of the critically ill or severe injury victim. Nutritional support is an integral part of the caring of the critically ill surgical patient, and the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN) have made recommendations toward providing early, aggressive nutritional support that enables patients to preserve their immune function, maintain lean body mass, and minimize metabolic complications.[5] This chapter addresses the areas of nutritional

assessment and management of the surgical patient, reviewing key metabolic principles and providing an overview of pertinent literature.

BASIC METABOLIC PRINCIPLES

Body Composition

Total body mass is composed of aqueous and nonaqueous components, with the former constituting approximately 55% to 60% of total body mass (total body water, TBW). Mineralized bone and adipose tissue make up the majority of the nonaqueous component. The relationship between total body mass and TBW is relatively constant for an individual and typically reflects the amount of body fat. Solid organs and muscle contain a higher proportion of water than bone and fat; therefore, young lean males have a higher proportion of their total body mass as water than obese or elderly individuals. Obesity, older age, and female gender shift the body composition to a greater fat mass (**Fig. 3.1**).[6]

The aqueous portion is divided into three functional fluid compartments: plasma (5% of body weight), interstitial or extracellular fluid (ECF; 15% of body weight), and intracellular fluid (ICF; 40% of body weight) (**Fig. 3.2**). In a typical 70-kg male, there are approximately 3.5 L of plasma, 10.5 L of interstitial fluid, and 28 L of intracellular volume while the remainder 28 kg represents the nonaqueous portion. Of the aforementioned, the body cell mass constitutes the metabolic engine of the body, while the extracellular component forms the supporting "scaffolding" for the body cell mass.

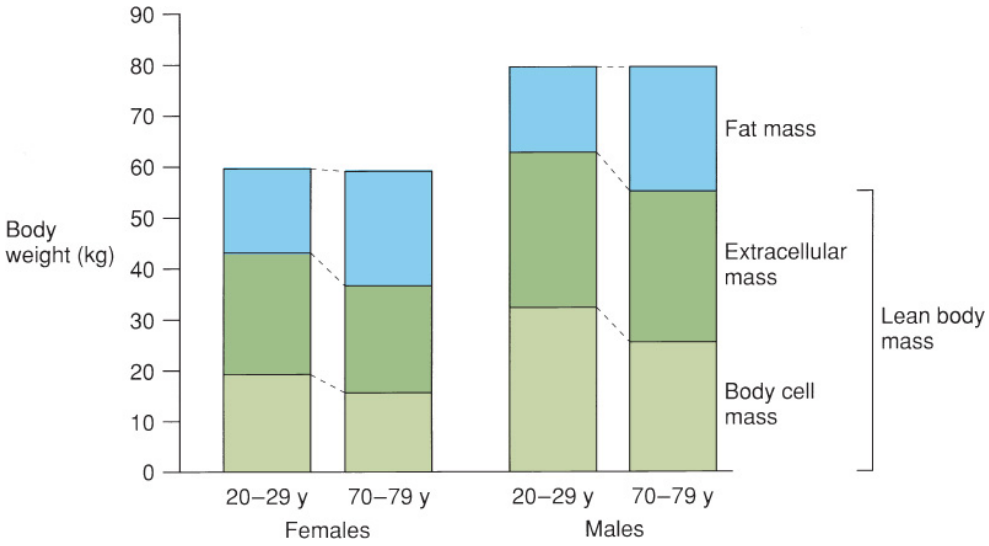

Figure 3.1 Body composition as a function of gender and age. (Data from Cohn SH, Vartsky D, Yasumura S, et al. Compartmental body composition based on total-body nitrogen, potassium, and calcium. *Am J Physiol-Endocrinol Metab* 1980;239(6):E524–E530.)

ENERGY AND SUBSTRATE METABOLISM

Measuring Energy Expenditure

In healthy individuals, total energy expenditure (TEE) reflects the activity of the fat-free mass (FFM) which primarily comprises organ systems that are highly metabolic, including the brain, heart, liver, and kidneys.[7] More specifically, TEE is the combination of basal metabolic rate (BMR), physical activity, and thermogenesis secondary to nutritional intake. The measurement of energy expenditure poses a challenge in the critically ill or surgical patient as this is a dynamic process that changes over the course of the disease process and is often not accurately measured by predictive equations. TEE can be measured by direct calorimetry which measures the total amount of heat produced by metabolic processes.[8] However, direct calorimetry is expensive and not widely available. In contrast, indirect calorimetry is a more feasible option.

Indirect Calorimetry

The gold standard for measuring resting energy expenditure and determining caloric need is indirect calorimetry. This method, based on thermodynamic principles, calculates heat produced through the measurement of oxygen consumed and carbon dioxide exhaled. Measurement by indirect calorimetry can be improved with proper patient selection. Patients should have stable hemodynamics and temperature, no chest tubes, and a fraction of inspired oxygen of <0.6 and should not be receiving nitric oxide.[9]

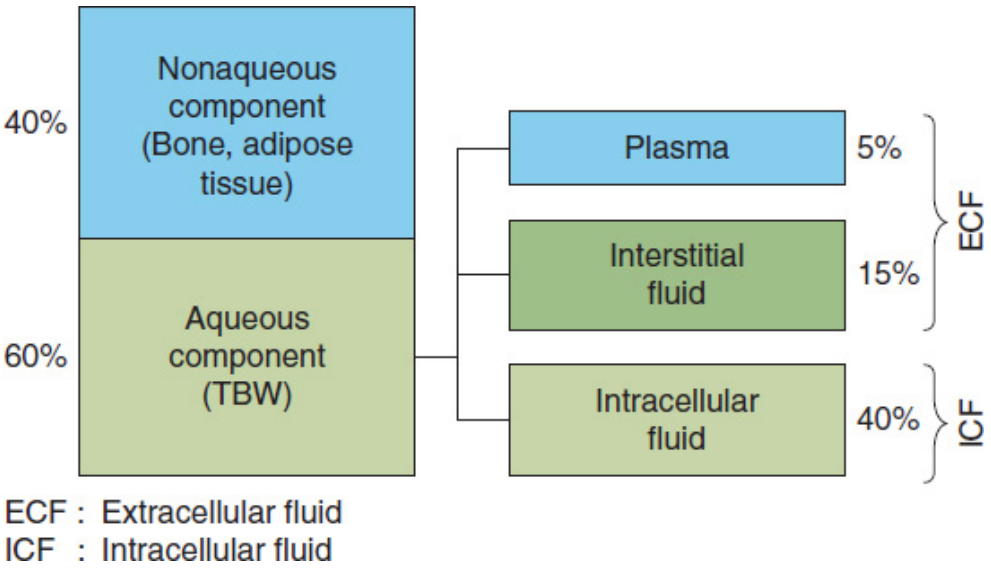

Figure 3.2 Aqueous and nonaqueous body composition.

Predictive Equations for Energy Expenditure

In most cases, energy expenditure is not measured, but estimated, on the basis of all metabolic activities that occur within the FFM. There are >200 predictive equations that have been developed for calculating energy expenditure that generally take into account body weight, height, age, and gender. When applied to critically ill or surgical patients, several equations will incorporate a stress factor to account for the increased metabolic state associated with illness or surgery. Several equations that predict basal energy expenditure, and hence daily caloric requirements, have been developed from the aforementioned variables, with the Harris–Benedict equation being among the most widely used (**Table 3.1**).[10]

Once the BMR has been calculated, minor adjustments based on exercise frequency and intensity can be made for estimation of the daily caloric requirement for an adult to maintain current weight.[10]

The Mifflin–St. Jeor equation appears to be even more accurate in estimating BMR in healthy individuals[11]:

$$\text{Men} \quad \text{BMR} = (10 \times \text{weight in kg}) + (6.25 \times \text{height in cm}) - (5 \times \text{age in years}) + 5$$

$$\text{Women} \quad \text{BMR} = (10 \times \text{weight in kg}) + (6.25 \times \text{height in cm}) - (5 \times \text{age in years}) - 161$$

1 For critically ill, or patients with highly inflammatory conditions, the estimated BMR is adjusted upward. Not surprisingly, basal energy requirements increase significantly with an active inflammatory response but minimally after elective surgery. The largest increases in energy expenditure are seen in patients with severe polytrauma or major burns.[12] Based on expert consensus from SCCM and ASPEN, in the absence of indirect calorimetry, either a predictive equation should be used or critical ill patients should receive 25 to 30 kcal/kg/day.[5]

Predicting Caloric Need for Underweight and Obese Patients

Indirect calorimetry is also the gold standard for estimating caloric needs in obese patients. When this is not available or not feasible, for critically ill obese patients, the Penn State University 2010 predictive equation is recommended with the Mifflin–St. Jeor equation as an alternative if the Penn State University (PSU) equation cannot be used.[13] However, in general, predictive equations are less accurate for estimating the caloric needs of underweight and obese patients.[5] Based on expert consensus, in the absence of indirect calorimetry, patients with body mass index (BMI) 30 to 50 should receive 11 to 14 kcal/kg (actual body weight)/day and patients with BMI > 50 should receive 22 to 25 kcal/kg (actual body weight)/day.[5] For patients with a BMI of 30 to 40, 2.0 g/kg (ideal body weight)/day of protein should be provided and patients with a BMI ≥ 40 should be provided 2.5 g/kg (ideal body weight)/day of protein.[5]

Table 3.1 The Harris–Benedict Equation and Adjustment Using the Harris–Benedict Principle

Men	BMR = 88.362 + (13.397 × weight in kg) + (4.799 × height in cm) − (5.677 × age in years)
Women	BMR = 447.593 + (9.247 × weight in kg) + (3.098 × height in cm) − (4.330 × age in years)
Little to no exercise	Daily kilocalories needed = BMR × 1.2
Light exercise (1–3 d/wk)	Daily kilocalories needed = BMR × 1.375
Moderate exercise (3–5 d/wk)	Daily kilocalories needed = BMR × 1.55
Heavy exercise (6–7 d/wk)	Daily kilocalories needed = BMR × 1.725
Very heavy exercise (twice per day, extra heavy workouts)	Daily kilocalories needed = BMR × 1.9

Adapted from Roza AM, Shizgal HM. The Harris Benedict equation reevaluated: resting energy requirements and the body cell mass. *Am J Clin Nutr* 1984;40(1):168–182.

Body Fuels

Human metabolism is organized in such a way that fuel consumption occurs in a hierarchical way when more than one energy source is present, with excess stored for the postprandial or fasting period. In the postprandial state, the body contains fuel reserves that it can also mobilize in an orderly fashion, as fasting is prolonged. The same fuel reserves are accessed during stress metabolism, although in a less orderly fashion (**Table 3.2**).

Calorically dense fat is by far the largest energy repository, providing 9 kcal/g when mobilized and oxidized. The ability of the body to store fat is essentially limitless. Protein comprises the next largest energy store in the

human body, yet amino acids when oxidized yield 4 kcal/g. Unlike fat, protein plays both structural and functional roles in the body; thus, in severe protein loss, major functional consequences can be expected. In malnutrition, proteolysis frees up amino acids to be used for gluconeogenesis to produce glucose, which, in turn, can be used as fuel. Carbohydrate reserves are minimal and exist in the form of glucose or glycogen in the liver. These can be depleted quickly, typically within 12 hours, unless replenished through nutrition. Carbohydrates, like protein, also yield approximately 4 kcal/g when mobilized for energy production (**Table 3.3**).

Carbohydrates

Carbohydrates are the most commonly used fuel by the human body, providing frequently >45% to 60% of daily energy requirements. Each gram of carbohydrate that is administered enterally yields approximately 4 kcal when broken down, whereas intravenously administered carbohydrates (such as dextrose-containing solutions) provide slightly less (approximately 3.4 kcal/g).

Table 3.2 Fuel Reserves of a Healthy, 70-kg Adult Male

Energy Source	kg	kcal Value
Fat	14	125,000
Protein		
Skeletal muscle	6	24,000
Other	6	24,000
Glycogen		
Muscle	0.15	600
Liver	0.075	300
Free glucose	0.02	80

The basic unit of carbohydrate metabolism in humans is glucose, and nearly all dietary carbohydrates are converted to glucose for energy production. Digestion of carbohydrates begins as proximally as the oral

cavity with food ingestion, where salivary amylase breaks down polysaccharides into smaller oligo- and disaccharides. This process continues in the duodenum and proximal jejunum with the pancreatic amylase. Oligosaccharidases that are present in the brush border of the proximal small bowel further hydrolyze oligosaccharides into di- or monosaccharides, most commonly glucose, to be absorbed by the gut mucosa. Once glucose reaches the bloodstream, it stimulates secretion of insulin from the endocrine pancreas (beta cells), which has major anabolic effects and stimulates protein synthesis, inhibits lipolysis, and upregulates glycogen production. Conversely, during stress, pancreatic glucagon exerts opposite effects: It promotes breakdown of glycogen, but also fat and protein, to be used as additional energy sources during a time when energy requirements are maximal. Deficiencies in carbohydrate digestion are rare in surgical patients, even in patients in whom the pancreatic exocrine function is significantly decreased. Patients with pre-existing celiac or Whipple disease may, however, have limited capacity to absorb carbohydrates.

The human central nervous system and circulating blood cells require glucose constantly for their energy requirements. In periods of extended fasting, after the liver has used up its stores of glycogen, the human body breaks down protein and uses the resulting amino acids to generate glucose, and even converts fat into ketones that can partly substitute glucose as an energy source. When glucose is reinstated through nutrition, these metabolic adaptations are completely reversed. During stress, gluconeogenesis and glycogen breakdown are accelerated and ketone production is minimized, leading to an abundance of glucose for use as the human body mounts an inflammatory response.

Table 3.3 Energy Value of Various Energy Sources

Energy Source	Energy Value
Fat	9 kcal/g
Carbohydrates (enteral)	4 kcal/g
Carbohydrates (intravenous)	3.4 kcal/g
Protein	4 kcal/g

Lipids

Lipids are the second most commonly used fuel for energy by the human body, accounting for 35% to 45% of daily caloric intake. Each gram of fat yields approximately 9 kcal of energy when oxidized. When lipids enter the proximal small bowel, cholecystokinin and secretin are released, which make the gallbladder contract and release bile into the duodenum. Bile salts contained in bile are necessary for lipid absorption, especially the long-chain fatty acids that are found in a typical Western diet, which occurs mostly in the distal ileum. Surgical resection of the distal ileum may lead to depletion of the bile salt pool and fat malabsorption.

Lipids are most commonly classified by the length of their contained hydrocarbon chains. Short-chain fatty acids typically refer to lipids containing two- to five-carbon length chains and are a product of dietary fiber fermentation in the colon by the intestinal flora. They are absorbed by, and are the preferred fuel for, the colonocytes. Medium-chain fatty acids (six- to nine-carbon length chains) are also not typically found in the human diet but are commonly used in numerous enteral nutrition formulas, as they are easier to digest, compared to longer-chain triglycerides. They are water soluble and hence require no emulsification or micelle formation for transport. Lipase is not required. The medium-chain triglycerides are absorbed directly into the portal circulation. Unlike the short- and medium-chain fatty acids, which can be produced from other dietary substrates, two long-chain fatty acids (more than nine-carbon length chains), linoleic and linolenic acids, are essential for human nutrition. These are not water soluble and require bile salts for emulsification as stated earlier, lipase for digestion, and micelle/chylomicron formation for transport. They gain access to the bloodstream via the lymphatic system (thoracic duct). Insufficient intake of these essential fats can lead to fatty acid deficiency, which can be prevented with provision of at least 3% to 4% of the daily calories as linoleic and linolenic acids. These two fatty acids are also a precursor of eicosanoids, significant mediators of the inflammatory response. On a cellular level, lipoprotein lipase is necessary for intake and carnitine for transport from the cytosol into the mitochondria for oxidation. Long-chain triglycerides are the main form of energy storage in the human body, given the numerous high-energy bonds they contain.

Protein

Protein is different from carbohydrate and lipids in that it contains nitrogen that neither fatty acids nor glucose does. It is also a key structural component, and there are no inactive protein stores. Essentially, all proteins are either functional or structural in the human body.

Proteins are polypeptides, containing numerous amino acids as their building blocks, and yield 4 kcal/g when used for energy production. Dietary protein is broken down into amino acids and smaller peptides by gastric pepsin and pancreatic proteases, the latter activated by enterokinase in the duodenum. These amino acids and oligopeptides get absorbed mostly in the proximal GI tract and travel to the liver, where they are recycled to synthesize new protein. In a healthy, 70-kg weighing adult male, >300 g of proteins are recycled daily. The branched-chain amino acids (BCAAs; leucine, isoleucine, and valine) are transported to muscle unaltered, while other amino acids are distributed to the intra- and extracellular pool for protein synthesis as needed. Excess amino acids are usually converted to glycogen or free fatty acids.

In addition to the dietary protein, intracellular proteins are continuously recycled and the resulting free nitrogen is excreted, mostly through urine. Most of the urine nitrogen is in the form of urea (85%), with smaller amounts excreted as creatinine and ammonia. Urinary nitrogen decreases significantly with protein-free diets (decreased intake) but increases during stress (greater turnover).

Amino acid metabolism generates ammonia, a highly toxic compound, which is converted into urea (nontoxic) in the liver. Glutamine and alanine serve as ammonia-transporting vehicles in a nontoxic form from the metabolically active peripheral tissues to the viscera. There, ammonia is resynthesized and either excreted (by the kidneys, where it also acts as a buffering system) or detoxified to urea (liver). Diseases that affect the functional capacity of either the kidneys or the liver can lead to significant ammonia build up in the body, with potentially toxic consequences to the central nervous system.

Provision of protein recommended for patients is dependent on clinical condition and comorbidities. SCCM and ASPEN recommend that critically

ill patients receive 1.2 to 2.0 g/kg of protein per day, with burn patients and polytrauma patients having higher protein needs.[5]

Vitamins

Vitamins A, D, E, and K are fat soluble and are absorbed in the small bowel in association with long-chain fatty acids. From there, they are transported to the liver (vitamins A and K) or the skin and subcutaneous tissue (vitamins D and E) for storage. Fat-soluble vitamins are required for normal immune function and play a significant role in wound healing. Daily vitamin A intake in patients on chronic corticosteroid regimens may counteract most of steroid-mediated adverse effects of wound healing.

Unlike vitamins A, D, E, and K, vitamins B_1 (thiamin), B_2, B_6, and B_{12}, along with vitamin C, niacin, folate, biotin, and pantothenic acid are water soluble and are absorbed in the proximal small bowel. From there, they are transferred to the liver with the portal circulation for use or storage. Water-soluble vitamins are required for normal amino and nucleic acid metabolism.

Deficiencies of vitamins B_1 (thiamin), B_9 (folate), and B_{12} can be associated with surgical procedures. Thiamin is an essential vitamin associated with carbohydrate metabolism and gluconeogenesis. Thiamin deficiency is commonly caused by alcoholism but may also be due to malabsorption (e.g., after Roux-en-Y gastric bypass), decreased nutritional intake (e.g., GI surgery, vomiting, intestinal obstruction), excessive losses (associated with loop diuretics and dialysis), and increased metabolism due to surgery or illness.[14] The central nervous system is affected by thiamine deficiency as seen in Wernicke encephalopathy, Wernicke–Korsakoff syndrome, and beriberi. Wernicke encephalopathy involves the triad of mental status changes, nystagmus, and ataxia. Wernicke encephalopathy may progress to Wernicke–Korsakoff syndrome, which is characterized by memory impairment. Beriberi involves muscular weakness and neuropathy.

Folate plays a role in protein metabolism and in the form of folic acid is often used to fortify numerous foods. Alcoholism and decreased nutritional intake are risk factors for folate deficiency. Folate deficiency may lead to anemia, weakness, and mouth sores. Additionally, folate supplementation is important for pregnant women to prevent neural tube defects in the setting of increased demand for embryonic DNA synthesis.

Electrolytes and Trace Elements

Electrolytes are important components of both the intra- and extracellular compartments, where they play a major role in maintaining electrical and osmotic balance across the body's plasma membranes. Such electrolytes include sodium (Na^+), potassium (K^+), calcium (Ca^{2+}), magnesium (Mg^{2+}), and chloride (Cl^-). Sodium is the main extracellular electrolyte and is important in maintaining volume homeostasis and in blood pressure control. Conversely, potassium is one of the key intracellular cations. The role of electrolytes is diverse and includes functions as varied as the conduction of electric signals, cotransport of larger molecules against their concentration gradient, muscular contraction, and participation in numerous essential biochemical reactions.

Trace elements play an important role in numerous metabolic, immunologic, and healing functions, and eight minerals have been identified as "essential." These include iron, iodine, zinc, chromium, copper, selenium, manganese, and molybdenum.

Iron is an integral component of the heme core in hemoglobin and of the mitochondrial cytochrome complex. Subtle impairments in central nervous, musculoskeletal, and immune system functions can be identified in patients with iron deficiency before microcytic anemia becomes clinically evident. Impaired cerebral, muscular, and immunologic functions can occur in patients with iron deficiency before anemia becomes clinically evident. Particular attention has to be paid to pregnant and lactating females, in whom iron requirements are even greater than the rest of the population.

Iodine is a key component of the thyroid hormonal system. Deficiencies are rare in the Western world, due to widespread use of iodinated salt. However, chronically malnourished patients can develop significant iodine deficiency, which can typically manifest clinically as diffuse goiter and hypothyroidism.

Zinc deficiency can manifest with skin discoloration and perioral rash, neuritis, hair loss, and alterations in taste and smell. Chromium deficiency presents as impaired glucose tolerance during prolonged fasting and is fairly common with total parenteral nutrition (TPN). Copper deficiency presents with microcytic anemia, typically unresponsive to iron, abnormal skin keratinization, and, in its most severe cases, pancytopenia. Selenium

deficiency, which can similarly be identified in cases of prolonged TPN administration, manifests as neuromuscular dysfunction or cardiac conduction defects, which in the most severe cases can lead to heart failure. Manganese deficiency can be identified as the underlying cause in a syndrome presenting as unintentional weight loss, hair color changes, and hypolipidemia. Molybdenum deficiency is associated with hypomethioninemia and hypouricemia, resulting in nausea and vomiting, tachycardia, and nonfocal central nervous system dysfunction (**Table 3.4**).

NUTRITIONAL ASSESSMENT

2 An accurate nutritional assessment is critical to identifying patients in need of nutritional support and determining the degree of nutritional support needed. Metabolism is altered to varying degrees by stress, namely, surgical injury, critical illness, infection, and physical trauma. In most cases, these alterations are short lived and reversible in a previously well-nourished individual, even if fasting is superimposed during acute illness. However, pre-existing malnutrition, even if mild, and prolonged poststressor fasting, intentional or not, can adversely affect healing, recovery, and overall outcomes after injury or surgery.[15] Factors such as weight loss and low preoperative albumin have been associated with poor outcomes after abdominal surgery.[16]

Subjective Global Assessment

Subjective global assessment (SGA) of a patient's nutritional status is commonly utilized to assess the presence and degree of malnutrition in surgical patients. It is one of the few clinical methods that has been validated as a reproducible method assessing a patient's nutritional status and has been consistently associated with clinical outcomes.[17] The SGA incorporates components of a patient's history, including weight loss, changes in nutritional intake, functional capacity, GI symptoms, and metabolic demand associated with underlying disease. Additionally, this assessment includes a focused physical examination to assess for edema, muscle wasting, and loss of subcutaneous fat.

Patients are classified as having (A) no evidence of malnutrition, (B) moderate or indeterminate malnutrition, and (C) severe malnutrition. Patients in this last category typically present with a recent history of unintentional weight loss and signs of tissue wasting (temporal and/or extremity most commonly). While the SGA can provide coarse information about the severity of malnutrition, it rarely yields clues pertaining to the underlying etiology (starvation vs. inflammation).

Table 3.4 Summary of the Daily Requirements of Vitamins, Electrolytes, and Trace Elements in a Per Os Diet by Healthy Adults

Vitamins	
Retinol (vitamin A)	1,000 µg
Thiamine (vitamin B_1)	1.4 mg
Riboflavin (vitamin B_2)	1.7 mg
Pyridoxine (vitamin B_6)	2.2 mg
Ascorbic acid (vitamin C)	60 mg
Niacin	20 mg
Folate	200 µg
Biotin	150 µg
Pantothenic acid	4–7 mg
Retinol (vitamin A)	1 mg
Vitamin D	5 µg
Vitamin E	10 mg
Vitamin K	75–150 mg
Electrolytes	
Sodium	90–150 mEq
Potassium	60–90 mEq
Calcium	1,300 mg
Magnesium	350 mg
Phosphorus	800 mg
Trace Elements	
Iron	10 mg
Iodine	150 µg
Zinc	15 mg
Chromium	5–200 µg
Copper	2–3 mg
Selenium	100 µg
Manganese	2.5–5 mg
Molybdenum	100–500 µg

Similar methods of assessing overall nutritional status encompassing dietary history, baseline health, and anthropometric and laboratory measurements have been described and used in certain patient subpopulations. These include the mini nutritional assessment, the malnutrition universal screening tool, the instant nutritional assessment, the geriatric nutritional risk index, among others. The SGA may be of limited use for critically ill patients and as such ASPEN and SCCM recommend the use of nutritional risk screening (NRS 2002) or NUTrition Risk in the Critically ill (NUTRIC score).[5]

NRS 2002 was developed to identify hospital patients who are at risk for malnutrition or are undernourished. This screening assesses weight loss, BMI, food intake, disease severity, and age.[18] The NUTRIC score is calculated based on age, Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores, number of comorbidities, days between hospital and intensive care unit (ICU) admission, and IL-6 if available.[19] High NUTRIC scores have been associated with worse clinical outcomes and long hospital and ICU lengths of stay.[20]

Anthropometric Measurements and Nutritional Indices

Anthropometric measurements have been used extensively to provide information regarding lean body mass, total fat stores, and overall nutritional health. Body composition studies aid in determining TBW, fat, and nitrogen. These anthropometric measurements can be easily performed at the bedside or an ambulatory setting and may include an individual's height and weight (which allow calculation of the BMI), triceps skinfold, midhumeral circumference, and other body part summations. The BMI is widely used as a measure of overnutrition (a BMI of 25 to 29.9 suggests overweight status, whereas a BMI > 30 defines obesity). The BMI is calculated from an individual's height and weight using the following formula:

$$\text{BMI} = \text{weight (kg)}/\text{height (m)}^2 = 703 * \text{weight (lb)}/\text{height (in)}^2$$

More advanced techniques and measurements include x-ray absorptiometry that allows a more accurate assessment of total fat and lean body mass. With the exception of the BMI, most anthropometric

measurements are operator dependent, and skill and experience are important in order to obtain accurate studies.

Nutritional indices provide a means of risk stratifying and objectively comparing individuals, as well as to guide nutritional support. The BMI is one of the most commonly utilized nutritional indices. It provides information on normal, overweight, or obese status. It also provides information on the degree of protein–calorie malnutrition in underweight individuals.

Serum Protein Levels

3 An ideal biochemical marker of malnutrition would be one that is highly sensitive and specific to nutrition intake. Although a single laboratory biomarker that could effectively describe a patient's nutritional status is lacking, numerous freely circulating serum transport proteins have been used. The most commonly utilized ones are albumin, prealbumin, transferrin, and retinol-binding protein (RBP), each with its own advantages and disadvantages. Many nutrition-unrelated parameters, most commonly inflammation, dilution secondary to large-volume resuscitation, and chronic liver failure, affect the levels of these serum markers. Although it is customary for markers of inflammation, usually the C-reactive protein, to be measured with the aforementioned biomarkers (commonly prealbumin), limited data exist to support this practice.[5,21,22]

Albumin

Albumin is a serum protein synthesized in the liver with a long half-life (approximately 20 days) and a relatively large total pool size. Only 5% of total body albumin is produced daily. Its main function is to carry molecules in the bloodstream and to help maintain intravascular oncotic pressure. Due to its large pool, long half-life, and relative slow turnover, it has been used as an indirect marker of protein intake, hepatic synthetic ability, and chronic nutritional status. Unfortunately, it is a negative acute-phase reactant, decreasing during the acute-phase response, and numerous nutrition-unrelated factors may affect its levels in either direction (**Tables 3.3** to **3.5**). Albumin is neither a sensitive nor specific marker for malnutrition, as patients with even severe starvation can have normal levels.[23–26] In critical care, hypoalbuminemia more commonly reflects illness acuity, especially during the acute phase, due to its function as a negative acute-phase reactant, its

redistribution to the interstitial space, and dilution secondary to large-volume resuscitation.[27]

Prealbumin

Prealbumin, also known as transthyretin or transthyretin-bound prealbumin, similar to albumin, is a visceral protein synthesized in its majority by the liver and to a smaller extent by the choroid plexus in the central nervous system. Its name prealbumin was originally given because it ran faster than albumin on electrophoretic gels. Its main function is to transport thyroxin (T4) and retinol (vitamin A) in the bloodstream. As a visceral protein, it is a small part of the total body protein pool, which includes serum and intracellular proteins. Consequently, it is similarly affected by many of the same factors that affect serum albumin concentrations. The main advantage of prealbumin over albumin is its shorter half-life (2 to 3 days), which makes it more sensitive and rapidly adaptable to acute, short-lived changes in nutrient intake. Like albumin, prealbumin is a negative-phase reactant, with values decreasing during the acute inflammatory response. Therefore, rising prealbumin levels may reflect improvement in nutritional status or resolution of the inflammatory condition. Prealbumin is commonly measured along C-reactive protein, and low levels of the former accompanied by high levels of the latter are commonly seen in inflammatory conditions, as opposed to malnutrition. While this practice is not well validated, a better use for prealbumin as a marker of overall nutritional status is to monitor trends.[28]

Table 3.5 Serum Proteins Used in Nutritional Status Assessment

Marker	Reference Range	Half-Life	Elevated in	Decreased in
Albumin	3–5 g/dL	14–20 d	Dehydration, marasmus, blood transfusions, and exogenous albumin administration	Aggressive resuscitation, ascites, eclampsia, liver failure, inflammatory states, nephrotic syndrome, protein-losing states, burns, trauma/postoperative states, kwashiorkor, cancer, collagen diseases, corticosteroid use, chronic bed rest, zinc deficiency, and pregnancy
Prealbumin	18–45 mg/dL	2–3 d	End-stage renal failure, corticosteroid use, and oral contraceptives	Postoperative states, hepatitis, liver failure, inflammatory states, dialysis, hyperthyroidism, pregnancy, and severe hyperglycemia
Retinol-binding protein	4–6 mg/dL	12 hrs	End-stage renal failure, diabetes, obesity, vitamin A overdose, corticosteroid use, and oral contraceptives	Postoperative states, hepatitis, liver failure, inflammatory states, and vitamin A deficiency
Transferrin	200–250 mg/dL	8–10 d	Iron deficiency, dehydration, pregnancy (third trimester), oral contraceptives, estrogens, chronic anemia, hepatitis, liver failure, hypoxia, and end-stage renal failure	Pernicious anemia, anemia of chronic disease, folate-deficiency anemia, aggressive resuscitation, chronic infectious states, iron overload, acute catabolic states, uremia, nephrotic syndrome, liver failure, kwashiorkor, old age, zinc deficiency, corticosteroids, and cancer

Adapted from Parrish CR. Serum proteins as markers of nutrition: what are we treating? *Practical Gastroenterology* 2006;43(10):48–64.

Retinol-Binding Protein

The majority of RBP is present in the bloodstream in the form of retinol-circulating complex that includes prealbumin, retinol (vitamin A), and RBP. It is catabolized in the kidneys, and its levels may be elevated in end-stage renal failure. RBP is dependent on vitamin A and zinc, as low levels of these conutrients inhibit mobilization of RBP in the liver.[29] To some extent, measuring the RBP provides the same information as measuring prealbumin. RBP is less commonly used as a marker of nutrition, as it has a short half-life (approximately 12 hours), levels are affected by renal failure, and the measurement assay is more costly.[28]

Transferrin

Transferrin has also been identified and used as a nutrition biomarker. It has a half-life between that of albumin and prealbumin (8 to 10 days) and fairly small total body pool size. However, because it plays a key role in iron transport, its levels are affected by iron status. Iron deficiency may lead to increased levels secondary to greater iron absorption. Under these

circumstances, it may be a better marker of total iron-binding capacity, rather than malnutrition.

Nitrogen Balance

Nitrogen balance is another marker for overall nutritional status. It is an indicator of whether protein intake and catabolism are in balance, and along with trends in prealbumin levels, it is a commonly employed method to assess progress in patients on nutritional support. Nitrogen balance is calculated from the amount of nitrogen entering minus the amount leaving the human body over a 24-hour period. Nitrogen intake is estimated from total protein intake divided by 6.25 (the average nitrogen content of human protein is approximately 16%). The main route of nitrogen excretion is the urine (≥90%). Nitrogen is also lost through the skin and stool, but this loss is usually small (<2 g/day), difficult to measure, and therefore typically accounted for with a constant of 2 in the nitrogen balance equation. Total urinary nitrogen (TUN) is ideally measured but is frequently substituted by urine urea nitrogen (UUN), because it is easier to estimate. In the latter case, an additional 2 to 3 g is typically added to the output side of the nitrogen balance equation to account for the unmeasured losses. The nitrogen balance equations are as follows:

Nitrogen balance (g/day) = Protein intake/6.25 - (TUN + 2)
Nitrogen balance (g/day) = Protein intake/6.25 - (UUN + 2 + 3)

A nitrogen balance of −2 to +2 g/day indicates nitrogen equilibrium and typically represents the goal in medically indicated nutritional support. More negative balances are managed with increases in protein intake, while more positive values typically reflect anabolism in recovering patients, or simply errors in measurement in the acutely ill (a positive nitrogen balance implies anabolism, but bedridden patients with active inflammation are not anabolic). Achievement of a positive balance has been associated with improved outcomes in certain critically ill patients.[12] Limitations of the nitrogen balance assessment include false-negative results in overfed patients; long time for the equation to reequilibrate after adjustments in nutritional support; and renal insufficiency and upper GI bleeding may

invalidate results (due to incomplete excretion of urea nitrogen and due to excess urea nitrogen production, respectively).

OVERFEEDING AND MALNUTRITION

Overfeeding

4 While adequate caloric intake is necessary to maintain weight and promote health, overprovision of calories can lead to overfeeding and obesity. Excess calories, especially as carbohydrates, can lead to increased CO_2 production (which may prolong ventilatory weaning), hyperglycemia (which can contribute to immunosuppression and increase the risk for infectious complications), lipogenesis (indicated by a respiratory quotient [RQ] > 1), and hepatic steatosis (which can interfere with normal liver function). Additionally, excessive nutritional support may lead to mineral or vitamin poisoning and severe electrolyte imbalances, with hypophosphatemia being the most common. To avoid overfeeding, specifically in critically ill patients with numerous active medical conditions, indirect calorimetry may be indicated to accurately estimate energy expenditure during the various stages of disease.

Malnutrition

Starvation

During short periods of fasting, insulin levels drop and glucagon levels rise in the plasma, while glycogen is being broken down in the liver to release glucose. Liver glycogen stores are typically depleted within 24 hours of fasting. After carbohydrate stores are used up, caloric needs are met by protein and fat degradation. During starvation, downregulated insulin results in net muscle wasting, as protein is broken down to release amino acids. These amino acids—most commonly alanine and glutamine—are used for gluconeogenesis in the liver. The resulting glucose is used primarily by the central nervous system and the hemopoietic system that rely heavily on glucose metabolism for their energy requirements. Hepatic gluconeogenesis

itself also requires energy, which is typically supplied by the free fatty acid oxidation. The drop in circulating insulin levels, along with the concomitant rise in plasma glucagon, activates hormone-sensitive lipase in fatty tissue that hydrolyzes triglycerides to release free fatty acids, which in turn help generate energy for the aforementioned gluconeogenesis. Both gluconeogenesis and fatty acid oxidation require the permissive effect of cortisol and thyroxin.

During starvation, the human body attempts to recycle energy sources to the greatest extent possible. Lactate produced by the white blood cells or the muscles during anaerobic metabolism is recycled back to glucose in the liver, through the Cori cycle. BCAAs, unlike glutamine and alanine, which are taken up by the liver, are secreted by the gland in order to provide skeletal and cardiac muscles an energy substrate. Once BCAAs are oxidized for energy, their residual amino groups are utilized to recycle alanine and glutamine, which, in turn, return to the liver to allow further gluconeogenesis. However efficient this conservation of energy and substrates may seem, gluconeogenesis from amino acids in the liver results in a significant loss of lean body mass, which may reach fatal levels after approximately 4 weeks. The brain adapts to prolonged starvation after about 7 to 10 days (chronic starvation) to use ketones derived from fat as its primary energy source. At this stage, the BMR decreases by as much as 30%, and all functions requiring significant amounts of energy expenditure slow down, including voluntary muscle activity and cardiac function.

Table 3.6 Metabolic Differences between the Response to Simple Starvation and Stress

	Simple Starvation	Stress/Inflammation
Basal metabolic rate	–	++
Presence of mediators	–	+++
Major fuel oxidized	Fat	Mixed
Ketone body production	+++	±
Hepatic ureagenesis	+	+++
Negative nitrogen balance	+	+++
Gluconeogenesis	+	+++
Muscle proteolysis	+	+++
Hepatic protein synthesis	+	+++

Starvation versus Inflammation as the Cause of Malnutrition

Both starvation and the systemic inflammatory response result in lean body mass loss, which should indicate nutritional support.[1–3] However, the two processes have key dissimilarities that differentiate one from the other. On the one hand, starvation leads to progressive loss of both lean mass and body fat, preservation of serum protein levels, and reversal of the metabolic response with feeding. The most common causes of starvation in the surgical patient are functional and include nausea and emesis, ileus, dysphagia, and malabsorption. On the other hand, during a significant inflammatory response, the BMR increases significantly (both anabolism and catabolism) and becomes relatively insensitive to feeding, and levels of acute-phase proteins change. Inflammation may additionally worsen malnutrition by interfering with caloric intake acutely (anorexia of acute illness) or in the

chronic state (cancer cachexia). The key differences between the metabolic response to simple starvation and injury are summarized in **Table 3.6**.

Substrate Metabolism Changes during Stress

5 During the neuroendocrine response to stress, metabolism of commonly used nutritional substrates undergoes significant changes.

Altered Carbohydrate Metabolism

Hyperglycemia occurs commonly after injury, and its intensity generally reflects the severity of the stressor. During the ebb phase, insulin levels are low and glucose production is only minimally elevated. During the flow phase, hepatic gluconeogenesis occurs at a faster pace from peripheral tissue–released precursors and hyperglycemia persists, while insulin levels are normal or elevated. This phenomenon suggests relative insulin resistance.

Altered Protein Metabolism

After a major injury, nitrogen losses increase. These correlate to the extent of trauma and the injury victim's pre-existing nutritional status. In patients not receiving nutrition, protein breakdown exceeds synthesis and negative balance results. Providing exogenous calories is important to maintain a neutral nitrogen balance.[30] Skeletal muscle is the chief source of the nitrogen lost in urine following extensive injury, and it appears that amino acid release from muscle is heavily skewed toward glucogenetic precursors (alanine and glutamine), even though these comprise less than 5% of muscle total protein.

In addition to skeletal muscle, the kidneys and the GI tract release alanine, which may be used for glucogenetic purposes, even though the majority enters metabolic pathways that favor the production of urea and ammonia to be excreted from the body.

Altered Lipid Metabolism

To support the increased metabolic rates after injury or elective surgery, triglycerides are released from adipose tissue for energy production. Glucose administration minimally affects this lipolysis, which appears to be

a result of continuous neuroendocrine stimulation. Although mobilization and oxidation of free fatty acids are accelerated in injured subjects, ketone synthesis is minimal and occurs independently of protein catabolism. When severely injured patients remain unfed, their fat and protein stores become depleted rapidly, and the resultant malnutrition increases their susceptibility to infectious complications, multiple-organ system failure, sepsis, and ultimately death.

Stressor-Dependent Adjustments to the Metabolic Response

Response to Elective Surgery and Accidental Injury

One of the earliest consequences of major surgery is the rise in levels of circulating cortisol in response to a sudden release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. This cortisol remains elevated for 24 to 48 hours after operation. Cortisol has generalized effects on tissue catabolism and mobilizes amino acids from skeletal muscle that provide substrates for wound healing and serve as precursors for the hepatic synthesis of acute-phase proteins or new glucose, as delineated earlier (**Fig. 3.3**). Associated with the activation of the adrenal cortex is stimulation of the adrenal medulla through the sympathetic nervous system, with release of epinephrine and norepinephrine. These circulating neurotransmitters play an important role not only in increasing vascular tone, which may be lessened from circulating cytokines, but also in promoting amino acid release from skeletal muscle, lipolysis in adipose tissue, and gluconeogenesis in the liver.

The neuroendocrine response to surgical trauma can also modify the various mechanisms that regulate salt and water excretion. Alterations in serum osmolarity and body fluid tonicity due to anesthesia, operative stress, and fluid resuscitation stimulate antidiuretic hormone (ADH) and aldosterone secretion. ADH and aldosterone promote water and sodium reabsorption in the renal tubules, respectively. Thus, weight gain from salt and water retention is not uncommon after major surgery. Edema occurs to a varying extent in all surgical wounds secondary to local cytokine release that

increases vascular permeability, and this local water accumulation is proportional to tissue trauma. This extravasated fluid eventually returns to the circulation as the postoperative inflammatory response subsides and diuresis commences, typically 2 to 3 days after surgery.

Glucagon from the endocrine pancreas is also released at greater rates postoperatively, while insulin levels decrease. This response appears to be associated with the increased sympathetic activity that typically follows surgical trauma. The rise in glucagon and the corresponding fall in insulin act as potent signals accelerating hepatic glucose synthesis.

This postoperative catabolic period, which may be worsened by inadequate caloric intake, has been termed the “adrenergic–corticoid phase,” which generally lasts 1 to 3 days, and is followed by the “adrenergic–corticoid withdrawal phase,” which may last an additional 1 to 3 days. An anabolic phase ensues, which can occur at a variable time during a surgical patient’s convalescence. In general, in the absence of significant postoperative complications, this stage starts 3 to 6 days after major abdominal surgery, usually when the bowel function returns and an oral diet is initiated. This phase is characterized by positive nitrogen balance and weight gain. Protein is synthesized at an increased rate, and return of lean body mass and muscular strength ensues.

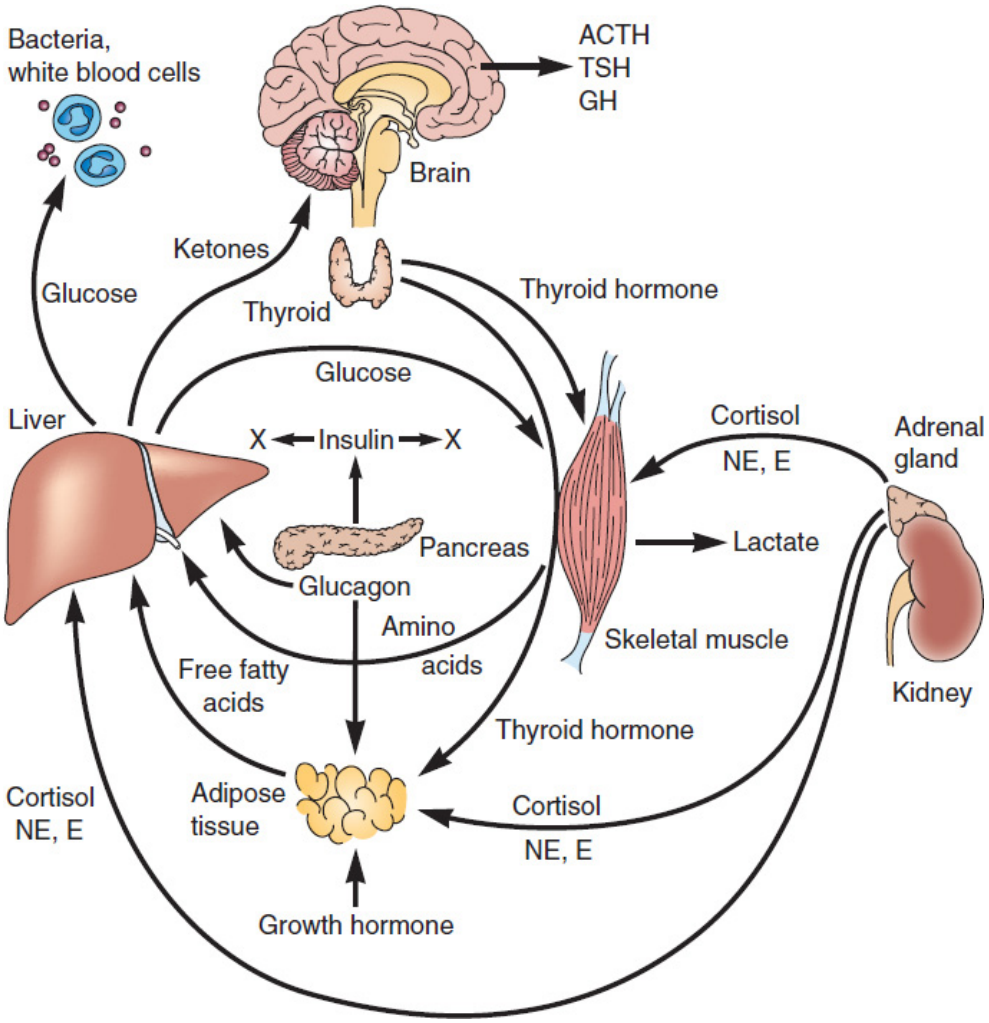

Figure 3.3 During sepsis, metabolism shifts to greater glucose synthesis and utilization, likely mirroring the greater metabolic needs of the pathogens and the mobilized host white blood cells.

Whether the body is injured within the carefully monitored confines of the operating room or accidentally, the response to tissue trauma is similar, although key differences exist. In accidental injury, tissue damage is uncontrolled and happens in a contaminated environment. The associated volume loss can be substantial and life-threatening. Pain and the sympathetic nervous system overexcitation are heightened and uncontrolled. As a consequence, the magnitude of the physiologic response to major accidental injury is considerable. In contrast, the elective tissue trauma inflicted occurs in a planned and monitored setting, and the team caring after the surgical patient perioperatively ensures appropriate resuscitation designed to attenuate such changes. Hydration during and after surgery is common, and

the latter typically happens in a clean field. At the same time, the anesthesiologist provides medications to minimize anxiety and fear to minimize the sympathetic nervous system response. Appropriately selected pharmacologic agents are used to minimize undesirable cardiovascular responses, and analgesic techniques are employed to minimize postoperative pain. As a result, the physiologic responses to elective surgery are generally of lesser magnitude than those following major accidental injury and are typically tolerated better (**Table 3.7**).

Metabolic Adaptations to Sepsis

The metabolic changes following invasive infection are not dissimilar to those seen after elective surgery and accidental trauma, although they are typically less predictable. Severe infection is characterized by fever, hypermetabolism, diminished protein economy, altered glucose dynamics, and accelerated lipolysis, much like the injured patient. Anorexia that commonly follows systemic infection is an added factor contributing to the loss of lean body mass.

Table 3.7 Differences between Elective Surgery and Accidental Injury

Insult	Elective Surgery	Accidental Injury
Tissue damage	Minimal and controlled, usually occurring in a clean environment; tissues are dissected with care along anatomic planes and reapproximated	Can be substantial; tissues torn in contaminated field. Debridement often necessary
Hypotension	Uncommon. Pre- and intraoperative hydration employed and volume status carefully monitored intraoperatively	May occur with significant blood loss and lead to shock. Fluid resuscitation often delayed
Pain, fear, and anxiety	Typically attenuated with perioperative analgesics and anxiolytics	Generally present in the first hours after trauma
Infectious complications	Relatively rare. Procedures take place in a sterile field, and preoperative administration of antibiotics is commonplace	More common due to contamination and tissue devitalization
Overall stress response	Controlled and of lesser magnitude. Starvation better tolerated	Controlled and proportional to the magnitude of the injury. Malnutrition poorly tolerated

Hypermetabolism and increased oxygen consumption are additional traits, with the latter reaching peak levels that may be 50% to 60% higher than baseline in severe sepsis. A portion of this metabolic acceleration can be attributed to the escalation in enzymatic reaction rates associated with fever. It is estimated that the BMR rises by 10% to 13% for every 1°C rise in central temperature. Glucose metabolism is increased to much greater levels in systemically infected subjects than in trauma victims. As an example, burn patients synthesize glucose at a rate approximately 50% above normal. If superinfection ensues, hepatic glucose production doubles, and it appears that the additional glucose requirements correlate with the bacterial burden and white blood cell activation (**Fig. 3.3**).

Increased proteolysis and nitrogen excretion leading to negative nitrogen balance typically occur following invasive infection, in a pattern that is similar to that described for injury. Visceral amino acid uptake is accelerated during sepsis, and this is matched by faster amino acid efflux from skeletal muscle. In infected burn patients, splanchnic amino acid uptake is amplified >50% above rates in uninfected burn victims with comparable injuries. These amino acids serve either as glucose precursors or as building blocks for acute-phase protein synthesis.

Fat is another major fuel utilized for energy in infected patients. Increased fat catabolism is particularly profound in patients during periods of inadequate nutritional support or relative starvation. Lipolysis is accelerated, among other reasons, by a heightened sympathetic activity, and serum triglyceride levels reflect the balance between synthesis in the liver and storage in the peripheral adipose tissue. Marked hypertriglyceridemia has been associated with certain gram-negative infections, but frequently triglyceride concentrations are normal or low, indicating enhanced utilization and clearance by other organs. Infected patients cannot convert fatty acids to ketones as efficiently in the liver, and do not adapt to starvation, as well as their fasted, unstressed counterparts. It is postulated that the low ketone state of infection is a consequence of the hyperinsulinemia, which in turn follows insulin resistance in high-degree catabolic states.

Trace elements and electrolytes (zinc, iron, potassium, magnesium, and inorganic phosphate) typically follow alterations in nitrogen balance. Although the iron-binding capacity of transferrin typically remains unchanged in early infection, free iron cannot be found in the plasma of patients with

severe pyrogenic infections. Similar changes are seen in zinc levels. These decreases cannot be totally accounted for by total body losses; rather, an accumulation of these elements appears to occur in the liver through not yet elucidated mechanisms. Unlike iron and zinc, serum copper levels generally rise, seemingly due to greater ceruloplasmin synthesis in the liver.

Metabolic Response to Cancer and Acquired Immunodeficiency Syndrome

Patients with cancer and acquired immunodeficiency syndrome (AIDS) have similar metabolic states, characterized by chronic malnutrition, typically a result of anorexia and treatment side effects, and prolonged low-grade inflammatory changes. Cancers of the aerodigestive tract interfere with taste, swallowing, and/or digestion, precluding adequate caloric and/or protein intake. Supplementation with zinc and B vitamins may help taste-related symptoms, and soft mechanical diets may allow greater caloric intake in patients with swallowing difficulties or proximal GI tract malignancies. The aggressive management of nausea and vomiting may also afford greater interest in food.[31]

Cancer- and AIDS-related cachexia is seen in the later stages of disseminated disease and represents a chronic catabolic state due to unrelenting inflammation that is difficult to reverse, even with adequate caloric and protein supplementation. Proinflammatory cytokines (TNF, IL-1, and IL-6) are constantly released in response to the tumor or an infectious source in AIDS, respectively, and lead to a chronic state of muscle wasting and fat loss. The cachexia of cancer and AIDS is difficult to manage, as removing the inflammatory stimulus can prove elusive. However, mitigation of the chronic, low-grade inflammatory response may be useful and so can aggressive nutritional supplementation and appetite stimulants.

Age and Gender

Certain patterns in the metabolic response to surgical pathology that occur with aging can be attributed to alterations in body composition. Although weight remains roughly stable, fat mass tends to increase with age while lean body mass tends to decline. The loss of strength that accompanies immobility, starvation, and acute surgical illness may have significant

consequences. Although the increased energy requirements after elective surgery occur essentially independent of age, the capacity of muscle to serve as a source of amino acids may be limited during acute surgical illness in the elderly and muscle strength may rapidly become inadequate for respiratory function.

In addition to a smaller muscle mass, older age is commonly associated with a greater prevalence of cardiovascular and pulmonary diseases. Relatively decreased arterial compliance, lower baroreceptor sensitivity, and a blunted response to the catecholamine surge may impair the cardiovascular homeostatic response during acute surgical illness. Thus, tissue oxygenation may not be able to meet the heightened demand.

Gender, in addition to age, may affect the body's ability to adapt to surgical stress. Observed differences in the metabolic response between men and women in general reflect differences in body composition. Lean body mass, as a proportion of total body weight, is lower in women than in men. This difference is thought to account for the lower net loss of nitrogen after major elective abdominal surgery in women. Women, in general, have approximately half the skeletal muscle mass of men of the same age. Therefore, young muscular men experience the greatest nitrogen losses during acute surgical illness, as opposed to elderly, sedentary women.[6]

NUTRITIONAL SUPPORT

Nutritional Support in Elective Surgery

With any patient undergoing an elective surgical procedure, consideration of perioperative nutrition is important. Malnutrition and underfeeding are risk factors for perioperative complications.[32–34] **Table 3.8** highlights the key aspects of perioperative care per the European Society for Clinical Nutrition and Metabolism (ESPEN). Patients undergoing major elective surgical procedures, particularly for cancers, should undergo nutritional screening as they are being prepared for surgery.[32]

Table 3.8 Key Aspects of Perioperative Care

- Integration of nutrition into the overall management of the patient
- Avoidance of long periods of preoperative fasting
- Reestablishment of oral feeding as early as possible after surgery
- Start of nutritional therapy early, as soon as a nutritional risk becomes apparent
- Metabolic control, e.g., of blood glucose
- Reduction of factors that exacerbate stress-related catabolism or impair gastrointestinal function
- Minimized time on paralytic agents for ventilator management in the postoperative period
- Early mobilization to facilitate protein synthesis and muscle function

From Weimann A, Braga M, Carli F, et al. ESPEN guideline: clinical nutrition in surgery. *Clin Nutr* 2017;36(3):623–650.

Most patients undergoing elective operations are adequately nourished and are typically only fasted for a few hours prior to surgery. The previous dictum that all patients must be made "NPO after midnight" is no longer recommended, and most patients can safely be fed clear liquids up to 2 hours prior to general anesthesia.[35] Preoperative intake of carbohydrate-based liquids ("CHO-loading") may impact postoperative insulin resistance and has been shown to be associated with overall reduction in length of hospital stay.[32] Early oral intake after most elective procedures is favored and may be associated with a reduction in the risk of postoperative ileus in some patients.[36] There are numerous studies that have demonstrated that it is safe to resume oral diet or enteral feedings early after GI surgery.[37,38] Early enteral nutrition within 24 hours should be initiated in all patients undergoing major head and neck or intestinal procedures for cancer.[32] ERAS has become standard of care in many countries and across numerous surgical disciplines. Most ERAS programs include components of nutritional assessment and reestablishment of early enteral nutrition postoperatively.[39]

6 Preoperative malnutrition is a clear risk factor for complications following elective surgery. There are a number of definitions and diagnostic criteria that can be applied, but proposed criteria are BMI < 18.5 kg/m^2 or a combined metric of weight loss >10% or >5% over 3 months and reduced

BMI or a low fat-free mass index (FFMI).[40] In patients who are determined to be malnourished preoperatively and in those patients at high risk of delayed postoperative nutrition initiation, nutritional support preoperatively may be indicated.[32] If the patient is malnourished preoperatively, or it is anticipated that the patient will be unable to take oral diet for more than 5 days postoperatively, nutrition should be instituted.[32] If a patient is unable to meet >50% of their nutritional needs for more than 7 days postoperatively, nutritional support is also recommended. As a general rule, enteral nutrition is preferred over parenteral nutrition. However, if adequate nutrition cannot be maintained by the enteral route, parenteral nutrition should be initiated after 7 days of enteral intolerance.[5]

Standard high-protein feeding formulas are adequate for most surgical patients. The choice of product and volume of feeding are based on the results of nutrition assessments. The majority of tube feeding formulas are rich in water-soluble dietary fiber, which is considered standard in the nutritional care of the surgical patient. Specific adjustments can be undertaken if special considerations (e.g., cardiac failure, renal failure, diabetes, etc.) are needed. In patients who present for elective surgery and who meet criteria for malnutrition, preoperative addition of balanced macronutrient and high-protein supplementation could be useful. This preoperative support should be initiated as soon as possible, even though it is estimated that the minimum time required to derive any benefit from this support is in the range of 2 to 4 weeks.[41]

Nutritional Support in Critical Care

While resuscitation, bleeding control, and preservation of the vital body functions, such as maintenance of gas exchange and supporting of adequate cardiac output, remain immediate priorities for survival in any critically ill surgical patient, it is increasingly recognized that nutritional support is an integral part of the metabolic care of the critically ill, and aggressive pursuit of target energy requirements is associated with optimal wound healing, recovery, and rehabilitation (**Fig. 3.4**). Critically ill patients who are typically quite catabolic often have anorexia that can be adaptive or maladaptive and may be unable to be fed by mouth volitionally for extended periods. Severe malnutrition can complicate the hospital course and

adversely affect outcomes. Numerous studies have demonstrated the association between energy deficit in critical illness and longer ICU stays, greater incidence of infectious complications, and even mortality.[5,42–44] The management of the nutritional support in critically ill patients is largely guided by the ESPEN guideline on clinical nutrition in the ICU[45] and the Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient from SCCM and ASPEN.[5] **Table 3.9** summarizes the recommendations for nutritional support in critically ill patients from SCCM and ASPEN.

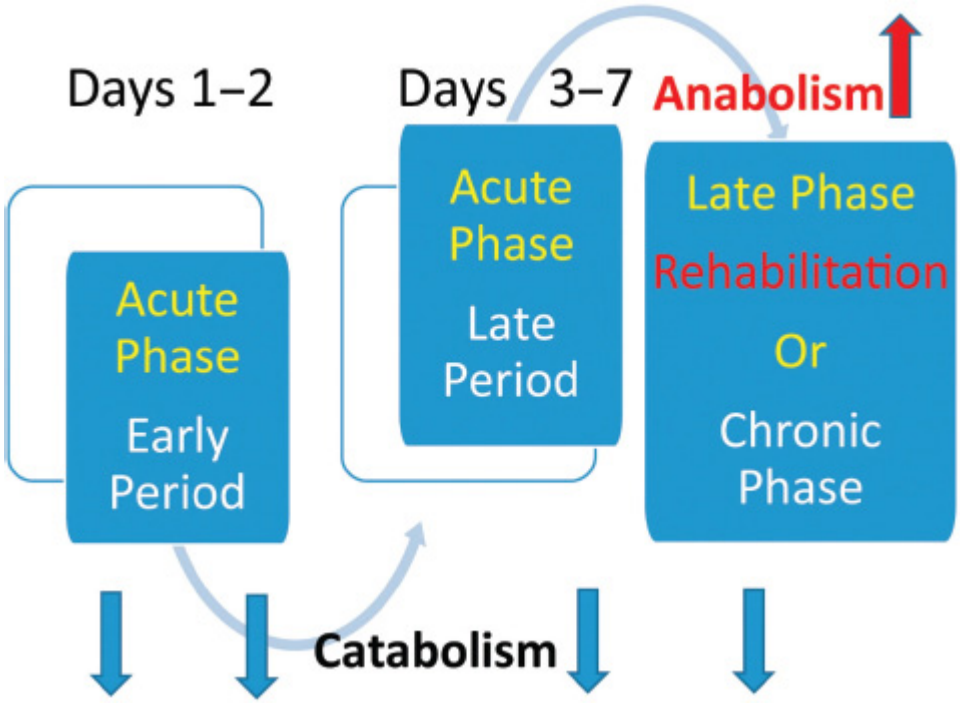

Figure 3.4 Description of the acute and late phases following infection/stress/injury. After injury, the acute phase is composed of an early period and a late period. Then the post–acute phase can be progressing to convalescence and rehabilitation or chronicity and prolonged inflammatory and catabolic syndrome (PICS). (From Martindale RG, McClave SA, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition: executive summary. *Crit Care Med* 2009;37:1757–1761.)

Table 3.9 Bundle Statements from the Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition's Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient

- Assess patients on admission to the intensive care unit (ICU) for nutrition risk and calculate both energy and protein requirements to determine goals of nutrition therapy.
- Initiate enteral nutrition (EN) within 24–48 hrs following the onset of critical illness and admission to the ICU, and increase to goals over the first week of ICU stay.
- Take steps as needed to reduce risk of aspiration or improve tolerance to gastric feeding (use prokinetic agent, continuous infusion, chlorhexidine mouthwash, elevate the head of bed, and divert level of feeding in the gastrointestinal tract).
- Implement enteral feeding protocols with institutionspecific strategies to promote delivery of EN.
- Do not use gastric residual volumes as part of routine care to monitor ICU patients receiving EN.
- Start parenteral nutrition early when EN is not feasible or sufficient in highrisk or poorly nourished patients.

From McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr* 2016;40(2):159–211.

Upon admission to the ICU, some assessment of nutritional risk should be performed. There are several validated tools, including the NUTRIC and NRS 2002, both of which evaluate nutritional status and disease severity. When available, indirect calorimetry is a useful adjunct to the evaluation of nutritional needs.[46,47] The finding that enteral nutrients exert a trophic effect on the cellular integrity and function of the gut mucosa has provided the rationale for initiating enteral feedings early in the 7 course of critical illness. In fact, evidence from multiple studies appears to support that critically ill patients who were fed earlier had better overall outcomes than those who did not.[48] Current recommendations are that critically ill patients receive enteral nutrition within 48 hours of ICU admission.[5,45] Despite early

enthusiasm for postpyloric feeds, it is now recognized that most patients can be fed safely into the stomach. If gastric feeding intolerance exists, prokinetic agents can be tried. If that fails, it is recommended to convert to postpyloric feeding via a nasojejunal tube.[45] Routine monitoring of gastric residual volumes is no longer recommended.[5] Interruptions in enteral feeding should be minimized to prevent inadequate nutrient delivery.

There is a great deal of controversy and disparate literature on the best quantity and quality of nutritional support. Current recommendations are that a comprehensive approach toward nutrition that considers the route, timing, and content of nutrition provided. The appropriate calorie intake to be provided to critically ill patients via enteral nutrition remains unclear. One metaanalysis of randomized controlled trials that compared the effect of initial underfeeding and full feeding in acutely critically ill patients demonstrated no significant difference in overall mortality between the underfeeding and fullfeeding groups. However, a subgroup analysis of the underfeeding subgroup that was feed more than one-third of the caloric requirements indicated that mortality was significantly lower in this group. There were no differences in the secondary outcomes evaluated.[49] A recent multicenter, double-blind, randomized trial evaluating energy-dense versus routine enteral nutrition failed to demonstrate a mortality benefit with the use of an energy-dense formulation.[50] There is also increasing recognition that provision of adequate protein is more important than goal calories via a carbohydrate substrate.[51] Current recommendations are to provide 1.2 to 2.0 g/kg of actual body weight per day of protein.[5] Requirements may be even higher in patients with burns or polytrauma. One noncontroversial issue is the avoidance of overfeeding. It should be a goal of all to avoid the provision of excessive amounts of nutrients by any route in the early phase of critical illness.

Another frequently asked question is whether it is safe to enterally feed patients who are requiring hemodynamic support with vasopressors. One randomized trial comparing enteral to parenteral nutrition in patients requiring vasoactives did not demonstrate reduction in mortality or the risk of secondary infections but an increased risk of GI complications in enterally fed patients, including intestinal ischemia.[52]

8 For years, parenteral nutrition was considered far inferior to enteral nutrition. Recently, this notion has been challenged with the recognition that

mortality in patients provided with parenteral nutrition was not different from mortality in those fed enterally.[53] However, infectious complications may be higher as was ICU length of stay in one study. This difference did not occur when the calories administered by parenteral and enteral routes were similar, suggesting that overfeeding may be responsible for the infectious complications of parenteral nutrition. Focusing specifically on patients after GI surgery, one meta-analysis confirmed the beneficial effects of enteral nutrition for a lower rate of infectious complications, anastomotic leaks, and shorter hospital length of stay[54] while another demonstrated shorter time to return of bowel function and shorter hospital length of stay[55] without mortality benefits. A recent multicenter, randomized trial found no difference in mortality, infectious complications, or hospital length of stay between the two groups.[56]

Both the ESPEN and ASPEN/SCCM guidelines strongly endorse the use of enteral over parenteral nutrition when possible.[5,45,57] In patients who are severely malnourished and cannot tolerate enteral nutrition, preoperative parenteral nutrition has been associated with fewer noninfectious complications than in patients who were not provided with nutritional supplementation.[58] In critically ill patients, if parenteral nutrition is to be used, the timing of when to initiate it is controversial. Current recommendations are for patients at high nutritional risk to have parenteral nutrition initiated as soon as possible.[5] For patients at low nutritional risk, current recommendations are to wait 7 days before starting parenteral nutrition if they are unable to take oral or enteral nutrition. The rationale on the delay in parenteral nutrition administration is based on complications associated with its use, such as infections, hyperglycemia, hypertriglyceridemia, and liver function abnormalities.[59–62] In certain select cases, “dual feeding” with parenteral and enteral nutrition may be warranted.[63–65]

Parenteral Nutrition Considerations

One significant downside of parenteral nutrition is the concern of disuse of gut enterocytes, which may exacerbate intestinal microflora translocation from the gut lumen to the mesenteric lymph circulation, worsening total bacterial load and stress, as well as cause a loss of gut mucosal immunity.

Evidence suggests that parenteral nutrition may accentuate stress and predispose to gut-derived infectious complications, and even multiple-organ failure,[66,67] but is associated with fewer GI complications.[53,56] Due to the high osmolarity of its content, parenteral nutrition must be delivered centrally to minimize the risk of venous sclerosis. Patients on parenteral nutrition therapy should be monitored regularly by measuring blood sugar, serum electrolytes, and liver function tests, as abnormalities in these laboratories are common. Parenteral nutrition–related complications can be broadly categorized into those that are access-related, metabolic, and infectious. A list of these complications is summarized in **Table 3.10**.

Hyperglycemia

Hyperglycemia is common in surgical patients. Hyperglycemia is a well-recognized side effect of parenteral nutrition. Current guidelines recommend a target blood glucose range of 140 or 150 to 180 mg/dL.[68] Most hyperglycemia can generally be controlled with subcutaneous or intravenous insulin administration if mild or moderate. Insulin can be added to parenteral nutrition once the daily insulin requirements have been calculated. It has been shown that stressed individuals can maximally oxidize up to 4 to 5 mg of glucose/kg/min. For a 70-kg man, this is equal to approximately 400 to 500 g/day (1,600 to 2,000 kcal/day). Therefore, it is common for patients to receive up to two-thirds of their daily caloric needs in carbohydrate form through parenteral nutrition. Excess glucose can result in hyperglycemia and glycosuria and can be converted to fat and deposited in the liver. Glycosuria, with its osmotic load, can lead to osmotic diuresis, which can be misinterpreted as a sign of adequate resuscitation status or transition to recovery phase, while the patient may actually be clinically worsening.

Provision of Fat

Fat is an important fuel for the critically ill, as stressed patients preferentially utilize endogenous fat as an energy source. Fat oxidation is only minimally affected by carbohydrate administration during stress, unlike traditional starvation, and glucose infusion above certain levels may lead to hepatic steatosis. Lipids are commonly added to parenteral nutrition formulations to help meet the caloric requirements, to provide the essential

fatty acids, and to minimize complications associated with the infusion of large amounts of carbohydrate-containing fluids. Inclusion of lipids in parenteral nutrition provides the essential linoleic acid, inhibits lipogenesis from carbohydrates, and helps lower the RQ, which may benefit patients with CO_2 retention. Lipid emulsions for parenteral nutrition solutions are mostly 18-carbon soy-based omega-6 fats containing primarily long-chain fatty acids. These formulations with a high omega-6 polyunsaturated fatty acid content (linoleic acid in particular) have been associated with an increase in complications.[69] Newer nutritional methods of modifying the catabolic response to injury and infection propose the use of omega-3 fatty acids, which may decrease eicosanoid synthesis and thereby diminishing the vasoconstriction, platelet aggregation, and immunosuppression that may occur when soy-based omega-6 derivatives are given. Studies suggest that n-3 fatty acids may be of benefit to the critically ill patient.[70]

Table 3.10 TPN-Related Complications

Complication	Etiology
Access-Related	
Pneumothorax	Air accumulation between the pleural leaflets from puncture/laceration
Carotid/Subclavian arterial injury	Accidental puncture of the adjacent arterial structure
Catheter malposition and arrhythmias	Tip of catheter may find its way into an unintended venous structure or the right atrium, causing arrhythmogenesis
Venous thrombosis	Thrombus formation in a major vein, due to alterations in blood flow and the presence of a foreign body
Metabolic	
Hyperglycemia	Excessive carbohydrate administration, glucose intolerance, or combination of the two
Hypoglycemia	Sudden cessation of TPN, while insulin stimulation has not subsided
CO_2 retention	Carbohydrate calories in excess of energy requirements
Azotemia	Excessive protein administration with inadequate calories
Essential fatty acid deficiency	Inadequate essential fatty acid administration
Hypertriglyceridemia	Rapid fat infusion or decreased fat clearance
Hypophosphatemia and hypokalemia	Sudden full-strength nutritional restitution in a starved patient (refeeding syndrome)
Any electrolyte abnormality	
Hemorrhagic diathesis	

	Excess or inadequate electrolyte supplementation Vitamin K deficiency
Infectious	
Septicemia Skin site cellulitis Pneumonia, other systemic infectious	Catheter tip becomes colonized with bacteria and continuously seeds bloodstream Skin flora enters the subdermal/subcutaneous space High n-6 fatty acid content adversely affects immune function

Electrolytes

The amounts of the various electrolytes provided to patients receiving parenteral nutrition vary, depending on volume status and preexisting electrolyte abnormalities. Careful monitoring of serum electrolyte levels is critical, especially during the acute phase of disease or in severely malnourished individuals, because as metabolism switches to the anabolic phase, potassium and phosphate can move rapidly into the intracellular compartment, leading to potentially fatal electrolyte abnormalities from refeeding syndrome.[71] Vitamin and trace mineral levels, although not as life-threatening, should be monitored as well. The composition of a standard parenteral nutrition solution is shown in **Table 3.11**.

Table 3.11 Composition of a Standard Total Parenteral Nutrition Formulation

Volume		
10% Amino acid solution		500 mL
50% Dextrose solution		500 mL
Fat emulsion		—
Electrolytes + vitamins + minerals		~50 mL
Total volume		~1,050 mL
Composition		
Amino acids		50 g
Dextrose		250 g
Total N		50/6.25 = 8 g
Dextrose kcal		250 g × 3.4 kcal/g = 840 kcal
mOsm/L		~2,000
	Usual Concentration	**Range of Concentrations**
Electrolytes to Total Parenteral Nutrition Solutions		
	60	0–150
	40	0–80
Sodium (mEq/L)	50	50–150
Potassium (mEq/L)	50	0–150
Acetate (mEq/L)	15	0–30
Chloride (mEq/L)	4.5	0–20
Phosphate (mEq/L)	5	5–15
Calcium (mEq/L)[a]		
Magnesium (mEq/L)		

[a]Generally added as calcium gluconate or calcium chloride: one ampule of calcium gluconate = 1 g of calcium = 4.5 mEq.

Enteral Nutrition Considerations

Enteral nutrition is generally safer and less expensive than parenteral nutrition, and numerous studies have demonstrated superiority of enteral nutrition compared to parenteral nutrition as discussed earlier and extensively in guidelines.[5,45,57] The GI tract can be used for administration of complex nutrients that cannot be provided as readily intravenously, such as polypeptides and fiber. Gut processing of many of these nutrients stimulates hepatic protein synthesis, while intravenous administration 9 bypasses the portal circulation altogether. In addition to the systemic benefits of enteral nutrition, enteral feedings afford significant local benefits on the gut mucosa itself. Enterocytes are being fed directly, and the absorptive surface of the mucosa is stimulated and maintained. Luminal nutrients, such as glutamine and short-chain fatty acids, are used as fuel by small bowel enterocytes and colonocytes, respectively.[72] The trophic effects of luminal nutrition are well documented, even if small amounts of enteral feedings are provided; evidence suggests that earlier enteral nutrition is preferable.[73,74] An additional immunologic benefit of enteral nutrition is that complex polypeptides and long-chain fatty acids stimulate the production of gut-derived immunoglobulin A, which is important in maintaining the mucosal immunity barrier. Luminal nutrients also help maintain a normal pH and flora, thus diminishing the risk of opportunistic bacterial overgrowth in the bowel.

In addition to the physiologic, metabolic, and immunologic benefits of enteral nutrition, safety and cost benefits exist. Enteral feedings are considered safer than parenteral nutrition as there is a less risk of hyperglycemia, which may be the reason why parenteral nutrition–nourished patients were at a greater risk for infectious complications. With the advent of aggressive hyperglycemia management, this risk may be eliminated and may partially explain the differences seen in older studies of parenteral versus enteral nutrition. Additionally, there are obvious cost benefits, as tube feedings are in general cheaper than parenteral nutrition formulations.

Gastrointestinal Function

Although enteral nutrition is generally the preferred method for nutritional support in malnourished patients or patients at risk for developing malnutrition, an intact and well-functioning GI tract is required. Postoperative ileus is frequent, reflects functional immobility of the GI tract,

and is typically proportional to the amount of manipulation the bowel sustained during the surgical intervention. Contraindications to enteral feedings are usually relative or temporary and include short, obstructed, or perforated bowel, a GI tract in discontinuity, protracted vomiting, fistulas, or active GI ischemia. ESPEN and the European Society of Intensive Care Medicine endorse contraindications to enteral nutrition and suggest withholding enteral nutrition in critically ill patients with uncontrolled shock, uncontrolled hypoxemia and acidosis, uncontrolled upper GI bleeding, gastric aspirate >500 mL/6 hr, bowel ischemia, bowel obstruction, abdominal compartment syndrome, and high-output fistula without distal feeding access.[45,75] The ASPEN/SCCM recommendations are similar.[5]

Complications of Enteral Nutrition

Despite the numerous benefits of enteral nutrition, it is not completely free of complications. These can be categorized into access-related, functional, and metabolic and are summarized in **Table 3.12**. In general, these can be avoided with meticulous care while inserting and maintaining feeding tubes, considering using nasal bridles,[76] ensuring head-of-bed elevation to minimize risk of aspiration, using motility agents when gastric motility is suboptimal, closely monitoring patients' metabolic profile and adjusting content, or adding bulking agents if osmotic diarrhea develops.

Enteral Feeding Formulations

Enteral feedings are generally categorized into intact or polymeric, hydrolyzed or monomeric, or modular. With the intact or polymeric formulations, protein, carbohydrate, and lipid molecules exist in an unaltered form. Hydrolyzed or monomeric formulations contain predigested proteins, simple sugars, and medium-chain triglycerides. Modular feeds typically contain one type of fuel, carbohydrate, lipids, or fat, and can be combined to address each patient's specific needs. Despite previous enthusiasm for specialty feeds for a variety of disease states, current recommendations are for standard polymeric enteral feeding formulas for medical patients. Postoperative surgical patients and patients with traumatic brain injury may benefit from immunomodulating enteral formulations, although the quality of

evidence is low.[5] Some of the most commonly used enteric feeding formulas and their metabolic characteristics are shown in **Table 3.13**.

Macro- and Micronutrient Selection

Protein

An additional topic of debate is whether selection of specific macro- and micronutrients included in nutritional formulas, be it enteral or parenteral, can afford specific benefits to patients receiving them, depending on the underlying pathology. Gluconeogenesis from amino acids (glutamine and alanine) released from muscle protein breakdown cannot be fully suppressed with exogenous glucose and insulin administration, due to the complex hormonal stress response the human body elicits during critical illness, which results in relative insulin resistance. It was postulated, therefore, that exogenous amino acid and oligopeptide infusion would help minimize lean body mass erosion.[77] Therefore, the optimal protein to total energy ratio in critical illness was previously unknown. More recent studies in critical ill populations suggest that provision of protein is more closely linked to outcome than provision of total energy in the forms of carbohydrates and fats.[5] In addition, the dose of protein required by critically ill patients appears to be higher than previously thought. At least two studies have demonstrated better outcomes when high-protein targets were met.[78,79]

Table 3.12 Enteral Nutrition–Related Complications

Complication	Etiology
Access-Related	
Feeding tube malposition, clogging, and accidental removal	The feeding tube can be misplaced in the tracheobronchial tree; it can become clogged with dense tube feedings or inadequately crushed medications or be accidentally removed
Oro/nasogastric or enteral tube perforation of the proximal gastrointestinal tract or tracheobronchial tree	Accidental puncture of the wall of the structure the feeding tube in placed into
Pressure ulcers at skin entry site and sinusitis	A foreign body is continuously pressing against healthy skin and increases risk of bacterial colonization of the nasal passages
Functional	
Nausea, vomiting, and abdominal distension	Usually due to delayed gastric emptying
Diarrhea	Usually polyfactorial, but high protein content and high osmolarity of enteral feedings are the most common culprits
Metabolic	
Electrolyte abnormalities	When enteral nutrition content is inadequate to cover daily needs. Hyperosmolarity may be a consequence when calorically dense enteral feedings are administered
Volume overload	From excess sodium and water loading, typically in patients with preexisting heart failure
Hyperglycemia	

	Less common than in patients receiving TPN but may manifest in patients with diabetes or impaired glucose tolerance or can herald sepsis

Glutamine

10 Glutamine is the most abundant nonessential amino acid and in humans, it is predominantly released with skeletal muscle proteolysis. It is one of the key precursors for hepatic gluconeogenesis at times of stress, and low glutamine levels have been associated with poor outcomes in critical illness, as it is an important nutrient necessary for the function of immune cells, enterocytes, and hepatocytes. It has been postulated that low glutamine levels are a consequence of muscle wasting, and a meta-analysis of early randomized controlled trials suggested that glutamine supplementation may help decrease infectious complications, hospital length of stay, and even mortality.[80] However, this finding has not been replicated in newer, higher-quality studies, and, in fact, it appears that aggressive glutamine supplementation may increase risk of death in patients with organ failure.[81–83] These findings do not support glutamine supplementation routinely. Its supplementation may be beneficial when depletion is severe or when the intestinal mucosa is damaged by chemo- and/or radiation therapy.[84] Similarly, arginine supplementation may be associated with a lower infectious risk and shorter hospital length of stay; however, no currently available evidence supports its use during critical illness.[85]

Table 3.13 Commonly Used Enteral Nutrition Formulations

Product Name	Calories (per mL)	Protein (g/L)	Carbohydrates (g/L)	Fat (g/L)	Fiber (g/L)	Osmolality (mOsm/L)	Special Features
Tube Feeding Formulations							
Osmolite 1 Cal	1.06	44	144	35	0	300	Isotonic
Jevity 1.2 Cal	1.2	56	169	39	18	450	High protein with fiber
Jevity 1.5 Cal	1.5	64	50	50	22	525	Concentrated calories with fiber
Promote with Fiber	1	63	138	28	14	380	Very high protein with fiber
Nepro with Carb Steady	1.8	81	161	96	13	745	Renal formula
TwoCal HN	2	84	219	91	5	725	Calorie and protein dense
Vital AF 1.2 Cal	1.2	75	111	54	5	425	Peptide-based elemental with high protein
Vital high protein	1	88	112	23	0	353	Peptide-based elemental with high protein
Pivot 1.5 Cal	1.5	94	172	51	7.5	595	Immune support
Vivonex RTF	1	50	176	12	0	630	Elemental (amino acids)

Product Name	Calories	Protein (g)	Carbohydrates (g)	Fat (g)	Fiber (g)	% Water	Special Features
Oral Supplements[a]							
Ensure Plus (per 8 fl)	350	13	51	11	3	76	High calorie and high protein
Glucerna Shake (per 8 fl)	220	10	26	9	3	84	Diabetic formula
Ensure Clear (per 6.8 fl)	200	7	43	0	0	84	Clear liquid
Juven (per 24 g)	80	14 (amino acids)	8	0	0	n/a	Helps build lean body mass to support healing
Pro-Stat Sugar free (per 30 mL)	100	15	10	0	0	n/a	Protein
Nutrisource fiber (per 4 g)	15	0	4	0	3	n/a	Fiber

[a]Per amount noted in product name column.
Adapted from Boston University Medical Center's Nutrition Formulary, 2014.

Fatty Acids

The omega-3 fatty acids, which are found in fish oil preparations, have been shown to have anti-inflammatory effects as opposed to omega-6 fatty acids, found in soybean oil, which appear to be proinflammatory.[86] Some initial studies suggested that administration of high omega-3 to omega-6 fatty acid ratio formulas may benefit critically ill patients.[87,88] However, more recent, higher-quality studies have failed to show a beneficial effect of omega-3 fatty acid preparations in either enteral or parenteral nutrition formulations.[89,90] Currently, the lack of high-quality evidence precludes any recommendation on the use of specific lipids in critically ill patients.

Micronutrients

Micronutrients—electrolytes, vitamins, and trace elements—are administered in critical illness to prevent deficiencies and associated complications. With repletion of micronutrient stores after starvation, refeeding syndrome can occur. Refeeding syndrome is associated with the reintroduction of feeding after a period of caloric deprivation and is characterized by hypophosphatemia. This can be life-threatening and present with lactic acidosis, cardiac arrhythmias, worsening respiratory failure, and even heart failure. Therefore, routine administration of physiologic doses of micronutrients during critical illness is warranted. Provision of therapeutic doses of trace elements (selenium, copper, zinc, and iron) and vitamins (E, C, and beta-carotene) with antioxidant activity has also been proposed[91]; however, a recent randomized controlled trial failed to demonstrate a benefit.[82] Selenium supplementation may also be beneficial in subjects with selenium deficiency, and the potential benefit is supported by a recent meta-analysis.[92]

Nutritional Access

Parenteral Nutrition Access

Parenteral solutions are administered through a central venous catheter, generally inserted in the subclavian or internal jugular vein, or through peripherally inserted central catheters (PICCs) that are typically inserted via veins of the antecubital fossa with the tip in the atriocaval junction. Current

recommendations are to choose the smallest device possible and always "reserve" one lumen to be dedicated to the parenteral nutrition administration.[57] Peripheral parenteral nutrition (PPN) can be infused through peripheral venous cannulas. Peripheral intravenous feedings may be used for infusion of protein, lipid, and lower concentration dextrose solutions. PPN is limited in caloric delivery, due to the large volumes it would require to meet daily demands, but it avoids central venous cannulation, which has considerable complications. It can be considered for short-term parenteral nutrition, for example, in the case of postoperative patients with ileus expected to resolve in a few days.

Enteral Nutrition Access

11 In the acute phase of surgical illness, enteral feedings are often administered through oral or nasal enteric feeding tubes. The tip of the tubes can either reside in the stomach—gastric—or the duodenum or proximal jejunum—"postpyloric." The stomach is easily accessed with a soft flexible feeding tube. Intragastric feedings provide several advantages compared to more distal GI tract feedings, as the stomach has the capacity and reservoir for bolus feedings. Feeding into the stomach stimulates the biliary and pancreatic axis, with trophic benefits for the entire small bowel. Finally, gastric secretions exert a dilutional effect on tube feeding osmolarity, reducing the risk of diarrhea. An important risk of intragastric feedings is regurgitation of gastric contents, with possible aspiration into the tracheobronchial tree. This risk is highest in patients with altered mental status or who are on neuromuscular blockade. Routine monitoring of gastric residual volumes is currently not recommended, as it has not been shown to be associated with a reduction in aspiration events.[93]

First-line therapy for patients with gastric feeding intolerance is the provision of prokinetic agents.[5] Placement of the feeding tube through the pylorus reduces the risk of regurgitation and is advisable in patients with gastric feeding intolerance that does not resolve with prokinetic agents.[5,94,95] Nasoduodenal/nasojejunal tubes are smaller in caliber and therefore more comfortable for patients; however, they are more prone to clogging. Patients who repeatedly remove their catheters may be candidates for feeding tube

bridles. Placement of nasogastric or nasoduodenal tubes should always be confirmed radiographically prior to initiation of feedings.

Patients with chronically impaired mental status, an inadequate swallowing mechanism, or dysphagia and those with oropharyngeal or proximal GI tract pathology may be candidates for longer-term transabdominal GI access. This access is traditionally provided through temporary Stamm gastrostomies, in which a small laparotomy incision is made, and the gastric lumen in the midportion of the gastric body is accessed, while a transabdominal large-bore feeding tube is secured in place with concentric purse string sutures. This procedure is more frequently performed with a minimally invasive laparoscopic approach now. Percutaneous endoscopic gastrostomy (PEG) tubes can be inserted and provide access for gastric feedings, without the need for laparotomy, general anesthesia, and even a trip to the operating room, as they can be performed at the bedside under endoscopic guidance. Using monitored anesthesia care, a gastroscope is advanced transorally into the stomach and helps transilluminate the anterior gastric wall through the abdominal wall. A small abdominal incision is made over the area of maximal transillumination, ideally over the midportion of the gastric body, and through an angiocatheter, a wire is advanced into the gastric lumen, which is snared and pulled back out of the mouth with the gastroscope. The wire is looped around the PEG tube and pulled through the abdominal wall in an antegrade fashion, until only the head of the feeding tube remains in the stomach, with the rest of it being extracorporeal. The inner part of the PEG tube is confirmed to be in correct position and the feeding tube is secured in place. This technique may be difficult in obese patients, whose abdominal walls can be hard to transilluminate. Fluoroscopic approaches can also be used.

Feeding jejunostomies can be considered following any major abdominal procedure if the need for prolonged enteral nutrition is anticipated and there is preference to feed the small bowel. A loop of proximal small bowel, typically 20 to 40 cm distal to the ligament of Treitz, is elevated and secured against the abdominal wall fascia of the left upper or lower quadrant and is accessed transabdominally with a feeding tube. The tube can be covered for a short distance with bowel serosa, called a Witzel jejunostomy. Feeding jejunostomies are standardly placed via a laparoscopic approach.[96] Dual-lumen transgastric jejunal feeding tubes have the lower morbidity of a

gastrostomy as compared to a jejunostomy with the benefit of small bowel feeding, as well as the passage of jejunostomy tubes through percutaneously placed gastrostomy tubes.

NUTRITIONAL CONSIDERATIONS IN SPECIAL POPULATIONS

Sepsis and Septic Shock

12 In the setting of severe inflammation and fever such as that occurs with sepsis, the BMR increases. Total energy requirements need to be assessed, increasing energy requirements by 20% to 30% for mild or moderate infection and approximately 50% above basal levels in severe infection. Many of the recommendations about nutritional support in the setting of sepsis have been previously discussed. Based on expert consensus, the ASPEN/SCCM guidelines suggest that critically ill patients receive enteral nutrition 24 to 48 hours as soon as the patient is hemodynamically stable.[5] Initiation of enteral nutrition while the patient is still in shock may aggravate impaired splanchnic perfusion.[97] The NUTRIREA-2 study demonstrated an increase in GI complications when patients on vasoactive agents were fed enterally early in the course of septic shock.[52] Provision of goal calories does not need to be achieved, but provision of goal protein has demonstrated benefit.[78] Supplemental parenteral nutrition or parenteral nutrition alone is not recommended early in the course of sepsis and septic shock but should be instituted if enteral nutrition is not feasible for a prolonged period.[45] Immunomodulating formulas should not be routinely used.

Acute Respiratory Failure

A condition commonly complicating surgical patients is respiratory failure with the need for prolonged mechanical ventilation. The main concern in mechanically ventilated patients is adequate gas exchange, which includes oxygen and CO_2 transport across the capillary–alveolar membrane. Not uncommonly the indication for ventilatory support is pulmonary infection, which along with a postoperative status, contributes to the overall

hypermetabolism. Hypermetabolism is accompanied by increased oxygen consumption, which drives CO_2 production, as more substrate must be oxidized to support the greater energy requirements. While nutrition commonly takes lower priority in ventilated patients, in whom all efforts are directed toward managing the underlying etiology for the respiratory insufficiency, consideration should be given to the content of the nutritional support, as they may facilitate or prolong weaning, especially in those with chronic CO_2 retention. Despite early enthusiasm for enteral formulations that were high in fat and low in carbohydrate to decrease CO_2 production, this strategy only results in lower CO_2 production in patients who are being overfed.[98] Fluid restriction with energy-dense enteral feeds may be appropriate in patients with fluid overload.[5]

Acute Renal Failure

Renal failure affects the body's ability to clear the by-products of protein metabolism but does not change the catabolic rate or the protein requirements. Therefore, a careful balance needs to be achieved between the need for protein and to limit uremia. When acute surgical stress is superimposed, consideration for potentially earlier or more aggressive renal support should be given so that the body is not restricted of protein, which is critical during the hypermetabolic phase of acute disease. Based on expert consensus, patients with acute renal failure should be placed on a standard enteral formulation, energy (25 to 30 kcal/kg/day) provision, with standard recommendations for protein (1.2 to 2 g/kg actual body weight per day).[5] Only if significant electrolyte abnormalities develop, a specialty formulation designed for renal failure should be utilized. In patients on renal replacement therapy, patients should receive increased protein, up to a maximum of 2.5 g/kg/day. Protein should not be restricted in patients with acute renal failure as a means to avoid or delay initiating renal replacement therapy.[5]

Acute Liver Failure

Patients with liver disease are often chronically malnourished. These individuals are protein depleted, yet tolerate protein poorly, due to their

likelihood to become encephalopathic with high nitrogen intake. Due to liver damage and portosystemic shunting, these patients can develop derangements in circulating levels of amino acids. The plasma aromatic to branched chain amino acid ratio is increased, favoring the transport of aromatic amino acids across the blood–brain barrier. These amino acids are precursors of neurotransmitters that can worsen encephalopathy and lethargy. Therefore, historically, protein restriction was used to help reduce hepatic encephalopathy. This strategy may worsen nutritional status, decrease lean muscle mass, and ironically lead to decreased ammonia elimination. Therefore, protein should not be restricted as a management strategy aimed at reducing hepatic encephalopathy.[99,100] Using solutions enriched in BCAAs and deficient in aromatic amino acids in liver failure patients has failed to show benefit in patients being treated with lactulose and luminal-acting antibiotics.[5]

Complications of Gastrointestinal Surgery

After GI surgery, whether elective or emergent, complications such as anastomotic leaks and enteroatmospheric or enterocutaneous fistulae can complicate nutritional management. In critically ill patients with surgical complications after abdominal or esophageal surgery who are unable to eat orally, enteral nutrition, rather than parenteral nutrition, should be utilized unless the patient is in discontinuity, has obstruction of the GI tract, or has abdominal compartment syndrome.[45] GI cutaneous or GI atmospheric fistulas with high output (commonly defined as having output >400 mL/24 hr) represent a classic indication for long-term parenteral nutrition. Oral intake in patients with such fistulas typically results in greater output, especially in fistulas involving the proximal GI tract, which can lead to dehydration and significant metabolic disturbances and adversely affect the ability of the fistula to heal. In the case of an unrepaired anastomotic leak or fistula, a feeding access distal to the defect should be the goal to allow for enteral nutrition.[45] If distal feeding access is not achieved, parenteral nutrition is appropriate. Parenteral nutrition has been shown to increase spontaneous rate of closure of enterocutaneous fistulas by improving overall nutritional status in the host or improving perioperative outcomes in those requiring surgical therapy. Somatostatin and analogs have been used to aid with fistulous output

and spontaneous closure with varying results. In patients who are treated via a damage control laparotomy approach or who have an open abdomen, early enteral nutrition is recommended[5] as long as there is intestinal continuity. Additional protein supplementation may be appropriate due to the high protein loss of the exudate.[101–103]

Burns

Burn victims often suffer from prolonged ileus, which encumbers enteral nutritional support. Even if the bowel is usable and patients are not on mechanical ventilation, they are frequently unable to consume adequate calories, due to anorexia of severe injury and extreme catabolism. Based on expert consensus, early (within 4 to 6 hours of injury if possible) enteral nutrition should be administered to all burn patients to meet estimated energy needs. Parenteral nutrition should only be reserved for those patients for whom enteral nutrition is not feasible or not tolerated. Enteral nutrition has been associated with fewer infections and improved survival when compared with parenteral nutrition.[104] Patients with burns should also be provided protein in the range of 1.5 to 2 g/kg/day.[5] Indirect calorimetry is recommended to assess energy needs in burn patients with routine repeated measures.

Acute Pancreatitis

Mild pancreatitis is defined by the absence of organ failure and local complications, while moderate to severe acute pancreatitis is defined by transient organ failure.[105] Differentiating patients with severe acute pancreatitis from those with mild severity helps identify those patients who will require early provision of nutrition therapy. ASPEN/SCCM recommends that the initial nutrition assessment in acute pancreatitis evaluate disease severity to guide nutritional therapy and that frequent reevaluation is performed.[5] Patients with moderate to severe acute pancreatitis should have a nasal or oral enteric tube placed and enteral nutrition with a standard polymeric formulation initiated at a low rate and advanced to goal as fluid volume resuscitation is completed.[5] This is based on studies that have demonstrated benefit from early enteral nutrition.[106–110] Parenteral nutrition

should be avoided when possible, but if the patient is unable to be fed enterally, parenteral nutrition should be instituted 7 days after the onset of the critical illness.[74] Probiotics may be beneficial in patients with acute pancreatitis, based on a meta-analysis from 2010.[111]

Trauma

Trauma patients have a high risk of developing septic complications and multiple-organ failure. Early enteral nutrition has been shown to reduce septic complications[112,113] and reduce the rate of organ failure when initiated within 24 hours.[114] Both ASPEN/SCCM and ESPEN recommend early enteral feeding with a high protein polymeric formulation in the immediate posttrauma period once the patient is hemodynamically stable.[5,45] Immunomodulating formulae may be considered in severely injured patients.[5] For patients with traumatic brain injury, early feeding is associated with decreased infection rates and better outcomes.[115]

Solid Organ Transplant

Malnutrition is a major factor influencing outcome after transplantation. Candidates for solid organ transplantation should have regular assessment of their nutritional status, and if meet criteria for malnutrition, oral nutritional supplements or even *tube feeding* is advised.[32] *Since there is* often a long preoperative waiting period, there is time to try to replete patients nutritionally. In addition to malnutrition, obesity remains a significant metabolic risk factor for the outcome of patients undergoing organ transplantation.[116] Despite some suggestion of benefit of immunomodulating formulas in the literature,[117] a consistent benefit has not been demonstrated. After solid organ transplantation, early intake, either orally or via a feeding tube, within 24 hours is recommended. *No strong recommendations are made for the use of probiotics, parenteral nutrition, or omega-3 fatty acid provision. Long-term nutritional monitoring and counseling are recommended.*[32]

Bariatric Surgery

Bariatric patients pose a special challenge, as they are at an increased risk for several macro- (usually protein) and micronutrient deficiencies (most commonly vitamins D and B_{12}, calcium, iron, folic acid, zinc, and selenium).[118–120] Nutritional support of the obese or post–weight loss surgery patient is particularly complex because of the balance needed between minimizing overfeeding and avoiding the hypercatabolic state. There is widespread consensus that early oral nutrition after bariatric surgery is appropriate.[121,122] Clinical practice guidelines recommend a preoperative assessment including screening for malnutrition and deficiency in vitamins and trace elements.[123] Early postoperative enteral nutrition is advocated and supplementation with protein in order to meet daily requirements of 60 g of protein per day.[32] Standard oral supplements should be avoided in bariatric patients as they can cause dumping syndrome. Postoperative nutritional follow-up by a dedicated team is essential to monitor weight loss and prevent deficiencies of micronutrients. ERAS principles have been applied and appear to be beneficial in bariatric surgery.[124] In case of a major complication requiring reoperation, recommendations are no different from those for patients undergoing any major *abdominal surgery*. Despite the excessive fat stores, critically ill postoperative bariatric patients should receive early and timely nutrition, as protein–calorie malnutrition does occur. Consideration for indirect calorimetry, which allows accurate estimation of the caloric requirements, is appropriate, and early involvement of a nutritionist is essential.

Geriatrics

Attention to appropriate nutritional support of the geriatric or frail patient is of paramount importance, both in the perioperative stage and in the ICU, given the multiple physiologic alterations seen in both frailty and older age. These alterations include greater ratio of fat to muscle mass, decreased cardiac and pulmonary reserves, poor dentition, polypharmacy, and a high incidence of malnutrition. Malnutrition rates may be as high as 85% in nursing home residents.[125,126] Compared to younger cohorts, elderly patients are more likely to have comorbid disease processes affecting their general nutritional status, including diabetes, cancers, cardiac, pulmonary, and renal

insufficiency. Given that a certain degree of lean body mass loss is to be expected in this demographic, a higher protein intake (>1.5 g/kg/day) should be the goal preoperatively in the elderly undergoing elective surgery or early in the recovery phase after emergency procedure or acute surgical illness.[127,128]

Obesity

Overweight and obese patients have become more prevalent in ICUs as the prevalence of obesity increases in the general population. As a general rule, an isocaloric high-protein diet can be administered to obese patients, preferentially guided by indirect calorimetry measurements and urinary nitrogen losses. It is still unclear whether overweight and obese critically ill patients have a higher nitrogen loss than patients with a normal BMI when adjusted for actual lean body mass. Other metabolic derangements are common such as decreased glucose tolerance, altered lipid metabolism, lack of micronutrients, and decreased gut motility.[129] Recommendations for early enteral nutrition apply similarly to overweight and obese patients as to other critically ill and postoperative patients.[45] High-protein hypocaloric feeding should be implemented to preserve lean muscle mass whenever feasible.[5]

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4

The Pathogenesis of Obesity and Metabolic Disease

Robert W. O'Rourke

Key Points

1. Obesity is a polygenic phenomenon, and up to 70% of the propensity to obesity is due to genetic influences.
2. Epigenetics and environment interact with genetics to produce the obesity phenotype.
3. Control of food intake via satiety and hunger is a dominant mechanism of body weight regulation, but other processes contribute, including but not limited to metabolic rate, adipocyte physiology, and the microbiome; alterations in these processes are linked to the development of obesity.
4. The hypothalamic feeding center (HFC) is a dominant central control site of energy homeostasis, with multiple afferent inputs and diverse efferent outputs to all organ systems.
5. Bariatric surgery regulates body weight via multiple mechanisms that are qualitatively different from responses to nonsurgical weight loss.
6. Nutrient excess is a key early trigger in the development of cell stress that underlies the pathogenesis of metabolic disease.
7. Adipose tissue acts as a critical nutrient "buffer" to protect other tissues from nutrient excess; as adipose buffering capacity is overwhelmed, nutrient excess overflows to all tissues, inducing metabolic disease.
8. Hepatic steatosis and peripheral and central insulin resistance are dominant features of metabolic disease, but metabolic disease encompasses all organ systems with pleiotropic pathology.

GENETICS OF OBESITY

Metabolic Thrift, Genetics, and Epigenetics

The *thrifty gene hypothesis*, proposed by geneticist Neel, posits that humans are predisposed to a *thrifty metabolism* by genes selected over eons of

evolution in environments characterized by food scarcity.[1] These genes were adaptive in our ancient past but lead to a blossoming of obesity in our modern *obesogenic environment*. While competing theories exist, such as predation release and genetic drift, Neel's hypothesis remains the basis of a modern understanding of obesity as a genetic phenomenon. *Quantitative analysis of twin studies,* in which phenotypic traits of thousands of twin pairs are analyzed using statistical methods based on Mendelian principles, consistently demonstrate that approximately 70% of the tendency 1 to obesity is due to genetics.[2] *Genome-wide association studies* (GWAS), which involve sequencing thousands of genomes and correlating single-nucleotide polymorphisms (SNPs) with phenotypic traits and disease states, permit study of genetics at the nucleotide level. GWAS studies have identified thrifty genes that Neel postulated decades earlier. Many obesity SNPs lie within genes associated with body weight regulation. Others lie in genes not clearly related to energy balance, but instead regulate neural and limb development, DNA repair, and other cellular functions, testament to the fact that the processes that regulate energy homeostasis overlap with all aspects of physiology. Emerging data demonstrate that the effect size of each individual SNP's contribution to the obesity phenotype is small, on the order of 1% to 3%, and that potentially hundreds of SNPs contribute to obesity. Obesity, like many chronic diseases, is a complex polygenic phenomenon. GWAS studies have so far identified over 50 SNPs that correlate with human obesity.[3]

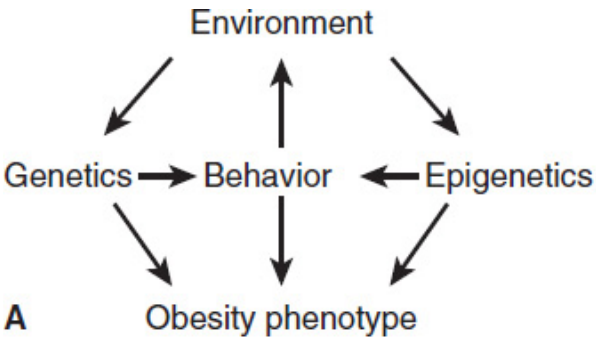
The *thrifty phenotype hypothesis* was proposed by Hales and Barker in 1992 to explain the observation that infants born to malnourished mothers are at increased risk of adult obesity and metabolic disease compared to offspring born of the same mothers during well-nourished pregnancies.[4] The fetus was presumed to be responding to instability in environmental food resources by adjusting its phenotype toward a thrifty metabolism, a phenomenon termed *fetal programming*. A similar response was subsequently observed in fetuses born of obese and diabetic mothers.[5] Excess or scarcity of nutrients may be interpreted similarly by the fetus as signs of unstable food resources, explaining the similar effect of maternal under- and overnutrition on offspring metabolic phenotype. Subsequent research demonstrated that these effects are mediated by *epigenetic* mechanisms, covalent modification of the genome independent of changes in

Watson–Crick base-pair sequence, 2 including but not limited to DNA methylation, glycosylation, and histone modification, changes that persist for one or more generations. Epigenetic modification of the genome is widespread, occurs primarily during fetal development but extends into adulthood, and regulates normal developmental processes as well as pathologic responses. Epigenetics allows the fetus to respond in utero to environmental cues delivered by changes in maternal homeostasis, the so-called "weather forecast" model.[6] Epigenetic modifications in response to fetal under- and overnutrition have been demonstrated in animals and humans, play an important role in disease pathogenesis, and suggest that intervention must occur early, prior to birth, to prevent adult obesity and metabolic disease.

Human Metabolic Diversity and Environment

The multiple thrifty SNPs in the human genome impart genetic heterogeneity that underlies the intrinsic variability of human body habitus and metabolism, with a wide range of body types from lean to obese, gynecoid and android obesity phenotypes, variability in age of onset, triggers, and severity of obesity, response weight loss interventions, as well as differences in satiety and hunger thresholds, metabolic rates, and multiple specific metabolic functions. *Metabolic diversity* has allowed humans to adapt to a wide range of habitats. Multiple examples exist of human subpopulations whose genetic heritages are adaptive in their native environments, but maladaptive in a modern obesogenic environment. Polynesians, for example, manifest a marked genetic propensity to obesity and insulin resistance, traits that provided a selective advantage in the ancient South Pacific environment, but which impart a high risk for obesity and metabolic disease in our modern environment. Similar human subpopulations metabolically adapted to specific niche environments but at high risk for metabolic disease in industrialized society include Inuit Eskimos, Aboriginal Australians, and Pima Indians (**Fig. 4.1**). Environment plays a critical role in the obesity phenotype. Modern environmental contributors include an excess of processed food and a structured *built environment* that discourages physical activity. Modern processed food is not only calorie dense but also highly palatable, stimulating central nervous system reward centers and

hunger/satiety circuits not designed for chronic stimulation, thus reinforcing overeating. Physical activity is markedly decreased in our modern environment. Paleolithic humans were estimated to have consumed 30% more calories than modern humans but engaged in significantly higher levels of physical activity.[7] Other factors also contribute, including disruption in Circadian rhythms, home temperature stability, and assortative mating patterns. An evolving field of environmental engineering has arisen to address these issues.



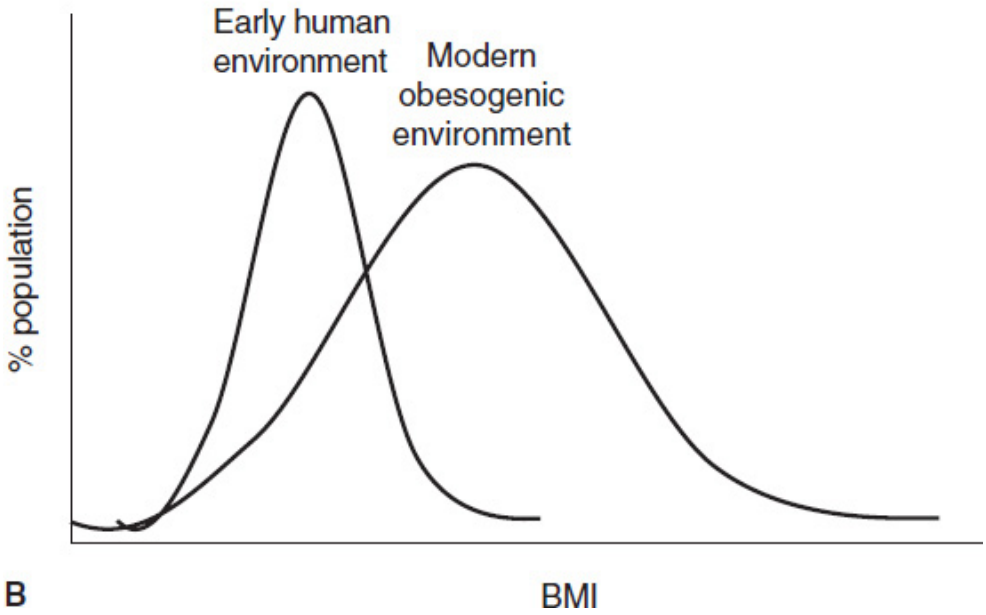


Figure 4.1 Interactions between environment and genetics dictate phenotype. **A:** Environment alters genetics over millennia, while the effects of environment on epigenetics take place over generations. In the case of humans, genetics dictates our behavior which in turn has led us to create an obesogenic environment, creating a vicious cycle that exacerbates the obesity epidemic. **B:** The obesity phenotype blossoms in a modern obesogenic environment, with the population BMI curve broadening and shifting rightward, with an increase in median BMI. The increase in median BMI is relatively modest, but a substantially larger percentage of people populate overweight and obese BMI ranges. Of note, the schematic graphs shown are similar to those that describe the shift in U.S. population BMI NHANES data from the late 1970s to the early 2000s.

3 PHYSIOLOGY OF OBESITY

The Adipostat

A dominant determinant of systemic metabolic homeostasis is the quantity of existent adipose tissue stores, the adequacy of which is determined by the hypothalamic feeding center (HFC). The HFC receives multiple afferent neural and hormonal inputs from all organ systems, including adipose tissue, and orchestrates a range of responses via efferent outputs that monitor and maintain adipose tissue stores, regulate all aspects of metabolism, and which together comprise the *adipostat*, the sum total of all processes that defend body weight. The amount of adipose tissue "deemed" adequate by the HFC varies among individuals and is dictated by multiple poorly understood thrifty genes which collectively determine the *adipostat set-point*. The hypothalamus of a lean person "considers" a lower amount of adipose tissue to be adequate, while the hypothalamus of an obese person requires higher levels of adipose tissue stores. Weight loss alerts the HFC to deviation from the adipostat set-point and triggers robust compensatory responses that restore adipose tissue mass to baseline levels, including increased hunger, decreased satiety, and decreased metabolic rate. HFC-mediated metabolic responses are characterized by tight regulation; deviation outside the range of these responses for more than limited periods of time is not possible based on conscious choice, explaining the high failure rate of diet-induced weight loss, and the lack of efficacy of liposuction for weight loss, as reduction in adipose tissue mass activates compensatory mechanisms that restore adipose tissue mass to set-point levels. Bariatric surgery–induced weight loss is an exception to this rule, inducing poorly understood paradoxical responses that bypass the adipostat. Multiple physiologic mechanisms comprise the adipostat and regulate body weight. Most important in humans are the collective satiety and hunger systems that regulate food intake. Also important are mechanisms that control metabolic rate, adipocyte physiology, and the microbiome.

Satiety and Hunger

Regulation of food intake is the dominant mechanism by which humans control body weight. Food intake is controlled by a family of proteins that regulate satiety and hunger primarily by acting on receptors within the hypothalamus. These diverse proteins are secreted by multiple organ

systems, including but not limited to adipose tissue, the gut, the liver, and skeletal muscle.

The Ob mouse, a mutant strain described in 1950, manifests an obese phenotype along with immune, endocrine, and reproductive abnormalities. The Ob mouse harbors an inactivating point mutation in the *leptin* gene (Gr *leptos*, thin). Leptin is a 16-kD satiety hormone secreted by adipose tissue in response to a meal that binds receptors in the HFC and induces satiety. Leptin mediates communication between adipose tissue, gut, and brain that signals the status of adipose tissue stores, which in turn dictates food intake. As such, leptin is a paradigmatic mediator of the adipostat and an example of the complex interorgan communication that underlies its function (**Fig. 4.2**). Soon after cloning of the leptin gene in 1994,[8] rare humans with leptin mutations were identified with an Ob phenotype that was reversed with administration of exogenous recombinant leptin. Similar therapy was ineffective in common human obesity, which is not due to a single leptin mutation, but rather is polygenic and characterized by hypothalamic resistance to leptin satiety effects. Nonetheless, the discovery of leptin led to an explosion of research, and over the ensuing decade multiple satiety and hunger proteins were described.

The control of feeding behavior and nutrient intake is a 4 highly regulated process centered in the hypothalamus, which integrates information regarding nutritional status, environment, and energy expenditure via central and peripheral orexigenic and anorexigenic signals. Peripheral messengers include signals from adipose tissue (*adipokines*), including leptin and adiponectin, *cytokines*, such as TNF-α and IL-6, and *gut peptides*. Among this diverse latter class of mediators, ghrelin is a dominant orexigen. Ghrelin is expressed primarily by oxyntic glands in the fundus of the stomach, but is also produced in the hypothalamus. Encoded by five exons, preproghrelin undergoes endoproteolytic processing and posttranslational modification to yield des-acyl ghrelin and acyl ghrelin. Acyl ghrelin, the active form, regulates feeding, metabolic activity, and insulin secretion. The ghrelin receptor is a member of the G protein–coupled receptor family and is widely distributed in central and peripheral tissues, including the pituitary gland, hypothalamus, pancreas, stomach, and intestine. In humans, plasma acyl-ghrelin levels increase with fasting and decrease after feeding, and intravenous administration of ghrelin induces hunger and stimulates oral

intake. Ghrelin secretion is increased by weight loss and caloric restriction, and depressed in obese subjects. Ghrelin antibodies and ghrelin receptor antagonists are under study as therapeutic agents.

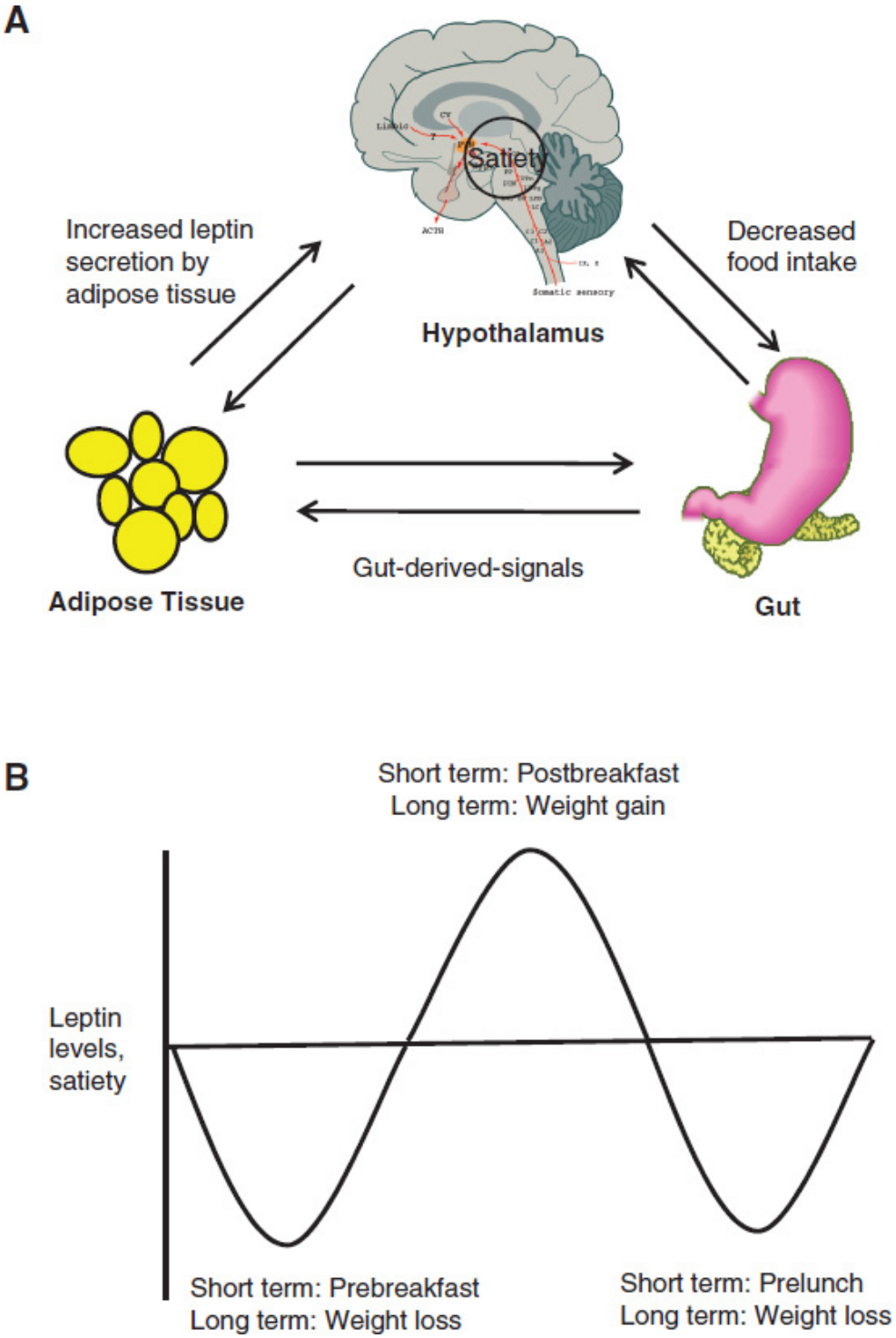


Figure 4.2 Leptin mediates communication between adipose tissue, gut, and brain. **A:** Signals from the gastrointestinal tract triggered by a meal circulate to adipose tissue and induce adipocyte leptin secretion. Leptin circulates to the hypothalamus, where it binds receptors in the arcuate nucleus to induce satiety, leading to decreased food intake. Leptin is one of many signals that mediate bidirectional communication between gut, adipose tissue, and brain. Other organ systems are

also involved, including immune and reproductive systems and the liver. **B:** Leptin regulates allostatic control of short-term and long-term food intake. Postprandial leptin secretion induces satiety for a period of hours, after which leptin levels and satiety wane, prompting food intake. Similarly, leptin, along with other mediators of food intake, controls long-term weight regulation: diet-induced weight loss leads to decreased adipose tissue mass, reducing peak postprandial leptin levels, leading to decreased postprandial satiety and increased food intake at each subsequent meal until adipose tissue mass is restored to set-point levels. In this manner, leptin functions as a component of the adipostat. This allostatic control provides an explanation for rebound weight gain after diet-induced weight loss.

The arcuate nucleus of the hypothalamus is a crucial site for the integration of fasting and feeding signals. Two types of neurons, with opposing actions on feeding behavior, have been identified in the arcuate nucleus. Neurons that express proopiomelanocortin (POMC) and cocaine and amphetamine-related transcript (CART) suppress food intake, reduce body weight, and increase energy expenditure. In contrast, neurons producing neuropeptide Y and agouti gene–related transcript (AgRP) are orexigenic. These cells act to stimulate food intake and reduce energy expenditure. Ghrelin, as well as leptin and multiple other gut peptides, adipokines, and cytokines, directly mediates the activities of these two types of neurons (**Fig. 4.3**).

Other adipokines that regulate satiety include adiponectin, visfatin, apelin, and lipocalin; gut peptides with diverse effects on food intake and metabolism include glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide-1 (GLP-1), nesfatin-1, oxyntomodulin, pancreatic polypeptide, cholecystokinin, amylin, glucagon, somatostatin, cholecystokinin, and insulin. Cytokines, including TNF-α and IL-6, in addition to immunoregulatory functions, also play important roles in the control of food intake. TNF-α, for example, mediates anorexigenic responses in the context of cachexia and inflammatory states. Virtually all adipokines, gut hormones, and cytokines have multiple overlapping functions that include regulation of satiety and hunger, immune function, glucose homeostasis, lipid metabolism, and endocrine and reproductive function (**Fig. 4.4**). This functional diversity speaks to the intimate association of energy homeostasis with all aspects of physiology.

Genetic polymorphisms in the melanocortin 4 receptor gene, which regulates satiety and hunger responses and the HFC set-point, are implicated in 5% of cases of human obesity. Similar polymorphisms associated with

obesity exist with the genes encoding leptin and its receptor, ghrelin, neuropeptide Y, adiponectin, GLP-1, and other genes associated with the control of satiety and hunger. These observations demonstrate that variability in the genes that regulate food intake contribute to the development of human obesity.

Metabolic Rate

In obese subjects who lose weight with diet, total energy expenditure is decreased up to 20% beyond that expected by loss of fat and fat-free mass alone, and is accompanied by a corresponding decrease in voluntary physical activity.[9] Compensatory decreases in energy expenditure counteract caloric restriction and contribute to adipostat responses that resist declines in adipose tissue mass. Studies of overfeeding and weight gain in obese subjects demonstrate converse changes with a compensatory increase in total energy expenditure. Importantly, overfeeding studies in twin cohorts demonstrate a significant genetic component to variability in energy expenditure responses to overfeeding, suggesting that variability in metabolic rate responses to weight loss contributes to the development of obesity in those at risk.[2] Differences in sympathetic nervous system activity contribute to variability in metabolic rate. Obese humans demonstrate decreased sympathetic nervous system activity, and higher levels of sympathetic nervous system activity predict successful diet-induced weight loss. Differences in endocrine responses also contribute, with obese humans manifesting differences in thyroid hormone and catecholamine balance associated with decreased metabolic rates. At the cellular level, differences in energy utilization and thermogenesis play an important role. Skeletal muscle energy utilization efficiency is increased in humans who achieve successful weight loss and decreased in those who gain weight. Furthermore, obese humans manifest decreased skeletal muscle nonexercise-induced thermogenesis and diet-induced thermogenesis,[10] suggesting that fundamental differences in cellular energy homeostasis contribute to obesity. The mechanisms underlying these variable cellular responses are not fully defined, but differences in uncoupling protein (UCP) function are implicated. UCP proteins uncouple oxidative phosphorylation from electron transport in mitochondria, creating a proton leak that generates heat rather than ATP. The

role of UCPs in the pathogenesis of obesity is an important area of active research. UCP function is highly variable and genetically determined in mice, and polymorphisms in UCP genes correlate with obesity and metabolic disease in humans, supporting a role for genetic variability in UCP function in obesity pathogenesis. Transgenic mice overexpressing UCP-1 under control of the adipose tissue–specific AP2 promoter are resistant to obesity, suggesting the potential for therapy for obesity based on manipulation of cellular thermogenesis and metabolic rate.

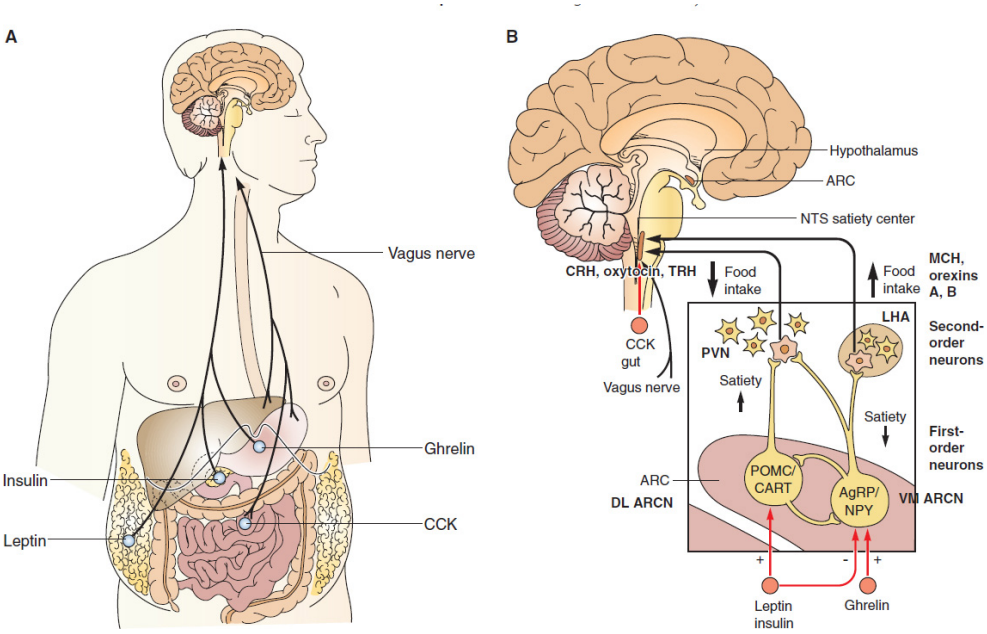


Figure 4.3 A simplified schematic of the hypothalamic feeding center and its primary afferent signals: Multiple hormones secreted by the gastrointestinal tract and adipose tissue act as afferent signals that regulate the arcuate nucleus (ARCN) within the hypothalamic feeding center function. These signals impact on first-order ARCN neurons, which in turn communicate with second-order paraventricular nucleus (PVN) and lateral hypothalamic area (LHA) neurons to coordinate behavioral and metabolic output. PVN signaling is primarily anorexigenic and catabolic, and is enhanced by leptin and insulin, while LHA signaling is primarily orexigenic and anabolic and inhibited by leptin and insulin. Higher-order anorexigenic PVN outputs include corticotropin-releasing hormone (CRH), oxytocin, and thyrotropin-releasing hormone (TRH); higher-order orexigenic LHA outputs include melanin-concentrating hormone (MCH) and orexins. **A** and **B**: Both pathways negatively regulate the other. Other peripheral and central mediators stimulate first- and second-order neurons as well, including ghrelin, CCK, GLP-1, serotonin, endogenous cannabinoids, and norepinephrine.

Adipocyte Physiology

Adipocytes arise from mesenchyme-derived *adipocyte stem cells* (ASCs), also termed *preadipocytes*. ASCs are pluripotent, and depending on the stage of differentiation, may give rise to adipocytes, fibroblast, myocytes, and other cell types. Multiple ASC subpopulations give rise to adipocytes of variable phenotypes, including white, brown, and beige. Evidence suggests that hematopoietic precursor cells may also give rise to adipocytes. Until recently it was thought that ASC proliferation did not occur in postnatal humans, and that adipocyte hypertrophy was the primary mechanism of increased adipose tissue mass in obesity. Recent data suggest that both hyperplasia and hypertrophy contribute to evolving obesity, with hyperplasia predominating during childhood and hypertrophy predominating during adulthood. These data derive in part from ingenious methods studying incorporation of C14 into adipocyte DNA in individuals born before and after mid-20th century nuclear bomb testing, which raised environmental C14 levels.[11] Data over the last decade demonstrate that ASC from obese humans demonstrate increased hyperplastic and hypertrophic capacities, contributing to progressive obesity.[12] Epigenetic programming of ASC during fetal development may account for differences in adipocyte function between obese and lean subjects. Defining regulatory mechanisms of ASC is an active area of research and will lead to methods to manipulate adipocyte biology.

The Microbiome

The microbiome plays an important role in energy homeostasis. Animals raised in germ-free environments manifest increased food intake, decreased body weight, and do not develop obesity and insulin resistance when fed a high-fat diet, demonstrating that gut microbiota contribute to nutrient digestion. Gut microbiota ferment non–host-digestible polysaccharides into monosaccharides and short-chain fatty acids that are absorbed by host enterocytes and colonocytes. Products of microbiota fermentation act not only as nutrients, but also regulate host metabolism: short-chain fatty acids induce satiety, mediated in part by increased secretion of GLP-1 and peptide YY and decreased secretion of ghrelin. Separate data demonstrate interactions between microbiota and adipose tissue, liver, skeletal muscle,

and central nervous system. These effects are mediated by short-chain fatty acids, activation of Toll-like receptors on host cells via lipopolysaccharide and other bacterial products, regulation of host systemic and cellular metabolism, and other diverse mechanisms.

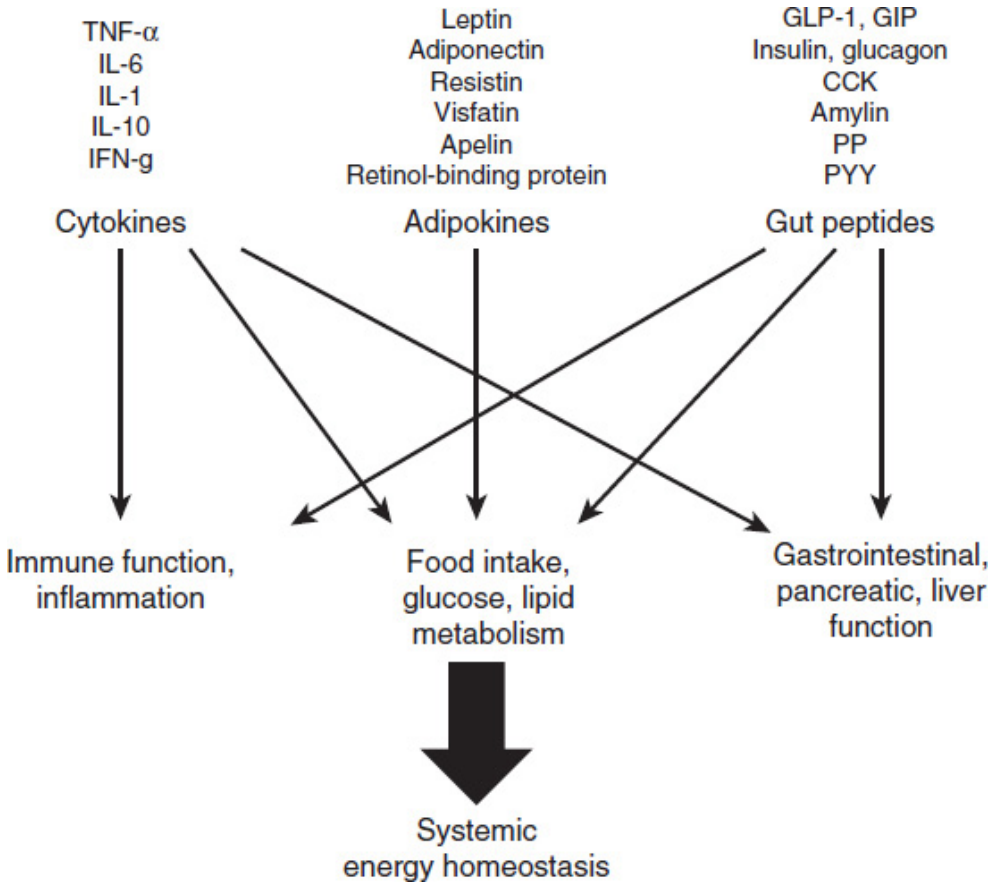


Figure 4.4 Primary peptide mediators of energy homeostasis: Cytokines, adipokines, and gut peptides regulate diverse aspects of metabolism to control global energy homeostasis. Each of these proteins has dominant functions within its primary family, but also demonstrates cross-regulatory functions in other domains. In addition, mediators participate in crosstalk at the level of cellular receptors and downstream intracellular signaling mediators. Shown are only partial lists of peptides and the physiologic functions they control.

Alterations in the microbiome contribute to obesity and metabolic disease. Germ-free mice, when colonized with stool from obese mice, gain more weight than mice colonized with stool from lean mice, demonstrating an obesity-specific microbiome. The ratio of gut Firmicutes/Bacteroidetes species is increased in obese mice and humans. Ongoing research has begun to identify specific subspecies within these broad categories of bacteria that

are altered in obesity and metabolic disease to provide a high-resolution picture of the microbiome in obesity. For example, obesity in mice and humans is associated with an increase in gram-negative gut bacteria, with a concomitant increase in lipopolysaccharide absorption from the gut, which has been postulated to contribute to obesity-associated inflammation and insulin resistance. The tools used to evaluate the microbiome are rapidly evolving. Sequencing of the microbial genome using ribosomal 16S is well established, while evolving technologies include shotgun sequencing of the metagenome and functional assays involving transfer of human microbiota in the form of stool into germ-free animals to study in vivo effects. Manipulation of the microbiome holds therapeutic promise. Prebiotic (nondigestible bacterial nutrients), probiotic (specific bacterial subspecies thought to confer systemic benefits), and tailored antibiotic therapies are areas of active research.

Bariatric Surgery and Weight Physiology

Bariatric surgery regulates body weight physiology via mechanisms that are qualitatively different than those observed in diet-induced weight loss. While restriction of caloric intake and nutrient malabsorption in the past were presumed mechanisms of surgery-induced weight loss, mounting evidence suggests otherwise. For example, little data exists to support that smaller gastric pouches or sleeves are associated achieve greater weight loss; in fact, larger sleeve diameters and antral pouches are associated with greater weight loss in response 5 to sleeve gastrectomy.[13] Other features of restriction are similarly counterintuitive: for example, weight loss after gastric bypass and sleeve gastrectomy is associated with increased gastric emptying rates compared to native anatomy. These observations suggest a complex relationship between weight regulation, metabolism, and gut anatomy and motility. Indeed, bariatric surgery somehow “sidesteps” normal compensatory responses that defend body weight in response to nonsurgical weight loss. For example, satiety is increased, hunger decreased, and metabolic rate increased after bariatric surgery, the opposite of diet-induced weight loss responses. Surgery also induces unique metabolic effects; diabetes often improves within days or weeks of gastric bypass, before substantial weight loss, the result of changes in gut hormone secretion

secondary to altered intestinal anatomy. Decades ago, it was observed that an oral glucose load elicits a greater insulin response than an intravenous glucose load, leading to postulation of the existence of *incretins*, gut hormones secreted in response to a meal that regulate systemic glucose metabolism. Subsequent research led to the discovery of GIP and GLP-1, incretins secreted by duodenal K-cells and ileal L-cells, respectively, in response to nutrient delivery to the small intestine. Incretins have diverse effects on glucose homeostasis, potentiating central insulin secretion and peripheral insulin sensitivity. Anatomic effects of gastric bypass, including diversion of the alimentary stream from the duodenum and proximal jejunum (the *foregut hypothesis*), and increased caloric delivery to the distal jejunum and ileum (the *hindgut hypothesis*), alter secretion of gut hormones and contribute to improvement in glucose homeostasis. While debate persists regarding the magnitude of these effects on diabetes remission after gastric bypass, an understanding of incretin physiology has led to the development of GLP-1 agonists as pharmacologic therapy for diabetes.

Gut anatomic derangements mediate additional metabolic changes. Gastric bypass and sleeve gastrectomy reduce secretion of the orexigenic hormone ghrelin from the gastric fundus, which may reduce hunger after surgery. Gastric bypass and sleeve gastrectomy are associated with increased secretion of peptide YY and oxyntomodulin, gut hormones secreted by L-cells in response to a meal that induce satiety, inhibit gut motility, and are central mediators of the "ileal brake" mechanism. Roux-en-Y anatomy alters bile acid metabolism, increasing serum levels of conjugated bile acids with beneficial effects on glucose and lipid metabolism. Bariatric surgery disrupts vagal and enteroenteric innervation of the gut and alters central nervous system satiety responses. Finally, bariatric surgery is associated with alterations in gut microbiota that contribute to weight loss and resolution of metabolic disease.

Summary

Satiety and hunger, metabolic rate, adipocyte physiology, and the microbiome are a few of many processes that regulate metabolism and are dysregulated in obesity. Differences in lipid and glucose metabolism, immune function, central and peripheral nervous system function, and multiple other processes

contribute to the wide variability of the obesity phenotype and metabolic diversity in humans, driven by genetic polymorphisms that were selected over eons of evolution. The question is often posed, should obesity should be considered a disease? Rather, obesity is better thought of as a maladaptive response to an environment that is radically different than that in which our species evolved. The obesity phenotype remains relatively underexpressed in environments of food scarcity, in which obesogenic genes acted to defend adipose tissue stores and enhance survival, but blossoms in our modern environment. An understanding of these intimate genetic–environment interactions will lead to novel therapy for obesity based on manipulation of environment and genetics. Elucidation of the physiologic mechanisms of weight regulation will similarly lead to next-generation therapy. Bariatric surgery provides a unique opportunity in this regard, as surgery-induced weight loss does not trigger adipostat-mediated defense of body weight in the same way as diet-induced weight loss. An emerging field of *metabolic surgery* is exploring operations designed to mimic metabolic effects of bariatric surgery (e.g., ileal transposition, foregut exclusion) in lean diabetic humans with promising results. As mechanisms underlying surgery-induced weight loss are deciphered, pharmacologic interventions developed through "reverse engineering" of bariatric surgery will emerge.

PATHOPHYSIOLOGY OF METABOLIC DISEASE

Obesity and Metabolic Disease

Obesity is associated with a range of pathology involving every organ system collectively referred to as metabolic disease. While underlying mechanisms are multiple, the root cause of metabolic disease is a failure of adipose tissue nutrient buffering capacity, leading to overflow of nutrients, metabolites, cytokines, and adipokines from adipose tissue to other tissues. The clinical effects of overflow differ depending on the target tissue, but the fundamental cellular responses to nutrient excess common to all tissues, adipose included, involve mechanisms by which cells control nutrient flux and respond to

nutrient excess. These cellular responses underlie the pathophysiology of metabolic disease.

6 Nutrient Excess

Energy homeostasis is the dominant overriding goal of all biologic systems. Metabolism (Gr. *metabole*, change) may be defined as the sum total of all chemical reactions and physiologic processes that regulate cellular and systemic energy homeostasis. At the cellular level, metabolic processes are fundamental to all metazoan life and are highly conserved across phyla; examples include the citric acid cycle and mitochondrial respiration, which utilize multiple enzymes, the structure and function of which are conserved from yeast to humans. At the systemic level, metabolic processes are central to maintaining homeostasis and interface with virtually every organ system and every physiologic process. The basic substrates of metabolism are macronutrients, fatty acids, amino acids, and carbohydrates, and their metabolites, along with micronutrients that catalyze reactions that synthesize and degrade macronutrients and higher-order macromolecules. Cellular nutrient flux provides substrate for synthesis of macromolecules via anabolic metabolic processes, which are in turn degraded via catabolic metabolic processes. Maintaining the balance between anabolism and catabolism at cellular and systemic levels is of critical importance. Cancer, for example, may be viewed as a metabolic imbalance that favors cellular anabolism over catabolism. Cachexia, in contrast, may be considered as a metabolic disorder that favors systemic catabolism over anabolism. The nutrient flux with which cells are constantly faced determines the balance between anabolism and catabolism and dictates organism-wide energy homeostasis. Nutrients are, much like oxygen, high energy-capacity molecules, capable of participating in energy-intensive, potentially damaging reactions. Fatty acid metabolites such as ceramides and diacylglycerols, and glucose metabolites including advanced glycation end products and glucosamines, trigger inflammation, oxidative stress, and insulin resistance. Cellular physiology has therefore evolved processes designed to control exposure, flux, and sequestration of these high-energy molecules. These cellular processes were selected by evolution to manage *transient* nutrient excess, but are not well adapted to *chronic* nutrient excess. Maladaptive cellular responses to chronic nutrient

excess underlie the pathogenesis of metabolic disease and occur in all cells, explaining the involvement of virtually every organ system in metabolic disease. These processes include fundamental cellular stress responses: *endoplasmic reticulum (ER) stress*, *oxidative stress*, and *inflammation*.

Cellular Responses to Nutrient Excess

The ER is a complex organelle present in all eukaryotic cells that orchestrates synthesis and intracellular transport of macromolecules. The rough ER, studded with ribosomes, is responsible for protein synthesis, while the smooth ER is responsible for lipid and carbohydrate synthesis. The ER receives a constant influx of nutrients, which it sequesters and directs toward macromolecule synthesis or degradation, carefully metering cellular nutrient exposure. In this capacity, the ER acts as a nutrient sensor, responding to changes in nutrient flux by balancing cellular anabolism and catabolism. The ER also responds to other cell stressors, including hypoxia, toxins, disturbances in electrolyte balance, and a host of other stimuli that alter cell homeostasis. Excess cellular nutrient flux, like other forms of stress, leads to a series of stepwise ER responses collectively referred to as the *ER stress response*. The initial ER stress response to modest increases in nutrient flux induces increased expression of *chaperone proteins* involved in macromolecule synthesis to accommodate increased anabolism of excess nutrients. If nutrient excess persists beyond cellular processing capacity, the ER stress response progresses to activate the *unfolded protein response,* which downregulates global protein expression. If nutrient excess persists beyond the capacity of the ER to maintain proper protein synthesis, then the unfolded protein response progresses to induce cell *apoptosis*. The unfolded protein response thus protects cells from modest increases in nutrient flux and induces cell death in the face of extreme nutrient excess.

Macromolecule synthesis generates reactive oxygen species (ROS) (e.g., superoxides, oxygen/hydroxyl free radicals, hydrogen peroxide) which, like nutrients, are highly energetic molecules capable of damaging cells. Cells have evolved multiple mechanisms to sequester ROS which together comprise the *oxidative stress response*, including antioxidant enzymes such as superoxide dismutase, glutathione peroxidase, and catalase, scavenging molecules such as ascorbic acid, urate, and divalent ions, and the thioredoxin

and glutaredoxin systems. The ER and mitochondria are primary cellular sites of control of oxidative stress. When nutrient flux, macromolecule synthesis, and ROS production exceed cellular antioxidant capacity, cells activate oxidative stress responses, which increase expression of antioxidant proteins, sequester ROS, and increase mitochondrial uncoupling, transiently reducing cellular ROS production. Oxidative stress responses overlap with ER stress responses, and if oxidative stress persists, the unfolded protein response is activated and leads to apoptosis.

Increased nutrient flux generates an *inflammatory response* designed to scavenge debris and byproducts from increased cell turnover that results from ER and oxidative stress responses. Testament to the close relationship between metabolism and inflammation, inflammatory and metabolic mediators demonstrate functional overlap. For example, TNF-α and leptin, in addition to their dominant functions in regulating inflammation and satiety, respectively, each play important reciprocal roles in regulating body weight and inflammation.[14,15] All satiety and hunger factors and inflammatory cytokines manifest dual immunoregulatory and energy homeostasis functions. In addition, molecular byproducts of metabolism trigger inflammation. Free fatty acids are ligands for Toll-like receptors, while advanced glycation end products trigger receptors of advanced glycation end products' pathways which activate innate immune effector cells, establishing a molecular link between metabolism and inflammation. Obesity is associated with a state of chronic systemic inflammation that plays a central role in the pathogenesis of metabolic disease. Serum cytokine levels are increased in obese animals and humans, and adipose tissue manifests a pan-leukocyte infiltrate, findings that directly correlate with the magnitude of obesity and severity of metabolic disease.

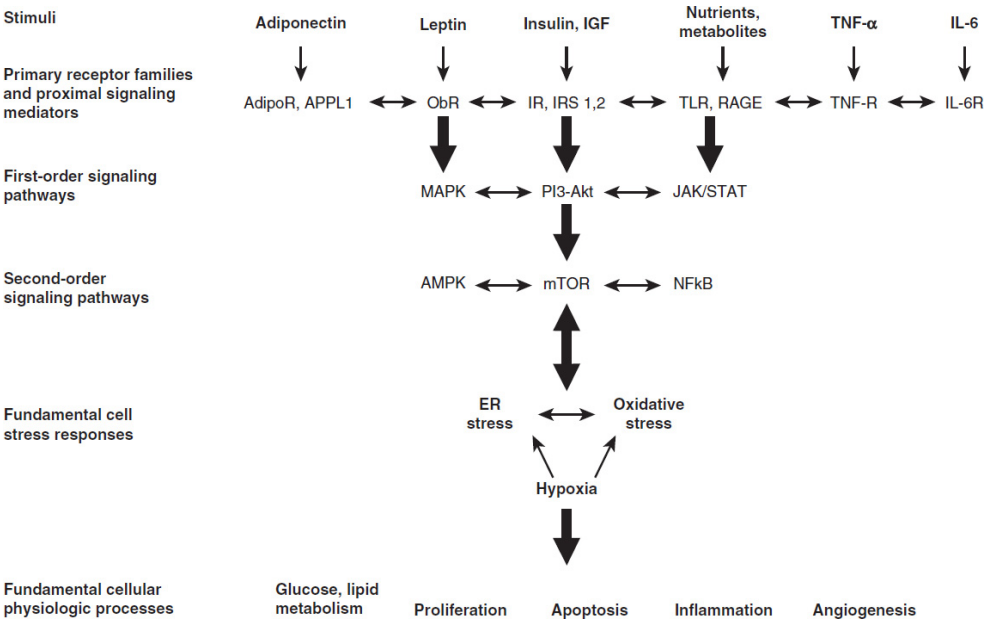


Figure 4.5 Highly simplified schematic of major cell signaling pathways that regulate energy homeostasis and cell stress responses: Primary stimuli for all cells include adipokines, insulin, IGF-1, nutrients and metabolites including free fatty acids, and their derivatives such as ceramide (which activate Toll-like receptors, TLR), glucose, fructose, and advanced glycation end products (which activate receptors for advanced glycation end products, RAGE), and cytokines. Primary intracellular signaling nexi include mitogen-activated protein kinases (MAPK), PI3-Akt, JAK/STAT signaling mediators, AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and NFkB, all of which are linked to ER stress and oxidative stress responses. These pathways engage in highly redundant crosstalk via cross-reactivity of intracellular signaling mediators and induction of gene transcription, and conspire to integrate multiple stimuli to regulate fundamental aspects of cell metabolism, survival, and death in response to nutrient availability and cell stressors such as hypoxia.

Increased ER stress, oxidative stress, and inflammation have been demonstrated in obese rodents and humans. An important aspect of cellular stress responses is that each potentiates the others via overlap in fundamental cell signaling pathways including PI3-Akt, MAPK, AMPK, mTOR, JAK-STAT, and NFκB. These signaling pathways are triggered by multiple stimuli that are dysregulated in obesity, including adipokines, cytokines, growth factors, and nutrients and metabolites, all of which participate in crosstalk, establishing a vicious cycle that perpetuates cell stress in the face of chronic nutrient excess (**Fig. 4.5**). These processes are common to all cells and affect all tissues in late-stage obesity, explaining the diverse manifestations of

systemic metabolic disease. But it is within adipose tissue that these processes are initiated and metabolic disease originates.

Adipose Tissue Failure

Adipocytes are exquisitely well designed to manage high levels of nutrients. Hypertrophy is an early response of adipocytes to chronic elevations in nutrient flux in early overweight and obesity. Free fatty acids are absorbed by adipocytes through pinocytosis mediated by fatty acid–binding proteins, as well as synthesized from glucose and glutamine via de novo lipogenesis, and stored in lipid droplets via a highly regulated process mediated by perilipin proteins. Virtually all cells are capable of storing lipid to some degree, but adipocytes have an extremely high capacity for lipid storage and hypertrophy. Adipocytes are one of only a few cell types that can enlarge to diameters greater than 100 microns, the diffusion distance of oxygen. Adipocyte diameter in humans correlates directly with the magnitude of obesity and the severity of metabolic disease; adipocytes in lean subjects are virtually all less than 100 microns in diameter, while those in obese subjects are greater than 100 microns, in some cases exceeding 200 microns.[16] Progressive adipocyte hypertrophy establishes a state of cellular hypoxia within adipose tissue that has been verified in obese mice and humans. Decreased adipose tissue capillary density and blood flow in obesity exacerbates hypoxia. This hypoxic state has broad effects on adipocyte metabolism, inducing insulin resistance, ER stress, oxidative stress, and inflammation, and inhibiting lipogenesis. Manipulation of hypoxic responses in adipocytes holds therapeutic promise. For example, targeting hypoxia-inducible factor-1α, a dominant cellular hypoxia response protein, ameliorates murine metabolic disease.[17]

Inflammation is a dominant feature of adipose tissue dysfunction in obesity, and is directly linked to insulin resistance and dysregulation of lipid metabolism at local (adipose tissue) and systemic levels. Hypoxia induces adipocyte apoptosis and necrosis which in turn recruits an inflammatory response designed to scavenge dead and dying adipocytes. Adipose tissue macrophages (ATMs) are a central component of this response. ATMs in obesity are altered in phenotype, shifting from a scavenging "M2" phenotype to an inflammatory diabetogenic "M1" phenotype.[18] ATMs are a dominant

source of inflammatory cytokines, including TNF-α, IL-6, and IL-1, all of which induce insulin resistance and aberrations in glucose and lipid metabolism in adipocytes via multiple mechanisms. Supporting a central role for ATMs in metabolic disease, obese mice transgenically engineered to lack macrophage homing molecules in adipose tissue do not develop macrophage infiltrates and are protected from diabetes. Agents that interfere with macrophage homing to adipose tissue in humans show promise as treatment for diabetes. Finally, adipose tissue inflammation involves more than macrophages, and is associated with a pan-leukocyte infiltrate that includes T cells, B cells, NK cells, NKT cells, and eosinophils. Therapy targeting these cell subpopulations is an area of active research.

As inflammation persists, adipose tissue undergoes fibrotic remodeling, with increased expression of matrix metalloproteases and collagens and increased extracellular matrix turnover. Adipose tissue fibrosis limits adipocyte hypertrophic and lipid storage capacity, accelerating adipocyte stress. Obese collagen VI knockout mice demonstrate increased adipocyte hypertrophic capacity due to decreased fibrosis and are protected from systemic metabolic disease.[19] These observations speak to a critically important role of the adipose tissue extracellular matrix in regulating adipocyte nutrient buffering capacity.

Adipose Tissue Overflow

7 As obesity progresses, adipose tissue buffering capacity is overwhelmed and cell stress responses, initially confined to adipose tissue, overflow into circulation and cause systemic metabolic disease (**Fig. 4.6**). Patients with rare congenital and acquired lipodystrophy syndromes characterized by a paucity of adipose tissue suffer from metabolic disease, including insulin resistance, hyperlipidemia, and hepatic steatosis, demonstrating that an absence of adipose tissue is as detrimental as its excess. In lipodystrophy and in obesity, adipose tissue nutrient buffering capacity is overwhelmed, and nutrients overflow to other tissues not well adapted to manage nutrient excess, inducing systemic metabolic disease.

Adipocytes reside in multiple discrete anatomic depots as well as within every organ and every tissue. Adipose tissue is more than simply a storage depot for lipid; only half the cells in adipose tissue are adipocytes, the

remainder comprising the so-called stromovascular cell fraction, which consists of immune leukocytes, fibroblasts, endothelial cells, ASCs, and other cell types. Adipose tissue is highly innervated with sympathetic and parasympathetic afferent and efferent fibers, and has important immunoregulatory and endocrine functions. Adipose tissue participates in robust communication with the central nervous system and all peripheral organs, orchestrating responses to alterations in nutrient availability, systemic health and metabolism, ambient temperature, and a host of other stimuli. Adipose tissue is a central regulator of systemic energy homeostasis.

Hibernating bears accumulate large amounts of adipose tissue without developing inflammation or other cellular stress responses, while in some humans, excess subcutaneous adipose tissue appears to protect against metabolic disease. These examples demonstrate that adipose tissue phenotype is as important as quantity with respect to systemic metabolic state. Adipose tissue may be broadly divided into white and brown phenotypes. White adipose tissue comprises the majority of adipose tissue in humans, is strongly associated with metabolic disease, increases with increasing obesity, and is a primary storage site for lipid. Brown adipose tissue, in contrast, comprises a minority of total adipose tissue in humans, has beneficial effects on metabolism, decreases with increasing obesity and age, and manifests lower lipid storage capacity. Brown adipocytes engage in higher levels of fatty acid oxidation and thermogenesis via expression of mitochondrial UCPs. White adipose tissue derives from mesodermal stem cells that migrate to sites of canonical depots in humans in early embryonic development and proliferate to form-defined depots in late fetal and early neonatal periods. White adipose tissue depots include visceral and subcutaneous, which may be further subdivided into omental, retroperitoneal, and mesenteric visceral adipose tissue compartments, and deep and superficial subcutaneous adipose tissue compartments, each with distinct functional characteristics. Brown adipose tissue develops in rodents during gestation from precursor cells that also give rise to myocytes and form-defined brown adipose tissue depots prior to birth. Brown adipose tissue in humans is less well understood; while most voluminous in the neonatal period, positron emission tomography scanning demonstrates cervical, supraclavicular, mediastinal, paraspinous, and perirenal brown adipose tissue depots in adult humans as well.[20] Recent data suggest that the

dichotomy between white adipose tissue and brown adipose tissue is overly simplistic, and that adipocyte phenotype spans a spectrum. An intermediate phenotype, termed *"brite"* (brown-in-white) or "*beige adipocytes,*" are found in white adipose tissue depots in rodents and humans. These cells manifest brown adipocyte functions, and are induced to proliferate by cold stress and β-adrenergic stimuli, suggesting phenotypic plasticity. Pharmacologic "browning" of adipocyte phenotype is an important area of research with preclinical and clinical trials in progress.

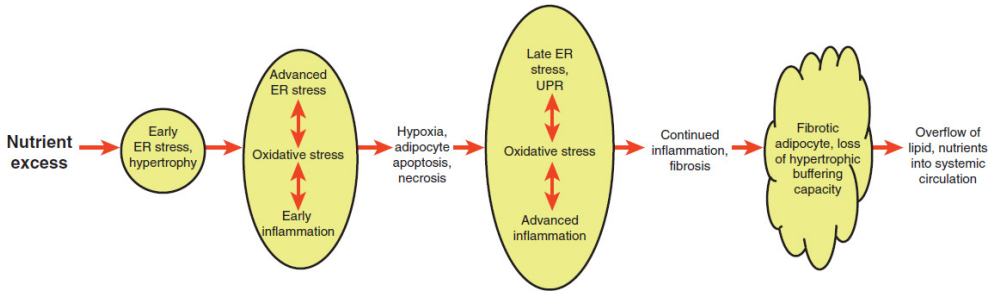


Figure 4.6 Nutrient excess and cell stress in adipocytes: Nutrient excess is an early signal that induces ER stress and hypertrophy in adipocytes. ER stress is tightly linked to oxidative stress and inflammation, and each of these processes induces and potentiates the others. As hypertrophy progresses, adipocyte diameter expands beyond the diffusion distance of oxygen, leading to cellular hypoxia, which exacerbates cell stress responses, leading to adipocyte apoptosis and necrosis via the unfolded protein response and other advanced cell stress responses. Adipocyte apoptosis and necrosis triggers recruitment of an advanced inflammatory response designed to scavenge dead and dying adipocytes. This inflammatory response is associated with fibrotic tissue remodeling which limits adipocyte hypertrophic and lipid buffering capacity of surviving adipocytes, leading to overflow of lipids, nutrients, metabolites, and inflammatory products from adipose tissue into the systemic circulation.

Adipose tissue is anatomically heterogeneous. Human obesity may be broadly classified into android and gynecoid phenotypes, defined by excess visceral and subcutaneous adipose tissue, respectively, with the former strongly associated with metabolic disease, while the latter is less strongly associated with metabolic disease, and in some studies has been shown to be protective. Surgical lipectomy of visceral adipose tissue but not subcutaneous adipose tissue ameliorates murine diabetes.[21] Similar studies of visceral omentectomy in humans demonstrate conflicting results, likely due to more complex human adipose tissue depot anatomy, but excess visceral adipose tissue as measured by waist circumference and imaging techniques

nonetheless correlates strongly with metabolic disease. The reasons for the disproportionate effect of visceral adipose tissue on metabolic disease are unclear. While the abdominal location of visceral adipose tissue plays a role, intrinsic differences between visceral and subcutaneous adipose tissues also exist, as visceral adipose tissue manifests higher levels of inflammation, lipolysis, β-adrenergic receptor expression, steroid sensitivity, insulin resistance, and adipocyte proliferation and differentiation relative to subcutaneous adipose tissue.

SYSTEMIC METABOLIC DISEASE

8 Mediators of Metabolic Disease

In addition to its distinct functional phenotype, visceral adipose tissue contributes disproportionately to metabolic disease via direct anatomic communication with the liver via the portal venous system. *Portal overflow* of free fatty acids, excess nutrients and metabolites, and hormones and cytokines from visceral adipose tissue to the liver is an early step in the progression to systemic disease. As obesity progresses, *peripheral overflow* extends beyond the liver to involve all tissues, including skeletal muscle, pancreas, vasculature, kidneys, lungs, and the central nervous system; inflammation and ER stress occur in the hypothalamus, and mediate reciprocal effects on adipose tissue and other organ systems via aberrations in CNS efferent outputs that exacerbate obesity and metabolic disease. In essence, adipose tissue dysfunction "metastasizes," inducing cell stress responses in all tissues that underlie the pathogenesis of metabolic disease (**Fig. 4.7**).

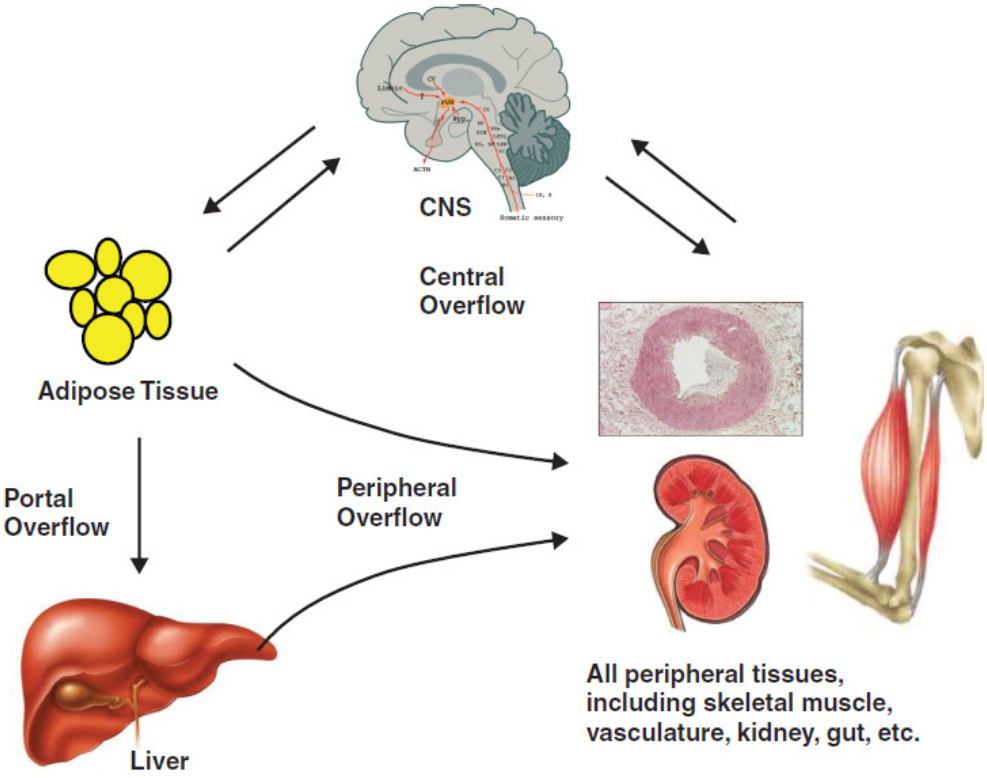


Figure 4.7 Adipose tissue overflow, interorgan communication, and systemic metabolic disease: As adipose tissue buffering capacity is overwhelmed, lipids, nutrients, cytokines, and adipokines overflow into the systemic circulation and cause systemic metabolic disease via the same cellular effects that initially unfold in adipocytes. Early overflow occurs via the portal system, which drains visceral adipose tissue venous effluent into the liver, which becomes the first site of systemic metabolic disease and an important secondary site of nutrient buffering via the development of hepatic steatosis. Overflow progresses to involve all peripheral tissues, inducing cell stress and disease in all organ systems. Overflow involves the central nervous system as well, as inflammation and cell stress have been documented in the hypothalamus in obesity, which in turn is thought to disturb peripheral metabolic function via alterations in CNS efferent signaling.

Nutrients and metabolites are central mediators of the systemic effects of adipose tissue overflow. Free fatty acids mediate systemic *lipotoxicity*, acting as ligands for Toll-like receptors and other immunostimulatory and cell stress–inducing receptor families. Lipid metabolites induce cellular insulin resistance, ER stress, and apoptosis. Metabolic products of glucose and fructose, including advanced glycation end products and glucosamines, mediate similar effects. Cytokines and adipokines overflow from adipose tissue as well. TNF-α, a dominant inflammatory cytokine expressed by adipose tissue macrophages, exerts proinflammatory and diabetogenic

effects. Leptin also promotes inflammation and regulates cellular glucose homeostasis. Expression of adiponectin, which attenuates inflammation and has beneficial effects of cellular metabolism, is decreased in obesity, as adipose tissue's cytokine and adipokine balance shifts toward a proinflammatory milieu. Metabolites, adipokines, and cytokines establish in multiple tissues the same cellular stress responses that initially unfold in adipose tissue, including ER stress, oxidative stress, and inflammation. Within target tissues, as in adipose tissue, these processes potentiate one another and exacerbate cell stress, leading to systemic metabolic disease.

Portal Overflow and Liver Disease

The liver is one of the first organs to be affected by adipose tissue failure, as portal overflow induces hepatic steatosis, the result of an imbalance in delivery and export of hepatocyte lipid. Sources of hepatic lipid include fats absorbed from the diet and delivered from the gut as chylomicrons, lipids synthesized by hepatocytes via de novo lipogenesis, and free fatty acids delivered from visceral and subcutaneous adipose tissues. Free fatty acids from adipose tissue constitute over 60% of lipid delivery to the liver.[22] Lipids are exported from the liver primarily in the form of very low–density lipoproteins (VLDL). Abnormalities in each of these aspects of hepatic lipid delivery and efflux have been identified in obese animals and humans. As lipid storage capacity is reached, hepatocytes experience ER, oxidative, and inflammatory stresses, causing steatohepatitis, a histologic entity characterized by Mallory bodies, hepatocyte ballooning and an inflammatory infiltrate consisting of macrophages (Kupffer cells) and other leukocytes. As in adipose tissue, TNF-α plays a central role in the hepatic inflammation; neutralization of TNF-α ameliorates steatohepatitis in mice and is under study as therapy in humans.[23,24] Interleukin-6 and other inflammatory cytokines have also been implicated in steatohepatitis. Steatosis is present in over 90% of patients with BMI >40, up to 30% of whom will develop steatohepatitis; 10% to 30% of patients with steatohepatitis will develop cirrhosis. Ethnic and genetic predispositions to steatohepatitis exist, with Asians and Hispanics at higher risk than Caucasians or Blacks. Weight loss reverses steatosis and halts progression of steatohepatitis.

Diabetes

Insulin resistance is a central metabolic response of all cells to stress, but it begins in adipose tissue. Free fatty acids are central mediators of cellular insulin resistance. Insulin regulates not only glucose homeostasis in adipocytes, but also lipid metabolism, inhibiting lipolysis and free fatty acid release. Early nutrient excess, with resultant ER and oxidative stress, induces insulin resistance in adipocytes, impairing adipocyte glucose uptake, attenuating insulin's inhibitory effects on lipolysis, and increasing free fatty acid release by adipocytes. Free fatty acids in turn activate Toll-like receptors on adipose tissue inflammatory cells, inducing inflammatory cytokine expression, including TNF-α. TNF-α induces insulin resistance by regulating expression and phosphorylation of genes involved in glucose homeostasis, including insulin receptor, insulin receptor substrates, the cell signaling nexus protein Akt, and glucose transporter molecules. TNF-α also promotes lipolysis, exacerbating insulin resistance and free fatty acid release by adipocytes. While other mediators contribute, TNF-α provides a cogent example of the vicious cycle in adipose tissue that contributes to worsening insulin resistance.

As adipose tissue lipid buffering capacity is overwhelmed, free fatty acids overflow into the systemic circulation, resulting in lipotoxicity, which underlies the pathogenesis of insulin resistance in peripheral tissues. Skeletal muscle, responsible for 70% of systemic glucose disposal, is a dominant site of systemic insulin resistance. Lipotoxicity triggers ER stress, oxidative, stress, and inflammation in skeletal muscle myocytes, contributing to insulin resistance via mechanisms described above. Skeletal muscle, like adipose tissue, becomes inflamed, with increased levels of macrophages and diabetogenic inflammatory cytokines. Circulating free fatty acids also have important metabolic effects on the liver and skeletal muscle. As lipid delivery to skeletal muscle and liver increases, energy production shifts from glucose utilization to fatty acid oxidation. Increased free fatty acid beta-oxidation leads to increased hepatic gluconeogenesis and reduced skeletal muscle glucose utilization, exacerbating hyperglycemia. The initial response of pancreatic beta cells to peripheral insulin resistance and hyperglycemia is a compensatory increase in insulin secretion, leading to hyperinsulinemia, a pathognomonic feature of early type 2 diabetes. As disease progresses,

lipotoxicity and cell stress responses induce pancreatic beta cell exhaustion, leading to decreased insulin secretion, and insulin resistance progresses to frank diabetes. Like obesity itself, genetics plays an important role in type 2 diabetes: Asian, Black, and Hispanic ethnicities are associated with increased risk and multiple diabetes-associated SNPs have been identified. Worldwide incidence is rapidly increasing; diabetes represents a dominant emerging health crisis.

Cancer

The incidences of almost all types of cancer increase in a dose-dependent manner with increasing BMI, with risk ratios range from 2 to greater than 6 depending on cancer type and BMI.[25] At the cellular level, energy homeostasis involves fundamental processes central to carcinogenesis, and signaling pathways activated by chronic overnutrition promote cell proliferation. Epidemiologic data suggest that long-term metformin use is associated with decreased cancer incidence, suggesting the potential for metabolism-based cancer therapy. Chronic inflammation, characteristic of obesity and a risk factor for cancer, activates NFκB and other signaling pathways that potentiate cell proliferation, increase production of ROS that may contribute to oncogenic mutation, and induce expression of inflammatory cytokines that act as cell mitogens. Overnutrition in obesity predisposes to a state of chronic anabolism and is associated with increased expression of multiple growth factors, including insulin, insulin-like growth factor-1, and leptin. Chronic inflammation on a background of chronic anabolism creates an ideal milieu for carcinogenesis. Steroids represent another putative molecular link between obesity and cancer. Steroid metabolism is aberrant in obesity and adipose tissue is a source of estrogen which may promote estrogen-responsive cancers. Finally, peritumor adipocytes have been implicated in carcinogenesis. In addition, adipocyte precursors home from adipose tissue depots to tumors and provide growth factors and energy substrates that promote tumor growth. The mechanisms by which obesity causes cancer are multiple, and as details are elucidated, metabolism-based therapy for cancer will emerge.

CONCLUSION

Obesity is associated with an increased risk of cardiovascular disease, including hypertension, atherosclerosis, and hyperlipidemia, the result of cell stress responses that afflict vascular tissue. Immune diseases including allergy, atopy, and autoimmune diseases, are increased in the obese, due in part to alterations in immune and inflammatory function. While mechanical stress due to excess weight are contributing factors to sleep apnea, osteoarthritis, and gastroesophageal reflux disease, fundamental cell stress mechanisms also contribute, as inflammation has been implicated in these diseases as well. The pan-systemic nature of metabolic disease provides opportunity for developing therapy that will simultaneously treat multiple obesity-related pathologies.

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5

Wound Healing

Katherine A. Gallagher

Key Points

1. Wound healing is a complex process that involves four major phases: hemostasis, inflammation, proliferation and remodeling.
2. Innate immune cells play a major role in the inflammatory phase of healing.
3. Macrophages are critical for the transition from the inflammatory to the proliferative phase.
4. Multiple factors can adversely impact healing including advanced age, poor nutrition, obesity, DM, steriods/chemotherapy.

The role of disease states including diabetes and cancer-related treatments including radiation, chemotherapy and steroids negatively influence wound repair. Hence, a thorough understanding of the pathways/processes involved in both normal and pathologic healing is essential. Thus, a fundamental understanding of the wound healing cascade is essential to surgical practice. Besides the controlled injury that occurs in elective surgery, all invasive surgical procedures cause soft tissue trauma regardless of the circumstances. All aspects of surgical care from patient selection, surgical instruments and technique, and postoperative management are needed to optimize tissue

healing and avoid complications. In addition to surgical procedures, there is the growing problem of people suffering from chronic wounds, particularly in diabetes is on the rise. Nonhealing wounds affect about 10 million people in the United States, with persons 65 years and older accounting for the majority of these events. The development of new data regarding the normal and pathologic wound healing responses both at the cellular levels and the biologic markers associated with healing will help develop new therapeutic strategies.

PHASES OF WOUND HEALING

1 Wound healing is a dynamic process that occurs in a programmed series of four phases: hemostasis, inflammation, proliferation, and remodeling.[1] These steps occur in a linear fashion under normal, nondiseased conditions. The timing of these four phases of wound repair is illustrated in Figures 5.1 and **5.2** and the major cell types involved are shown in **Figure 5.3**.

Hemostasis

The hemostasis phase begins almost instantaneously after injury. The tissue response is mediated by: (1) blood leaking into the wound, (2) proteins stored in the ECM, and (3) locally resident surviving cells following injury.

Following injury, hemostasis occurs and is characterized by the recruitment of platelets and circulating coagulant factors to the wound site to initiate clotting.[2] Concurrent with platelet recruitment, injured cells release damage signaling factors, which activate resident macrophages,[3–6] as well as damage associated molecular patterns (DAMPs).[7] Together, these stimulate recruitment of polymorphonuclear neutrophils (PMNs) from the vasculature to defend against pathogens.[3,5,7] As platelets aggregate to the exposed collagen bed, they secrete cytokines and growth factors such as platelet-derived growth factor, that promote clotting and serve to further recruit PMNs.[8] Once PMNs begin to migrate to the wound, this initiates the inflammation stage.

The plasma membrane of each platelet contains specific receptors for collagen known as the glycoprotein Ia/IIa complex. When plasma membrane

receptors come into contact with collagen of the ECM (type I) and the basement membrane of the vascular endothelium (type IV), platelets bind and anchor to the site. Simultaneously, platelet activation occurs and the platelet changes from a rounded amorphous shape to a flattened configuration and discharges the contents stored cytoplasmic granules in an event known as the platelet release reaction. These bioactive factors serve a dual purpose in hemostasis and wound healing. Platelet anchoring is strengthened by von Willebrand factor (vWF) released by damaged endothelium and activated platelets. Platelet binding is also characterized by rapid vascular restriction and the formulation of a stable fibrin clot. Platelets are the main cellular players of the first phase. Platelet-derived functions that achieve hemostasis include: adhesion, aggregation, and formation of a procoagulant surface that facilitates the generation of thrombin and results in a fibrin plug. In addition, platelets express and release substances that promote tissue repair and influence future processes such as angiogenesis, inflammation, and the immune response. They contain large secreted pools of biologically active proteins, including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF) as well as cytokines. The therapeutic use of platelets in a fibrin clot has a positive influence in clinical situations requiring rapid healing, dental implant surgery, orthopedic surgery, muscle and tendon repair, skin ulcers, hole repair in eye surgery and cardiac surgery are situations where the use of autologous platelets accelerates healing.

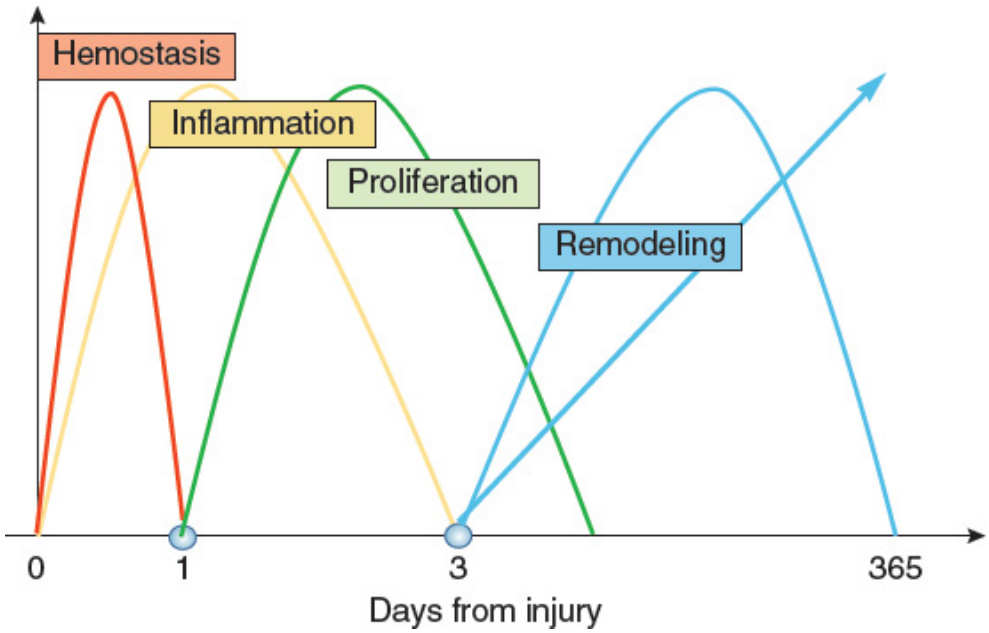

Figure 5.1 Four phases of wound healing: plotted against "Time" on the x-axis, the four phases shown in different colors occur sequentially, and overlap. Overall the total time period for completion is 1 year.

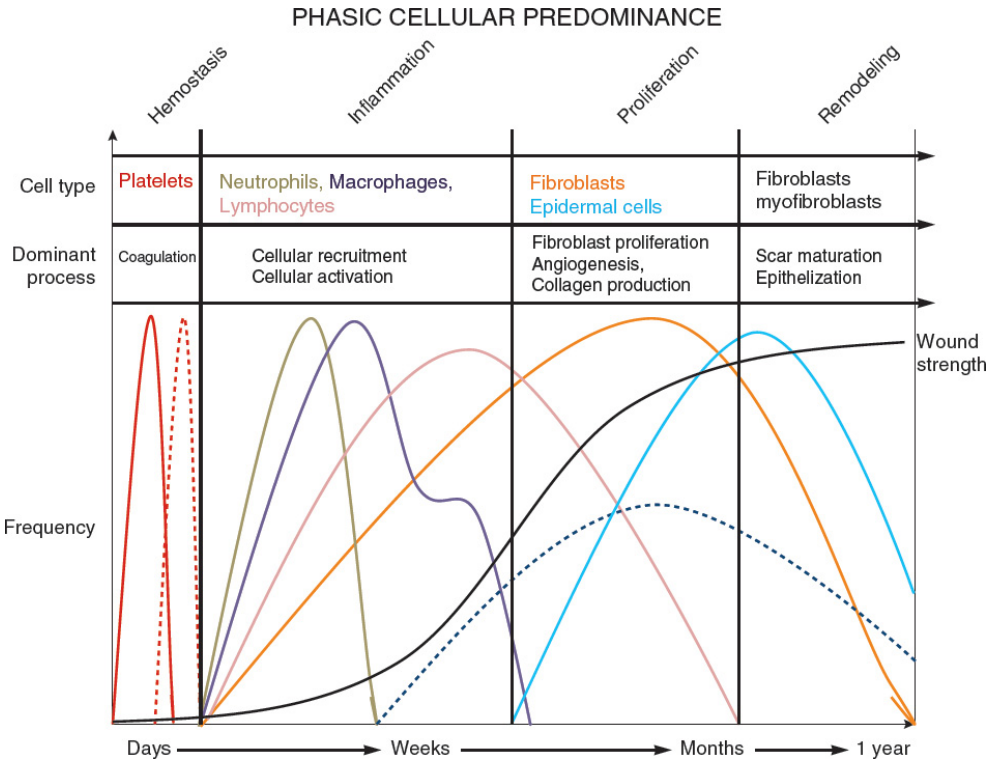

Figure 5.2 The dominant cells, physiologic process as well as the temporal distribution of the four phases of wound healing.

The growing platelet plug inside the vessel is stabilized by fibrin polymerized from circulating fibrinogen. The vascular response is mediated by local factors modulated by the systemic control of sympathetic nervous system. Vasoconstriction, mediated by catecholamines and prostaglandins (thromboxane and PGF 2a), normally is limited to the time required to achieve hemostasis. Vasodilation and alteration in capillary permeability soon follow mediated by histamine, prostaglandins (PGE2 and PGI2), VEGF released from resident interstitial mast cells and damaged endothelium. This causes increased blood flow and controlled delivery of fluid, leukocytes, macrophages, and relevant plasma proteins to the wound environment which facilitates the inflammatory phase. Platelets release two factors with particular importance for would healing: PDGF and TGF-β which in turn stimulate chemotaxis and proliferation of inflammatory cells.

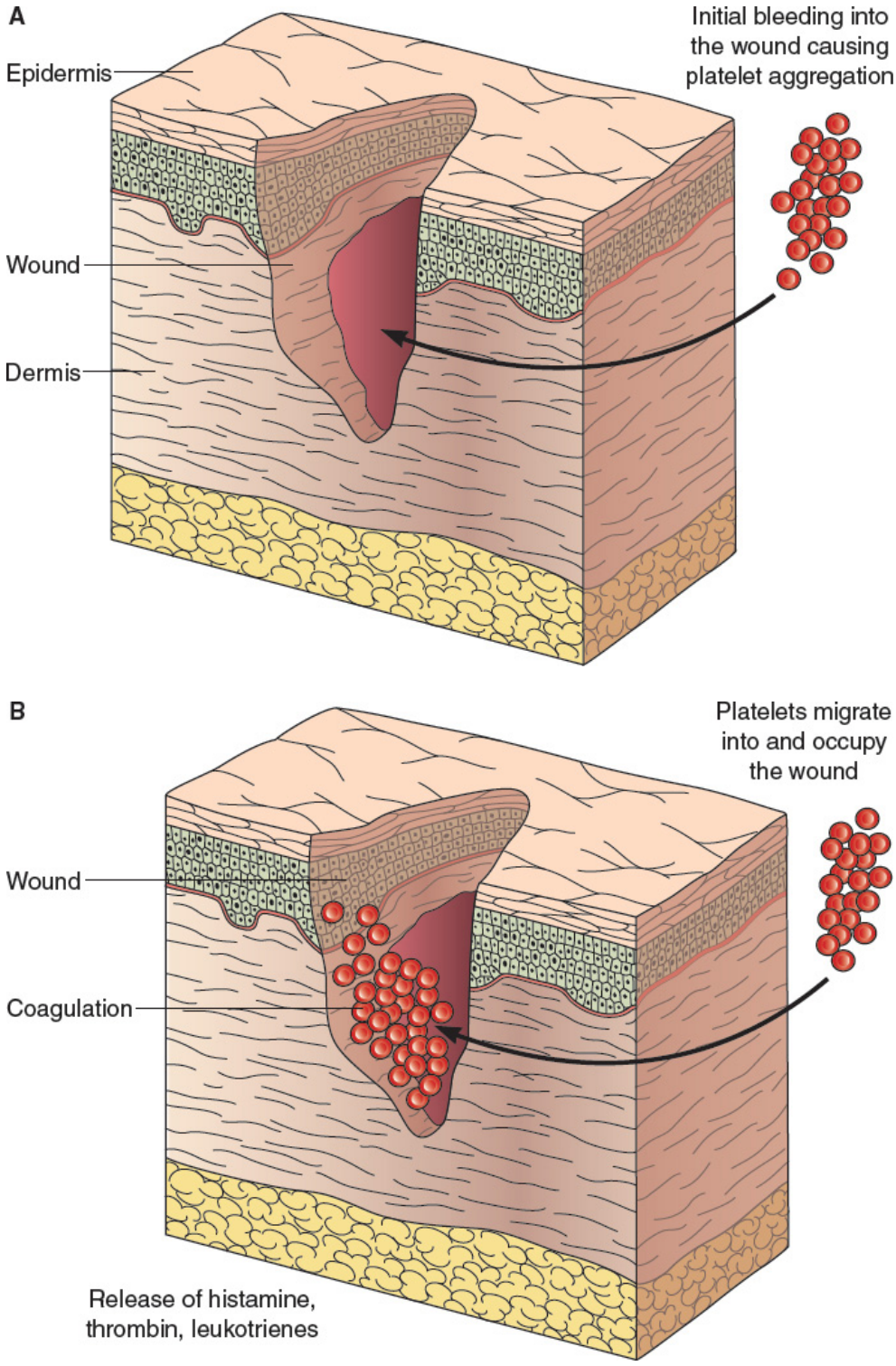

Figure 5.3 **A**: Diagrammatic wound healing model. Platelets, the first cells to arrive at the wound are critical to create a clot and establish hemostasis. **B**: Phase 1—Hemostasis.

Inflammatory Phase

The second phase of healing involves inflammation (acute then chronic) that begins following the hemostasis phase. 2 The cells involved in this phase are mainly immune cells, as shown in **Figure 5.4**. Neutrophils (PMNs) dominate during the early part of the inflammation phase; however, their presence is short lived as they start to wane after 24 to 48 hours.[9] 3 PMNs set the stage for the appearance of macrophages, the most important cellular mediator of the inflammatory phase of wound healing (**Fig. 5.5**). Neutrophils release chemokines that are responsible for recruiting circulating monocytes from the peripheral blood to the wound site. Recruited monocytes that differentiate into macrophages and dendritic cells, along with F4/80+ resident tissue macrophages, carry out the critical steps of the inflammatory phase of wound healing.[10,11] However, the specific roles of recruited monocytes/macrophages, dendritic cells, and tissue macrophages in wound healing are unclear.[12] Wound macrophages initially display a "classical" activation state, indicated by expression of proinflammatory cytokines such as IL-12, IL-1β, IL-6, TNF-α, and iNOS. Proinflammatory, or M1-like, macrophages work to clear debris and recruit additional inflammatory cells. As the inflammatory phase progresses, macrophages phagocytose apoptotic cells in the wound and chemokines are released (e.g., CXCL12), promoting the transition from a proinflammatory state to one promoting tissue repair and remodeling.[13,14] This occurs as the predominant macrophage phenotype in the wound transitions to an "alternatively activated" state, or M2-like, secreting anti-inflammatory cytokines such as IL-4, IL-10, IL-13, and TGF-β.[10,15] In vivo, macrophages exist along a spectrum and the distinct phenotypes seen in vitro (e.g., M1, M2) are rarely seen.[10,16,17]

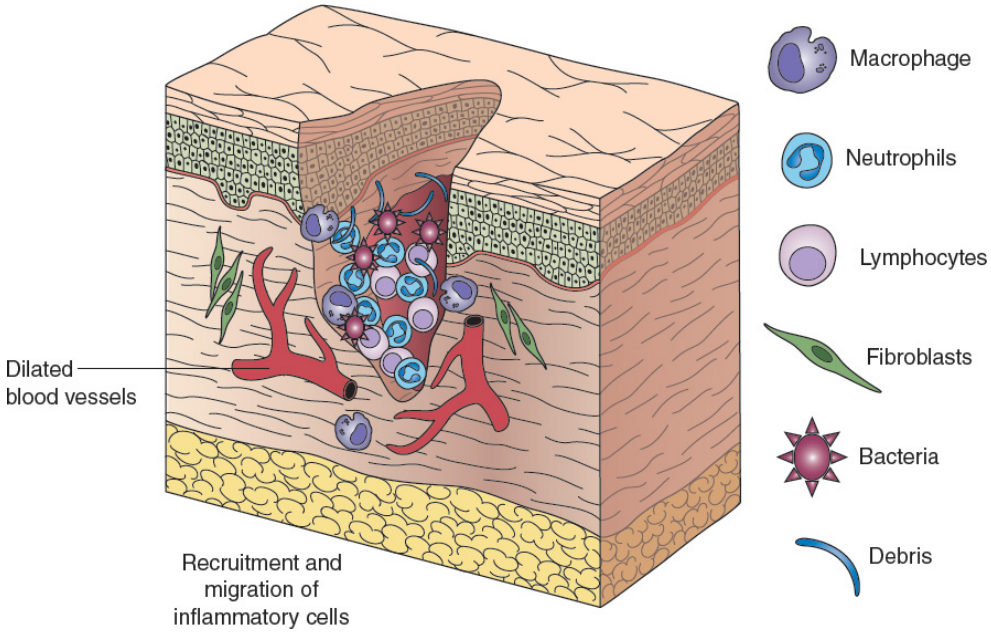

Figure 5.4 Phase 2—Inflammation.

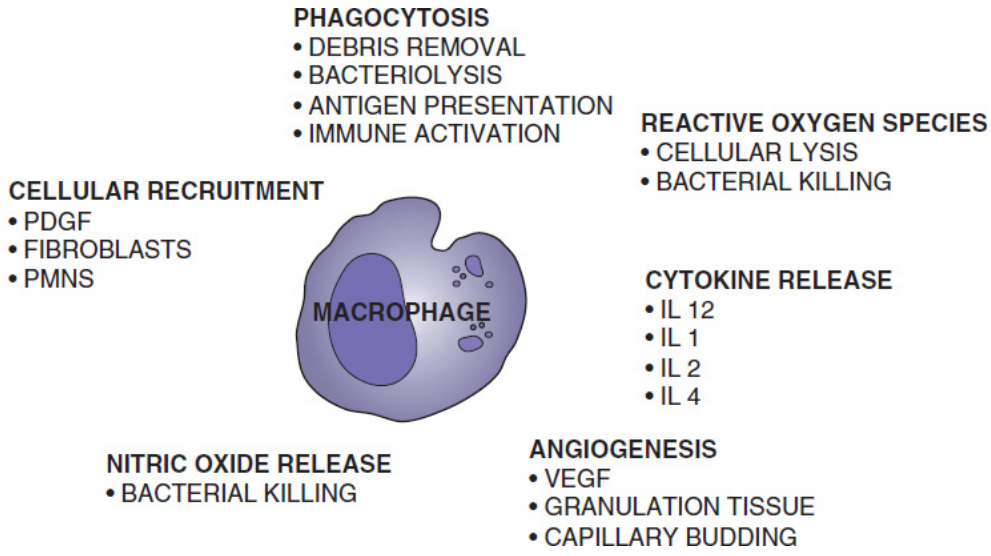

Figure 5.5 Macrophage functions.

The mechanisms underlying monocyte-macrophage phenotype plasticity in vivo are complex, but are under intense investigation. An early step in this transition of monocyte-macrophages from the proinflammatory to the anti-inflammatory phenotype, and thus the initiation of tissue repair, is the ingestion of apoptotic PMNs and other immune cells by monocyte-macrophages. Apoptotic neutrophils have been found to secrete a variety of signaling molecules, such as lysophosphatidylcholine, which attract

monocyte-macrophages via the chemotaxis receptor G2A, causing subsequent engulfment of these cells.[18] As wound healing progresses, monocyte-macrophages show increased expression of MerTK, a cell-surface tyrosine kinase involved in phagocytosis of apoptotic cells; these $MerTK^{+}Ly6C^{lo}$ monocyte-macrophages demonstrate the ability to produce VEGF and TGF-β.[19] Indeed, it appears that phagocytosis of these apoptotic cells triggers the release of these growth factors and augments other tissue repair processes. In one study, Voll et al.[20] demonstrated that coculture of LPS-activated monocyte-macrophages with apoptotic lymphocytes inhibited monocyte-macrophage expression of proinflammatory mediators such as TNF-α and increased release of anti-inflammatory cytokines. These findings were replicated in a subsequent study where human peripheral blood monocytes failed to upregulate expression of proinflammatory mediators IL-1β, IL-8, and TNF-α, but demonstrated increased TGF-β expression in monocyte-macrophages that engulfed apoptotic PMNs compared with naive monocyte-macrophages.[21]

In addition to the cellular and molecular mechanisms underlying monocyte-macrophage plasticity, the maturing field of epigenetics has become a new focus in the investigation of monocyte-macrophage–mediated inflammation (**Fig. 5.6**). A number of epigenetic alterations have been associated with MΦ polarization.[22,23] Histone deacetylases (HDACs) are a group of epigenetic regulators associated with influencing monocyte-macrophage phenotype via alterations in chromatin conformation. For example, HDAC3 has been found to promote proinflammatory and inhibit anti-inflammatory monocyte-macrophage polarization.[24–26] In Mullican et al.,[25] mice lacking HDAC3 in monocyte-macrophages displayed a gene expression profile recapitulating in vitro M2 activation. Furthermore, a chromatin immunoprecipitation assay revealed localization of HDAC3 to a subset of sites bound by PU.1, a major determinant of the monocyte-macrophage epigenome.[27,28]

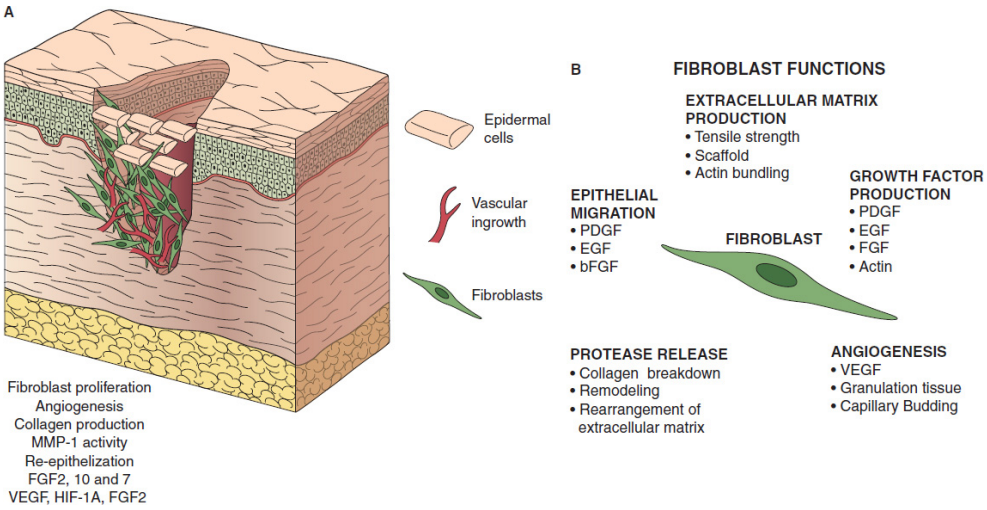

Figure 5.6 **A**: Phase 3—Proliferation. Vast array of cells are recruited into the wound bed and carry out diverse functions including proliferation and deposition of ECM. **B**: Fibroblast functions.

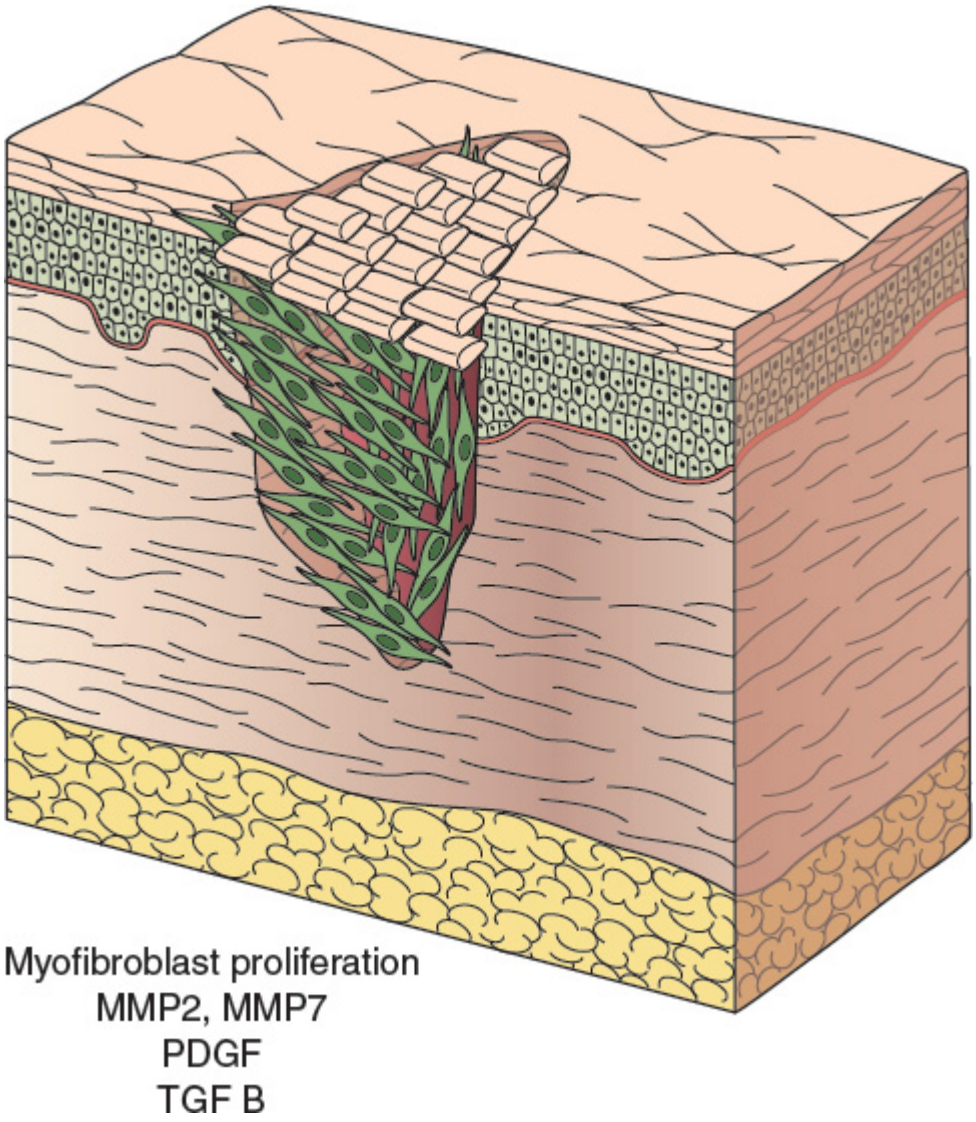

Figure 5.7 Phase 4—Remodeling and maturation.

Epigenetic enzymes also play a role in monocyte-macrophage phenotype skewing in type 2 diabetes (T2D) and metabolic syndrome. Hyperlipidemia has been shown to induce DNA methylation and repress anti-inflammatory cytokines; similarly, a genome-wide analysis for promoter methylation in MΦs revealed hypomethylation of M1 genes and hypermethylation of M2 reparative genes.[29] DNA methyltransferase 3b has been found to promote M1 activation in obese mice by DNA methylation of peroxisome proliferator-activated receptor γ1 promoter. Furthermore, knockdown of DNA methyltransferase 3b enhances M2 activation and suppresses the M1 response.[30]

Given the role of epigenetic factors in the systemic inflammatory milieu of type 2 diabetes (T2D) and metabolic syndrome, attention has recently turned to epigenetic alterations present within diabetic wounds (**Fig. 5.7**). Alterations in histone methylation have been linked to impairments in diabetic wound healing. As mentioned previously, pathologic expression of IL-1β contributes to impaired wound healing.[31] In a study by Kimball et al.,[10] monocyte-macrophages isolated from wounds of a diet-induced obese mouse model of T2D expressed increased IL-1β after stimulation with LPS, and chromatin immunoprecipitation analysis revealed increased histone H3 lysine (H3K) 4 (H3K4; activation mark) and decreased H3K27 (repressive mark) methylation, suggesting an epigenetic mechanism underlying IL-1β expression. Another epigenetic event that strongly influences healing is decreased global methylation through a reduction of (H3K27) trimethylation.[32] Gallagher et al.[33] discovered that, in diet-induced obese mice, the IL-12 promoter exhibited increased demethylation of the repressive H3K27me3 mark in bone marrow progenitor cells, circulating blood monocytes and tissue monocyte-macrophages. This allowed increased expression of proinflammatory IL-12. Further, the histone demethylase enzyme JMJD3 was decreased at the IL-12 gene, suggesting that these monocyte-macrophages were epigenetically preprogrammed toward a proinflammatory phenotype, ultimately negatively impacting wound healing.[33]

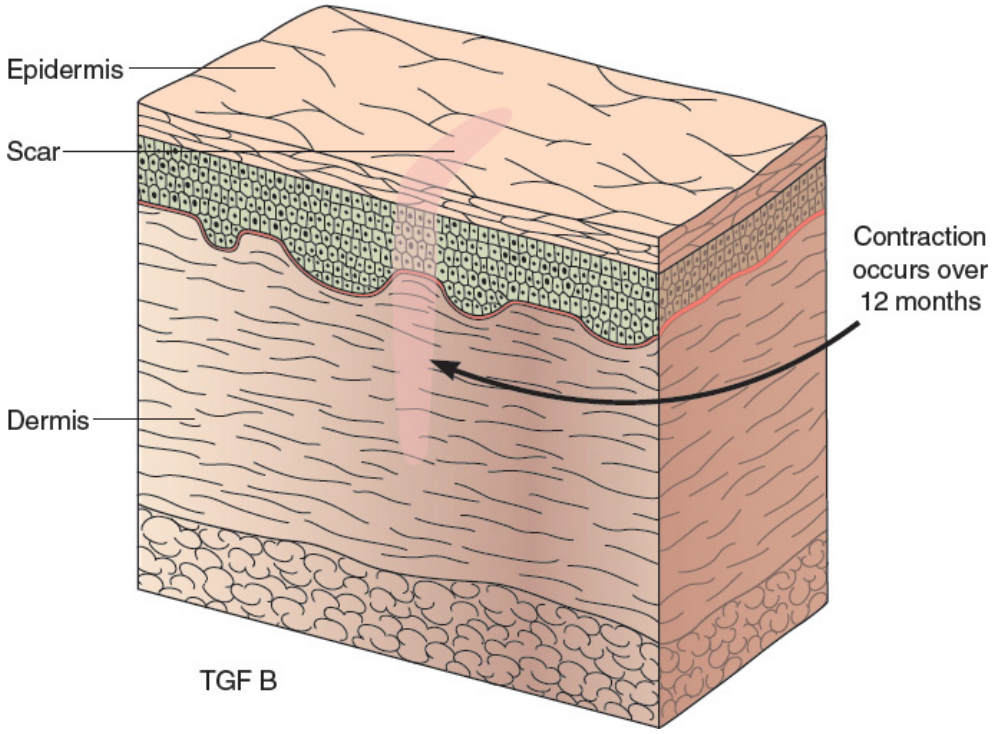

Figure 5.8 Contraction of scar—This process occurs over the course of 1 year.

MicroRNAs regulate gene expression and interact with epigenetic enzymes through a complicated feedback network. It has recently been demonstrated that hyperglycemia leads to changes in the microRNA signature in wound healing, and they have been found to play a role in the dysregulated inflammation of diabetic wounds.[34–36] For example, miR-125b epigenetically enhances monocyte-macrophage activation by increasing the responsiveness to IFN-γ and concurrently inhibits the reparative phenotype by targeting the M2 transcription factor IRF4.[37] Thus, although this field of study is in its relative infancy, there is great potential for continued exploration of the epigenetic mechanisms in inflammatory disease and diabetic wound healing.

Proliferation Phase

The subsequent proliferation phase is characterized by the recruitment and activation of keratinocytes and fibroblasts. During this phase, growth factors stimulate keratinocytes to re-epithelialize the wound.[15] During this time, the provisional matrix established by platelets during hemostasis is replaced by granulation tissue. Fibroblasts secrete proteinases and matrix

metalloproteases (MMPs) to degrade the provisional matrix while simultaneously secreting collagen and other extracellular matrix (ECM) proteins into the granulation tissue.[38]

The defining characteristic of the proliferative phase of healing is ECM production, as shown in **Figure 5.8**. The provisional ECM is a protein scaffold that stabilizes wound edges and provides a framework for migration of PMNs, macrophages, fibroblasts, and other cells into the wound from surrounding tissues. As the inflammatory phase slows the proliferative phase begins and becomes dominant, fibroblasts replace macrophages as the most numerous cell type. Like macrophages, fibroblasts are multifunctional. They are responsible for new tissue formation, collagen production and the laying down of the ECM (**Fig. 5.9**). Angiogenesis occurs simultaneously as new capillaries form and blood vessels penetrate the provisional matrix sprouting from vessels of the surrounding uninjured tissues. Vasculogenesis a process dictated by endothelial progenitor cells (EPCs) from bone marrow, that form de novo blood vessels. The processes that actually coordinate formation of ECM and new tissue with angiogenesis are not well defined. Signaling pathways that stimulate new tissue formation involve the role of low oxygen tension that increases the expression "hypoxia-induced factor" (HIF) by vascular endothelial cells. SDF-1α has been shown to be a key chemokine that promotes vasculogenesis.[39]

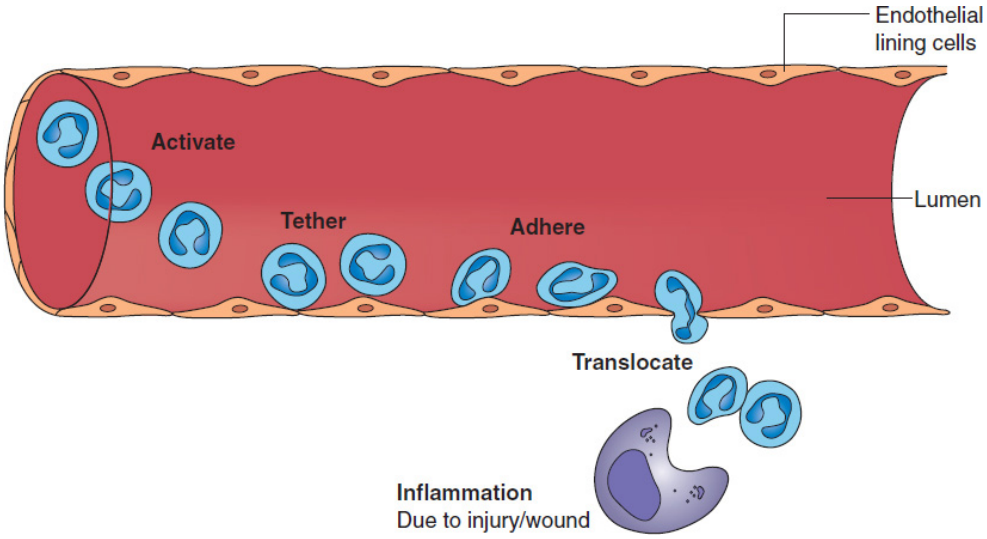

Figure 5.9 The biochemical factors that elicit migration of cells from intravascular compartment into the wound site.

As the proliferative phase progresses the predominant cell in the wound site is the fibroblast. This multifunctional cell of mesenchymal origin mainly produces and deposits the new matrix for structural integrity at the level of the wound bed. The ECM is primarily collagen. At least 23 individual types of collagen have been identified—type I is present mostly in scar tissues.[40] Fibroblasts produce collagen via their attachment to the cables of the provisional fibrin matrix.[41] During this process, there is an important step involving hydroxylation of proline and lysine residues.[42] The collagen molecule transforms itself into the classical triple helical structure and thereafter its nascent chains are modified through glycosylation[43]; this procollagen molecule is released into the extracellular space.[44] The hydroxyproline in collagen gives the molecule its stable helical conformation,[45] whereas fully hydroxylated collagen has higher stability, unhydroxylated forms are fragile, similar to collagen produced under anaerobic disease conditions or vitamin C–deficient states (scurvy), where in the collagen undergoes denaturation easily and can break.

Finally, collagen released into the extracellular space undergoes further processing by cleavage of the procollagen N- and C-terminal peptides. Cross-linking steps give collagen its strength and stability over time.[46]

Remodeling Phase

The final phase of wound healing is the remodeling phase and begins once granulation tissue is present. Here, fibroblasts differentiate into contractile myofibroblasts that contract the wound and the collagen III deposited in the ECM during the proliferation phase is exchanged for collagen I which has a higher tensile strength.[47] Once healed, the site is mechanically functional but many structural components, for example, hair follicles, may not recover and the healed site has, at maximum, ~70% of the original tensile strength.[15]

The remodeling phase is characterized by continued synthesis and degradation of the ECM components trying to establish a new equilibrium—and the formation of an organized scar (**Fig. 5.10**). Collagen degradation occurs[48] via the action of specific collagenases that are secreted by various cells; fibroblasts, neutrophils, and macrophages each of which can cleave the collagen molecule at differing specific locations on all three chains, and break it down to characteristic three-quarter and one-quarter pieces. These

collagen fragments undergo further denaturation and digestion by other proteases. Several molecules including TGF-β play a major role in the remodeling phase.

CLINICAL CONSIDERATIONS

Multiple clinical pathologies can impair wound healing as illustrated in **Figure 5.9**.

Chronic versus Acute Wounds

Wounds heal within a reasonable time of 4 to 6 weeks. Those 4 that do not are termed chronic. As shown in **Table 5.1**, a variety of factors and disease conditions impair wound healing and result in chronic nonhealing wounds. Reasons that lead to chronicity instead of normal healing, are complex—but the salient points are detailed below. The most important concept is a persistent proinflammatory condition that paradoxically leads to increased degradation of matrix proteins, and an unstable wound that is recalcitrant to healing.

Advanced Age and Gender

Many clinical and animal studies at the cellular and molecular level have examined age-related changes and delays in wound healing. It is commonly recognized that, in healthy older adults, the effect of aging causes a temporal delay in wound healing, but not an actual impairment in terms of the quality of healing.[49] Delay wound healing in the aged is associated with an altered inflammatory response, such as delayed T-cell infiltration into the wound area with alterations in chemokine production and reduced macrophage-phagocytic capacity.[50] Overall, there are global differences in wound healing between young and aged individuals.

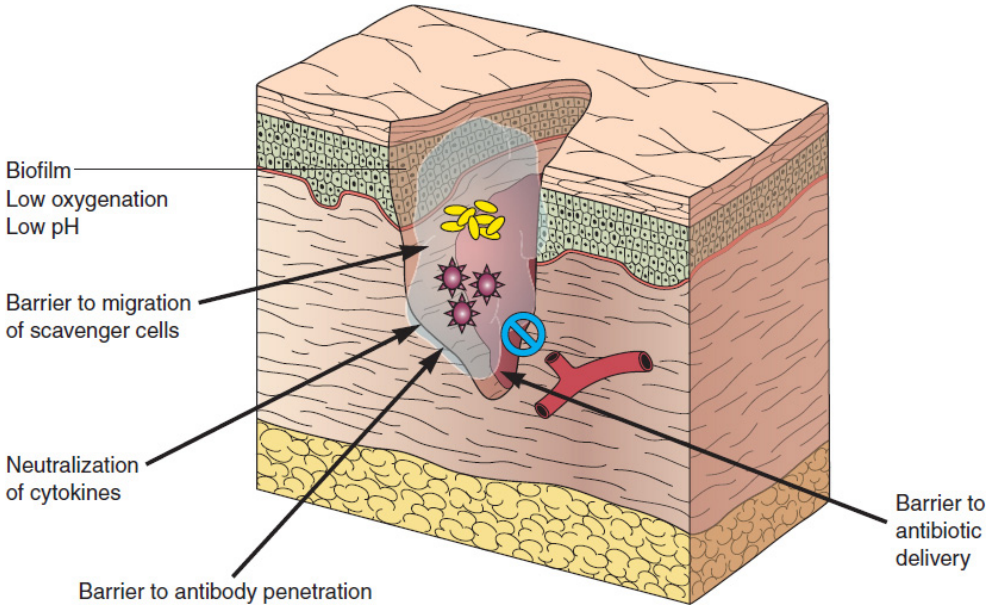

Figure 5.10 Effects of biofilm on wound healing.

Sex hormones play a role in age-related wound healing deficits. Compared with aged females, aged males have been shown to have delayed healing of acute wounds. A partial explanation for this is that the female estrogens (estrone and 17β-estradiol), male androgens (testosterone and 5α-dihydrotestosterone, DHT), and their steroid precursor dehydroepiandrosterone (DHEA), appear to have significant effects on the wound healing process.[51] It was recently found that the differences in gene expression between elderly male and young human wounds are almost exclusively estrogen regulated.[52] Estrogen effects wound healing by regulating a variety of genes associated with regeneration, matrix production, protease inhibition, epidermal function, and genes primarily associated with inflammation.[53] Studies indicate that estrogen can improve the age-related impairment in healing in both men and women, while androgens regulate cutaneous wound healing negatively.

Several treatments to reduce the age-related impairment of healing have been studied. Interestingly, exercise has been reported to improve cutaneous wound healing in older adults as well as aged mice, and the improvement is associated with decreased levels of proinflammatory cytokines in the wound tissue. Improved healing response may also be due to an exercise-induced anti-inflammatory response in the wound.[54]

Table 5.1 Cellular and Biologic Events That Frame the Normal Wound Healing Process

Phase	Cellular and Biophysiologic Events
Hemostasis	Vascular constriction Platelet aggregation, degranulation, and fibrin formation (thrombus)
Inflammation	Neutrophil infiltration Monocyte infiltration and differentiation to macrophage Lymphocyte infiltration
Proliferation	1. Re-epithelialization 2. Angiogenesis 3. Collagen synthesis 4. ECM formation
Remodeling	1. Collagen remodeling 2. Vascular maturation and regression

ECM, extracellular matrix.

Nutrition

Malnutrition or specific nutrient deficiencies can have a profound impact on wound healing after trauma and surgery. Patients with nonhealing wounds and experiencing nutrition deficiency often require special nutrients, energy, carbohydrates, proteins, fat, vitamins, and mineral metabolism all can affect the healing process.[55]

Glutamine is the most abundant amino acid in plasma and is a major source of metabolic energy for rapidly proliferating cells such as fibroblasts, lymphocytes, epithelial cells and macrophages, glutamine improves nitrogen balance and diminishes immunosuppression and plays a critical role in stimulating the early inflammatory phase of wound healing. Major surgery, trauma, and sepsis require supplementation of glutamine. Oral glutamine

supplementation has been shown to improve wound breaking strength and to increase levels of mature collagen.[56]

Lipids are used as nutritional support for surgical or critically ill patients to help meet energy demands and provide essential building blocks for wound healing and tissue repair. Polyunsaturated fatty acids (UFAs), consist mainly of two families, n-6 (omega-6 found in soybean oil) and n-3 (omega-3 found in fish oil). Although fish oil has been widely touted, effects of omega-3 fatty acids on wound healing are not conclusive. They have been reported to affect proinflammatory cytokine production, cell metabolism, gene expression, and angiogenesis in wound sites.[57]

Vitamins, Micronutrients, and Trace Elements

Vitamins C (L-ascorbic acid), A (retinol), and E (tocopherol) show potent antioxidant and anti-inflammatory effects. Vitamin C had many roles in wound healing and a deficiency in this vitamin has multiple effects on tissue repair. Vitamin C deficiencies result in impaired healing and have been linked to decreased collagen synthesis and fibroblast proliferation, decreased angiogenesis, and increased capillary fragility. Also, vitamin C deficiency leads to impaired immune response increased susceptibility to wound infection. Similarly, vitamin A deficiency leads to impaired wound healing. The biologic properties of vitamin A include antioxidant activity, increased fibroblast, proliferation, modulation of the cellular differentiation and proliferation, increased collagen and hyaluronate synthesis, and decreased MMP-mediated ECM degradation.[1]

Obesity

The prevalence of obesity continues to increase among adults, children, and adolescents in the United States, with more than 30% of adults and 15% of children and adolescents classified as obese in a recent study. Obesity is well known to increase the risk of many diseases and health conditions, which include coronary heart disease, type 2 diabetes, cancer, hypertension, dyslipidemia, stroke, sleep apnea, respiratory problems, and impaired wound healing. Obese individuals frequently face wound complications, including skin wound infection, dehiscence, hematoma and seroma formation, pressure ulcers, and venous ulcers.[58] An increased frequency of wound

complications has been reported for obese individuals undergoing both bariatric and nonbariatric operations.[59] In particular, a higher rate of surgical site infection occurs in obese patients.

The function of adipose tissue used to be considered as primary caloric storage. However, more recent findings have documented that adipose tissue secretes a large variety of bioactive substances that are collectively named adipokines. Both adipocytes as well as resident macrophages in adipose tissue are known to produce bioactive molecules including cytokines, chemokines and hormone-like factors such as leptin, adiponectin, and resistin. Adipokines have a profound impact on the immune and inflammatory response.[60] The negative influence of adipokines on the systemic immune response seems likely to influence the healing process, although direct proof for this is lacking. Impaired peripheral blood mononuclear cell function, decreased lymphocyte proliferation, and altered peripheral cytokine levels have been reported in obesity. Importantly, many of the obesity-related changes in peripheral immune function are improved by weight loss.[61]

Diabetes Mellitus

Over 30 million people over the age of 18 in the United States have diabetes mellitus.[62] Additionally, another 86 million live with "pre-diabetes," a condition that can progress to type 2 diabetes (T2D).[62] The overall prevalence of diabetes continues to increase, thereby contributing to increasingly high healthcare costs.[62] Diabetes-related healthcare expenditure was 548 billion USD in 2013, accounting for 11% of the total adult healthcare cost, and is projected to exceed 627 billion USD by 2035.[63] Further, it is estimated that approximately 7 million people go undiagnosed thus delaying disease treatment and management.[62] Nonhealing wounds that result in lower limb amputation, are among the most common complications associated with diabetes and account for more than 200 billion USD annually in healthcare costs and loss of productivity.[64] Importantly, amputation is associated with high mortality rates of 16.7% at 12 months and over 50% at 5 years, rates that are worse than many cancers.[65]

Impaired wound healing in diabetes is the result of a combination of factors that promote inflammation and disrupt epithelialization and wound closure. Although this process is complex, it has been shown that neutrophils

and macrophages recruited to the site of the wound are critical components of the healing process.[66–68] During the normal healing process, macrophages are initially proinflammatory and then transition to an anti-inflammatory phenotype where they promote tissue repair and transition to the next phase of healing.[67,69,70] In diabetic wounds, however, this macrophage transition is altered, causing them to remain in a proinflammatory state and prevent wound resolution.[11,33,71,72] The factors driving the macrophage transition are not fully understood but recent evidence suggests that epigenetics plays a role in regulating macrophage function in both normal and diabetic wound healing.[33,73–76] These processes include DNA methylation of CpG islands, and methylation of histone tails.

Additionally, re-epithelialization is delayed in diabetic wounds due to impaired keratinocyte and fibroblast function brought on by hyperglycemia and accumulation of advanced glycation end-products (AGEs)[77–80] and epigenetic regulation has also been implicated in these processes.[81–83]

The etiology of nonhealing diabetic foot ulcerations is multifactorial due to a combination of peripheral neuropathy, peripheral artery disease, and altered immune function.[84] These factors work together to predispose the diabetic patient to ulceration and infection. Despite the cause of the wound, it is failure of the wound to heal that is responsible for considerable morbidity and mortality associated with diabetes. Neuropathic edema makes the diabetic foot susceptible to ulceration and infection[85] and ischemia resulting from occlusive arterial disease reduces blood flow,[86] both contributing to delayed healing in the diabetic wound. Additionally, recruitment of EPCs is impaired in diabetes due to reduced nitric oxide (NO) production which, ultimately, results in impaired angiogenesis.[39] However, the most direct effects on wound healing come from functional alterations in cells activated by the immune response, including platelets, macrophages, neutrophils, endothelial cells, fibroblasts, and keratinocytes; all contributing to a failure to progress through the normal phases of wound healing.

Platelets

Platelets are key constituents of hemostasis and are responsible for some of the earliest events in response to injury, initially forming a platelet plug. As healing progresses, however, the clot must be degraded in order for re-epithelialization to occur. Sustained high glucose and insulin resistance

causes platelets to release high levels of fibrinogen and plasminogen activator inhibitor 1 (PAI-1) making them more adherent to the vascular endothelium and more likely to aggregate.[87,88] Additionally, under diabetic conditions, platelets have been shown to be less responsive to NO released from the vascular endothelium which normally reduces aggregation at the vessel wall.[89] Exacerbating this, defects in insulin signaling cause the vascular endothelium to produce less NO.[90,91] Thus, platelet dysfunction in diabetes contributes to development of microvascular disease that is well established in diabetic patients. Hence, in the setting of wound healing, the platelet phenotype induced by diabetes hinders wound healing by reducing coagulation during hemostasis.

Neutrophils

Neutrophils are important components during the inflammatory phase of wound healing, working to clear pathogens. However, sustained recruitment and activation of neutrophils are associated with chronic, nonhealing wounds.[92–94] Elevated levels of neutrophil-derived proteases are believed to contribute to persistent inflammation and delayed wound healing.[92,93] In addition to proteases, neutrophils release extracellular traps (NETs) composed of decondensed chromatin lined with cytotoxic proteins to kill microbes.[94] It has been shown that the protein responsible for NET formation, peptidyl deiminase 4 (PAD4), is elevated in neutrophils from diabetic mice and humans making them more susceptible to NETosis and potentially contributing to persistent inflammation and tissue damage in diabetes.[94]

Monocytes/Macrophages

Monocytes are recruited to the wound site very early during the inflammatory phase where they differentiate into macrophages and dendritic cells. Despite the lack of clarity regarding the in vivo definition of these cells, there is substantial evidence that infiltrating monocytes/macrophages are critical for establishing the initial inflammatory phase as well as promoting the transition from a proinflammatory to anti-inflammatory environment.[33,67,69] In diabetic wounds this transition does not occur and macrophages remain in a persistent inflammatory state where they promote the destruction of the surrounding tissue both directly and indirectly by recruiting other proinflammatory

immune cells.[33,95,96] It has been recently reported that Ly6C^{Hi} monocytes/macrophages, which have been shown to promote inflammation, normally transition to Ly6C^{Lo}, which are more regenerative; however, in diabetic wounds, a second wave of Ly6C^{Hi} macrophages are recruited during the reparative phase and fail to transition to the anti-inflammatory Ly6C^{Lo} cells contributing to a sustained proinflammatory environment.[10] Furthermore, it has been shown that hyperglycemia and formation of AGEs impede the phagocytic capacity of macrophages ability to clear apoptotic neutrophils thereby promoting a sustained proinflammatory state.[97,98] Since the transition from a pro- to anti-inflammatory state is partly stimulated by neutrophil clearance, this results in a higher number of proinflammatory macrophages present in the wound. Additionally, studies have shown that monocyte-macrophage infiltration is sustained in diabetic mouse models due to alterations in expression of P-selectin and macrophage chemoattractant protein 1 (MCP-1).[95]

Endothelial Cells

Endothelial cells line the luminal surface of blood vessels and are responsible for regulating vasoconstriction and dilation by expression of vasoactive factors such as endothelial nitric oxide synthase (eNOS).[99] Reduced eNOS expression is associated with peripheral neuropathy and peripheral artery disease and contributes to decreased peripheral blood flow which, in turn, slows wound healing.[100] Additionally, EPCs are required for neovascularization of the wound and eNOS stimulates mobilization of EPCs from the bone marrow[39,101]; thus the observed decrease in eNOS also contributes to impaired local angiogenesis during diabetes.

Keratinocytes and Fibroblasts

The late phase of wound healing is carried out by keratinocytes and fibroblasts. In nonhealing diabetic wounds, a variety of alterations in keratinocyte function contribute to diminished epithelialization including defective keratinocyte migration and proliferation,[102,103] gap junction abnormalities,[104] chronic inflammation and infection,[95,105] reduced angiogenesis,[39,101] oxidative stress,[105] and abnormal expression of MMPs.[82,106,107] The mechanisms associated with these processes have been reviewed elsewhere.[108–110]

Alterations in fibroblast function also contribute to dysfunctional epithelialization and delayed healing in diabetic wounds. These are primarily involved with decreased proliferation, increased apoptosis, and impaired migration to the wound site.[79,80,111] Alterations in both keratinocytes and fibroblasts can be induced directly by hyperglycemia and AGE formation.[77,78,81,112,113] Moreover, crosstalk between the two cell types is important for re-epithelialization and is dependent on a delicate balance between proinflammatory and anti-inflammatory cytokine expression in the wound.[114]

In summary the impaired healing that occurs in individuals with diabetes, involves hypoxia, dysfunction in fibroblasts and epidermal cells, impaired angiogenesis and neovascularization, high levels of MMP, damage from reactive oxygen species and advanced glycation end products, decreased host immune resistance and neuropathy.

MEDICATIONS AND DIETARY SUPPLEMENTS

Glucocorticoid Steroids

Systemic glucocorticoids, which are frequently used as anti-inflammatory agents, are well known to inhibit wound repair via global anti-inflammatory effects and suppression of cellular wound responses, including fibroblast proliferation and collagen synthesis. Systemic steroids cause wounds to heal with incomplete granulation tissue and reduced wound contraction.[115] Glucocorticoids also inhibit production of HIF-1, a key transcriptional factor in healing wounds.[116] Beyond effects on repair itself, systemic corticosteroids may increase the risk of wound infection. While systemic corticosteroids inhibit wound repair, topical application produces quite different effects. Topical low-dosage corticosteroid treatment of chronic wounds has been found to accelerate wound healing, reduce pain and exudate, and suppress hypergranulation tissue formation in 79% of cases. While these positive effects are striking, careful monitoring is necessary to avoid a potential increased risk of infection with prolonged use.[117]

Peripheral Vascular Disease

Total disease prevalence based on objective testing has been evaluated in several epidemiologic studies and is in the range of 3% to 10%, increasing to 15% to 20% in persons over 70 years.[118] Peripheral vascular disease (PVD) is an independent risk factor for subsequent ulceration and limb loss in diabetes. It is present in 50% of patients with diabetic foot ulcer (DFU), a proportion that may be increasing. Those with DFU and peripheral arterial disease (PAD) are less likely to heal and more likely to require amputation compared to patients without PAD. It is therefore essential that PVD is identified in all patients with diabetes.

Patients with PVD commonly suffer from chronic toe and foot sores, cramping leg muscles when walking or numbness, weakness or heaviness in the muscles. Other chronic PVD symptoms include:

- Numbness in the extremities
- Weakness and atrophy of calf muscles
- A feeling of coldness in legs or feet
- Changes in the color of the feet: feet will turn pale when elevated and turn dusky red when in the dependent position
- Hair loss over the dorsum of the feet, thickening toenails
- Painful ulcers and/or gangrene in tissue, typically in the toes

Traditional wound care algorithms include aggressive detection of PAD and treatment with revascularization for all patients with PVD and lower extremity wounds—in order to prevent limb amputation. This is covered in data in other chapters.

Cigarette Smoking

It is well known that smoking increases the risk of heart and vascular disease, stroke, chronic lung disease, and many kinds of cancers. Similarly, the negative effects of smoking on wound healing outcomes have been known for a long time.[119] Postoperatively, patients who smoke show a delay in wound healing and an increase in a variety of complications such as infection, wound rupture, anastomotic leakage, wound and flap necrosis, epidermolysis, and a decrease in the tensile strength of wounds.[120]

Most studies have focused on the effects of nicotine, carbon monoxide, and hydrogen cyanide from smoke. Nicotine interferes with oxygen supply by inducing tissue ischemia, since nicotine can cause decreased tissue blood

flow via vasoconstrictive effects.[121] Nicotine stimulates sympathetic nervous activity, resulting in the release of epinephrine, which causes peripheral vasoconstriction and decreased tissue blood perfusion. Nicotine also increases blood viscosity caused by decreasing fibrinolytic activity and augmentation of platelet adhesiveness. In addition to the effects of nicotine, carbon monoxide in cigarette smoke also causes tissue hypoxia. Carbon monoxide binds to hemoglobin with an affinity 200 times greater than that of oxygen, resulting in a decreased fraction of oxygenated hemoglobin in the bloodstream. Hydrogen cyanide, another well-studied component of cigarette smoke, impairs cellular oxygen metabolism, leading to compromised oxygen consumption in the tissues. Beyond these direct tissue effects, smoking increases the individual's risk for atherosclerosis and chronic obstructive pulmonary disease, two conditions that might also lower tissue oxygen tension.[66,122]

Chemotherapy and Radiation

Chemotherapy Drugs

Most chemotherapeutic drugs are designed to inhibit cellular metabolism, rapid cell division, and angiogenesis and thus inhibit many of the pathways that are critical to appropriate wound repair. These medications inhibit DNA, RNA, or protein synthesis, resulting in decreased fibroplasia and neovascularization of wounds.[123] Chemotherapeutic drugs delay cell migration into the wound, decrease early wound matrix formation, lower collagen production, impair proliferation of fibroblasts, and inhibit contraction of wounds.[115] In addition, these agents weaken the immune functions of the patients, and thereby impede the inflammatory phase of healing and increase the risk of wound infection. Chemotherapy induces neutropenia, anemia, and thrombocytopenia, thus leaving wounds vulnerable to infection, causing less oxygen delivery to the wound, and also making patients vulnerable to excessive bleeding at the wound site.

Radiation

Radiation is one of the most commonly used therapies for the treatment of multiple types of human cancer.

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6

Hemostasis

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Key Points

1. During the time that thrombin forms, natural anticoagulant mechanisms oppose further thrombin formation and help to localize thrombin activity to areas of vascular injury. Just as thrombin generation is key to coagulation, antithrombin is the central anticoagulant protein.
2. The endothelial cell acts as a nonthrombogenic surface, and inflammation tips the balance to procoagulant state.
3. Thrombosis and inflammation are closely linked, and may perpetuate each other. Leukocytes and chemokines are involved with normal DVT resolution. These essential inflammatory mechanisms may drive vein wall injury.
4. Both acquired and inherited factors contribute to pathologic thrombosis; often occurring together.
5. Factor VIII and IX deficiency states are involved in hemophilia A and B and von Willebrand disease.

BASIC CONSIDERATIONS

Coagulation is an essential homeostatic mechanism for survival, and involves tightly controlled processes to maintain vascular integrity, including thrombosis localization, amplification, and neutralization. These coordinated steps occur at the vessel, cellular, and subcellular levels. Thrombosis, directly or indirectly, is the underlying leading cause of death in the world, and is an essential part of surgery.

Platelets form the initial hemostatic plug after vascular injury, and are locally activated and aggregation induced (**Fig. 6.1**). Platelet aggregation is mediated by receptors that are part of the mammalian integrin family. This family includes the β_1 family, mediating platelet

interaction with cells, collagen, fibronectin, and laminin; the β_2 family, present on leukocytes mediating interactions between leukocytes and other cells important in inflammation; and the β_3 family (cytoadhesion), including the megakaryocyte-specific glycoprotein (Gp) IIb/IIIa receptor and the vitronectin (Vn) receptor present on platelets and other cells.[1] Platelet aggregation is mediated by GpIIb/IIIa, which binds fibrinogen, von Willebrand factor (vWF), fibronectin, Vn, and thrombospondin to activated platelets. These high-density receptors are hidden on inactivated platelets and become exposed on the surface of activated platelets.

Two platelet activation routes are thought to occur physiologically.[2] Without direct vessel damage, platelet activation may occur via tissue factor (TF) deencryption and activation by protein disulfide isomerase (PDI), with factor VIIa generation and activation of platelets. Alternatively, subendothelial collagen may directly bind to GpVI and vWF, leading to platelet capture and activation. Of note, PDI inhibition can directly block experimental thrombus formation.[3]

Once stimulated, activated platelets contract, with externalization of negatively charged procoagulant phospholipids, including phosphatidylserine and phosphatidylinositol (termed platelet factor 3). This allows the coagulation proteins to assemble on the surface membrane of platelets, accelerating the coagulation reaction.[4] During platelet activation, granules release calcium and serotonin, and membranes are exposed that are rich in receptors for factors Va and VIIIa,[5,6] as well as fibrinogen, vWF, and ADP, a potent activator of other platelets. vWF is responsible for platelet adhesion through binding to GpIb,[7] whereas fibrinogen forms bridges between activated platelets by binding to GpIIb/IIIa on adjacent stimulated platelets.[8] Platelets also release polyphosphates that activate factor XII and the intrinsic pathway.[9]

While long thought to be a bystander in venous thrombosis (VT) as compared to the arterial system, the role of the platelet is now thought to play a critical role, as well as direct later inflammatory cell actions.[10,11] First, recent clinical trials suggest antiplatelet therapy may reduce recurrent VTE.[12] Second, in stasis and nonstasis experimental murine VT, genetic deletion of vWF was associated with significantly reduced VT size and not restored with recombinant factor rVIII.[13] Intravital microscopy also showed direct association of leukocytes and platelets in a growing acute thrombus. Consistently, platelets via $GpIb_2$, may promote VT by colocalizing leukocytes and coagulation factors at the site of injury or stasis in the vein.[14]

Once the platelet plug has formed, the stage is set for coagulation protein assembly (**Fig. 6.2**). Initiating agents for coagulation include subendothelial collagen and TF, usually from vascular injury.[1,2] There is also growing evidence that blood-borne TF associated with leukocytes, or circulating in soluble form, is also involved with venous thrombogenesis.[15,16] Leukocyte adhesion to platelets may trigger leukocyte activation, causing recruitment of blood-borne TF onto the surface of leukocytes associated with thrombus, or recruitment of TF-positive leukocytes onto the growing thrombus.[17] TF, both blood-borne and local, activates the extrinsic pathway of coagulation by complexing with activated factor VII (VIIa), activating factors IX and X to factors IXa and Xa.[16,18] Factor Xa, activated factor V (Va), ionized calcium, and factor II (prothrombin) form on the platelet phospholipid surface

to initiate the prothrombinase complex, which catalyzes the formation of thrombin faster than can be achieved with factor Xa alone.

Thrombin is central to coagulation and acts to cleave fibrinopeptide A (FPA) from the α chain of fibrinogen and fibrinopeptide B (FPB) from the β chain. This leads to the release of fibrinopeptides and the formation of new fibrin monomers, which then cross-link, resulting in fibrin polymerization. Thrombin also activates factor XIII, which catalyzes the cross-linking of fibrin to make the clot firm, activates platelets, and activates factors V and VIII, two nonenzymatic cofactors, to Va and VIIIa. This is important because only activated factors Va and VIIIa are involved in coagulation. Factor XIIIa also cross-links other plasma proteins, such as fibronectin and α_2-antitrypsin, resulting in their incorporation into clot.

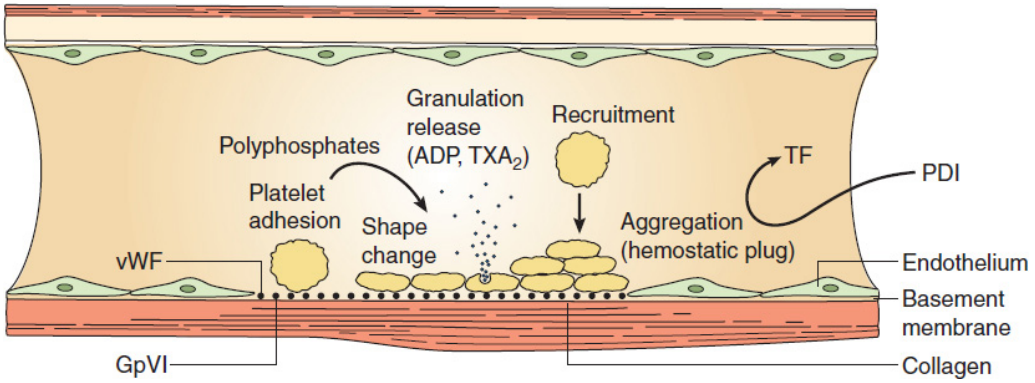

Figure 6.1 Primary hemostasis is achieved initially with a platelet aggregation as illustrated. Note that platelet adhesion, shape change, granule release, followed by recruitment and the hemostatic plug at the area of subendothelial collagen (binds to GpVI) exposure are the initial events for thrombus formation. Platelets can also be activated by PDI with deencryption of TF.

The intrinsic pathway of blood coagulation requires activation of factor XI to XIa. This may occur by both the contact activation system through activation of factor XII, plasma prekallikrein, and high–molecular-weight kininogen and, more important, through thrombin with negatively charged surfaces.[19] Factor XIa activates factor XI autocatalytically and also catalyzes the conversion of factor IX to IXa. After activation, factor VIIIa dissociates from vWF and assembles with factors IXa and X. Factor IXa, factor X, ionized calcium, and thrombin-activated factor VIII (VIIIa) then assemble on the platelet surface in a complex called the *Xase complex* to catalyze the activation of factor X to Xa. Factor Xa then shunts into the prothrombinase complex for further amplification of thrombin formation.

The importance of a mechanism of factor XI activation independent of the contact activation system is apparent because patients deficient in those factors of the contact activation system, including factor XI, have abnormal prolongation in bleeding, whereas patients deficient in factor XII, prekallikrein, and high–molecular-weight kininogen do not.[20] The contact activation system is the most important coagulation process involved in extracorporeal bypass circuits, including cardiopulmonary bypass and extracorporeal membrane oxygenation.

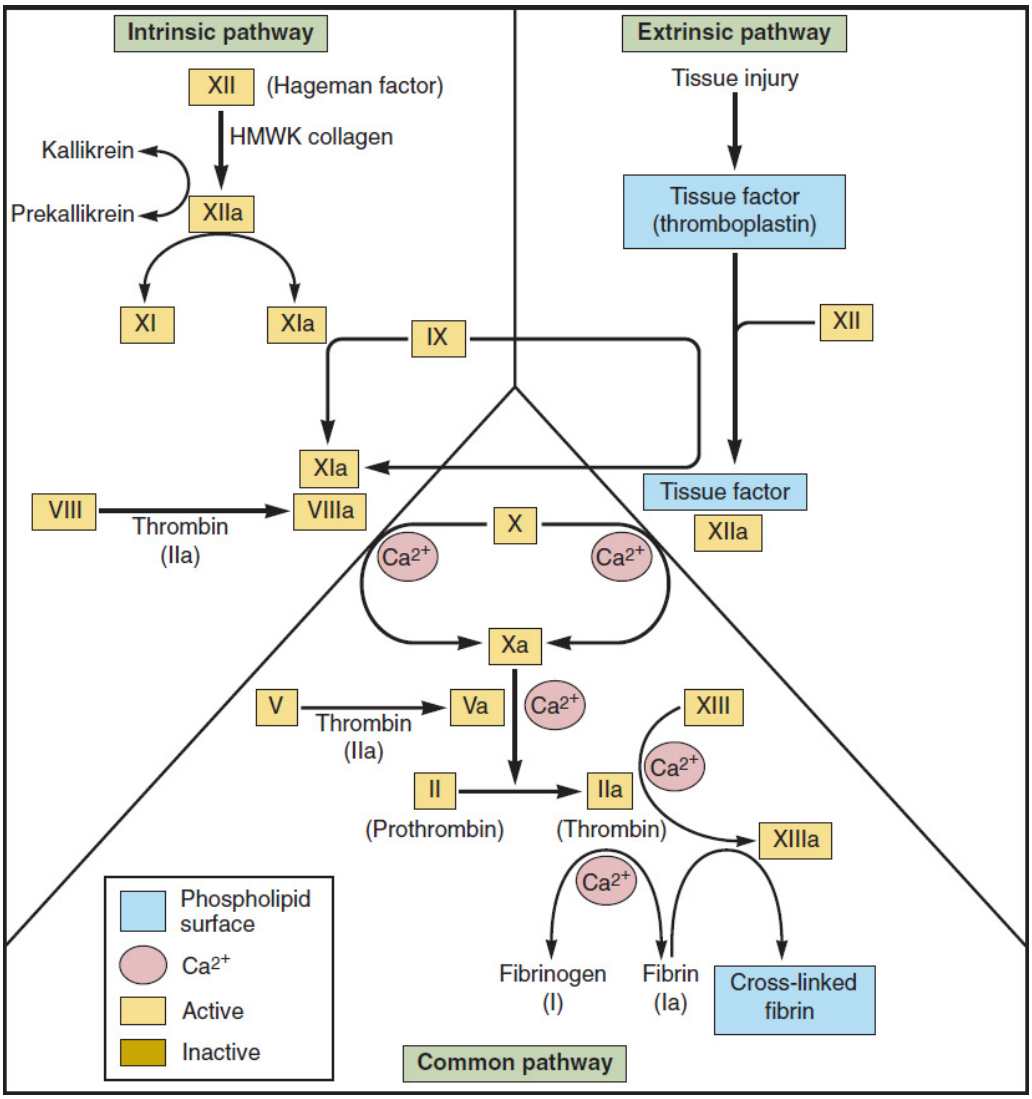

Figure 6.2 The classical pathway showing the interface between the intrinsic pathway, extrinsic pathway, and the common pathway is illustrated with the ultimate production of thrombin. This catalyzes fibrin from fibrinogen, and then cross-links the fibrin to form a stable clot.

NATURAL ANTICOAGULANT MECHANISMS

1 At the same time that thrombin forms, natural anticoagulant mechanisms oppose further thrombin formation and help to localize thrombin activity to areas of vascular injury.[2] Just as thrombin generation is key to coagulation, antithrombin (AT) is the central anticoagulant protein (**Fig. 6.3**). This glycoprotein of 70-kD molecular weight binds to thrombin, preventing the removal of FPA and FPB from fibrinogen, prevents the activation of factors V and VIII, and inhibits the activation and aggregation of platelets. In addition, AT directly inhibits factors IXa, Xa, and XIa.

A second natural anticoagulant is activated protein C (APC), which inactivates factors Va and VIIIa, thus reducing the Xase and prothrombinase complex acceleration of the rate of

thrombin formation. In the circulation, protein C is activated on endothelial cell surfaces by thrombin complexed with one of its receptors, thrombomodulin (TM).[21–23] The formation of this thrombin–TM complex accelerates the activation of protein C compared with thrombin alone. Thrombin, at the same time, by binding to TM, loses its platelet-activating activity as well as its enzymatic activity for fibrinogen and factor V. Protein S is a cofactor for APC.

Another innate anticoagulant is tissue factor pathway inhibitor (TFPI). The protein binds to TF–VIIa complex, inhibiting the activation of factor X to Xa and the formation of the prothrombinase complex.[24] A fourth natural anticoagulant is heparin cofactor II.[25] Its concentration in plasma is estimated to be significantly less than that of AT, and its action is implicated primarily in the regulation of thrombin formation in extravascular tissues. Finally, thrombin is inactivated when it becomes incorporated into the clot.

FIBRINOLYSIS

In addition to natural anticoagulants such as proteins C and S, physiologic clot formation is balanced by a contained process of clot lysis, which prevents thrombus formation from proceeding outside of the injured area (**Fig. 6.4**). The central fibrinolytic enzyme is plasmin, a serine protease generated by the proteolytic cleavage of the proenzyme, plasminogen. Its main substrates include fibrin, fibrinogen, and other coagulation factors. Plasminogen, tissue plasminogen activator (tPA), and α_2-antiplasmin (α_2-AP) become incorporated into the fibrin clot as it forms. Plasminogen activators are serine proteases that activate plasminogen, by cleavage of a single arginine–valine peptide bond, to the enzyme plasmin. Plasminogen activation provides localized proteolytic activity.[26] The major endogenous plasminogen activators include tPA and urokinase, and intrinsic factors, such as factor XII, prekallikrein, and high–molecular-weight kininogen. These later factors of the contact system are more important in clot lysis than thrombus formation. These enzymes may also liberate bradykinin from high–molecular-weight kininogen, resulting in an increase in vascular permeability, prostacyclin (PGI_2) liberation, and tPA secretion. Finally, APC has been found to proteolytically inactivate the inhibitor to tPA, thus promoting tPA activity and fibrinolysis.[27] Thrombin promotes tPA release from endothelial cells as well as the production of plasminogen activator inhibitor (PAI-1) from endothelial cells.[28,29]

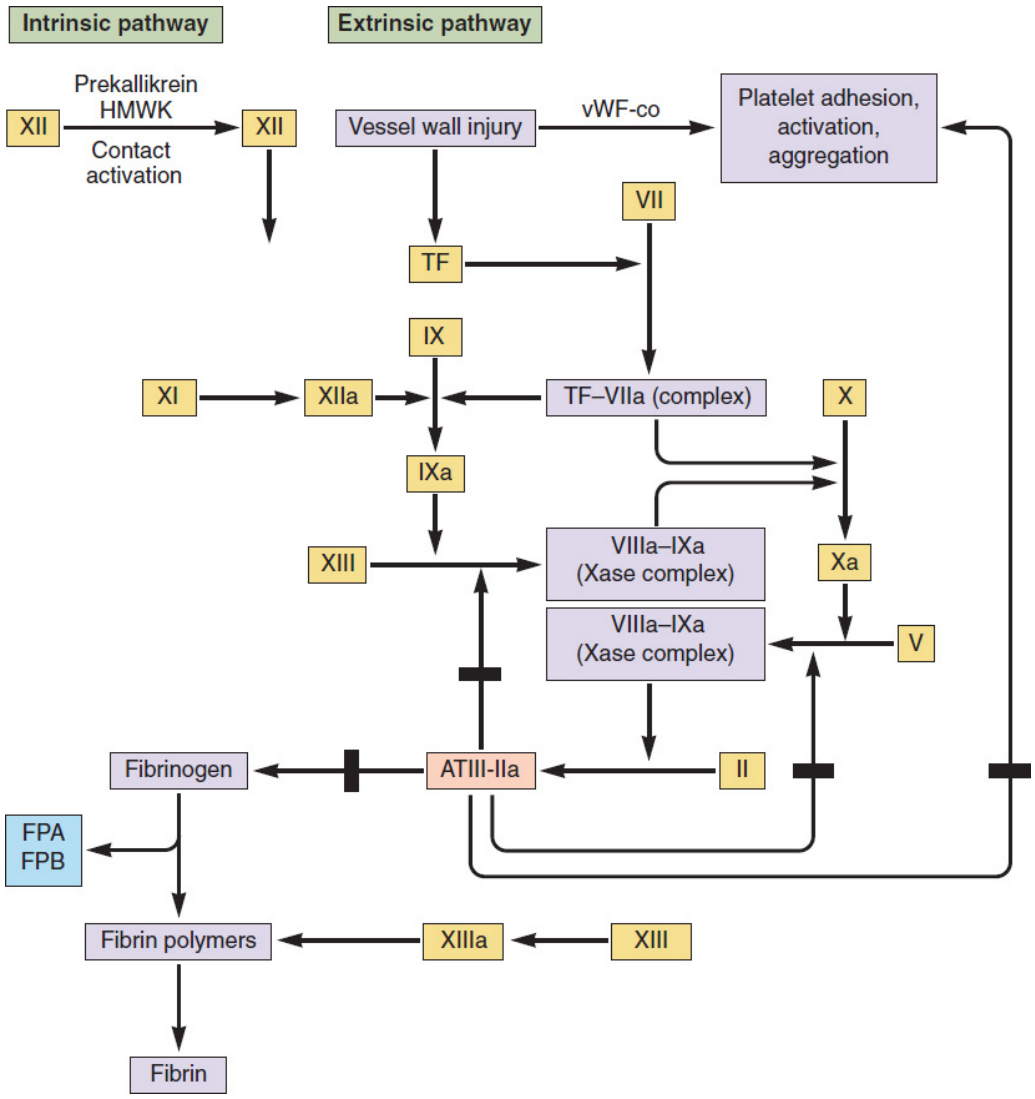

Figure 6.3 Antithrombin is a primary anticoagulant. Note antithrombin complexes with IIa to inhibit fibrin polymerization, as well as factor Xa, and inactivates factors Va and VIIIa.

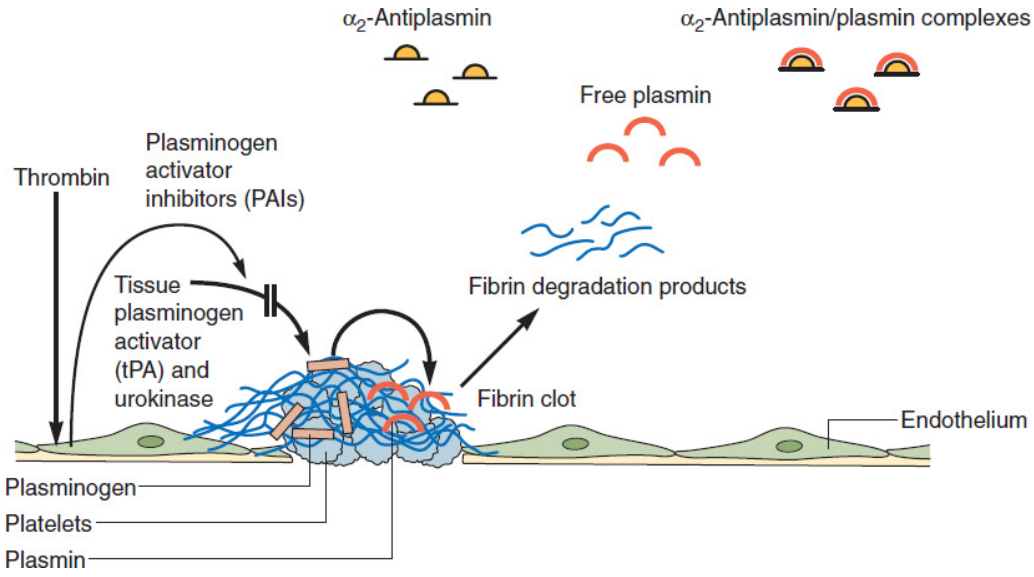

Figure 6.4 Hemostasis with thrombus production is a tight and intricate process that is locally confined. Balancing thrombus production are tissue plasmin activator and urokinase plasminogen activator which activate plasmin and cause thrombolysis. These are balanced by plasminogen activator inhibitor-1 and α_2-antiplasmin. Free plasmin is complexed rapidly. Fibrin degradation products, such as D-dimer, are produced.

Fibrin, when digested by plasmin, yields one molecule of fragment E and two molecules of fragment D. In physiologic clot formation, fragment D is released in dimeric form (D-dimer),[20] and is a marker for fibrinolysis of formed clot. An elevated D-dimer level after treatment of DVT is one biomarker that has been found to accurately predict an ongoing risk of recurrent VTE.[30,31]

Two primary inhibitors of plasmin are important. First, α_2-AP is released by endothelial cells and complexes with plasmin. In physiologic fibrinolysis, α_2-AP is bound to fibrin and excess plasmin is readily inactivated. In plasma, PAI-1 is the primary inhibitor of plasminogen activators.[32] It is secreted in an active form from liver and endothelial cells and stabilized by binding to Vn. PAI-1 levels are elevated by hyperlipidemia, and PAI-1 elevation appears to synergize with factor V Leiden genetic abnormalities.[33]

In summary, coagulation is an ongoing process of thrombus formation, inhibition of thrombus formation, and thrombus dissolution. The central mediators are TF, platelets, thrombin, and plasmin. Abnormalities in coagulation occur when one process—thrombus formation, thrombus inhibition, or fibrinolysis—overcomes the others and dominates the delicate balance.

ENDOTHELIUM AND HEMOSTASIS

2 Through its ability to express procoagulant and anticoagulant factors, vasoconstrictors and vasodilators, as well as key cell adhesion molecules and cytokines, the endothelial cell is a key regulator of hemostasis (**Fig. 6.5**).[34] The vascular endothelium maintains a vasodilatory

and local fibrinolytic state in which coagulation, platelet adhesion and activation, and leukocyte activation are suppressed.

Vasodilatory endothelial products include adenosine, nitric oxide (NO), and PGI_2. A nonthrombogenic endothelial surface is maintained by four main mechanisms, including endothelial production of TM and subsequent activation of protein C, endothelial expression of surface heparan and dermatan sulfate, constitutive expression of TFPI by endothelium (which is markedly accelerated in response to heparin), and local production of tPA and urokinase plasminogen activator (uPA).[34,35] Finally, the elaboration of NO and interleukin (IL)-10 by the endothelium inhibits leukocyte adhesion and activation.

During states of endothelial disturbances such as injury, a prothrombotic and proinflammatory state of vasoconstriction is driven by the endothelial surface. Endothelial release of platelet-activating factor (PAF) and endothelin-1 promotes vasoconstriction.[35] Endothelial cells increase production of vWF, TF, PAI-1, and factor V to augment thrombosis with exposure to prothrombotic stimuli. Finally, in response to endothelial injury, endothelial cells are activated, resulting in increased surface expression of cell adhesion molecules, promoting leukocyte adhesion and activation.

THROMBOSIS, INFLAMMATION, AND RESOLUTION

After VT, an acute to chronic inflammatory response occurs in the vein wall and thrombus progressing from thrombus amplification, to organization, and vein recanalization (often at the expense of vein wall fibrosis and vein valvular damage). Initially, there is an increase in neutrophils (PMN) in the vein wall followed by monocytes/macrophages. Cytokines, chemokines, and inflammatory factors (e.g., tumor necrosis factor [TNF]) facilitate inflammation. The ultimate response of the vein wall depends on proinflammatory and anti-inflammatory mediator balance at the interface between the leukocyte, activated platelet, and endothelium.[36]

Cell Adhesion Molecules

Selectins (P- and E-selectins, sP-sel, sE-sel) have been found to be intimately involved in thrombosis (**Fig. 6.6**).[37] P selectin is the first upregulated glycoprotein on activated platelets (α granules) and endothelial cells (Weibel–Palade bodies). They mediate the adhesion of leukocytes, platelets, and even cancer cells in inflammation and thrombosis. sP-sel is released from activated platelets and endothelial cells and levels rise significantly during pathologic conditions.[38–40] The P-selectin receptor is P-selectin glycoprotein ligand-1 (PSGL-1). P-selectin: PSGL-1 interactions trigger the release of procoagulant microparticles (MPs) that support fibrin formation, thrombus growth, and increase monocyte TF expression.

sP-sel has been studied as a biomarker for DVT,[38,41–43] and combining sP-sel with Wells score (clinical pretest probability of DVT) establishes the diagnosis of DVT. An sP-sel (≥90 ng/mL) combined with Wells score (≥2) showed a better PPV (91%) than D-dimer (≥500 ng/mL) combined with Wells score (≥2), which was 69%.[44] E-selectin, upregulated after P-

selectin, is an important regulator of thrombus formation and fibrin content in a mouse VT model.[45,46] Endotoxin-induced TF-mediated coagulation is enhanced in humans carrying the *S128R* E-selectin allele,[47] and patients homozygous for the *S128R* E-selectin allele have an increased risk for VTE recurrence.[48] E-selectin has been shown to be efficient at raising the affinity and avidity of two (CD18) integrins which support neutrophil trafficking to sites of acute inflammation and recruit platelets and red blood cells.[49]

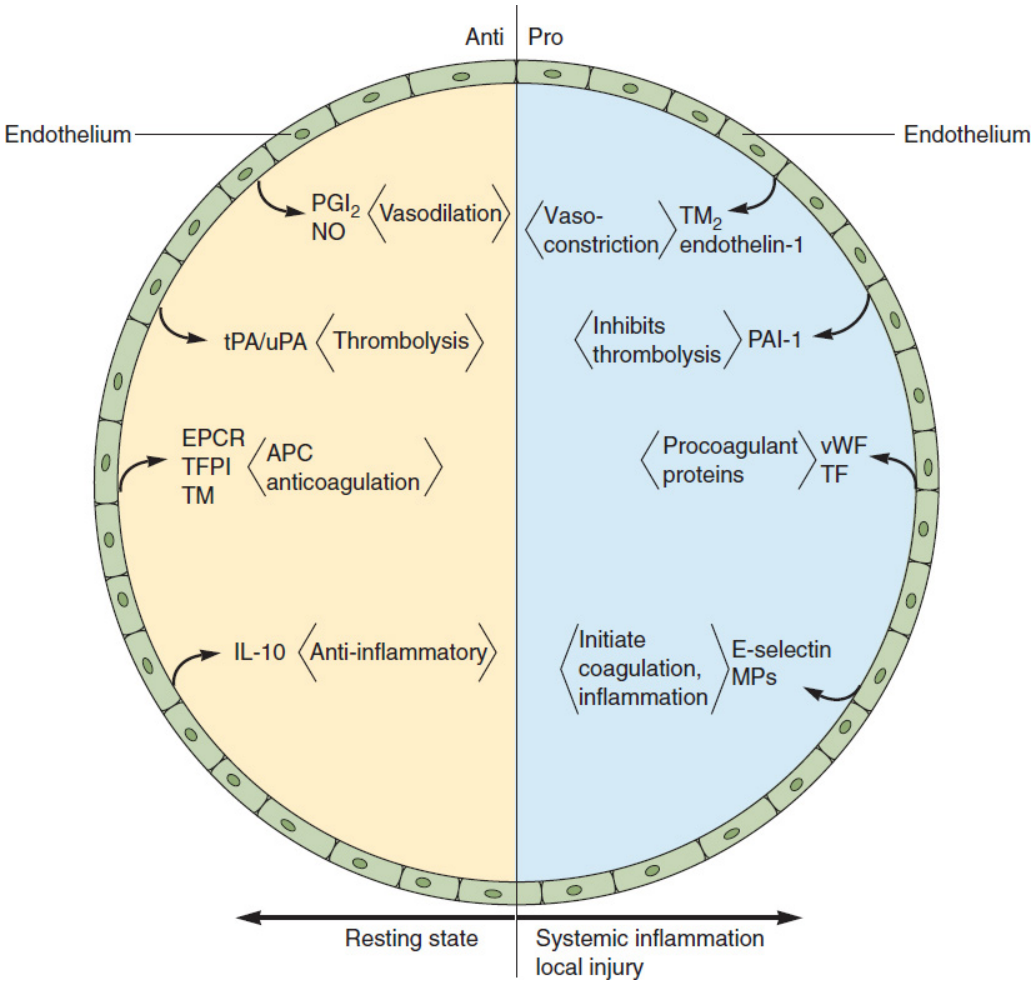

Figure 6.5 The endothelium is a primary interface allowing both anticoagulant functions in the resting state, with prostacyclin, NO, plasminogen activators, and thrombomodulin. Procoagulant proteins are expressed on activated endothelium including selectins, von Willebrand factor, TF, as well as PAI-1.

Other factors of importance to venous thrombogenesis include vWF, a factor that stabilizes procoagulant factor VIII to promote the initiation and formation of stable thrombus at the site of vascular inflammation and TF. Using a ferric chloride model of vein wall injury, it has been shown that occlusive thrombus formation is dependent on vWF.[50] TF activity is increased in cells treated with chemotherapy and in circulating MPs. Patients with cancer have elevated MPs, suggesting a role for TF in the pathogensis of cancer-associated DVT.[51] In addition, cancer patients with VTE were found to have elevated levels of MP TF compared to cancer patients without VTE.[52,53]

Leukocytes and Thrombosis

Inflammatory cells are important to the process of thrombus recanalization and organization (**Fig. 6.7**).[54,55] Thrombus resolution resembles wound healing, and involves profibrotic growth factors, collagen deposition, matrix metalloproteinase (MMP) expression, and activation.[56,57] As the thrombus resolves, a number of proinflammatory factors are released into the local environment, including interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α).[58] The cellular sources of these different mediators are probably leukocytes and smooth muscle–like cells within the resolving thrombus and adjacent vein wall. The fact that leukocytes invade the thrombus in a specific sequence suggests their importance in the normal thrombus resolution.[59]

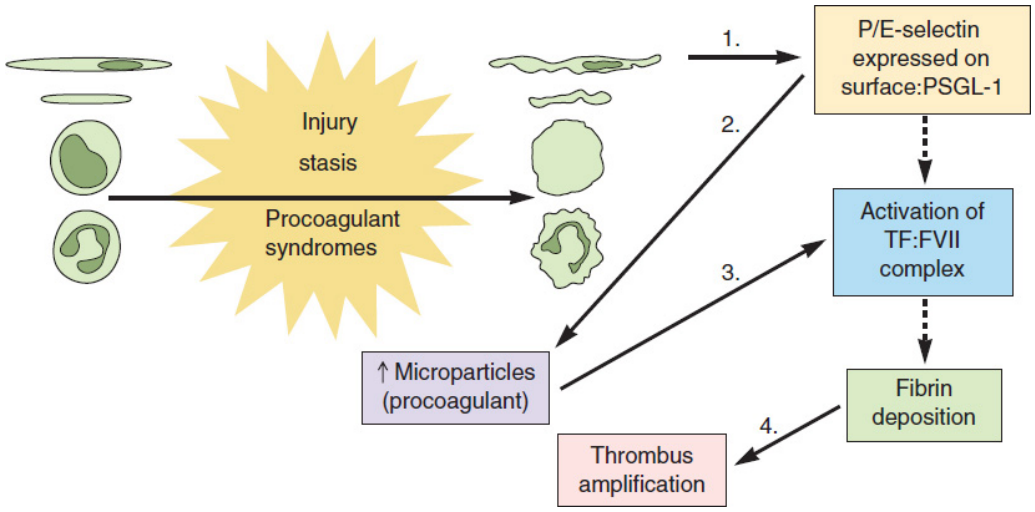

Figure 6.6 The interaction between stasis injury and procoagulant syndromes is represented by Virchow triad. Endothelial and vascular injuries cause leukocytes and platelets to express P- and E-selectins and the PSGL-1 receptor. Microparticles are released which express TF. This stimulates the coagulation pathway, fibrin production, and thrombus amplification.

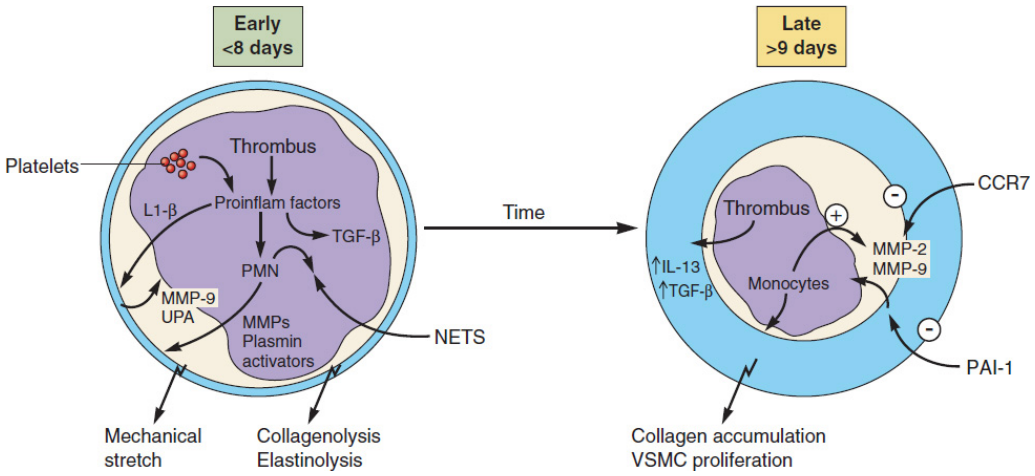

Figure 6.7 The proposed resolution mechanism involves both early thrombolysis with a large distending clot and then, over time, a fibrotic thrombus that resembles scar tissue as produced. Note proinflammatory factors, as well as neutrophils (releasing NETs), platelets, and MMP are present early with subsequent vein wall injury related to collagenolysis and elastinolysis. Later, vascular smooth muscle cell proliferation appears to occur, with thrombus resolution with increased profibrotic growth factor such as IL-13 and TGF-β. This promotes collagen accumulation. Both PAI-1 and CCR7 are protective against fibrosis.

The first cell type in the thrombus is the PMN. Although 3 PMNs may cause vein wall injury, they are essential for early thrombus resolution by promoting both fibrinolysis and collagenolysis.[60,61] It is likely the timing of PMN influx and the amount of perithrombus blood flow that tip PMN activities towards thrombosis or thrombolysis. In a rat model of stasis VT, neutropenia was associated with larger thrombi at 2 and 7 days, and was correlated with increased thrombus fibrosis and significantly lower thrombus levels of both uPA and MMP-9.[60] Conversely, in a nonstasis VT model, PMNs promote thrombosis.[14] Through processes that also involve the initial activation of leukocytes and platelets, PMNs form neutrophil extracellular traps (NETs), which are extracellular fragments of DNA containing histones and antimicrobial proteins.[14,62] The NETs provide a scaffold for thrombus formation, are proinflammatory, and are prothrombotic.[63]

In order to investigate if plasma DNA is a surrogate for NETs in patients with DVT, and to determine correlations with other biomarkers of DVT studied in our laboratory, patients presenting to our diagnostic vascular laboratory were investigated.[64] Patients were divided into positive for DVT by ultrasound, leg pain but negative for DVT by ultrasound, and control volunteers. Circulating DNA was significantly elevated in DVT patients, compared with controls. Of interest was a significant positive correlation of circulating DNA with C-reactive protein, D-dimer, vWF, and the Wells score (all $p < 0.01$).

The monocyte/macrophage is likely the most important cell for later DVT resolution.[58] Monocyte influx into the thrombus peaks at day 8 after thrombogenesis, and correlates with elevated MCP-1 levels, which has been associated with DVT resolution.[65] Targeted deletion of CC receptor-2 (CCR-2 KO) in the mouse model of stasis thrombosis was associated with late impairment of thrombus resolution, probably via impaired MMP-2 and MMP-9

activities.[66] Indeed, precedent exists in humans that the monocytic activation state may predict long-term DVT resolution.[67]

Thrombi have been found to contain increasing amounts of both tPA and uPA activities as they resolve, and this activity is expressed by invading monocytes.[68,69] In a recent study, mice genetically deleted for uPA had impaired thrombus resolution with reduced monocyte infiltration at the margins of the thrombus, with few neovascular channels present.[70] Mice gene deleted for tPA, however, were not similarly affected, suggesting that uPA, not tPA, is responsible for this activity.

The local venous environment is by definition hypoxic. A major angiogenic growth factor is hypoxia-inducible factor-1 alpha (HIF-1α). Experimental data in a stasis model of VT suggest that thrombosis stimulates increased vein wall HIF-1α, and that by exogenous stimulation of HIF-1α expression, thrombus recanalization was increased and associated with accelerated VT resolution.[71] Thus, thrombus resolution is in part dependent on neovascularization. The effect of mechanical stretch, such as by a VT, may also stimulate HIF-1α as well as MMP-2 and MMP-9, both leading to reduced vein contractility.[72]

Recent data linking inflammation to fibrosis demonstrate that inhibition of the inflammatory response can decrease vein wall fibrosis. In a rat model of stasis DVT, treated with either low–molecular-weight heparin (LMWH) or an oral inhibitor to P-selectin 2 days after establishment of thrombosis, inhibition of P-selectin significantly decreased vein wall injury (independent of thrombus size).[73] The mechanism accounting for this protective effect is not yet known, but probably does not involve leukocyte blockade, because no differences in influx of monocytes into the vein wall were observed.

Loss of venous endothelium likely also contributes to the vein wall fibrosis, as well as the predisposition to recurrent thrombosis. An experimental model of DVT showed lower expression of homeostatic endothelial genes such as NO and TM than in controls, which correlated with loss of vWF positive cell luminal staining.[74] Other investigators have found that prolonged venous stasis is associated with decreased plasminogen activators, probably related to loss of endothelium, as well as early vein wall dysfunction.[75,76]

Associated with the early biomechanical injury from DVT is an elevation of profibrotic mediators, including transforming growth factor-beta (TGF-β), interleukin-13 (IL-13), IL-6, and monocyte chemotactic protein-1 (MCP-1).[73,77,78] These mediators are present within the vein wall and thrombus and may drive the fibrotic response. Although exogenous MCP-1 may hasten DVT resolution, it promotes organ fibrosis in vivo. The profibrotic growth factor TGF-β is also present in the thrombus and is activated with normal thrombolysis.[79] TGF-β may be a key mechanism promoting vein wall fibrosis.[80]

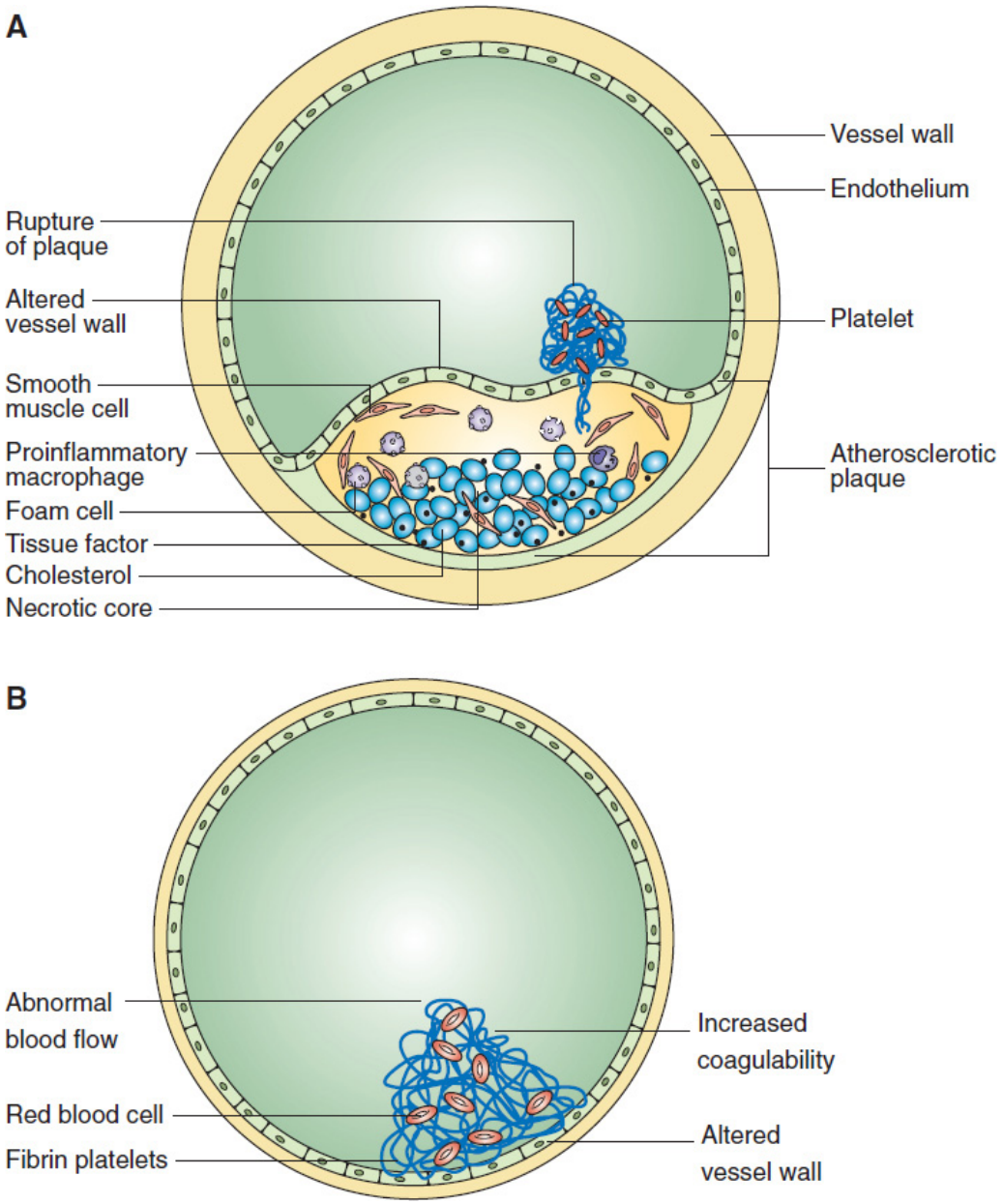

Figure 6.8 Depicted in **A** is the typical atherosclerotic thrombotic nidus, which includes rupture of a plaque, composed of smooth muscle, foam cells, and leukocytes. Platelets are the primary intermediary in arterial thrombosis, as well as TF. In figure **B**, increased coagulability, as well as vessel wall changes with procoagulant TF expression, promotes thrombosis.

Late fibrosis has been observed in our mouse model of DVT, which demonstrated a significant increase in vein wall collagen after stasis thrombogenesis.[77,81–83] Based on experimental studies, elastinolysis and collagenolysis seem to occur early, as measured by an increase in vein wall stiffness, persisting through 14 days, and are accompanied by elevated MMP-2 and MMP-9 activities.[77,81] Correlating with this increase in fibrosis is altered procollagen I and III gene expression, as well as an increase in MMP-2 and MMP-9 gene expression and activity. Genetic deletion of MMP-2 or MMP-2/9 is associated with

decreased midterm vein wall fibrosis, possibly by modulating vein wall elastin/collagen metabolism as well as monocyte influx.[56,57] It has been demonstrated that decreasing inflammation with a selectin inhibitor or with neutralizing IL-6 can also decrease vein wall fibrosis.[45,73,78] Moreover, the thrombus size itself does not drive the vein wall injury response; rather, the mechanism of thrombosis seems more important.[77,84] Lastly, PAI-1 overexpression is associated with decreased vein wall fibrosis, in part by decreased MMP-2/9 activity.[82]

ARTERIAL VERSUS VENOUS THROMBOSIS

Thrombosis in the arterial system occurs somewhat differently than in the venous system (**Fig. 6.8**). The elements required for the initiation of DVT were described by Virchow as stasis, endothelial injury, and hypercoagulability of the blood. In the arterial circulation, endothelial vascular injury (whether acute or chronic) is key to thrombosis. This is most clearly demonstrated by the typical atherosclerotic plaque. In advanced lesions, the lipid core of the plaque is rich in inflammatory cells, cholesterol crystals, and TF (generated by activated macrophages within the plaque).[85] Plaque ulceration exposes highly thrombogenic lipid to the bloodstream, activating coagulation, platelet aggregation, and leading to the deposition of clot.[86] Platelet deposition occurs at the apex of stenosis, the point of maximal shear force. The blood flow velocity itself regulates how quickly both thrombi form and dissolve.[87]

A platelet-rich thrombus is observed in arterial thrombus, while in contrast, venous blood stasis and changes in its composition (leading to hypercoagulability) incite the formation of thrombus from local procoagulant events, including small endothelial disruptions at venous confluences, saccules, and valve pockets.[11] Hypercoagulable states have classically been highly associated with VTE, but do play a role in cardiovascular disease as well.[88,89] Moreover, HMG-CoA reductase inhibitors (statin) not only decrease atherothrombotic events, but also incident VTE,[90] suggesting some common pathogenic pathways.

PROCOAGULANT STATES

Acquired Procoagulant States

Most thrombotic clinical episodes have an identifiable cause, although environment risks and genetic predispositions to thrombosis may account for many of the VTEs that manifest clinically.[11] Risk factors for arterial thrombosis are primarily related to atherosclerosis, and are detailed elsewhere.

Table 6.1 Acquired Hypercoagulable States

Risk	Relative Risk of VTE
Malignancy	++++
Trauma	++
Indwelling catheters	+
Surgery	++++
Pregnancy	+
HRT/OC	+
Lupus anticoagulant	+++
Obesity	+
Postoperative infection	++++
IBD	+++
Prolonged immobility	++

HRT, hormone replacement therapy; IBD, inflammatory bowel disease; OC, oral contraceptive; +, low risk; ++, moderate risk; +++, high risk; ++++, very high risk.

The most common risk factors for VTE are prior DVT, malignancy, immobility, intravenous catheters, increased age, major 4 surgery, trauma, infections such as pneumonia and urinary tract infection, and certain chemotherapies (**Table 6.1**).[91–93] Certain medications such as oral contraceptives and hormonal replacement therapies also increase the risk of VTE.

Of primary importance to surgeons is how best to estimate perioperative VTE risk, and apply appropriate prophylaxis. This can be done with a screening form, such as that devised by Caprini et al.[94] and Pannucci et al.[95] Essentially, this is a focused assessment of VTE risks related to current illnesses and history that may not be fully covered in the routine history and physical. The recommendations are also well detailed in the routinely updated American College of Chest Physicians VTE evidence-based guidelines.[96,97] The higher the risk, the more intensive the prophylaxis is. For example, an outpatient hernia patient may require no prophylaxis outside of early ambulation, whereas a hip replacement in an obese patient would be best treated with anticoagulation as well as sequential compression devices for the lower extremities. However, all patients should be assessed for VTE risk.

Malignancy

Cancer represents an independent risk factor for the development of VTE, with a sixfold increased risk in cancer patients. Importantly, cancer patients undergoing surgical procedures have twice the risk of development of postoperative DVT.[98] Highest rates of VTE are seen in

pancreas, stomach, and lung cancer. The malignancy itself activates a procoagulant phenotype by expression of TF by malignant cells, release of TF-bearing MPs, and increased activation of NETs—the downstream effects of which have been outlined above.[99]

Despite considerable evidence supporting the use of prophylactic anticoagulation in cancer patients, many do not receive optimal pharmacoprophylaxis for DVT while inpatient.[100] An extended duration of therapy—28 days—was found to be associated with a decreased incidence of DVT at the end of the study period; consequently, current guidelines recommend extended thromboprophylaxis in cancer patients after an operative intervention.[97]

Inflammatory Bowel Disease

Since the first half of the last century, a link between inflammatory bowel disease (IBD) and VTE has been recognized. While there does appear some correlation between thrombosis and the inflammatory nature of the disease, the link between the inflammatory and coagulation cascades does not tell the whole story. There are several possible mechanisms for this increased tendency toward thromboembolic events under active investigation, including spontaneous platelet activation through the CD40–CD40L pathway.[101]

A recent retrospective cohort study of the National Surgical Quality Improvement Program database demonstrated that the presence of IBD is an independent risk factor for postoperative VTE with an odds ratio of 2.[102] Interestingly, there appears to be an increased tendency to form clot in unusual locations, such as cerebral and hepatic veins. Currently, guidelines recommend only standard pharmacologic thromboprophylaxis for patients with IBD.

Trauma

As with other acquired prothrombotic states, the systemic inflammatory milieu is associated with VTE in trauma patients. Activation of inflammatory pathways through TNF-α with increased circulating TF and procoagulant MP induces a prothrombotic state.[103] Incidence of VTE in trauma patients is around 2%, and this may be higher in patients with other risk factors, such as old age, obesity, and prolonged immobility after bone fractures.[104,105] LMWH with application of pneumatic compression devices has been shown to be the preferred thromboprophylaxis in trauma patients, and this is reflected in anticoagulation guidelines.[96] However, optimal dosing regimens are not well defined.

Lupus Anticoagulant/Antiphospholipid Syndrome (Antiphospholipid Antibody)

Antiphospholipid antibody syndrome is a particularly virulent hypercoagulable state that results in both arterial thrombosis and VTE. For the diagnosis of antiphospholipid syndrome, both clinical and laboratory criteria are necessary (**Tables 6.2** and **6.3**). The prolongation in the aPTT is strictly a laboratory phenomenon. The dilute Russell viper venom time confirms the presence of a lupus anticoagulant. There is imperfect agreement between diagnostic tests for this abnormality. Approximately 80% of patients with a prolonged aPTT will have a

positive antiphospholipid antibody, but only 10% to 50% of patients with a positive antiphospholipid antibody will have a prolonged aPTT.[106]

Table 6.2 Diagnostic Criteria for Antiphospholipid Antibody Syndrome

Clinical Criteria (must have ≥1)	1. ≥1 clinical episode of, objectively confirmed, arterial, venous, or small vessel thrombosis. 2. Pregnancy morbidity: ≥1 unexplained fetal death at ≥10-wk EGA; ≥1 premature birth (≤34th wk of gestation) due to eclampsia, severe preeclampsia, or placental insufficiency; ≥3 unexplained consecutive spontaneous abortions at <10-wk EGA.[107]
Laboratory Criteria (must have ≥1)	1. LA (+) ≥2 occasions, at least 12 wks apart, according to ISTH guidelines (prolonged PL-based clotting assay, lack of correction with 1:1 mix, and correction with excess PL). 2. ACLA and/or anti-β_2 glycoprotein-I antibody (medium or high immunoglobulin G [IgG] and/or IgM isotype titer ≥2 occasions, at least 12 wks apart using standardized ELISA assays).

Hypercoagulability Testing

Clinical signs of possible thrombophilia include thrombosis at a young age (<40), unprovoked thrombosis, recurrent thrombosis, thrombosis at unusual locations such as the mesentery, CNS venous sinus, and portal vein, a family history of thrombosis, particularly unprovoked, severe, and in those <50 years of age.[126] Testing for hereditary defects in patients with thrombosis with no family history has pros and cons. On the pro side, testing may improve understanding of pathogenesis of thrombosis, identify and counsel affected family members, and obviate expensive diagnostic testing (e.g., CT scans) looking for a malignancy. On the con side, testing may identify patients with defects whose management would change, with the potential for overaggressive management, insurance implications for the patient arise, and the rather costly testing.

In order to determine the efficacy of hypercoagulable testing, a multicenter international observational registry on clinical characteristics, treatment patterns, and outcome in consecutive patients with symptomatic, objectively confirmed acute VTE was done. In this study, 22,847 patients were enrolled and 4,503 tested for thrombophilia. Of the total patient

population, 8.4% had factor V Leiden, 6.8% had PTG20210A, and 3% had activated protein C resistance (APC-R). The authors concluded that for the low incidence and in accordance with the recommendations made by other authors and international bodies, "the undertaking of thrombophilia testing on patients with a first episode of VTE is not advisable."[127]

A hypercoagulable screen should include routine coagulation tests such as the aPTT and platelet count, AT activity and antigen assay, protein C antigen and activity levels, protein S antigen level, and mixing studies to identify a lupus anticoagulant (if indicated); APC-R assay and factor V Leiden gene analysis; prothrombin G20210A genetic analysis; homocysteine level; an antiphospholipid antibody screen that includes anticardiolipin antibody; fibrinogen level; FVIII, FIX, and FXI levels and a functional plasminogen assay.

Inherited Procoagulant States

Defects with High Risk for Thrombosis

Inherited procoagulant states at high risk for thrombosis consist of antithrombin III (AT) deficiency, protein C deficiency, and protein S deficiency (**Table 6.3**). AT is a serine protease inhibitor (SERPIN) of thrombin, kallikrein, and factors Xa, IXa, VIIa, XIIa, and XIa. It is synthesized in the liver and has a half-life of 2.8 days. Protein C and its cofactor protein S are both vitamin K–dependent factors synthesized in the liver with half-lives of 4 to 6 hours and 12 to 14 hours, respectively. The majority of cases of protein C or protein S deficiency are inherited as autosomal dominant. Protein deficiency is divided into a type I deficiency (quantitative) and a type II deficiency (qualitative). Patients heterozygous for protein C deficiency usually have antigenic protein C levels less than 60% of normal.[128,129] Protein S is a cofactor to protein C in inactivating FVa and FVIIIa, and is regulated by complement C4b-binding protein.

Table 6.3 Severity and Frequency of VTE due to Hypercoagulable States

	Frequency (%) VTE	Thrombotic Phenotype	Diagnostic and Therapeutic Considerations
High Risk for Thrombosis			
▪ AT deficiency	0.5–3	Venous >> arterial ▪ May have thrombosis at unusual sites. ▪ Inherited cases become apparent by age 50 yrs.[108] ▪ Homozygous patients die in utero. ▪ Can be acquired from liver or kidney disease, sepsis, DIC, or malnutrition.[109]	Suspect in patients who cannot be adequately anticoagulated on heparin. Anticoagulation with direct thrombin inhibitors is recommended; alternatively, may administer FFP with heparin. Lifelong anticoagulation recommended following the first VTE.
▪ Protein C deficiency	3	Venous >> arterial ▪ Patients often present between ages 15 and 30 with VTE.[110] ▪ Homozygous patients die at birth from purpura fulminans. ▪ Can be acquired from liver failure, DIC, and nephrotic syndrome.	If asymptomatic heterozygote carriers, aggressive thromboprophylaxis is recommended in the perioperative period. Lifelong anticoagulation is recommended following first episode of thrombosis. Patients are at particular risk of warfarin-induced skin necrosis and must undergo bridging anticoagulation with heparin, LMWH, or direct thrombin inhibitor.[111]
▪ Protein S deficiency	3–6	Venous >> arterial ▪ Cofactor to protein C;	If asymptomatic heterozygote carriers, aggressive

		deficiency results in clinical state identical to protein C deficiency. ▪ Acquired deficiency can occur in liver disease, nephrotic syndrome, OCP use, pregnancy, and during breastfeeding.[112]	thromboprophylaxis is recommended in the perioperative period. Lifelong anticoagulation is recommended following the first episode of thrombosis. Patients are at particular risk of warfarin-induced skin necrosis and must undergo bridging anticoagulation with heparin, LMWH, or direct thrombin inhibitor.[111]
▪ Antiphospholipid antibody syndrome	3–5	Venous > arterial ▪ Associated with thrombosis, fetal loss, stroke, MI, visceral infarction, extremity gangrene, and graft thrombosis. ▪ May be induced by medications, cancer, and certain infections.[113]	Treatment is with warfarin followed by heparin; direct oral anticoagulants are associated with higher thrombosis risk.[113,114] For recurrent fetal loss, LMWH is recommended. Anti-Xa levels should be used to monitor LMWH/heparin levels.
Lower Risk for Thrombosis			
▪ Factor V Leiden (FVL)	20–60	Venous >> arterial Combined defects with protein C or S deficiency or prothrombin G20210A increase thrombotic risk.[115,116]	Diagnosis is made with a clot-based functional assay and genetic analysis to determine hetero- vs. homozygosity. Long-term anticoagulation is not necessary after first episode of thrombosis in a heterozygote, but

			is recommended after recurrent thrombosis.[117]
▪ Hyper-homocysteinemia	10	Arterial ~ venous ▪ Can be acquired via smoking, coffee consumption, diabetes, cancer, hypothyroidism, and low dietary levels of folate and vitamins B_6 or B_{12}. ▪ Common medications that increase levels: metformin, methotrexate, theophylline, levodopa, and anticonvulsants.[118]	Diagnosis is made via fasting homocysteine levels or after a methionine oral loading regimen. Treatment is through/by folate supplementation. Anticoagulation choice and duration should not be influenced by diagnosis of hyperhomocysteinemia.
▪ PT G20210A	4–6	Venous >> arterial ▪ Thrombosis risk is increased in combination with FVL and pregnancy. ▪ Most prevalent in Caucasians.[119]	Long-term anticoagulation is recommended for patients with recurrent thrombosis or when diagnosed in conjunction with FVL.[120]
▪ Dysfibrinogenemia	1–3	Venous > arterial Common presentations include VTE and digit ischemia.[121]	Standard anticoagulation according to guidelines.[122,123]
▪ Dysplasminogenemia	<1	Arterial ~ venous	Standard anticoagulation according to guidelines.[122,123]
▪ Elevated factors VIII, IX, and XI	1	Venous > arterial Thrombosis risk is dose responsive,	Diagnosis is with activity assays; however, factor VIII carrier is vWF

	for example, factor VIII:C above the 90th percentile is associated with fivefold increased risk of VTE.[124] Acquired and environmental factors precipitate VTE.[125]	which is an acute phase reactant and must be accounted for, usually by measuring ESR or CRP. Standard anticoagulation according to guidelines.[123]

AT, antithrombin; HITTS, heparin-induced thrombocytopenia and thrombosis syndrome; PAI-1, plasminogen activator inhibitor-1; VTE, venous thromboembolism.

Defects with Lower Risk for Thrombosis

Resistance to APC (Factor V Leiden)

Resistance to APC has been reported to be present in 20% to 60% of cases of idiopathic VTE and is the most common underlying abnormality associated with VTE. This disorder is present in 1% to 2% of the general population.[130–132] As a result of the substitution of a single amino acid, glutamine for arginine, at position 506 in the protein for factor V, caused by a nucleotide substitution of guanine for adenine at 1,691 in factor V gene, hypercoagulability is conferred by resistance to inactivation of factor Va by APC.[110,133,134] Factor V Leiden accounts for 90% of APC-R (**Table 6.3**).

Prothrombin G20210A Polymorphism

Prothrombin (factor II), a vitamin K–dependent factor synthesized in the liver, becomes thrombin when activated. A genetic polymorphism in the distal 3′ untranslated region of the gene for prothrombin, a transition from guanine to adenine at the 20210 nucleotide of the prothrombin gene, has been described in patients with VTE.[135] This results in a normal prothrombin but at increased levels.[120,136,137] This polymorphism confers an increased risk for VTE by 2.8-fold, is associated with 4% to 6% of patients with VTE, and is the second most common cause for hypercoagulability in Caucasians (**Table 6.3**).[117,119,138–140]

Hyperhomocysteinemia

Hyperhomocysteinemia has been a known risk factor for atherosclerosis and vascular disease for more than 25 years, though a direct cause and effect relationship has not been established.[141,142] However, a recent meta-analysis suggests the risk of VTE to be 2.5-fold with elevated homocysteine levels.[143] Two enzyme deficiencies, N^5,N^{10}-methylenetetrahydrofolate reductase (MTHFR) or cystathionine β synthase, are responsible for elevated homocysteine levels.[144] Although mutations in these enzymes are not infrequent, the common polymorphism in MTHFR alone is not a factor in either the elevation of plasma homocysteine or thrombosis (**Table 6.3**).[145]

Other Disorders Associated with Thrombosis

Defective Fibrinolysis/Dysfibrinogenemia/Lipoprotein(a)

Abnormal plasminogens (dysplasminogenemias), although rare (<1%), have been described in cases of spontaneous arterial thrombosis or VTE (**Table 6.3**).[146] Both type I quantitative and type II qualitative deficiency states have been described. Numerous molecular defects have been classified. Defective thrombin binding or resistance to plasmin-mediated breakdown has been described.[147] Although not clearly documented, defects in plasminogen activators, tPA or uPA, may incite thrombotic events.[148] Elevated PAI-1 has been associated with DVT and myocardial infarction.[146]

Lipoprotein(a), associated with LDL, has both atherogenic and prothrombotic properties.[149–151] It prevents plasminogen from binding to cells or fibrin and inhibits fibrinolysis.[152] Elevated levels of lipoprotein(a) have been associated with VTE in childhood; it is a weak thrombotic risk factor in adults (**Table 6.3**).[153–155]

Abnormal Platelet Aggregation

It has been recognized for some time that there are patients who have thrombosis and may have hyperactive/hyperresponsive platelets but this entity is poorly defined. Diabetes mellitus, which is known to be associated with hyperactive platelets and hyperlipidemic states, may be a contributing factor. Hyperactive platelets have been noted during graft thrombosis in peripheral vascular reconstructions.[156] Although platelet aggregation assays may be helpful in making the diagnosis, these assays are not commonly performed or standardized and, thus, the incidence and importance of platelets to thrombosis are not well known. Bleeding time measurements are not specific, and not recommended for making this diagnosis. This condition has been called “sticky platelet syndrome” and both arterial and venous events have been reported.[157]

Standard anticoagulant treatment is recommended for this condition. Aspirin and the thienopyridine derivatives such as clopidogrel may be useful, but their utility is unknown.[158]

Elevated Procoagulant Factors: VIII, IX, and XI

Elevated prothrombotic factors have only recently been associated with primary and recurrent VTE (**Table 6.3**).[117,159]

Disseminated Intravascular Coagulation

DIC is a primary form of acute thrombosis. Causes of DIC include sepsis, trauma, pancreatitis, obstetric complications such as abruptio placentae or amniotic embolism, transplant rejection, malignant tumors, certain snake bites, hematologic malignancies, and hepatic failure. Coagulation in DIC is activated by the release of TF into the circulation causing unregulated activation of the coagulation cascade, leading to massive thrombin production and fibrin generation. Fibrinolysis then becomes activated as well, leading to bleeding in the later, hemorrhagic stages of the syndrome because of the consumption of clotting factors, depletion of fibrinogen, and unchecked plasmin activity. The diagnosis of DIC is a clinical one, which requires consideration of the gestalt of the patient. Laboratory values in DIC reveal a downtrend in platelet count—even within the normal range,

decreased fibrinogen level, prolonged PT, and concomitant elevation in fibrin split products and the presence of a positive D-dimer test. The treatment of DIC requires treatment of the underlying condition. The need for platelet or plasma transfusion is based on the presence of hemorrhage, rather than on particular laboratory values.[160]

BLEEDING DISORDERS

Although the surgeon deals more often with procoagulant states than bleeding disorders, it is important to recognize these disorders when they occur.

Coagulation Factor Deficiency

Coagulation factor deficiency states are important causes of 5 bleeding and the most common are factor VIII and IX deficiency states, termed hemophilia A and B, and type I von Willebrand disease (vWD).

Hemophilia A is inherited as a sex-linked recessive deficiency of factor VIII, with fewer cases secondary to spontaneous mutation. The incidence of this abnormality is approximately 1 in 5,000 births.[161] Clinical findings range from bleeding into joints and muscles, epistaxis, hematuria, and bleeding after minor trauma, to prolonged postoperative bleeding, retroperitoneal bleeding, and intramural bowel hemorrhage. Laboratory screening tests usually reveal a prolongation of the aPTT along with decreased factor VIII levels; other test results are normal. The minimum level of factor VIII required for hemostasis is 30%, and spontaneous bleeding is uncommon with factor VIII levels greater than 5% to 10% of normal. Levels less than 2% constitute severe, 2% to 5% moderate, and greater than 5% mild deficiency.[162] Although the half-life of factor VIII is 2.9 days in normal subjects, the half-life of factor VIII concentrates is only 9 to 18 hours.[161] Levels between 80% and 100% of normal should be attained for surgical bleeding or life-threatening hemorrhage. Acquired deficiency has been reported to occur with the development of antibodies to factor VIII after therapy. Inhibitor antibodies develop in approximately 10% to 15% of patients with hemophilia A, although the incidence of antibody formation may be much higher in previously untreated patients and in those with severe hemophilia A.

Recombinant factor VIII preparation has been developed and tested in children and infants. Despite the development of low levels of inhibitors in 20% of children at a mean 9 days after first administration, these inhibitors either disappeared or remained at low levels.[163]

Factor IX deficiency (Christmas factor), known as hemophilia B, is transmitted as an X-linked recessive trait. It may also be acquired because of enhanced factor IX clearance in states such as the nephrotic syndrome, abnormal protein production in vitamin K deficiency, and acquired specific inhibitors to factor IX in various autoimmune diseases, such as SLE. It is clinically indistinguishable from hemophilia A, and laboratory screening tests reveal a prolonged aPTT, with other test results normal, although a greater proportion of patients have only mild or moderate deficiency.[164] Severe deficiency (approximately 30% of cases)

is defined as a level of activity less than 4% of normal, whereas moderate deficiency is reported with activity levels between 20% and 40%.[162] Treatment consists of plasma or factor IX concentrates and vitamin K. It has been recommended that levels greater than 30% be achieved for hemostasis.

vWF causes platelet adhesion to collagen, initiating platelet plug formation. It also forms a complex with factor VIII in the blood. Produced in endothelial cells and megakaryocytes (compared with the liver for factor VIII), it has a circulating half-life of 6 to 20 hours. vWD, a deficiency of vWF, is the most common of the inherited coagulation disorder. A number of different subtypes have been identified for its deficiency state, and the syndrome is transmitted as both autosomal dominant (heterozygous) and autosomal recessive (homozygous) forms. Variants include types I and III (quantitative decreases in normal-appearing vWF) and type II (qualitative abnormalities in structure and function of vWF).[165] vWF deficiency is probably as common as hemophilia A, although the true incidence may surpass what is generally appreciated because many mild cases probably remain undiagnosed.

The classic syndrome is caused by a reduction of factor VIII activity (although not as great as in hemophilia A) and vWF (vWF–factor VIII complex). Clinical manifestations include easy bruisability, mild to moderate epistaxis, gingival bleeding, menorrhagia, rare joint or muscle bleeding, prolonged bleeding following surgery, and subcutaneous bleeding. Spontaneous bleeding is not as common as in hemophilia A.

Abnormal laboratory tests include a prolonged bleeding time; a decreased level of factor VIII activity; decreased immunoreactive levels of the vWF; and abnormal platelet aggregation response to ristocetin. The most reliable source of vWF is cryoprecipitate, although many concentrates of factor VIII have vWF present and show promise. Desmopressin acetate (DDAVP) is available for the treatment of mild cases of type I vWD and types 2a and 2b; serum levels of 25% to 50% are needed for hemostasis. In other type II states and type III vWD, factor VIII concentrates are necessary. Recombinant factor VIII/vWF concentrates that avoid the infectious risks of transfusion are available.

Rare Factor Deficiencies

Other specific factor deficiencies are much less common and receive only a brief mention here. These include factors II, XI, V, VII, and X. These can be measured by serum assays, although this is not routinely available in many hospitals. The treatments are primarily FFP concentrates to give back the clotting factors.

Deficiencies of fibrinogen can also lead to bleeding disorders. This is the only factor deficiency state in which the TCT is prolonged. It is generally believed that a fibrinogen level of 100 mg/mL should be achieved to stop bleeding related to fibrinogen abnormalities. Fibrinogen deficiency may also occur from consumption during DIC and from primary fibrinolytic states.

Platelet Disorders

Platelet disorders are another important cause of bleeding. Inherited defects of platelet receptors include defects of GpIIb/IIIa (Glanzmann thrombasthenia), characterized by impaired platelet binding to vWF, fibrinogen, and fibronectin. In patients with defects in GpIb (Bernard–Soulier syndrome), the absolute number of platelets is decreased, the platelets are larger, and platelet aggregation and adhesion are abnormal. Acquired deficits occur in uremia; both GpIb and GpIIb/IIIa receptors are defective, resulting in impaired adhesion and aggregation. Acquired deficits also occur in patients who previously received platelet transfusions and then acquired immune-mediated antiplatelet antibodies.

Abnormalities in Fibrinolysis

Abnormalities in fibrinolysis may play a role in abnormal bleeding disorders. Genetic or acquired deficiencies in α_2-AP may be associated with bleeding, whereas deficiencies in factor XIII (fibrin-stabilizing factor) may lead to highly lysable clot. α_2-AP deficiency is treated with ε-aminocaproic acid or tranexamic acid. Homozygous patients with factor XIII deficiency and less than 1% of normal plasma activity often show bleeding from the umbilical cord at birth, bleeding after trauma or surgery, and delayed bleeding 24 to 36 hours later. Screening test results include a shortened euglobulin lysis time. A specific assay for factor XIII activity exists. Treatment consists of FFP, cryoprecipitate, and factor XIII concentrates.

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7

Inflammation

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Key Points

1 Innate immunity, arm of the immune system poised in advance of any prior stimulus, provides the initial defense against invading pathogens. Subsequent more targeted reinforcement is provided by the adaptive immune system, which possesses extensive capacity to learn and tailor the response to repeated exposures and thereby manifests an exquisite specificity for subsequent exposure to individual microbes. Both are comprised of cellular and humoral components.

2 Implicit with the capacity for pathogen elimination is the potential for destruction of host tissues. Numerous regulatory mechanisms provide temporal and spatial control of the inflammatory processes, including programmed cell death (i.e., apoptosis).

3 Damage-associated molecular patterns (DAMPs) are the endogenous equivalent of PAMPs, represent danger signals or "alarmins," and share many characteristics similar to cytokines. These are released following nonprogrammed cell death, such as necrosis, or secreted as mediators by cells and regulate the inflammatory response.

4 The T_H1 inflammatory response (i.e., cell-mediated immunity or delayed-type hypersensitivity) is induced by IL-12 derived from phagocytes, provides one major arm of the adaptive immune response; it is mediated by $CD4^+$ and $CD8^+$ lymphocytes, innate lymphocytes type 1 (IL-C1) and macrophages, which regulate production of opsonizing and complement fixing antibodies and are effectors of phagocyte-dependent responses.

5 The principal stimulus for T_H2 differentiation is IL-4, which is derived from T cells, mast cells, and basophils. As the cellular effectors of humoral immunity, T_H2 responses are another major arm of the adaptive immune response mediated by T_H2 $CD4^+$ cells, IL-C2, B cells, plasma cells, and antibodies.

6 Over 60 randomized-controlled clinical trials have been conducted to assess the efficacy of modulating injurious inflammation, in particular systemic cytokine concentrations, in reducing mortality

from either trauma or sepsis. The only "biologic" adopted by the medical community as a potential therapeutic is the combination of corticosteroids and fludrocortisone in the management of sepsis.

7 T_H17 effecters are upregulated by IL-6 and IL-23 and can drive proinflammatory or tissue protective responses driven by the release of the cytokine IL-17A/F. Sources of this cytokine include T_H17 cells and IL-C3.

8 The complement system is integral to both innate and adaptive immunity and has the capacity to independently eliminate organisms and facilitate host defense by marking foreign particles for phagocytosis through opsonization. Complement activation products can also drive inflammation (i.e., C3a and C5a).

9 Additional systems, including the vascular (i.e., vasodilatation, adhesion receptors, kinin cascade), neuroendocrine (i.e., ACTH, AVP, CRH), and coagulation cascades integrate with the immune system and share similar mediators and their receptors as to orchestrate an intense, coordinated response to any injurious/septic insult.

10 Our immune system differentiates pathogens and damaged cells from self, using evolutionarily ancient sets of recognition molecules called pattern recognition receptors (PRRs), which bind conserved molecular structures found in large groups of pathogens, termed pathogen-associated molecular patterns (PAMPs), an example being the toll-like receptors (TLRs).

Our intimate understanding and appreciation for the complexity of the integrated mechanisms collectively called "inflammation" has exponentially evolved since Celsus in 1c AD first described the four cardinal signs and symptoms: "rubor et tumor cum calor et dolore," redness and swelling with heat and pain.[1–3] Centuries lapsed until John Hunter postulated that inflammation provides a survival mechanism to preserve the host. Ironically, he commented that an exuberant inflammatory response could be deleterious.

This is all too true, as the pathologic sequelae of excessive inflammation (i.e., ARDS, MODS) are encountered ever more frequently as technology affords survival of the initial insult.[1–3] The 19th century witnessed milestone contributions to our understanding of this process, as Rudolph Virchow detailed the cellular pathology of inflammation, Julius Cohnheim provided microscopic details of the acute phases of inflammation (vasodilatation, edema formation, and leukocyte emigration), and Elie Metchnikoff described the events of phagocytosis.[1,4,5] The integration of these new data created a novel paradigm of cellular and humoral concepts of inflammation, both of which were deemed critical in host defense against foreign pathogens.

In the 20th century, technologic advancements in molecular biology and biochemistry facilitated more detailed investigation and enabled the rapid expansion of knowledge of the many interwoven facets of inflammation. Evidence began to accumulate that the ramifications of these processes extended beyond the regional confines of the inciting insult. Many humoral mediators, in addition to local effects, influenced distant targets as well, such as the liver and neurohormonal centers. Recently we have come to appreciate that the immune system, endocrine system, and nervous system comprise a singular collaborative network sharing similar mediators and their cognate receptors. Such an integrative view, introduced by J. Edwin Blalock, when combined with Hans Selye's concept of stress, led to the contemporary understanding of sickness behavior, defined by Robert Dantzer as a highly organized strategy of the organism to fight infections and to respond to other environmental stressors. Hence, what originated nearly 2 millennia ago as a simple concept founded upon a constellation of signs and symptoms now is considered an intense, coordinated interplay of the nervous, vascular, endocrine, and immune systems to any injurious insult. It is the culmination of millions of years of evolution, and without it, life would be an arduous, painful, and brief existence, at best.

INNATE VERSUS ADAPTIVE IMMUNITY

1 Innate immunity, a system comprised of both cellular and humoral components, "stands" in anticipation of and prepared to respond to any stimulus and provides our initial security against invading microbes.[6]

Evolutionarily conserved across phyla, it notably provides the primary defense mechanism for invertebrates, as well. The response is typically uniform and consistent with each successive infection, though recent data suggest that like the adaptive arm, it too can "learn," or rather, "be trained."[7,8] Subsequent reinforcement is provided by the more specific and targeted efforts of the adaptive immune system, which mounts responses of increased magnitude and defensive capabilities with each successive insult.[6] This exquisite specificity for individual microbes, the capacity to "learn," "remember," and modify subsequent responses to repeated exposures, has provided the impetus for the name; though as aforementioned, the term "innate immune memory" has been adopted by the scientific community.[8]

CELLULAR COMPONENTS

Neutrophils

Neutrophils are integral to both innate and humoral immunity, providing the initial defense against invading viral, bacterial, and parasitic pathogens. This vital contribution is highlighted by the fact that 55% to 60% of hematopoietic output is the production of neutrophils.[9] On exiting the marrow, neutrophils circulate for approximately 7 to 10 hours and then emigrate into the tissues where they reside for an additional 1 to 2 days (**Table 7.1**).[10,11] Upon sensing minute concentration gradients of microbial products and inflammatory mediators, they rapidly accumulate to the site of infection to ingest and dispose of a wide array of pathogens with their vast microbicidal armamentarium. This pathogenicity, however, carries with it an implicit capacity for host injury and accordingly, neutrophil function must be tightly regulated.

Recruitment

Neutrophil recruitment, conceptually, is a sequence of events progressing from (1) initial adhesion to activated endothelium, to (2) subsequent extravasation and emigration toward the inflammatory focus, to (3) the ultimate elimination of foreign microorganisms through phagocytosis, the

generation of reactive oxygen species (ROS), and the release of antimicrobial substances.[6]

After injury or microbial invasion, hyperemia as a consequence of local and regional vasodilation facilitates the delivery of leukocytes to the focus of injury. Extravasation of plasma creates edema, and in combination with the release of vasoactive substances leads to hemoconcentration, which promotes the peripheral margination of leukocytes.[12,13] Circulating neutrophils transiently interact with the endothelial cell surface molecules during a process called "rolling" that involves a series of loose and reversible attachments between the neutrophil and endothelium (**Fig. 7.1**). These interactions are prerequisite to subsequent tighter cell–cell interactions, mediated by the family of selectin receptors, which bind with their counterligands, the sialyl Lewis family and other fucosylated and sulfated structures. E-selectin and P-selectin are present on endothelium and L-selectin is found on leukocytes.[6]

In response to a variety of inflammatory mediators (thrombin, histamine, complement fragments, oxygen species, lipopolysaccharide [LPS], and cytokines such as IL-1, TNFα and IFNγ), the endothelium expresses P- and E-selectin, which binds to the cell surface glycoprotein P-selectin glycoprotein ligand 1 (PSGL-1) or sialyl Lewis of neutrophils. Endothelial cells also translocate ligands for neutrophil L-selectin and release mediators like platelet-activating factor (PAF) and IL-8. Cytokines such as TNFα, granulocyte-macrophage colony-stimulating factor (GM-CSF), and G-CSF increase the affinity of leukocyte L-selectin for its counterreceptor. In addition to mechanical anchorage, these selectins induce signal transduction pathways that influence subsequent cell function. P-selectin facilitates neutrophil degranulation and superoxide production, and cross-linking L-selectin primes the neutrophil for increased superoxide production.[14–16]

After rolling, L-selectin is rapidly shed in preparation for leukocyte diapedesis and emigration into the interstitium (**Fig. 7.1**). The receptors mediating this process are members of the β_2-integrin family: leukocyte function antigen 1 (LFA-1, CD11a/CD18) and Mac-1 (CD11b/CD18); the expression of which is enhanced by prior selectin binding. Both integrin receptors engage the intercellular adhesion molecules ICAM-1 and ICAM-2; yet, each provides additional important functions. Leukocyte emigration is

primarily an LFA-1-dependent process, as mice deficient in this receptor exhibit reduced neutrophil attachment to ICAM-1 and endothelial cells. By contrast, mice lacking Mac-1 demonstrate impaired degranulation, superoxide production, and phagocytosis. Mac-1 also binds fibrinogen, heparin, and factor X and is implicated in neutrophil phagocytosis-induced apoptosis, a process essential for resolution of the inflammatory process (*vida infra*). The very late antigen 4 (VLA-4) binds vascular cellular adhesion molecule 1 (VCAM-1) and may provide an additional mechanism for tight adhesion. In addition to providing mechanical anchorage, these receptors interact with the cytoskeleton and other structural proteins and signaling cascades and are thought to represent a *biochemical* link between the external environment and intracellular signal transduction cascades that induce a cellular phenotype more appropriate for the inflammatory environment (**Fig. 7.2**).[17–19]

Table 7.1 Leukocyte Subsets

Cell	Neutrophil	Monocyte	Lymphocyte	Eosinophil	Basophil
Size (μm)	13	16–20	9–16	12–16	15
Differential (%)	40–75	2–6	20–45	1–6	<1
Life span	6 h to 7 d	1 d to years	Months to years	8 to 12 d	1 year
Activators	G-CSF, IL-8	M-CSF, GM-CSF, IFNγ, TNFα	IL-2, IL-12 (T_H1), IL-4 (T_H2)	G-CSF, IL-5	G-CSF, IL-3

(G, M)-CSF (granulocyte, monocyte) colony-stimulating factor; IL, interleukin; T_H, helper T cell; TNF, tumor necrosis factor.
Modified from Burkitt G, Young B, Heath JW, eds. *Wheater's Functional Histology: A Text and Colour Atlas*. 3rd ed. Edinburgh, New York: Churchill Livingstone; 1993.

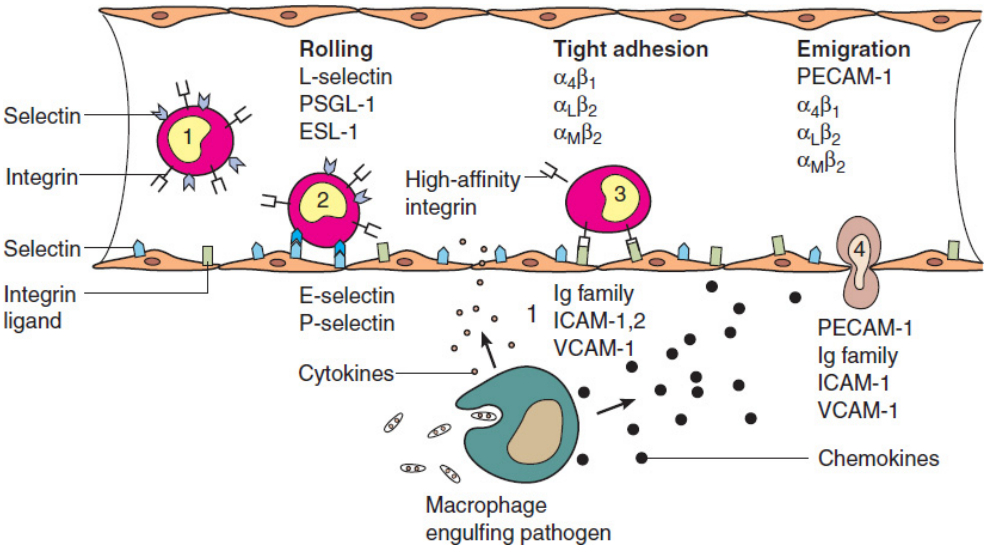

Figure 7.1 Leukocyte recruitment. **1.** Circulating leukocytes express integrins in a low-affinity conformation. **2.** Exposure to activated endothelium leads to rolling, which is mediated by L-selectin and P-selectin on the neutrophil and E-selectin on endothelium. **3.** Leukocyte exposure to cytokines released by macrophages phagocytosing pathogens induces a high-affinity integrin conformation integrins. Tight leukocyte-endothelial adhesion involves integrin engagement with counterligand expressed on the endothelium. **4.** Subsequent exposure to chemokines leads to diapedesis, which is further mediated by the family of β_1 and β_2 integrins. (Redrawn from Abbas AK, Lichtman AH. *Cellular and Molecular Immunology*. Philadelphia, PA: Saunders, 2003.)

Now tightly adhered, neutrophils must diapedese between endothelial cells and across the basement membrane on their trek toward the focus of inflammation. Platelet/endothelial cell adhesion molecule 1 (PECAM-1) and integrin-associated protein are integral to transmigration (**Fig. 7.1**).[17,18,20,21] PECAM-1 is concentrated along the intercellular junctions of endothelial cells, and both leukocyte and endothelial PECAM-1 appear to be essential for neutrophil and monocyte diapedesis. Other candidate receptors include the β_1 integrins, or VLAs, which possess affinity for many constituents of the extracellular matrix, including laminin, fibronectin, and collagens, the β_3 family of integrins including the glycoprotein (gp) IIβIIIα and the vitronectin receptor.[6] Further "directions" for migration to the focus of inflammation are delivered by the concentration gradients of chemotactic factors; examples include, complement C5a, IL-8, LTB_4, and the bacterial product fMLP.[22–24]

The clinical significance of even minor derangements in any aspect of this process is evident in the disease leukocyte adhesion deficiency, characterized by complete absence of CD18, and therefore all β_2 integrins. Patients usually succumb to recurrent skin and mucosal infections within the initial 10 years of life.[6]

Phagocytosis

Upon initial encounter with a foreign pathogen the neutrophil readies the "machinery" for microbial elimination. Phagocytosis is facilitated by opsonization, a process in which microbes are bound by immune globulins and complement and by subsequent binding to their cognate cell surface receptors, FcγRs and Mac-1, are rendered more accessible to the neutrophil.[25–27] Neutrophils constitutively express low-affinity immune globulin receptors FcγRII and FcγRIII and can be induced to express high-affinity FcγRI by incubation with IFNγ or cross-linking β_2 integrins.[9,28] Complement-dependent phagocytosis is mediated by interactions between the leukocyte Mac-1 receptor and the complement opsonin iC3b.

Once engaged, FcγRs are phosphorylated on tyrosine residues within an immunoreceptor tyrosine activation motif (ITAM) by the Src-family kinases.[28] These phosphorylated sites serve as docking regions for a variety of proteins, in particular Syk. The importance of Syk is underscored by the observation that mice deficient in Syk are incapable of ingesting IgG-opsonized particles. A series of enzymes are subsequently activated including phosphoinositol 3-kinase, phospholipase C, and protein kinase C. Ultimately, the actin cytoskeleton undergoes rearrangement and the local plasmalemma is remodeled as the phagosome is formed and physically excluded from the external environment.[6,28]

This immature phagosome undergoes a series of maturation steps, whereby it acquires the machinery necessary for the killing and disposal of internalized microorganisms. Alterations in cytosolic calcium concentration induce the fusion of secretory vesicles and granules containing the microbicidal armamentarium with the immature phagosome.[28] Proteins effected by calcium concentration and that may govern phagosomal maturation include synaptogamins, actin, calmodulin, and the Src family of kinases.[28] The SNARE (soluble N-ethylmaleimide-sensitive-fusion-protein

attachment protein receptor) proteins are thought to assist in fusion by engaging cognate receptors on the target membrane and approximating the two membranes. Antibodies to the SNARE 5 syntaxin 6 and SNAP-23 inhibited exocytosis of azurophilic and specific granules, respectively.[28]

Neutrophil Granules and Secretory Vesicles

Neutrophils exhibit an oxygen-dependent "respiratory burst" pathway that generates toxic oxygen derivatives and an oxygen-independent pathway that utilizes toxic proteinases.[29] These two microbicidal arms are compartmentalized into four distinct granules or vesicles (**Table 7.2**).[30] They are mobilized in a hierarchical fashion in response to gradual elevations in the intracellular calcium level.[31] They also contain adhesion molecules and important inflammatory mediators that help further orchestrate the involvement of other cells.

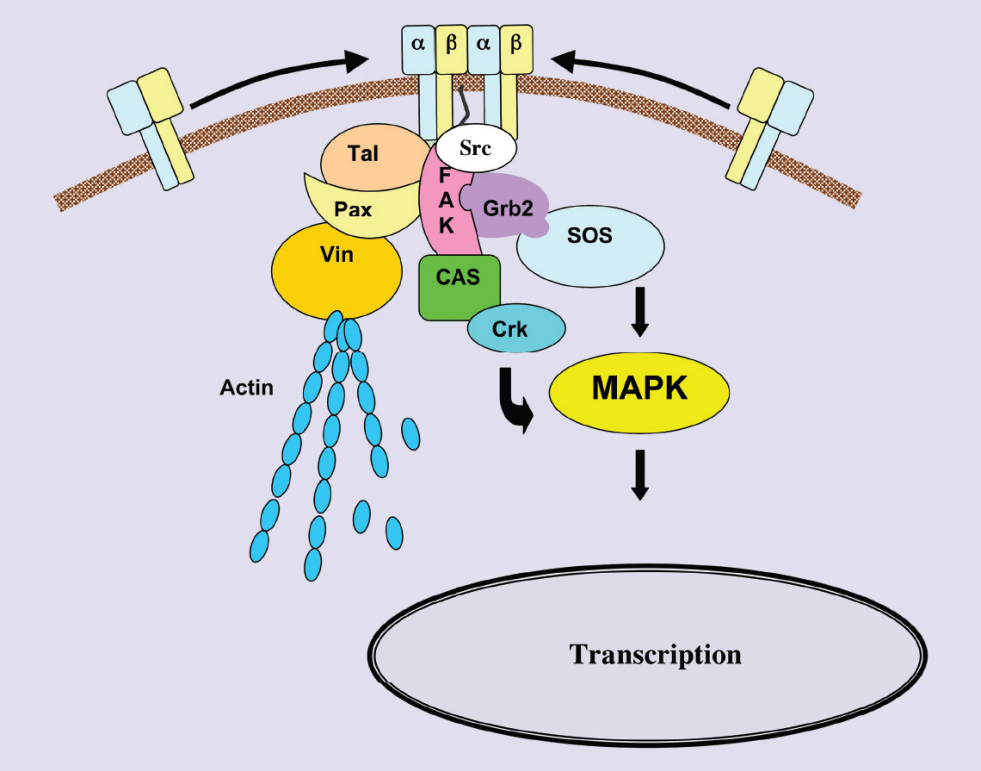

Figure 7.2 Integrin signaling. Integrins comprise a large family of cell surface receptors that are composed of two subunits, α and β, and are activated by dimerization. The cytoplasmic tails are devoid of enzymatic activity, and hence, signal transduction is effected by adaptor proteins that connect the receptor to the cytoskeleton, cytoplasmic kinases, and transmembrane growth factor receptors. As integrins bind the extracellular matrix they become clustered and associated with the cytoskeletal proteins talin, paxilin, and vinculin and signaling complexes. Actin stress fibers form, which increase integrin clustering. Ultimately, focal adhesion kinase (FAK) is recruited via interactions with talin and paxillin or with the β-integrin subunit. Subsequent autophosphorlyation on tyrosine 397 provides a binding site for the Src homology 2 (SH2) domain of Src. The Src kinase phosphorylates a number of focal adhesion components including paxillin and tensin and pl30CAS, a docking protein that recruits Crk, which can subsequently activate proximal elements in the JNK cascade of the MAPK family. FAK may also be phosphorylated by Src on tyrosine 925, creating a binding site for the complex of the adaptor Grb2 and Ras guanosine 5'-triphosphate exchange factor mSOS. These interactions also lead to activation of MAPK cascades, and ultimately the induction of a variety of genes. (Redrawn from Giancotti F, Ruoslahti E. Integrin signaling. *Science* 1999:1028–1032.)

Primary, or azurophil (affinity for the dye azure A) granules (**Table 7.2**). Myeloperoxidase (MPO) within these granules generates hypochlorous acid (HOCl) from products generated by NADPH oxidase; this is what imparts the characteristic greenish color of pus.[13,31] Other major constituents include

(1) α-defensins, cytotoxic proteins that scaffold into transmembrane pores within the microbial cell wall and perturb the maintenance of vital transmembrane gradients, and (2) bactericidal/permeability-increasing protein (BPI), which binds to gram-negative organisms and induces rearrangement of membrane lipids and inhibits growth.[31–34] Elastase cleaves constituents of the extracellular matrix, including proteoglycans, collagen (types I, III, IV), and fibronectin and, of course, elastin.[35] Azurocidin is chemotactic for monocytes and stimulates LPS-induced release of IL-6 and TNFα from monocytes.[6,31]

Specific granules are rich in antimicrobial substances that are released extracellularly (**Table 7.2**).[30] Lactoferrin, by sequestering iron, inhibits bacterial growth and can bind bacterial cell membranes and induce irreversible membrane damage and lysis.[31] Phospholipase A_2 (PLA_2) degrades bacterial membrane phospholipids. Lysozyme, present in all granules, is a cationic antimicrobial peptide that cleaves peptidoglycan polymers of bacterial cell walls. Gelatinase and collagenase are other extracellular matrix degrading enzymes.[31] These granules also possess receptors for a variety of extracellular matrix proteins and cell surface ligands (i.e., β_2-integrin Mac-1) that strengthen neutrophil adherence to the endothelium. In addition to the mechanical function of cellular anchorage, engagement of these receptors with their respective counterligands induces phenotypic alterations such as degranulation and enhanced ROS production.[6,31]

Table 7.2 Neutrophil Granules and Secretory Vesicles

Azurophil Granules	Specific Granules	Gelatinase Granules	Secretory Vesicles	
Myeloperoxidase (MPO)	Lysozyme	Gelatinase	Plasma proteins	M
Lysozyme	Phospholipase A_2	Lysozyme		E
Cathepsins	Gelatinase	β_2-microglobulin		M
Elastase	Collagenase	Acetyltransferase		B
Proteinase 3	Lactoferrin			R
Azurocidin	TNF			A
BPI	β_2-microglobulin			N
Defensins	Histaminase			E
iNOS	Heparinase			
α1-antitrypsin	uPA			
α-mannosidase				
Sialidase				
Acid mucopolysaccharide				
β-glycerophosphatase				
Elastase				
CD63	Mac-1	Mac-1	Mac-1	C
CD68	SNAP proteins	SNAP proteins	SNAP proteins	Y
	CD15	Cytochrome b558	Cytochrome b558	T
	CD66	fMLP R	CR1	O
	CD67	DAG-deacylating enzyme	CD14	S
	Cytochrome b558	uPA R	CD45	O
	Fibronectin R		fMLP R	L
	Laminin R		uPA R	
	Vitronectin R		C1q R	
	Thrombospondin R			
	fMLP R			
	uPA R			

BPI, bactericidal/permeability-increasing protein; CD, cluster of differentiation; CR1, complement component C3b; fMLP, N-formylmethionine-leucyl-phenylalanine; iNOS, inducible nitric oxide synthase; R, receptor; uPA, urokinase-type plasminogen activator.
Modified from Faurschou M, Borregaard N. Neutrophil granules and secretory vesicles in inflammation. *Microbes Infect* 2003:1317–1327.

Gelatinase granules contain matrix metalloproteases, zymogens that upon proteolytic activation degrade the interstitial matrix including collagens, fibronectin, proteoglycans, and laminin; this may facilitate neutrophil extravasation and migration (**Table 7.2**). They too are a source of cell surface adhesion molecules.[6,31,34]

Secretory vesicles are dense with the β_2 integrins LFA and Mac-1, the complement receptor (CR1), the LPS receptor CD14, and the FcγRIII. Through fusion with the plasmalemma, the cell surface is enriched with these receptors, which facilitates firm neutrophil-endothelial engagement, leukocyte recruitment, and the capacity to respond to a variety of stimuli.[6,31] Not surprisingly, because of the essential nature of leukocyte recruitment, secretory vesicles possess the lowest threshold for release and are released

earliest, followed by gelatinase, specific, and azurophil granules (**Table 7.2**).[31]

Oxidative Burst and Oxidant Metabolites

The generation of toxic oxygen metabolites and ROS is the cardinal characteristic of the neutrophil, though is also a defensive quality of the monocyte/macrophage. Their essential antimicrobial properties are equally destructive to host tissues and implicated in the pathophysiology of many inflammatory disorders (**Table 7.3**). Thus, a delicate balance must be maintained between ensuring elimination of the offending pathogen and minimizing host damage.

A free radical is any species possessing one or more unpaired electrons. They are categorized under the broader term ROS or reactive nitrogen species (RNS), which encompasses all molecules capable of radical formation. Despite a very brief existence (10^{-11} to 10^{-6} seconds) extensive damage may occur through the induction of free radical chain reactions. Species underlying both physiologic and pathophysiologic inflammation include the following: the superoxide anion ($O_2^{\bullet -}$), the hydroxyl radical (•OH), hydrogen peroxide (H_2O_2), the singlet oxygen, and the reactive nitrogen intermediates nitric oxide (NO), and peroxynitrite ($ONOO^-$) (**Table 7.3**). Counterintuitive to their role in microbial killing and tissue injury, recent data also support as an intracellular signal.[36] In the context of signal transduction, ROS modulate the immune response by activating neighboring inflammatory cells and inducing cytokine secretion.[37,38]

Numerous regulatory mechanisms provide temporal and spatial control of the ROS production. The NADPH oxidase complex itself exists in a disassembled state, and only upon cell activation and the need for ROS production, are the subunits approximated to enable enzymatic function.[39] In addition, high plasma and tissue concentrations of proteinase inhibitors provide continuous surveillance and systemic control. However, such regulation is incomplete as evidenced by such diseases as rheumatoid arthritis, chronic obstructive pulmonary disease, and autoimmune vasculitis, which are the consequence of damage due to neutrophil-derived products.[39]

NADPH oxidase is a heteromeric complex composed of six subunits: flavocytochrome b558, the electron-transporting apparatus comprised of

gp91(phox) and p22(phox); the cytosolic complex p40(phox), p47(phox) and p67(phox); and the oxidase factor rac-2 (**Fig. 7.3**).[39] Microorganisms or high concentrations of chemoattractants bind to cell surface receptors and initiate oxidase activation, heralded by phosphorylation of p47(phox). Cytochrome b558 (gp91 and p22), which exists within the plasmalemma and the membranes of specific granules and secretory vesicles, is recruited by phagocytosis and granule fusion. Phosphorylation of p47(phox) induces a conformation change that enables its incorporation within the membrane, where it facilitates the translocation of rac2 and p67(phox) and stabilizes the association of this cytosolic complex with cytochrome b558, thereby rendering the complex functional.[39]

Table 7.3 Major ROS and Their Metabolism

ROS Molecule	Main Sources	Enzymatic Defense Systems	Products
Superoxide ($O_2^{\bullet -}$)	Leakage from electron transport chain Activated phagocytes Xanthine oxidase Flavoenzymes	Superoxide dismutase Superoxide reductase	$H_2O_2 + O_2$ H_2O_2
Hydrogen peroxide (H_2O_2)	From $O_2^{\bullet -}$ via superoxide dismutase NADPH oxidase Glucose oxidase Xanthine oxidase	Glutathione peroxidase Catalase Peroxiredoxins	$H_2O + GSSG$ $H_2O + O_2$ H_2O
Hydroxyl radical ($O_2^{\bullet -}$)	From $O_2^{\bullet -}$ and H_2O_2 via transition metals		
Nitric oxide (NO)	Nitric oxide synthases	Glutathione/TrxR	GSNO

NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; TrxR, thioredoxin.

Modified from Nordberg J, Arner E. Reactive oxygen species, antioxidants, and the mammalian thioredoxin system. *Free Radic Biol Med* 2001:1287–1312.

At the redox center of the oxidase an electron is transferred from NADPH to oxygen, thereby generating superoxide.[40]

$$O_2 + e^- = O_2^{\bullet -}$$

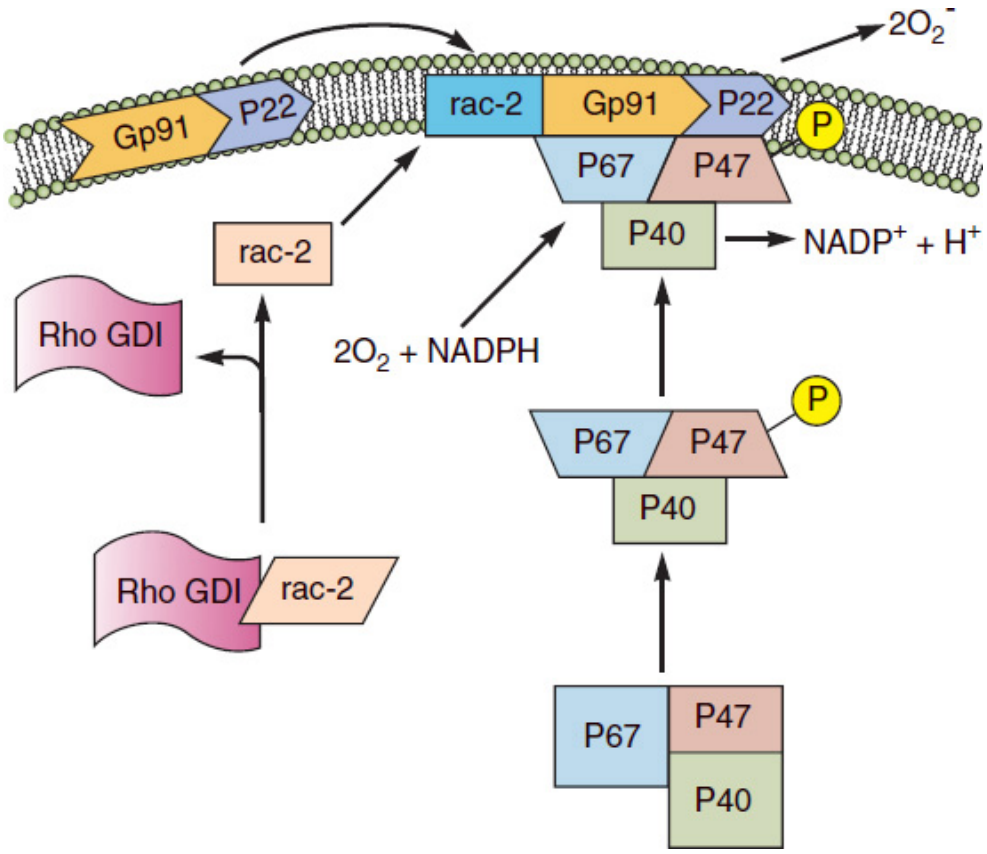

Figure 7.3 NADPH oxidase assembly. In the resting neutrophil, the cytochrome subunits gp91 and p22 are tightly bound in the membrane. P47(phox), p67(phox) and rac-s complex are in the cytosol. On activation, GDI releases rac-2, and p47(phox) becomes phosphorylated. This causes translocation of rac-2, p47(phox), and p67(phox) to the membrane and complex formation with the cytochrome components, thereby completing the assembly of the active oxidase. (Redrawn from Burg ND, Pillinger MH. *Clin Immunol* 2001;1:7–17.)

Other mechanisms of superoxide production include uncoupling of xanthine dehydrogenase system, uncoupling of mitochondrial and ER electron transport chains, and nonenzymatic reactions such as autooxidation of hemoglobin.[41,42]

Superoxide is relatively weak and of low bactericidal potency. However, its membrane permeability and role as a reactant in reactions yielding highly toxic products confers upon it a high potential for cellular and tissue

damage.[40] Superoxide can spontaneously or enzymatically (superoxide dismutase) dismutate into hydrogen peroxide.[39,40]

$$2H^+ + 2O_2\cdot^- \Leftrightarrow H_2O_2 + O_2$$

It can also be converted to the more potent hydroxyl radical through the metal-catalyzed Haber-Weiss reaction[39,40]

$$H_2O_2 + O_2\cdot^- + Fe^{3+} \Leftrightarrow O_2 + OH^- + \cdot OH + Fe^{2+}$$

or through the Fenton equation[39,40]

$$H_2O_2 + Fe^{2+} \Leftrightarrow Fe^{3+} + OH^- + \cdot OH + Hb\text{-}Fe^{2+} + H_2O_2 \Leftrightarrow Hb\text{-}Fe^{3+} + OH^- + \cdot OH$$

Under physiologic conditions, lactoferrin found in neutrophil-specific granules provides the iron catalyst for the Haber-Weiss reaction. In the Fenton reaction, superoxide or other reducing agents such as lactate or ascorbate donate electrons to generate the ferrous ions required to react with hydrogen peroxide to produce the hydroxyl radical.[39,40,43]

The hydroxyl anion is highly reactive and induces DNA strand breaks and base hydroxylations leading to ATP depletion and gene mutations. It can attack lipid side chains of membrane phospholipids to form hydrogen peroxide and lipid hydroperoxides in a process called lipid peroxidation. These products disrupt membrane function, serve as substrates for the production of cytotoxic aldehydes, and can uncouple calcium-ATPase thereby increasing cytosolic calcium concentration, which too is toxic. Recent data support a mechanism by which oxidation of critical sulfhydryl residues on the ryanodine receptors induces an “open” configuration and a leak of intracellular ER calcium into the cytosol.[44] This elevation of cytosolic calcium can activate calcium-dependent proteases and phospholipases that propagate cellular damage.[43]

Superoxide reacts with NO to produce peroxynitrite ($ONOO^-$) and hydroxyl radical.[40,45]

$$NO^\bullet + O_2\bullet^- \Leftrightarrow ONOO^- + H^+ \Leftrightarrow ONOOH \Leftrightarrow \bullet OH + NO_2\bullet$$

The hemoprotein MPO yields the potently bactericidal HOCl from the reactants chloride and H_2O_2. HOCl oxidizes amino acids, nucleotides, and hemoproteins, can activate neutrophil collagenases and permit unabated elastase injury by inhibiting α1-antitrypsin, and contribute to hydroxyl radical and singlet oxygen production.[37,43,46] Though short-lived, subsequent reactions with secondary amines generate secondary chloramines, which are equally toxic but much more stable. These metabolites can oxidize similar cellular components. They can combine with halide anions to generate toxic free halides or with taurine chloramines that induces MAC complement formation.[37,43,46]

In light of the central role of MPO during inflammation and pathogen elimination, it is surprising that MPO deficiency is common and relatively benign. Though MPO-deficient neutrophils show early depressed bacterial killing, bactericidal function normalizes within 60 minutes.[47] It is hypothesized that though bacterial killing is impaired, postphagocytosis oxidase-dependent neutrophil apoptosis is normal, resulting in appropriate regulation of the inflammatory response.[47]

Singlet oxygen, a highly reactive and extremely short-lived species, is formed by an input of energy to O_2 that reverses the spin direction of one of the outermost unpaired electrons away from a parallel spin. It is produced during reactions of the MPO-H_2O_2-halide system and is a potential product of superoxide dismutation and the Haber-Weiss reaction. It is highly electrophilic, reacting with compounds containing electron-rich double bonds and may react with membrane lipids to produce peroxides.[43]

The highly destructive potential of ROS, for both host, as well as, pathogen obligates continuous tight spatial and temporal regulation. The oxidase complex itself exists spatially disaggregated; only upon cellular activation are its constituents assembled and enzymatic function restored (**Fig. 7.3**).[39,47] As elegant and intricate as are the mechanisms by which ROS production is controlled, so too are the mechanisms by which these products are removed when no longer needed. Superoxide is eliminated by spontaneous and enzymatic (superoxide dismutase) dismutation to H_2O_2 (**Fig. 7.4**). H_2O_2 is subsequently reduced to oxygen and water by catalase.[40,43] In the extracellular environment, this function is performed by GSH peroxidase, a selenium-dependent enzyme that reduces H_2O while

oxidizing reduced GSH to its oxidized form. N-acetylcysteine (NAC) is a reducing agent that restores GSH and is used in the treatment of acetaminophen toxicity. More contemporary preclinical data support therapeutic utility in a variety of related inflammatory disease states. A systematic review concluded that NAC exhibits an ameliorative effect against obesity-related comorbidities, in part, by attenuating abnormal proinflammation and limiting oxidative damage.[48] Similar conclusions were reported of the protective effects of NAC against diabetes-associated cardiovascular complications by reducing oxidative stress.[49] NAC has also been shown to reduce hepatocellular injury in an animal model of warm liver ischemia/reperfusion.[36] Similarly purported mechanisms are invoked to support its prophylactic use in reducing contrast-induced nephropathy in patients undergoing iodinated contrast imaging procedures; however, equipoise persists in actual clinical efficacy.[50–52] Mechanisms of preventing hydroxyl radical-induced tissue damage include the binding of transition metal ions by albumin, ceruloplasmin, haptoglobulin, lactoferrin, and transferrin.[37,40,43] Taurine, an endogenous amino acid, is a scavenger for HOCl. It, in combination with its derivative taurolidine, is being investigated as an agent to reduce perioperative inflammation.[53] Other antioxidants that may assist in controlling the reaction include vitamins E (tocopherol) and C. Vitamin C has many antioxidant properties, including the ability to regenerate α-tocopherol. It can prevent activation of neutrophil-derived collagenase and is a powerful scavenger of HOCl, superoxide, singlet oxygen, and hydroxyl radicals. However, clinically, the recent CITRIS-ALI randomized trial of patients with sepsis and severe acute respiratory failure did not observe significant improvements in organ dysfunction scores or alterations in markers of inflammation and vascular injury in the cohort administered a 96-hour infusion of vitamin C compared with placebo.[54] Carotenoids have long double bonds to attract and sequester free radicals. Uric acid is a powerful scavenger of water-soluble radicals such as HOCl and singlet oxygen. It can also bind copper and iron ions to suppress hydroxyl radical formation. Stress proteins or heat-shock proteins (HSPs) are induced by oxygen radicals and ischemia and may play a role in defense. Furthermore, heme oxygenase-1 (HO-1) catalyzes the cleavage of heme to biliverdin, which is subsequently converted to bilirubin, an efficient free radical scavenger.[37,40,43]

All of the aforementioned participants of the NADPH oxidase are vital for health, as evidenced by those who suffer from chronic granulomatous disease (CGD).[39,47] These patients have deficient superoxide production and experience ineffective inflammatory reactions to infection. They commonly suffer from repeated bacterial infections (pneumonia, cutaneous abscesses and hepatic and perihepatic abscess, and osteomyelitis) by organisms that are catalase positive (*Staphylococcus aureus*). Organisms that produce large amounts of peroxide are less of a threat as the neutrophils can utilize bacterial peroxide to produce toxic metabolites. The use of prophylactic antibiotics and IFNγ has reduced the frequency of serious infections in this patient population.[39,47]

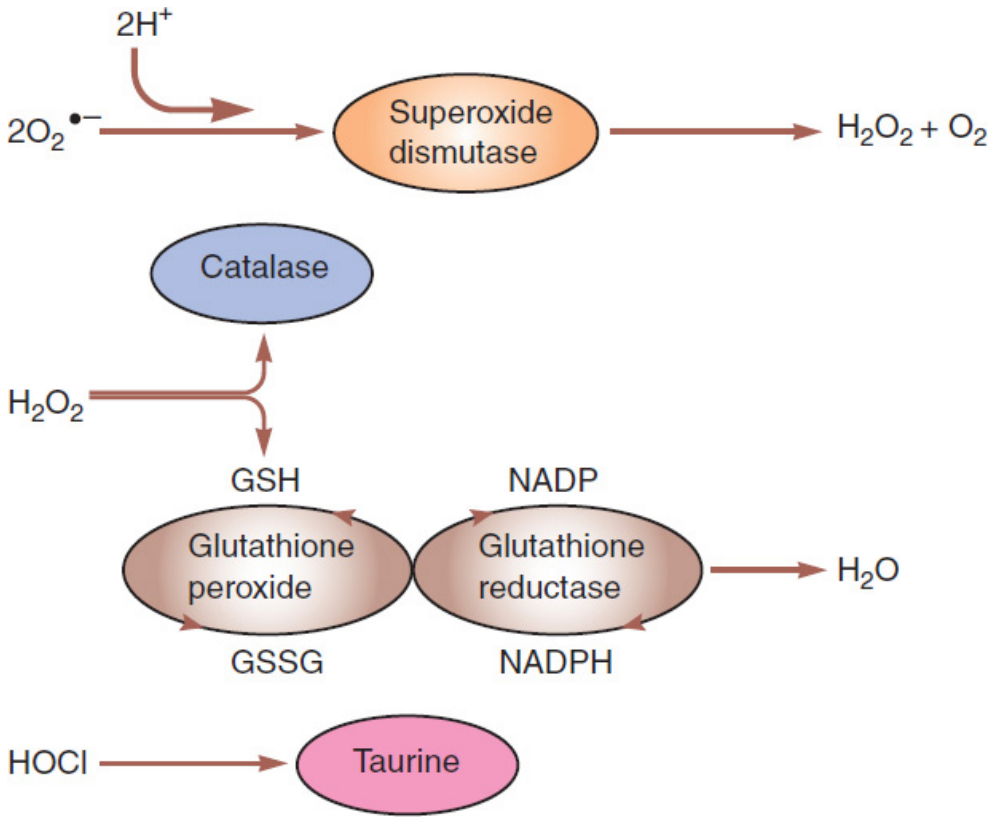

Figure 7.4 Scavengers of ROS. (Redrawn from Klebanoff SJ. In: Gallin JI, Snyderman R, eds. *Inflammation: Basic Principles and Clinical Correlates*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:723.)

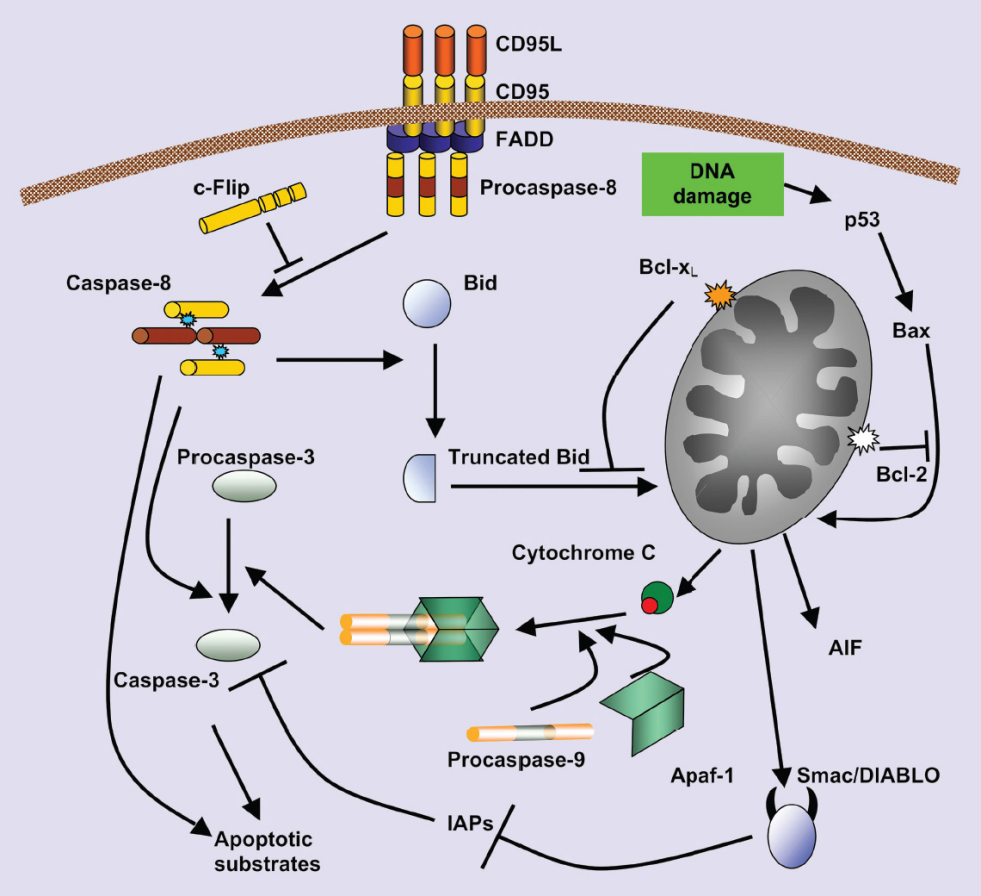

Figure 7.5 Apoptosis. Apoptosis is an integral component in the regulatory mechanisms that limit and resolve inflammation. Unlike cell necrosis, which is characterized by loss of membrane integrity, cellular edema and lysis, and release of intracellular products that incite an inflammatory reaction, apoptosis is a physiologic process of programmed cell death, characterized by DNA fragmentation and plasma membrane blebbing, with the compartmentalization of cytoplasmic and membrane particles into apoptotic bodies consisting of cytoplasmic and membrane fragments. Cytoplasmic contents are not released and consequently, an inflammatory response is not induced. Neutrophils are programmed to undergo apoptosis constitutively, and the signal transduction pathways culminating in apoptosis are activated early in acute inflammation. Subsequent neutrophil apoptotic particles are phagocytosed by resident macrophages. This is the preferred mechanisms for clearing neutrophils from inflammatory foci, and has also been implicated in the clearance of eosinophils, monocytes, and lymphocytes.

Apoptosis plays a prominent role in the immune system. Most developing T cells undergo apoptosis during the selection process in the thymus. Termination of the cellular immune response also involves cytokine-induced apoptosis. Apoptosis can be used by lymphocytes as a means of effecting death in other cells. CTLs kill target cells by inducing apoptosis via a Fas-induced pathway and a perforin- and granzyme-mediated pathway. Increased apoptosis has been observed in lymphoid tissues of patients dying of sepsis, suggesting that excessive lymphocyte apoptosis may contribute to fatal sepsis.

Inducers of apoptosis include oxidant stress, radiation, viral infection, trauma, and cytokines. Many of the pathologic agents that induce apoptosis at low concentrations can cause necrosis at higher concentrations. Apoptogenic stimuli activate the apoptotic pathway through both receptor-dependent and independent pathways. The sphingomyelin breakdown product, ceramide, is implicated as a transducer of apoptosis. DNA damage secondary to radiation or oxygen radical formation results in the accumulation of the tumor suppressor gene p53. p53 promotes non–receptor-mediated modulation of apoptosis.

Receptor-mediated pathways involve the "death receptors" that belong to the TNF receptor superfamily. Ligands shown to induce apoptosis include FasL, TNF, TNF-related apoptosis-inducing ligand (TRAIL), nerve growth factor, and CD40L. The best-characterized death receptors are Fas bound by FasL and TNFRI bound by TNF and lymphotoxin a. Although primarily produced by macrophages, TNF is expressed on many cell types, whereas FasL is restricted to the surfaces of CTL, macrophages, and neutrophils. TNF and FasL also differ in that FasL directly activates a cell death pathway, whereas TNF does so indirectly and concurrently stimulates pathways that inhibit apoptosis. Independent and divergent proinflammatory signaling pathways by TNF lead to the induction of NFKB, an inhibitor of apoptosis. The mechanism by which several cytokines, including IL-1, IL-6, and GM-CSF, inhibit apoptosis is through induction of NFKB and apoptosis is one of many factors that ultimately determine the cell's fate.

Ligation of death receptors recruits "death domain" containing adaptor proteins that interact with the receptor's intracellular death domain. This interaction initiates the enzyme cascade responsible for apoptosis effector mechanisms, the caspases. All signaling pathways converge on the activation of cysteine proteases related to IL-1/3 converting enzyme called caspases. Caspases propagate apoptotic signaling by cleaving/activating other caspases, and eventually execute terminal events in apoptosis by cleaving specific target proteins. Caspases 8 and 10 activate apoptosis signaling by linking Fas-associated death domain protein (FADD) with the caspase cascades. Caspases 3 and 7 are the executor molecules in the nucleus that cleave death substrates, including nuclear structural proteins, protein kinases, and proteins involved in cell cycle regulation or DNA fragmentation. Cytochrome C release from mitochondria is a key component in the activation of caspases. Cytochrome C release, and therefore apoptosis, is inhibited by Bcl-2, the primary death protection protein that belongs to the Bel family of pro- and antiapoptotic proteins involved in the regulation of apoptosis. CD95L binds CD95, induces receptor clustering and the formation of a death-inducing signaling complex. This complex recruits, through the adaptor molecule Fas-associated death domain (FADD) protein, procaspase-8, resulting in caspase-8 activation; this event can be blocked by the caspase homologue c-FLIP. These diverse response pathways converge on mitochondria, often through the activation of a proapoptotic member of the Bcl-2 family. Unlike Bcl-2, which is primarily membrane-associated, Bax, Bad, Bim, and Bid, can shuttle between the cytosol and organelles. Proapoptotic signals redirect these proteins to the mitochondria. Proapoptotic and antiapoptotic Bcl-2 family members converge on the mitochondrium to compete to regulate cytochrome c exit. If the proapoptotic camp wins, an array of molecules is released from the mitochondrial compartment. Principal among these is cytochrome c, which associates with Apaf-1 and then procaspase-9 to form the apoptosome. The death receptor and mitochondrial

pathways converge at the level of caspase-3 activation. Caspase-3 activity is antagonized by the ZAP proteins, which themselves are antagonized by the Smac/DIABLO protein, integration between the death receptor and mitochondrial pathways is provided by Bid, a proapoptotic Bcl-2 family member. Caspase-8–mediated cleavage of Bid greatly increases its prodeath activity, and results in its translocation to mitochondria, where it promotes cytochrome c exit. (Redrawn from Hengartner MO. The biochemistry of apoptosis. *Nature* 2000;407:770–776.)

Neutrophil Extracellular Traps (NETs) and NETosis

The antimicrobial weapons possessed by neutrophils to fulfill the task of pathogen elimination are vast. To this arsenal another distinct "weapon" has been described: NETs. NETosis is a process in which neutrophils extrude a lattice of chromatin and histones; it is postulated that this functions to entrap invading pathogens, which are then killed. The characteristic feature is the presence of neutrophil nuclear DNA in the extracellular space. Attached to this DNA backbone is an array of microbicidal agents that are typically compartmentalized inside the azurophilic, specific and gelatinase granules: neutrophil elastase (NE), cathepsin G, and MPO. Distinct from apoptosis, the process does lead to cell death, though clearly contributes to pathogen control. It is conserved in various vertebrates, insects, and even plants. Several microorganisms exhibit mechanisms of resistance to NETs, which may be additional evidence highlighting the importance of this process.

Pathogens (i.e., bacteria, fungi, viruses, and protozoa) and their subcellular components, such as LPS, M1 protein, and fMLP induce NET formation. Similarly, sterile insults, inflammatory stimuli (e.g., PAF, IL-8, TNFα, HMGB1, NO), and chemical compounds (PMA, ionomycin) all can stimulate NETosis. The process begins with engagement of the aforementioned stimuli with TLRs, Fc receptors, cytokine, and CRs located on the neutrophil cell surface. Subsequent calcium release stimulates PKC activity and assembly of functional NADPH oxidase, leading to ROS and NO production. ROS are requisite for NET formation, as antioxidant scavengers (e.g., N-acetylcysteine) attenuate the process. Interestingly, individuals with CGD, a disease characterized by insufficient ROS production, inefficiently produce NETs. The chromatin undergoes decondensation followed by mixing of nuclear and cytoplasmic components with granulate antimicrobial contents. Plasma membrane rupture ensues with the release of chromatin decorated with granular proteins into the extracellular space.[55–57]

NETs are able to trap almost all pathogens, including those too large to be phagocytosed. Indeed, it is proposed that trapping by NETs is one of the most important functions that limits microbial spread. The antimicrobial functions of NETs are mediated by the microbicidal compounds accompanying the chromatin: NE, MPO, histones, cathepsin G, proteinase 3, lactoferrin, calprotectin, and antimicrobial peptides such as defensive or the cationic LL37. However, the histones H1, H2A, H2B, H3, and H4 themselves also possess powerful antimicrobial and proinflammatory effects.

As fundamental as NETosis is for microbial defense, recent data suggest that excessive NETosis or ineffective NET clearance may underlie several pathologic conditions or syndromes characterized by excessive inflammation, including autoimmunity, cancer, and thrombosis.[55–57] Furthermore, methods of dissolving NETs (e.g., DNAase) may offer therapeutic utility.

During acute lung injury (ALI) a high concentration of stimulating factors promotes NETosis and the release of neutrophilelastase, LL-37, and ROS, which may exacerbate injury. Cystic fibrosis is characterized by peribronchial neutrophil infiltration and an inflammatory response that includes both upper and lower airways. Studies show that neutrophil cytotoxins, NETs and high concentrations of extracellular DNA are thought to underlie the high mucus viscosity and are associated with increased mucus clogging and lung injury in cystic fibrosis.[55–57] Degrading DETS appears to help manage CT airway disease.[58]

Several autoimmune diseases are also characterized by perturbed NETosis, and more than 70% of NET components are potent autoantigens, and the neutrophils from patients with various autoimmune diseases appear more prone to NETose.[55–57] NETs have been identified in rheumatoid arthritis, systemic lupus erythematosus (SLE) and antineutrophil cytoplasmic antibodies (ANCA)-associated vascularitis, psoriasis, and gout. In fact, an imbalance between NETosis and NET degradation may be a causal mechanism of autoimmune diseases themselves.[59,60] Small vessel vasculitis is characterized by ANCA reactive against PR3 and MPO. Externalization of IL-17 in the extracellular traps of neutrophils and mast cells is now thought to be central to the pathogenesis of psoriasis. In SLE, an imbalance between NET formation and clearance may underlie the systemic tissue damage that

occurs. In fact, decreased NET degradation correlates with renal disease. NETs may also activate complement, thereby amplifying the disease.

NETs may also serve as a link between inflammation and thrombosis. NETs are also rich in bioactive molecules that promote thrombosis and induction of NETosis is one mechanism by which antiphospholipid antibodies may cause thrombotic events in patients with antiphospholipid syndrome.[61] They can provide a stimulus and scaffold for thrombus formation by promoting platelet and RBC adhesion and by concentrating effector proteins and coagulation factors. Activated endothelium produces compounds that, upon contact with neutrophils, stimulate NETosis, which in turn, promotes endothelial damage.[55–57]

Regulation of Neutrophil Activity

In addition to the previously described mechanisms for controlling the inflammatory response of neutrophils, there is substantial evidence supporting the role of apoptosis in halting and 2 resolving neutrophil-derived inflammation (**Fig. 7.5**).[62] Within 90 minutes of phagocytosis, over 250 genes are induced, of which more than 30 encode proteins integral to at least three distinct apoptotic pathways.[62] These observations suggest that the mechanism-inducing apoptosis is initiated quite proximal in the inflammatory cascade, in fact, just subsequent to phagocytosis. The timely execution of a controlled cell death program in human PMNs is essential for preventing damage to healthy tissues and for the resolution of infection. Furthermore, evidence suggests that the phenotype of other immune cells, including monocytes and macrophages, is altered after encountering and phagocytosing apoptotic neutrophils. Thus, apoptotic neutrophil particles may function to downregulate the inflammatory function of neighboring cells. In some circumstances of infection or trauma, neutrophil apoptosis may be delayed, which might contribute to prolonged or a failure to resolve inflammation.

The inflammatory capacity of neutrophils is also transcriptionally regulated. Genes encoding proinflammatory mediators or signal transduction molecules such as receptors for IL-8, IL-10, IL-13 are downregulated early after activation and decrease rapidly after the initiation of apoptosis.[62] In addition, regulating oxidative stress and ROS achieve high priority as the genes involved in glutathione and thioredoxin metabolism and heme

catabolism are upregulated as is the production of reduced glutathione.[62] Hence, activation-induced apoptosis in neutrophils stimulates self-directed regulation, an event that likely facilitates removal of neutrophils by macrophages. As aforementioned, removal of apoptotic neutrophils by activated macrophages also appears to serve a role in modifying their function and halting the inflammatory response.

Mononuclear Phagocytes

Monocytes circulate for about 1 to 2 days, whereafter, they constitutively hone to a particular tissue (i.e., lung, peritoneum) to differentiate into macrophages possessing a phenotype specific to the resident tissue (dendritic cells [DCs] of the skin, Kupffer cells of the liver) (**Table 7.1**).[6,63,64] Resident macrophages are typically found at interfaces with blood (liver and spleen) and with lymph, where they can readily detect, ingest, and destroy invading organisms.[43] Mononuclear cells function as antigen presenting cells in T cell-mediated adaptive immune responses, presenting antigen in the appropriate context to effector T cells. They provide services integral to both innate and adaptive immune responses. Evidence also supports their role in providing an "alarm" both locally and systemically through the release of intracellular proteins (i.e., HMGB1, IL-1α) expressing damage-associated molecular patterns 3 (DAMPs) that can function as a danger signal (*vida infra*). Like neutrophils, circulating monocytes are generated through myelopoiesis in the bone marrow. At steady state these monocytes are characterized by cell surface markers. In humans $CD14^+$ monocytes are described as proinflammatory and rapidly egress into tissues under inflammatory conditions to become macrophages. $CD16^+$ monocytes are referred to as patrolling monocytes and remain in the circulation where they "patrol" and repair damaged endothelial cells. Under systemic stress as seen after trauma or sepsis, emergency myelopoiesis or demand adaptive myelopoiesis is induced and massive numbers of primed neutrophils and monocytes are released into the circulation.

Recruitment

Monocytes are recruited and emigrate to foci of inflammation utilizing similar mechanisms of adhesion and diapedesis as described for neutrophils (**Fig. 7.1**). PAF, C5a, the CC chemokines (i.e., MCP family members), RANTES, and MIP-1α, are potent monocyte-macrophage chemotaxins.[65,66] The selectin family of adhesion receptors mediates the initial tethering of monocytes to endothelial cells.[22] Firm adhesion to the endothelium involves the interactions β_1 and β_2 integrins on monocytes with the endothelial adhesion molecules ICAM-1 and VCAM-1.[22]

Phagocytosis

Phagocytosis involves the IgG receptor (FcγR) and the receptor for the complement factor C3b. Terminal sugar patterns on microbial surfaces also allow recognition by macrophages for nonspecific phagocytosis through the mannose lectin pathway.[26] However, phagosomal maturation differs from that which occurs in the neutrophil. Monocytes and macrophages have an endocytic pathway targeting the phagosome to a lysosome.[28] After endocytosis of a receptor–ligand complex, the contents of a vesicle are targeted to an early endosome; the ligand and receptor dissociate, and the receptor is then recycled to the cell surface.[28] This early endosome undergoes a series of maturation steps in which it is acidified (pH 5.5–6.0). This acidification is requisite for optimal protease and hydrolase activity involved in pathogen killing. It may also be integral for phagosome maturation as titrating the acidity inhibits phagosome-lysosome fusion.[28] Ultimately, the endosome fuses with a lysosome, which is characterized by its extreme acidity (pH <5.0) and elevated concentration of proteases.[28] Lysosomes are the terminal destination of phagocytosed material targeted for degradation.

After fusion, MPO released into phagosomes can react with hydrogen and halides to yield toxic hypohalous acids, superoxide anion, hydrogen peroxide, and hydroxyl radical (**Table 7.3**). Macrophages may also use peroxidase generated by adjacent neutrophils, eosinophils, and monocytes and acquired through endocytosis to generate these ROS. In addition to supporting the inflammatory response, macrophages also play an important immunoregulatory role in inflammation by scavenging apoptotic neutrophils at sites of inflammation.[43]

Activation

IFNγ derived primarily from T cells and innate lymphocytes (i.e., natural killer cells) is the primary activator of macrophages and yields what has been entitled "M1" macrophages; these are generalized as "inflammatory macrophages" and produce proinflammatory cytokines, phagocytose microbes, and initiate the immune microbicidal response. They also produce NO and ROS.[6,64,67] Optimal M1 macrophage activation requires both interferon IFNγ and a sensitizing agent (T_H1 4 activation), both of which can be provided by activated T lymphocytes. CD40 ligand on T cells can bind CD40 on macrophages to sensitize the cell. Alternatively, membrane-associated TNFα or lymphotoxin from lymphocytes can activate macrophage TNFα synthesis and thereby sensitize the macrophage to IFNγ.[43] IL-10 promotes monocyte maturation and macrophage differentiation.[68] Other activators include GM-CSF, TNFα, IL-1, and LPS.

Activated monocytes and M1 macrophages can produce approximately 100 different products, including GM-CSF, M-CSF, G-CSF, IL-1, TNFα, G-CSF, and NO.[43,69] Mononuclear phagocytes are important sources of chemoattractants such as IL-8, PAF, and leukotriene B_4 (LTB_4) that recruit neutrophils and other leukocytes. Their release of HMGB1 and other damage-associated molecular patterns (DAMP) molecules serves an endogenous "danger" signals to other immune cells in the local environment (**Table 7.4**). These bind to various pattern recognition receptors (PRRs) to alter cell function. However, systemic release of HMGB1 may also be causally related to mortality in such inflammatory states as sepsis and trauma.[70,71] The respiratory burst and subsequent production of toxic ROS mirrors that of neutrophils.

Alternatively, 5 exposure to IL-4, IL-10 or IL-13 (T_H2 activation) induces M2 macrophages. They produce low levels of proinflammatory cytokines, typically are not involved in antigen presentation or NO production. Through the high expression of arginase, M2 elaborate either polyamines to induce proliferation or proline to induce collagen production, and thus, are associated with wound healing and tissue repair. Recent metabolism studies have shown that alterations in the metabolic profile of macrophages shape their activation state and function; specifically, the plasticity of phenotype is postulated, in part, to be dictated by use or disuse

of oxidative metabolism. M1 macrophage metabolism is characterized by aerobic glycolysis, fatty acid synthesis and a curtailment in the tricarboxylic acid (TCA) cycle. Alternatively, the metabolic signature of M2 macrophages is characterized by fatty acid oxidation and a predominant use of oxidative metabolism for ATP generation. The teleologic purposes of these metabolic differences are likely many and varied, though include the use of metabolites in signal transduction, autocrine modulation of activation state, epigenetic modifications, and antimicobicidal properties.[72] This dichotomous characterization, though helpful, has come under scrutiny for its oversimplification of what is a more likely a spectrum of macrophage phenotypes. More advanced molecular techniques (e.g., single-cell RNA seq) suggest that in response to septic or sterile insult, several distinct monocyte/macrophage populations emerge, each with a distinct genomic signature and likely, function.

Table 7.4 Monocyte/Macrophage Products

Product	Functions
Enzymes	
Lysozyme	Antimicrobial
Urokinase	Plasminogen activation and fibrinolysis
Collagenase	Connective tissue degradation
ACE	Vasopressor
Cytokines	
IL-1	Multiple
TNFα	Multiple
Interferon α/β	Antiviral, immune modulation
IL-6	Acute-phase response
IL-10	Anti-inflammatory
IL-12, IL-18	Stimulate IFN γ production
IL-8	Neutrophil chemoattraction
FGF	Fibroblast growth
GM-CSF	Granulocyte, macrophage differentiation
MIP-1 α/β	Chemoattractant
MCP-1	Monocyte recruitment
RANTES	Monocyte/T_H cell recruitment
Complement proteins	Opsonization, complement activation
Coagulation Factors	Coagulation
Adhesion, matrix molecules Fibronectin, proteoglycan	Localization, migration
Transport proteins	
Transferring	Iron transport
B_{12}-binding protein	Vitamin transport
Bioactive lipids	
Cyclooxygenase	Inflammation
Lipooxygenase	Inflammation

PAF	Platelet activation
Reactive oxygen intermediates Superoxide, hydrogen peroxide Oxygen singlet	Antimicrobial
Reactive nitrogen intermediates NO, nitrates, nitrites	Antimicrobial
Defensins	Antibacterial

ACE, angiotensin-converting enzyme; FGF, fibroblast growth factor; GM-CSF, granulocyte/macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; MCP, membrane cofactor protein; MIP, macrophage inflammatory protein; NK, natural killer; PAF, platelet activating factor; RANTES, regulated on activation, normally T-cell expressed and secreted; TNF, tumor necrosis factor.

Modified from Gordon S. Development and distribution of mononuclear phagocytes: relevance to inflammation. In: Gallin Jl, Snyderman R, eds. *Inflammation: Basic Principles and Clinical Correlates*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

Antigen Presentation

T cells recognize only those antigens associated with surface MHC molecules. MHC class I molecules are expressed on all nucleated cells, whereas MHC class II molecules are restricted to antigen-presenting cells (APC). After phagocytosing pathogen, mononuclear cells process and display antigen to T cells, and in doing so, initiate the development of the adaptive response (i.e., antibody formation). There is evidence that the HSP receptor CD91 may also participate in this process (*vide infra*). This processed antigen is presented on the APC cell surface in the context of major histocompatibility complex (MHC) molecules that are specifically recognized by T-cell receptors (TCRs) and essential for T-cell activation. $CD4^+$ T cells, or helper T cells (T_H), recognize antigen coexpressed with MCH class II molecules and induce B cell differentiation into either memory or antigen-specific antibody-producing plasma cells. These T_H cells can also induce macrophage production of NO, ROS, and other inflammatory mediators. $CD8^+$ cytotoxic T lymphocytes (CTLs) recognize antigen in the context of MHC class I molecules and induce target cell lysis; they destroy host cells infected with intracellular pathogens or cells of malignant potential.[73] Activated mononuclear phagocytes release IL-12, a potent

stimulus for T_H cells and the production of inflammatory cytokines, and elaborate IL-15 the function of which mirrors that of IL-2.[74,75]

The three professional APC are DCs, macrophages, and B cells. DCs are a specialized APC, which process and present antigen to naïve T cells. Monocytes stimulated with GM-CSF, IL-4, or IL-13 differentiate toward DCs. Maturation of the DCs requires TNFα or LPS stimulation.[43] Epidermal Langerhans cells, after encountering antigen, migrate through the lymphoid organs and differentiate into mature DC. DCs are particularly effective at presenting viral antigen. They present antigen in the context of both MHC I and MHC II, and thereby induce both a T_H1 and T_H2 response, respectively. DCs can also present antigens derived from apoptotic cells in the context of MHC I.[76–78] Antigen presentation through MHC I activates $CD8^+$ lymphocytes to become cytotoxic.

Macrophages present antigenic peptides from ingested pathogens that persist in the phagosomes. These peptides, usually of bacterial origin, are expressed in conjunction with MHC II molecules. B cells, by contrast, bind specific soluble molecules (insect toxins, venom, and allergens) via immunoglobulin. This is endocytosed, processed, and presented on surface MHC II.[43,78–80]

Lymphocytes

B, T, and NK cells comprise this lineage of inflammatory cells (**Table 7.1**). B and T cells are central to the adaptive immune response, whereas NK cells lack antigen specificity and primarily function during innate immune response. NK cells are the first line of defense against many viral infections. The loss of surface expression of MHC class I molecules as occurs with virus-infected cells serves as a target for NK cells.[43,81] Alternatively, NK cells bind cell-bound antibody and participate in antibody-dependent cell cytotoxicity. Cells targeted by either mechanism are induced to undergo cell death.

B Lymphocytes

B cells, though of bone marrow origin, attain full maturation within extramedullary sites such as lymph nodes, the spleen, and the mucosal lymph

nodules of tonsils and Peyer patches. With activation, B cells differentiate into antibody-producing plasma cells, which through the elaboration of antibody, aid the neutralization of viruses and bacterial toxins, and facilitate opsonization for phagocytosis and complement activation.[6] Activation requires antigen binding to cell surface receptors and stimulation by T_H cell–derived cytokines; they do not need the assistance of APCs. Polyclonal B-cell activation can occur in a T-cell–independent mechanism if the antigen has a large repeating polymeric sequence.[43,82]

T Lymphocytes

Development of T lymphocytes begins within the marrow and is completed in the thymus. The final population profile is determined by apoptotic processes of both positive and negative selection.[83] Any protein or antigen of *host* origin is presented by APCs, and thymocytes reactive to these self-proteins are deleted.[84] Alternatively, expansion of cell lines recognizing foreign, or rather non–self antigen, occurs through positive selection. IL-7 provides the stimulation for proliferation and differentiation of developing T cells. Ultimately, two lines of mature cells, $CD4^+$ and $CD8^+$, will develop.[85]

Lymphocytes, the smallest of the leukocytes, constitute approximately 20% of circulating leukocytes.[6] Most circulating lymphocytes are T cells, and 60% of those are $CD4^+$, a marker of a T_H phenotype. The other 40% are $CD8^+$, called cytotoxic T cells, T_C. The normal ratio of $CD4^+/CD8^+$ is 2:1.[6] Lymphocytes continuously recirculate through lymph nodes, spleen, lymphatics, lymph nodules, and blood, providing continuous surveillance. Encounter with a particular antigen initiates activation toward an effector T cell. Activation of a T cell requires binding to its specific antigen plus a costimulatory signal provided by the interaction between costimulatory molecules on the APC and their cognate receptors on the T cell.[43]

Naïve T cells circulate continuously between blood and lymphoid organs, making contact with many APCs and the epitopes of the antigens they express.[86] Initially, lymphocytes enter the cortical region of lymph nodes by migrating across the high endothelial venules, a process mediated by the Selectin family of receptors. L-selectin, which is found constitutively on all lymphocytes, binds sialyl Lewis carbohydrate on the endothelium.[43] For example, L-selectin on lymphocytes binds GlyCAM-1 on the high endothelial

venules in lymph nodes. In mucosal tissues, L-selectin and endothelial MAdCAM-1 guide emigration. Migration across the endothelium requires integrins, in particular LFA-1 and its interaction with ICAM-1 and ICAM-2 on endothelial cells.[87] Most lymphocytes are carried back to the blood by the efferent lymphatics. If a T lymphocyte recognizes its specific antigen on the surface of an APC, it remains for several days, then returns to the blood as an armed effector T cell.[43]

Adhesion molecules mediate many of the transient interactions between T cells and APCs that are required for the T cell to sample each antigen it encounters. Lymphocyte LFA-1 can bind the APC in a loose, reversible fashion by any of the ICAM molecules on APCs. If a match between T cell and antigen is found, conformational changes in LFA-1 greatly increase its affinity for ICAM-1 and ICAM-2 to stabilize the interaction. The T cell can then proliferate and differentiate into an effector cell. Effector T cells lose surface expression of L-selectin and no longer circulate through lymphoid tissue. Instead they express VLA-4, an integrin, which binds vascular endothelium at sites of infection, and the cell is retained at the focus. Effector T cells have increased LFA-1 and CD2 adhesion molecule expression that facilitate tight binding to target cell.[88,89] Though a predominant purpose of integrins is cellular adhesion and the mechanical processes of cell recruitment, intracellularly they interact extensively with a variety of signal transduction pathways (e.g., mitogen-activated protein kinases [MAPKs]). Signals induced by and specific to components of the extracellular milieau to which the integrins are exposed (e.g., microbe, fibronectin) cultimate in changes to the cell phenotype, rendering it better suited for the "current" environmental conditions (i.e., microbe vs. sterile injury).

Antigen binding in the appropriate context provides the signal for clonal expansion and differentiation of T cells into effector and memory lymphocytes. The appropriate contact is comprised of antigen complexed with MHC class II molecules on APCs, costimulators, and cytokines produced by the APCs and by the T cells themselves. This first encounter of naïve T cells with antigen is the primary immune response, which serves to induce the formation of effector and memory T cells. These activated T cells hone to peripheral tissues where, upon reexposure to their specific antigen, they activate macrophages to eliminate phagocytosed microbes and induce B-cell differentiation and antigen-specific antibody secretion. The $CD8^+$ CTLs

kill infected host cells and tumor cells that display class I MHC associated antigen. Naïve T cells require activation by DCs, whereas effector T cells can respond to antigens presented by a wider variety of APCs, such as macrophages and B lymphocytes. Not surprisingly, differentiated effector and memory T cells possess lower thresholds for costimulation and require lower antigen concentration for activation than naïve T cells.

In general, antigen presented on MHC II molecules is the prototypical stimulus for $CD4^+$ T-cell activation and the subsequent production of a variety of cytokine mediators, including IL-2, which stimulate further expansion and activation. However, the circumstances under which this activation occurs may dictate disparate paths of differentiation, producing T-cell subsets with distinct cytokine profiles and effector functions. These differing phenotypes have been utilized to characterize two distinct subsets: T_H1 and T_H2.[74,75,90] IL-12 derived from phagocytes infected with intracellular pathogen provides the necessary signal for T_H1 differentiation.[43] IL-12 also stimulates production of IFNγ, the principal macrophage activator, by NK cells and $CD4^+$ lymphocytes. Interferons stimulate T_H1 development by augmenting phagocytic IL-12 production and by maintaining IL-12 receptor expression on $CD4^+$ T cells. The principal effector action of T_H1 cells is the activation of macrophages through the production of IFNγ, GM-CSF, TNFα, CD40L, and FasL.[43,74,75,90] They regulate production of opsonizing and complement fixing antibodies and are effectors of phagocyte-dependent responses. This inflammatory response, also referred to as cell-mediated immunity or delayed-type hypersensitivity, provides one major arm of the adaptive immune response; it is mediated by $CD4^+$ and $CD8^+$ lymphocytes and macrophages.

The principal stimulus for T_H2 differentiation is IL-4, which is derived from T cells, mast cells, and basophils.[74,75,90] These cells are the cellular effectors of humoral immunity and provide the other major arm of the adaptive immune response, which is mediated by T_H2 $CD4^+$ cells, B cells, plasma cells, and antibodies. They produce IL-4, IL-5, and CD40L, thereby inducing B-cell activation and antibody production, and a host of other proinflammatory and anti-inflammatory cytokines.[43] Activation of mast cells and eosinophils by extracellular pathogens is associated with activation of

T_H2 cells. T_H2 cells quell the inflammatory response by inhibiting macrophage functions and T_H1 responses. They are considered the anti-inflammatory arm of cell-mediated inflammation. Helper T cells that express both T_H1 and T_H2 patterns of cytokine expression have been called T_H0 cells, and further studies will certainly discern other subsets of T cells.[6,90]

T-cell activation, differentiation, and expansion are orchestrated by the T cell itself. The responding T cell, in an autocrine fashion, serves as both source and target of a variety of mediators stimulating growth. The principal autocrine growth factor is IL-2, which is induced by signaling regulated by the phosphatase calcineurin (*vida infra*).[91] IL-15 stimulates the proliferation of $CD8^+$ T cells, especially memory cells of the $CD8^+$ subset. After antigen exposure, the numbers of T cells specific for that antigen may increase to about 1 in 10 for $CD8^+$ and 1 in 1,000 to 10,000 for $CD4^+$ cells.[6]

After activation, some proliferating T cells will differentiate into effector cells that eliminate antigens and activate other immune cells. Mature $CD4^+$ cells induce the activation of mononuclear phagocytes and B cells. $CD8^+$ cells differentiate into CTL that recognize viral and other intracellular pathogen antigens that are presented in the context of MHC class I molecules and induce target cell death by releasing the cytotoxins perforin and granzymes from cytoplasmic granules. Granzymes are serine proteases that trigger DNA fragmentation and apoptosis. Perforin stimulates cell membrane pore formation that facilitates granzyme entrance into cells. Apoptosis can also be induced by the binding of Fas ligand on CTL to fas on the target cell. CTLs also release the cytokines IFNγ, TNFα, and CC chemokines. IFNγ and certain CC chemokines have antiviral properties, and both are potent activators of macrophage function. IL-2 produced by CTL and local helper $CD4^+$ lymphocytes expands the CTL, and IL-12 released by APC stimulates CTL activity. As with $CD4^+$ cells, early evidence suggests that the population $CD8^+$ may be divided into T_C1 and T_C2 cells based on their cytokine profiles and effector functions.[43,73–75]

Other T cells will mature into long-lived functionally quiescent memory cells. Upon antigen reexposure, a cell surface rich in adhesion molecules (i.e., integrins, CD44) facilitates rapid and efficient migration to peripheral sites of infection.[6] These cells accumulate over time and in the adult human comprise more than half of the circulating T cells.

Mere antigen exposure is insufficient for activation of naïve T cells. Proliferation and differentiation require costimulatory signals provided by molecules on APCs. The best characterized costimulator pathway involves the T-cell surface molecule CD28 and its counterligands B7-1 and B7-2 expressed on activated APCs.[6,43] CD28 delivers signals that enhance T-cell survival, by increasing expression of the anti-apoptotic protein Bcl-X, the production of cytokines such as IL-2 and the IL-2 receptor, and the differentiation of immature T cells. In vitro, purified populations of $CD4^+$ cells challenged with antigen by APCs that express B7, proliferate and secrete cytokines. This does not occur if B7 is absent. The costimulatory signal must come from the same APC that provides the initial signal. DCs are the most potent APC because they express both classes of MHC molecules and the B7 molecules, whereas macrophages and B cells must be activated to express the costimulatory molecules. This expression of costimulators is regulated so as to ensure that T-cell activation is temporally and spatially appropriate. For instance, during T-cell activation, engagement of CD40 ligand with CD40 induces upregulation of B7 costimulators on the APCs. In addition, it increases the secretion of cytokines such as IL-12 that promote T-cell differentiation, and cytokines are secreted that promote T-cell differentiation and activation. A protein CTLA-4, expressed on activated T cells, is homologous to CD28 and binds B7-1 and B7-2. Unlike CD28, CTLA-4 functions to terminate T-cell responses and plays a role in self-tolerance.

The differentiation of naïve $CD8^+$ T cells to CTL requires a stronger costimulatory signal. This can be provided by either DCs, as they have the greatest intrinsic costimulatory activity, or by a $CD4^+$ helper T lymphocyte. Naïve helper T cells attached to the same APC as the $CD8^+$ T cell can be activated to elaborate IL-2. Attached effector T helper cells stimulate the APC to express more costimulatory molecules. In the case of virulent viruses, cytotoxicity can substitute for CD28 costimulation, and so the typical costimulatory signal is not required for activation. For less virulent viruses, costimulation is necessary for CTL induction.[43,92] The absence of costimulation results in an unresponsive, or anergic T cell. This step has been shown to be mediated by the serine/threonine kinase calcium/calmodulin-dependent protein kinase (CaMK) II (see below).[93] Anergic T cells do not produce IL-2 and therefore cannot proliferate and

differentiate into effector cells even when presented with antigen at a later time.[43]

The affinity of most TCRs for peptide-MHC complexes is low, with dissociation constants on the order of 10^{-5} to 10^{-7} and an estimated TCR–antigen interaction of less than 10 seconds. Furthermore, on any APC fewer than 1,000 of the 10^5 available MHC molecules are likely to be displaying any one peptide at any particular time. Therefore, one APC can engage a small fraction of the 10^4 to 10^5 antigen receptors on a single T cell.[6] Activation of an individual T cell may require multiple sequential engagements of that cell's antigen receptors by peptide–MHC complexes on APCs. With engagement, there is clustering of membrane receptors, tyrosine phosphorylation of several proteins, and recruitment and activation of adaptor proteins.

TCRs are devoid of enzymatic activity and must utilize other proteins to effect signal transduction.[6] After TCR-MHC engagement, several membrane surface proteins and intracellular signaling proteins are rapidly recruited: TCR complex, CD4 or CD8, receptors for costimulators such as CD28, and enzymes and adaptor proteins.[6] After TCR clustering, activated tyrosine kinases associated with and phosphorylate tyrosine residues on CD3 and TCR (**Fig. 7.6**). These phosphorylation sites provide docking sites for other tyrosine and protein kinases, such as Lck, a Src family tyrosine kinase, and ZAP-70, a tyrosine kinase. These kinases become activated with phosphorylation. Activated ZAP-70 phosphorylates several adaptor proteins that subsequently induce a variety of signal transduction cascades. Adaptor proteins contain structural domains that bind other proteins and thereby facilitate the correct spatial orientation that is required for signal transduction. The ras pathway is also activated, which is an early step in the activation of the MAPKs that can activate a variety of transcription factors. Ras is a member of a family of guanine nucleotide-binding proteins (GDP/GTP) that are involved in diverse activation responses in different cell types. This pathway is an amplification process by which few upstream kinases lead to the activation of several downstream kinases. Ultimate activation of the terminal extracellular–regulated kinase (ERK 1/2) leads to the phosphorylation of the protein ELK, which stimulates the transcription of fos, a component of the activation protein 1 (AP-1) transcription factor (**Table 7.5**). Concomitantly, c-Jun N-terminal kinase (JNK) is activated,

which phosphorylates c-Jun, the second component of AP-1. The third member of the MAPK family, p38, is also activated. The activities of the MAPKs are terminated by specific protein tyrosine/threonine phosphatases that are regulated by the MAPKs themselves. Hence, the entire system is self-regulated by a negative feedback system.[6] From a clinical therapeutic standpoint, the anti-inflammatory properties of statins is postulated to be mediated, in part, by inhibition of GTPase isoprenylation and the secondary pathways they regulate in inducing immune cell activation.[94] A variety of clinical trials have been and are being conducted to determine the efficacy of statin therapy, or avoiding statin withdrawal, to mitigate inflammation, particularly in the context of cardiovascular disease.[95–99]

Activation of TCR also leads to the induction of phospholipase C (PLC), in particular PLCγ1 (**Fig. 7.6**). Phosphorylated PLCγ1 catalyzes the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PIP_2) into inositol 1,4,5-triphosphate (IP_3) and diacylglycerol (DAG), and activates enzymes that generate additional active transcription factors. IP_3 increases cytosolic calcium that leads to a large influx of both intracellular and extracellular calcium with subsequent activation of calcium- and calmodulin-dependent proteins. Calcineurin, a calcium/calmodulin-dependent phosphatase is integral to T-cell activation via modulation of the activation of the transcription factors NFATs and NFκB (**Table 7.5**).[4,19] These transcription factors are essential for the induction of cytokine transcription, in particular IL-2 production. However, in the absence of costimulation, activation of the CaMK II opposes the actions of calcineurin as described above and produces an anergic cell.[93] DAG activates protein kinase C, which activates additional transcription factors. Three transcription factors that are activated in T cells and appear critical for most T-cell responses are NFATs, AP-1, and NFκB (**Table 7.5**). Regulation of those kinases operant in T-cell signaling involves protein tyrosine phosphatases. Through dephosphorylation they modulate TCR signaling. Two phosphatases induced with TCR clustering are SHP-1 and SHP-2.

The role of PKC and calcium signaling in T-cell function is made evident by studies in which pharmacologic activation of PKC and/or elevation of intracellular calcium concentration stimulates T-cell cytokine secretion and proliferation.[6] Similarly, elevating mononuclear phagocyte cytosolic calcium

concentration augments a proinflammatory phenotype, characterized by elevated cytokine production with exposure to LPS. These biologic pathways are clinically relevant. Derangements in calcium homeostasis and hypocalcemia are nearly universal in patients suffering from a variety of critical illness: trauma, burns, septic shock. Translationally oriented studies underscore the prevalence of derangements in calcium homeostasis, and moreover, that pharmacologic calcium supplementation to treat hypocalcemia is associated with heightened inflammation and more severe organ dysfunction.[100]

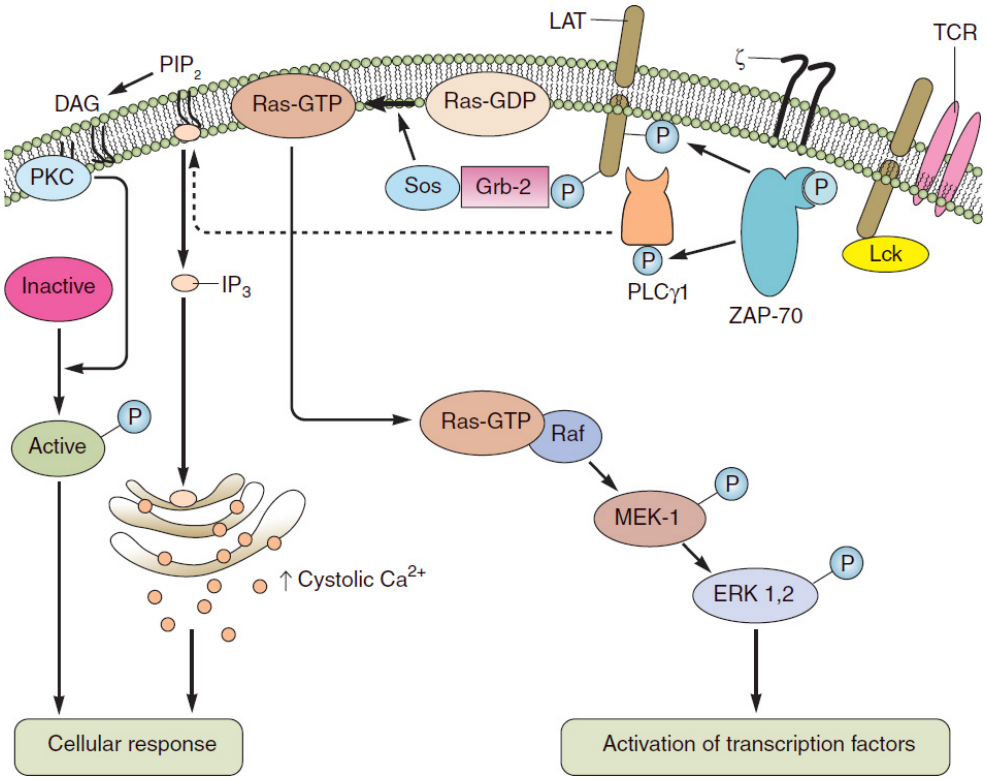

Figure 7.6 T-cell signaling and activation. (Redrawn from Abbas AK, Lichtman AH. *Cellular and Molecular Immunology*. Philadelphia, PA: Saunders, 2003.)

Table 7.5 Transcription Factors

Transcription Factor	Stimuli	Effector Genes
AP-1	TNF, IL-1, UV light, H_2O_2, LPS, stress, ROS, hypoxia	TNF, IL-1, IL-2, IL-5, IFN-γ, ICAM-1, E-selectin, GM-CSF, MMPs, COX-2
NFκB	TNF-IL-1, UV light, H_2O_2, LPS, ROS	IL-1, IL-2, IL-6, IL-8, IL-12, TNF, E-selecting, VCAM-1, ICAM-1, MIP-1, MCP-1, RANTES, iNOS, eotaxin, PLA_2, G-CSF, GM-CSF, IFN-β
STAT	IFNs, CSFs, GFs, IL-1 to IL-15	FOS, E-selectin, Myc, ICAM-1, Fc γRI
NFAT	TCR, BCR, FcεR, FcγR, histamine and thrombin receptors	IL-2, IL-3, IL-4, IL-5, IL-8, IL-13, TNF, GM-CSF, IFN-γ, CD40L, FASL

AP, activator protein; CSF, colony-stimulating factor; COX, cyclooxygenase; GF, growth factor; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MMP, matrix metalloproteinase; MPO, myeloperoxidase; NF AT, nuclear factor of activated T cells; NFkB, nuclear factor kappa-B; PLA_2, phospholipase A_2; ROS, reactive oxygen species; STAT, signal transducer and activator or transcription; TNF, tumor necrosis factor; UV, ultraviolet; VCAM, vascular cell adhesion molecule.

Modified from Gallin JI, Snyderman R, eds. *Inflammation: Basic Principles and Clinical Correlates*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.

A third mechanism of T-cell activation involves lipid antigens, such as cell wall protein from intracellular bacteria. These antigens bind CD1, an MHC-related cell surfacemolecule that presents these antigens to certain subtypes of T cells. A superantigen is an unprocessed bacterial or retroviral product that binds the MHC molecule and the TCR outside the usual antigen-

binding sites. This engagement leads to a polyclonal and nonspecific stimulation of a large proportion of the T-cell population. An overwhelming activation of all arms of the immune system ensues and underlies much of the pathophysiology of toxic shock syndrome (TSS). Intravenous gamma globulin (IVIG), by binding this antigen, is thought to be of therapeutic benefit.

Several important regulatory molecules in cell-mediated immunity are expressed on the cell surface of lymphocytes, including T-cell immunoglobulin- and mucin-domain containing molecule-3 (TIM-3), lymphocyte activation gene 3 protein (LAG3), and programmed death-1 (PD-1). These "checkpoint inhibitors" are responsible for maintaining immune balance through the inhibition of an aggressive immune response, though they have also been associated with immune, particularly lymphocyte, exhaustion. TIM-3 is a transmembrane protein expressed on $CD4^+$ and $CD8^+$ T cells and limits the duration and magnitude of T-cell responses. However, the upregulation of TIM-3 is associated with the proliferation, apoptosis, and functional failure of lymphocytes; it has been found in several malignancies and portends a poorer prognosis. LAG-3 is a member of the immunoglobulin superfamily, is expressed on activated $CD4^+$, $CD8^+$, and NK cells, and functions as a negative regulator of T-cell homeostasis. It has been shown to be expressed on tumor infiltrating lymphocytes (TILs) and correlates with functionally exhausted T cells and inferior cancer outcomes. PD-1 is a type 1 transmembrane receptor that belongs to the immunoglobulin superfamily. It was originally identified as a coinhibitory molecule on T cells; interactions with its ligands PD-L1 and PD-L2 activate downstream signals and suppress T-cell activation. It has also been identified on DCs, macrophages and some nonhematopoietic cells, such as the endothelium and astrocytes. PD-1 maintains tolerance and preventing autoimmunity, however, it is also associated with lymphocyte exhaustion and in the context of cancer biology, has been shown to correlate with worse tumor biology and clinical outcome. Importantly blocking these molecules, notably PD-1, has been shown to revert the functional impairment of exhausted T cells. This appreciation has led to an explosive development of a wide variety of small molecular inhibitors and monoclonal blocking antibodies that now support immunotherapies for the treatment of severe sepsis and several cancers: including renal cell carcinoma, head and neck squamous cell carcinoma, cervical, uterine and breast cancer; and a variety of lymphomas.[101]

Eosinophils

Eosinophils are marrow-derived granulocytes that share some properties of neutrophils, act in conjunction with basophils and mast cells as primary effectors in allergen inflammation and are involved in the eradication of helminthic infections (**Table 7.1**). Upon exiting the marrow, their intravascular half-life is but a few hours, whereafter they enter the mucosa of the lung, gastrointestinal, and genitourinary tracts.[43,102] IL-3, GM-CSF, and IL-5 promote eosinophil differentiation, the induction of effector functions, and survival, the last by inhibiting apoptosis.[102] Emigrating through inflamed endothelium they release inflammatory mediators and toxic agents from cytoplasmic granules. They generate superoxide anion and hydrogen peroxide, though less efficiently than neutrophils. They express IgE receptors and stimulate histamine release from basophils and mast cells through major basic protein (MBP). They can also regulate basophil and mast cell function by releasing enzymes that inactivate histamine and slow-reacting substance of anaphylaxis (SRS-a).

Recruitment and Activation

Eosinophils are recruited primarily to sites of parasitic infection and allergen challenge. Mast cells and macrophages responding to either secrete mediators (IL-5, PAF, LTB-4) that upregulate expression of endothelial adhesion molecules. Eosinophils themselves are more responsive to CC chemokines (MIP-1α, RANTES, and MCP-3) and the cytokines produced with T_H2 activation. Engagement of eosinophil β_1 integrin VLA_4 with VCAM-1 and fibronectin on the endothelium initiates the process of emigration. IL-4 can activate both the binding and the upregulation of endothelial cell VCAM-1. Diapedesis and tissue infiltration also involve members of the β_2-integrin family (Mac-1 and LFA) similar to that which mediates neutrophil recruitment.[43,103]

Eosinophils are activated by IL-3, GM-CSF, IL-5, PAF, CC chemokines, and C3a and C5a of complement. IL-5 is a potent activating agent and enhances the ability of eosinophils to release granule contents on FcR cross-linking. A positive feedback cycle ultimately is established, in which

recruited eosinophils produce cytokines and chemokines that recruit more eosinophils and other leukocytes.

Granules

Eosinophils possess a compartmentalized armamentarium of toxic substances that assist in the elimination of organisms, in particular helminths. Their specific granules contain GM-CSF and MBP, the latter of which is cytotoxic to parasites and normal cells. Further, it functions as a stimulus for histamine release from mast cells and basophils.[104] The granule matrix contains eosinophil peroxidase (EPO), eosinophil-derived neurotoxin, lysosomal enzymes, catalase, TNFα, TGFβ, and eosinophilic cationic proteins that stimulate formation of transmembrane pores to increase target cellular permeability.[105] EPO is released extracellularly on target cell surfaces where it generates hydrogen peroxide and hydrogen halides. Approximately 30% of oxygen consumed by stimulated eosinophils is utilized in the formation of halogenating species. Thiocyanate may be the major halide for the EPO–H_2O_2 system.[106] If ingested by a neighboring phagocyte, EPO can combine with H_2O_2 and halides to form hypohalous acids. EPO also stimulates neutrophil aggregation and adhesion to endothelial cells. Although they express Fc receptors for IgG, IgA, and IgE, they are relatively insensitive to activation by antigen-mediated cross-linking of these receptors. However, they can kill microorganisms by antibody-dependent cell-mediated cytotoxicity (ADCC).[6,43]

The primary targets of eosinophils are extracellular parasites. The size of these pathogens prohibits phagocytosis, and their integument is relatively resistant to the microbicidal products of neutrophils and macrophages; however, they can be killed by MBP, which is released after cross-linking of Fc-bound IgE coating the parasite. The T_H2 response to parasitic invasion produces IL-4, IL-5, and IL-13. IL-4 stimulates the production of specific IgE antibodies, which opsonize helminths. IL-5 activates eosinophils, which bind to the IgE-coated helminthes via Fc receptors. Activated eosinophils then release their granule contents and generate ROS and hypohalous acids. EPO also stimulates neutrophil aggregation and adhesion to endothelial cells. The sparse uncompartmental granules contain Charcot–Leyden crystals and have lysophospholipase activity. Finally, eosinophils produce and release lipid

mediators such as PAF, prostaglandins, and leukotrienes, which probably contribute to the process of allergic diseases.[6,107,108]

Basophils and Mast Cells

Basophils and mast cells are central to the development of allergic inflammation and produce cytokines, lipid mediators, vasoactive amines, and proteases that can also participate in nonallergic inflammatory responses (**Table 7.1**). Both cells share a common progenitor cell, which diverges early during differentiation. The primary growth factors for basophil development are IL-3 and GM-CSF, whereas stem cell factor is the primary stimulus for mast cell maturation.[109] Although basophils and mast cells are distinct cell types, they are often grouped together because of their similarity of their granule content, the stimuli inducing activation, and in their effector functions.[43]

Mature basophils constitute only 0.5% to 1% of the circulating leukocytes. Mast cells are primarily tissue-fixed residents of connective tissue. Engagement of IgE-bound antigen with the high-affinity IgE antibody receptor, FcεR, provides the primary stimulus for basophil and mast cell activation and degranulation. In addition, diverse agents such as contrast media, opiates, anaphylatoxins, chemokines, and neuropeptides may serve as activators. Basophils and mast cells elaborate both preformed, as well as, newly synthesized inflammatory mediators. The main basophil proteoglycan is chondroitin sulfate A, whereas mast cells contain heparin, chondroitin sulfate, and chondroitin sulfate E and also store neutral proteases.[110] The lipid mediators LTB_4, LTC_4, and PGD_2 are synthesized de novo in response to stimulation. The leukotrienes are powerful vasoconstrictors, bronchoconstrictors, and chemoattractants for neutrophils and eosinophils. PGD_2 inhibits platelet aggregation and is chemotactic for neutrophils. Both basophils and mast cells synthesize and secrete histamine. Histamine, or 2-(4-imidazolyl)-ethylamine, is formed by the carboxylation of histidine. It is stored in preformed granules at acid pH as a complex with proteins and proteoglycans. Mast cells carry greater quantities of histamine than do basophils. The classic vasoactive properties of arteriolar dilatation, increased vascular permeability, and bronchoconstriction are mediated by

the H_1 receptors. H_2 receptors are involved in modulation of the immune response and stimulating gastric output and mucus secretion. H_3 receptors participate in neuroconduction.[43,110,111]

Platelets

Though classically considered in the context of hemostasis, studies confirm that platelets are also integral to normal and pathologic inflammation and link the processes of hemostasis, inflammation, and tissue repair. They are activated in a variety of sterile inflammatory conditions, such as trauma,[112,113] idiopathic pulmonary fibrosis,[114] thromboembolic disease,[115] diabetes,[116] cardiovascular disease,[117] sickle cell disease,[118] and autoimmune disease[119] such as rheumatoid arthritis, and inflammatory bowel disease, a testimony to their role in inflammation.[120] They also have been shown to be critical regulators of early immune response in sepsis, with multiple effects on platelet function regulated by pathogens.[121–123] Upon activation, they release factors that enhance vascular permeability, chemokines, microbicidal proteins, and mitogens for endothelial cells, smooth muscle cells, and fibroblasts. They assist leukocytes in promoting the inflammatory reaction and killing microbes by providing an adhesive surface to facilitate emigration, by stimulating adhered leukocytes, and by further modulating chemokine synthesis (**Table 7.6**).[120,124]

Humans possess about 150 to 400 × 10^9 platelets per liter of blood.[120] Thrombopoiesis is regulated by thrombopoietin (TPO) as well as a variety of other mediators (IL-3, IL-4, IL-6, IL-7, and IL-11). In fact, human IL-11 is in clinical use to stimulate thrombopoiesis in patients undergoing chemotherapy.[125] After release from the marrow, platelets circulate with a half-life of approximately 12 days. Interferon α is inhibitory for megakaryocyte growth, and the elevated levels induced with some viral and inflammatory conditions may explain the relative thrombocytopenia observed in these conditions.[120,126] However, thrombocytopenia is exceptionally common in critical illness with complex and multifactorial etiologies.[127]

Table 7.6 Platelet-Derived Mediators
Chemoattractants C5a 12-HETE
PAF α-Granule proteins
PDGF PF-4 RANTES
Growth factors Transforming growth factors α and β Fibroblast growth factor PDGF
Antimicobial activity Cationic bactericidal protein IgE-mediated oxidant production by platelets directed at schistosomes
Vascular reactions Prostaglandin E_2 Prostaglandin I_2 Prostaglandin $F_2\alpha$ Serotonin PDGF Serotonin PAF Cationic proteins Vascular endothelial growth factor

HETE, hydroxyeicosatetraenoic acid; PAF, platelet activating factor; PDGF, platelet-derived growth factor; PF-4, platelet factor 4; RANTES, regulated on activation, normal T cell expressed and secreted.

Klinger MHF, Jelkmann W. Role of blood platelet in infection and inflammation. *J Interferon Cytokine Res* 2002;22:913–922.

Recruitment and Activation

Platelets are activated by and aggregate in response to thrombin or activated endothelium. Clot formation triggers the release of vasoactive agents (PGE_2, PGI_2, $PGF_{2\alpha}$, and PDGF) and inflammatory mediators. Serotonin, PGE_2, and PAF increase vascular permeability. The adhesion molecule PECAM-1 and the β_3 integrins mediate platelet plug formation, endothelial cell adhesion, and leukocyte emigration. The integrin IIb/IIIa and P-selectin facilitate platelet interactions with other inflammatory cells, with P-selectin serving as a critical ligand for leukocytes with recognition by PSGL-1. The α granules are rich in membrane-bound P-selectin; upon fusion with the cell surface membrane they enhance the cell surface density of this receptor. On stimulation, both receptors are expressed on the platelet surface in an activated state. IIb/IIIa binds various adhesive proteins containing the RGD sequence (i.e., fibrinogen), which serve as a mechanical link to other platelets, leukocytes, and the endothelium. Possibly the immobilization of activated P-selectin–expressing platelets on the vessel wall may biochemically and functionally promote the adhesion of neutrophils to endothelial cells.[120,126]

Platelets are a primary source of chemoattractants for neutrophils. Neutral proteinases released from stimulated platelets cleave complement factor C5, liberating the chemoattractant C5a. PDGF binds strongly to the extracellular matrix, providing a long-acting source of chemoattractant. Platelet factor 4 (PF4) is a cationic protein that penetrates the vascular wall and is a chemoattractant. Activated platelets also bind monocytes via P-selectin and PSGL-1 and induce the expression and secretion of monocyte chemotactic protein-1 (MCP-1) and IL-8. Thrombospondin released from activated platelets mediates monocyte binding to platelets. Together these substances promote leukocyte margination, activation, and recruitment to the sites of injury, and the chemoattractant effect of platelets for neutrophils has been linked to subsequent neutrophil activation and NET production.[43]

Granules

The vasoactive substances and inflammatory mediators of platelets are either stored in cytoplasmic granules or synthesized de novo. A platelet contains about 35 α *granules* and 5 *dense bodies*. The dense granules contain adenosine diphosphate (ADP), adenosine triphosphate (ATP), serotonin, and

calcium that are required during the earlier stages of inflammation. ADP is the principal platelet agonist during platelet aggregation and augments the oxidative burst of neutrophils. Serotonin increases vascular permeability and enhances the superoxide production by macrophages.[120]

The more abundant α granules contain fibrinogen, RANTES, MIP-1α, thrombospondin, P-selectin, PF4, PDGF, TGFβ, β-thromboglobulin, high–molecular-weight kininogen (HMWK), high mobility group box 1 (HMGB1), and many other biologically active proteins. PF4 and β-thromboglobulin initiate leukocyte recruitment and activation. PF4 induces neutrophil adherence to unstimulated endothelium and the release of secondary granules. It inhibits monocyte apoptosis and promotes macrophage differentiation. PF4 can also stimulate histamine release from basophils. RANTES is deposited on the endothelium and recruits monocytes from the circulation. PAF induces platelet aggregation, increases vascular permeability, enhances phagocyte-free radical formation, and the adhesion of platelets to neutrophils. HMGB1 is a critical regulator of platelet activation and aggregation, and direct release of HMGB1 by platelets has been shown to regulate neutrophil function and NET production in trauma, autoimmune disorders, and sepsis. Platelet activation appears to occur in allergic asthma and may precede the delayed accumulation of eosinophils in the lung after allergen exposure. The α granules also carry several important growth factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and TGFβ. VEGF promotes extravasation and aids recruitment of leukocytes. PDGF is chemotactic for neutrophils and monocytes. TGFβ is chemotactic for and activates neutrophils and monocytes early during inflammation, but displays immunosuppressive effects during later stages of inflammation.[120]

Platelets are an important source of eicosanoids, including thromboxane, prostaglandins $F_{2\alpha}$ and E_2. $PGF_{2\alpha}$ causes vasoconstriction, whereas PGE_2 vasodilates and modulates pain.[128,129] Thromboxane synthetase in platelets is responsible for the production of TXA_2, a potent vasoconstrictor that also increases vascular permeability and stimulates platelet aggregation. Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit platelet function by inhibiting TXA_2 production. As this effect is irreversible, new platelets must be produced (7 to 10 days) to restore normal clot formation. In emergent circumstances (management of intracranial hemorrhage) platelet

administration is requiredoften utilized, however, the ability of transfused platelets to “reverse” the effects of antiplatelet agents is controversial, with a recent meta-analysis demonstrating no improvement in mortality in patients who received platelet transfusion in the setting of traumatic brain injuries with a history of prehospital antiplatelet agent use. As most means of platelet function testing (aggregation, adhesion, activation) required laborious or sophisticated testing means, there is a substantial limitation inherent in the lack of rapid platelet functional assays. Light transmission aggregometry-based testing has been developed to detect aspirin and P2Y12 inhibition in a point-of-care fashion, which has been validated in cardiovascular disease, particularly for the monitoring of aspirin resistance. These point-of-care devices are used in other acute care settings, although often without validation, to monitor platelet function and response to transfusion. Recently, an aspirin response test has been developed that assists in guiding therapy and targeting transfusion to those with functional evidence of platelet inhibition. It has also assisted in monitoring the response to transfusion.

Platelets participate in transcellular lipoxygenase metabolism (LO), which refers to the production of eicosanoids through interactions with neighboring inflammatory cells. Endothelial cells utilize platelet-derived endoperoxides to synthesize PGI_2. Platelets interact with neutrophils in several pathways, providing a direct link between thrombosis and inflammation, including the direct stimulation of NET production referenced above. 12-HETE released from activated platelets can be used by unstimulated neutrophils to produce the chemoattractant 12,20-HETE. 12-HETE and 5-HETE from activated platelets and neutrophils, respectively, can combine in either cell type to form 5,12 diHETE, an anti-inflammatory compound, which diverts production away from the proinflammatory leukotrienes. 12-LO from platelets and LTA_4 formed by neutrophils can produce the intermediate 5(6)-epoxytetraene. This intermediate produces lipoxins A_4 and B_4 that have primarily counterinflammatory functions.[43,124,128,130]

In addition to modulating inflammation platelets possess some direct microbicidal activity. Platelets are activated and degranulate when exposed to certain bacteria. Electron microscopic studies have shown that activated platelets internalize bacteria and viruses. The α granules contain antibacterial proteins called thrombocidins (TC) in humans that support the

killing of adherent bacteria. The two antibacterial proteins isolated from human platelets (TC-1, TC-2) are bactericidal for *Escherichia coli* and *S. aureus*.[120] Additionally, platelets are able to engulf bacteria independently, including *S. aureus*, demonstrating a direct role in microbial interaction and clearance.[131]

Myeloid-Derived Suppressor Cells

Myeloid-derived suppressor cells first came to attention a decade ago as a heterogeneous population of myeloid cells with potent immune-regulatory activity generated in the context of a variety of disease states. They are now appreciated as universal regulators of immune function in many pathologic conditions. They represent a pathologic state of activation of monocytes and relatively immature neutrophils, possessing a distinct set of genomic and biochemical features, the most salient of which is their ability to inhibit T-cell function and thereby contribute to the pathogenesis of various diseases from cancer to obesity.[132]

Under physiologic conditions in response to infection or injury, GM-CSF drives myelopoiesis, and G-CSF and M-CSF induce the differentiation of granulocytes and macrophages. However, in pathologic statues characterized by unresolved inflammation (e.g., cancer), low level production of these factors persists and favors the development of MDSCs. The first group of signals is driven by factors produced by tumors or tissue stroma in response to chronic infection and inflammation: GM-CSF, G-CSF, M-CSF, S-SCF, and VEGF. The transcriptional factors/regulators STAT3, STAT5, IRF8, C/EBP-β and NOTCH are active during this stage. The second group of signals includes inflammatory cytokines and DAMPs: IFNγ, IL-1β, IL-4, IL-6, IL-13, TNF, and HMGB1, which signal via NF-κB, STAT1, and STAT6.

The distinguishing feature of MDSCs is immune suppression. M-MDSCs are more suppressive than granulocyte MDSCs. MDSCs have an immature phenotype and morphology; relatively weak phagocytic activity; increased background levels of ROS and NO, and high expression of arginase, PGE_2 and a number of anti-inflammatory cytokines. This persistent and aberrant state of activation fails to eliminate the threat, but rather, inhibits adaptive

immunity. In the context of cancer, this supports tumor progression and metastasis.

Early oncology studies reported a positive correlation of MDSC numbers in the peripheral blood with cancer stage and tumor burden. In a meta-analysis, elevated numbers of MDSCs in the circulation proved to be an independent indicator of poor outcomes in subjects with solid tumors and shorter progression-free interval and/or overall survival in subjects. More recent studies suggest a value in prognosticating response to chemotherapy; the frequency of M-MDSCs is negatively correlated with response.

A similar pathologic role for MDSCs has been characterized in several types of infection. Studies have shown that bacteria can induce or modulate MDSCs. During *S. aureus* infection, M-MDSC and PMN-MDSCs suppress T-cell function, thereby exacerbating the infection. An expansion of PMN-MDSCs and M-MDSC has been reported to occur in tuberculosis, fungi, gram-positive or gram-negative pathogens, and chronic HCV infection. These can be but are not always associated with disease persistence and adverse outcome.

MDSC populations have also been characterized in autoimmune diseases, including SLE and rheumatoid arthritis, obesity, wherein it may contribute to the increased risk of infectious disease, and pregnancy, a state characterized by maternal–fetal tolerance.

NONCELLULAR COMPONENTS

Cytokines

Cytokines are soluble protein mediators secreted by the cells of the innate and adaptive immunity in response to microbes and other antigens, including intra- and extracellular proteins, and mediate many of the functions of these cells (**Table 7.7**). They mediate and modulate the host response to both pathogen-associated molecular patterns (PAMPs) on bacteria, viruses, fungi, and parasites and damage-associated molecular patterns (DAMPs) released during trauma, burns, allograft rejection, ischemia/reperfusion injury, and autoimmune disease. They govern lymphocyte differentiation during adaptive immunity and activate effector cells of both arms of inflammation to

eliminate microbes. Cytokines play important roles in tumor biology and angiogenesis. Though essential for a normal immune response, excessive cytokine release underlies a variety of pathophysiologic inflammatory states such as acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS).[133–136] So essential is their function to health and disease that modulating cytokine biology nearly comprises an entire domain of drug development, and they been targeted in several preclinical and clinical trials.

Cytokine secretion is brief, and as they typically are not stored preformed, necessitates transcription and de novo synthesis, which is also transient as the messenger RNA is unstable. Their functions are pleiotropic and redundant, which has been interpreted to represent a teleologic safety mechanism. However, such protective characteristics greatly limit the therapeutic utility of either cytokine administration or blockade. In fact, 6 over 60 randomized-controlled clinical trials have been conducted to assess the efficacy of modulating inflammation, on reducing mortality in a variety of contexts: trauma, sepsis. The majority have involved manipulating systemic cytokine concentrations. Only one valid biologic, activated protein C, was briefly FDA approved for use; it was subsequently removed from the market due to a lack of benefit.[137] Corticosteroids have regained favor by the medical community for the treatment of severe sepsis and septic shock. The recent APROCCHSS (Activated Protein C and Corticosteroids for Human Septic Shock) trial confirmed earlier studies demonstrating that a 7-day course of the corticosteroid hydrocortisone in combination with the mineralocorticoid fludrocortisone reduced 28-day mortality: relative risk 0.88 (95% confidence interval, 0.78 to 0.99).[138] A updated meta-analysis similarly concluded that in critically ill patients with sepsis, corticosteroids probably result in a small reduction in mortality.[139] However, the exact mechanism conferring such benefit remains to be identified and may not be immunomodulatory in nature.

Cytokines often influence the synthesis and actions of other cytokines, such as IL-1–induced T-cell IL-2 production; this interaction may be synergistic (additive or multiplicative) or antagonistic. They may function in an autocrine, paracrine, or even endocrine function, although the inability to correlate plasma cytokine concentrations with the extent of tissue damage

suggests that they are designed for local rather than systemic inflammation.[6,43,133]

Cytokine actions are mediated by specific membrane receptors on target cells to which they bind with high affinity (Kd α 10^{-10} to 10^{-12}). Hence, only minute quantities are necessary to elicit a response. Such efficiency is accompanied by a narrow therapeutic index and potential for unwanted global effects (i.e., MODS) with even small systemic concentrations. The receptors and the cells expressing them are regulated by external stimuli, which provide some degree of specificity to the response, even though the cytokines themselves are not antigen specific. Receptor binding alters cellular gene transcription (induction or suppression) that may result in proliferation, differentiation, and the acquisition of new or suppression/enhancement of pre-existing functions.[6]

All cytokine receptors consist of at least one transmembrane protein with an extracellular portion for ligand binding and an intracellular domain mediating signal transduction. Current receptor classification is based on structural homologies among the extracellular cytokine binding domains. Type I cytokine receptors contain a domain with two conserved pairs of cysteine residues and a membrane proximal sequence of tryptophan-serine-X-tryptophan-serine, where X is any amino acid (WSXWS). Type II resemble type I receptors, however the WSXWS motif is absent. The Ig superfamily consists of receptors with extracellular Ig domains. TNF receptors belong to a family of receptors with conserved cysteine-rich extracellular domains. Finally seven-transmembrane α-helical receptors mediate the functions of cytokines called chemokines through GTP-binding (G) proteins.[6]

Translating ligand engagement to the signaling events that alter cellular phenotype involves a variety of signaling cascades dependent upon the structure of the cytoplasmic tail of the particular receptor (**Table 7.7**). This is another method by which to classify cytokine receptors. These individual signaling cascades will be discussed in the context of the various cytokines and respective receptors employing them.

Table 7.7 Cytokines

Cytokine	Receptor	Signal Transduction	Cellular Source	Targets	Effects	
TNFα	TNF R	TRAFS Death domains	Mo/Mϕ, MC, Ba, Eo, NK, B, T, fibroblast, Epithelia	Endothelium PMN Many cells	↑ inflammation, coagulation, adhesion molecules ↑activation ↑ apoptosis ↑ fever, APP, catabolism	INNATE/EARLY CYTOKINES
IL-1	Ig family	IRAK	Mo/Mϕ, B, EC, Epithelial, Fibroblast	Endothelium PMN Mo	↑ inflammation, coagulation, adhesion molecules ↑ activation and emigration ↑ activation and emigration ↑ shock, fever, APP production	
Chemokines/ Il-8	7 transmembrane	G protein	Mo/Mϕ, T, PMN, F, EC, Ep	PMN T Mo/Mϕ EC Ba	↑ activation, adherence, and migration ↑ emigration ↑ emigration ↑ adhesion molecules ↑ histamine release	
IL-12	Type I	JAK/STAT	Mϕ	T NK	T_H1 differentiation, interferon-γ synthesis, ↑ cytolytic activity	
Interferons (Type I:)	Type II	JAK/STAT	All	All	Antiviral, antitumor, increases MHC I activates T, Mϕ, NK cells	
IL-10	Type II	JAK/STAT	Mo/Mϕ, T, B, MC	Mo/ Mϕ T B, NK, MC	↓ IL-12, costimulators, MHC II ↓ T_H1 differentiation	
IL-6	Type I	JAK/STAT	Mo/Mϕ, B, F, EC, Ep	T B Mo/ Mϕ E	differentiation ↑ antibody-producing cells APP synthesis	
IL-15	Type I	JAK/STAT	Mϕ	NK T	Proliferation Proliferation	
IL-18	Ig family	IRAK	Mϕ	T, NK	↑ interferon γ	

IL-2	Type I	JAK/STAT	T	T B NK	T activation and proliferation, Fas apoptosis ↑ proliferation, antibody synthesis ↑ proliferation and activation Mo/Mϕ activation	A D A P T I V
IL-4	Type I	JAK/STAT	T, Ba, MC	T B Mo/Mϕ	T_H2 differentiation and proliferation, ↓ T_H1 Isotype switching to IgE ↓ interferon-γ-mediated function	E / L A T E
IL-5	Type I	JAK/STAT				
Interferon-γ	Type II	JAK/STAT	T, NK	Mϕ T B	Mϕ activation T_H1 differentiation IgG secretion ↑ MHC I and II ↑ antiviral ↑ fever, anorexia, shock, capillary leak ↑ APP synthesis, inflammatory cytokine induction	C Y T O K I N E S
TGF-β			All	T Mϕ B	↓ T proliferation and effector functions ↓ Mϕ function ↓ proliferation ↑ matrix protein synthesis	
Lymphotoxin	TNF R	TRAFS Death domains	T	PMN	Recruitment and activation	
IL-13	Type I	JAK/STAT	T	Mo/Mϕ B EC	↓ Mϕ function switching to isotype IgE ↑ adhesion molecules and CC chemokines	

Modified from Abbas AK, Lichtman AH. *Cellular and Molecular Immunology*. 5th ed.; 2003;179, 181–182.

Early Cytokines/Innate Immunity

TNFα

TNFα is the principal initiating mediator of the inflammatory response to gram-negative bacteria and other infectious pathogens. It is an important early mediator of inflammation and is essential for the normal initiation, maintenance, and repair of tissue injury. However, aberrant production may

underlie the pathologic sequelae of many inflammatory and infectious states (i.e., MODS, rheumatoid arthritis, Crohn disease). Mononuclear phagocytes are the principal source of TNFα, usually in response to the potent prototypical stimulus lipopolysaccharide of gram-negative organisms.[140,141] TNFα production may be augmented by concomitant stimulation with IFNγ, IL-4, and IL-10, whereas, corticosteroids are suppressive.[142] Secondary sources include mast cells, NK cells, and T and B lymphocytes. Other stimuli inducing production and release include complement C5a, GM-CSF, hypoxia, IL-1, NO, ROS, and TNFα itself.[43]

TNFα is expressed on the cell membrane as a bioactive protein and is cleaved into its soluble form by a specific TNFα-converting enzyme. There are two distinct TNF receptors present on virtually all cell types (**Fig. 7.7**).[143] Ligand binding to TNF-RII leads to recruitment of TNF receptor-associated factors (TRAFs) that ultimately activate the transcription factors NFκB and AP-1, and thereby influence gene expression and cellular phenotype.[6] Alternatively, binding to TNF-RI activates caspases and triggers apoptosis, in addition to signaling transcription factors. The manner by which either a proinflammatory or apoptotic path is chosen is unknown, although the net effect of TNFα binding is probably the culmination of differential adaptor protein expression and downstream signal transduction cascades. TNF-RI appears to be more important in host defense as knockout TNF-RI mice show a greater degree of impairment in host defense than mice lacking TNF-RII.[6]

Shedding of extracellular domains of the two TNFα receptors by metalloproteinases, can further alter the biologic activity of TNFα by decreasing the number of cell-signaling sites on target tissues and increasing the amount of circulating inhibitors. Unlike other members of the TNF family that are primarily involved in regulation of cell proliferation, TNFα has both proinflammatory and apoptosis-inducing properties.[133,144]

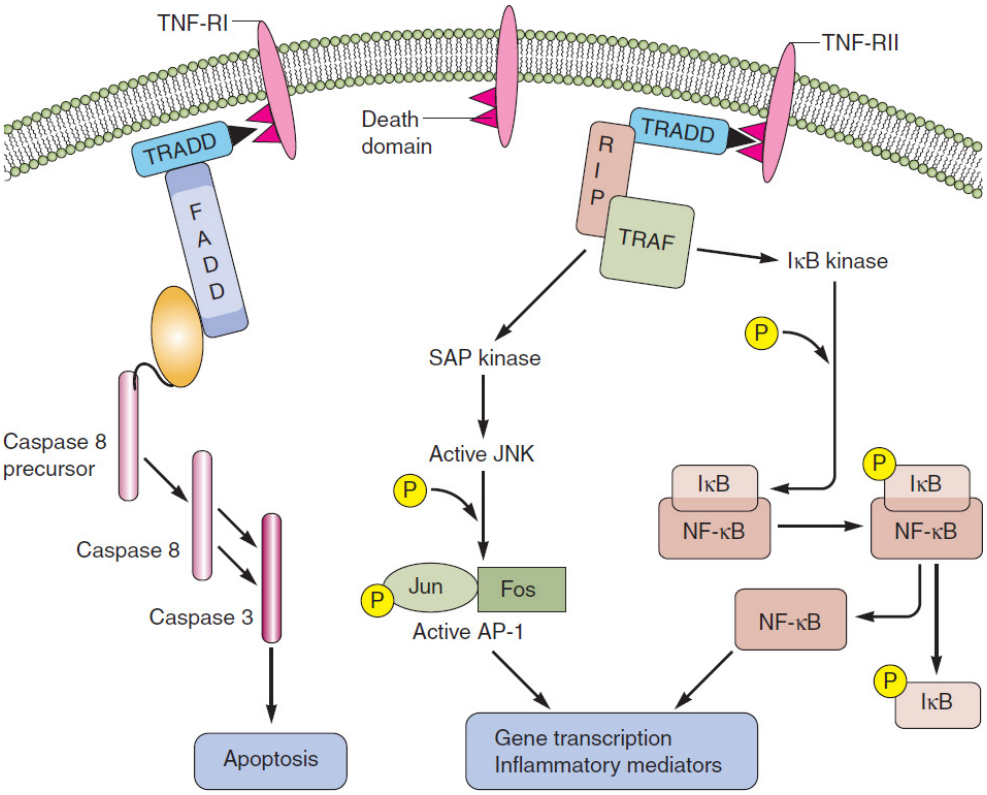

Figure 7.7 TNF receptor–signaling pathway. (Redrawn from Abbas AK, Lichtman AH. *Cellular and Molecular Immunology*. Philadelphia, PA: Saunders, 2003.)

The principal function of TNFα is to recruit neutrophils and monocytes to foci of infections and to activate these cells to eradicate microbes. TNFα activates the endothelium to upregulate the expression of the adhesion molecules E- and P-selectin, ICAM-1, PECAM-1, and VCAM-1. It potently stimulates these cells and macrophages to secret chemokines (IL-8, MIP-1α, and Gro-α) that enhance the affinity of leukocyte integrins for their ligands and induce leukocyte chemotaxis and recruitment.[145] TNFα also can induce HMGB1 release by activated macrophages, which generates a forward feedback mechanism, as HMGB1, by signaling through RAGE (*vida infra*), also induces TNFα release.[146,147] TNFα by stimulating the release of tissue factor, PAF, von Willebrand factor, and thromboplastin generates a state of hypercoagulability. By inhibiting tissue-type plasminogen activator and thrombomodulin, it suppresses fibrinolysis, decreases protein C and S activation, and increases thrombin formation. However, TNFα also induces the release of a variety of anticoagulants (prostacyclin), fibrinolytics

(urokinase-type plaminogen activator), and vasodilators (NO, PGE_2), which may offset or balance the tendency toward procoagulation. Most likely, the ultimate effect of TNFα depends on the location and quantity in which it is produced and the vascular bed with which it interacts.[6,133]

Though clearly vital for host defense and microbial elimination, in severe infections, exuberant production and aberrant release of TNFα, wherein it possess endocrine function, can cause a plethora of pathologic sequelae. These systemic effects include fever by stimulating the production of PGE_2 by the hypothalamus (hence the name endogenous pyrogen), acute-phase protein production by the liver, cachexia, inhibition of myocardial contractility and vascular tonus, and intravascular thrombosis due to loss of normal anticoagulant properties of the endothelium and the production of tissue factor. TNFα is central to the pathogenesis of severe sepsis and septic shock, and either state can be reproduced by the exogenous administration of TNFα.[148,149] The organ dysfunction characteristic of these states may result from the hypercoagulability and subsequent tissue ischemia induced by this cytokine. Antagonists of TNFα can prevent mortality in experimental models, however several clinical trials with anti-TNFα antibodies or with soluble TNFα receptors in sepsis have been to no avail.[6,148] Greater clinical efficacy with anti-TNFα therapy has been achieved in treating the more chronic inflammatory diseases of rheumatoid arthritis, psoriasis, and Crohn disease.[150,151]

Soluble TNF receptors formed by proteolytic processing of both types of receptors bind and neutralize TNFα and serve as an endogenous regulator of cytokine activity.[43] TNFα also directly induces the expression and release of TNFα inhibitors, including IL-10, corticosteroids, and prostanoids, which in a negative feedback loop suppresses TNFα production and processing.[133] Hence, TNFα serves as its own regulator.

Interleukin 1

Interleukin 1 possesses similar functions to TNFα in mediating a proinflammatory host response to insult; it is frequently released concomitantly with TNFα (**Table 7.7**).[152] The major source of IL-1 is the mononuclear phagocyte. Synthesis and release are induced by LPS, cytokines such (TNFα, IL-2, TGF-β, all the interferons), antigen–antibody complexes,

C5, and hypoxia.[133] IL-1 is also produced by neutrophils, B cells, helper T cells, epithelial cells, fibroblast, renal mesangial cells, and endothelial cells. There are two forms of IL-1: IL-1α and IL-1β. Both forms are active, bind to the same receptors and mediate the same effects. Most IL-1 found in circulation is IL-1β.[6]

The two IL-1 receptors (IL-1R) are members of the Ig superfamily. IL-1RI is universally expressed and transduces the majority of IL-1 responses.[153,154] IL-1RII expression is restricted to B cells, but may be induced on other cells. There is little evidence that this latter receptor serves any function, and in fact, may serve as a decoy.[155] The cytoplasmic portion of IL-1RI is homologous to a domain of toll-like receptors (TLRs), which mediate the cellular responses to endotoxin (**Fig. 7.8**). Engagement of IL-1 with IL-1RI induces the activation of the IL-1 receptor-associated kinase (IRAK) and the subsequent induction of the transcription factors NFκB and AP-1.[6,154]

The functions of IL-1 mirror those of TNFα, and synergy between the two cytokines is evident.[152] IL-1 activates endothelial cells to increase cell surface expression of adhesion molecules and the production of prostaglandins, PAF, and a variety of colony-stimulating factors (CSFs). In doing so, it facilitates the recruitment and activation of appropriate leukocyte populations for specific localized immune responses. IL-1 also induces a procoagulant state by suppressing fibrinolysis through enhanced plasminogen activator inhibitor-1 and decreased tissue-type plasminogen activator activity. It increases thrombosis by stimulating tissue factor-like procoagulant and thromboplastin production and suppressing thrombomodulin release. It induces the synthesis of PAF, a potent vasoconstrictor and stimulus for platelet and leukocyte activation. However, similar to TNFα, it also stimulates the production of prostacyclin and urokinase-type plasminogen activator, which promotes an antithrombotic state.[156] At larger concentrations, its effects become systemic causing fever, the synthesis of acute-phase proteins, cachexia, myalgia, somnolence, and hypotension. It stimulates arachidonic acid and prostaglandin metabolism, and the release of pituitary stress hormones. It stimulates collagenase release and is a potent mitogen for neutrophils. Though similar in effect to TNFα, probably by activating similar signaling cascades and transcription factors, IL-1 does not induce apoptosis. Even at high concentrations IL-1 does not cause the physiologic derangements of septic shock.[43,152]

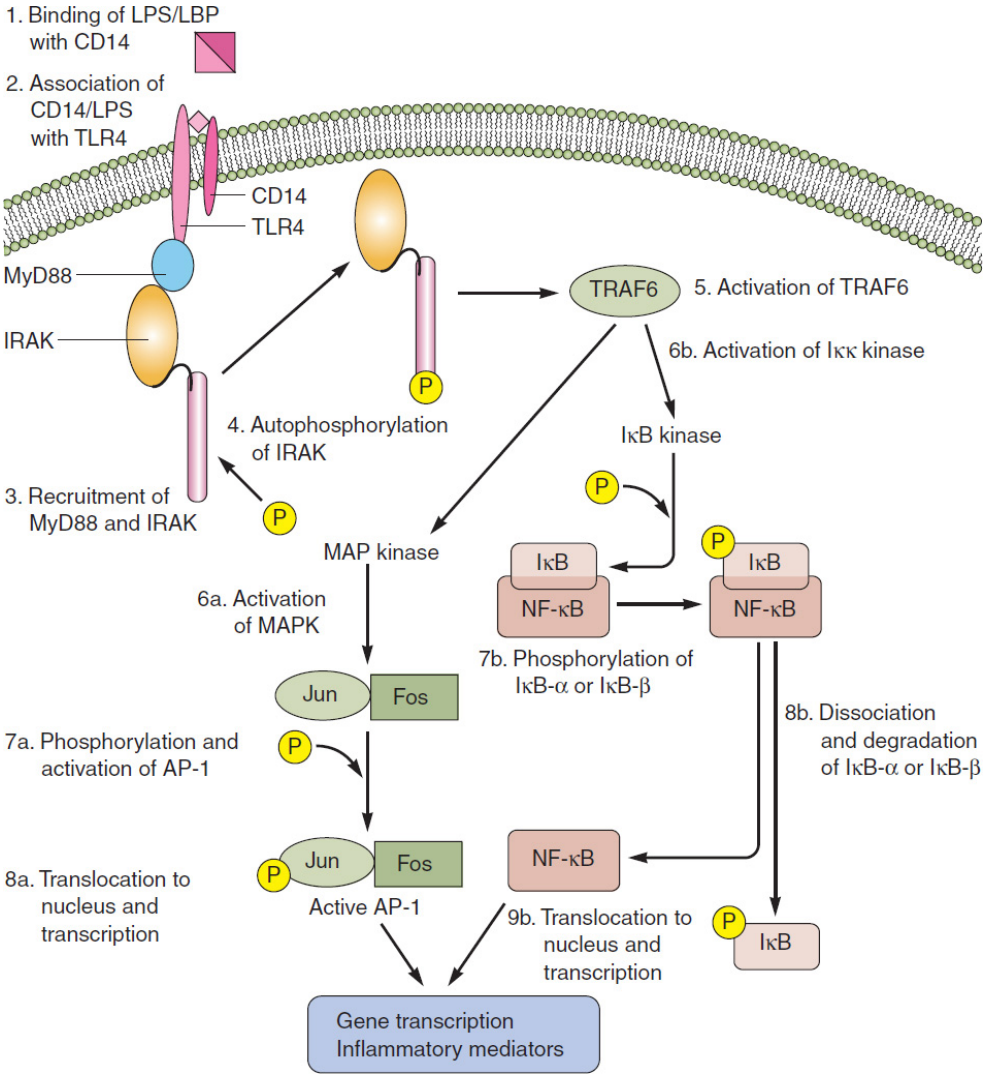

Figure 7.8 Toll-like receptor (TLR)-signaling pathway. (Redrawn from Abbas AK, Lichtman AH. *Cellular and Molecular Immunology*. Philadelphia, PA: Saunders, 2003.)

Mononuclear cells produce the natural inhibitor of IL-1, IL-1Ra. This IL-1 structural homologue is an inactive competitive inhibitor and may function as an endogenous regulator of IL-1. As occurred with immunomodulatory agents of TNFα, early attempts to inhibit IL-1 were shown not been of clinical benefit in human trials of sepsis.[43] However, greater awareness of the heterogeneity of sepsis as a disease, supported posthoc analyses and additional clinical trials that have yielded more encouraging results. A reanalysis of a phase III trial of a human IL-1 receptor antagonist (i.e., anakinra) for severe sepsis focused on a subgroup of patients experiencing what is termed macrophage activation syndrome, a fulminant cytokine storm

characterized by fever, disseminated intravascular coagulation, hepatobiliary dysfunction, cytopenias, and hyperferritenemia. In this subgroup, anakinra was associated with improved 28-day survival.[157] Similar "positive" results were obtained in a separate study of IL-1Ra stratified by plasma IL-1 concentration; benefit was observed with IL-1Ra in the cohort with elevated plasma IL-1 concentrations.[158]

Chemokines

This large family of cytokines primarily orchestrates leukocyte chemotaxis, hence the name (**Table 7.7**).[159–164] Those bound on the endothelial surface induce leukocyte integrins to express a high-affinity state for their ligands, which is critical for tight leukocyte adherence and subsequent migration into the extravascular space. However, they also assist in orchestrating the migration of immune cells into lymphoid organs. Unlike other chemoattractants, members of this family possess a degree of cellular specificity, influencing the recruitment of discrete subsets of leukocytes. They mediate their effects both directly, as well as indirectly through the induction of other mediators such as histamine and ROS. Though some chemokines, in particular those regulating cell traffic through tissues, are constitutively produced (MIP-3β and RANTES), most necessitate cellular stimulation for synthesis and release, in particular, those involved in inflammatory reactions. They are typically produced by macrophages, leukocytes, endothelial cells, fibroblasts, and many other cell types stimulated by LPS, phagocytosis, and inflammatory cytokines such as IL-1, TNFα, IL-6, and IFNγ.[43]

Chemokines can be classified into four families based on the number and location of N-terminal cysteine residues.[164] The two major families are the CC chemokines, in which the cysteine residues are adjacent, and the CXC chemokines, in which one amino acid is interposed between these cysteine residues. This amino acid sequence appears to account for the disparate influence, either promotion or inhibition, on neutrophil chemotaxis. The three amino acids that immediately precede the first cysteine are critical in defining receptor binding and neutrophil activation.[165,166] This area has been designated the ELR motif. The other two chemokine families are represented by lymphotactin (C chemokine) and fractalkine (CX3C chemokine).[43]

Chemokine receptors are seven transmembrane receptors that signal by G proteins and the formation of the second messengers, IP_3 and DAG (**Fig. 7.6**). Currently 7 CXC chemokine receptors, 10 CC, and 1 receptor each for the last 2 subfamilies have been identified and defined. The pattern of cellular expression of the receptors determines the specificity of the cellular response to binding.[6,164,166]

CXC chemokines primarily govern the chemoattraction and activation of neutrophils, and to a lesser degree, lymphocytes, in particular T cells. At least 17 different chemokines have been identified. They are clustered on chromosome 4 and demonstrate 20 to 50% homology at the amino acid level. IL-8 is the prototypical CXC chemokine.[136] It is produced by an array of immune and nonimmune cells including monocytes, alveolar macrophages, neutrophils, keratinocytes, mesangial cells, epithelial cells, fibroblasts, and endothelial cells. TNFα and IL-1 are key molecules for inducing IL-8. It is chemotactic for all granulocytes and influences nearly every aspect of neutrophil function. IL-8 stimulates neutrophil degranulation, phagocytosis, transendothelial migration and shedding of L-selectin, upregulation of β_2 integrins, and augments superoxide production. It is also a potent angiogenic factor and binds to both the CXCR1 and CXCR2, receptors that also engage the chemokines GCP-2, GRO-α, and ENA-78. ENA-78 is a potent neutrophil chemotaxin produced by the endothelium in response to TNFα or IL-1, neutrophils, or monocytes. Studies have demonstrated that ELR-containing CXC chemokines are angiogenic, whereas those lacking this motif are angiostatic.[43,133,165–167]

The interferon-influenced chemokines, IP-10 (CXCL10) and Mig (CXCL9) do not target neutrophils, and the ELR motif is absent. They induce IFNγ production and may play a more prominent role in mediating the inflammatory response to viral infections and autoimmune disorders. Mig is chemotactic for TILs, activated T cells, and monocytes and promotes CTL activity. IP-10 is chemotactic for monocytes, T cells, and NK cells and augments T-cell adhesion. Both chemokines bind the CXCR3 receptor found on IL-2–activated T cells. IFNγ attenuates the expression of both IL-8 and ENA-78, and hence may serve as an important mechanism to the control and regulate inflammation.[43,133] Stromal cell–derived factor-1 (SDF-1/CXCL12) is the only known ligand for the CXCR4 receptor and in the presence of IL-7

stimulates proliferation of pre–B-cell clones and growth of bone marrow B progenitor cells. The receptor has gained much interest since it was identified as a coreceptor for HIV-1. Platelet factor 4 and neutrophil-activating protein-2 are CXC chemokines of platelet origin. PL-4 has angiostatic properties and inhibits the growth of various cancer cell lines in a manner that appears to be related to its angiostatic properties. It binds heparin with high affinity to stimulate coagulation.[43]

There are at least 27 distinct members of *CC* chemokines, whose function is to recruit monocytes, granulocytes, T cells, NK cells, and DCs. Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES) is produced by stimulated T cells, platelets, and endothelial cells and is constitutively produced in resting T cells, which implies a homeostatic function. MIP-1α and β are produced by activated T cells and are chemotactic for neutrophils, monocytes, eosinophils, basophils, and T lymphocytes. They are also mitogenic for hematopoietic progenitor cells and upregulate TNFα, IL-1, and IL-6. The membrane cofactor protein (MCP) family of chemokines influences the recruitment of monocytes and T cells. Their influence upon the function of these target cells is dictated by the cell's specific profile of receptor expression. MCP-1 (also known as CCL2) is produced by nonlymphocytic cells (endothelial cells, epithelial cells, fibroblasts, smooth muscle cells, macrophages, and mast cells). CCL2 is critical for the mobilization of inflammatory ($LY6C^{hi}$) monocytes from the bone marrow and their recruitment to peripheral tissues and sites of inflammation.[168,169] Binding to CCR1 enhances chemotaxis, whereas activation of CCR2 increases the release of intracellular substances such as histamine and leukotrienes from basophils.[43]

Lymphotactin is the only member of the *C* chemokine family and is produced by $CD8^+$ lymphocytes, thymocytes, and NK cells, and, to a lesser degree, by DCs and activated mast cells. It selectively recruits lymphoid cells.[43]

Fractalkine is the sole *CX3C* chemokine and is produced by the endothelium. In its membrane-bound form it may act as a solid-phase adhesion molecule, but upon cleavage serves as a soluble chemoattractant for lymphoid cells and monocytes.[43]

Interleukin 12 (NK Cell Stimulatory Factor, Cytotoxic Lymphocyte Maturation Factor)

IL-12 is integral in the innate immune response (**Table 7.7**). It is produced early during innate immune reactions and is critical for initiating a sequence of responses involving macrophages, NK cells, and T lymphocytes that results in the eradication of intracellular microbes. It stimulates subsequent adaptive responses that confer further host protection against these pathogens. Hence, it is an important link between innate and adaptive immune responses. IL-12 is primarily derived from activated mononuclear phagocytes and DCs, and most importantly stimulates IFNγ from T cells and NK cells. There are two pathways leading to IL-12 production: (1) T-cell dependent and (2) T-cell independent pathway. During innate immunity, LPS, infection by intracellular bacteria, and viral infections may induce IL-12 production. In addition interactions between CD40 ligand and CD40 on activated lymphocytes and APC, respectively, induce the release of APC IL-12.[170,171] Thus, IL-12 is produced during the induction of and the effector phases of cell-mediated immune response when APCs present antigens to T cells.[6,43]

The IL-12 receptor is a heterodimer composed of β_1 and β_2 subunits, the latter of which is involved in signaling, although both are required for engaging ligand. The receptor signals through the JAK/STAT pathway (**Fig. 7.9**).[6] This signal transduction pathway is employed by numerous cytokines including interferons, IL-6, IL-12, IL-2, IL-7, IL-9, IL-4, and IL-10. A characteristic of this cytokine is the generation of a positive amplification loop, which heightens the inflammatory response. Expression of the IL-12 receptor is induced by IFNγ. Activated NK cells and T_H1 cells produce IFNγ that potentiates macrophage IL-12 production. IL-12 stimulates further production of IFNγ by NK cells and T lymphocytes, which continues to fuel the reaction in a positive feedback mechanism. Ultimately, IFNγ activates macrophages to kill and degrade phagocytosed microbes. IL-12 potentiates bacterial LPS-induced macrophage TNFα production. IL-12 antagonists reduce mortality in experimental models of LPS-induced septic shock; however, there is no evidence of their efficacy in human clinical trials.[6]

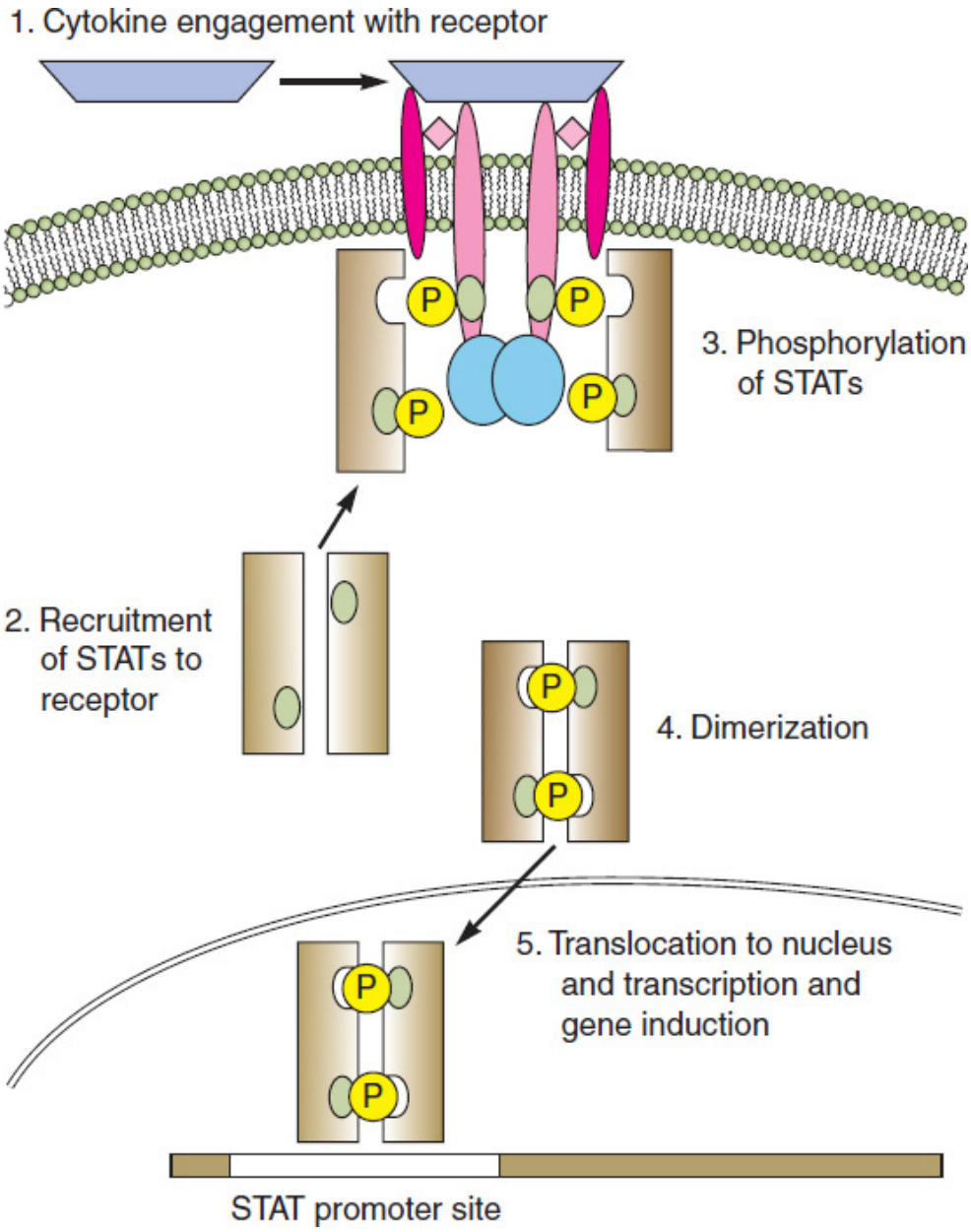

Figure 7.9 JAK/STAT-signaling pathway. JAK (Janus Kinase) components are associated in an inactive form with the cytopasmic portion of cytokine receptors. Cytokine binding leads to receptor aggregation. Adjacent JAK proteins become activated and phosphorylate each other and tyrosine residues. Through the Src homology domain, STAT proteins bind phosphotyrosine residues on the cytoplasmic portion of cytokine receptors. Bound STAT proteins are phosphorylated by bound JAK proteins and subsequently dissociate. Phosphorylated STAT proteins dimerize and then move to the nucleus where they induce transcription by binding to STAT-binding regions within the promoter. (Redrawn from Abbas AK, Lichtman AH. *Cellular and Molecular Immunology*. Philadelphia, PA: Saunders, 2003.)

$CD4^+$ helper T lymphocytes, under the influence of IL-12, differentiate into T_H1 cells, which subsequently activate phagocytes in cell-mediated immunity. IL-12 enhances the cytolytic functions of activated NK cells and $CD8^+$ CTLs, and suppresses T_H2 cell differentiation and effector activity. The inhibition of T_H2 and IL-4 activity confers antiallergic properties to IL-12. IL-12 knockout mice demonstrate diminished IFNγ production and defective T_H1 cell development and cell-mediated immunity against intracellular organisms.[6,43]

Recent data support the potential for anti–IL-12 therapy in the long-term management of rheumatoid arthritis and Crohn's disease. The CERTIFI trial evaluated ustekinumab, a monoclonal antibody to the p40 subunit of IL-12 and IL-23, in adults with moderate-to-severe Crohn disease that were resistant to anti-TNF treatment. They observed that the cohort allocated to ustekinumab had an increased rate of response to induction; for those who responded, maintenance therapy with ustekinumab resulted in significantly increased rates of clinical remission. Similarly, the more recent UNITI-IM-UNITY Study Group showed that among patients with moderately to severely active Crohn's disease, a significantly higher response was observed in those receiving ustekinumab, and subcutaneous administration maintained remission in patient who had a clinical response to induction therapy.[172]

Interleukin 6

IL-6 regulates the acute-phase response to inflammation, characterized by altered thermoregulation (i.e., fever), perturbation in nitrogen balance (i.e., cachexia and catabolism), and the generation of the acute-phase reactants of innate immunity by the liver (**Tables 7.7** and **7.8**).[133,173] It functions in both innate and adaptive immunity to enable the host to recover. Despite in vitro data demonstrating that a variety of cells can produce IL-6, the most prominent in vivo sources of IL-6 are monocytes and macrophages stimulated with LPS or IL-1 or fibroblasts and endothelial cells stimulated with TNFα.[174] Steroids inhibit the induction of IL-6. The receptor for IL-6 consists of cytokine-binding protein and a signal-transducing subunit, which belong to the type I cytokine receptor family. It signals through the JAK-STAT pathway (**Fig. 7.9**).[6]

In conjunction with IL-1 and TNFα, IL-6 regulates the systemic manifestations of the acute-phase response.[173] It potentiates the immune response by inducing B-cell differentiation and activating T cells. It interacts with TNFα to enhance T-cell proliferation and promotes neutrophil activation and accumulation. In adaptive immunity, IL-6 stimulates the growth of B lymphocytes that have differentiated into antibody-producing plasma cells. IL-6 antagonizes LPS-induced TNFα production and TNFα-induced IL-1 production.[175,176]

The SIRROUND-T was a multinational, randomized, double-blind, placebo-controlled, parallel-group phase 3 study that tested the efficacy and safety of sirukumab, a human monoclonal antibody that selectively binds to IL-6 with high affinity, in patients with active rheumatoid arthritis refractory to anti-TNF therapy.[177] In patients who received sirukumab, showed significantly improved signs and symptoms of the disease compared to placebo. The proportions of patients who achieved an American College of Rheumatology criteria (ACR2) was 40% with sirukumab and 24% with placebo control ($p < 0.001$).

Table 7.8 Acute-Phase Proteins

Acute-Phase Protein	Function	
C-reactive protein	Opsonin	**I**
Serum amyloid A	Apolipoprotein	**N**
α_1-acid clycoprotein	Platelet inhibitor	**C**
Fibrinogen	Coagulation, tissue repair	**R**
α_2-macroglobulin	Antiprotease	**E**
α_1-protease inhibitor	Antiprotease	**A**
α_1-antichymotrypsin	Antiprotease	**S**
Haptoglobulin	Antooxidant	E
Hemopexin	Antioxidant	
Ceruloplasm	Antioxidant	
C3	Complement	
Factor b	Complement	
C1 inhibitor	Complement	
C4b-binding protein	Complement	
Mannose-binding lectin	Complement	
Albumin	Transport	**D**
Prealbumin	Transport	**E**
Transferrin	Transport	**C**
		R
		E
		A
		S
		E

High Mobility Group Box 1 Protein (HMGB1)

HMGB1 was initially identified as an architectural chromatin-binding factor that bends DNA and directs protein assembly on specific DNA targets. It is abundant, ubiquitous, and evolutionarily conserved, as evident by the 99%

amino acid homology between rat and human proteins.[70] Thirty years after its original discovery, Tracey and colleagues demonstrated that HMGB1 acts as a late mediator of mortality in murine endotoxemia and sepsis. HMGB1 appeared 8 hours poststimulation and plateaued at 16 to 32 hours, very distinct from the acute rise and fall of early mediators (TNFα, IL-1β) of severe sepsis and septic shock.[70] Recent studies show that systemic concentrations are elevated in those patients who die of sepsis.[178]

HMGB1 is the prototypical damage-associated molecular pattern (DAMP). When cells die by necrosis (i.e., nonprogrammed cell death), HMGB1 is released into the extracellular medium. In contrast, apoptotic cells modify their chromatin so that HMGB1 irreversibly binds, and thus is not release.[179,180] However, HMGB1 is also released by activated cells of many types, via an active process that necessitates shuttling the protein from nucleus to cytoplasm; this event does not require further synthesis.[179–181] Acetylation of HMGB1 appears essential for release, however acetylation of histones as occurs during apoptosis, strengthens its interaction with chromatin and inhibits release.[179,180] Recent studies have shown that nucleocytoplasmic shuttling of HMGB1 involves serine phosphorylation by CaMKIV that enables it to be translocated to the cytoplasm by 14-3-3 and CRM1 chaperones.[182,183] Subsequent release of cytoplasmic HMGB1 appears to involve active secretion through a secretory lysosomal pathway.[179,181] The liver is a major source of circulating HMGB1 in sepsis.[184]

HMGB1 has many of the intercellular signaling activities characteristic of cytokines and therefore is often classified as a proinflammatory cytokine and potent regulator of the inflammatory response. In light of the fact that it is released by immune and nonimmune cells responding to bacterial challenge or by injured cells, it may mediate inflammation consequent to sepsis or trauma. After release, signaling is thought to occur by binding to RAGE with subsequent activation of p21ras, MEK, the MAPK kinases, and NFκB.[146,185] This receptor is expressed on mononuclear phagocytes, vascular smooth muscle cells and neurons. Blocking studies of antibodies to RAGE failed to completely prevent cellular activation suggesting the presence of an alternate receptor. Recent studies suggest that both TLR2 and TLR4 may mediate HMGB1-induced activation of NFκB in macrophages and neutrophils. This observation is very important as it demonstrates that a receptor classically

considered specific for microbial danger signals may interact with an endogenous molecule.[70,146,185] Binding to TLRs results in inflammatory signaling while binding to RAGE results in HMGB1 uptake. Here HMGB1 carries PAMPs such as LPS and DNA into cells where these can activated intracellular PRRs.

In a series of elegant studies, anti-HMGB1 antibodies conferred a dose-dependent protection in animal models of endotoxemia, even when the first dose of anti-HMGB1 antibodies was delayed for 2 hours.[71] This occurred without changes in TNFα, IL-1β, or MIP-2 concentrations. Even more striking are the in vivo CLP models, in which anti-HMGB1 administration up to 24 hours after CLP significantly increased survival, 72% versus 28%.[71] This wider therapeutic window may enable the development of inhibitors of HMGB1 for treat of sepsis.[146,186–188] These observations have stimulated the search for other inhibitors of HMGB1. Ethyl pyruvate a nontoxic food additive, dose-dependently inhibits HMGB1 release, and confers significant protection against the lethality of sepsis, even when the first dose is administered 24 hours after the onset of sepsis. In addition, it inhibits the translocation of NFκB and p38 MAPK signaling.[146,186,189,190] However, few clinical trials have been conducted, and those that have do not suggest clinical benefit.[191]

HMGB1 is also elevated during hemorrhage shock.[192] In a clinical case, serum HMGB1 levels increased significantly within 24 hours of hemorrhagic shock and returned toward basal levels as the clinical condition improved.[193] HMGB1 also appears to mediate cell damage and death in other noninfectious insults. In a model of warm liver ischemia reperfusion, HMGB1 inhibition attenuates hepatocellular injury.[36] Interestingly, this protection, as well as reduced systemic concentrations of HMGB1, was also afforded by inhibiting CaMK.[36]

High levels of HMGB1 have also been found in other conditions of sterile inflammation such as rheumatoid arthritis.[194–196] In human arthritis, overexpression of HMGB1 at the site of joint inflammation may be detected in the synovial fluid of rheumatoid arthritis patients.[195,196] HMGB1 may in fact amplify the effect of local cytokines as suggested by its ability to stimulate macrophages derived from synovial fluid of rheumatoid arthritis patients to release TNFα, IL-1β, and IL-6.[194,197] Hence, HMGB1 may serve as a signal of danger from endogenous threats or perturbations.

Interleukin 15

IL-15 is produced by various cells in response to LPS and other stimuli, though the principal cellular source is mononuclear phagocytes (**Table 7.7**). It is structurally homologous to IL-2, as is its receptor and the IL-2R. IL-15 stimulates the proliferation of NK cells similar to the manner by which IL-2 functions later in the adaptive immune response. It also acts as a T-cell growth and survival factor especially for long-lived memory $CD8^+$ T cells.[6]

Interleukin 17

7 IL-17 is an inflammatory cytokine involved in host defense, tissue repair, the pathogenesis of inflammatory disease and cancer progression. The IL-17a gene was initially identified in T cells, and subsequent studies have characterized a distinct family of IL-17 members: IL-17B–IL-17F.[198]

IL-17A and IL-17F signal through the IL-17RA and IL-17RC receptor subunits to mediate qualitatively similar but quantitatively distinct signals, with the following graded signaling potency: IL-17A > IL-17A–IL-17F > IL-17F. Whereas IL-17RA is ubiquitously expressed, the more restricted expression of IL-17RC limits IL-17 signaling mostly to nonhematopoietic epithelial and mesenchymal cells. Subsequent to receptor binding, IL-17 signaling induces inflammatory gene expression via the transcription factor NF-κB and the activation of MAPK pathways.[198]

IL-17's main effect is to regulate innate immunity. IL-17 induces neutrophils, by indirectly stimulating the release of G-CSF, CCL2, and the CXC chemokines from nonhematopoietic cells. IL-17 deficiency is nearly always associated with reduced activation of neutrophils. IL-17 contributes to the response to extracellular bacteria and intracellular pathogens such as *Mycobacterium tuberculosis*. Patients with mutations of IL-17RA genes experience a mucocutaneous infection with *Candida albicans* and *S. aureus*. This also provides a causal between the early loss of T_H17 cells during HIV infection and elevated incidence of opportunistic fungal infections.[198]

While regulated IL-17 activity supports a physiologic response to infection and tissue injury, chronic IL-17 activity is pathogenic and promotes cancer and autoimmunity. IL-17 has been shown to promote tumorigenesis and tumor progression. However, the observation of its role in autoimmunity has inspired intense interest in the IL-17 family of cytokines for potential

therapeutic use. Mouse models of arthritis show that T_H17 rather than T_H1 cells are dominant instigators of autoimmunity. Accordingly, blockade or deletion of IL-17 and IL-23 in mice reduced disease signs. This has rapidly "come to the bedside." The biologic ustekinumab has been approved for use, and its success has spurred development of more specific therapies directed against IL-17–IL-17R and IL-23. The efficacy of the biologics secukinumab and ixekizumab, which are monoclonal antibodies to IL-17, in psoriasis is particularly striking. These drugs also work in psoriatic arthritis and ankylosing spondylitis and in a subgroup with rheumatoid arthritis. In preclinical settings, blockade of IL-17 also ameliorates pathologies triggered by environmental challenges in models of asthma and COPD.

Interleukin 18

IL-18 is structurally homologous to IL-1 and utilizes a similar IRAK-signaling pathway (**Table 7.7**). Macrophages responding to microbial challenge or exposure to LPS are the principal source. Its primary function is to stimulate the production of IFNγ by NK cells and T cells, and in synergizing with IL-12, augments cell-mediated immunity. Knockout mice lacking IL-18 are deficient in IFNγ production, and concomitant IL-12 deficiency eliminates all IFNγ production and any T_H1 response.[6]

Interferons (Type I)

Type I interferons possess potent antiviral and antitumor properties (**Table 7.7**). It is from this ability to "interfere" with viral infection that the name is derived. They are subcategorized into α and β interferons. Mononuclear phagocytes are the major source of interferon α, whereas many cell types produce interferon β. The most potent stimulus inducing the synthesis and release of either is viral infection, particularly double-stranded RNA produced during viral replication. Other inducers include IL-1, TNFα, LPS, and antigen-activated T cells. Both groups bind to the same cell surface receptor and induce similar responses by signaling through the JAK/STAT pathway (**Fig. 7.9**).

These cytokines provide the first line of defense against viral infection and promote cell-mediated immunity against intracellular pathogen. They are secreted from virally infected cells to protect neighboring uninfected ones by

inducing the synthesis of a number of enzymes that interfere with viral RNA or DNA transcription and viral replication. Through enhanced expression of class I MHC molecules, the type 1 interferons facilitate recognition of class I–associated viral antigens on infected cells by CTLs and increase the efficiency of CTL-mediated killing. Type I interferon stimulates the development of T_H1 cells by promoting these cells to express IL-12 receptor. They can also stimulate B-cell development, proliferation, and immunoglobulin heavy chain switching from IgM to IgG.[199–201] Knockout mice lacking the receptor for these cytokines are susceptible to viral infections. Interferons are currently in clinical use for hepatitis B and C infection, multiple sclerosis, CML, and Kaposi sarcoma.[199–201]

Interleukin 10 (Cytokine Synthesis Inhibiting Factor)

IL-10 inhibits activated macrophages and APC and functions in a counterregulatory mechanism to suppress innate immune reactions (**Table 7.7**). It is produced mainly by macrophages, and hence functions by negative feedback. T lymphocytes, particularly the T_H2 subset, B cells, and some other nonlymphoid cells produce IL-10, in response to a variety of stimuli including LPS, TNFα, IL-2, IL-4, and IL-13.

IL-10 binds to a type II (interferon) receptor. Though the manner by which it effects curtailment of the inflammatory response is unknown, its presence inhibits NKκB activation and the generation of inflammatory mediators. Thus, it may inhibit, in some manner, the activation of signal transduction cascades and gene activation in proinflammatory pathways.[6,202]

IL-10 terminates many of the functions of activated macrophages and participates in reestablishing homeostasis as the infection resolves. It downregulates proinflammatory cytokine (TNFα, IL-1, IL-6, and IL-8) production, suppresses the production of IL-12 and inhibits IFNγ production and the innate and cell-mediated immune responses.[6,74,133] It represses the expression of costimulators and class II MHC molecules on APC, thereby terminating T-cell activation and inhibiting cell-mediated immunity.[6] In neutrophils it inhibits cytokine release, superoxide generation, migration, and even survival.[203] In combination with IL-4 it inhibits IFNγ release and IL-12 production to limit differentiation and function of T_H1 cells, favoring a T_H2 profile.[74]

IL-10 knockout mice develop inflammatory bowel disease, which is hypothesized to result from unregulated macrophage reaction to enteric microbes.[204] In observational studies of ARDS or MODS, serum IL-10 levels were often elevated, and those patients with the highest systemic concentrations died.[202] It is unclear whether this is actually a pathologic response, or merely a marker of disease severity. Contemporary belief is that IL-10 is not a mediator of immunosuppression, but rather, important for immunoregulation.

Late Cytokines/Adaptive Immunity

Interleukin 2 (T-Cell Growth Factor)

Interleukin 2 stimulates the growth and proliferation of T lymphocytes and is responsible for T-cell clonal expansion after antigen recognition (**Table 7.7**).[205] IL-2 is produced by $CD4^+$, and to a lesser extent $CD8^+$ T cells. The receptor is heterotrimeric, consisting of three noncovalently associated proteins, α, β, and γ. The α and β chains are involved in cytokine binding, and the β and γ chains mediate signal transduction.[6] Antigen recognition enhances the expression of functional IL-2 receptors, which confers a degree of specificity, as those T cells recognizing antigen are preferentially induced to proliferate in response to IL-2. Though, the α chain appears on T-cell activation and binds IL-2, signal generation necessitates the β and γ chains. Cells expressing the complete α, β, and γ complex bind IL-2 with higher affinity (Kd of 10^{-11} M), and growth stimulation of such cells occurs at a low IL-2 concentration.[6] Upon antigen receptor-mediated T-cell activation, IL-2R α is rapidly upregulated, which reduces the concentration of IL-2 needed to stimulate growth. Therefore, antigen-stimulated T cells are more responsive to IL-2 than naïve T cells. This receptor signals through numerous signal transduction pathways including the JAK/STAT, PI 3 kinase, and MAP kinase pathways (**Figs. 7.6** and **7.9**).

IL-2 functions in an autocrine and paracrine fashion to induce the proliferation of the antigen-specific cells. After exposure to IL-1, there is a rise in cyclins and activation of cyclin-dependent kinases that stimulates the progression of the cell cycle from the G1 to the S phase. A reduction in p27, an inhibitor of cyclin–kinase complexes, facilitates this progression, and the

induction of Bcl-2, an antiapoptotic protein, facilitates survival. It also stimulates the production of other cytokines such as IFNγ and IL-4.[6]

IL-2 promotes the proliferation and differentiation of many immune cells. NK cells are stimulated to grow and transform into lymphocyte-activated killer (LAK) cells. In combination with IFNγ and IL-12, IL-2 can trigger a positive feedback cycle of NK activation. IL-2 stimulates B-cell growth and antibody synthesis. Repeated activation of $CD4^+$ T cells in the presence of IL-2 sensitizes these cells to apoptosis by fas-fas-ligand. IL-2 may also stimulate the development of regulatory T cells, and IL-2 knockout mice develop autoimmunity. Knockout mice lacking the γ chain develop X-linked severe combined immunodeficiency syndrome. This is probably due to an inability of immature T cells to respond to IL-7.

Our understanding of these mechanisms has enabled the development of several immunomodulatory drugs. Daclizumab (anti-Tac) is a humanized monoclonal antibody that binds, thereby inhibiting, the α subunit of the IL-2 receptor of T cells. Both the DECIDE and SELECT trials provide compelling data supporting the clinical utility of IL-2 receptor inhibition in the management of multiple sclerosis. The Ruxolitinib (JAK1 inhibitor) is an orally available biochemical inhibitor of JAK1/2 that has been approved for us in the treatment of myeloproliferative disorders and is currently under investigation for chronic graft versus host disease. Tofacitinib (JAK3 inhibitor) has been approved to treat adults with moderately and severely active rheumatoid arthritis who have had an inadequate response to methotrexate. It is also used to treat psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis. IL-2 has been used in the management of cancer, in particular renal cell carcinoma, and investigation continues to determine clinical applications.[206–209]

Interleukin 4

IL-4 is the major stimulus for the production of IgE antibodies and for the development of T_H2 cells from naïve $CD4^+$ T cells (**Table 7.7**). The principal cellular sources are $CD4^+$ T cells, mast cells, and basophils. The IL-4 receptor belongs to the type I cytokine receptor family and signals through the JAK/STAT pathway (**Fig. 7.9**).[210] IgE is integral in orchestrating the defense against parasitic infections. It stimulates IgE production and mast

cell/eosinophil-mediated reactions and induces B-cell Ig heavy chain class switching to the IgE isotype. However, IL-4 also serves a counterregulatory role by inducing T_H2 cell differentiation and growth. IL-4 antagonizes the macrophage-activating effects of IFNγ and thus inhibits cell-mediated immunity.

Interleukin 5

IL-5 is produced by T_H2 cells, IL-C2, and activated mast cells and activates eosinophils (**Table 7.7**). It signals through the type I cytokine receptor and the JAK/STAT pathway (**Fig. 7.9**). IL-5 is an inducer of eosinophil growth, differentiation, and activation, and also participates the eradication of helminthic infection. IL-5 also stimulates the proliferation of B cells and the production of IgA antibodies.[6]

Interleukin 13

IL-13 is produced by T_H2 cells and some epithelial cells and is structurally homologous and functionally similar to IL-4 (**Table 7.7**). The receptor is found mainly on nonlymphoid cells and can be activated by either IL-13 or IL-4. IL-13 downregulates the expression of Fcγ on monocytes and macrophages, thereby decreasing antibody-dependent cellular cytotoxicity. It increases 15S-HETE and lipoxin A_4, both of which antagonize proinflammatory leukotrienes. However, they can increase the expression of MHC class II and costimulatory molecules on monocytes, and thereby serve an immunostimulatory function. The major action is to inhibit the activation of macrophages, drive macrophages toward M2, and to antagonize IFNγ.[211]

Interferon γ (IFNγ)

IFNγ is produced by NK cells, T_H1 cells, and $CD8^+$ cells and as the principal stimulus for macrophage activation, provides necessary functions during both innate and adaptive immune responses (**Table 7.7**). It modulates cellular differentiation, cytotoxicity, cytokine production, cellular adhesion, and oxidative metabolism. During innate immunity, NK cells secrete IFNγ upon exposure to pathogen or stimulation by IL-12. $CD8^+$ T cells and the T_H1 subset of $CD4^+$ T cells produce it in response to MHC-bound peptide antigen

with a costimulatory signal. The IFNγ receptor is composed of two homologous proteins belonging to the type II cytokine receptor family and functions through the JAK/STAT pathway (**Fig. 7.9**).[6]

The antiviral and antitumor properties of IFNγ are redundant with those of type I interferons. In concert with TNFα and IL-12 it forms one arm of a positive feedback loop fueling the activation of both NK cells and macrophages. Stimulated macrophages activate NK cells by releasing TNFα and IL-12. These NK cells produce IFNγ, which further stimulates macrophages to secrete more TNFα and IL-12.[212,213]

IFNγ induces the genes encoding the enzymatic machinery required for generating ROS generation and provides the principle stimulus for macrophages to kill phagocytosed microbes. It regulates the expression of MHC class I and class II molecules and costimulators of APC, and induces the transcription of enzymes regulating antigen processing.[212,213]

IFNγ synergizes with TNFα to activate the endothelium and upregulate adhesion molecule expression; in doing so it facilitates lymphocyte recruitment and leukocyte recruitment. Interferon promotes the differentiation of naïve $CD4^+$ cells into T_H1 cells and inhibits the proliferation of T_H2 cells, in part, by inducing IL-12, the major T_H1-inducing cytokine, from activated mononuclear phagocytes. It promotes B-cell switching to certain IgG subclasses, notably IgG2a, and inhibits the switching to IL-4–dependent isotypes such as IgE and IgG1. These IgG subclasses bind the Fcγ receptors on phagocytes and activate complement, thereby promoting phagocytosis of opsonized microbes. It activates PMNs and stimulates the cytolytic activity of NK cells. The net effect is to promote macrophage-rich inflammatory reactions while inhibiting IgE-dependent eosinophil-rich reactions. IL-10, by suppressing macrophage release of TNFα and IL-12, negatively regulates IFNγ production.

IFNγ also demonstrates counterregulatory properties. It selectively inhibits LPS-induced expression of CXC chemokines. It upregulates macrophage production of IP-10, MIG, and ELR-negative chemokines that inhibit neutrophil chemotaxis and activation and decreases macrophage release of ELR-positive CXC chemokines (e.g., IL-8), which are chemotactic for neutrophils.[6]

Transforming Growth Factor β (TGFβ)

TGFβ is a homodimer synthesized and secreted by activated T cells, macrophages, and many other cells (**Table 7.7**). It is primarily immunosuppressive and inhibits the proliferation and activation of lymphocytes and other leukocytes. It promotes wound healing by increasing extracellular matrix protein synthesis and stimulating mononuclear cell and fibroblast influx.[214–216] Though the family consists of three closely related isoforms, most cells utilize TGFβ. Its effects are mediated through two high-affinity TGF receptors (types I and II) that signal through a serine/threonine kinase domain that phosphorylates transcription factors called SMADS.[6]

TGFβ inhibits the proliferation and differentiation of T cells and the activation of macrophages. It favors differentiation of $CD4^+$ cells to the T_H2 subset and inhibits MHC class II surface expression. By suppressing the expression of MHC class II antigen, it abrogates the adaptive immune response. Macrophages demonstrate diminished ROS production and TNFα and NO release. It directly counteracts the influence of proinflammatory cytokines on PMNs and endothelial cells, and in combination with IL-4, IL-13, and IL-10 can antagonize the production or effects of these proinflammatory mediators. Knockout mice, deficient in TGFβ develop uncontrolled inflammatory lesions.[6,43]

Cytokines that Stimulate Hematopoiesis

Cytokines are necessary for normal hematopoiesis. Several of the cytokines stimulated during both innate and adaptive immune responses are mitogenic for and induce differentiation of bone marrow progenitor cells. CSFs are cytokines made by activated T cells, macrophages, endothelial cells, and bone marrow stromal cells that stimulate increased production of inflammatory leukocytes by bone marrow progenitors. Receptors for granulocyte-macrophage colony-stimulating factor (GM-CSF) and G-CSF are of the class I family of cytokine receptors. GM-CSF is expressed by T and B cells, macrophages, mast cells, fibroblasts, and endothelium in response to stimuli such as IL-1, IL-2, LPS, and TNFα. It stimulates neutrophils, monocytes, macrophages, and DCs and is a powerful inducer of hematopoiesis. It enhances cytokine release, degranulation, and phagocytosis

of opsonized particles in neutrophils. In monocytes and macrophages, it enhances cytotoxicity and cytokine release. It promotes the activity of APCs and the maturation of bone marrow cells into DCs and monocytes.[217] G-CSF is produced by macrophages, endothelial cells, fibroblasts, and bone marrow stromal cells. It functions as an endocrine hormone to mobilize neutrophils and induces subsequent leukocyte proliferation and maturation. In 1991, the FDA approved the use of G-CSF for use in patients with neutropenia.[218,219]

Stem cell factor or c-Kit ligand is synthesized by marrow stromal cells and binds to a cell surface tyrosine kinase receptor on pluripotent stem cells that is the protein product of the cellular proto-oncogene c-kit. Its effects appear to be permissive, as it is corequisite for stem cell responsiveness to other CSFs, yet in isolation does not stimulate colony formation. It may also play a role in sustaining the viability and proliferative capacity of immature T cells in the thymus.[6]

IL-3 is a product of $CD4^+$ T cells that promotes the differentiation of immature marrow progenitors into all known mature cell types. It also promotes the growth and development of mast cells. Surprisingly, despite these important functions, murine knockouts do not manifest noticeable impairment of hematopoiesis.[6]

IL-7 is secreted by bone marrow stromal cells and promotes the growth and survival of immature precursors committed to the B and T lymphocyte lineages. Knockout mice, deficient in IL-7 or its receptor, are lymphopenic and possess diminished populations of B and T cells.[6]

The Complement System

8 The complement system is integral to both innate and adaptive immunity. It has the capacity to independently eliminate organisms and to facilitate host defense by marking foreign particles for phagocytosis through opsonization. Many pathophysiologic inflammatory diseases, immune complex diseases, ischemia/reperfusion injury, and ARDS are considered consequences of excessive or unregulated induction of this system.[220–223]

The system consists of 3 pathways comprised of approximately 30 serum and cell surface proteins that interact with one another and with other molecules of the immune system in a highly coordinated fashion. These cascades involve the sequential proteolytic activation of zymogens to

generate enzymes with proteolytic activity. This mechanism for activation amplifies the response because each individual enzyme activated can cleave numerous zymogens in the next step and generate multiple activated enzyme molecules. Ultimately, the products of complement activation adhere to microbial cell surfaces or to antibody-bound microbes and other antigens to directly or indirectly eliminate these pathogens. Temporal and spatial regulation to the focus of infection is ensured both by the transience of activation of these enzymes in the absence of microbes or antigens and by several circulating proteins that provide surveillance.[220,222]

The complement cascade is divided into three distinct pathways: (1) the classical pathway (humoral immunity), which is activated by antibody bound to antigen, (2) the alternative pathway (innate immunity) in which complement is activated by components of microbial cell surfaces, and (3) the mannose/lectin pathway (innate immunity), which is activated by a plasma lectin that binds to mannose residues on microbes. Despite differences in which the cascade is activated, all three complement pathways ultimately result in the cleavage of C3 and share the same late cascade.[220,222]

The alternative pathway functions in the absence of antibody and is phylogenetically the oldest pathway (**Fig. 7.10**). Bacteria, viruses, fungi, and parasites all function as stimuli. Initial activation begins with the cleavage of C3 and the stable attachment of its product C3b to the microbial surface. Bound C3b finds factor B, which is subsequently cleaved by a plasma serine protease called factor D to generate Bb. The C3bBb complex is called the alternative pathway C3 convertase and functions to cleave more C3. In doing so the convertase serves as an amplification step in both the classical and alternative pathways. Properdin prolongs the half-life of C3 convertase by delaying the release of Bb from C3bBb. C3b is the recognition component of the alternate pathway and is responsible for the opsonization of bacteria. C3a in conjunction with C5a and C4a induces acute inflammation by activating mast cells and neutrophils. These inflammatory mediators play a significant role in increasing blood vessel permeability, vasodilatation, edema formation, neutrophil adhesion and activation, chemotaxis, and the release of toxic oxygen species and lysosomal enzymes from phagocytic cells. The binding of another C3b to this complex generates the alternative pathway C5 convertase, C3bBb3b.[6,220,222]

Activation of the alternative pathway is restricted to the cell surface of microbes, as mammalian cells possess several regulatory proteins to rapidly degrade any C3bBb. Excessive amplification is regulated by factors H and factor I. H accelerates the decay and delays the formation of C3bBb. It also acts as a cofactor for I to degrade C3 into iC3b, which is unable to bind B to generate C3 convertase. Decay acceleration factor (DAF) hinders C3 convertase assembly and mediates its dissociation in all three pathways. Also, the protein properdin, which stabilizes this alternative pathway C3 convertase, has a higher affinity for microbial than mammalian cell surfaces.[6,220,222]

The classical pathway is the primary mediator of adaptive humoral immunity and is initiated by binding of the complement protein C1 to IgG or IgM molecules engaged with antigen (**Fig. 7.10**). Other substances such as lipid A in endotoxin and mitochondrial membranes may activate this pathway independent of antigen–antibody complexes in vitro.[220,224]

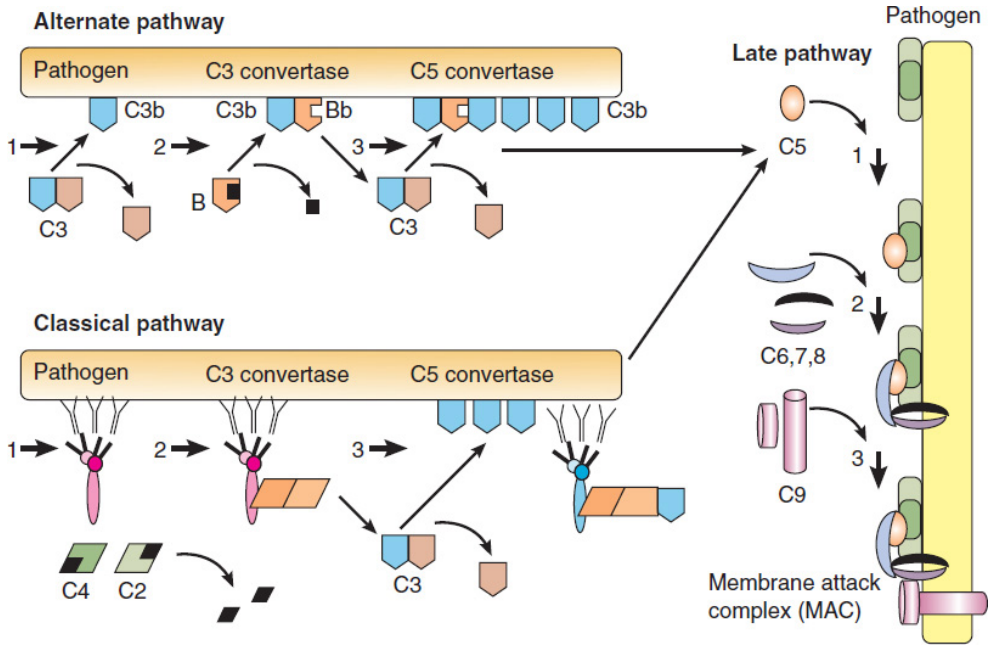

Figure 7.10 Complement pathways. Alternate pathway: 1. C3 is cleaved to C3b. 2. C3b binds and cleaves B to Bb to form C3 convertase (C3bBb). 3. Another C3b binds C3 convertase to form C5 convertase (C3bBbC3b). Classical pathway: 1. C1 binds immunoglobulin. 2. C1 binds and cleaves C4 and C2 to C4b and C2a to form C3 convertase (C4b2a). 3. C4b2a binds another C3b to generate C5 convertase (C4b2aC3b). Late pathway: 1. C5 converatse cleaves C5 to form C5b, which integrates into the plasmallema. 2. C6–8 are recruited, forming the C5b-8 complex. 3. C5b-8 recruits numerous C9 subunits, which form a pore in the pathogen cell wall. (Redrawn from Abbas AK, Lichtman AH. *Cellular and Molecular Immunology*. Philadelphia, PA: Saunders, 2003.)

C1 is a calcium-dependent trimeric protein consisting of C1q, which recognizes and binds the Fc region of the immunoglobulin, and C1r and C1s, which are proteases. C1q engages the Fc portion of the immunoglobulin μ and γ heavy chains. Each Fc region has a single C1q binding site, yet for activation, each C1q molecule must bind to two Ig heavy chains. Hence, multiple antibodies must be approximated for activation, which restricts activation to foci of immunoglobin engagement. IgM exists as a pentamer enabling it to bind to two C1q molecules, and hence it is more efficient at complement activation.[6,220,224]

Interaction between C1q and the immunoglobin Fc region induces a conformational change in C1q that activates C1r, which subsequently cleaves and activates C1s. C1s cleaves C4 to generate C4b and C4a. The C4a anaphylatoxin possesses properties similar to those described for C3a. C4b

localizes to immune complexes on the cell surface. C2, after complexing with C4b, is cleaved by C1s, thereby generating the classical C3 convertase C4b2a complex, which has the ability to cleave C3. The C3b generated can bind Bb, producing more C3 convertase and amplifying the signal. The key early steps of the alternative and classical pathways are analogous: C3 and factor B of the alternative pathway are homologous to C4 and C2 in the classical pathway. C3b can also combine with the classical C3 convertase to generate C4b2a3b, the classical C5 convertase.[6]

Numerous regulatory mechanisms exist to restrict activation to sites of inflammation. Excessive classical C3 convertase activity is prevented by the rapid decay of C2a from the complex, which renders the complex unstable. C1 inhibitor covalently binds C1s, reducing the half-life of activated C1 to only 13 seconds. C4-binding protein enhances spontaneous dissociation of C4b2a and also acts as a cofactor for C3b/C4b inactivator, which degrades C4b.[43]

The mannose-binding lectin (MBL) pathway is activated by microbial polysaccharides bound to circulating lectins; MBL serves as the recognition unit of the MBL pathway. This pathway recognizes polysaccharides with high mannose content and other oligosaccharides with characteristic linkages found exclusively on pathogens and not on normal host components. Binding is calcium-dependent and results in the activation of MBL-associated serine proteases (MASP-1 and MASP-2). Activated MASP-2 cleaves and activates C4 and C2 in the same fashion as the classical complement pathway. Subsequent steps of complement activation of the MBL pathway mirror those of the classical complement pathway.[220,225,226]

The C5 convertases generated during either the classical or alternative pathway initiate a cascade of events that culminates in the formation of the cytocidal membrane attack complex (MAC). Specifically, C5 convertase cleaves C5, yielding C5a and C5b. C6 and C7 bind to generate the C5b67 complex. This hydrophobic moiety penetrates deeply into the lipid bilayer as a high-affinity receptor for C8. Binding of C8 forms the complex C5b–8 that recruits numerous C9 subunits, which polymerize to form pores in the plasma membrane of bacteria. The pores structurally resemble the membrane pores formed by perforin, the cytolytic granule protein found in CTLs and NK cells. Their diameter may span 100 angstroms, which prevents the maintenance of vital ionic gradients, induces osmotic lysis, and ultimately the

death of target cells or pathogens. Patients with deficiencies in the terminal components of C5, C6, C7, and C8 are susceptible to meningococcal and gonococcal infections.[6,227] By contrast, recent studies suggest that aberrant induction of the complement system, specifically C5a, plays an integral role in inducing paralysis of the innate immunity and the development of ARDS and MODS.

The effects of complement are in part mediated through several CRs. Opsonization and phagocytosis are important mechanisms for pathogen destruction, and phagocytic cells express receptors for complement factor C3 components. Complement receptor type 1 (CR1), the C3b receptor for C3b and C4b, mediates engagement of and facilitates phagocytosis of complement bound microbes and the clearance of immune complexes from the circulation. It is expressed on a variety of cells including RBC, neutrophils, monocytes, eosinophils, and T and B cells. RBCs facilitate elimination by transporting these opsonized particles to the liver and spleen where the immune complexes are removed by phagocytes. CR2 stimulates humoral immune response by enhancing B-cell activation by antigen and by promoting the trapping of antigen–antibody complexes in germinal centers. In humans, this receptor is the receptor for EBV. CR3 and CR4 are β_2 integrins that bind the iC3b-processed fragment of C3 and promote macrophage and neutrophil phagocytosis of iC3b-opsonized antigen.[6,43]

This entire cascade is under strict regulation to ensure that activation is restricted to sites of inflammation and infection. This regulation is needed as low-level activation is always occurring, and if not quelled, would certainly damage normal tissues. Even when locally activated, byproducts may damage nearby cells and tissues. Several circulating proteins function to do this. C1r and C1s are inhibited by C1 inhibitor, a serine protease inhibitor that mimics C1r and C1s. C1 inhibitor targets activated C1qrs, and after attachment, C1r–C1s dissociate and activation of classical complement ceases. This inhibition prevents the accumulation of active C1r–C1s, thereby limiting the duration during which active C1r–C1s can initiate the cascade.[6] C1 inhibitor also inhibits other circulating inflammatory serine proteases including kallikrein and factor XII, both of which can activate the formation of bradykinin.[6] Hereditary angioneurotic edema is an inherited deficiency of

C1 inhibitor and manifests as acute intermittent edema of the skin and mucosa causing abdominal pain, vomiting, diarrhea, and airway obstruction.

MCP, CR1, and decay-accelerating factor (DAF) are regulatory proteins that bind to C3b and C4b deposited on cell surfaces and competitively inhibit the binding of other components of the C3 and C5 convertases, such as Bb and C2a, and thereby block further progression of the cascade. These proteins are only produced by mammalian cells. Deficiency of an enzyme required to form the linkages necessary to express DAF underlies paroxysmal nocturnal hemoglobinuria, a disease characterized by recurrent intravascular hemolysis due to unregulated complement activation on the surface of erythrocytes. Cell-associated C3b is proteolytically degraded by a plasma serine protease called factor I which is active only in the presence of regulatory proteins such as MCP, factor H, C4BP, and CR1. MAC formation is inhibited by CD59, a membrane protein that incorporates itself into growing MACS and inhibits the incorporation of C9. It is not present in microbes. The function of these regulatory proteins may be overcome by increasing amounts of complement activation.[6]

Several disease states are considered either the consequence of or propagated by aberrant complement activation, and thus, considerable interest exists in understanding methods of modulating this cascade and thereby restoring complement homeostasis. Paroxysmal nocturnal hemoglobinuria is a rare acquired disorder characterized by chronic complement-mediated intravascular hemolysis. Eculizumab is a humanized monoclonal antibody that binds to the terminal complement component C5, inhibiting the cleavage of C5 by C5 convertase into C5a. Similarly, Ravulizumab is a new complement C5 inhibitor that through high-affinity binding to C5 inhibits C5a and C5b formation. Both have demonstrable efficacy in preventing immune activation and hemolysis and treating paroxysmal nocturnal hemoglobinuria.[228,229] They are also used in the treatment of hemolytic uremic syndrome. Other studies are in progress to test the ramifications of targeting the complement pathway in age-related macular degeneration, aquaporin-4–positive neuromyelitis optic spectrum disorder, and Guillain–Barré syndrome.[230–233]

9 Lipid Mediators

Eicosanoids

Eicosanoids are 20-carbon lipid inflammatory mediators that are derived from membrane arachidonic acid and are involved in numerous homeostatic processes and inflammation. These lipid mediators are not stored in tissues but are synthesized de novo within seconds in response to a variety of stimuli, including mechanical trauma, specific cytokines, growth factors, and other mediators (**Fig. 7.11**). Although most cells are capable of producing eicosanoids, neutrophils and macrophages are the predominant sources. They are rapidly degraded in the circulation, which limits their role primarily to that of autocrine and paracrine mediators of local inflammatory changes.[234–236]

The liberation of the precursor molecule, arachidonic acid, is the major rate-limiting step. The family of PLA_2, in particular type IV cytosolic PLA_2, is responsible for eicosanoid production; cells lacking type IV PLA_2 are devoid of eicosanoid synthesis.[237] Many PLA_2 are transcriptionally regulated by IL-1 and TNFα, whereas others are regulated by the MAP kinase pathway and by calcium-dependent translocation to membranes. Once formed, arachidonic acid metabolism proceeds along one of two pathways.[234–236]

Cyclooxygenase Pathway (Prostaglandins)

Cyclooxygenase catalyzes the initial step of a series of reactions that converts arachidonic acid to prostanoids (**Fig. 7.11**). There are two isoforms, COX1 and COX2; the former is constitutively expressed, whereas COX2 is inducible. COX2 is considered more important during inflammatory processes such as fever, hyperalgesia, and edema formation. Either enzyme catalyzes the conversion of arachidonic acid to the endoperoxidase PGG_2, which is subsequently converted to PGH_2. PGH_2 serves as the precursor to numerous specific prostaglandins. All of these products possess very short half-lives and are rapidly inactivated.[237,238]

Prostaglandins mediate their effects through G protein signaling (**Table 7.9**). Prostacyclin (PGI_2) is produced by the endothelium as a potent vasodilator and inhibitor of platelet aggregation and adhesion; these characteristics enhance tissue perfusion. PGI_2 inhibits neutrophil chemotaxis and activation and interacts synergistically with PGE_2 to increase vascular

permeability through the bradykinin pathway. PGE_2 is the predominant anti-inflammatory prostaglandin and is produced by nearly all inflammatory cells. It is produced in response to IL-1 and mediates the hypothalamic fever response and synergizes with bradykinin and histamine to mediate pain. It is a bronchodilator, inhibits both IL-1 production and T-cell responsiveness to IL-1, and at low concentrations suppresses TNFα production. It also inhibits neutrophil chemotaxis and activation and T_H1 lymphocyte proliferation.[237,238] There is some suggestion from animal studies that PGE_2, PGE_1, and PGI_2 may be beneficial in response to sepsis through their endogenous counterregulatory properties. Administration of each of these has been shown to improve survival in several animal models of hypovolemic and traumatic shock, though clinical trials have failed to identify benefit.[238] PGD_2 is a potent bronchoconstrictor that inhibits neutrophil chemotaxis and activation. TXA_2, PGG_2, and PGH_2 oppose the actions of prostacyclin by promoting platelet aggregation and inducing bronchoconstriction. TXA2 produced by platelets and macrophages is a powerful vasoconstrictor that induces neutrophil accumulation and increases vascular permeability.[234–236,239] There is substantial evidence that TXA_2 plays a significant role in early acute-phase organ injury.[238]

Lipoxygenase Pathway (Leukotrienes and Lipoxins)

Leukotrienes and lipoxins are leukocyte-derived molecules synthesized by the oxidation of arachidonic acid by 3 lipoxygenase (LO) enzymes: 5-LO, 12-LO, and 15-LO (**Fig. 7.11**). 5-LO associates with the perinuclear membrane protein 5-LO–activating protein (FLAP) to catalyze the formation of 5-hydroperoxyeicosatetraenoic acid (5-HPETE). 5-HPETE is subsequently converted to LTA_4 by the combined efforts of a dehydrase and 5-LO. LTA_4 serves as the precursor for either LTB_4 or LTC_4. LTC_4 can in turn be successively hydrolyzed to the dipeptide derivative LTD_4 and the LTE_4. Additional LO activity results in the production of 12-HPETE, 12-HETE, and 15-HPETE. These compounds exhibit biologic activity, although they are not as potent as the leukotrienes or prostaglandins. The leukotrienes are inactivated by oxidation followed by dehydration.[235–237,239,240]

The major lipoxygenase product of neutrophils is LTB_4, though macrophages may also synthesize this compound. This compound is potently chemotactic for both neutrophils and eosinophils. By upregulating endothelial cell surface adhesion molecules, it promotes leukocyte recruitment. It increases vascular permeability, either directly or through interaction with neutrophils and endothelial cells. LTB_4 has also been shown to induce hyperalgesia.[130,237]

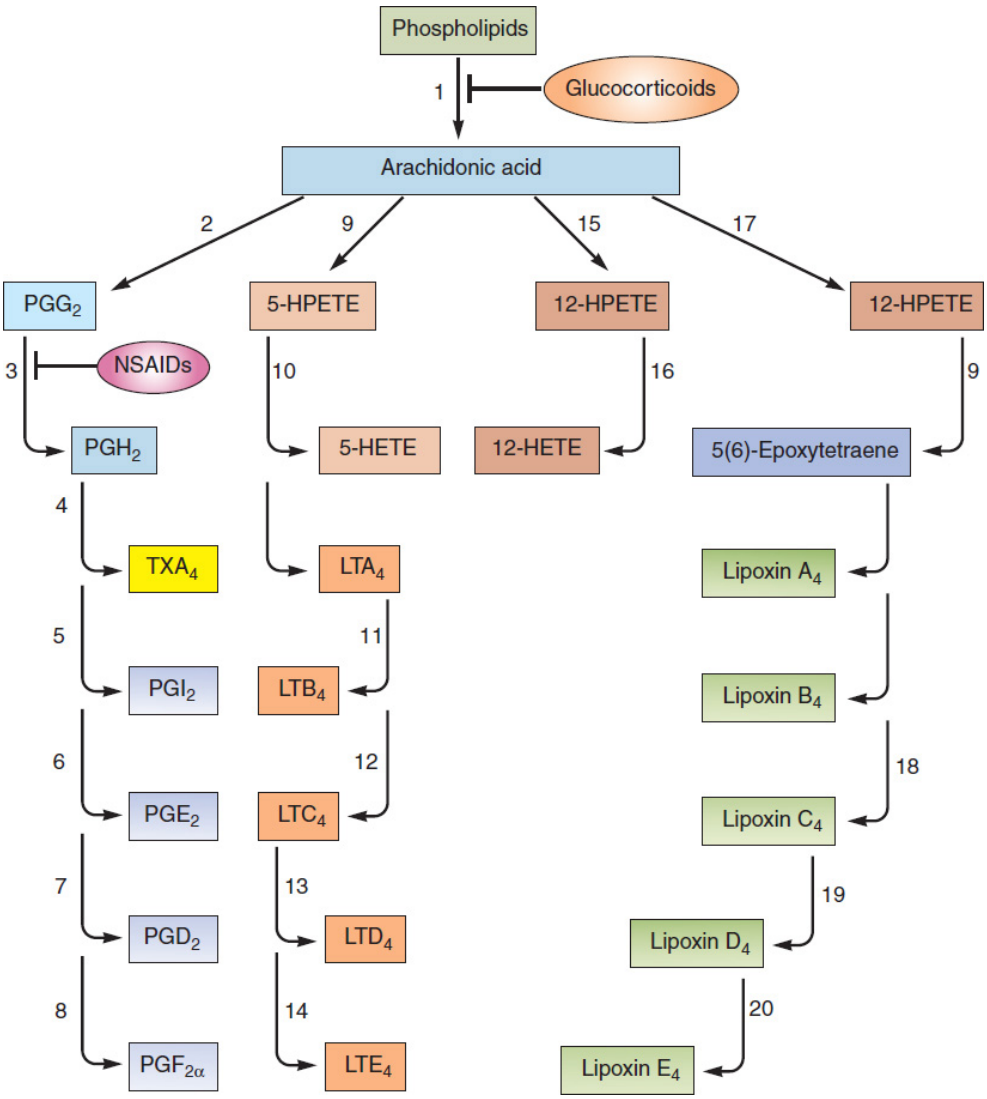

Figure 7.11 Eicosanoid production. 1. Phospholipases; 2. Cyclooxygenase; 3. Hydroperoxidase; 4. Thromboxane synthetase; 5. Prostacyclin synthetase; 6. E-isomerase; 7. D-isomerase; 8. F-reductase; 9. 5-Lipoxygenase; 10. Glutathione peroxidase; 11. Hydrolase; 12. Glutathione S-transferase; 13. γ-Glutamyl transpeptidase; 14. Cysteinyl glycinase; 15. 12-Lipoxygenase; 16. Peroxidase; 17. 15-Lipoxygenase; 18. GSH-cis-11-trans lipoxin A_4; 19. α-Glutamyl transferase; 20. Dipeptidase.

LTC_4, LTD_4, and LTE_4 comprise the family of slow-reacting substances of anaphylaxis (SRSA), compounds synthesized by mast cells during anaphylactic reactions. LTC_4 is the major eicosanoid product of eosinophils and the only mast cell-derived product of LO. These three leukotrienes are potent vasoconstrictors and the most powerful bronchoconstrictors in

humans, being three orders of magnitude more potent than histamine. They also increase vascular permeability and are vasodilatory in skin.[47,237]

Lipoxins are biosynthesized by several routes in a tissue-specific manner. Current evidence implicates the eosinophil. A 5(6)-epoxytetraene intermediate can be formed by 5-LO activity on 15-HPETE. This reaction, when carried out in blood vessels, requires the interaction of platelets and neutrophils. On mucosal surfaces, 12-LO and 5-LO activity on LTA_4 can result in formation of this lipoxin intermediate through leukocyte–epithelial interactions. The 5(6)-epoxytetraene intermediate is then converted to lipoxin A_4, lipoxin B_4, or lipoxin C_4, the last of which serves as the precursor for lipoxins D_4 and E_4.[128,241,242]

Though many of the functions of lipoxins have yet to be elucidated, they appear to counterregulate the actions of leukotrienes. They inhibit leukotriene production by downregulating 5-LO as 15-LO is upregulated. The anti-inflammatory cytokines IL-4 and IL-13 further contribute to suppression of inflammatory responses by enhancing 15-LO activity. In addition to inhibiting synthesis, lipoxins inhibit the actions of LTB_4 and LTD_4. Lipoxins A_4 and B_4 are potent vasoactive compounds. Lipoxins influence smooth muscle and vascular tonus by increasing NO and prostacyclin production, increasing arachidonate release, and reversing endothelin-induced vasoconstriction. Counterinflammatory functions of lipoxin A_4 include inhibition of leukotrienes, fMLP, and other chemoattractants. Lipoxin A_4 also downregulates LTB_4-mediated delayed-type hypersensitivity reactions.[128,241–243]

Table 7.9 Prostanoid Effects

	PGG_2	PGH_2	PGI_2	PGE_2	TXA_2
Chemotaxis	↑	↑	↓	↓	↑
Bronchial resistance	↑	↑	↓	↓	↑
Platelet aggregation	↑	↑	↓	↓	↑
Systemic vascular resistance			↓	↓	↑
Pulmonary vascular resistance	↑	↑	↓	↓	↑

A large number of anti-inflammatory drugs, many of which are in clinical use, act by interfering with eicosanoid synthesis. The anti-inflammatory properties of corticosteroids are mediated at least in part by the inhibition of PLA_2 through the induction of lipocortin. They have been shown to selectively inhibit COX2 activation without affecting COX1. NSAIDs block the synthesis of both prostaglandins and thromboxanes by inhibiting COX activity. In contrast to the other NSAIDs, aspirin inhibits COX in an irreversible manner, and restoration of platelet function necessitates the administration of platelets. Aspirin, by either acetylating COX2 or by inducing the oxidation of arachidonic acid by cytochrome p450 or 5-LO, has been shown to stimulate the formation of 15R-HETE in endothelial or epithelial cells. These 15-epilipoxins exhibit higher potency in suppressing inflammation because of their prolonged half-lives. A potential complication of NSAID use and COX inhibition is the shunting of arachidonate through the 5-LO pathway and subsequent greater production of proinflamamtory leukotrienes (asthma). Such consequences minimize any benefit achieved from reducing other eicosanoid levels. In addition, NSAIDs act systematically in a nonselective manner, so that inhibition of prostaglandin synthesis can result in dangerous side effects in locations where prostaglandins normally exert cytoprotective effects (stomach).[238,242,244]

Platelet-Activating Factor (PAF)

PAF is a heterogeneous mixture of 1-0-alkyl-2-acetyl-sn-glycero-3-phosphocholines that plays a prominent role in both physiologic and pathologic inflammatory states. It does not exist preformed but is rapidly produced by activated cells. Synthesis involves either the remodeling of membrane phospholipids by PLA_2, usually more important under inflammatory conditions, or by de novo synthesis as occurs in resting cells. De novo synthesis is regulated by substrate availability and involves a constitutively active enzyme that produces PAF in small basal amounts.[245] The membrane phospholipid precursor is present in high amounts in neutrophils. Other cells that can synthesize PAF include platelets, basophils, monocytes, eosinophils, mast cells, and vascular endothelial cells. Similar to eicosanoid production, the synthesis of PAF is initiated by calcium-dependent activation of PLA_2, which yields 1-0-alkyl-sn-

glycerophosphocholine (lyso-PAF); subsequent acetylation generates PAF. PAF may be released from the cell, or it may be converted back to lyso-PAF by an acetylhydrolase and to the precursor ether-phosphatidylcholine.[245]

The actions of PAF are mediated by G-protein activation. As the name implies, PAF induces platelet aggregation and degranulation; yet also possesses many other critical functions for inflammation. Its vasoactive properties include vasodilation and increased permeability, and it is an equally potent bronchoconstrictor. PAF enhances arachidonic acid metabolism, leading to increased leukocyte motility, degranulation, and free radical formation. PAF plays an integral role in promoting activation and adherence of inflammatory cells to the endothelium.[246] During the early inflammatory response, activated endothelial cells synthesize and express PAF on the cell surface. Leukocytes tethered by selectins to the endothelium are activated by endothelial PAF, which results in the induction of tight integrin-dependent adhesion and subsequent emigration and chemotaxis toward the inflammatory focus. Acyl-PAF, the major acetylated lipid from mast cells, basophils, and endothelial cells, is a less potent derivative of PAF that likely plays a similar role in the regulation of neutrophil recruitment. PAF also promotes platelet and neutrophil aggregation, thereby contributing to the prothrombotic state of acute inflammation. In circumstances of persistent pathologic stimuli, PAF may be liberated systemically, thereby causing the sequelae of an excessive inflammatory response. As a mediator of sepsis, PAF augments endotoxin-induced hypotension and neutrophil and platelet accumulation in the lungs. There is evidence that the NO-induced hypotension in experimental models of endotoxemia is mediated by PAF.[247] PAF infusion leads to a shock state that is similar to septic shock in that there is tissue hypoperfusion despite adequate fluid resuscitation. In animal studies, PAF has been shown to contribute many manifestations of sepsis including coronary vasoconstriction, reduced cardiac contractility, reduced preload, peripheral vasodilation, pulmonary vasoconstriction, increased microvascular permeability, gastrointestinal hemorrhage, and thrombocytopenia.[238] Two prospective randomized, placebo-controlled trials of PAF inhibition in sepsis have suggested a benefit.[238]

PAF acetylhydrolase, an enzyme regulated by dexamethasone, estrogen, and PAF itself, is the enzyme responsible for degradation of PAF.

Kinins

Kinins (i.e., bradykinin and lysyl bradykinin) are small vasoactive peptides generated during the inflammatory response (**Fig. 7.12**). Three sources and mechanisms of kinin formation occur during inflammation: (1) plasma proteins; (2) tissue proteins; (3) cellular proteinases.[248–251]

Production of Bradykinin

Biosynthesis commences with the activation of Hageman factor (HF), or factor XII of the coagulation cascade (**Fig. 7.12**). HF is activated by exposure to anionic surfaces such as the basement membrane of injured endothelium, heparin, or lipid A of endotoxin. It can also be proteolytically cleaved and activated by kallikrein. Prekallikrein circulates complexed with HMWK, a nonenzymatic protein. Kininogen enhances the binding of prekallikrein to negatively charged surfaces. Activated HF converts prekallikrein to kallikrein, which in turn activates more HF in a positive feedback cycle. HFf, a cleavage product of activated HF, is also capable of activating prekallikrein. Kallikrein in plasma, tissues, and secretions specifically cleaves HMWK to release the nonapeptide bradykinin. In addition to bradykinin production, kallikrein participates in the activation of plasminogen and C1q of the complement system; yet another link between inflammation and the coagulation system. The only major plasma inhibitor of activated HF is C1 inhibitor. The primary inhibitors of kallikrein in plasma are C1 inhibitor and α_1 macroglobulin.[43,248]

Kinin Production in Tissue

Lysyl-bradykinin (kallidin) is the cleavage product of either HMWK or low–molecular-weight kininogen (LMWK) by tissue kallikreins, which are proteins distinct from their plasma counterparts. LMWK is present in higher concentrations intracellularly compared with HMWK. Whereas both HMWK and LMWK can be converted to lysyl-bradykinin by tissue kallikrein, only HMWK is cleaved by plasma kallikrein. Kallidin itself can be converted to bradykinin by a plasma aminopeptidase. Both kallidin and bradykinin use the same receptors and perform similar functions, but kallidin is approximately 85% as potent as bradykinin. Tissue kallikrein is synthesized from a

preproenzyme and is converted intracellularly to tissue prokallikrein by enzymes that are not yet well characterized. The secreted prokallikrein is then converted to tissue kallikrein extracellularly by plasmin or plasma kallikrein. The only significant inhibitor of tissue kallikreins is α_1-proteinase inhibitor.[43,248]

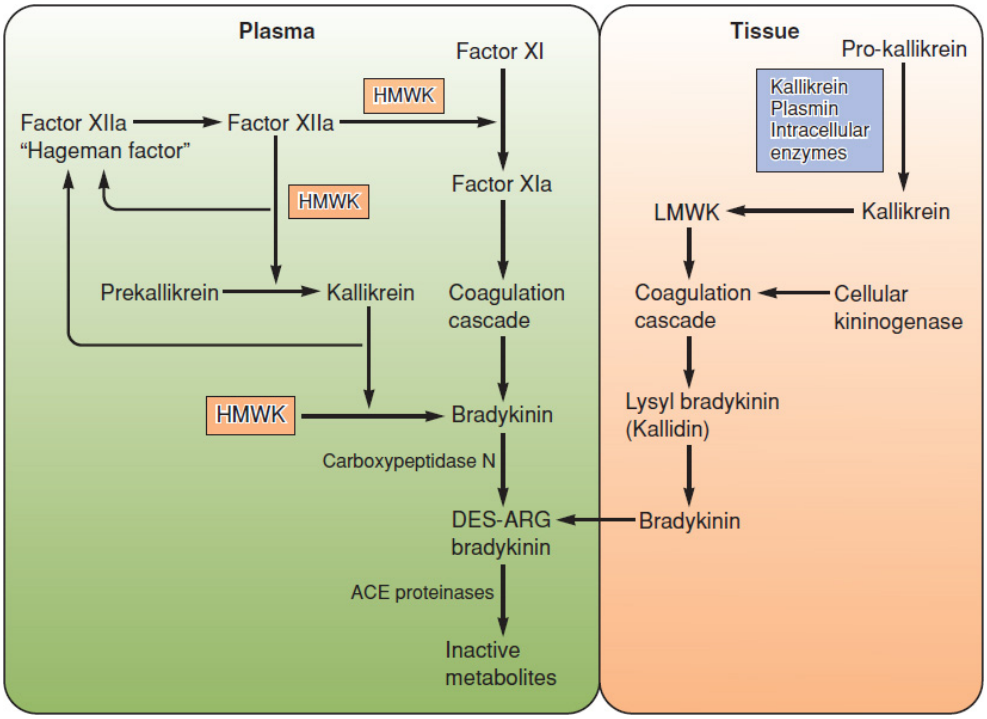

Figure 7.12 Kinin pathway. (Modified from Proud D, Kaplan AP. Kinin formation: mechanisms and role in inflammatory disorders. *Annu Rev Immun* 1988;6:49.)

Cellular Kininogenase Activity

Neutrophils, mast cells, and basophils are sources of kininogenase activity. Neutrophils produce leukokinins by way of cathepsin D. Their role in inflammation is unclear. Bradykinin is metabolized sequentially to the partially active eight-amino acid peptide, des-Arg-bradykinin, by carboxypeptidase N, and then to inactive five-amino acid and three-amino acid fragments by the angiotensin-converting enzyme (ACE). ACE is the predominant enzyme to inactivate bradykinin in the pulmonary vasculature. Arginine released as a byproduct of the carboxypeptidase N reaction may contribute further to the modulation of inflammation by acting as a substrate for the formation of NO.[43,248,252]

There are three kinin receptors, of which two are well characterized.[248,250] B1 receptors are expressed primarily on the vasculature under pathologic conditions such as tissue injury. They bind des-Arg-bradykinin and des-Arg-kallidin and mediate the hypotension characteristic of sepsis and pain.[248,253] Both B1 and the more widely distributed B2 receptors are G-protein–coupled receptors. Activation of B2 receptors stimulates IP and phospholipase C (PLC), resulting in the accumulation of the second messengers IP_3, DAG, and calcium. The B2 receptors are more important in mediating the effects of inflammatory kinins, such as bradykinin and lysyl-bradykinin. These kinins induce arteriolar dilatation and mediate pain. Similar to histamine, bradykinin increases the gaps between postcapillary venule endothelial cells leading to increase in vascular permeability. It is a potent constrictor of bronchial, uterine, and gastrointestinal smooth muscle, and the coronary and pulmonary vasculature.[250] Activation of endothelial B2 receptors stimulates production of NO to further enhance vasodilatation. Kinins have been implicated in mediating the antihypertensive and cardioprotective effects of ACE inhibitors.[254] ACE, in addition to catalyzing the formation of angiotensin II from angiotensin I, promotes the hydrolysis of bradykinin to inactive metabolites. In addition, bradykinin can modulate platelet function by stimulating endothelial cell secretion of PGI_2 and thromboxane through activation of PLA_2.[248]

Hereditary angioedema (HA) is an autosomal dominant disorder caused by a deficiency of C1 esterase inhibitor, which has a regulatory role in the classic complement pathway and in coagulation, fibrinolytic, and kallikrein–kinin cascades. The disease is characterized by recurrent attacks of angioedema of the skin, larynx, and gastrointestinal tract. Reduced activity of C1 esterase inhibitor results in an elevated plasma level of bradykinin, which has now been shown to be a key mediator of HA. The idiopathic angioedema due to ACE inhibitor therapy is hypothesized to involve a similar mechanism of elevated bradykinin concentration. Icatibant, a new bradykinin-recpetor antagonist was tested in a two-blind, randomized, multicenter trial (For Angioedema Subcutaneous Treatment—FAST 1 and 2 trials) in patients with HA presenting with cutaneous or abdominal attacks.[255] In FAST-2, the median time to first improvement of symptoms was

significantly shorter with icatibant compared to tranexamic acid: 2.0 versus 12.0 hours ($p < 0.001$).

Neuropeptides

Neuropeptides may provide a neuroendocrine link between psychological stress and inflammatory diseases such as psoriasis and inflammatory bowel disease. Like cytokines, their actions are pleiotropic and redundant. Neuropeptides execute their inflammatory and immunomodulatory effect by binding to specific G-protein–coupled receptors on the surfaces of target cells, and the resultant effect may be proinflammatory, anti-inflammatory, or both. For example, substance P mediates the hypothalamic fever response to PGE_2 induced by IL-1 and TNFα, whereas adrenocorticotropic hormone (ACTH), arginine vasopressin (AVP), and α-melanocyte–stimulating hormone (α-MSH) suppress it. The pituitary peptides prolactin, corticotropin-releasing hormone (CRH), and AVP have been shown to augment immune responses by enhancing T_H1 activity.[43,256,257]

Tachykinins are important proinflammatory neuropeptides that mediate pain and vasodilatation and promote the classic inflammatory signs of erythema and edema. Substance P stimulates monocyte and neutrophil influx and neutrophil phagocytosis. Its inflammatory effects appear to be mediated by the proinflammatory cytokines TNFα and IL-1 from mast cells, monocytes, macrophages, bone marrow, and endothelial cells. During allergic inflammation, substance P stimulates histamine release from mast cells. As an effector of immune function, substance P promotes T-cell proliferation and antibody production. Substance P released locally by nerve terminals is important in mediating the perception of pain.[43,248]

CRH induces the release of IL-1, IL-6, and superoxide anion from macrophages and negatively regulates its own proinflammatory effects through cortisol release. Cortisol downregulates production of proinflammatory cytokines such as IL-1, TNFα, and IL-2, metalloproteinases, and iNOS, and through this negative feedback loop, inhibits the production of CRH, ACTH, and AVP. AVP, growth hormone, and prolactin are other important proinflammatory neuropeptides.[43,256,257]

Vasoactive intestinal peptide (VIP) and its homologues display both proinflammatory and anti-inflammatory effects. VIP is widely distributed throughout the central and peripheral nervous systems and serves as a chemoattractant for macrophages, neutrophils, and T cells, and may play an important role in granulomatous reactions. VIP stimulates the release of histamine and IL-5 and is a potent vasodilator. It inhibits IL-6, TNFα, and IL-12 release and iNOS expression in activated macrophages. VIP has also been shown to stimulate the production of the anti-inflammatory cytokine IL-10 by macrophages and to inhibit T lymphocyte proliferation and the production IL-2 and IFNγ.[258]

Somatostatin and α-MSH are primarily anti-inflammatory in action. Somatostatin, which colocalizes with substance P in sensory nerves, inhibits IgE formation and NK cell activity, whereas α-MSH inhibits leukocyte chemotaxis, IFNγ production, and downregulates T_H1 activity. ACTH, calcitonin, and β endorphin are other neuropeptides with predominantly anti-inflammatory properties.[43]

Calcitonin gene-related peptide (CGRP) is an immunomodulator that inhibits the activity of T cells and macrophages, in part through the induction of IL-10. It also is an inhibitor of antigen presentation. CGRP promotes vasodilatation and neutrophil influx, and synergizes with bradykinin and histamine to promote edema formation.

Nitric Oxide (NO)

Endogenous NO was first discovered in 1987, and NO was the first gaseous molecule shown to be synthesized for the purpose of cell signaling.[259] NO is a weakly reactive radical that diffuses short distances from cell to cell independent of membrane channels or receptors. Its half-life is short because of its rapid inactivation by hemoglobin and other endogenous substances; thus, it functions primarily in a paracrine and autocrine fashion. The enzyme NO synthase (NOS) catalyzes the formation of NO and citrulline from the substrates L-arginine and oxygen.[67,260–262] NOS contains prosthetic groups for flavin-adenine dinucleotide, flavin mononucleotide, tetrahydrobiopterin, iron protoporphyrin IX, and zinc. Three isoforms of NOS have been identified. The calcium-dependent constitutive isoforms, neuronal NOS (nNOS) and endothelial NOS (eNOS), generate the small amounts of NO necessary for those processes maintaining physiologic homeostasis, such as neurotransmission and endothelial regulation of vascular tone. The expression of inducible NOS (iNOS), however, requires stimulation and produces larger, sustained amounts of NO that possess both cytoprotective and cytotoxic properties. This distinction is not absolute, as certain cell populations express low basal levels of iNOS, and constitutive NOS transcripts can be enhanced by certain stimuli such as shear stress and hypoxia.[67,260–262]

Many of the physiologic effects of NO are mediated by the activation of soluble guanylate cyclase. Increased levels of intracellular cyclic guanosine monophosphate trigger a reduction in calcium concentration and promote vascular smooth muscle relaxation and the inhibition of platelet aggregation and adhesion. The cellular response to NO also likely involves multiple signal transduction mechanisms, including the MAPK pathway.

Inflammation secondary to endotoxemia, hemorrhagic shock, and ischemia/reperfusion are associated with increased NO production by iNOS. First described in macrophages, iNOS can be expressed in essentially any cell type in response to immunologic stimuli. Unlike nNOS and eNOS, iNOS does not depend on elevations in intracellular calcium levels for its activity.[67,260–262] Important inducers of iNOS upregulation include LPS, IL-1, TNFα, and IFNγ. Expression is primarily transcriptionally regulated,

although stabilization of iNOS mRNA also appears to play a role. IFNγ stabilizes iNOS mRNA, whereas TGFβ can destabilize it. Transcription of the iNOS gene is controlled by NFκB, IFNγ-responsive element, and TNF-responsive element. Induction of iNOS can be inhibited by glucocorticoids, thrombin, macrophage deactivation factor, PDGF, IL-4, IL-8, IL-10, and IL-13.[67,260–262] Dexamethasone may inhibit iNOS induction by impairing the DNA-binding capacity of NFκB and by increasing levels of IκB.[263,264]

The endothelial dysfunction and vascular hyporeactivity that characterizes septic shock is consequential, in part, to iNOS production of NO.[265] NO has been shown to be the effective mediator of the negative myocardial inotropy of TNFα, IL-6, and IL-2 and the TNFα-induced vasodilatation in the systemic and microcirculations.[266] NO may indirectly increase prostaglandin production by increasing the catalytic activity of cyclooxygenase and decrease leukotriene production by inhibiting 5-lipoxygenase.[267] NO plays an autoregulatory role in the T_H1 subset of T_H cells by limiting their own proliferation.[268]

NO can mediate tissue injury in inflammation by modulating organ perfusion, mediating interactions with neutrophils, contributing to proinflammatory signaling, and by regulating apoptosis.[269] Whereas eNOS primarily regulates perfusion during homeostasis, both eNOS and iNOS modulate organ flow in pathophysiologic states. Basal NO production from eNOS prevents the adherence of neutrophils to the endothelium and inhibits chemotaxis under physiologic conditions. Animal studies have demonstrated that pharmacologic inhibition of iNOS or genetic deletion of iNOS attenuates neutrophil accumulation in organs after ischemia/reperfusion injury.[270] Conversely, similar experiments in endotoxemia implicate an antiadhesive role for iNOS, suggesting that the effect of induced NO on neutrophil accumulation is insult specific.[269] Activated neutrophils can be stimulated by fMLP, PAF, LTB_4 to produce NO. NO produced by neutrophils at sites of inflammation can combine with superoxide to form peroxynitrite as another means of effecting toxicity.[43,271]

The reaction of NO with superoxide is the only reaction that outcompetes the reaction of superoxide with superoxide dismutase. Small amounts of peroxynitrite are produced under basal conditions from constitutively produced NO and superoxide from mitochondria and other cellular sources.

However, endogenous antioxidants such as GSH, vitamins E and C, and superoxide dismutase likely limit its toxicity. A low concentration of peroxynitrite has been shown to inhibit neutrophil adhesion. Higher concentrations of peroxynitrite can initiate a wide range of toxic oxidative reactions through a peroxynitrous acid intermediate. These include the initiation of tyrosine nitration, lipid peroxidation, and direct inhibition of mitochondrial respiratory enzymes. The balance between superoxide and NO determines the reactivity of peroxynitrite; excess NO reduces the oxidation elicited by peroxynitrite. In addition, peroxynitrite may contribute to cytotoxicity by a more indirect pathway. Peroxynitrite-induced single strand breaks in DNA activate the nuclear enzyme poly (ADP-ribose) synthetase, leading eventually to irreversible energy depletion of the cells and necrotic-type cell death.[43,45]

iNOS plays a key role in host defense, with NO or peroxynitrite-exhibiting potent antimicrobial activity against a number of pathogens including viruses, fungi, and bacteria. Although microbicidal susceptibility to NO-mediated killing can vary considerably between species, essential roles have been identified in tuberculosis and bacterial peritonitis.[272] Induced NO has been shown to be essential for the upregulation of the inflammatory response in hemorrhage shock and other inflammatory processes. NO produced by iNOS leads to the activation of NFκB.[273] This is followed by the induction of proinflammatory cytokines and increased leukocyte recruitment and activation.

NO possesses both pro- and antiapoptotic effects depending upon the circumstances. NO derived from eNOS may inhibit apoptosis.[274] Proapoptotic effects appear to be associated with pathophysiologic conditions in which iNOS is upregulated. Low concentrations of peroxynitrite have also been shown to induce apoptosis, whereas higher concentrations promote cell necrosis in vitro. The role of NO-mediated apoptosis in the regulation of the inflammatory response is yet to be more clearly defined.

NO, typically delivered by inhalation, has been subjected to intense investigation for clinical efficacy in a variety of diseases: pulmonary embolism, ARDS, and sick cell pain crisis.[275–277] It has even been added to the cardiopulmonary bypass circuit to provide myocardial protection during cardiac surgery.[278] No study, however, provides definitive data to support

clinical efficacy, and thus, NO as a therapeutic has not been widely incorporated into clinical care.

In summary, NO mediates tissue injury both directly through the formation of peroxynitrite, as well as, indirectly through the amplification of the inflammatory process. Like many mediators, NO has dual regulatory functions, and it is therefore difficult to characterize NO as distinctly pro- or anti-inflammatory. In general, basal levels of NO produced by constitutive NOS may confer anti-inflammatory effects, whereas induced NO may tend to promote the upregulation of the inflammatory response. It is likely that an optimal level of NO is necessary in host defense; too little NO may be as harmful as too much.

Heme Oxygenase (HO)

HO catalyzes the breakdown of heme to iron, biliverdin, and carbon monoxide (CO).[279] Three isoforms of HO have been identified. HO-2 is constitutively expressed in many tissues, whereas HO-3 expression appears to be limited to the brain. HO-1 is not expressed constitutively in most tissues, but is rapidly upregulated by both heme and nonheme cellular stresses, including hypoxia, redox stress, and inflammation. Additionally, NO is a potent inducer of HO-1. HO-1 has profound antiapoptotic and anti-inflammatory effects. These cytoprotective effects have been attributed to the individual catalytic products of heme metabolism. Biliverdin is converted to bilirubin by biliverdin reductase, and bilirubin has been demonstrated to act as a potent intracellular antioxidant. CO alone can mimic many of the actions of HO-1 and has been shown to protect in models of sepsis, hemorrhagic shock, and ischemia/reperfusion when administered as an inhaled gas. The mechanism of action of CO has both similarities and dissimilarities with NO, and is an area of active investigation.[279]

Hydrogen Sulfide

Hydrogen sulfide (H_2S) is a colorless, flammable gas, with the typically malodor of putrid eggs. It is highly lipophilic and freely penetrates the cell wall, which greatly facilitates its biologic activity.[280] Recent evidence

highlights the widespread distribution of H_2S in the plasma, brain, and other tissues. H_2S is formed in mammalian cells largely by the activity of two pyridoxal phosphate-dependent enzymes, cystathione γ lyase (CSE) and cystathionine β synthetase (CBS) that utilize cysteine and homocysteine to form H_2S.[281] Large amounts of these enzymes occur in the brain (CBS), liver (CSE), kidney (CSE), and blood vessels (CSE). Interestingly, lipopolysaccharide exposure induces the expression of CSE, suggesting that H_2S may regulate inflammation.[280] Both pro- and anti-inflammatory actions have been described. H_2S levels and CSE expression are increased in animal models of endotoxemia, sepsis, and hemorrhagic shock.[280,282,283] It has been shown to increase leukocyte attachment and rolling in jejunal blood vessels and to increase ICAM-1 expression.[284] In human monocytes, H_2S donors induce the formation of proinflammatory cytokines and chemokines via an NFκB mechanism.[285] Inhibitors of CSE reduce the inflammation in these animal models of sepsis and hemorrhage. By contrast, H_2S decreases LPS-induced upregulation of NFκB in RAW 264.7 macrophages, and H_2S-releasing derivatives of diclofenac exhibit greater anti-inflammatory activity in endotoxic shock.[280,281,286]

RECOGNITION AND ACTIVATION PROCESSES

Exogenous and Endogenous Danger Recognition

Multicellular organisms have evolved an essential mechanism of surveillance, defense, and repair of injured cells. Implicit with this system is the ability to differentiate pathogens and damaged cells from self. The initial response is orchestrated by the evolutionarily ancient and more universal innate immune system, which employs monoclonal sets of recognition molecules called PRRs.[287,288] PRRs bind conserved molecular structures found in large groups of pathogens, termed PAMPs. PAMPs are a diverse set of microbial molecules, which share a number of different recognizable

biochemical features that alert the organism to intruding pathogens.[287–289] These PAMPs are recognized by cells of innate and acquired immunity, primarily through the toll-like PRRs. Activation induces several signaling pathways, most notably NFκB.[287,289] Consequent to this activation, an immune response is triggered to destroy the pathogen and/or pathogen-infected cells, and an adaptive response is initiated to select pathogen-specific T cells and antibodies for future occasions.

However, pathogens are not the only causative agents of tissue and cell damage. Cells, and thus tissues, can be injured by various noxious insults: heat, cold, chemicals, radiation, ischemia, or direct mechanical injuries. Evolution has enabled us to deal with these damages, which though not caused by pathogens, still necessitate repair. It is becoming apparent that specific receptors exist by which to recognize extrinsic threats (i.e., pathogen) and intrinsic altered self (cytokines, oxidized mitochondrial DNA, HSPs, and uric acid).[289]

Damage-Associated Molecular Patterns (DAMPs)

DAMPs, the endogenous equivalent of PAMPs, represent danger signals or "alarmins" and share many characteristics similar to cytokines.[289] DAMPs may be released following nonprogrammed cell death, such as necrosis, and under such circumstances tend to elicit inflammation. By contrast, programmed cell death (i.e., apoptosis) incorporates mechanisms such as acetylation, to minimize the release of these mediators and any subsequent inflammatory response. Cells of the immune system also can be induced to secrete these mediators.[289] This secretion may occur by specialized secretion systems or by the classical ER-Golgi secretion pathway.[289] Under these circumstances, DAMPs may facilitate the inflammatory response by aiding the recruitment of innate immune cells, most notably DC. In doing so, they indirectly orchestrate the subsequent adaptive immune response and facilitate tissue repair.[289] The prototypical alarmin, HMGB1, has already been discussed.

S100 Proteins

The family of S100 proteins incorporates over 20 related calcium-binding proteins.[289] S100A8 and S100A9 form heterocomplexes in the cytosol of granulocytes, monocytes, and macrophages, whereas S100A12 exists as homodimers in the cytoplasm of granulocytes. S100 proteins are actively secreted at sites of inflammation via a nonclassical pathway. The receptors mediating their effects are still being defined, though it appears that S100A12 and S100B interact with RAGE, whereas S100A8/9 may interact with TLR receptors. S100 proteins have been shown to induce increased vascular permeability and a prothrombotic effect. Recent studies implicate S100 proteins in the pathogenesis of autoimmune arthritis and psoriasis.[289]

Uric Acid

Uric acid is released after cellular injury, and upon exposure to the extracellular environment, precipitates to form monosodium urate (MSU).[289] Uric acid stimulates dendritic maturation and, when coinjected with antigen in vivo, significantly enhances the generation of responses from $CD8^+$ T cells.[289] It has significant proinflammatory properties that are best evidenced in the disease gout, in which uric acid accumulates in tissues and induces inflammation-dependent arthritis. MSU crystals engage the inflammasome, resulting in the production of IL-1β and IL-18.[289] Macrophages from mice deficient in IL-1R or in various components of the inflammasome, such as caspase-1, ASC, and NALP3 are defective in MSU-induced cytokine secretion and have reduced inflammation.[289] Extracellular uric acid is eliminated by uricase.[289]

Mitochondrial DAMPs (MTDs)

The concept of circulating mitochondrial DAMPs, in particular mitochondrial DNA, as an etiology of inflammatory responses was definitively established over a decade ago, when investigators observed that mitochondrial DAMPs (MTDs) were released in consequence to tissue and injury. By signaling through innate immune pathways identical to those activated in sepsis MTDs could recapitulate a “sepsis-like” state.[290] Since then an explosive amount of investigation has defined a role for MTDs in the pathologic sequelae of additional diseases: tumor microenvironment, inflammation and biology; cardiac complications postcardiopulmonary

bypass surgery; liver inflammation and oxidative stress; and chronic neuroinflammation.[291–293] Subsequent studies have identified pattern recognize receptors, notably TLR 9, as the cognate receptor. Studies are underway to determine the clinical ramifications of scavenging circulating mitochondrial DNA as a potential therapeutic for systemic inflammation and multiple organ dysfunction.[294]

Receptors for Danger Recognition

10 Innate immunity is not antigen specific, but rather programmed to respond to groups of evolutionarily conserved macromolecules that represent "patterns of danger" and signal a potential threat to the host. PRRs identify these pathogen-associated molecular patterns (PAMPs) and include the TLRs and NOD-like receptors. Recent studies highlight the promiscuity of these PRRs in also recognizing and mediating DAMP-dependent signaling. In fact, multiple positive feedback loops between DAMPs and PAMPs and their overlapping receptors may represent the molecular basis for the observation that infections, as well as, nonspecific stress factors, can trigger flares of autoimmune diseases (i.e., rheumatic).[195] Additional, novel receptors have subsequently been identified and designated PRRs, including RAGE.[288,289]

CD14

The prototypical receptor identifying external infectious threat (i.e., gram-negative infection) is CD14. CD14 was identified as the LPS receptor when transfection of CD14-negative CHO cells with CD14 conferred responsiveness to LPS.[295] Its critical role in LPS recognition is underscored by the LPS-hyporesponsive phenotype of CD14-deficient mice. It has been identified on cells of the myeloid lineage, B cells, liver parenchymal cells, and fibroblasts. Differential expression is observed; ranging from high levels on peritoneal and pleural macrophages to lower levels on Kupffer cells, alveolar macrophages, monocytes, and PMN. Expression may be modified; human PMNs express low levels of CD14 that is upregulated by TNFα, G-CSF, GM-CSF, and fMLP. Prototypically, CD14 binds LPS bound to LPS-binding protein (LBP) in combination with MD-2 and presents it to TLR4.[295] MD-2 is required for cellular responsiveness to LPS, as demonstrated by

both transfection studies and an analysis of a CHO cell line with mutated MD-2 gene. Most of the available evidence indicates that a complex of TLR4/MD-2/CD14 directly binds LPS.[295] CD14 is also important in TLR2 signaling, whereby it presents bacterial products other than LPS.

Toll-Like Receptors (TLRs)

CD14 is a glycosylphosphatidylinositol-linked receptor devoid of any transmembrane domain. This, in combination with the identification of a soluble form of CD14, necessitated identifying the manner by which LPS induced activation.[296] In 1996, the toll protein in Drosophila was shown to be necessary for an effective immune response to the fungus *Aspergillus fumigatus*.[287] In 1998, Poltorak et al. discovered that the *lps* gene in LPS-hyporesponsive C3H/HEJ mice encoded a murine member of the TLR family. These data provided the initial evidence that mammalian TLRs function as PRRs.[297] Subsequent studies have confirmed that TLR4 is the "LPS receptor" and that it is essential for the defense against gram-negative microorganisms.[295]

Thirteen mammalian TLR receptors have been characterized in humans and mice. Each recognizes a specific set of conserved microbial molecules, and as a family, they can detect most microbes.[295] Interestingly, the subcellular localization of different TLRs correlates to some extent with the molecular patterns of their ligands and their function.[298] TLR1, TLR2, and TLR4 are located on the cell surface and are recruited to phagosomes after activation by their respective ligands. They are the receptors mediating the response to exogenous insults including bacterial infection and trauma. By contrast, TLR3, TLR7, and TLR9, all of which are involved in the recognition of nucleic-acid like structures (i.e., viral DNA), are expressed intracellularly.[287,299]

TLR4 is required for the innate response to gram-negative organisms and LPS, though other TLR, such as TLR2, can also recognize and mediate this response.[288] TLR4 has been shown to trigger the response to additional ligands, including lipoteichoic acid (LTA) and peptidoglycans from gram-positive bacteria and the fusion protein of the respiratory syncytial virus.[300] Polymorphisms in the receptor confer variability in function. Individuals with the D299G polymorphism in TLR4 demonstrate increased risk of gram-

negative infections, and other studies have linked this with an increased incidence of SIRS.[301] In addition, this polymorphism has been associated with alterations in the susceptibility to other inflammatory and potentially infectious processes (carotid artery atherosclerosis, coronary artery disease).[301] HSP60 of Chlamydial origin has been found in atherosclerotic plaques and can bind TLR4. Perhaps recognition of HSP60 by human TLR4 might exacerbate the inflammatory component of atherosclerosis, whereas people with the D299G polymorphism might be at least partly protected from this exacerbation.[301] TLR4 has been well characterized as a PRR for DAMPs, including HSPs (HSP60, HSP70, gp96), hyaluronate, heparan sulfate, and other matrix proteins. Because of its ability to recognize endogenous proteins, TLR4 is implicated in a variety of diseases, including arthritis and atherosclerosis.[195,299] Eritoran is a synthetic lipid A antagonist that blocks lipopolysaccharide from binding at the cell surface MD2-TLR4 receptor. Despite TLR4 possessing such a fundamental vantage point in immune signaling, the randomized, double-blind, placebo-controlled multinational phase 3 trial ACCESS did not observe a benefit in the treatment of patients with severe sepsis.[302]

TLR2 recognizes lipoproteins derived from the cell wall of bacteria such as *Treponema pallidum* and *Mycoplasma fermentas*, LTA from gram-positive bacteria (i.e., *Streptococcal* sp.), lipopeptides, LPS and lipid A.[288,299,300] It also can recognize a host of DAMPs, including the HSPs, fibronectin, fibrinogen, heparan sulfate, and hyaluronate. Recent data suggest that TLR2 forms heterodimers with other TLR, including TLR1 or TLR6 to recognize these DAMPs. A likely consequence of this cooperation is an increased repertoire of ligand specificities. The R753Q polymorphism in the TLR2 is associated with decreased response to these bacteria and may increase susceptibility to staphylococcal infections or tuberculosis.[299,301]

Additional TLRs involved in inflammation include TLR9, which recognizes unmethylated CpG motifs present in bacterial DNA; most of the host mammalian genome is methylated. TLR9–ligand engagement occurs intracellularly, in either endosomes or lysosomes, presumably following bacterial lysis. Data support that TLR9 recognizes host DNA released by dead or dying cells and may participate in autoimmune diseases such as SLE.[287] Immunotherapy with a TLR9 vaccine consisting of AMB a 1, a ragweed-pollen antigen, conjugated to a phosphorothioate

oligodeoxyribonucleotide immuostimulatory sequence of DNA appeared to offer long-term clinical efficacy in the treatment of ragweed allergic rhinitis.[303] TLR7 is of particular relevance for respiratory allergies. TLR7 polymorphisms have been strongly linked with susceptibility to asthma and other atopic disorders.[304] TLR7 agonists effectively prevent T_H2-mediated airway disease in animal models. A recent randomized, double-blind, placebo-controlled trial concluded that a novel selective TLR7 agonist (GSK2245035) reduced allergic reactivity to nasal challenge in a cohort of patients with allergic rhinitis.[304] Similar observations were reported in studies of TLR8 and TLR9 agonists.[305,306] TLR5 recognizes flagellin of bacterial flagella.[307] TLR3 recognizes double-stranded RNA of both viral and endogenous sources. Because of the later characteristic, TLR3 has been implicated in autoimmune arthritis. A recent trial tested the efficacy of TLR3 receptor blockade with CNTO3157, an inhibitory monoclonal antibody, in rhinovirus-induced experimental asthma exacerbations in healthy subjects and patients with mild-to-moderate stable asthma. The investigators concluded that CNTO3157 is ineffective in attenuating the effect on lung function, asthma control, and symptoms in patients.[308]

TLRs induce signal transduction via their cytoplasmic toll-interleukin-1 receptor (TIR) domains that promotes the subsequent expression of a variety of host defense genes. These include inflammatory cytokines and chemokines, antimicrobial peptides, costimulatory molecules, MHC molecules, and other effectors. A considerable portion of the functional response is mediated by activating intracellular signaling pathways that culminate in the induction of the transcription factor NFκB. Specifically, the CD14/MD-2/TLR4 complex, upon engagement with LPS-LBP recruits the adaptor protein MyD88, which engages the serine/threonine kinase IRAK. IRAK undergoes autophosphorylation and recruits TRAF6. Ultimately, activated IκK phosphorylates and targets for degradation the NFκB inhibitor IκB, which enables the nuclear translocation of NFκB and transcription of inflammatory genes. AP-1 and members of the MAPK transduction cascade are also activated by this mechanism. This pathway is critical to the production of IL-12, TNFα, and IL-6. All TLRs signal through this conserved signaling cascade, and for some MyD88 (TLRs 2, 6, 9) is their sole receptor-proximal

adaptor. For instance, MyD88 is essential for clearance of *S. aureus* a gram-positive bacteria, which signal through TLRs 2, 6, 9.[287,288,300]

Subsequent studies utilizing MyD88-deficient mice suggested that alternate TLR pathways existed. These mice, in response to many TLR ligands, including peptidoglycan and unmethylated CpG motifs, did not activate NFκB or MAPK. Surprisingly, however, LPS could still activate NFκB and MAPK, though in a delayed fashion. Subsequently, a MyD88-independent pathway has been characterized that is utilized by TLR4 and utilizes a distinct adaptor protein called TIR domain-containing adaptor protein TIRAP or Mal. A dominant negative mutant of TIRAP specifically impairs TLR4- and TLR2- but not IL-1R or TLR9-induced NFκB, indicating a specificity of TIRAP for the TLR4 pathway. A third TIR-containing adaptor molecule, TIR-domain containing adaptor inducing IFN-β (TRIF) also appears to mediate a MyD88-independent pathway.[287,288,300]

Most of this research has occurred in the realm of sepsis and provided insight into the manner by which organisms identify infectious threats and activate the inflammatory pathway to preserve the host. However, several circumstances of sterile inflammation suggest a role of the TLRs in mediating inflammation in response to endogenous danger signals (uric acid, mitochondrial DNA, HMGB1).[295] Hepatocellular injury consequent to ischemia/reperfusion (I/R) has been shown to be dependent on TLR4.[36]

RAGE

RAGE is an immunoglobulin superfamily molecule that belongs to the multiligand receptors that recognize families of ligands rather than a single polypeptide.[135,289,309,310] It has a single transmembrane spanning domain and a highly charged cytoplasmic tail that though lacking known signaling motifs, is critical for cellular activation. Though RAGE knockout mice are viable and fertile, they display a wide range of defects. Most of these defects are subtler than expected, leading to the suggestion that other receptors with overlapping function might exist. Signaling appears to necessitate clustering into a particular orientation, which facilitates binding of cytosolic-signaling complexes.[135,309] Its ligands include products of nonenzymatic glycosidation (e.g., advanced glycation endproducts or AGEs), the amyloid-β precursor protein, the S100/calgranulin family of proinflammatory cytokine-like

mediators, and the high mobility group 1 DNA-binding proteins (HMGB-1). Its expression is upregulated at sites of diverse pathologies including atherosclerosis and Alzheimer disease. In fact, RAGE-mediated cellular stimulation is thought to increase expression of the receptor itself, thereby generating a positive feedback mechanism and perpetuating the proinflammatory state.[135,309,310]

Recent studies demonstrate the activation of multiple signal transduction cascades subsequent to ligand binding, including the family of MAPKs (p38, ERK 1/2, and JNK) and the rho GTPases (cdc42 and rac).[310] Like TLRs and IL-1R, RAGE engagement leads to NFκB activation, suggesting that both receptor usage and signaling pathways evoke similar responses when cells are activated by PAMPs and DAMPs. It is currently hypothesized that RAGE–ligand interaction induces a new heightened basal state of activation. With a superimposed stimulus, cellular perturbation is magnified. Rather than returning to homeostasis, cellular signal transduction mechanisms favor augmented dysfunction.[135,309]

Studies have implicated RAGE to be an important receptor during various acute and chronic inflammatory processes, including tumor biology. RAGE expression and function directly correlated with tumor growth in RAGE-transfected C6 glioma cells. In a murine tumor model, mice treated with soluble RAGE, which functions as a decoy, exhibited a reduction in lung metastases, cellular invasion, and expression of matrix metalloproteinases.[310]

RAGE has also been identified as a receptor for S100A12, a member of the S100/calgranulin family of proinflammatory mediators. Endothelial cells cultured with S100A12 displayed RAGE-dependent expression of VCAM-1 and tissue factor. Mononuclear phagocytes displayed S100A12-RAGE chemotaxis, expression of tissue factor, and elaborated IL-1 and TNFα. In vivo studies of delayed-type hypersensitivity demonstrated reduced inflammatory response when mice were treated with anti-RAGE F(ab')2, anti-S100 F(ab')2, or soluble RAGE. Treated animals also displayed reduced NFκB activation and IL-1 and TNFα expression.[310]

The angiopathy of diabetes is thought to be consequent to inflammatory processes generated by elevated glucose concentrations. Hyperglycemia has been demonstrated to activate numerous signaling cascades. One process that might mediate these effects is through the nonenzymatic formation of

advanced glycation endproducts AGEs.[135,309,310] AGE–RAGE interactions on endothelium lead to the expression of procoagulant tissue factor and VCAM-1 and macrophages released tissue factor. Animals treated with soluble RAGE showed decreases in atherosclerotic lesion area and number and a marked reduction in lesion complexity. Also, treated animals had reduced expression of adhesion molecules, tissue factor, MCP-1, and matrix metalloproteinases.[135,309,310]

CD91

The immunologic properties of HSPs were discovered by their ability to elicit antitumor immunity. It was later discovered that this antigenic specificity was determined by the peptides they chaperoned. APCs can bind and internalize HSP–peptide complexes derived from virus-infected cells or tumors and represent them on major histocompatibility MHC class I molecules. In addition, APC engagement of HSP–peptide complexes induces maturation, the expression of costimulatory molecules, and the induction and release of cytokines (TNFα, IL-1, IL-12, IL-6, GM-CSF, MIP-1, RANTES, and NO).[311,312]

CD91 had been identified as a receptor for the serum protein α_2 macroglobulin, a natural protease inhibitor that like HSPs is found across many species. In fact, α_2 macroglobulin is the evolutionary precursor of the C3 complement component. By binding pathogen proteases utilized during invasion and shuttling them for endocytosis, α_2 macroglobulin hinders pathogen invasion.[311,313]

However, such a method of host defense would be ineffective for intracellular pathogens that gain access by alternative means, such as mimicking host proteins and developing ligands for host receptors. Hence, another method of signaling danger is necessary. It is currently thought that upon cell death, HSPs contained within the cell transfer information regarding the infected intracellular environment to CD91. This large cell surface receptor, complexed with the HSPs, is internalized and delivers antigen to the classical MHC class I pathway. The MHCs bind and present them to $CD8^+$ T cells. On recognizing nonself, T cells are induced to proliferate and mediate killing. This mechanism could be generalized to

implicate CD91 and HSP interactions in the recognition of all cellular stress that culminates in injury and death.[313]

CD91 was first identified by Binder et al. as the receptor for gp96 and then by Basu as a common receptor for other HSPs (HSP70, HSP90, and calreticulin).[314,315] This large multidomain 600-kD protein possesses multiple binding sites for at least 32 ligands. The binding of this receptor to many members of the HSP family has been corroborated by several independent functional and structural studies.[313]

Several in vivo studies suggest a physiologic relevance for HSP–CD91 interaction. Mice immunized with tumor-derived gp96–peptide complexes reject a subsequent tumor challenge. If CD91 antiserum is mixed with the HSP–peptide inoculum, the mice fail to reject the tumors. Srivastava et al. noted that blocking of CD91 completely inhibits the phenomenon of re-presentation of peptides that are carried or chaperoned by HSPs, suggesting that not only is CD91 a receptor for HSPs, but it may also be the sole receptor involved in antigen representing.[312,315]

HSPs have been shown to chaperone antigenic peptides (tumor, viral, minor histocompatibility antigens) from all cellular compartments. The family of HSPs thus appears to be a universal mechanism for antigen capture, and they permit a high-efficiency antigen uptake through a receptor-mediated mechanism.

Evidence that HSP–peptide–CD91 interactions serve to signal cellular stress is beginning to culminate. Basu et al. demonstrate that HSP70, HSP90, gp96, and calreticulin are released from cells as a result of necrotic cell death, but not apoptotic cell death.[314] Similarly, Melcher reported that tumor cells undergoing necrotic death are highly immunogenic as compared to those undergoing apoptotic death.[316] Actual necrosis may be unnecessary as stressed cells and cancer cells have been reported to express cell surface HSP molecules, which may activate APCs. Li et al. observed that physical contact of tumor cells artificially engineered to express cell surface HSPs with immature DCs elicits a powerful maturation of DCs.[317]

Other HSP Receptors

CD40 was reported as a receptor for HSP70 when anti-CD40 antibodies were observed to inhibit macrophage chemokine secretion in response to

mycobacterial HSP70. Subsequently, Becker noted the association of recombinant GST-tagged CD40 with murine HSP70.[318,319] They further demonstrated enhanced binding after the APCs were stimulated with LPS. As LPS induces expression of a number of cell surface molecules, the authors concluded that CD40 mediates recognition and binding of HSP70.[320]

CD36 has been implicated as a receptor for gp96. Transfection of CD36 into CD36-negative cells has been shown to enhance gp96 binding. In addition, $CD36^{-/-}$ macrophages have a 52% reduction in gp96 binding compared with wild-type controls, suggesting that some role for CD36 as an HSP receptor.[320]

LOX-1, a member of the same scavenger superfamily as CD91 and CD36 has been postulated to be an additional receptor for endocytic uptake of HSP70 and chaperoned peptides by human DCs. Anti–LOX-1 antibodies and LOX-1 ligand-acetylated albumin competed with HSP70 for binding to DCs.[156]

Both TLRs and CD14 have been implicated as receptors for HSPs, such as HSP70.[321] HSP70 stimulates macrophage IL-12p40 production that is partially abrogated by inhibiting downstream TlR-signaling cascades. In addition, human HSP60–activated NFκB and TNFα production by 293 T cells transfected with either TLR-2 or TLR-4 and MD-2.[322] HSP60 also activated JNK kinase and IKK kinase signaling and TNFα production by macrophages, an effect that was partially eliminated by knocking out MyD88 or TRAF6. Similar functional studies have proposed that CD14 might serve as an HSP70 receptor in APCs. All of these studies heavily suggest a role of TLRs or CD14 in HSP binding, although several investigators call into question the potential for contamination with LPS to be mediating much of these effects.[320]

AUTOPHAGY

Autophagy is an ancient cytoplasmic homeostatic process governing cellular biomass quantity, quality, and distribution through the recycling of cytoplasmic proteins and organelles to support vital functions during periods of stress (i.e., starvation).[323,324] It literally originates from the Greek words *auto* meaning "self" and *phagein* meaning "to eat." Fundamental for

embryologic development and survival, it integrates extensively with apoptosis and may itself function as a form of programmed (type II) cell death.[324–326] Hence, it is not surprising that it is preserved in all eukaryotic organisms, from yeast to humans.

Macroautophagy is coordinated by specialized autophagy-related proteins (ATGs) that sequester large protein aggregates, dysfunctional organelles, and even microorganisms and target them for lysosomal degradation. In the setting of nutrient deprivation, the mechanisms orchestrating this dynamic process involve the main growth rheostat mammalian target of rapamycin (mTOR) and adenosine monophosphate (AMP) kinase, a sensor of cellular energy status.[324,327–332] Prototypically, AMP kinase, sensing-reduced cellular energy (i.e., elevated AMP) inhibits mTOR, a negative regulator of autophagy, thereby inducing autophagy.[327,332–334]

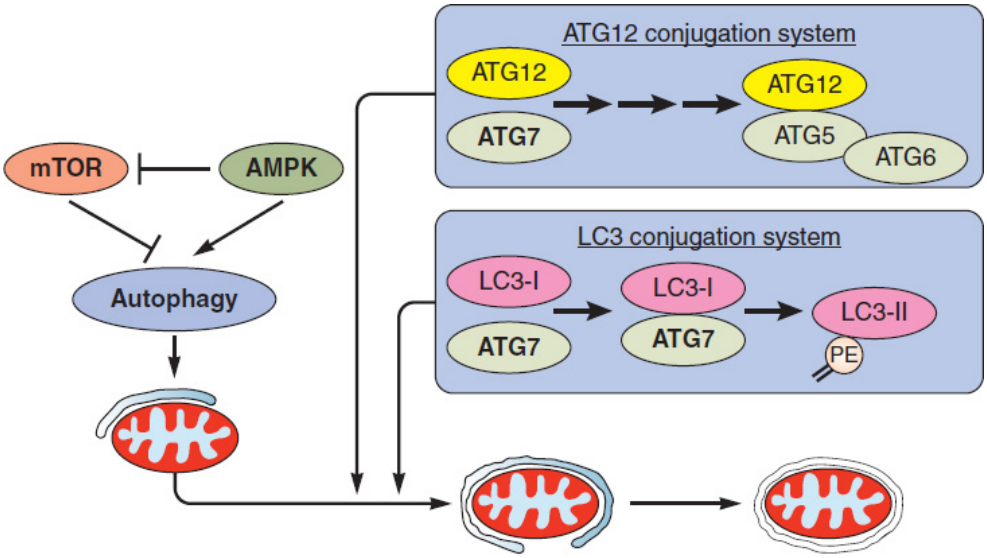

Figure 7.13 Autophagy/mitophagy. Autophagy is inhibited by the metabolic growth rheostat mTOR that inhibits autophagy when ATP and nutrients are plentiful. Sepsis and metabolic stress lead to inhibition of mTOR and initiation of the isolation membrane. Atg12-ATG5-Atg16L and LC3-II localize to the phagophore to capture selected targets for degradation. Upon completion of autophagosome formation, the Atg12-Atg5-Atg16L complex dissociates while LC3-II remains on it. The autophagosome ultimately fuses with the lysosome to form an autolysosome, where its contents are degraded.

Autophagy is initiated by complex formation of ULK1 and ULK2, the class III phosphatidylinositol-3-phosphate kinase VPS34, and ATG14-like protein, ATG14L. This initiates the ATG conjugation cascade in which ATG5 and

ATG12 complex with ATG16L1 to form an isolation membrane around the target (**Fig. 7.13**). The complex facilitates the addition of a phosphatidylethanolamine group to LC3-1 to form LC3-II. LC3-II together with other factors leads to elongation and closure of the autophagosome, which is then targeted for fusion with the lysosome, forming the autolysosome (**Fig. 7.13**).

Though the quintessential function of autophagy is to digest and recycle portions of the cytoplasm during starvation, it has recently been described as an important effector arm of immune cells responding to exogenous (i.e., PAMP: LPS)[335,336] and endogenous (DAMP: HMGB1) stimuli.[323,333,336–340] It is proposed that competition with microorganisms for nutrients, and thus nutrient deprivation, may have served as a sign of invading organisms and thereby supported the emergence of eukaryotic autophagic mechanisms of pathogen elimination. However, a host of other PAMPs and DAMPs and mediators may induce autophagy. In Mϕ, LPS induces autophagy through mechanisms dependent on TLR4, TRIF, RIP1, and p38 MAPK.[335,341] Cytosolic pathogens, such as viruses, can induce autophagy, or rather xenophagy. DAMPs, such as DNA, ATP, and HMGB1 may also induce autophagy, the later through RAGE. The induction of autophagy by the inflammatory cytokine IL-1β is critical for control of *M. tuberculosis*. Similarly, TNFα stimulates autophagy in restricting intracellular bacteria. By contrast, T_H2 cytokines such as IL-4 and IL-13 and NO inhibit autophagy.

During innate immunity, autophagy has been shown to be important in the elimination of intracellular microbes, through LC3-associated phagocytosis and xenophagy. This latter process of selectively degrading intracellular pathogens, involves sequestosome 1-like receptors (SLRs) that recognize molecular motifs on invading pathogens. These SLRs help to clear microorganisms that gain entry to the cytoplasm if they escape the defenses that are controlled by conventional PRRs. Microbial polymers, such as DNA, that are present in the cytoplasm might function as autophagy-inducing PAMPs, as in the case of *M. tuberculosis* infections. The critical importance of autophagy to cell survival is also supported by the defenses several microbes (Listeria, Shigella, Legionella) exhibit to combat the autophagy machinery.

Autophagy can assist PRRs by delivering cytosolic PAMPs to endosomal TLRs (i.e., TLR7) and stimulate their activity.[342–344] Nucleic acid receptors called RIG (retinoic acid inducible gene)-I–like receptors (RLRs) recognize viral RNA, and induce the production of type I IFN to thwart viral invasion. The interaction between TLRs and autophagy may also serve to augment antigen presentation by DCs.

Autophagy limits the activation of the inflammasome, a cytoplasmic complex that responds to PAMPs and DAMPs by inducing the proteolytic processing and secretion of IL-1β and IL-18. It does so by clearing the cytoplasm of debris, such as damaged or depolarized mitochondria that can function as endogenous agonists. Inhibition of autophagy leads to the release of the products, such as mitochondrial DNA and ROS.[342–344] Autophagy also affects the secretion of pro- and anti-inflammatory mediators. In senescent cells, it regulates the secretion of IL-6 and IL-8. It reduces immunoglobulin secretion from plasma cells, and thus, may be important in negatively regulating antibody production.

During adaptive immunity, autophagy contributes to MHC class II presentation. Classically this is described in the context of presenting cytoplasmic antigen (e.g., virus or self-antigen) to endosomal receptors, such as TLR7 (*supra vide*). Thus, autophagy is implicated in autoimmune disorders, such as autoimmune colitis and Crohn disease. The link between autophagy and inflammatory diseases has also been reported. Polymorphisms in ATG16L1 and IRGM are linked to Crohn disease. IRGM polymorphisms may be a risk factor for SLE, and rheumatoid arthritis has been associated with variations in the ATG5 gene. In summary, autophagy influences adaptive immune responses through its effects of antigen presentation, naïve T-cell repertoire selection, T-cell homeostasis, and T_H cell polarization.[342–344]

Interestingly, nonimmune cells, such as hepatocytes and renal tubular cells also exhibit TLR signaling and respond to the stress of sepsis or lipopolysaccharide by inducing autophagy.[36,338,345–348] Studies suggest that these mechanisms are similarly induced in vivo in the early response to sepsis, and regulate bronchoalveolar cytokine/chemokine production and neutrophil accumulation. Others have shown that sepsis induces similar AMPK- and mTOR-dependent mechanisms of autophagy in the Mφ, kidney, and liver.[341,345,349–351] This mechanism may be critically important for cell

survival, as it has been shown that augmenting mTOR- or AMPK-dependent autophagy during CLP sepsis attenuates mitochondrial injury and reduces AKI (**Fig. 7.7**).[348] In summary, recent data support a fundamental role of autophagy in nearly every arm of immunity as an antimicrobial effector of TLRs.[326,338,339,341,342]

In the field of cancer biology, autophagy has been shown to be one potential mechanism by which cancers establish treatment resistance to chemotherapy. This paradigm has been well characterized in pancreatic cancer, in which transcriptional control of autophagy–lysosome drives pancreatic cancer metabolism and is critical for tumor growth and progression.[352,353] Early studies of hydroxychloroquine, which nonselectively inhibits autophagy by decreasing autophagosome–lysosome fusion, suggested benefit in enhancing the sensitivity of tumors to systemic chemotherapy.[354,355] However, a recent phase 2 randomized clinical trials comparing gemcitabine and nab-paclitaxel with or without hydroxychloroquine in patients with advanced pancreatic cancer failed to observe a prolongation in 1-year all-cause survival.[356]

Mitophagy, autophagy directed at the removal of damaged mitochondria, is considered of particular importance in protecting against organ injury, such as acute kidney injury (AKI).[357] At least two mechanisms are involved in the sequestration and elimination of defective mitochondria: Atg7 and PINK1/Parkin. Atg7 is an autophagy protein that is required for the initiation of ubiquitin-like conjugation pathways of autophagy. During erythroid maturation, Atg7 serves a nonredundant role in mitochondrial clearance through canonical autophagosomal pathways.[358,359] Alternatively, PINK1 accumulation at the outer mitochondrial membrane of dysfunctional mitochondria selectively recruits Parkin, which in turn promotes their selective degradation by mitophagy.[360–363] Conditions that induce mitochondrial dysfunction and depolarization strongly induce this pathway, which is important for cell survival.[364] Indeed, endogenous Parkin production and exogenous Parkin overexpression have been found cytoprotective in different conditions of stress, including sepsis. Not surprising, due to the potential for release of cytochrome C and ROS, it is vital that a cell possess a programmatic mechanism for the elimination of defective mitochondria.

THE STRESS RESPONSE

The stress response is the cellular reaction to any perturbation or disruption in equilibrium and serves to restore homeostasis. Inducers of the stress response include physical stresses (burns, radiation, trauma), chemical agents and mediators (toxin, heavy metals, cytokines, ROS), infectious agents (bacteria, viruses, parasites), and allergens. It is often referred to as the heat-shock response after the identification in the 1960s of the HSPs, a group of genes expressed after exposure to heat.[365] However, subsequent investigations delineated additional cellular proteins that are expressed in response to a wide variety of insults. Clinically, expression of HSP has been observed under conditions in which oxygen delivery is compromised, as in hemorrhage or ischemia.[366]

Activation of the stress response is characterized by both morphologic and metabolic cellular alterations. Morphologic alterations include the accumulation of unprocessed forms of mRNA in the nucleolus, and increased numbers of actin microfilaments in the cytoplasm. Changes in cellular metabolism include a rapid reduction in intracellular ATP levels, most likely correlated with alterations in the integrity of mitochondria. The stress response is characterized by transient downregulation of most cellular products and by the upregulation of stress proteins.[367] It is the induction of stress proteins that confers the primary adaptive and protective effects of the stress response.

After expression of stress genes, cells become resistant to subsequent stresses. Members of the stress protein family include HO (*supra vida*); the multiple-drug resistance (MDR) gene product P-glycoprotein; ubiquitin, involved in targeting proteins for degradation; scavengers such as superoxide dismutase, ferritin, and metallothioneins; and the glycolytic enzymes enolase and glyceraldehyde 3-phosphate dehydrogenase. The most extensively characterized are the HSPs.[43]

HSPs are molecular chaperones that may either be constitutively expressed or induced upon cellular stress.[368] Classification is based upon their molecular mass and degree of homology. The most extensively studied is the HSP70 family, members of which possess a mean molecular mass of 70 Kd and greater than 70% homology. Members of the HSP70 family bind ATP and are induced under conditions of energy depletion and stress. HSP70

is integral in cellular adaptation to and survival during environmental stresses. Both HSP72 and HSP73 are present in the cytosol and nucleus. The former is constitutively expressed, whereas, expression of HSP72 is exclusively induced. In most studies HSP72 is used as a marker of HSP induction.[43,366,369,370]

The HSP60 family members are also referred to as chaperones. The glucose-regulated protein group of HSP is induced with glucose starvation, inhibitors of N-glycosylation, and calcium ionophores. The decrease in glucose content may affect the pool of sugar donors during protein glycosylation. The low–molecular-weight HSP (molecular masses of 20 to 30 Kd) may be important regulatory components of the actin-based cytoskeleton.[366]

HSP regulation of transcription occurs through the activation of heat-shock elements in the gene promoters. Two heat-shock transcriptional factors (HSFs) have been identified, HSF1 and HSF2. HSF1 activates transcription of the HSP72 gene in response to heat, heavy metals, and other inducers of the stress response. With stimulation, unbound HSF1 oligomerizes, translocates to the nucleus, and binds to the HSP promoter to activate the transcription of the gene. HSF2 is not activated by the classic inducers of heat-shock genes, but may be important in controlling the activities of HSP gene expression in the normal or unstressed cell.[43,366,369,370]

HSP can play multiple roles in modulating the inflammatory response. A number of conditions such as rheumatoid arthritis, ARDS, and asthma have been shown to benefit experimentally from increased HSP expression.[365–367,370] Functions of HSP include enhancement of immune responses, thermotolerance, regulation of apoptosis, hemostasis, and cytoprotection against ROS and other inflammatory mediators. HSP–CD91 interaction is integral to the processing and representation of antigen by APCs. HSP may shift the balance between T_H1 and T_H2 toward an increase in more anti-inflammatory T_H2 cells. ROS, including H_2O_2, hydroxyl radical, and peroxynitrite, activate HSP synthesis. In the presence of iron, ROS also induce the oxidation-specific stress proteins HO and ferritin, which afford protection against oxidative stress by binding iron and preventing it from participating in the Fenton reaction. Mechanisms of HSP-mediated cytoprotection from the toxic effects of ROS include the maintenance of

cellular GSH levels (HSP27) and mitochondrial protection (HSP70). Hence, ROS induce a cytoprotective response that counteracts their own toxicity. Other inflammatory mediators such as NO have also been shown to induce expression of HSP.[43]

HSP may participate in intracellular signaling pathways that modulate the production or function of inflammatory mediators. For example, HSP90 has been shown to facilitate signaling that leads to NO formation by eNOS.[371] HSP70 has been reported to prevent apoptosis, which may promote propagation rather than resolution of inflammation. In addition, the body's immune response to bacterial and parasitic stress proteins likely protects the host from infection. The bacterial homologue of HSP60, GroEL, is a major target of the mammalian humoral response to bacterial infections. Many activators of HSF1 are potent inhibitors of the proinflammatory transcription factor NFκB. Aspirin and other NSAIDs activate HSF while inhibiting NFκB. Therefore, the anti-inflammatory effects associated with the stress response might be related more to the inhibition of NFκB activation.[366,372]

The Acute-Phase Response

The acute-phase response consequent to trauma or cellular injury is characterized by alterations in hepatic metabolism; activation of the central nervous system, leading to fever and adaptive behaviors; altered hematopoiesis; activation of complement and the fibrinolytic and coagulation cascades; and the release of neuropeptides, kinins, and hormones. It is a rapid, nonspecific response that accompanies both acute and chronic inflammatory disorders. Many of the processes induced during the acute-phase response are mediated by cytokines. IL-6, IL-1, and TNFα play particularly central roles.[373,374] Though considered a defense mechanism promoting host survival, aberrant or unregulated production of many of these inflammatory mediators can be lethal.

Acute-Phase Proteins

An acute-phase protein is defined as a protein whose concentration increases by at least 25% during inflammation (**Table 7.8**).[374,375] These changes are primarily due to altered hepatic synthesis and typically occur within

approximately 6 hours of the inciting stimulus. The function is to restore homeostasis: hemostatic functions (fibrinogen), microbicidal and phagocytic functions (complement components, C-reactive protein [CRP]), antithrombotic properties (plasminogen, protein S), antioxidant properties (haptoglobin), and antiproteolytic actions (α_2 macroglobulin, α_1 protease, α_1 chymotrypsin). The negative acute-phase proteins albumin, prealbumin, transferrin, and retinol-binding protein decrease by at least 25%. Levels of the negative acute-phase proteins albumin and transferrin drop almost immediately after operation and remain depressed for several days. The rapid initial loss of these proteins is likely due to increased vascular permeability and loss to the extravascular space. The magnitude of the response is proportional to the severity of the stress. Whereas trauma and burns lead to significant increases in acute-phase reactants, exercise and psychiatric illness induce more moderate responses.

The two major acute-phase proteins in humans are CRP and serum amyloid A (SAA). CRP, named because of its reaction with pneumococcal C-polysaccharide, displays both proinflammatory and anti-inflammatory effects. It has been shown to activate complement, recognize foreign pathogens, bind phagocytic cells, and enhance activation of tissue factor, the main initiator of coagulation. CRP can also inhibit superoxide production by neutrophils and inhibit neutrophil adhesion by decreasing surface expression of L-selectin. Changes in plasma or serum CRP, although nonspecific, may reflect the magnitude of an inflammatory process, and may aid the differentiation of inflammatory from noninflammatory conditions. Measurement of CRP is more precise than the erythrocyte sedimentation rate (ESR); the latter largely depends on plasma fibrinogen levels and is influenced by a variety of other, unrelated factors in the circulation. SAA may promote chemotaxis and adhesion of phagocytes during inflammation.[43]

C1 inhibitor is of special interest as an acute-phase protein because of its effects outside of the complement cascade. This antiprotease inhibits the activity of HF, limiting kinin production and factor XI production. Thus, enhanced expression of a complement inhibitor protein during acute inflammation may also influence coagulation, fibrinolysis, and kinin pathways.

Systemic Manifestations of the Acute-Phase Response

Systemic manifestations include neuroendocrine changes, shifts in the hematologic profile, and metabolic and chemical alterations. The classic neuroendocrine manifestation is fever. IL-1, IL-6, and TNFα mediate the fever response by resetting the hypothalamic temperature setpoint through the synthesis of PGE_2. The secretion of neuropeptides, such as CRH and AVP, and of hormones, such as glucagon, insulin, thyroxin, and aldosterone, is also characteristic of the acute-phase response. CRH and AVP are released by the hypothalamus and increase ACTH and cortisol levels. The rise in plasma cortisol levels occurs rapidly and may function to inhibit the fever response and cytokine gene expression, thereby serving a potential negative regulatory function in the acute-phase response. Glucocorticoids also stimulate macrocortin synthesis, which by inhibiting synthesis of PLA_2, limits the availability of arachidonic acid for prostaglandin synthesis. Glucocorticoids increase the rate of synthesis of certain acute-phase proteins involved in connective tissue repair and clotting, as well as antioxidants and antiproteinases. They also may function to counteract the hypoglycemic response to insulin overproduction during infection or stress.

Other alterations include a prominent leukocytosis, thrombocytosis, and the "anemia of chronic disease." Metabolic changes include altered lipid metabolism and negative nitrogen balance. Changes in the chemical and enzymatic profile include increased hepatic production of metallothionein, iNOS, HO, manganese superoxide dismutase, and glutathione (GSH). Plasma levels of zinc and iron are noted to drop, whereas copper levels increase slightly. This persists for the duration of inflammation and is likely due to sequestration induced by IL-6, glucocorticoids, and catecholamines. Low levels of iron and zinc may confer protective antimicrobial effects because they are essential micronutrients for microbial growth.[43]

Mediators of the Acute-Phase Response

Bacterial products such as LPS are probably the most potent activators of tissue macrophages, the initiators of the acute-phase response. LPS, through its interactions with LBP, CD14, and TLRs, induces macrophage synthesis of ROS, including NO; lipid derivatives (e.g., PGE_2, thromboxane A_2, and

PAF); and acute-phase cytokines (e.g., TNFα, IL-6). Additional mediators inducing the synthesis of acute-phase cytokines in the absence of bacterial infection include free radicals, prostaglandins, and the release of DAMPs from injured tissues.[43] Indeed the response to the sterile insult of trauma mirrors much of what is observed during severe sepsis, a similarity that may be the consequence of substantial overlap in signaling mechanisms, such as TLR4.

Acute-phase cytokines can be proinflammatory (IL-1, TNFα, IFNγ, IL-8) or anti-inflammatory (IL-10, IL-4, IL-13, TNFβ). However, it is IL-6 and IL-6-type cytokines that are most critical in the acute-phase response. IL-6 is the major inducer of acute-phase proteins synthesis and, together with IL-1 and TNFα, is responsible for the systemic features classically associated with the acute-phase response (fever, anorexia, leukocytosis, and hormonal changes).[43]

In addition to the aforementioned cytokines, IFNγ is a potent inducer of complement components. The anti-inflammatory cytokine TGFβ stimulates synthesis of antiproteases, urokinase, and negative acute-phase proteins. IL-4 is inhibitory to some acute-phase proteins. Growth factors, including hepatocyte growth factor and TGFβ are also able to modulate the synthesis of acute-phase proteins. Glucocorticoids augment the response to cytokines, and insulin attenuates the cytokine-induced rise in acute-phase proteins.[43]

Effects of the cytokines are influence by cytokine receptors, receptor antagonists, and hormones. IL-1RA competes with IL-1 and attenuates the acute-phase response in vivo. Soluble receptors for IL-1 and TNFα act as antagonists. In contrast, soluble receptors for IL-6 act as agonists.

Regulation of Acute-Phase Cytokines and Proteins

Several major families of transcription factors participate in the upregulation of acute-phase cytokines and proteins, the most important being NF-IL-6, AP-1, and NFκB.[376] NF-IL-6 participates in the expression of the cytokines IL-1, TNFα, IL-6, and IL-8. Activation through the NFκB is probably the predominant pathway. The triggering of IL-6 in monocytes in vitro by IFNγ involves a change in the amount of the phosphorylated transcription factor Sp1, together with the induction and activation of IFN-regulatory factor.

All known acute-phase proteins are regulated primarily at the transcriptional level. Activation of TNFα and IL-1 receptors triggers signaling pathways that activate transcription factors AP-1 and NFκB. Many type I acute-phase proteins genes contain response elements for NFκB, NF-IL-6, and AP-1. Acute-phase protein responses to IL-6 are mediated through the JAK-STAT signal transduction pathway. In addition, both IL-1 and IL-6 signal transduction mechanisms activate the MAPK pathway that activates transcription factors NF-IL-6, linking the IL-1 and IL-6 pathways.

Reperfusion Injury

Prolonged tissue ischemia produces irreversible injury and cell death. Timely restoration of perfusion may salvage some tissue, though paradoxically can induce injury as well. Reperfusion injury is the damage caused by the restoration of blood flow in previously ischemic tissue (i.e., myocardial ischemia, transplantation, vascular surgery). Injury is the direct consequence of activation of the inflammatory response, especially complement activation and neutrophil recruitment. Components of the complement cascade promote tissue damage through the generation of anaphylatoxins and by the formation of the MAC. Invading neutrophils injure tissue through the generation of ROS and the release of proteolytic enzymes. Recent evidence points to TLR4 as a sensor of tissue stress, the signal of which is probably through release of DAMPs from ischemic cells.[36]

Alterations in the microvascular endothelium are central to the pathophysiologic process of reperfusion injury. Early loss of constitutive NO production facilitates neutrophil adherence, the upregulation of cell adhesion molecules such as P-selectin, and inhibits vasorelaxation and perfusion.[377] Low oxygen tension induces the conversion of xanthine dehydrogenase to xanthine oxidase. Reperfusion and reoxygenation yield the formation of superoxide anion and H_2O_2 and induce oxidant injury. Neutrophils and other cellular effectors are progressively recruited and activated, releasing ROS, cytokines, and NO, further contributing to increased vascular permeability and tissue injury. PAF released by neutrophils activates circulating platelets and promotes vascular plugging. Platelets also release factors that enhance platelet–neutrophil adhesion. Both cell types also release vasoconstricting

agents that can further exacerbate no-reflow. Capillary plugging by neutrophils and platelets can impair local blood flow and cause the "no-reflow phenomenon."[43]

Neutrophils mediate direct toxicity to the surrounding tissue through the elaboration of ROS and granule contents. Peroxynitrite formed by the reaction of NO and superoxide can contribute directly to tissue injury during reperfusion. Neutrophil granule proteases such as elastase, collagenase, and gelatinase alter the vascular permeability and are highly destructive to local tissue. The significance of the neutrophil in mediating these effects are apparent in neutrophil depletion studies demonstrating attenuated tissue injury when compared to subjects with normal numbers of neutrophils.[378] Animal studies using blocking monoclonal antibodies to selectins and β_2 integrins show improved organ function ischemia/reperfusion.[379]

The mechanism by which complement is activated with reperfusion is not completely understood. Ischemia may alter the cell's plasma membrane or through the exposure of basement membrane or subcellular organelle components, creating a complement-activating surface. Alternatively, binding of natural antibody may lead to induction of these cascades.[223] Complement activation has been shown to occur in the setting of therapeutic thrombolysis. The generation of plasmin-dependent fibrinolytic agents and plasmin after tissue plasminogen activator administration has been associated with complement activation.[380]

Anaphylatoxins are important effectors of complement-mediated injury. They alter vascular permeability, induce smooth muscle cell contraction, and stimulate the release of histamine from mast cells and basophils. C3a and C5a are potent chemoattractants especially for neutrophils. C5 can be activated by an abundance of oxygen free radicals. The subsequent generation of the MAC perturbs the maintenance of vital ion gradients, induces cell lysis, and facilitates neutrophil recruitment. In addition it can induce the expression of numerous inflammatory mediators, including cytokines (TNFα, IL-1, IL-8), ROS, prostaglandins, leukotrienes, and cell surface adhesion molecules.[381]

Systemic Inflammatory Response Syndrome

The inability of host defenses to control a localized inflammatory process or an unchecked inflammatory response can result in SIRS, defined as the presence of any two of the following physiologic parameters: (1) a temperature greater than 38°C or less than 36°C; (2) leukocytosis (>12,000), leukopenia (<4,000), of more than 10% bands; (3) pulse greater than 90 beats per minute; (4) tachypnea (respiratory rate greater than 20 or $PaCO_2$ <32 mm Hg).[382] Infection underlies a significant minority of cases, as only a third of patients with SIRS will have a documented infection and meet the criteria for sepsis. In one prospective study, 26% of patients with SIRS developed sepsis and 7% died.[383] In fact, SIRS is so nonspecific insofar as facilitating diagnosis that it has been removed as a criterion in the new definitions of sepsis (Sepsis-3).[384]

SIRS may be initiated by infectious or noninfectious causes, such as trauma, autoimmune reactions, or pancreatitis. Gram-negative organisms, rich in LPS, induce a potent inflammatory response mediated through the CD14/TLR4/MyD88 pathway previously described and account for the majority of infectious SIRS cases. Gram-positive organisms can generate a similarly impressive degree of inflammation either through TLR2 or alternative mechanisms. Streptococcal superantigen may induce a global and nonspecific activation of T cells that culminates in massive systemic elaboration of cytokines and cardiovascular collapse termed TSS. Trauma, either through tissue injury (HMGB1-RAGE, HSP-CD91) or the ischemia/reperfusion consequent to hemorrhage can culminate in inflammatory pathophysiology indistinguishable from that accompanying these other inflammatory states. As the growing evidence continues to support the promiscuity of TLR and other signaling pathways, we are replacing the former concept distinct receptor-signaling mechanisms for each stimulus with one that emphasizes the similarities, overlap, and integration. Though there are clearly mechanisms by which host distinguishes normal self from endogenous (trauma) and exogenous (infection) dangers, there is considerable overlap, and all stimuli appear to converge upon similar signaling mechanisms in attaining the goal of preserving the host.

The development of SIRS has been described as progressing through stages: Stage I—local cytokine production recruits inflammatory cells to the injured site; Stage II—an acute-phase response is initiated and small

quantities of cytokines are released into the circulation to enhance the local response; and Stage III—homeostasis cannot be reestablished.[385] Enhanced levels of CRP, the major acute-phase protein in humans, occur in SIRS/sepsis, and clinical resolution is preceded by a drop in CRP levels.

The elaboration of proinflammatory cytokines (IL-1, TNFα, and IL-6) is central to the pathogenesis of SIRS regardless of the initiating stimulus. Their release triggers increased expression of adhesion molecules, leukocyte recruitment, and the production of secondary proinflammatory mediators, such as chemokines. Endotoxin is one of the most powerful triggers of SIRS. LPS activates the complement and coagulation cascades, induces endothelial cell activation, and increases TNFα and IL-1 synthesis, and the late release of HMGB1. Noninfectious tissue injury (i.e., sterile), perhaps through the release of DAMPs such as mitochondrial DNA, may too induce a similar inflammatory response. LPS, TNFα, and IL-1 also induce increased production of NO by iNOS. PGI_2 and arachidonic acid, together with NO contribute to decreased systemic vascular resistance and hypotension. Autocrine and paracrine NO production also results in myocardial depression. Increased vascular permeability promotes extravasation of fluid and edema formation. Activated endothelial cells express tissue factor, PECAM, and TXA_2, which promote a procoagulant local environment that predisposes to microthrombi formation. Adherent leukocytes further exacerbate organ injury by mechanically impeding microvascular blood flow and by damaging the endothelial cells and surrounding connective tissue. The results are end-organ hypoperfusion, inadequate oxygen delivery, initiation of anaerobic metabolism, and organ failure. The metabolic and nutritional sequelae of this activated cytokine milieu include fever, catabolism, cachexia, and altered fat, glucose, and trace mineral metabolism.

SIRS is counteracted by the concomitant induction of an anti-inflammatory response termed the compensatory anti-inflammatory response syndrome (CARS).[385] Many of the proinflammatory mediators that participate in SIRS modulate the immune function of lymphocytes and mononuclear cells. Proinflammatory mediators can inhibit their own synthesis or enhance the synthesis of natural antagonists by negative feedback mechanisms. Thus, at any given time, the clinical manifestation is SIRS, CARS, or an intermediate, mixed inflammatory response syndrome. The spectrum of features that

characterizes these syndromes has been termed CHAOS (cardiovascular shock, homeostasis, apoptosis, organ dysfunction, and immune suppression). Studies employing a variety of specific anticytokine agents have failed to observe an improvement in the outcome of patients with SIRS or sepsis.

Chronic Inflammation

There are no clear boundaries between an acute and a chronic inflammatory response. In general, if the source of an acute inflammatory process is incompletely eliminated, a state of chronic inflammation eventually ensues. Chronicity is usually not characterized by the signs classically associated with acute responses, such as swelling, heat, or redness. Pain is minimal if not absent. Microscopically, a mononuclear cell infiltrate predominates (lymphocytes, monocytes, plasma cells) with proliferation of fibroblasts and vascular elements.

Many agents can create a state of chronic inflammation, including persistent infectious agents, remnants of dead organisms, foreign bodies, and metabolic byproducts. Ultimately, chronicity of inflammation is a result of the immune response to a persistent antigen. Furthermore, a chronic inflammatory response can develop in the absence of a preceding acute response, such as infections with agents of low toxicity such as mycobacterium and treponema. $CD4^+$ T cells and macrophages are the primary cellular orchestrators of chronic inflammatory response.[386] T_H1 cell-mediated immune responses are protective against most microbes and usually result in the elimination of the pathogen. If the microbe persists, the ongoing T_H1 response results in inflammatory tissue injury. Cytokines and growth factors released by T lymphocytes and macrophages stimulate proliferative responses. Neutrophils and eosinophils contribute to the release of proteolytic enzymes and oxygen derivatives. Eosinophilia occurs with chronic parasitic infections and hypersensitivity conditions. Fibroblasts are actively recruited by chemoattractants such as fibrin, collagens, and cytokines. Local IL-1 stimulates fibroblast proliferation and collagen production. Irreversible tissue damage can occur through the replacement of normal parenchyma with fibrous connective tissue. Fibroblasts can release metalloproteinases that degrade normal tissue, further contributing to tissue

destruction. Mast cells are elevated in chronic conditions and may play a part in cell-mediated immune responses. Inflammatory cyst formation may occur as a result of epithelial hyperplasia.

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8

Surgical Infections

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Key Points

1. Surgical infections include intra-abdominal infections (appendicitis, cholecystitis/cholangitis, diverticulitis, colitis including *Clostridium difficile* colitis, pancreatitis, and peritonitis), soft tissue infections (necrotizing and nonnecrotizing), surgical site infections (SSIs), and hospital-acquired infections that occur in surgical patients (pneumonia, central line–associated bloodstream infections [CLABSI], and catheter-associated urinary tract infections [CAUTI]).
2. Early appropriate empiric broad-spectrum antimicrobial therapy, to cover all potential causative pathogens, is an important adjunct to source control in the treatment of surgical infections. Inappropriate antimicrobial therapy is associated with increased mortality.
3. Any of these surgical infections can result in sepsis or septic shock.
4. A key concept in surgical infections is "*source control,*" defined as any physical intervention to remove or eliminate a focus of invasive infection (drainage, debridement, and device removal) and to restore optimal anatomic function.
5. Pathogen identification and appropriate deescalation of antimicrobial therapy are of paramount importance in treatment of surgical infections, as increasing prevalence of multidrug-resistant pathogens has been identified in both abdominal and skin surgical infections.
6. Complicated intra-abdominal infection (cIAI) extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis.
7. Recommendations for specific antimicrobial therapy for cIAI are based on whether the infection is "community acquired" or "health care associated."
8. In patients with intra-abdominal infections who have undergone an adequate source control procedure, fixed-duration antibiotic therapy for 4 days is noninferior to longer duration antimicrobial therapy until resolution of physiologic abnormalities, with no difference in SSI, recurrent intra-abdominal infection, or death.

9 The two surgical procedures indicated for *C. difficile* colitis treatment include the following: (1) total abdominal colectomy (for peritonitis, colonic perforation, ischemia, necrosis, toxic megacolon with impending perforation, septic shock with organ failure) and (2) diverting loop ileostomy and intraoperative colonic lavage for toxin reduction. The second option is associated with colonic preservation.

10 The initial treatment of infected pancreatic necrosis is percutaneous catheter or endoscopic (transgastric/transduodenal) drainage with additional drain placement as required.

11 Lack of clinical improvement of necrotizing infected pancreatitis with initial percutaneous drainage warrants consideration of minimally invasive techniques for pancreatic necrosectomy including video-assisted retroperitoneal debridement, minimally invasive retroperitoneal pancreatectomy, or transluminal direct endoscopic necrosectomy.

12 Acute bacterial skin and skin structure infections are defined as bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration), including cellulitis, wound infection, and abscess.

13 Early operative debridement is the major determinant of outcome in necrotizing soft tissue infections. Delayed definitive debridement remains the single most important risk factor for death.

INTRODUCTION

1 Surgical infections include intra-abdominal infections (appendicitis, cholecystitis, diverticulitis, colitis, and pancreatitis), soft tissue infections (necrotizing and nonnecrotizing), surgical site infections (SSIs), and hospital-acquired infections that occur in surgical patients (pneumonia, central line–associated bloodstream infections [CLABSIs], and catheter-associated urinary tract infections [CAUTIs]).[1] Appropriate therapy of surgical

infections to optimize patient outcomes includes four steps: (1) early diagnosis, (2) early initiation of appropriate empiric broad-spectrum antimicrobial therapy, (3) adequate source control (surgical or interventional radiology), and (4) pathogen identification and appropriate deescalation of antimicrobial therapy (**Table 8.1**).

The initial management of all surgical infections should include the initiation of early empiric antimicrobial therapy to cover all potential possible pathogens, since early and appropriate empiric antibiotic therapy improves patient outcomes (**Table 8.2**).[2] The choice of early empiric antimicrobial therapy is guided by the specific site of infection, the common pathogens associated with that infection, and by local and regional antibiograms. The goal of antimicrobial therapy is to achieve antibiotic levels at the site of the infection that exceed the minimum inhibitory concentration of the microbial pathogens present.

Table 8.1 Appropriate Therapy of Surgical Infections

1. Early diagnosis of surgical infection
2. Early initiation of appropriate empiric broad-spectrum antimicrobial therapy
3. Adequate source control
4. Pathogen identification and appropriate deescalation of antimicrobial therapy

Early Use of Appropriate Broad-Spectrum Antimicrobial Therapy

2 Early use of appropriate broad-spectrum antimicrobial therapy is an important adjunct to appropriate surgical management of surgical infections. Numerous studies have confirmed that inappropriate empiric antibiotics (i.e., antibiotics that do not cover the causative pathogens) are associated with increased mortality.[3] In patients who manifest sepsis or septic shock, every hour delay of antimicrobial therapy is 3 associated with increased mortality.[4] The Surviving Sepsis Guidelines recommendations are listed in **Table 8.3**.

Source Control

4 Source control is defined as any physical intervention to remove or eliminate a focus of invasive infection (drainage, debridement, and device removal) and to restore optimal anatomic function.[5] In surgical infections, antimicrobial agents are used in conjunction with adequate source control of the initial infection. Adequate source control can be accomplished by either surgical or percutaneous interventional radiologic techniques. A number of factors have been identified that predict failure of source control for intra-abdominal infections (**Table 8.4**).

Pathogen Identification

5 Pathogen identification is extremely important, in part related to increased prevalence of multidrug-resistant pathogens that are associated with surgical infections. Whenever possible, high-quality specimens should be obtained from source control procedures for Gram stain and culture in order to identify causative pathogens and determine antimicrobial susceptibility of the bacterial isolates identified. This will enable appropriate deescalation of antimicrobial therapy from broad-spectrum therapy to directed potential single antimicrobial agent therapy.

Table 8.2 Spectrum of Activity of Specific Antimicrobials for Specific Pathogens

Antibiotic	Gram Negative	Gram Positive	Resistant Gram Negative	Resistant Gram Positive	Anaerobe	Pseudomonas
Beta-lactam/beta-lactamase inhibitor	+	+	#	0	+	#
First-generation cephalosporins	0	+	0	0	0	0
Second-generation cephalosporins	#	#	0	0	0	0
Third-generation cephalosporins	+	+	#	0	0	#
Fourth-generation cephalosporins	+	+	#	0	0	#
Fifth-generation cephalosporins	0	+	0	+	0	0
Tigecycline	+	+	+	+	+	0
Glycopeptides	0	+	0	+	0	0
Carbapenems	+	+	#	0	+	#
Quinolones	+	+	0	0	#	#

0, no activity; +, activity; #, activity, but varies by product within class.

Table 8.3 Antimicrobial Therapy, Surviving Sepsis Guidelines 2016

1. Recommend administration of intravenous antimicrobials be initiated as soon as possible after recognition and within 1 hr for both sepsis and septic shock (strong recommendation, moderate quality of evidence)
2. Recommend empiric broad-spectrum therapy with one or more antimicrobials for patients presenting with sepsis or septic shock to cover all likely pathogens (including bacterial and/or fungal or viral) (strong recommendation, moderate quality of evidence)
3. Recommend that empiric antimicrobial therapy be narrowed once pathogen identification and sensitivities are established and/or adequate clinical improvement is noted (Best Practice Statement)
4. Suggest empiric combination therapy (using at least two antibiotics of different antimicrobial classes) aimed at the most likely bacterial pathogens for the initial management of septic shock (weak recommendation, low quality of evidence)
5. Recommend daily assessment for deescalation of antimicrobial therapy in patients with sepsis and septic shock (Best Practice Statement)

Adapted from Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Crit Care Med* 2017;45(3):486–552.

Table 8.4 Clinical Factors Predicting Failure of "Source Control" for Intra-Abdominal Infection
Delay in the initial intervention (>24 hrs)
High severity of illness (APACHE [Acute Physiology and Chronic Health Evaluation] II score ≥15)
Advanced age
Comorbidity and degree of organ dysfunction
Low albumin level
Poor nutritional status
Degree of peritoneal involvement or diffuse peritonitis
Inability to achieve adequate drainage or debridement
Presence of malignancy

INTRA-ABDOMINAL INFECTIONS

Classification

6 Complicated intra-abdominal infection (cIAI) extends beyond the hollow viscus of origin into the peritoneal space and is associated with either abscess formation or peritonitis. "Uncomplicated" intra-abdominal infection involves intramural inflammation of the gastrointestinal tract and has a substantial probability of progressing to cIAI if not adequately treated.

Diagnosis

Patients with cIAI present with abdominal pain and gastrointestinal symptoms. A comprehensive abdominal physical examination must be performed in these patients. If peritonitis is present, evaluation for emergent laparotomy without diagnostic studies is considered. If peritonitis is not present, recent evidence-based guidelines recommend that computed

tomography (CT) scan of the abdomen and pelvis is the diagnostic imaging modality of choice to evaluate for cIAI and its source.[6,7]

Treatment

7 Early appropriate empiric systemic antimicrobial therapy to cover all potential causative pathogens and early source control are the mainstays of treatment of cIAIs. In order to select appropriate empiric antimicrobial agents for use, cIAIs are further classified as "community-acquired" or "health care-associated."

Community-Acquired Complicated Intra-Abdominal Infection

For patients who have "community-acquired" cIAI, determination of whether the disease is "mild/moderate (appendicitis, mild diverticulitis)" or "severe (fecal peritonitis, perforated diverticulitis)" facilitates appropriate antimicrobial treatment (**Table 8.5**). Patients with "severe" community-acquired cIAI should have antibiotics that cover *Pseudomonas* and *Enterococcus* pathogens, and both single-agent and combination-agent regimens are available for use. A number of antimicrobials are no longer recommended for use in community-acquired cIAI:

- Ampicillin/sulbactam is not recommended because of high resistance of *Escherichia coli* to this agent (B-II).
- Cefotetan and clindamycin are not recommended for use because of increasing resistance of the *Bacteroides fragilis* group to these agents (B-II).
- Because of the availability of less toxic agents demonstrated to be of at least equal efficacy, aminoglycosides are not recommended for routine use in community-acquired cIAI in adults (B-II).

Health Care–Associated Complicated Intra-Abdominal Infection

For patients with "health care–associated" cIAI, separate evidence-based guideline recommendations for empiric antimicrobial treatment are provided (**Algorithm 8.1**). Specific antimicrobials are recommended based on

whether the patient and/or institution have high risk for infection with multidrug-resistant pathogens. Quinolone-resistant *E. coli* have become common in many communities, and quinolones should not be used unless hospital antibiograms confirm greater than 90% susceptibility of *E. coli* to quinolones. In patients with health care–associated cIAI, carbapenems are an excellent single-agent regimen for empiric treatment.

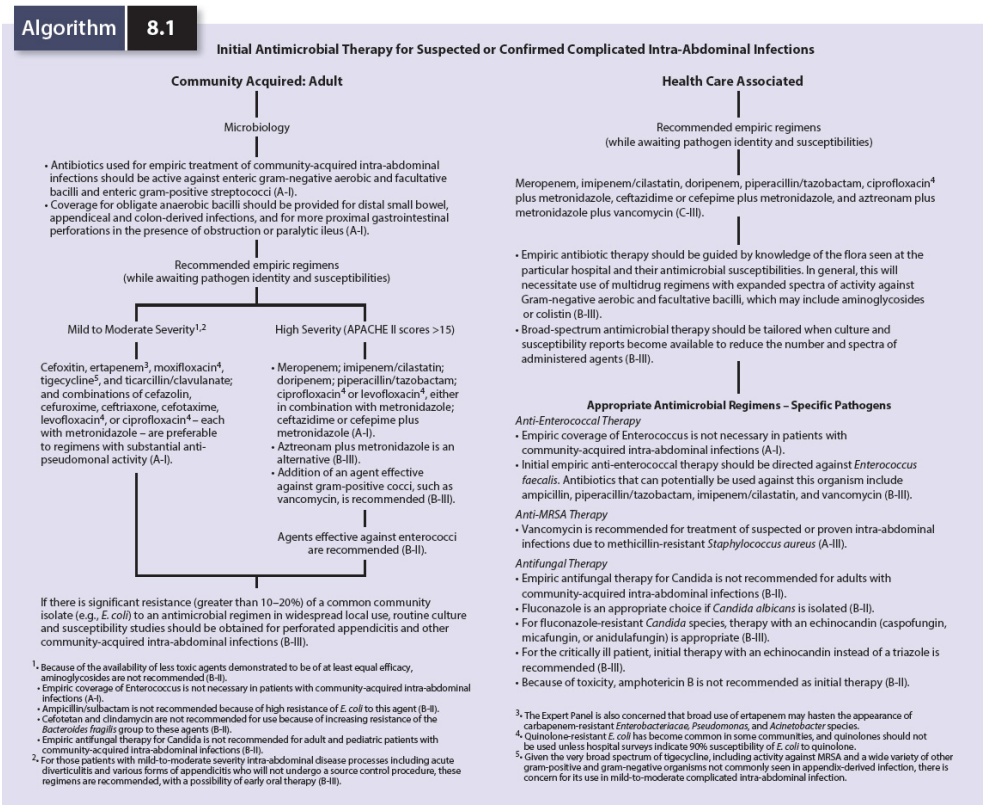
Table 8.5 Empiric Antimicrobial Treatment of Extrabiliary cIAIs, Community Acquired

	Community-Acquired Infections in Adults	
	Mild to Moderate	**Severe**
Single agent	▪ Cefoxitin ▪ Ertapenem ▪ Moxifloxacin ▪ Tigecycline ▪ Ticarcillin/clavulanic acid	▪ Imipenem/cilastatin ▪ Meropenem ▪ Doripenem ▪ Piperacillin/tazobactam
Combination regimen	▪ Cefazolin,[a] cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole	▪ Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole

- Ampicillin/sulbactam is not recommended because of high resistance of *Escherichia coli* to this agent (B-II).
- Cefotetan and clindamycin are not recommended for use because of increasing resistance of the *Bacteroides fragilis* group to these agents (B-II).
- Because of the availability of less toxic agents demonstrated to be of at least equal efficacy, aminoglycosides are not recommended for routine use in community-acquired IAI in adults (B-II).

[a]Caution—local antibiograms should direct use of this agent.

Adapted from Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010;11(1):79–109.



Algorithm 8.1 Empiric antimicrobial treatment of extrabiliary cIAIs, community acquired versus health care associated. (Adapted from Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010;11(1):79–109.)

Duration of Antibiotics for Complicated Intra-Abdominal Infection

Duration of antibiotics for treatment of cIAI has long been [8] controversial. A recent important randomized controlled trial examined the efficacy of short-course (4 days) antimicrobial therapy in patients with intra-abdominal infections who had undergone an adequate source control procedure. Fixed-duration antibiotic therapy for 4 days was noninferior to longer duration antimicrobial therapy until resolution of physiologic abnormalities, with no difference in the composite endpoints of SSI, recurrent intra-abdominal infection, or death.[8]

SPECIFIC INTRA-ABDOMINAL INFECTIONS

Appendicitis

Appendicitis is common with over 300,000 hospital discharges in the United States per year. Although appendectomy provides definitive source control for the treatment of acute nonperforated appendicitis, intravenous (IV) antibiotics should be administered preoperatively with a dose repeated intraoperatively if the surgery is prolonged, a number of controversies in diagnosis and management of appendicitis persist.[9]

Antibiotics versus Appendectomy

In patients with uncomplicated appendicitis (nonperforated, no abscess, or phlegmon), appendectomy is definitive source control. But a number of recent randomized trials have confirmed that acute nonperforated appendicitis can be treated successfully with antibiotics alone. A meta-analysis of six studies with 1,201 patients reported that in patients treated with antibiotics alone, 7 ± 4% failed to respond and required appendectomy, and acute appendicitis recurred in 14 ± 11%. A normal appendix was found in 7.3 ± 5.1% of patients at appendectomy. Complications were considerably less likely to occur with antibiotic treatment than with appendectomy. Major surgical complications included enterocutaneous fistula and reoperation.[10]

A Cochrane meta-analysis of five trials with 901 patients reported that 73.4% of patients who were treated with antibiotics and 97.4% of patients who underwent appendectomy were cured within 2 weeks without major complications (including recurrence) within 1 year.[11] Another meta-analysis included only four trials and reported that efficacy was significantly higher for surgery but rates of perforated appendicitis were not different, and complication rates were significantly higher for surgery.[12] The most recent meta-analysis included 11 trials with 2751 patients and concluded for both uncomplicated and complicated adult acute appendicitis, nonoperative management with antibiotics was associated with significantly fewer complications and a shorter length of stay but a lower effective rate and higher relapse rate.[13]

The APPAC trial enrolled 530 patients in Finland with uncomplicated appendicitis confirmed by CT scan and randomized to early appendectomy

or antibiotic treatment (ertapenem for 3 days, then oral levofloxacin and metronidazole for 7 days) with 1-year follow-up. In the antibiotic group, 70 patients (27.3%) underwent appendectomy within 1 year of initial presentation for appendicitis. Antibiotic treatment did not meet the prespecified criterion for noninferiority compared with appendectomy. But it was notable that 72.7% of patients with uncomplicated appendicitis treated with antibiotics alone did not require subsequent appendectomy.[14,15] In the 5-year follow-up, 39.1% of patients who were randomized to antibiotics underwent appendectomy.[16] In the 7-year follow-up, long-term quality of life was similar, but patients who received antibiotics and later underwent appendectomy were less satisfied than patients with successful antibiotics or appendectomy.[17]

The trials published to date were primarily from European countries, used antibiotics not available in the United States and had minimal use of laparoscopic appendectomy or CT scan for diagnostic imaging.[18] Further high-quality randomized trials are therefore needed to determine which patients are most likely to benefit from antibiotic therapy alone. The Comparison of Outcomes of Antibiotic Drugs and Appendectomy (CODA) trial[19] just completed enrollment in the United States (n = 1552 randomized with parallel observation cohort over 4 years), and aims to compare patient-reported and clinical outcomes in patients randomized to antibiotics (10-day course) or appendectomy. Although appendectomy remains the standard treatment for acute appendicitis, antibiotic treatment alone may be used as an alternative treatment in patients with contraindication to surgery (or where surgery is high risk).

Laparoscopic versus Open Appendectomy

Appendectomy can be performed by laparoscopic or open approach. A large retrospective review (2005–2008) of laparoscopic versus open appendectomy using the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) reported that 76.4% were performed laparoscopically and 23.6% performed open. Open appendectomy was associated with increased morbidity, SSI, and mortality.[20]

A Cochrane review of 67 trials was updated in 2010 and reported that laparoscopic appendectomy was associated with lower SSI rates but higher

intra-abdominal abscess rate. Laparoscopic approach was associated with shorter hospital length of stay, faster return to normal activity, and decreased postoperative pain. This review concluded that laparoscopic appendectomy should be considered the preferred approach where surgical expertise and equipment are available.[21]

Time to Appendectomy and Perforation Risk

It has long been thought that appendiceal luminal obstruction leads to appendiceal perforation without timely surgical intervention. This belief led to attempts to decrease time from presentation and diagnosis of acute appendicitis to operating room start time. With the advent of early appropriate empiric systemic antimicrobial therapy, this fundamental concept is no longer true. As discussed previously, in patients with uncomplicated appendicitis, antibiotic treatment alone does not lead to appendiceal perforation. Furthermore, using data from the Washington State Surgical Care and Outcomes Assessment Program (SCOAP) with 9,048 adult patients who underwent appendectomy, there was no association between appendiceal perforation and in-hospital time prior to surgery. This study confirmed that appendiceal perforation is most commonly a prehospital occurrence, and timing of surgery should be determined based on all factors relevant to the surgeon and patient.[22]

Abscess or Phlegmon Management

In patients with periappendiceal abscess or phlegmon, current evidence (mainly retrospective studies) supports nonoperative management with IV transitioned to oral antibiotics and percutaneous drainage if possible. A meta-analysis of 19 retrospective studies from 1969 to 2005 reported that nonsurgical treatment failed in only 7.6% of patients and immediate appendectomy was associated with higher morbidity. Similar findings were confirmed in a more recent review.[23] Routine interval appendectomy is not recommended since the risk of recurrence is low (7.4%). But either colonoscopy or repeat CT imaging is recommended due to the risk of a malignant disease (1.2%) or important benign disease (0.7%) identified during follow-up.[24]

Interval Appendectomy after Initial Nonoperative Management

A large retrospective cohort study reported that 3% of patients were initially treated with nonoperative management. Of these, 15% had an interval appendectomy and the remaining 85% did not. Of the 864 patients who did not undergo interval appendectomy, only 39 patients (5%) had recurrence of appendicitis after a median follow-up of 4 years.[25] Routine interval appendectomy after initial successful nonoperative treatment is therefore not justified based on the evidence to date. In a meta-analysis including 2,771 patients initially treated nonoperatively for appendiceal phlegmon or abscess, 31 patients were found to have a malignant diagnosis and a lower rate of inflammatory bowel disease. Peri-Appendicitis Acuta Randomized Clinical Trial[26] patients either to interval appendectomy or MRI after initial successful nonoperative treatment of periappendiceal abscess, and all patients underwent colonoscopy. An interim analysis of 60 patients confirmed a high rate of neoplasm (17%) with all inpatients with age >40 years, and the trial was prematurely terminated. These data highlight the need for follow-up with either CT scan or colonoscopy after successful nonoperative management.[24] Although a retrospective study in pediatric appendicitis reported a 2.8-fold higher rate of recurrent appendicitis in patients with an appendicolith, this study is limited by small sample size (n = 96) and a higher overall rate of recurrent appendicitis than all other published studies.[27] See also chapter on Appendiceal Diseases.

Biliary Infections

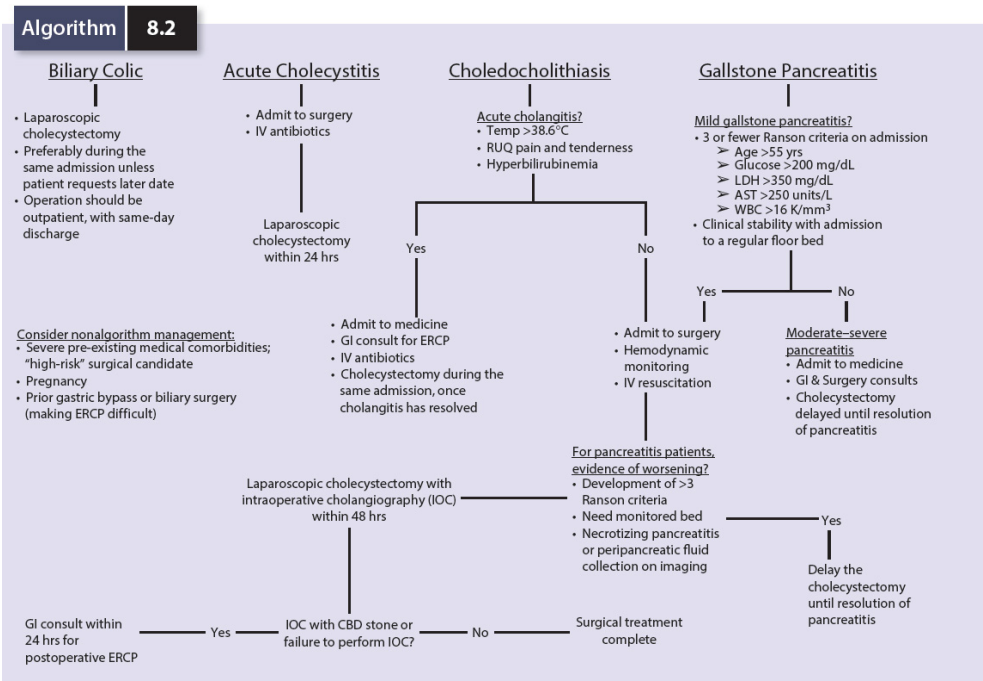
Biliary infections include acute cholecystitis which may be calculous or acalculous, may include choledocholithiasis or not, and cholangitis.[28] Acute cholecystitis and ascending cholangitis are primary inflammations of the gallbladder and bile ducts, respectively, which are caused by infection and possible biliary obstruction.

Acute Cholecystitis

Acute cholecystitis is inflammation of the gallbladder resulting from obstruction of the cystic duct and subsequent bacterial invasion and

overgrowth. Cholelithiasis is the cause of cystic duct obstruction in more than 90% of cases of acute cholecystitis in the United States. Acalculous cholecystitis is more common in critically ill patients and the pathophysiology is transmural ischemia. Acalculous cholecystitis carries higher morbidity and mortality rates than calculous cholecystitis.

The diagnosis of acute cholecystitis is made based on the common constellation of right upper quadrant tenderness, leukocytosis, and fever. Initial diagnostic imaging is right upper quadrant ultrasound to evaluate for gallstones, gallbladder wall thickening, and pericholecystic inflammation (sensitivity 88% to 94%, specificity 78% to 80%). If ultrasound is inconclusive or is discordant with the clinical evaluation, then cholescintigraphy (99mTc-hepatobiliary iminodiacetic acid, HIDA scan) is recommended, and nonvisualization of the gallbladder confirms acute cholecystitis with sensitivity of 96% and specificity of 90% (**Algorithm 8.2**).[29,30] Contrast-enhanced CT scan imaging is recommended for diagnosis of emphysematous cholecystitis or complications such as pericholecystic abscess, perforation, and peritonitis. The Tokyo Guidelines classify severity grading for acute cholecystitis into Grade I (mild), II (moderate) and III (severe) based on clinical, laboratory, and imaging criteria, with higher severity grades associated with worse outcomes, prolonged hospital length of stay, and conversions to open surgery (**Table 8.6**). Treatment recommendations are then based on severity classification and coexistent comorbidities and ASA classification.[31]



Algorithm 8.2 Biliary infections and algorithm for diagnosis and management. (From Demehri FR, Alam HB. Evidence-based management of common gallstone-related emergencies. *J Intensive Care Med* 2016;31(1):3–13.)

Early systemic antimicrobial treatment is indicated for acute cholecystitis to cover the causative pathogens, including aerobic, enteric, gram-negative bacilli (i.e., *E. coli*, Klebsiella, Enterobacter, and Proteus), and aerobic gram-positive organisms (i.e., Enterococcus and Streptococcus). Anaerobes are uncommon, identified in approximately 15% of isolates. Clostridial organisms can be identified in cases of emphysematous cholecystitis confirmed by identification of gas in the gallbladder wall.

Cholangitis

Cholangitis signs/symptoms include jaundice, fever, right upper quadrant tenderness, hyperbilirubinemia, and leukocytosis. Ultrasound confirms common bile duct dilation (>7 mm). Acute cholangitis has long been diagnosed on the basis of clinical signs of Charcot triad (jaundice, fever, right upper quadrant abdominal pain), which provides highly specific diagnostic criteria, but very low sensitivity (about 26%).

Appropriate evidence-based recommendations for diagnosis and treatment from the Tokyo Guidelines are provided in **Tables 8.7** and **8.8**. For treatment recommendations, urgent biliary drainage (<24 hours) is indicated in severe

cholangitis or when (1) obstructive biliary stones are associated with moderate acute cholangitis OR (2) mild acute cholangitis is not responding to IV antibiotics and fluid resuscitation.

For patients with biliary infections, specific evidence-based guideline recommendations for antimicrobial treatment are classified into four patient populations (**Table 8.9**). For patients undergoing cholecystectomy for acute cholecystitis with complete source control (i.e., complete cholecystectomy), antimicrobial therapy should be discontinued within 24 hours of the operation unless there is evidence of infection outside the wall of the gallbladder. For patients with gallbladder perforation or pericholecystic abscess, antimicrobial treatment should be continued until signs and symptoms of infection are resolved (normal WBC count, no fever, abdominal findings resolved).[32] For acute cholangitis, antimicrobial therapy should be continued for 4 to 7 days after source control is obtained. See also chapter on Calculous Biliary Disease.

Diverticulitis

Diverticulitis is a common intra-abdominal infection. Its pathophysiology is associated with altered gut motility, increased luminal pressure, and an altered colonic microenvironment.

Uncomplicated diverticulitis is treated with systemic antibiotics and usually resolves. Antimicrobial treatment of diverticulitis is the same as for cIAI which is reviewed above. In a cohort study of 2,366 patients hospitalized in the Kaiser Permanente system and followed for 8.9 years, only 13.3% had a first recurrence and 3.9% had a second recurrence.[33] Antibiotic therapy alone is associated with a very high success rate for complicated acute diverticulitis with abscess size <4 cm diameter,[34,35] and percutaneous drainage of abscesses >4 cm successfully resolve in 80% of patients with a low complication and reintervention rate.

Table 8.6 Severity Grading for Acute Cholecystitis: Tokyo Guidelines 2018

Severity of Acute Cholecystitis		Treatment
Mild (Grade I)	Does not meet the criteria of "Grade II" or "Grade III" acute cholecystitis Also defined as acute cholecystitis in a healthy patient with no organ dysfunction and mild inflammatory changes in the gallbladder, making cholecystectomy a safe and low-risk operative procedure	Early laparoscopic cholecystectomy if the patient meets the criteria of CCI ≤5 and ASA-PS ≤2
Moderate (Grade II)	Acute cholecystitis associated with any one of the following conditions: ▪ Elevated WBC count (>18,000/mm^3) ▪ Palpable tender mass in the right upper abdominal quadrant ▪ Duration of complaints >72 hrs ▪ Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary	Early laparoscopic cholecystectomy by experienced surgeons if the patient meets the criteria of CCI ≤5 and ASA-PS ≤2 If not, after medical treatment and/or gallbladder drainage, laparoscopic cholecystectomy would be indicated

	peritonitis, emphysematous cholecystitis)	
Severe (Grade III)	Acute cholecystitis associated with dysfunction of any one of the following organs/systems: ▪ Cardiovascular dysfunction (hypotension requiring vasopressors) ▪ Neurologic dysfunction (decreased level of consciousness) ▪ Respiratory dysfunction (PaO_2/FiO_2 ratio <300) ▪ Renal dysfunction (oliguria, serum creatinine >2 mg/dL) ▪ Hepatic dysfunction (elevated PT/INR >1.5) ▪ Hematologic dysfunction (platelet count <100,000/mm^3)	Lap-C is indicated with strict criteria: favorable organ system failure, and negative predictive factors, with CCI ≤3 and ASA-PS ≤2 and who are being treated at an advanced center (where experienced surgeons practice) If the patient is not considered suitable for early surgery, early/urgent biliary drainage is recommended followed by delayed Lap-C once the patient's overall condition has improved.

CCI, Charlson comorbidity index; ASA-PS, American Society of Anesthesiologists physical status classification system.

Adapted from Yokoe M, Hata J, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholecystitis (with videos). *J Hepatobiliary Pancreat Sci* 2018;25:41–54; Okamoto K, Suzuki K, Takada T, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis. *J Hepatobiliary Pancreat Sci* 2018;25:55–72.

Surgery for acute diverticulitis is indicated for patients who present with peritonitis and/or sepsis or who do not improve with medical management and/or percutaneous drainage of associated abscess/infection. Although less than 25% of patients will develop generalized peritonitis after colonic perforation, it is severe with high mortality. Surgical options include simple colostomy formation in the setting of profound inflammation (rarely performed), traditional sigmoid resection with colostomy (Hartmann procedure), and sigmoid resection with a primary colocolonic or colorectal anastomosis with or without a diverting loop ileostomy. Laparoscopic surgery is preferred to open surgery when possible.[36]

Table 8.7 Diagnosis of Cholangitis: Tokyo Guidelines 2018

Systemic inflammation	▪ Fever and/or shaking chills ▪ Laboratory data: evidence of inflammatory response (WBC, CRP, etc.)
Cholestasis	▪ Jaundice (total bilirubin ≥2 mg/dL) ▪ Laboratory data: abnormal liver function tests (ALP, GGT, AST, and ALT)
Imaging	▪ Biliary dilatation ▪ Evidence of the etiology on imaging (stricture, stone, stent, etc.)
Diagnosis of cholangitis	Suspected: presence of 1 item in A + 1 item in either B or C Definite: presence of 1 item in A, 1 item in B, and 1 item in C

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase/aspartate transaminase; CRP, C-reactive protein; GGT, γ-glutamyl transferase; WBC, white blood cell.

Adapted from Kiriyama S, Kozaka K, Takada T, et al. Tokyo Guidelines 2018: Diagnostic criteria and severity grading of acute cholangitis (with videos). *J Hepatobiliary Pancreat Sci* 2018;25:17–30.

Since recurrence after recovery from an uncomplicated episode of diverticulitis is rare and two or more recurrences are not associated with increased risk of complications, elective colectomy following two episodes of diverticulitis is no longer recommended. Decisions regarding surgical intervention and colectomy must therefore be based on individual potential risks and benefits of colon resection.[37]

For patients who require surgical intervention, the specific treatment that is associated with the best outcome is controversial. Hinchey proposed a practical clinical classification of diverticulitis based on the severity of peritoneal contamination (**Fig. 8.1**) identified at operation.[38] The modified Hinchey classification includes Hinchey Ia (confined pericolic inflammation–phlegmon) and Ib (confined pericolic abscess) and considers classification based on radiologic imaging with CT scan as well. The majority of Hinchey Ib–II cases can be successfully managed nonoperatively. Furthermore, the majority of patients with Hinchey I–II disease who are successfully managed without surgery are unlikely to experience any further acute diverticulitis and therefore, surgery should not be routinely offered to avoid future episodes. A personalized patient-specific approach for elective surgery should be used.

Increasing Hinchey classification is associated with increased mortality. The mortality for patients with Hinchey III is reported as 6% but increases greatly to 35% for fecal peritonitis (Hinchey IV). A systematic review comparing surgical treatments for Hinchey III or IV colonic diverticulitis confirmed that primary resection with anastomosis has a significant advantage with lower mortality compared to Hartmann procedure. Furthermore, laparoscopic peritoneal lavage with subsequent surgical resection, if indicated, had lower surgical morbidity and hospital length of stay compared to the primary resection and anastomosis group.[39] The 2019 EAES/SAGES Diverticulitis Guidelines recommend "Lavage may be considered in selected Hinchey III patients by surgeons with appropriate expertise and the ability to closely watch for and manage complications. The lower stoma rate should be weighed against the higher risk of complications and re-intervention." See also chapter on Diverticular Disease.

Table 8.8 Treatment of Acute Cholangitis by Severity Classification: Tokyo Guidelines 2018 Criteria

Severity of Acute Cholangitis	
Mild (grade I)	Does not meet the criteria of "severe" or "moderate" acute cholangitis at time of initial diagnosis
Moderate (grade II)	Acute cholangitis associated with any two of the following conditions: ▪ Abnormal WBC (>12,000, <4,000/mm^3) ▪ High fever (≥39°C) ▪ Age ≥75 years old ▪ Hyperbilirubinemia (total bilirubin ≥5 mg/dL) ▪ Hypoalbuminemia (<lower limit of normal × 0.7)
Severe (grade III)	Acute cholangitis associated with the onset of dysfunction in at least one of the following organs/systems: ▪ Cardiovascular dysfunction (hypotension requiring vasopressors) ▪ Neurologic dysfunction (disturbance of consciousness) ▪ Respiratory dysfunction (PaO_2/FiO_2 ratio <300) ▪ Renal dysfunction (oliguria, serum creatinine >2 mg/dL) ▪ Hepatic dysfunction (elevated PT/INR >1.5) ▪ Hematologic dysfunction (platelet count <100,000/mm^3)
Assessment of Urgency of Draining **Urgent** biliary drainage (<24 hrs) is indicated when:	

a. severe (grade III) acute cholangitis is present.
b. obstructive biliary stones are associated with severe or moderate acute cholangitis.
c. mild acute cholangitis is not responding to IV antibiotics and fluid resuscitation.

Early (but not urgent) ERCP (<72 hrs) is recommended for patients with mild acute cholangitis who respond to medical therapy.

ERCP, endoscopic retrograde cholangiopancreatography; PT/INR, prothrombin time and international normalized ratio.

Adapted from Kiriyama S, Kozaka K, Takada T, et al. Tokyo Guidelines 2018: diagnostic criteria and severity grading of acute cholangitis (with videos). *J Hepatobiliary Pancreat Sci* 2018;25:17–30; Miura F, Okamoto K, Takada T, et al. Tokyo Guidelines 2018: initial management of acute biliary infection and flowchart for acute cholangitis. *J Hepatobiliary Pancreat Sci* 2018;25:31–40.

Table 8.9 Antimicrobials for Treatment of Biliary Infections

Community-acquired acute cholecystitis of mild to moderate severity ▪ Cefazolin ▪ Cefuroxime ▪ Ceftriaxone
Community-acquired acute cholecystitis of severe physiologic disturbance, advanced age, or immunocompromised state ▪ Imipenem/cilastatin ▪ Meropenem ▪ Doripenem ▪ Piperacillin/tazobactam ▪ Ciprofloxacin, levofloxacin, or cefepime, each in combination with metronidazole
Acute cholangitis following bilioenteric anastomosis of any severity ▪ Imipenem/cilastatin ▪ Meropenem ▪ Doripenem ▪ Piperacillin/tazobactam ▪ Ciprofloxacin, levofloxacin, or cefepime each in combination with metronidazole
Health care–associated biliary infection of any severity ▪ Imipenem/cilastatin ▪ Meropenem ▪ Doripenem ▪ Piperacillin/tazobactam ▪ Ciprofloxacin, levofloxacin, or cefepime, each in combination with metronidazole ▪ Vancomycin added to each regimen

Adapted from Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Surg Infect (Larchmt)* 2010;11(1):79–109.

Clostridium Difficile Colitis

The incidence and severity of *Clostridium difficile* infection (CDI) has increased, particularly in surgical patients who have been exposed to prior antimicrobial therapy. There has been a substantial change in the management of CDI related to the emergence of the NAP1/BI/027 strain which is associated with higher toxin production and more severe forms of disease. CDI may be associated with mild to moderate diarrhea or colonic ileus and obstipation to severe colitis.[40,41]

Early diagnosis of CDI is imperative. Recommended testing includes two steps, using a glutamine dehydrogenase assay for the Clostridium difficile antigen, followed by enzyme immunoassay toxin testing. Polymerase chain reaction (PCR) confirmatory testing is used if the antigen is positive and toxin is negative.[42] Radiologic testing is helpful, and CT may show colonic mucosal edema (thumbprinting or target sign), ascites, inflammation, and fat stranding and the "accordion sign" which indicates alternating edematous colonic haustra separated by transverse mucosal ridges filled with enteral contrast.

Initial management of CDI is cessation of all antibiotics if possible. The 2017 Update[43] to the 2010 SHEA/IDSA Guidelines have evidence-based recommendations for CDI based on severity of disease (**Fig. 8.2**).[44] Vancomycin or Fidaxomicin are now first-line therapy, and enteral metronidazole is no longer recommended except if the other agents are not available. Fidaxomicin (a macrocyclic antibiotic with a narrow antimicrobial spectrum against *C. difficile*, staphylococci, and enterococci) may also be considered for recurrent CDI or where risk of recurrence is high. A multicenter, multinational randomized trial confirmed decreased recurrence rates compared to oral Vancomycin, and is U.S. Food and Drug Administration (FDA) approved with a recommended treatment dose of 200 mg PO BID.[45] A monoclonal antibody against toxin B (bezlotoxumab) was safe and effective for prevention of recurrent CDI and may be a good therapeutic option for severe CDI as well.[46] Fecal microbiota transplantation is associated with symptom resolution and may be effective in recurrent CDI, but has no role in primary CDI treatment.

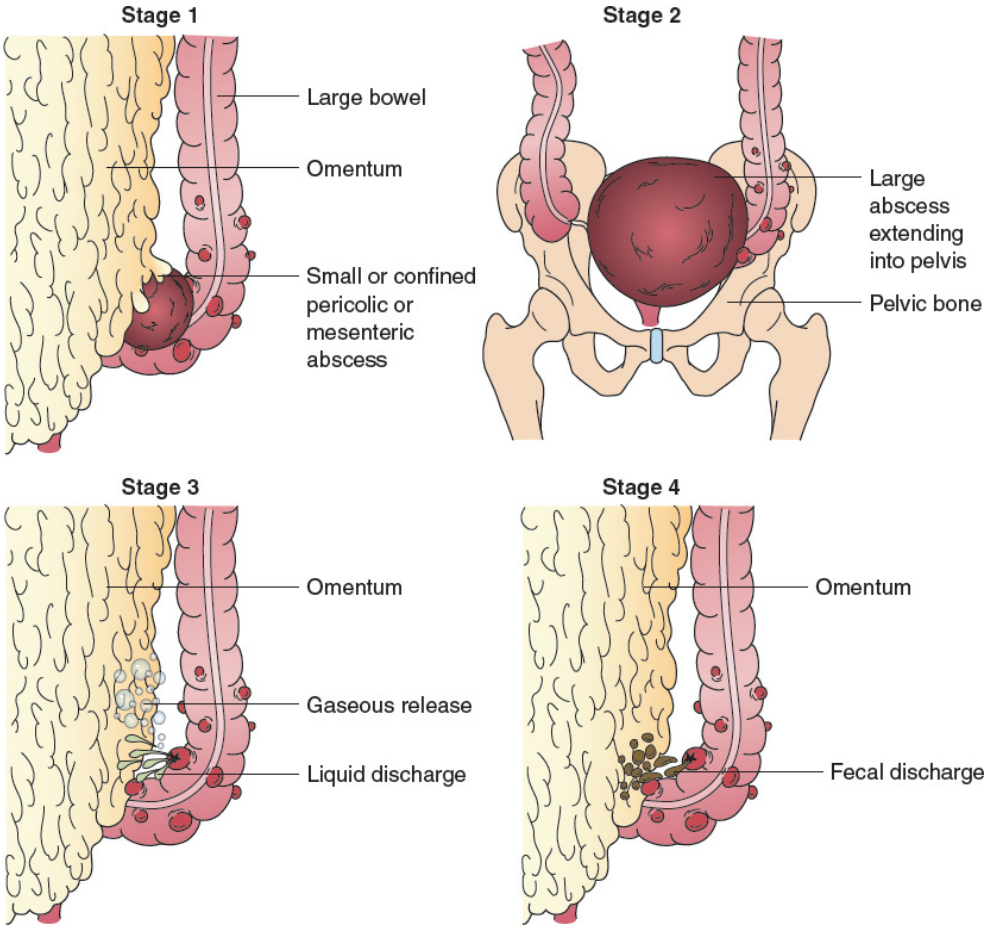


Figure 8.1 Hinchey classification scheme. Patients with stage 1 disease have small, confined, pericolic, or mesenteric abscesses, whereas those with stage 2 disease have larger abscesses, often confined to the pelvis. Stage 3 disease, or perforated diverticulitis, is present when a peridiverticular abscess has ruptured and caused purulent peritonitis. Rupture of an uninflamed and unobstructed diverticulum into the free peritoneal cavity with fetal contamination, the so-called free rupture, signifies stage 4 disease and carries the highest risk of an adverse outcome.

CDI may warrant surgical intervention. Surgical consultation should occur very early in the course of disease in patients with severe and complicated CDI. The indications for surgical management of CDI patients are not clearly defined, but severe disease, worsening clinical condition despite appropriate treatment, and peritonitis or shock states are all potential indications. 9 The two surgical procedures indicated for CDI treatment include (1) total abdominal colectomy (for peritonitis, colonic perforation, ischemia, necrosis, toxic megacolon with impending perforation, septic shock with organ failure) and (2) diverting loop ileostomy and intraoperative colonic lavage for toxin reduction while preserving the colon (**Fig. 8.3**). This new

treatment strategy resulted in reduced mortality compared with the historical population who had undergone total abdominal colectomy (19% vs. 50%), and preservation of the colon was achieved in 93% of patients.[47] A retrospective multicenter study compared total colectomy versus loop ileostomy for CDI treatment and reported that loop ileostomy was associated with decreased mortality.[48] No randomized studies have been published to date comparing these two options.

Pancreatitis

A new classification of acute pancreatitis has been implemented and is based on local disease (whether pancreatic necrosis is present or not, whether it is sterile or infected) and systemic determinants (whether organ failure is present or not, whether it is transient or persistent) of severity (**Table 8.10**). Early management requires goal-directed fluid resuscitation (with avoidance of overresuscitation and abdominal compartment syndrome), assessment of severity of pancreatitis, diagnostic CT imaging to assess for necrotizing pancreatitis, consideration of endoscopic retrograde cholangiopancreatography (ERCP) for biliary pancreatitis, and early enteral nutrition support. Antibiotic prophylaxis for severe acute or necrotizing pancreatitis is not recommended.[49]

Necrotizing pancreatitis is high risk for progression to necrotizing *infected* pancreatitis. Therapeutic antibiotics are required for treatment of documented infected pancreatic necrosis. Causative pathogens include gram-negative microbes and an increase in gram-positive organisms has been reported.[50] Therefore broad-spectrum IV antimicrobials are recommended.

10 The initial treatment of infected pancreatic necrosis is percutaneous catheter or endoscopic (transgastric/transduodenal) drainage with a second drain placement as required. The "step-up" approach consisted of percutaneous drainage followed, if necessary, by minimally invasive retroperitoneal necrosectomy. The minimally invasive step-up approach, as compared with open necrosectomy, reduced the rate of the primary composite endpoint (12% vs. 50%, including major complications [new-onset multiple organ failure or multiple systemic complications, perforation of a visceral organ or enterocutaneous fistula, or bleeding] or death), but the mortality rate did not differ significantly between groups (19% vs. 16%).[51,52]

The long-term follow-up of patients in the PANTER trial confirmed the step-up approach for necrotizing pancreatitis to be superior to open necrosectomy, without increased risk of reinterventions.[53]

11 Lack of clinical improvement after these initial procedures warrants consideration of minimally invasive techniques for pancreatic necrosectomy including video-assisted retroperitoneal debridement (VARD), minimally invasive retroperitoneal pancreatic necrosectomy (MIRP), or transluminal direct endoscopic necrosectomy (DEN).[54] VARD and MIRP use the tract created by percutaneous drainage catheters as a guide for placement of a laparoscope into the retroperitoneum so that debridement and lavage can be performed under direct visualization. Open necrosectomy is associated with substantial morbidity, but to date no randomized trial has documented superiority of either minimally invasive or open surgical technique. Additional trials are underway to address this (**Algorithm 8.3**). See also chapter on Acute Pancreatitis.

Clinical Definition	Supportive Clinical Data	Recommended Treatment[a]	Strength of Recommendation/ Quality of Evidence
Initial episode, non-severe	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	▪ VAN 125 mg given 4 times daily for 10 days, OR ▪ FDX 200 mg given twice daily for 10 days ▪ Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Strong/High Strong/High Weak/High
Initial episode, severe[b]	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	▪ VAN, 125 mg 4 times per day by mouth for 10 days, OR ▪ FDX 200 mg given twice daily for 10 days	Strong/High Strong/High
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	▪ VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)
First recurrence	…	▪ VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR ▪ Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (e.g., 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR ▪ FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Low Weak/Low Weak/Moderate
Second or subsequent recurrence	…	▪ VAN in a tapered and pulsed regimen, OR ▪ VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR ▪ FDX 200 mg given twice daily for 10 days, OR ▪ Fecal microbiota transplantation[c]	Weak/Low Weak/Low Weak/Low Strong/Moderate

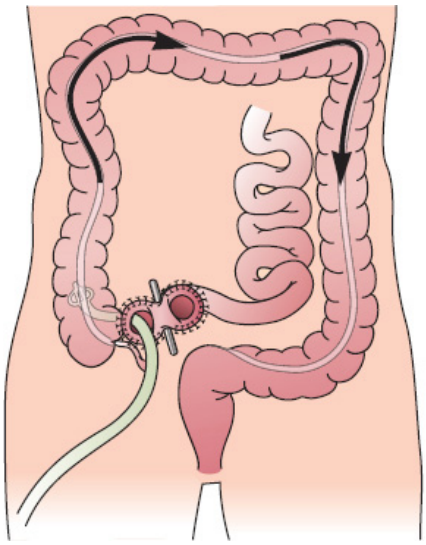
Abbreviations: FDX, fidaxomicin; VAN, vancomycin.
[a]All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment and clinicians should consider extending treatment duration to 14 days in those circumstances.
[b]The criteria proposed for defining severe or fulminant *Clostridium difficile* infection (CDI) are based on expert opinion. These may need to be reviewed in the future upon publication of prospectively validated severity scores for patients with CDI.
[c]The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation.

Figure 8.2 Treatment of initial episode of *Clostridium difficile* infection.

SKIN AND SOFT TISSUE INFECTIONS

Skin and soft tissue infections (SSTIs) span a broad spectrum of clinical entities from limited cellulitis to rapidly progressive necrotizing fasciitis, which may be associated with septic shock or toxic shock syndrome and associated organ failure.[55,56] These SSTIs may result in critical illness and require management in the intensive care unit (ICU).[57,58] Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as the most common identifiable cause of severe SSTIs, therefore initiation of empiric anti-MRSA antimicrobials is warranted in all cases of severe SSTIs. In addition, appropriate critical care management, including fluid resuscitation, organ support, and nutritional support are necessary components of treatment of severe SSTIs.

The complex interplay of environment, host, and pathogen is important to consider when evaluating SSTIs and planning therapy. The key to a successful outcome in caring for patients with severe SSTIs is (1) early diagnosis and differentiation of necrotizing versus nonnecrotizing SSTI, (2) early initiation of appropriate empiric broad-spectrum antimicrobial therapy with consideration of risk factors for specific pathogens, (3) "source control," that is, early aggressive surgical intervention for drainage of abscesses and debridement of necrotizing soft tissue infections (NSTIs), and (4) pathogen identification and appropriate deescalation of antimicrobial therapy.



1. Creation of diverting loop ileostomy.
2. Intraoperative antegrade colonic lavage with 8 L of warmed PEG3350/electrolyte solution via ileostomy.
3. Postoperative antegrade colonic enemas with vancomycin (500 mg in 500 mL x 10 days) via ileostomy.

Figure 8.3 Diverting loop ileostomy with antegrade colonic irrigation for CDI.

Before surgery is started:

1. Place the patient in lithotomy position with easy access to rectum.
2. Place a fluid collection bag (commonly used by urology) under the patient's rectum for drainage collection.
3. Place a rectal drainage tube (large Malecot catheter, large Foley catheter, #9 or #10 endotracheal tube, or other large catheter).
4. Have 8 L of warmed polyethylene glycol 3350/electrolyte solution (GoLYTELY; Braintree Laboratories) available in OR for intraoperative colonic irrigation, and dulcolax suppository.

Intraoperatively:

1. Ensure that the colon is viable and without perforation.
2. Create a loop ileostomy (laparoscopic or open).
3. Place a 24-Fr Malecot catheter into the efferent limb of the ileostomy and advance into the right colon through the ileocecal valve. Secure to skin with sutures.
4. Infuse 8 L of warmed polyethylene glycol 3350/electrolyte solution (GoLytely; Braintree Laboratories) into the 24-Fr Malecot catheter via the efferent limb of the ileostomy.
5. Once colonic lavage is completed, perform rectal examination to empty rectum, place dulcolax suppository in rectum to encourage colonic emptying.
6. Instill antegrade colonic enema with vancomycin (500 mg in 500 mL) via ileostomy efferent limb, continue postoperatively.

(Adapted from Neal MD, Alverdy JC, Hall DE, et al. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. *Ann Surg* 2011;254:423–427; discussion 427–429.)

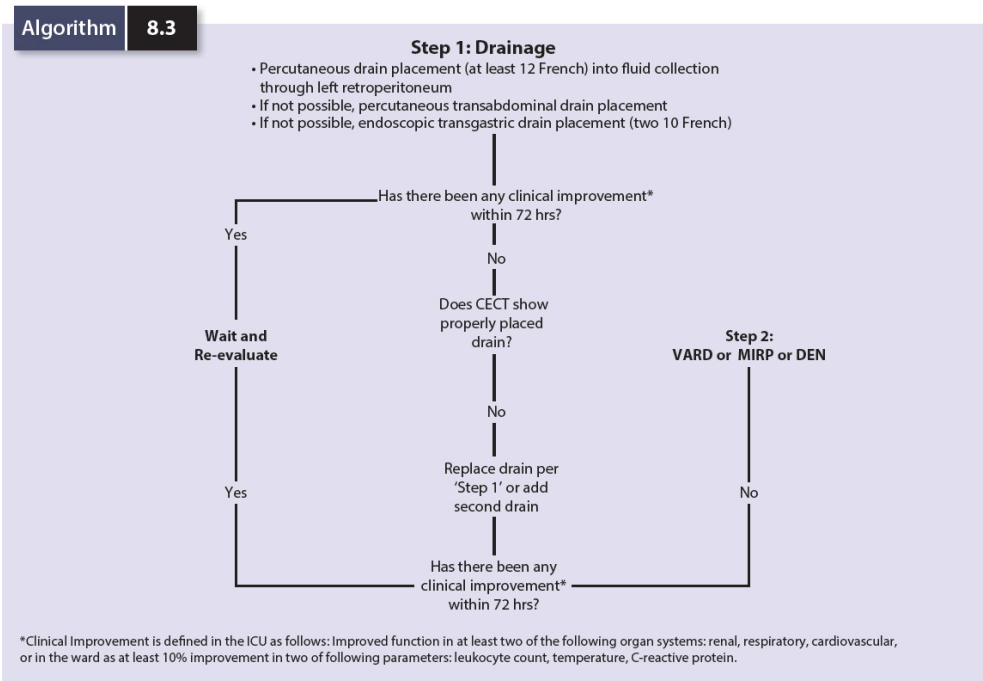
Table 8.10 New International Classification of Acute Pancreatitis: Determinants of Severity of Acute Pancreatitis by the 2011 World Congress of the International Association of Pancreatology

Mild AP	No evidence of necrosis or organ failure		
Moderate AP	Evidence of sterile necrosis or transient organ failure		
Severe AP	Evidence of infected necrosis or persistent organ failure		
Critical AP	Evidence of infected necrosis and persistent organ failure		
Local Determinant: Peri/Pancreatic Necrosis	**Systemic Determinant: Organ Failure**		
Nonviable tissue located in the pancreas alone, or in the pancreas and peripancreatic tissues, or in peripancreatic tissues alone. It can be solid or semisolid (partially liquefied) and is without a radiologically defined wall	Defined for three organ systems on the basis of the worst measurement over a 24-hr period In patients without pre-existing organ dysfunction, defined as either SOFA score of 2 or more in the assessed organ system are: ▪ Cardiovascular: need for inotropic agent ▪ Renal: ≥171 μmol/L (≥2 mg/dL) ▪ Respiratory: PaO_2 ≤30 mm Hg (≤40 kPa)		
Sterile necrosis	No proven infection in necrosis	Transient organ failure	Evidence of organ failure in the same organ system for

			less than 48 hrs
Infected necrosis	At least one is present: 1. Gas bubbles within peri/pancreatic necrosis on CT 2. Positive culture by image-guided fine-needle aspiration 3. Positive culture obtained during the first drainage and/or necrosectomy	Persistent organ failure	Evidence of organ failure in the same organ system for 48 hrs or more

SOFA, sepsis-related organ failure assessment; CT, computed tomography.

Adapted from Dellinger EP, Forsmark CE, Layer P, et al; Pancreatitis Across Nations Clinical Research and Education Alliance (PANCREA). Determinant-based classification of acute pancreatitis severity: an international multidisciplinary consultation. *Ann Surg* 2012;256:875–880.



Algorithm 8.3 Step-up approach to management of necrotizing infected pancreatitis. (Adapted from Besselink MG, van Santvoort HC, Nieuwenhuijs VB, et al; Dutch Acute Pancreatitis Study Group. Minimally invasive 'step-up approach' versus maximal necrosectomy in patients with acute necrotizing pancreatitis (PANTER trial): design and rationale of a randomized controlled multicenter trial [ISRCTN13975868]. *BMC Surg* 2006;6:6.)

Classification of Skin and Soft Tissue Infections

The FDA previously classified SSTIs into two broad categories for the purpose of clinical trials evaluating new antimicrobials for the treatment of SSTIs: **uncomplicated** and **complicated** (Table 8.11). **Uncomplicated** SSTIs include superficial infections such as cellulitis, simple abscesses, impetigo, and furuncles. These infections can be treated by antibiotics and/or surgical incision for drainage of abscess alone. In contrast, **complicated** SSTIs include deep soft tissue infections that require significant surgical intervention such as infected ulcers, infected burns, and major abscesses, and these patients also have significant underlying comorbidities, that is, disease states which complicate (and usually delay) response to treatment. Complicated SSTIs are a significant clinical problem, in part related to the increasing resistance of infecting bacteria to current antibiotic therapies.

Uncomplicated Skin and Soft Tissue Infections

Uncomplicated SSTIs are associated with ***low*** risk for life- or limb-threatening infection. These patients can be treated with empiric antibiotic therapy according to likely pathogen and local resistance patterns.

Table 8.11 Comparison of Old and New Classification of SSTIs by FDA

- Uncomplicated
  - Superficial infections, such as:
    - simple abscesses
    - impetiginous lesions
    - furuncles
    - cellulitis
  - Can be treated by antibiotics or surgical incision alone
- Complicated
  - Deep soft tissue, such as:
    - infected ulcers
    - infected burns
    - major abscesses
  - Significant underlying disease state which complicates response to treatment
  - Requires significant surgical intervention and antimicrobials

New FDA Definition (October 2013):

ABSSSI defined as bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration), including the following:

- **Cellulitis/erysipelas:** A diffuse skin infection characterized by spreading areas of redness, edema, and/or induration
- **Wound infection:** An infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration
- **Major cutaneous abscess:** An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration

From https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acute-bacterial-skin-and-skin-structure-infections-developing-drugs-treatment. Accessed September 24, 2020.

Complicated Skin and Soft Tissue Infections

Complicated SSTIs are associated with ***high*** risk for life- or limb-threatening infection. In these patients, it is of paramount importance to initiate appropriate and adequate broad-spectrum initial empiric antimicrobial therapy with coverage for MRSA, and to consider the need for surgical intervention for abscess drainage or debridement.

Patients with complicated SSTIs require hospitalization for treatment. Specific circumstances that warrant hospitalization include the presence of tissue necrosis, sepsis, severe pain, altered mental status, immunocompromised state, and organ failure (respiratory, renal, hepatic). SSTIs can lead to serious potentially life-threatening local and systemic complications. The infections can progress rapidly, and early recognition and proper medical and surgical management is cornerstone of therapy.

12 In October 2013, the FDA changed the SSTI terminology and issued final guidance for the treatment of acute bacterial skin and skin structure infections (ABSSSI).[59] This guidance defined ABSSSI as cellulitis, erysipelas, wound infection, and major cutaneous abscess. An ABSSSI is defined as a bacterial infection of the skin with a lesion size area of at least 75 cm^2 (lesion size measured by the area of redness, edema, or induration). The minimum area of involvement of 75 cm^2 is chosen to select patients with acute bacterial skin infections for which a reliable control drug treatment effect can be estimated for the conduct of new antimicrobial treatment trials. While the FDA generally requires two phase III trials to support approval of drugs to treat ABSSSI, this guidance stated that a single phase III study that is supported by additional independent evidence may suffice.

Patients with the following infection types can be enrolled in ABSSSI clinical trials:

- **Cellulitis/erysipelas:** A diffuse skin infection characterized by spreading areas of redness, edema, and/or induration.
- **Wound infection:** An infection characterized by purulent drainage from a wound with surrounding redness, edema, and/or induration.
- **Major cutaneous abscess:** An infection characterized by a collection of pus within the dermis or deeper that is accompanied by redness, edema, and/or induration.

Unfortunately, this new guidance does not address less serious skin infections, such as impetigo and minor cutaneous abscess, or more serious

infections needing more complex treatment regimens, such as infections resulting from animal or human bites, NSTIs, diabetic foot infection, decubitus ulcer infection, myonecrosis, osteomyelitis, and ecthyma gangrenosum.

Early Diagnosis and Differentiation of Necrotizing versus Nonnecrotizing SSTI

Another classification for SSTIs that is commonly used is the differentiation of **NSTIs** from **nonnecrotizing infections**. This differentiation is critical since necrotizing infections warrant prompt aggressive surgical debridement. Clinical clues to the diagnosis of NSTIs are listed in **Table 8.3**. The differentiation of necrotizing infections from nonnecrotizing infections is critical to achieving adequate surgical therapy.[60] A clear approach to these infections must allow rapid identification and treatment of NSTIs because they are limb threatening and life threatening.

When "hard clinical signs" (bullae, crepitus, gas on x-ray, hypotension with SBP <90 mm Hg, or skin necrosis) of NSTI are present, establishing the diagnosis of NSTI is not difficult. However, hard signs of NSTIs are often absent on presentation, thus potentially delaying diagnosis and surgical intervention. Studies have documented that less than 50% of patients with a definitive diagnosis of NSTI presented with "hard clinical signs" of NSTI.[61] Admission of white blood cell count >15,400 × 10^9/L and/or serum sodium <135 mEq/L was documented to help differentiate NSTI from non-NSTI and aided in early diagnosis.[62,63] The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score is also helpful as a laboratory aid in distinguishing necrotizing from nonnecrotizing SSTIs (see NSTI section below). In retrospective studies, CT scan has been shown to have a negative predictive value of 100% and a positive predictive value of 76% in diagnosing NSTI.[64]

If there is any question regarding the possible diagnosis of an NSTI, it is imperative to proceed with surgical intervention and to be certain that the surgical incision is continued down to the fascial and muscle level to make a definitive diagnosis.

Early Initiation of Appropriate Empiric Broad-Spectrum Antimicrobial Therapy with Anti-MRSA Coverage and Consideration of Risk Factors for Specific Pathogens

Antimicrobial therapy is an essential element in the management of severe SSTIs. As in all serious life-threatening infections, it is important to initiate **early** and **appropriate** empiric antimicrobial therapy. It is well established that prompt appropriate treatment of hospitalized infections reduces mortality.[2] Similar findings were reported in studies of patients with ventilator-associated pneumonia[65] and sepsis.[66] A study of ICU patients found that the higher mortality rate associated with inappropriate initial therapy is still observed when antibiotics are switched from an inappropriate to an appropriate treatment.[67]

Furthermore, appropriate and timely antibiotic therapy improves treatment outcomes for SSTIs caused by MRSA.[68] In a study of 492 patients with community-onset MRSA SSTIs, 95% of episodes treated with an active antibiotic within 48 hours were treated successfully, compared with an 87% rate of successful treatment in patients who did not receive an active antibiotic. In logistic regression analysis, failure to initiate active antimicrobial therapy within 48 hours of presentation was the only independent predictor of treatment failure. Similarly, in a study of patients admitted to the hospital with MRSA sterile-site infection, multivariate analysis found inappropriate antimicrobial treatment to be an independent risk factor for hospital mortality.[69]

An empiric treatment algorithm for SSTI directed against community-associated MRSA (CA-MRSA) in the emergency department that promotes both the use of antibiotics likely active against CA-MRSA and early incision and drainage of abscesses was examined. Clinical failure occurred in only 3% of cases treated according to the algorithm, compared with 62% of those not treated according to the algorithm. Furthermore, among cases that underwent immediate incision and drainage, initial treatment with antibiotics active in vitro against the MRSA isolate was associated with a decreased clinical failure rate when compared to those treated with inactive antibiotics (0% vs. 67%).[70]

Empiric antibiotic therapy should be initiated in **all** patients with SSTIs. IV broad-spectrum antimicrobial therapy should be initiated when an infection is severe or progresses rapidly, when there are signs of systemic illness, when the patient has comorbidities or is immunosuppressed, for very old or young patients, when an abscess cannot be completely drained, and when the infection does not respond to incision and drainage.[71]

Timely initiation of antimicrobial therapy is also important in the treatment of severe SSTIs, particularly if associated with septic shock. In a study of 2,731 adult patients with septic shock, a strong relationship between the delay in effective antimicrobial initiation and in-hospital mortality was noted.[4] Administration of an antimicrobial effective for isolated or suspected pathogens within the first hour of documented hypotension was associated with a survival rate of 79.9%. Each hour of delay in antimicrobial administration over the ensuing 6 hours was associated with an average decrease in survival of 7.6%. By the second hour after onset of persistent/recurrent hypotension, in-hospital mortality rate was significantly increased relative to receiving therapy within the first hour. In multivariate analysis (including Acute Physiology and Chronic Health Evaluation II score and therapeutic variables), time to initiation of effective antimicrobial therapy was the single strongest predictor of outcome. Interestingly, only 50% of septic shock patients received effective antimicrobial therapy within 6 hours of documented hypotension.

Necrotizing Soft Tissue Infections

NSTIs are aggressive soft tissue infections that cause widespread necrosis, and can include necrotizing cellulitis, fasciitis, and myositis/myonecrosis.[72,73] Establishing the diagnosis of NSTI can be the main challenge in treating patients with NSTI, and knowledge of all available tools is key for early and accurate diagnosis.[74] There have been a number of recent advances in the definition, pathogenesis, diagnostic criteria, and treatment of NSTIs.[75,76]

Patients with NSTIs require prompt aggressive surgical debridement, appropriate IV antibiotics, and intensive support. Despite aggressive treatment, their mortality and morbidity rates remain high, with some series reporting mortality rates of 25% to 35%.[77] A high index of suspicion should

be used in conjunction with laboratory and imaging studies to establish the diagnosis as rapidly as possible. Successful treatment requires early, aggressive surgical debridement of all necrotic tissue, appropriate broad-spectrum systemic antibiotic therapy, and supportive care (fluid resuscitation, organ and critical care support) to maintain oxygenation and tissue perfusion. Delayed definitive debridement remains the single most important risk factor for death. Early operative debridement is the major determinant of outcome in NSTIs.

A recent single-institution series of 166 patients documented that the overall mortality rate was 17% and limb loss occurred in 26% of patients with extremity involvement.[78] Independent predictors of mortality included white blood cell count greater than 30,000 × $10^3/\mu L$, creatinine level greater than 2 mg/dL, and heart disease at hospital admission. Independent predictors of limb loss included heart disease and shock (systolic blood pressure <90 mm Hg) at hospital admission. Clostridial infection was an independent predictor for both limb loss and mortality and was highly associated with IV drug use and a high rate of leukocytosis on hospital admission.

A 30-day postoperative mortality risk calculator for NSTI was developed using the NSQIP which identified seven independent variables that correlated with mortality: age older than 60 years, functional status, requiring dialysis, American Society of Anesthesiologists (ASA) class 4 or higher, emergent surgery, septic shock, and low platelet count. The receiver operating characteristic area was 0.85, which indicated a strong predictive model that can aid physicians in the decision-making process.[79]

13 Early operative debridement is the major determinant of outcome in NSTIs. However, early recognition of NSTIs is difficult clinically. A novel diagnostic scoring system for distinguishing NSTIs from other severe soft tissue infections based on laboratory tests routinely performed for the evaluation of severe SSTIs is called the LRINEC score (**Table 8.12**).[80] The LRINEC score was initially developed in a retrospective observational study including 145 patients with necrotizing fasciitis and 309 patients with severe cellulitis or abscesses admitted to the two tertiary care hospitals. The cutoff value for the LRINEC score was 6 points with a positive predictive value of 92% and negative predictive value of 96%. The LRINEC score is a robust score capable of detecting clinically early cases of necrotizing

fasciitis. The variables used are routinely measured to assess severe soft tissue infections. Patients with a LRINEC score of ≥6 should be carefully evaluated for the presence of necrotizing fasciitis.

Table 8.12 The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) Score

Variable, Units	Score
C-reactive protein, mg/L	
<150	0
≥150	4
Total white cell count, per mm^3	
<15	0
15–25	1
>25	2
Hemoglobin, g/dL	
>13.5	0
11–13.5	1
<11	2
Sodium, mmol/L	
≥135	0
≤135	2
Creatinine, μmol/L	
≤141	0
>141	2
Glucose, mmol/L	
≤10	0
>10	1

The maximum score is 13; a score ≥6 should raise the suspicion of necrotizing fasciitis and a score of ≥8 is strongly predictive of this disease.

Since the initial development of the LRINEC score, a number of other cohort studies have validated its utility in the diagnosis of NSTIs. A

multicenter study in 229 patients with NSTIs from 2002 to 2005 reported an overall mortality rate of 16% and amputation rate of 26%. This study also documented that a LRINEC score ≥6 was associated with a higher rate of both mortality and amputation.[81]

Diagnostic Imaging in Necrotizing Soft Tissue Infections

NSTIs necessitate prompt aggressive surgical debridement for satisfactory treatment in addition to antimicrobial therapy. Because of the rapidly progressive and potentially fatal outcome of this condition, if imaging cannot be performed expeditiously, delaying treatment is not justified. Plain film findings may reveal extensive soft tissue gas. CT examination can reveal asymmetric thickening of deep fascia in association with gas, and associated abscesses may also be present. MR imaging can also assist in the diagnosis of NSTIs.[82] MR imaging has been documented to effectively differentiate between necrotizing and nonnecrotizing infections of the lower extremity and other areas of the body, but should not delay prompt surgical intervention in NSTIs management.[83–85]

Microbiology of Necrotizing Soft Tissue Infections

Necrotizing fasciitis and myonecrosis are typically caused by infection with *group A streptococcus (GAS)*, *Clostridium perfringens*, or, most commonly, aerobic and anaerobic organisms as part of a polymicrobial infection that may include *S. aureus*. In case series, CA-MRSA has recently been described as a predominantly monomicrobial cause of necrotizing fasciitis.[86,87] A retrospective review of patients presenting with necrotizing fasciitis indicated that MRSA was the most common pathogen, accounting for one-third of the organisms isolated.[88]

NSTIs have been classified into two types, either polymicrobial (**type I**) or monomicrobial (**type II**). Polymicrobial infections are more common, due to both aerobic and anaerobic organisms, and commonly occur in the trunk and perineum. NSTIs that are monomicrobial in origin commonly occur in the limbs and are typically caused by infection with GAS, *C. perfringens,* or *S. aureus*. NSTIs are categorized into these two specific types based on the microbiologic etiology of the infection, and this classification does impact on

the specific antimicrobial agents required for treatment of these NSTIs. Increasingly, MRSA has been identified as the causative microbe in NSTIs, but a separate category for this NSTI does not currently exist.[89–93] Given this finding, anti-MRSA empiric antimicrobial therapy should be initiated in all patients with NSTIs and pathogen-directed antimicrobial therapy should be considered once tissue culture results are available.

Uncommon microbiologic causes of NSTIs and primary sepsis include *Vibrio* and *Aeromonas* species, virulent gram-negative bacteria, and members of the Vibrionaceae family that thrive in aquatic environments.[94] These NSTIs are likely to occur in patients with hepatic disease, diabetes, and immunocompromised conditions.[95] These organisms are found in warm sea waters and are often present in raw oysters, shellfish, and other seafood. The diagnosis of vibrio NSTIs should be suspected when a patient has the appropriate clinical findings and a history of contact with seawater or raw seafood.[96] Early fasciotomy and culture-directed antimicrobial therapy should be aggressively performed in those patients with hypotensive shock, leukopenia, severe hypoalbuminemia, and underlying chronic illness, especially a combination of hepatic dysfunction and diabetes mellitus. The rates of amputation and mortality are very high in these patients, and early definitive management is of paramount importance.[97–99] A study of 125 patients identified that a LRINEC score of 2 or greater and the presence of hemorrhagic bullous/blistering lesions in patients with *Vibrio vulnificus* SSTI are associated with a 12-fold increased risk for the presence of NSTI and necrotizing fasciitis.[100]

Pyomyositis

Myositis is a rare infection that may lead to serious and potentially life-threatening local and systemic complications.[101] The infection can progress rapidly, and early recognition and proper medical and surgical management is therefore the cornerstone of therapy. With the increasing prevalence of community-associated MRSA as a pathogen in severe SSTIs, pyomyositis is more common than in past years.[102,103] Myositis often occurs in muscle sites that have been compromised by injury, ischemia, malignancy, or surgery. The predominant pathogens are *S. aureus,* GAS, gram-negative aerobic and

facultative bacilli, and the indigenous aerobic and anaerobic cutaneous and mucous membranes local microflora.

CT scan imaging is a rapid and sensitive diagnostic test and commonly demonstrates diffuse enlargement of the involved muscle and may demonstrate the presence of fluid or gas collections within the muscle suggesting the presence of abscesses. MRI is more sensitive in showing early inflammatory changes prior to development of abscesses in myositis.[104] Emergency surgical exploration is warranted in order to define the nature of the infective process which is accomplished by direct examination of the involved muscles. Surgical intervention is required to perform appropriate abscess drainage and debridement and also to evaluate for necrotizing myositis. Fasciotomies and extremity amputation are sometimes necessary.

SURGICAL SITE INFECTIONS

Epidemiology

SSI is the leading nosocomial infection among surgical patients and the second most common nosocomial infection overall. In the United States, greater than 40 million inpatient and outpatient surgical procedures are performed each year and 2% to 5% are complicated by SSIs. SSIs result in increased length of stay (7 days) and additional cost ($400 to $2,600 per infection; total $130 to $845 million per year).[58,105–107] Among the four health care–associated infections (pneumonia, SSI, urinary tract infection, and bloodstream infection), SSIs are the second most common health care–associated infection, accounting for 17% of all health care–associated infections among hospitalized patients. A similar rate was obtained from the National Healthcare Safety Network (NHSN) hospitals reporting data in 2006–2008 (15,862 SSI following 830,748 operative procedures, with an overall rate of nearly 2%).[108]

Definitions

SSIs are defined in three specific categories by the Centers for Disease Control and Prevention (CDC), including superficial incisional SSI, deep

incisional SSI, and organ/space SSI (**Fig. 8.4**, Table 8.13), dependent on the depth of the infection at the surgical incision site. In addition, the SSI must occur within 30 days after the operative procedure if no implant is left in place or within 1 year if implant is in place and the infection appears to be related to the operative procedure. More specific criteria regarding these definitions are available in the CDC Guideline for Prevention of Surgical Site Infection.[109]

Risk Factors for Surgical Site Infection

SSI risk is strongly associated with wound classification, with low risk for SSI in *clean* and *clean–contaminated* wound classes, and high risk for SSI in *contaminated* and *dirty–infected* wound classes. Three independent variables have been shown to be associated with SSI risk, initially developed by the National Nosocomial Infections Surveillance System (NNIS). The NHSN was established in 2005 to integrate and supersede three legacy surveillance systems at the CDC: the NNIS system, the Dialysis Surveillance Network (DSN), and the National Surveillance System for Healthcare Workers (NaSH). Similar to the NNIS system, NHSN facilities voluntarily report their health care–associated infection surveillance data for aggregation into a single national database.

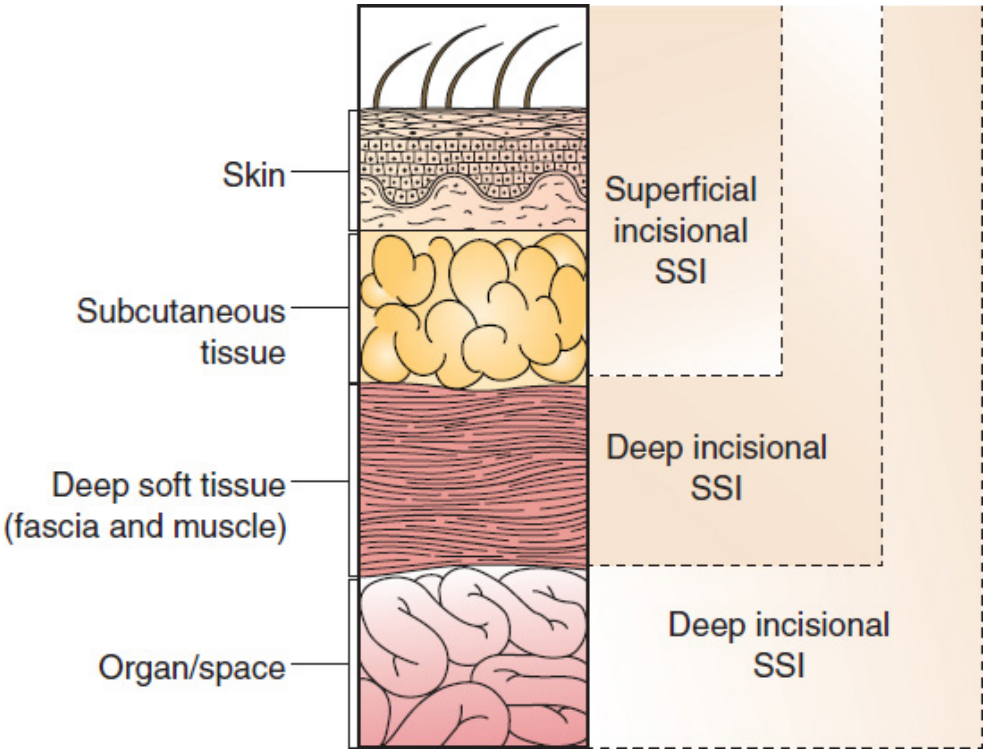


Figure 8.4 Surgical site infection (SSI) definitions by CDC.
Cross-section of the abdominal depicted.
Superficial incisional SSI involves only the skin and subcutaneous tissue layer of the incision.
Deep incisional SSI involves deep soft tissues (e.g., fascia and muscle layers) of the incision.
Organ/Space SSI involves any part of the body, excluding the skin incision, fascia or muscle layers, that is opened or manipulated during the operative procedure (e.g., intra-abdominal abscess or thoracic empyema).

Table 8.13 CDC/NHSN Classification of Surgical Site Infections (SSIs)

Type of SSI	Definition
Superficial incisional	Infection occurs within 30 days after the operative procedure and involves only skin and subcutaneous tissue of the incision and patient has at least one of the following: a. Purulent drainage from the superficial incision b. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision c. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, and superficial incision is deliberately opened by surgeon and is culture positive or not cultured. A culture-negative finding does not meet this criterion d. Diagnosis of superficial incisional SSI by the surgeon or attending physician
Deep incisional	Infection occurs within 30 days after the operative procedure if no implant[a] is left in place or within 1 yr if implant is in place and the infection appears to be related to the operative procedure and involves deep soft tissues (e.g., fascial and muscle

	layers) of the incision, and patient has at least one of the following: a. Purulent drainage from the deep incision but not from the organ/space component of the surgical site b. A deep incision spontaneously dehisces or is deliberately opened by a surgeon and is culture positive or not cultured when the patient has at least one of the following signs or symptoms: fever (38°C), or localized pain or tenderness. A culture-negative finding does not meet this criterion c. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination d. Diagnosis of a deep incisional SSI by a surgeon or attending physician

[a]Implant: A nonhuman-derived object, material, or tissue (e.g., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during an operative procedure and is not routinely manipulated for diagnostic or therapeutic purposes.

From Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309–332.

The NHSN SSI Risk Index includes an ASA score greater than 2, classification of wound as contaminated or dirty, and prolonged duration of operation.[110,111] Although the risk of infection increases within the wound

classification, it has been shown to be also dependent within each wound class on the NNIS classification.

Basic SSI Risk Index

The index used in NHSN assigns surgical patients into categories based on the presence of three major risk factors:

1. Operation lasting more than the duration cut point hours, where the duration cut point is the approximate 75th percentile of the duration of surgery in minutes for the operative procedure
2. Contaminated (class 3) or dirty/infected (class 4) wound class
3. ASA classification of 3, 4, or 5

The patient's SSI risk category is simply the number of these factors present at the time of the operation.

The laparoscopic surgical approach is associated with decreased SSI incidence, and a modified risk index (category 1 when procedure was performed with a laparoscope) has been created to address this approach.

Additional patient-specific risk factors for SSI have also been identified that are not included in this risk index, including the presence of anemia, blood transfusion intraoperatively, and colonization with resistant pathogens.[111,112] This SSI Risk Index warrants reevaluation for the future, particularly with regard to resistant pathogens and other patient-specific risk factors that are not modifiable prior to surgical intervention. It is of paramount importance to include an SSI risk assessment in all future clinical trials where SSI is a primary outcome measure.

Surgical Site Infection Prevention

Preventive measures for SSI include antimicrobial prophylaxis, sterilization methods, proper ventilation of operating rooms, use of barriers, no shaving, clipping if hair removal is required, proper surgical skin preparation and surgical techniques, maintenance of normothermia, glycemic control, and the provision of supplemental oxygen.[107] The National Surgical Infection Prevention (SIP) project was initiated as the first component of the Surgical Care Improvement Project (SCIP). Initiated in 2003, the SCIP partnership

sought to substantially reduce surgical mortality and morbidity through collaborative efforts.

Despite evidence of effectiveness of preoperative antimicrobials for SSI prevention and the publication of guidelines for antimicrobial prophylaxis, it was recognized that use was often suboptimal. As part of the SIP initiative, three SIP performance measures were developed:

- SIP-1: **Antibiotic timing:** Proportion of patients in whom IV antimicrobial prophylaxis is initiated within 1 hour before incision.
- SIP-2: **Antibiotic selection:** Proportion of patients are given prophylactic antimicrobials consistent with published guidelines.
- SIP-3: **Antibiotic discontinuation within 24 hours:** Proportion of patients whose antimicrobial prophylaxis is discontinued within 24 hours after surgery.

Numerous studies document that antimicrobial prophylaxis for SSI is most effective when provided 30 to 60 minutes prior to the initial surgical incision, allowing adequate blood and tissue concentrations at the time of skin incision. Risk of SSI increases when antimicrobial prophylaxis is given too early (more than 2 hours prior to skin incision) or too late (after skin incision). In a recent study of 4,472 patients, SSI risk increased incrementally as the interval of time between antibiotic infusion and the surgical incision increased. These data from a large multicenter collaborative study confirmed lower SSI risk when surgical antimicrobial prophylaxis with cephalosporins and other antibiotics with short infusion times were given within 30 minutes prior to surgical incision.[113]

In addition, the correct antimicrobial must be administered to cover the potential causative pathogens, dependent on the surgical procedure performed. The SCIP pocket card (**Table 8.14**) provides a list of the recommended preoperative antimicrobials for specific surgical procedures. The recent publication of the "Clinical practice guidelines for antimicrobial prophylaxis in surgery" by the American Society of Health-System Pharmacists, Infectious Diseases Society of America, Surgical Infection Society, and Society for Healthcare Epidemiology of America provides evidence-based national recommendations.[114]

Table 8.14 Recommended Preoperative Antimicrobials for Specific Surgical Procedures

Prophylactic Antibiotic Regimen Selection for Surgery	Prophylactic Antibiotic Regimen Selection for Surgery
Surgical procedure: CABG, other cardiac or vascular	**Surgical procedure: hip/knee arthroplasty**
Approved antibiotics Cefazolin, cefuroxime, or vancomycin[a] If β-lactam allergy: vancomycin[b] or clindamycin[b]	**Approved antibiotics** Cefazolin or cefuroxime or vancomycin[a] If β-lactam allergy: vancomycin[b] or clindamycin[b]
Surgical procedure: hysterectomy	**Surgical procedure: colon**
Approved antibiotics Cefotetan, cefazolin, cefoxitin, cefuroxime, or ampicillin/sulbactam If β-lactam allergy: clindamycin + aminoglycoside, or clindamycin + quinolone, or clindamycin + aztreonam OR metronidazole + aminoglycoside, or metronidazole + quinolone	**Approved antibiotics** Cefotetan, cefoxitin, ampicillin/sulbactam, or [c]ertapenem OR cefazolin or cefuroxime + metronidazole If β-lactam allergy: clindamycin + aminoglycoside, or clindamycin + quinolone, or clindamycin + aztreonam OR metronidazole with aminoglycoside, or metronidazole + quinolone
Surgical procedure: special considerations	**Surgical procedure: special considerations**

[a]Vancomycin is acceptable with a physician/APN/PA/pharmacist documented justification for its use (see data element *Vancomycin*).

[b]For cardiac, orthopedic, and vascular surgery, if the patient is allergic to β-lactam antibiotics, vancomycin or clindamycin is an acceptable substitute.

[c]A single dose of ertapenem is recommended for colon procedures.

The first report of the National SIP Project baseline results from a systematic random sample of 34,133 Medicare inpatients undergoing surgery in U.S. hospitals in 2001 documented that only 55.7% of patients received a dose of parenteral antimicrobial prophylaxis within 1 hour before surgical incision. Antimicrobial agents consistent with published guidelines were administered to 92.6% of patients and antimicrobial prophylaxis was discontinued within 24 hours of surgery end time for only 40.7% of patients. Interestingly, only 28% of these surgical patients had compliance with all three of these performance measures.[115]

We have truly made remarkable progress in the United States with appropriate perioperative antimicrobial prophylaxis since that initial published report. Compliance with SIP-1 measure (antibiotics within 60 minutes prior to incision) increased from 55.7% to 91.6%; compliance with SIP-2 measure (guideline antibiotics) increased from 92.6% to 95.8%; and compliance with SIP-3 (antibiotics discontinued) increased from 40.7% to 87.7%.

Additional Strategies for Surgical Site Infection Prevention

Surgical Hand Antisepsis

Surgical hand antisepsis, to destroy bacteria, is routinely carried out before undertaking invasive procedures. A recent review of 10 trials confirmed that alcohol rubs used in preparation for surgery by the surgical team are as effective as aqueous scrubbing in SSI prevention. There is no evidence to suggest that any particular alcohol rub is better than another. Evidence from four studies suggests that chlorhexidine gluconate–based aqueous scrubs are more effective than povidone iodine–based aqueous scrubs in terms of the numbers of bacterial colony–forming units on the hands.[116]

Chlorhexidine as Skin Surgical Site Preparation

Preoperative skin antisepsis of the surgical site is performed to reduce the risk of SSI by removal of skin microorganisms. A review of six randomized controlled trials identified significant heterogeneity and the trial results could not be pooled. There was no evidence of a benefit in four trials associated with the use of iodophor-impregnated drapes.[117] More recent studies have documented that chlorhexidine provided superior skin decontamination compared to povidone-iodine.[118–121] The most recent Cochrane systematic review found evidence that preoperative skin preparation with 0.5% chlorhexidine in alcohol was associated with lower SSI rates following clean surgery than alcohol-based povidone-iodine paint.[122]

Appropriate Hair Removal

The preparation of the surgical site has traditionally included the routine removal of body hair, however, some studies have suggested that this is deleterious. A Cochrane systematic review of 11 randomized clinical trials, and 3 trials (n = 3,193) comparing shaving with clipping, found that there were statistically more SSIs with shaving than clipping. If it is necessary to remove hair, clipping results in fewer SSIs than shaving using a razor.[123]

Normothermia Maintenance during Surgery

Perioperative hypothermia is common and adversely affects clinical outcomes. The primary beneficial effects of warming are mediated through increased blood flow and oxygen tension at the tissue level. Hypothermia may facilitate SSI in two ways. First, sufficient intraoperative hypothermia triggers thermoregulatory vasoconstriction. Second, considerable evidence indicates that mild core hypothermia directly impairs immune function including T-cell–mediated antibody production and nonspecific oxidative bacterial killing by neutrophils. Randomized controlled trials have documented that perioperative warming is associated with a significant reduction in SSI and this simple SSI preventive strategy should be implemented in all surgical patients.[124–126]

Normoglycemia Maintenance during Surgery

Perioperative hyperglycemia has been associated with increased SSIs and previous recommendations have been to treat glucose levels above 200

mg/dL. Recent studies have questioned the optimal glycemic control regimen to prevent SSIs. A recent Cochrane Database systematic review included five randomized controlled clinical trials with a total of 773 patients randomized. Due to heterogeneity in patient populations, perioperative period, glycemic target, route of insulin administration, and definitions of outcome measures, combination of the results of the five trials into a meta-analysis was not appropriate. The authors concluded that there is insufficient evidence to support strict glycemic control in the intra- and postoperative period among surgical patients for the prevention of SSIs.[127] A Cochrane review of 12 trials that randomized diabetic patients to intensive or conventional glycemic control perioperatively concluded that no significant differences were identified in patients with diabetes mellitus. However, post hoc analysis indicated that intensive glycemic control was associated with greater incidence of hypoglycemia episodes.[128]

There are no randomized trials evaluating immediate preoperative glycemic control in any setting or intra/postoperative glycemic control in non-ICU patients. High-quality evidence for strict glycemic control in the intra- and/or postoperative period among surgical ICU patients, cardiac and noncardiac, to reduce SSIs, independent of other potential benefits, is also lacking. Further large, adequately powered, well-designed randomized trials are necessary to identify the ideal target for perioperative glycemic control in patients at high risk for SSIs. Future trials should report all nosocomial infections as well as SSIs. Given the heterogeneity seen in the included trials, it would appear that trials should be targeted at very specific populations and attempts to draw broader conclusions should not be made. At present, we should strive at least to maintain blood glucose <200 mg/dL in the perioperative period in our surgical patients.

Supplemental Oxygen in Perioperative Period

Several randomized controlled trials have been conducted to assess the benefit of perioperative supplemental oxygen in SSI reduction, yet meta-analyses have arrived at different conclusions.[129–131] On careful review, a number of problems with the conduct of these trials are noted: (1) SSI definition was not consistent with CDC definitions; (2) the interval for assessment of SSI was variable, ranging from 15 to 30 days; (3) SSI was

captured retrospectively in some studies and was not always a primary outcome measure; (4) no assessment of the patient's individual risk factors for SSI was performed; (5) no control of perioperative antibiotic prophylaxis timing or selection was performed; and (6) there was variable provision of high FiO_2 supplemental oxygen in each of the studies.[132]

The first institutional priority should be to universally implement all the evidence-based practices that reduce SSIs. The "SSI Bundle" from the Institute for Healthcare Improvement includes (1) appropriate use of antibiotics, (2) appropriate hair removal, (3) perioperative glucose control, and (4) perioperative normothermia.[133] The additional provision of increased inspired oxygen concentrations should be considered as an additional quality improvement measure, particularly in institutions with high SSI rates. A collaborative of 44 hospitals implemented the SSI preventive strategies discussed above and documented a significant reduction in the SSI rate, from 2.3% to 1.7%, representing a 27% reduction from the first to the last 3 months of the 1-year project.[134] Finally, prospective SSI surveillance, including postdischarge surveillance, should be instituted to obtain accurate information regarding institutional SSI rates.[135]

Surgical Site Infection and Colorectal Surgery

Surgical care bundles have been documented to be effective in reducing SSIs in patients undergoing colorectal surgery and therefore should be implemented.[136] Surgeons have held a long-standing belief that mechanical bowel preparation is an efficient strategy to reduce SSI and anastomotic leak rates following elective colorectal surgery. Recent systematic reviews have found that there is no statistically significant evidence that patients benefit from mechanical bowel preparation either in SSI or anastomotic leak rates.[137] In contrast, the use of nonabsorbable enteral antimicrobials covering aerobic and anaerobic colonic bacteria, in addition to IV preoperative antibiotics, is associated with a significant reduction in SSI by at least 75%.[138–140]

Treatment of Surgical Site Infection

Once superficial or deep incisional SSI is diagnosed, "pathogen identification" is of paramount importance. In years past, the surgical incision was opened and dressing changes were initiated with no culture of the surgical site obtained. In today's era of multidrug-resistant pathogens, a Gram stain and culture of the surgical site should always be obtained in order to determine the optimal antimicrobial therapy that is required for SSI treatment.

SSI treatment includes four strategies for successful treatment: (1) early empiric antimicrobial therapy; (2) decision-making regarding whether the surgical site should be opened; (3) pathogen identification; and (4) deescalation of antimicrobial therapy once culture results are available.

For organ/space SSI, "source control" and "pathogen identification" are both high priorities in order to achieve successful treatment. In the case of intra-abdominal abscess, source control can be provided by either interventional radiology percutaneous drainage or open surgical drainage of the abscess. Abscess fluid should be sent for Gram stain and culture, and empiric antimicrobial treatment should be deescalated once culture results are available.

Current Challenges in Surgical Site Infection

There are a number of growing challenges in SSI, including resistant pathogens, our increasingly elderly population, more patients with chronic diseases or immunocompromised states undergoing surgery, and increasing patients undergoing surgery for solid organ transplantation and placement of prosthetic devices. MRSA was reported to be the most common cause of SSI in vascular surgery patients (n = 772 over a 2-year period) in 2004.[141,142] MRSA has emerged as the leading cause of postoperative infection in vascular surgery patients, and is associated with substantial morbidity, increased hospital length of stay, and higher incidences of amputation and graft removal.

Comparison of the causative pathogens for SSI in U.S. hospitals documents that *S. aureus* increased from 22.5% (1986–2003) to 30% (2006–2007), with MRSA now the leading causative pathogen, comprising 49.2%

of all isolates.[142,143] In a study of 8,302 patients readmitted to U.S. hospitals with culture-confirmed SSI from 2003 to 2007, it was noted that the proportion of infections due to MRSA significantly increased from 16.1% to 20.6% and was associated with higher mortality rates, longer length of stay, and higher hospital costs.[144] Based on this important finding, some have strongly advocated for active screening for nasal carriage of MRSA prior to elective surgery with modification of antimicrobials for SSI prevention based on those results.[145–147] Eradication of MRSA before surgery appears to lower SSI rates due to MRSA and is recommended.[148,149] In contrast, a prospective interventional cohort study that employed a universal rapid MRSA admission screening strategy among 21,754 surgical patients at a Swiss teaching hospital reported that nosocomial MRSA infection, including SSI, did not decrease, but relatively low rates of MRSA infection were present at the start of this study.[150]

An "MRSA bundle" has been developed including five components:

1. MRSA nasal screening of patients upon admission, transfer, and discharge using PCR
2. Contact isolation of positive patients
3. Standardized hand hygiene
4. Cultural transformation campaign with staff and leadership engagement through positive deviance
5. Ongoing monitoring of process and outcome measures

Implementation of the MRSA bundle was associated with a significant decrease in MRSA transmission from 5.8 to 3.0 per 1,000 bed-days, significant reduction in MRSA nosocomial infections (2.0 to 1.0 per 1,000 bed-days), and a significant decrease in overall SSIs, with a 65% reduction in orthopedic MRSA SSIs and a 1% decrease in cardiac MRSA SSIs.[151]

The advent of CA-MRSA[152,153] has also significantly impacted SSI. Recent studies document that CA-MRSA is replacing traditional health care–associated or nosocomial MRSA strains in SSI among inpatients.[154] A report from a large community hospital in St. Louis, MO, examined the rates of SSI due to *S. aureus* in a total of 122,040 surgical procedures in an earlier period (2003–2006) versus later period (2006–2007). MRSA was identified as the SSI pathogen in 40% of all inpatients in both time periods. Interestingly, the percentage of clindamycin-susceptible MRSA

(distinguishing CA-MRSA) as an SSI causative pathogen for inpatients rose from 9% in the early period to 19% in the later period. This increase in the rate of CA-MRSA SSI was observed only among inpatients, not among ambulatory patients. Similarly, CA-MRSA has emerged as a leading cause of health care–associated infections among patients with prosthetic joint SSIs.[155]

The use of perioperative intranasal mupirocin for SSI prevention, particularly in patients with MRSA nasal colonization, remains controversial. Reviews of multiple clinical trials documented that no reduction in SSI was seen in general surgery or cardiac surgery patients; however, in nongeneral surgery patients, the use of mupirocin was associated with a reduction in SSI.[148,149,156]

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9

Shock

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Key Points

1. Shock is the clinical syndrome that results from inadequate tissue perfusion.
2. Shock can be caused by hypovolemic, cardiogenic, extracardiac obstructive, and distributive conditions.
3. Hypovolemic shock due to ongoing fluid, blood, and/or plasma loss leads to progressive cardiovascular deterioration, ultimate hypotension, oliguria, confusion, irreversible cell injury, and death.
4. Cardiogenic shock results in decreased tissue perfusion due to intrinsic cardiac pump failure.
5. Extracardiac obstructive shock attenuates cardiac pump function due to external compression of inflow and outflow (tamponade, tension pneumothorax, etc.).
6. Septic and traumatic shock, forms of distributive shock, are systemic inflammatory responses to infection or tissue injury with cellular breakdown, producing severe hypotension requiring massive volume resuscitation and high risk of multiple organ failure and death.
7. Complications of an episode of shock include ischemia–reperfusion injury from oxidant stress; potential secondary immunosuppression with enhanced nosocomial infection risk; hypothermia and coagulopathy; and multiple organ failure syndrome, including abdominal compartment syndrome (ACS).
8. Treatment of shock requires goal-directed volume resuscitation with treatment of the underlying etiology and careful monitoring of adequacy of end-organ perfusion to avoid under- and overresuscitation.

INTRODUCTION

The current accepted concept of shock was first described in 1929 by Cannon[1] as inadequate blood flow that results 1 in cellular hypoxia.

Persistence of cellular hypoxia results in dysfunction at both cellular and organ levels. Although shock can result from a number of etiologies, it was Blalock who first described the four major causes: hematogenic, neurogenic, cardiogenic, and vasogenic.[2,3] In fact, Blalock was the first to recognize the third-space fluid loss that follows shock resuscitation that is greater than the quantity of initial blood loss.[4] As a result, therapy began to focus not only on restoring intravascular volume but also on replacing fluid lost to the interstitium with a balanced salt solution. Investigators then became increasingly intrigued by the fact that, at some point, shock becomes irreversible and is no longer responsive to further volume resuscitation. As stated nearly a century ago by Wiggers, "at a certain stage adequate circulation cannot be restored by merely filling the system, as one does an automobile radiator."[5] Other "unknown" factors sustain the shock state, blood pressure cannot be restored, improvements are only transient, and death occurs shortly thereafter due to progressive organ dysfunction.

The current concept of shock has led to a reclassification into four distinct groups—hypovolemic, cardiogenic, extracardiac obstructive, and distributive—that may occur independent of each other, or more characteristically synergistic with each other.[6] Early recognition and prompt treatment are essential to modern treatment. If delayed, uncorrected critical oxygen delivery deficits occur that lead to irreversible shock. However, it is believed that future therapies will move beyond simple recognition, fluid resuscitation, and cardiovascular support. Thus, investigators are increasingly looking to gain an understanding of the chain of events that occur, which lead to organ damage and irreversibility. This chapter describes these events, discusses the therapeutic approaches utilized in current management, and offers a brief perspective on what may lie ahead in the future.

EVALUATION OF SHOCK

It is critically important to the patient's ultimate outcome that recognition and treatment of shock occur before decompensation. The clinical assessment must be guided by the knowledge that the severity of symptoms and signs of shock vary between patients and the type of shock present. The patient is

evaluated based on clinical appearance, hemodynamic measurements, physiologic responses, and biochemical analyses.

Early during various shock states, vasoconstriction frequently causes the skin to be cool leading to poor capillary refill. However, this must be contrasted to shock states induced by either neurogenic or septic states in which vasodilation is present causing the skin to be warm, with good capillary refill. Common to the various shock states is the presence of hyperventilation, a compensatory response due to progressive metabolic acidosis. As shock progresses, decreased cerebral blood flow and increased catecholamine stimulation may lead to anxiety and restlessness. With continued shock, lethargy may result. True coma, however, seldom results due to shock alone, unless complete cardiovascular collapse occurs or severe hypoxia develops.[7]

The initial hemodynamic assessment should include evaluation of the rate and character of the pulse; the blood pressure; and, in some cases, the central venous pressure (CVP), invasive or noninvasive cardiac assessment, and pulse pressure variation (PPV).[8] Tachycardia is a normal response to volume loss but also to pain, anxiety, and fear, all of which are commonly present. Assessment of the pulse may be helpful in determining the proper diagnosis. Because of the body's ability to compensate for hypovolemia, changes in blood pressure do not occur reliably until nearly 30% of blood volume has been lost. However, the pulse pressure usually narrows, even in compensated shock, because of the effects of vasoconstriction on the diastolic blood pressure. Importantly, the CVP does not reflect true blood volume, but the state of the venous tone. Although changes in CVP in response to treatment or from continuing hemorrhage may be more revealing than a solitary measurement, this remains debatable. Pulmonary artery catheters (PACs) are no longer routinely placed secondary to misuse or overuse in the past with associated morbidity and mortality.[9] As a result, invasive monitoring using PPV, and noninvasive measures such as echocardiography have become more commonly used to assess volume status and cardiac function.[10]

An indirect but extremely valuable measure of perfusion and volume status is urine output. A urinary catheter should be inserted in every patient being evaluated for shock. Hourly urine output should be 0.5 to 1 mL/kg for adult patients, at least 1 mL/kg for most pediatric patients, and 1 to 2 mL/kg for

patients younger than 2 years of age. Lack of adequate urine output in the setting of previous normal kidney function should cause the provider to be highly concerned about the continued presence of inadequate perfusion and cellular hypoxia.

Although the physical examination is important in the identification of shock, used alone it can fail to diagnose compensated shock. As a result, biochemical markers are used as a means to identify shock in its early stages. Biochemical analysis of shock is based on the shift from aerobic to anaerobic metabolism in underperfused tissues. This shift is marked by the production of lactate that can be measured in the circulation. Resuscitation of shock results in a decrease in serum lactate levels, and the time required to normalize serum lactate levels appears to be an important prognostic factor for survival.[11–15]

Another biochemical marker useful in the resuscitation of shock is the base deficit. This is defined as the amount of a fixed base (or acid) that must be added to an aliquot of blood to restore the pH to 7.40. Base deficit values have been categorized as normal (2 to −2), mild (−3 to −5), moderate (−6 to −9), and severe (>−10). Changes in base deficit toward normal with volume infusion can be used to judge the efficacy of resuscitation.[16–18] Base deficit has been shown to be superior to pH values in assessing the normalization of acidosis after shock resuscitation, and the time required for normalization of base deficit has perhaps even greater prognostic significance than that of lactate.[16,19] Furthermore, severe abnormalities in base deficit are associated with development of chronic critical illness (CCI), and thus early identification and correction may lead to improvement in the development of CCI.

The biochemical changes associated with the hypoperfusion of shock occur even with compensation. Because of the potential difficulties in diagnosing compensated shock, an arterial and/or venous blood gas analysis including base deficit and lactate should be obtained for every patient suspected of being in shock. Additionally, any patient with a lactate of ≥4 mmol/L or base deficit of ≥6 mEq/L should be considered to be in shock until proven otherwise.[17,20,21]

Additionally markers that can be used to determine the degree of shock include central and mixed venous oxygen saturation. Although the etiology of the shock state cannot be determined based on these measurements, they do

provide a global assessment of perfusion. Improvement in these values toward normal indicates reversal of hypoperfusion, and thus may be used to guide the resuscitation ("endpoints of resuscitation").[22–24]

TYPES OF SHOCK

Although several different classifications for shock have been described, the most widely accepted classification of shock was proposed by Weil and Shubin in 1971.[6] This classification divides the shock syndrome into four distinct categories (**Table 9.1**). 2 Despite this separation, however, there is considerable overlap between the categories, with some patients presenting with more than one factor at the same time. Given this overlap, it is helpful to evaluate the hemodynamic pattern in order to elucidate the etiology and appropriately manage the patient (**Table 9.2**).

3 Hypovolemic Shock

Hypovolemic shock is the form of shock most commonly encountered in surgical practice (**Table 9.2**). The essential feature is a reduction in intravascular volume to a level that prevents the heart from being able to pump sufficient blood to vital organ systems. Substantial blood (>20% circulating volume) or plasma (via soft tissue, enteric sequestration, gastrointestinal, urinary, or other insensible losses) losses are required to produce this syndrome.

The signs and symptoms of shock vary with both the severity and duration of fluid loss. A review of the Advanced Trauma Life Support classification system of the American College of Surgeons is useful to comprehend the manifestations and physiologic changes associated with hemorrhagic shock in adults.[22] Blood volume is estimated at 7% of ideal body weight, or approximately 4,900 mL in a 70-kg patient (**Table 9.3**).

Class I: Mild hemorrhage, up to 15% of total blood volume. This condition is exemplified by voluntary blood donation. In the supine position, there are no measurable changes in heart or respiratory rates, blood pressure, or pulse pressure. Capillary refill is normal. This degree of hemorrhage

requires little or no treatment, and blood volume is restored within 24 hours by transcapillary refill and the other compensatory methods.

Class II: Loss of 15% to 30% of blood volume (800 to 1,500 mL). Clinical symptoms include tachycardia and tachypnea. The systolic blood pressure may be only slightly decreased, especially in the supine position, but the pulse pressure is narrowed (because of the diastolic increase from adrenergic discharge). Urine output is reduced only slightly (20 to 30 mL/hr). Mental status changes (e.g., anxiety) are frequently present. Capillary refill is usually delayed. Patients with class II hemorrhage usually can be resuscitated with crystalloid solutions, but some may require blood transfusion.

Class III: Loss of 30% to 40% of blood volume (up to 2,000 mL). Patients with class III hemorrhage present with inadequate perfusion that is obvious; marked tachycardia and tachypnea; cool, clammy extremities with significantly delayed capillary refill; hypotension; and significant changes in mental status (e.g., confusion, combativeness). Class III hemorrhage represents the smallest volume of blood loss that consistently produces a decrease in systolic blood pressure. The resuscitation of these patients requires blood transfusion in addition to administration of crystalloids.

Class IV: Loss of more than 40% of blood volume (more than 2,000 mL), representing life-threatening hemorrhage. Symptoms include marked tachycardia, a significantly depressed systolic blood pressure, and narrowed pulse pressure or unobtainable diastolic pressure. The mental status is depressed and the skin is cold and pale. Urine output is negligible. These patients require immediate transfusion for resuscitation and frequently require immediate surgical or other (e.g., angiographic embolization) intervention.

In practice, individual susceptibility to blood loss varies greatly and is affected by age, pregnancy, pre-existing disease, prescription and nonprescription medications (e.g., beta-blockers), adequacy of compensatory mechanisms, and other factors that are poorly characterized. Presence of these factors should lead the provider to consider early use of invasive monitoring as an adjunct to appropriate fluid resuscitation.

Table 9.1 Classification System and Causes of Shock

Classification	Etiology	Cause
Hypovolemic	Hemorrhagic	Trauma Gastrointestinal
	Nonhemorrhagic	Absolute fluid loss (renal, gastrointestinal) Redistributive or "third spacing"
Cardiogenic	Myocardial	Ischemia Infarction Contusion Cardiomyopathy Myocarditis Pharmacologic/toxic (beta-blockers, calcium channel blockers, tricyclic antidepressants, anthracycline)
	Valve failure	Metabolic (hypophosphatemia, hypocalcemia, acidosis) Infection Injury Ruptured papillary muscle Stenosis Ischemia Pharmacologic/toxic Metabolic
	Arrhythmias	
Extracardiac Obstructive	Extrinsic compression	Mediastinal tumors
	Increased intrathoracic pressure	Tension pneumothorax

	Intrinsic vascular flow obstruction	Positive-pressure ventilation Pulmonary embolism Air embolism Tumors (myxoma) Proximal aortic dissection Aortic coarctation Acute pulmonary hypertension Tamponade Pericarditis
Distributive	SIRS related	Trauma Sepsis Pancreatitis Burns Drugs
	Anaphylactic/anaphylactoid	Venoms
	Neurogenic	Spinal cord injury Vasodilators
	Toxic/pharmacologic	Benzodiazepines
	Endocrine	Adrenal insufficiency Thyroid Myxedema

SIRS, systemic inflammatory response syndrome.

Hypovolemia due to plasma losses may also lead to hypovolemic shock. The clinical findings of hemorrhagic shock are typically present, but significant differences do exist. Hemoconcentration, elevated blood urea nitrogen (BUN) and creatinine, and hypernatremia are typical of acute plasma and/or free water losses and are not necessarily present in other forms of shock. Appropriate evaluation of preload and urine output should be followed, with specific considerations for unique electrolyte abnormalities associated with specific plasma and fluid losses (e.g., gastric vs. colonic losses).

Cardiogenic Shock

Cardiogenic shock occurs as a result of decreased cardiac output (CO) despite adequate intravascular volume with resulting tissue hypoperfusion. It is caused by a primary problem with the cardiac muscle, electrical conduction system, or valves. The most common cause is anterior wall myocardial infarction, although in surgical patients it may be precipitated by pulmonary embolus, myocardial contusion, or pulmonary hypertension.[25]

Table 9.2 Hemodynamic Patterns in Shock

Type	CO	SVR	PAOP	CVP	SvO_2
Hypovolemic	↓	↑	↓	↓	↓
Cardiogenic					
Left ventricular MI	↓	↑	↑	N, ↑	↓
Right ventricular MI	↓	↑	N, ↓	↑	↓
Extracardiac Obstructive					
Pericardial tamponade	↓	↑	↑	↑	↓
Pulmonary embolism	↓	↑	↑	↑	↓
Distributive					
Early	↑, N, ↓	↑, N, ↓	N	N, ↑	N, ↑
Early after fluid administration	↑	↓	N, ↑	N, ↑	↑, N, ↓
Late	↓	↑	N	N	↓

CO, cardiac output; CVP, central venous pressure; MI, myocardial infarction; N, normal; PAOP, pulmonary artery occlusion pressure; SvO_2, mixed venous oxygen saturation; SVR, systemic vascular resistance.

Distinguishing cardiogenic shock from other shock etiologies is occasionally difficult. It is not uncommon to see combined cardiogenic and hypovolemic shock in the elderly patient, with one often being the precipitating event for the other. The hallmarks of the hemodynamic and neuroendocrine response to systemic hypoperfusion from other causes are also typical of cardiogenic shock. Eliciting a history of pre-existing cardiac disease, and physical findings such as pulmonary rales, cardiac murmurs, an S3 gallop, and jugular venous distention may be helpful. An electrocardiogram may detect significant ischemia or other pathology. A chest radiograph may reveal bilateral pulmonary infiltrates typical of

cardiogenic edema, and cardio-specific serum tests (troponin I and creatine phosphokinase [CPK]) may indicate myocardial damage.

Manifestations of cardiogenic shock develop as a consequence of failure of peripheral perfusion, the associated adrenergic response, and the inability of the heart to accommodate blood returning from the lungs and the periphery. In the absence of sepsis or tissue injury, however, there is not usually an associated increase in the metabolic needs of the peripheral tissues. Sympathetic-mediated constriction of the peripheral vasculature attempts to maintain central blood pressure and perfusion of cerebral and coronary circulations. The clinical findings of cardiogenic shock may thus be similar to those of hypovolemic shock because both involve induction of the adrenosympathetic response.

Diminished or ineffective contractile activity of the right or left side of the heart allows blood to accumulate in the respective venous circulations. Shock from an acute left ventricular myocardial infarct occurs when more than 40% of the left ventricle is involved and may be present in approximately 20% of Q-wave infarcts.[25] Shock from an acute right ventricular myocardial infarct, on the other hand, is rare and only occurs in approximately 10% of all inferior wall infarcts.[23] Not only does the diagnosis of each infarct vary, but also the treatment and support vary significantly.

In any patient in shock, especially in those with compromised cardiac function, consideration should be given to the institution of mechanical ventilation. The work of breathing can be considerable, especially for the patient in a state of agitation or distress. Oxygen needs are decreased through intubation and mechanical ventilation. In this manner, the patient can be comfortably sedated with a secure airway; the work of breathing is undertaken by the ventilator, and gas exchange can be optimized. If there is a tenuous balance between myocardial oxygen needs and availability, the balance can thus be shifted in the patient's favor.

Table 9.3 Classification of Hemorrhagic Shock

	Class I	Class II	Class III	Class IV
Blood Loss (mL)	Up to 750	750–1,500	1,500–2,000	>2,000
Blood Loss (%)	Up to 15	15–30	30–40	40
Heart Rate	<100	>100	>120	>140
Blood Pressure	Normal	Normal	Decreased	Decreased
Pulse Pressure	Normal	Decreased	Decreased	Decreased
Respiratory Rate	14–20	20–30	30–40	>35
Urine Output (mL/hr)	>30	20–30	5–15	Minimal
Mental Status	Normal	Mildly anxious	Anxious and confused	Confused and lethargic
Fluid Replacement	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Like other forms of shock, cardiogenic shock tends to be self-perpetuating. Myocardial perfusion depends on the pressure gradient between the coronary artery and the left ventricle and the duration of diastole. Both are compromised by the hypotension and tachycardia that characterizes this condition. High-volume fluid resuscitation, sometimes necessary for treatment of other forms of shock, is poorly tolerated and likely to be detrimental to an individual with cardiogenic shock.

Extracardiac Obstructive Shock

4 A subset of patients with perceived evidence of cardiogenic shock do not have intrinsic cardiac disease but have pump failure due to extrinsic compression that limits diastolic filling and CO. Cardiac tamponade, tension pneumothorax, diaphragmatic herniation of abdominal viscera, mediastinal hematoma, massive pulmonary embolism, and, occasionally, positive-pressure mechanical ventilation may all precipitate shock by exerting constricting pressure on the myocardium. The key to diagnosis and appropriate therapy is the physical examination, supplemented by use of appropriate diagnostic modalities.

Distributive Shock

Distributive shock occurs in a state of inappropriate oxygen utilization associated with the systemic inflammatory response syndrome (SIRS). Classically, SIRS is triggered by sepsis, but SIRS is associated with other immune processes including trauma, pancreatitis, and other types of tissue injuries. However, other types of distributive disturbances can occur unrelated to inflammation that may be directly due to loss of vascular tone from spinal cord injury, endocrine dysfunction, or anaphylaxis.

Septic Shock

5 Septic shock is defined as sepsis that is associated with hypotension, despite adequate fluid resuscitation.[26] It occurs when bacterial products interact with cells of the immune system, leading to elaboration of mediators that cause circulatory disturbances and direct and indirect cell damage leading to the clinical manifestations of shock.[27] Hemodynamic changes are defined as early (warm or hyperdynamic) or late (cold or hypodynamic). These stages are primarily characterized by the degree of ventricular contractility and peripheral vasomotor impairment present, but can be misclassified if not appropriately evaluated. Early septic shock is distinguished by peripheral vasodilation, flushed and warm extremities, and a compensatory elevation in CO. Although an increase in venous capacitance diminishes venous return to the heart, CO is maintained via tachycardia and the decrease in afterload due to systemic vasodilation.

Late septic shock is characterized by impaired myocardial contractility due to local and systemic release of cardiac depressants, worsening peripheral perfusion, vasoconstriction, extremity mottling, oliguria, and hypotension. Peripheral oxygen utilization may be severely impaired by bacterial toxins, such as lipopolysaccharide (LPS) and the inflammatory products of the host's own immune response, resulting in metabolic dysfunction and acidosis despite a high systemic oxygen delivery. This inappropriate oxygen utilization and systemic shunting lead not only to confusion regarding the adequacy of resuscitation but also to progressive cell death. Together, both systemic hypoperfusion and the altered tissue metabolism create a vicious cycle that propagates the inflammatory response

initiated in reaction to the initial infectious challenge leading to progressive cellular injury.

Due to both volume deficits and cardiovascular dysfunction, persistent perfusion deficits are common and contribute significantly to multiple organ failure and mortality. In fact, the fluid volume required for treatment may exceed that required for treatment of other forms of shock due to persistent microvascular endothelial capillary leak. As a result of this profound leak, interstitial and total body fluid balances become extreme, leading to the potential development of marked hypoxia and the abdominal compartment syndrome (ACS).

Although appropriate early resuscitation and cardiovascular support are essential to the treatment of septic shock, as important are early infection source control and appropriate administration of antimicrobials. In fact, numerous investigators have demonstrated that even a few hours delay in initiation of antimicrobial therapy is associated with a significant increase in mortality.[28]

Traumatic Shock

The major contributor to shock after injury is hypovolemia due to hemorrhage. Even when hemorrhage ceases or is controlled, patients can continue to suffer loss of plasma volume into the interstitium of injured tissues and develop progressive hypovolemic shock. In addition, tissue injury evokes a broader pathophysiologic immunoinflammatory response and a potentially more devastating degree of shock than that produced by hypovolemia alone.

The degree to which direct tissue injury and an inflammatory response participate in the development and progression of traumatic shock distinguishes it from purely hypovolemic shock. Thus, traumatic shock results from direct tissue or bony injury, resulting in not only hypovolemia caused by fluid and blood loss but also an immunologic and neuroendocrine response to tissue destruction and devitalization. This combined insult complicates what might otherwise be straightforward hemorrhagic shock by inducing a systemic response that utilizes many of the inflammatory mediators present in septic shock.[28] These mediators propagate and intensify the effects of the

initial hypovolemia and make subsequent multiple organ failure far more likely than occurs with hypovolemic shock alone.

Although this condition can lead to increased fluid requirements, common problems associated with this condition such as rhabdomyolysis should be aggressively evaluated and treated with optimal resuscitation.[24] In addition, common patient characteristics are known to alter traumatic shock resuscitation, in particular, morbid obesity that can result in delayed correction of metabolic acidosis and increased risk for organ dysfunction.[29]

Thus, initial management of the seriously injured requires the assurance of an airway, breathing, and circulation; later management requires appropriate volume resuscitation and control of ongoing losses. Control of hemorrhage is a major concern and demands priority over attention to other injuries. After resuscitation and control of volume losses, efforts become necessary to minimize the potentially lethal postshock sequelae, including acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), and CCI.

Neurogenic Shock

Neurogenic shock is defined as failure of the nervous system to provide effective peripheral vascular resistance, resulting in inadequate end-organ perfusion. Warm, flushed, flaccid extremities; paraplegia; confusion; oliguria; and hypotension are the classic clinical findings. Injury to the proximal spinal cord, with interruption of the autonomic sympathetic vasomotor pathways, disrupts basal vasoconstrictor tone to peripheral veins and arterioles. Profound vasodilation of all microvascular beds below the level of cord injury diminishes venous return to the heart, reduces CO, and precipitates hypotension. Injuries at or above the fourth thoracic vertebrae may disrupt sympathetic enervation to the heart, resulting in significant bradycardia and severe decompensation.

Similar to the initial therapy for shock resulting from hypovolemia, treatment of the relative hypovolemia due to vasodilation of neurogenic shock requires intravenous volume resuscitation. Restoration of the pathologically expanded intravascular space improves preload and CO and may reverse hypotension. However, maintenance of adequate hemodynamics often requires vasopressor support in an effort to avoid the administration of

excessive fluids. Monitoring cardiac preload should be considered to determine adequate (but not excessive) filling volume, as loss of vasomotor capacity within the pulmonary circulation predisposes these patients to pulmonary edema. As spinal cord injury is often associated with other traumatic injuries, the diagnosis of isolated neurogenic shock must be a process of exclusion.

Physiologic Response to Hypovolemia

Common to each shock state is usually an initial decrease in circulating intravascular volume. This reduction is due directly to fluid loss or secondarily to fluid redistribution. This reduction in circulating fluid volume initiates both a rapid and sustained compensatory response. Within minutes, a rapid compensatory response occurs primarily due to adrenergic output. Sustained responses, in contrast, occur slower and result in intravascular fluid reabsorption and renal conservation of water and electrolytes (**Algorithm 9.1**).

Acute Response

Hypovolemia results in the initial secretion of epinephrine and norepinephrine from the adrenal gland due to decreased afferent impulses from arterial baroreceptors. Catecholamine release is acute and limited to the first 24 hours following the onset of hypovolemia. This results in vasoconstriction, tachycardia, and increased myocardial contractility. Adrenergic-induced vasoconstriction of the systemic capacitance of small veins and venules shifts blood back to the central venous circulation, thus increasing right-sided filling pressures. Left-sided filling and pressure are augmented by pulmonary vasoconstriction. Concomitantly, vasoconstriction occurs in the skin, kidneys, and viscera, effectively shunting blood to the heart and brain. Adrenergic-induced vasoconstriction increases cardiac filling and causes increased contractility and reflex tachycardia, all of which combine to increase stroke volume (SV) and CO.

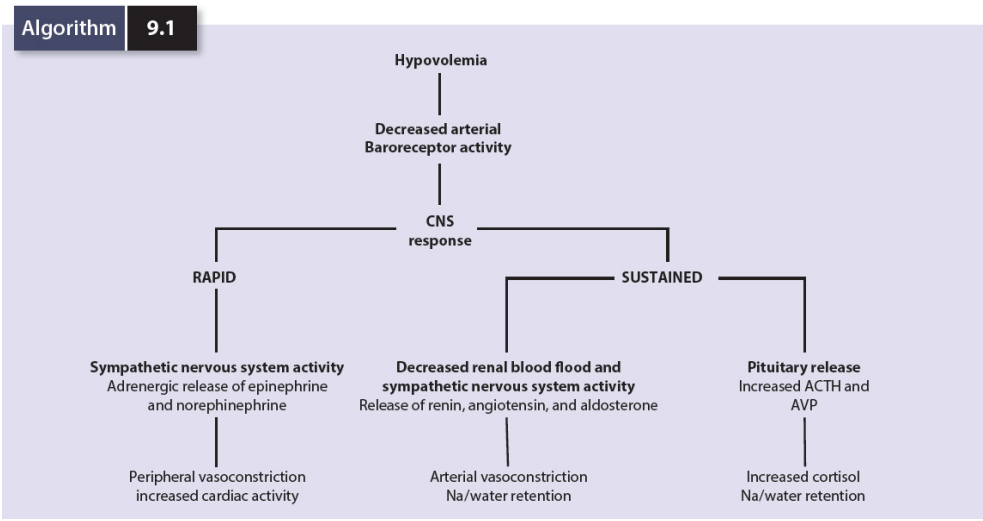
Adrenergic-mediated vasoconstriction affects arterioles, pre- and postcapillary sphincters, and small veins and venules. Due to this specific vasoconstriction, decreased hydrostatic pressure distal to the precapillary

sphincter occurs that leads to reabsorption of interstitial fluid (water, sodium [Na^+], and chloride [Cl^-]) into the vascular space. This functions to restore circulating blood volume and is known as transcapillary refill.[30]

Sustained Response

Sustained compensatory responses include the release of vasoactive hormones and fluid shifts from the interstitium and the intracellular space to the intravascular compartment. Decreased renal blood flow, increased adrenergic activity, and compositional changes in tubular fluid lead to the secretion of renin from the juxtaglomerular complex. Renin results in increased formation and release of angiotensin I by the liver. Circulating angiotensin I is rapidly converted to angiotensin II by the lungs and is the most potent known arterial and arteriolar vasoconstrictor. Angiotensin II also stimulates the release of pituitary ACTH. Increased circulating levels of both angiotensin II and ACTH result in increased secretion of aldosterone. As a result, reabsorption of Na^+ in the distal renal tubules in exchange for potassium (K^+) and hydrogen ions occurs.

Additionally, due to hypovolemia and increased serum osmolarity, reduced stimulation of arterial baroreceptors occurs, leading to the release of arginine vasopressin (AVP) This hormone not only functions as a potent vasoconstrictor but also causes increased reabsorption of water by increasing water permeability and passive Na^+ transport in the distal renal tubule. The overall net effect of aldosterone and AVP is to decrease glomerular filtration and increase salt and water tubular reabsorption in an effort to replace circulating intravascular volume deficits.



Algorithm 9.1 Neurohormonal response to hypovolemia. CNS, central nervous system; ACTH, adrenocorticotropic hormone; AVP, arginine vasopressin.

Finally, the increased release of the stress hormones (epinephrine, ACTH, cortisol, and glucagon) leads to glycogenolysis, lipolysis, and protein catabolism, causing a negative nitrogen balance and high extracellular concentration of glucose due to decreased insulin release and resistance. This leads to increased glucose utilization by insulin-independent tissues such as the brain and heart. In addition to glucose, products of anaerobic metabolism from hypoperfused cells accumulate in the extracellular compartment, inducing hyperosmolarity. This extracellular hyperosmolarity draws water from the intracellular space, increasing interstitial osmotic pressure, which in turn drives water, Na^+, and Cl^- across the capillary endothelium into the vascular space.

ORGAN-SPECIFIC COMPENSATORY RESPONSES TO SHOCK

Cardiac and Microvascular Response

Cardiovascular physiology is profoundly affected by shock. Reduced SV is caused by an absolute or relative loss of preload. Intrinsic neuroendocrine and renal compensatory responses, along with additional intravenous fluid, are needed to increase ventricular end-diastolic volume. Restoration of

adequate preload alone is often sufficient to return CO to levels required to overcome peripheral perfusion deficits. However, some cases are complicated by acquired myocardial contractility derangements. Contractile function under these conditions is less a function of preload and more related to intrinsic myocardial dysfunction.

A defining characteristic of shock is compromise of microvascular perfusion. Far from being a passive conduit, the microvasculature actively participates in the response to shock. Arteriolar vessels are innervated by sympathetic nerves, as are small veins and venules. The vasoconstriction of hypovolemic shock and the vasodilation of septic and neurogenic shock are a result of these autonomic responses. The majority of the circulating blood volume resides in the venous system, and normal physiologic compensation mechanisms rely on this venous blood pool as an autotransfusion reservoir. Collapse of underperfused veins passively propels blood toward the heart, while α-adrenergic venoconstriction actively mobilizes the venous pool. Profound peripheral vasoconstriction via α-adrenergic, vasopressin, angiotensin II, and endothelin-1 stimulation of arteriolar and precapillary smooth muscle sphincters selectively diminishes perfusion to dermal, renal, muscle, and, significantly, splanchnic vascular beds to preserve perfusion of critical central organs, primarily the central nervous system (CNS) and myocardium.[31]

The capillary endothelial monolayer maintains a semipermeable barrier between the intra- and extraluminal spaces and is compromised by shock.[43] Circulating inflammatory mediators and byproducts of infection (LPS, thrombin, tumor necrosis factor alpha [TNF-α], interleukin [IL]-1, nitric oxide, and endothelin-1) generated in response to traumatic or septic shock have been shown to induce and sustain endothelial capillary leak. Although the exact mechanisms of endothelial monolayer dysfunction are unclear, the only available therapies to reverse microvascular decompensation are timely restoration of peripheral perfusion, rapid elimination of infectious and necrotic tissue, and pharmacologic and mechanical support of cardiopulmonary function.[32,33]

Neuroendocrine Response

The neuroendocrine reaction to shock consists of involuntary responses by the hypothalamus, autonomic nervous system, and secretory endocrine glands and is directed toward restoration of tissue perfusion and a redirected utilization of metabolic substrates. The autonomic response is initially triggered by hypoxia, hypotension, or hypovolemia detected by aortic and carotid baroreceptors and chemoreceptors (**Algorithm 9.2**). Subsequently, sympathetic vasoconstriction of specific vascular beds, induced by direct synaptic release of norepinephrine, results in redistribution of circulating blood volume from tissue of low metabolic activity to more metabolically demanding organs. CO, diminished by loss of preload, is augmented by inhibition of cardiac vagal activity and a resulting reflex tachycardia.

Circulating epinephrine and norepinephrine alter several aspects of glucose utilization, availability, and metabolism. The hyperglycemia of stress results from catecholamine-induced glycogenolysis, gluconeogenesis, and decreased pancreatic insulin release. Simultaneously, hypothalamic stimulation of the anterior pituitary induces release of ACTH, which in turn prompts cortisol and aldosterone release by the adrenal cortex. Elevated serum cortisol contributes to postinjury hyperglycemia by increasing gluconeogenesis, enhancing lipolysis, and diminishing peripheral utilization of glucose and amino acids. The pancreatic response is characterized by a decrease in insulin release and an increase in glucagon secretion, which further stimulates hepatic gluconeogenesis. The combined actions of catecholamines, cortisol, and glucagon are synergistic and create a shock-related hyperglycemia that is often refractory to insulin treatment.

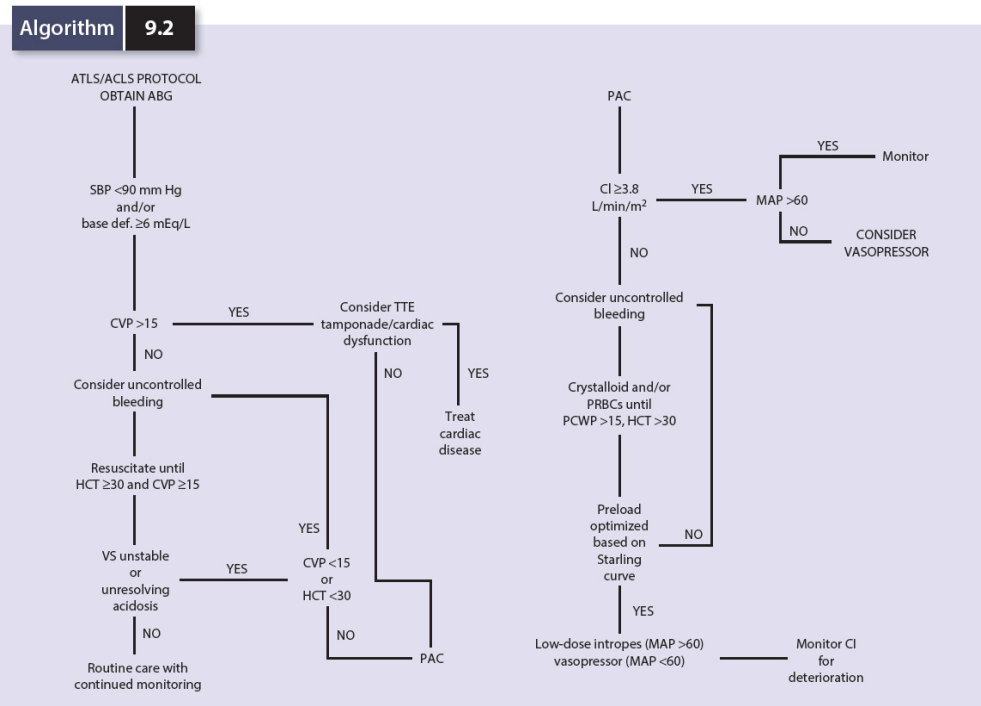
Renal juxtaglomerular secretion of renin in response to adrenergic stimulation and renal hypoperfusion triggers the formation of angiotensin I in the liver, which is subsequently converted to angiotensin II by the lungs. Angiotensin II, a potent vasoconstrictor, augments shock-induced catecholamine-mediated peripheral and splanchnic vasoconstriction and stimulates aldosterone release from the adrenal cortex. Renal tubular reabsorption of sodium in response to elevated circulating aldosterone creates highly concentrated, low-volume urine. Vasopressin secretion by the posterior pituitary similarly contributes to compensatory restoration and maintenance of intravascular volume by promoting water reabsorption by the renal distal tubules and by causing peripheral and splanchnic

vasoconstriction. A major result is a prolonged severe hypoperfusion of the splanchnic vascular bed, further augmenting the deleterious host response.

Immunoinflammatory Response

Many shock-inducing events, particularly those associated with septic or traumatic shock, simultaneously trigger a massive systemic inflammatory response. Although inflammatory mediators (TNF-α, ILs, chemokines, etc.) play an integral role in the recovery of local tissue to trauma and infection, an uncontrolled systemic inflammatory response contributes to organ failure. Immunologically active cells involved in the systemic inflammatory response include nucleated blood cells (monocytes, polymorphonuclear leukocytes [PMNs]) and platelets, microvascular endothelial cells, and tissue macrophages. These cells generate and secrete scores of signal-amplifying inflammatory mediators ranging in complexity from individual molecules (nitric oxide) to large multisubunit, extensively modified proteins (TNF-α, IL-1, etc.). Even transient systemic elevation of any of these mediators has profound physiologic consequences.

Local tissue destruction, microbial contamination, and infection similarly activate the coagulation cascade and induce platelet aggregation and release of numerous platelet-, endothelial-, and clot-derived vasoactive mediators. Persistent, profound, and recurring microvascular hypoperfusion of the splanchnic and other organs likewise causes local tissue ischemia, parenchymal cell injury, microvascular coagulation, activation of inflammatory cells, and release of inflammatory mediators. Circulating monocyte, lymphocyte, and PMN adherence to activated endothelium results in extraluminal transmigration of these inflammatory cells into tissues remote from the area of injury. This hyperdynamic immunologic response, with continued generation of proinflammatory mediators, is responsible for the progression of MODS.[34–37]



Algorithm 9.2 Shock resuscitation algorithm. ATLS, advanced trauma life support; ACLS, advanced cardiac life support; SBP, systolic blood pressure; CVP, central venous pressure; HCT, hematocrit; VS, vital signs; TTE, transthoracic echocardiography; PAC, pulmonary artery catheter; CI, cardiac index; MAP, mean arterial pressure.

Regulation of the systemic inflammatory response has been an active area of shock research for several decades. Elimination of particular inflammatory mediators from the systemic circulation, or inhibition of particular cell–cell interactions in experimental animal systems, has been shown to improve outcomes after shock resuscitation.[38–42] However, to date, all efforts to regulate this response have proven ineffective or even harmful.

Pulmonary Response

The lung is the organ system most sensitive to systemic insult and injury and is frequently the first organ to fail in the progression to MODS. ARDS represents a high-mortality form of pulmonary insufficiency that is often precipitated by sepsis or traumatic shock. It is triggered and perpetuated by the numerous inflammatory mediators created in the hypoperfused microvasculature elsewhere in the body.[38–43]

Renal Response

Direct sympathetic-induced renal vasoconstriction increases afferent arteriole resistance in response to shock. This effect is reinforced by elevated circulating angiotensin II and catecholamines. The resulting decrease in renal blood flow and glomerular filtration rate (GFR), along with elevated circulating aldosterone and vasopressin and anti-diuretic hormone (ADH), produce oliguria and prerenal azotemia. Acute tubular necrosis (ATN) may result from prolonged decreases in renal cortical blood flow, as well as from toxins generated during sepsis. Oliguric renal failure, like the pulmonary insufficiency of ARDS, is a common component of MODS.

Distinguishing low urine output due to oliguric renal failure from the oliguria of decreased renal perfusion pressure can be aided by analyzing urine sodium and osmolality. Renal hypoperfusion usually results in urine sodium of less than 20 mEq/L with an osmolality of greater than 400 mOsm/kg, whereas acute tubular injury impairs sodium reabsorption and is associated with a low urinary osmolality. A fractional excretion of sodium of less than 1% may also help determine whether the cause is renal or prerenal.

Hepatic Response

Ischemic injury to liver is not apparent early during shock. However, the liver plays an important role in the regulation of shock and subsequent tissue injury through both the release of acute-phase reactants and lack of clearance of potential toxic agents. As shock continues, hepatic necrosis occurs, leading to the release of aspartate aminotransferase and alanine aminotransferase. Continued shock results in attenuated synthesis of coagulation factors, albumin and prealbumin. Although progressive ischemia can occur, leading to complete loss of glycogen stores and marked hypoglycemia, this condition is rare without pre-existing liver disease, significant direct liver injury, or hepatic artery occlusion.

Genetic Regulation of the Response to Shock

Individuals vary considerably in their susceptibility to shock and in their ability to recover from its consequences. Unique host-specific responses have been identified as important determinants of the outcome of sepsis and septic shock. Genetic predispositions in an individual's immunoinflammatory response may dictate whether infection is adequately or inadequately countered. These differences in response may be partially explained by single-nucleotide polymorphisms (SNPs) in the genetic sequences for various inflammatory mediators. These subtle nucleotide variations may affect the transcription or translation of associated genes or the secretion or function of the corresponding proteins.

The recognition that genetic background may regulate the response to severe sepsis and septic shock has led to the identification of an array of genetic markers associated with enhanced risk of septic mortality. These SNPs are in genes encoding proteins involved in pathogen recognition (Toll-like receptors 2, 4, and 5; CD14; and mannose-binding lectin), cytokine expression (TNF-α, IL-1, IL-6, and IL-10), and several other genes involved in mediating and controlling the innate immune response and the inflammatory cascade.[44,45]

Investigation into genetic polymorphisms should provide important insights into the pathophysiology of shock. SNP identification leading to early diagnosis of individuals at risk of developing or dying from the complications of shock may allow therapies to become more preemptive and effectively targeted.

LOSS OF COMPENSATORY RESPONSES TO SHOCK

If shock is prolonged, the arteriolar and precapillary sphincters become refractory and relax, while the postcapillary sphincter remains in spasm. Therefore, the capillary hydrostatic pressure increases, and Na^+, Cl^-, and water are moved into the interstitium, leading to depletion of intravascular volume.

Cellular membrane function is also impaired with prolonged shock. The normal negative membrane potential approaches neutrality, leading to

increased permeability and interstitial flooding by K^+. This is caused, at least in part, by a decrease in the normal function of the adenosine triphosphate–dependent Na^+–K^+ membrane pump that is a result of cellular hypoxia. The loss of the membrane potential difference leads to cellular swelling due to an intracellular influx of Na^+ and fluid.

In addition to these cellular effects, severe and prolonged shock results in the development of progressive organ dysfunction. Although the mechanisms responsible are incompletely understood, it appears that the vital organs, in particular the lung early on, are limited in their ability to protect themselves during shock. As a result, direct endothelial injury occurs, resulting in leakage of various inflammatory mediators, which in turn results in accumulation of interstitial fluid and subsequent reduction in nutrient and gaseous diffusion. This condition, along with progressive microcirculatory thrombosis, is responsible for the late organ dysfunction characteristic of uncompensated shock.

COMPLICATIONS OF SHOCK

Ischemia–Reperfusion Injury

Inadequate microvasculature flow results in activation of leukocytes and converts local endothelial cells to a proinflammatory, prothrombotic phenotype. On reperfusion, the reintroduction of oxygen prompts these cells to generate superoxide anion, hydroxyl radicals, and hydrogen peroxide, further injuring local tissue. Microvascular endothelial adherence, monolayer transmigration, and local oxidative burst by activated neutrophils, along with the profound loss of endothelial monolayer integrity (i.e., microvascular capillary leak), contribute to massive interstitial edema after reperfusion. Although all tissues are sensitive to varying degrees, ischemia–reperfusion injury appears to be most detrimental to the pulmonary vasculature and the splanchnic circulations. Pulmonary interstitial edema and alveolar fluid accumulation are associated with the development of ARDS, whereas extensive visceral edema may contribute to development of ACS and mesenteric ischemia.

Multiple Organ Dysfunction Syndrome and CCI

6 The development of MODS is complex, but appears to depend on changes in the splanchnic and pulmonary microcirculations. These vascular beds appear to be major sites of the activation and subsequent immunoinflammatory mediator production. As splanchnic microcirculatory flow decreases in response to homeostatic vasoconstrictive responses during hypovolemia, excessive and prolonged hypoperfusion of the gut results in extensive microvascular injury and subsequent activation of endothelium, neutrophils, and macrophages. In addition, mucosal barrier disruption permits translocation of bacteria and bacterial toxins to circulate and reach the large tissue-fixed macrophage population in the liver. Extensive activation of the Kupffer cells in the liver results in the release of inflammatory mediators that cause distant organ injury through the systemic activation of other immune cells.

Not only is a proinflammatory innate phase present, but there is also a concurrent anti-inflammatory adaptive phase that is evolutionarily designed to counter the locally generated hyperimmune response and check systemic spread of proinflammatory mediators. If the concurrent anti-inflammatory response syndrome results in excessive immunosuppression, it may contribute to susceptibility to primary and secondary infections that can further perpetuate organ failure.[46] These variable inflammatory responses can lead to the development of MODS, and associated chronic dysfunction termed CCI.

Abdominal Compartment Syndrome

ACS is a highly morbid complication of reperfusion injury to the splanchnic viscera. This syndrome appears to be increasingly prominent due to aggressive resuscitation techniques that enable salvage of profoundly hypotensive and hypovolemic patients. Splanchnic ischemia and reperfusion result in extensive visceral capillary leak and interstitial edema of the bowel. Excessive volume resuscitation during this phase leads to grossly edematous viscera within the closed space of the abdomen, which dramatically

increases intra-abdominal pressure, and compromises intra-abdominal organ function, increases renovascular resistance, limits diaphragmatic excursion, and may decrease CO and elevate intracranial pressure. The clinical hallmarks of ACS are a distended and tense abdomen, diminished tidal volume, pulmonary edema, decreased CO, oliguria, and elevated urinary bladder pressure. Presence of all or a major part of this syndrome should prompt consideration of an urgent operative laparotomy to decompress the abdomen and treat by leaving the abdomen open.

Hypothermia

Hypothermia (core temperature <35°C) is common during severe shock, as the energy-dependent homeostatic processes (such as maintaining body temperature) are impaired. This reduction in oxygen delivery directly contributes to progressive hypothermia if uncorrected due to loss of ATP generation and heat production. Furthermore, prehospital and postadmission exposure can exacerbate hypothermia through conductive, convective, and evaporative heat loss, which should all be minimized. In addition, the administration of room temperature intravenous fluids and of cold-stored blood also contributes to hypothermia.[47] Hypothermia increases fluid requirements and independently increases acute mortality rates.[48] As the core temperature decreases, the rate of oxygen consumption also decreases, to approximately 50% of normal at 28°C. A leftward shift in the oxyhemoglobin dissociation curve also occurs with hypothermia but is partially compensated by the acidosis. CNS effects progress from confusion and loss of manual dexterity to obtundation and frank coma as the core temperature decreases from 35° to 26.5°C. The heart rate decreases to approximately half of baseline at 28°C, with a concomitant decrease in CO. All cardiac electrical conduction intervals are prolonged, consistent with the changes in heart rate, and both atrioventricular dissociation and refractory ventricular fibrillation occur at 28°C. Other potential physiologic effects include ileus and pancreatitis (from cold enzyme activation) at temperatures lower than 35°C.

Compensatory responses to hypothermia include increased excretion of catecholamines, resulting in doubling of the basal metabolic rate, and increased production of thyroid hormones, further increasing the basal metabolic rate to five times baseline. Shivering can increase heat production

as well, but it represents a significant energy expenditure and has been shown to be inhibited during episodes of hypotension or hypoxemia.[49] Compensatory responses to hypothermia are lost at temperatures below 30°C or 31°C, and a state of complete poikilothermy is reached.

The treatment for hypothermia is to primarily to treat the underlying cause of shock. However, in situations of severe hypothermia, reversal of shock may need to be accompanied by passive and active rewarming. The core temperature should be obtained on admission of patients in shock. Patients whose core temperatures are 33° to 35°C can be treated with passive rewarming, warm blankets, and hot packs. Patients with core temperatures lower than 33°C require active rewarming. If the patient is unconscious, airway control should first be obtained. Because severe hypothermia causes vasoconstriction, noninvasive blood pressure measurements may not be feasible or accurate, and an arterial line should be placed for monitoring and blood gas sampling. The inspired gas through the ventilator should be heated to 41°C and fully saturated with water vapor to increase heat conductance in the lung. The intravenous fluids should also be warmed. Commercially available rapid infusion systems with countercurrent heating elements should be used. For extreme hypothermia, continuous mechanical arteriovenous rewarming either by cardiac bypass or extracoporial membrane oxygenation can be performed for both circulatory support and rewarming. Recently developed microtechnology permits core rewarming by percutaneous placement of countercurrent warming coils directly in the inferior vena cava (IVC). Finally, other warming methods include lavage of heated saline through nasogastric and thoracostomy tubes as well as peritoneal lavage, but are not as effective.

Coagulopathy

Coagulopathy is a frequent problem complicating shock, especially in those patients who have received large volumes of crystalloid solution and blood for resuscitation. Although this problem is incompletely understood, it is clear that coagulation defects during shock are multifactorial. The presence of shock, the fluid volume required for resuscitation, the presence of hypothermia, and pre-existing diseases all influence the likelihood and severity of coagulopathy.[50]

A major factor in coagulopathy is usually due to the dilutional thrombocytopenia that occurs after massive volume resuscitation. Although bleeding times can be prolonged with platelet counts less than 100,000 cells/mL, platelet counts of 50,000 cells/mL or greater are usually adequate for surgical hemostasis. Dilutional thrombocytopenia becomes more likely with infusions of more than one blood volume. Each unit of platelets administered increases the platelet count by 10,000 to 15,000 cells/mL. Control of surgically remediable hemorrhage is prudent before platelet transfusion to prevent the loss of the transfused platelets.

Dilution of other coagulation factors also plays a role in development of coagulopathy. Factors V and VIII are the most labile in banked blood, but levels of less than 10% of normal for factors VII, X, XI, XII, and XIII are all associated with abnormalities in hemostasis, as demonstrated by prolonged partial thromboplastin time and prothrombin time. Fresh-frozen plasma can be administered as a source of all the soluble coagulation factors. The administration of cryoprecipitate may be necessary as a concentrated source of factor VIII and fibrinogen, particularly if adequate hemostasis is not obtained with the use of fresh-frozen plasma. Recent support has emerged to suggest the addition of tranexamic acid (TXA) for patients suffering from exsanguinating hemorrhage.[51] TXA prevents fibrinolysis, and thus results in more rapid control of hemorrhage. The benefits are primarily seen in the subset of patients with severe hemorrhagic shock, when TXA is given within the first 3 hours. Although TXA theoretically could be associated with thrombotic complications including pulmonary embolism, myocardial infarction, and stroke, data so far has does not show this association. Other agents continue to show promise in rapidly reversing anticoagulants including the use of prothrombin concentrates.[52,53]

Finally, evidence has suggested that coagulopathy and hemorrhage can be minimized following massive blood loss if early aggressive use of fresh-frozen plasma is administered. Coagulopathy is present after massive injury, even before blood component therapy is begun. Both civilian and military experience with a 1:1 ratio of packed red blood cells to fresh-frozen plasma has been associated with reduced mortality.[54–57] However, this practice has been associated with an increase in the development of ARDS and organ dysfunction due to poorly defined mechanisms.[58] Thus, generalization of this

data to all patients with hemorrhage other than the massively injured should be performed with caution as demonstrated in the PROPRR study.[59]

TREATMENT

Fluid Therapy

Early investigators of hemorrhagic shock noted that decreased CVP and a reduction in total body oxygen delivery (DO_2) were key early findings. If the decrease in oxygen delivery was severe or prolonged, a reduction in total body oxygen consumption ensued. After adequate fluid resuscitation, oxygen delivery and consumption increased above the baseline value for several hours, as if the body was paying back an "oxygen debt." Failure of the patient to achieve this hyperdynamic response to resuscitation was almost always fatal. Because early death from shock appeared to be explained by the dynamics of oxygen delivery and utilization, therapy focused on restoring hemodynamics and oxygen transport with fluid and inotropes.

The provision of additional fluid beyond the amount of blood loss was associated with improved survival in both clinical and experimental studies of hemorrhagic shock, leading to widespread acceptance of aggressive fluid infusion. However, some researchers have recently described a significant increase in mortality associated with crystalloid overresuscitation and have postulated that excessive fluid administration increases the clinical risk of ARDS, MODS, increased intracranial pressure, and ACS.[60–62] Because massive volumes of fluid are only provided to patients with severe shock, it is unclear if it is the excessive fluid or the associated underlying shock that increases the risk of ARDS, organ failure, or death after massive fluid resuscitation.[63]

A minimum of two large-bore (14- to 16-gauge) intravenous catheters should be established in adults. Isotonic fluid is then infused at the same time as blood is obtained for arterial blood gas analysis, screening, and typing. Fluid can be infused up to 200 mL/min through a 14-gauge catheter and up to 220 mL/min through a 7-French catheter. A fluid challenge of 10 to 25 mL/kg is administered to the hypotensive patient and the response assessed. However, patients with a shock state consistent with hypovolemia due to

hemorrhage should undergo early blood and blood product resuscitation rather than crystalloid infusion, and early activation of a massive transfusion protocol instituted. Sustained hypotension despite active blood product resuscitation in this patient population should warrant early surgical intervention for control. In patients that are in shock due to nonhemorrhage etiologies, the initial crystalloid therapeutic challenge is an effective trial in determining the amount of pre-existing or continuing volume loss. If the blood pressure returns to normal and is stabilized, the volume loss was relatively small, and the only treatment required may be infusion of isotonic fluid. If the increase in blood pressure is transient after fluid bolus, then hemorrhage or continued fluid losses should be considered. If hypotension persists, and no evidence of hemorrhage is found, carefully assessment of other etiologies of shock should then be investigated including septic, neurogenic, and cardiac with the potential need for vasopressor support.

Crystalloids

Balanced salt solutions are the most commonly used resuscitative fluids, and their use to restore extracellular volume significantly decreases the transfusion requirement after mild–moderate hemorrhagic shock. Lactated Ringer solution is isotonic, readily available, and inexpensive. It rapidly replaces the depleted interstitial fluid compartment and does not aggravate any pre-existing electrolyte abnormalities. Previous investigations have shown that administration of lactated Ringer solution does not lead to aggravation of the lactic acidosis that is present in shock.[64] In fact, animal models have demonstrated that the use of blood plus lactated Ringer solution results in a more rapid return to normal lactate and pH than dose-shed blood alone. As volume and perfusion are restored, lactate is mobilized and metabolized to bicarbonate in a single pass through the liver. In fact, mild metabolic alkalosis may occur 1 or 2 days after large-volume resuscitations with lactated Ringer solution. Normal saline solution is also effective for resuscitation of hypovolemic patients. Concerns about inducing hypernatremic, hyperchloremic metabolic acidosis with massive resuscitation volumes should be evaluated.

Colloids

Colloids have the theoretic advantages of increasing the colloid oncotic pressure and requiring smaller volumes for resuscitation than crystalloids.[65] Colloids commonly used for volume expansion in hypovolemia include albumin, dextran 70, dextran 40, and hydroxyethyl starch. Although each has unique individual characteristics, currently there is little justification for the routine addition of colloids to balanced salt solutions for volume replacement during shock. In fact routine use of colloid such as hydroxyethyl starch may be associated with increased risk of mortality without any benefit.[66]

Albumin solutions have been used during resuscitation to increase colloid oncotic pressure and, hypothetically, to protect the lung from interstitial edema; however, there is a relatively rapid flux of albumin across the pulmonary capillary membranes and relatively rapid clearance through the pulmonary lymphatics. In fact, colloid albumin infusion has been demonstrated to prolong the resuscitation phase and delay postresuscitation diuresis. Additionally, albumin may serve to depress circulating immunoglobulin levels and suppress albumin synthesis.

Dextran 40 and dextran 70 are polysaccharides with molecular weights of 40 and 70 kD, respectively. Dextran 40 (10%) is hyperoncotic and initially exerts a volume-expanding effect. However, because of its lower molecular weight, it is more rapidly excreted. Thus, dextran 40 is commonly used in cases of peripheral vascular disease and hyperviscosity syndromes. Dextran 70, conversely, is provided as a 6% solution and does not exert a hyperoncotic effect. The volume expansion is somewhat greater than the amount infused, and because of its large molecular size the effect is maintained for up to 48 hours. The dextran preparations, however, cause decreased platelet adhesiveness and decreased factor VIII activity. They also carry an incidence of allergic reaction of up to 5% and anaphylaxis of 0.6%.[65,67]

Hydroxyethyl starch is an amylopectin with volume-expanding effects for approximately 36 hours. It has side effects similar to those of dextran, but with less frequency. The incidence of anaphylaxis is 0.006%. A new hydroxyethyl starch, pentastarch, has a lower molecular weight and fewer hydroxyethyl groups than hydroxyethyl starch. Pentastarch has a shorter duration of action (2.5 hours) and has been reported to have even fewer side effects.[67,68]

The controversy regarding use of crystalloids versus colloids in resuscitation has not been fully resolved. Both types of solutions can restore circulating volume. The effects of the solutions on pulmonary function are at issue and are summarized as follows: (a) the use of crystalloid solutions decreases plasma oncotic pressure, thereby leading to lung edema at lower microvascular pressures; and (b) colloids given in the face of pulmonary injury can extravasate, promoting edema because of the reduced plasma interstitial oncotic gradient. In fact, a previous meta-analysis of colloid versus crystalloid resuscitation after hemorrhagic shock demonstrated a higher mortality rate among the colloid-resuscitated patients, partly because of pulmonary complications.[69] Therefore, since colloid infusion has not demonstrated a significant benefit over crystalloid resuscitation alone, it is not currently recommended in the management of hypovolemic shock.[70,71]

Resuscitative Strategy

7 Aggressive fluid resuscitation is clearly a lifesaving modality and a key strategy in the treatment of shock and prevention of secondary consequences (**Algorithm 9.2**). However, resuscitation is not a substitute for early hemorrhage control, and indiscriminate fluid loading causes problematic edema in the lungs, gut, brain, and other organs. The amount of fluid used for resuscitation should be titrated to carefully selected hemodynamic and oxygen transport endpoints.

Permissive Hypotension

Elevation of systemic arterial pressure in patients with disruption of the arterial system or major solid organ injury, especially after penetrating trauma, may cause acceleration of hemorrhage, disrupt natural clotting mechanisms, and cause dilution of clotting factors. Laboratory and clinical evidence support judicious use of intravenous fluids until hemorrhage is controlled by surgery, angiography, or direct pressure for penetrating trauma.[72] Fluid resuscitation for patients with multisystem blunt trauma, especially with concomitant traumatic brain injury, represents a more complicated decision process, as maintaining cerebral perfusion pressure is a competing priority. Avoidance of both excessive fluid administration and

prolonged hypoperfusion is best achieved in all patients not by maintenance of a marginal blood pressure, but by rapid surgical or angiographic intervention to control bleeding.

Transfusion

Anemia prompts clinical concerns because it may signify blood loss or hematologic disease, but it rarely causes tissue ischemia. The hemoglobin level that causes concern should depend on the adequacy of other mechanisms involved in oxygen delivery such as arterial oxygen saturation and CO, the specific clinical situation, and the organ systems most at risk, balanced against the risk of transfusion. Clinical evidence suggests that hemoglobin values above 7 mg/dL are adequate in most patients, including the critically ill, but this has not been explored during shock. In one prospective randomized trial in critically ill patients, it was clearly demonstrated that a reduction in complications and improvement in survival were noted when lower hemoglobin values were accepted.[73] However, this study excluded patients with hypovolemia, acute coronary syndrome, and sepsis. Although the role of transfusion during shock remains problematic, it appears in patients without shock these thresholds of transfusion are even acceptable for elderly patients with significant cardiac disease.[74]

Given this limitation, currently it is held that most patients with class I or II shock can be resuscitated with balanced salt solutions alone. Patients who lose more than 25% to 30% of total blood volume require blood for resuscitation, as do patients with persistent evidence of inadequate end-organ perfusion.[20] The decision about the extent of blood cross-match prior to being transfused is determined in part by the urgency of the situation. Blood that has been fully typed and cross-matched carries the least risk of transfusion reactions, but it also takes the most time to obtain. Other transfusion options include the use of type O or type-specific blood (**Table 9.4**).

Type O Blood

Type O (universal donor) blood is immediately available without a cross-match. Because type O blood contains no AB cellular antigens,

administration of packed red blood cells is relatively safe in patients with any blood type. Males should be transfused type O Rh-positive blood, while prepubescent females and females of childbearing age should be given type O Rh-negative blood to avoid sensitization that would complicate future pregnancies. The administration of more than four units of type O blood to a non–O-blood-type patient, however, theoretically can result in an admixture of blood type. A pretransfusion blood specimen should be sent to the blood bank when the patient is admitted, and type-specific blood should be transfused as soon as it is available.

Type-Specific Blood

Type-specific blood is available from most blood banks within 5 to 10 minutes of receipt of the blood specimen, while the patient is being resuscitated with balanced salt solutions. Although not cross-matched, this blood can be administered safely, as demonstrated in both military and civilian experiences.[75]

Autotransfusion

Autotransfusion involves collection of the shed blood and its reinfusion through a filter back into the patient. Autotransfusion can be as simple as aspiration of the blood into a citrate-containing collection chamber, followed by reinfusion through a 40-mm filter. A more elaborate system, the Haemonetics autotransfuser (Haemonetics Corp., Braintree, MA), centrifuges the collected blood and delivers washed, packed red blood cells for reinfusion. The advantages of autotransfusion include transfusion with warm, compatible blood without delays and with no risk of transmission of hepatitis, human immunodeficiency virus, or other blood-borne pathogens.

Autotransfused blood can produce disseminated intravascular coagulation and activation of fibrinolysis. In addition, collection of blood from the peritoneal cavity after hollow viscus injury, even with cell washing, may lead to bacterial contamination of the autotransfused blood.[76] Successful autotransfusion of contaminated blood has been demonstrated, but blood obtained from enteric-contaminated cavities probably should not be used, except perhaps in extreme circumstances.[77] Despite the potential benefits, investigators have found that the autotransfuser was used in only 26% of the

trauma patients for whom it was prepared.[78] Currently, no evidence exists that autotransfusion improves outcome compared to exclusive homologous blood transfusions in trauma patients.

Endpoints of Resuscitation

Endpoints of resuscitation can be categorized as either global or regional indicators of perfusion. Blood pressure and pulse are global measures and are relatively poor determinants of the adequacy of tissue oxygenation. They must also be interpreted in the context of patient age and pre-existing medical conditions. Tachycardia is a component of SIRS and does not always resolve with increased preload. Arterial pressure is maintained by myriad compensatory mechanisms, even in the face of a significant volume deficit, and interpretation is complicated by highly variable baseline pressures, age, and pre-existing medical conditions.

Base deficit and serum lactate are also global indicators of perfusion and may help in the detection of patients who are in otherwise compensated shock. Acidosis arising from regional tissues may not be apparent in peripheral blood samples, as is frequently the case in patients with intestinal ischemia, in whom systemic acidosis is a late finding. An elevated base deficit and lactate can be caused by electrolyte abnormalities, accelerated glycolysis or pyruvate production, and/or decreased clearance by the liver. They may also reflect dysfunction caused by a period of hypoperfusion that has already resolved and that does not need further treatment. A positive response toward correction, however, is indicative of appropriate resuscitation.

Table 9.4 Comparison of Blood Availability

Blood	Typing	Antibody Screen	Cross-Match	Time
Type O	No	No	No	Immediate
Type Specific	Yes	No	No	<10 min
Type and Screen	Yes	Yes	Yes	20–30 min
Type and Cross-Match	Yes	Yes	Yes	45–60 min

A PAC has obvious appeal as a monitor because ensuring adequate 8 oxygen delivery is paramount in the treatment of shock (**Algorithm 9.2**). A progressive decline in systemic oxygen delivery (DO_2) results in an increase in the oxygen extraction ratio, evident as a reduction in pulmonary mixed venous oxygen saturation. When DO_2 is reduced below the level needed to maintain normal tissue metabolic activity, anaerobic metabolism occurs. This is evident as a decrease in total body oxygen consumption (VO_2). Adequate resuscitation requires eliminating any pathologic decrease in VO_2 by restoring oxygen delivery to an adequate level. In clinical practice, however, there is no precise level of VO_2 that can be used as an endpoint, as tissue oxygen needs vary according to the patient's condition, level of sedation, body temperature, and other factors, and are affected by endogenous and exogenously administered catecholamines.

Oxygen consumption may be especially difficult to interpret in patients with late-stage sepsis because acquired defects in mitochondrial respiration may prevent utilization of oxygen, resulting in decreased consumption and progressive acidosis despite normal or high DO_2.

The adequacy of resuscitation can also be assessed by measurement of end-organ function and perfusion, in addition to global measures. Blood flow to the most vital organs (brain and heart) is preserved during shock at the expense of flow to the skin, muscles, gut, and, ultimately, kidneys. Detection of ischemia in less vital organs could theoretically identify patients in compensated shock who have otherwise normal global indicators.

Low urine output (<0.5 to 1.0 mL/kg/hr) is an indicator of inadequate end-organ perfusion, but inappropriate urine output may initially be maintained by peripheral venoconstriction and maintenance of CO due to tachycardia. The use of gastric tonometry to measure intramucosal pH has highlighted the uneven recovery from shock by visceral organs. Persistent visceral hypoperfusion, as demonstrated by intramucosal acidosis despite correction to normal hemodynamics, is associated with organ failure and poor outcomes. Unfortunately, direct measurement of visceral hypoperfusion, as well as hypoperfusion in other regional vascular beds, requires use of technically challenging, labor-intensive devices that often produce variable unreliable results and has not yet had widespread application. Presently, the goal of therapy is to restore tissue perfusion, both global and regional as

measured by organ function, and to normalize cellular metabolism while avoiding excessive use of fluids and inotropes.

Recently, several biomarkers, in addition to base deficit and lactate, have demonstrated potential promise. Among the most promising is procalcitonin for the early recognition of sepsis. However, in addition to being significantly elevated during sepsis, procalcitonin has recently been demonstrated, similar to lactate and base deficit, to be prognostic of outcome from hypovolemia based on rate of clearance.[79] Thus, this biomarker along with potential others may lead to early recognition and treatment of shock.

MONITORS

Central Venous Pressure

CVP has been used as a surrogate for venous return to the right heart and extended to represent preload. Preload is often diminished in the setting of shock and must be optimized in order to maintain adequate oxygen delivery. The venous system serves a capacitance function containing roughly two-thirds of our circulating blood volume. It is a compliant system that, in a healthy state, functions to maintain adequate venous return to the heart over a variable total blood volume. In states of shock, this capacitance function may be overcome by too low a circulating volume—as in the setting of hypovolemic or hemorrhagic shock—or by dysregulation—as in the setting of neurogenic or septic shock. CVP may be measured directly via an appropriately positioned central venous catheter. The catheter tip should ideally be positioned at the cavoatrial junction—roughly 2 cm caudal to the carina on chest x-ray.[80] Intravenous fluids are administered to achieve adequate preload. Despite challenges for the ability for CVP to determine preload, CVP still remains used clinically.[81] In the surviving sepsis campaign, CVP is pushed to a goal of 8 to 12 mm Hg, which is thought to optimize preload.[20] This, however, has been called into question in recent years with several investigators suggesting that there is no survival benefit to achieving such high CVPs.[20] It has certainly been demonstrated that CVP is not a perfect measure of venous return to the right heart or cardiac preload as there are several intrinsic cardiopulmonary factors that influence both CVP

and CO. The role of CVP may be most useful at its extremes and when used within the context of the patients' clinical situations. A CVP <5 mm Hg in the setting of a young, otherwise healthy trauma patient with ongoing hemorrhage is likely consistent with hypovolemic shock and warrants volume resuscitation. Alternatively, a CVP of 15 mm Hg in an elderly patient with known congestive heart failure does not alone provide adequate information as to a patient's volume status nor should it guide resuscitation. As such, CVP is one measure that can help to guide shock resuscitation when evaluated in the proper context.

Pulmonary Artery Catheter

Hemodynamic monitoring utilizing a flow-directed PAC was a standard in the treatment of shock for decades, and was considered to be essential for the optimal management of certain forms of shock. However, as a result of a multicenter study that reported that use of a PAC was associated with increased mortality, the indications for PAC use have been questioned.[82,83] Clinicians may not always interpret PAC data appropriately. In a multicenter study of physicians' knowledge and interpretation of PAC data, nearly half (47%) were unable to appropriately determine the wedge pressure from a clear tracing, and a similar percentage (44%) could not identify the determinants of oxygen delivery.[83] Studies have demonstrated improved outcome when patients are managed in ICUs staffed by specialists in critical care, despite their more frequent use of PACs.[84]

An additional consideration regarding the controversy over the utility of PACs is that currently used endpoints for PAC-guided resuscitation may be inappropriate. For example, efforts to augment systemic oxygen delivery have not demonstrated any benefits and, in fact, harm may be caused by this approach, whereas treatments used to alter the variables ascertained with the catheter may themselves cause harm (fluid overload, excessive inotropes, blood transfusions). Finally, PACs are associated with specific complications, including the risk of central venous catheter insertion, endocarditis, and pulmonary artery injury, which may outweigh any potential benefits. As the safety and utility of the PAC have not yet been evaluated with prospective clinical trials in specific shock states, its usefulness in the management of shock remains to be determined.

Minimally Invasive CO Monitors

Newer versions of invasive cardiac monitoring have been developed, including the LiDCO (Cambridge, United Kingdom), PiCCO (PULSION medical system, Munich, Germany), and FlowTrac (Edwards Lifesciences, Irvine, United States) devices. Common to each is the need for an arterial line that is used to determine CO and PPV.

The LiDCO device combines pulse contour analysis with lithium dilution to determine SV. In combination with lithium chloride dilution, CO can be calculated and continuously measured following calibration. This device has been studied against PAC, and demonstrated to have good correlation.

The PiCCO device is a pulse counter device that requires a central line in addition to arterial cannulation. The device combines pulse contour analysis with transpulmonary thermodilution CO to determine hemodynamic parameters. This device is more invasive than LiDCO given the additional need for central venous access. Although this device has demonstrated to be reliable under most instances, sustained hemodynamic instability has resulted in significant errors in comparison to PAC.

The FlowTrac device is a pulse contour device that only requires an arterial line. Unlike the other devices, it does not need external calibration and relies on a linear relationship between pulse pressure and SV to determine hemodynamic parameters. Similar to the LiDCO device, this device has demonstrated good correlation to PAC under a number of different conditions. The only noted problem is during periods of severe vasoconstriction of the radial artery at which time CO is poorly determined. However, this problem most likely occurs with other devices that rely on the radial artery for analysis.

Arterial Wave Contour Analysis

Analysis of the arterial wave contour in a mechanically ventilated patient has been shown to be a marker of fluid responsiveness. This is a dynamic measurement, and as such, provides more information than static measures such as CVP or PCWP. Inspiration during positive-pressure ventilation increases intrathoracic pressure and decreases venous return to the right heart. This, in turn, leads to a decrease in left ventricular preload, a lower

SV, and a decreased CO. This effect is more pronounced in the hypovolemic patient, and calculation of PPV has been consistently shown to predict fluid responsiveness in critically ill patients. PPV is a measure of percent change in the pulse pressure over the respiratory cycle, with a PPV greater than 12.5% being consistent with fluid responsiveness.[81] Arterial wave contour analysis relies on patients having a sinus rhythm, no spontaneous respiratory function, and a tidal volume of at least 8 mL/kg. Interpretation of PPV and other arterial wave contour measurements should be cautioned outside of these parameters.

Bedside Ultrasound and Echocardiography

Improved ultrasound technology—better image quality and improved portability—over the past several years has led to its frequent use in the emergency department and intensive care settings. Ultrasound offers the benefits of being noninvasive, real time, accurate, and reproducible. A focused cardiac ultrasound can provide information on both left and right ventricular function as well as volume status. Additionally, a pericardial effusion is easily identified and may be leading to tamponade physiology. Valvular disease is much more difficult to identify and may require a formal transthoracic or transesophageal echo.[85]

In addition to assessment of cardiac function, ultrasound has demonstrated use in assessment of volume status and fluid responsiveness in shock states. Measurement of the superior vena cava (SVC), IVC, and left ventricular stroke area (LVSA) have proved helpful in guiding resuscitation. Measurement of the SVC and LVSA are performed via transesophageal echocardiography, which limits their routine use in patient management. However, SVC and LVSA variation over the respiratory cycle has been demonstrated to be predictive of fluid responsiveness.[86,87] Measurement of the IVC is performed using bedside ultrasound. The IVC is identified just caudal to the diaphragm, and an anterior–posterior dimension is recorded at the end of expiration. In the setting of trauma and shock, an IVC diameter of <1 cm is consistent with a transient responder and correlates with fluid responsiveness.[88,89] The use of ultrasound in critical care settings is growing and will continue to do so as technology and provider experience improves.

PHARMACEUTICAL SUPPORT

Therapeutic adjustments of preload and afterload form the basis of treatment strategies in all forms of shock. Optimal volume resuscitation should always precede measures to augment the contractile function of the heart. Inotropic augmentation of CO may, therefore, be required when restoration of venous preload fails to provide sufficient CO to satisfy tissue oxygen demands. The effect of inotropic agents depends on the specific adrenergic receptor affinity, chronotropic effects, and demands placed on myocardial oxygen consumption of the individual agents (**Table 9.5**). Vasodilators reduce demands on the myocardium and augment cardiac function via reduction in systemic vascular resistance (SVR) or afterload or by dilating the venous system and reducing cardiac preload. Afterload reduction may preserve SV in the face of a failing myocardium, whereas venodilation reduces pulmonary capillary wedge pressure and pressure-driven pulmonary edema. Agents that increase afterload may be needed when blood pressure falls below the autoregulatory range of the coronary, cerebral, and renal vascular beds.

Inotropes and Vasopressors

Dopamine

Dopamine is an endogenous sympathetic amine that is a biosynthetic precursor of epinephrine and functions as a central and peripheral neurotransmitter. The effects of dopamine vary from individual to individual, and are altered with increasing doses. The highest-affinity receptors are occupied at low-serum concentrations (infusions <2 to 3 μg/kg/min) and consist of dopaminergic receptors in the renal and splanchnic beds that serve to augment regional blood flow, increase urine output, and cause natriuresis. However, multiple studies, including prospective randomized trials, have failed to demonstrate that low-dose dopamine prevents acute renal failure or decreases the need for dialysis in critically ill patients. At modest concentrations (3 to 5 μg/kg/min), dopamine occupies cardiac β_1-adrenergic receptors and increases myocardial contractility and heart rate. Higher doses (>5 μg/kg/min) cause an increase in heart rate and blood pressure. α-Adrenergic receptors are stimulated at higher-dose ranges (>10 μg/kg/min),

resulting in elevation of blood pressure and peripheral vascular resistance. Dopamine is, therefore, an effective agent for increasing blood pressure in hypotensive patients after appropriate fluid resuscitation. Because the relationship among a specific dose, receptor affinity, and clinical effect is unique to each patient, individual titration is required to achieve the desired effect.

Dobutamine

Dobutamine, a synthetic catecholamine, has a predominant affinity for β-adrenergic receptors. At clinically relevant doses (5 to 20 μg/kg/min), dobutamine enhances myocardial contractility with mild to moderate changes in heart rate. It also induces peripheral vasodilation, which limits its utility in patients with hypotension. It is an appropriate agent when CO augmentation, not blood pressure support, is required and when a drop in peripheral resistance and preload is clinically tolerable or beneficial. Treatment of cardiogenic shock following myocardial infarction or cardiac dysfunction following shock and reperfusion typically requires support of myocardial contractility and reduction of peripheral resistance, which makes dobutamine an excellent choice in this setting.

Epinephrine

Epinephrine, the endogenous adrenal catecholamine, is released physiologically in response to stress. It has a broad spectrum of systemic actions, including significant cardiovascular effects. When epinephrine is administered as a pharmacologic agent (0.01 to 0.05 μg/kg/min), β_1-adrenergic effects predominate, causing increased SV, heart rate, and contractility, along with modest β_2-receptor stimulation. At higher infusion rates, α-adrenergic receptors are stimulated, which overcome β_2-mediated peripheral vasodilation, resulting in an increase in blood pressure and SVR. Renal and splanchnic vasoconstriction, cardiac dysrhythmias, and increased myocardial oxygen demands limit the prolonged use of high-dose epinephrine. Transient increases in serum lactate have also been noted, possibly due to impaired regional blood flow. Epinephrine should be considered as a potential short-term agent for use in patients with impaired cardiac function not responsive to other agents such as dobutamine.

Table 9.5 Pharmacodynamics of Inotropic/Vasoconstrictor Agents

		Sites of Action				Hemodynamic Response			
Drug	Metabolism	Heart β_1	Heart β_2	Vessels α	Vessels β_2	Renal Perfusion	CO	SVR	BP
Isoproterenol 1 mg/250 mL 1–2 µg/min initially	Renal	+++	+++	0	+++	+/–		–	+/–
Dobutamine 250 mg/250 mL 3 µg/kg/min initially	Hepatic	+++	0/+	0/+	0/+			–	0/+
Dopamine 200 mg/250 mL 2–5 µg/kg/min low dose 20–50 µg/kg/min high dose	Hepatic	+++	+	0	Low dose High dose		Low dose High dose	0/+	
Epinephrine 2 mg/250 mL 2 µg/min initially	Renal	+++	+++	+++	++	–		–	
Norepinephrine 4 mg/250 mL 4 µg/min initially	Renal	++	++	+++	0	–	+/–		
Phenylephrine	Renal	0	0	+++	0	–	–		

α (alpha), vasoconstrict peripheral arterioles; β_1 (beta-1) myocardial inotropy, chronotropy, enhance atrioventricular conduction; β_2 (beta-2) chronotropy, vasodilate mesenteric/skeletal bed, bronchodilation; dopaminergic, vasodilate mesenteric/renal bed. BP, blood pressure; CO, cardiac output; SVR, systemic vascular resistance.

Norepinephrine

Norepinephrine, the sympathetic neurotransmitter, also has concentration-dependent cardiovascular effects. It should be considered as a drug with predominantly α-constrictor effects and less pronounced β-stimulation and is, therefore, appropriate for use in patients who remain hypotensive despite dopamine administration or as a dopamine alternative. Combined α- and β-stimulation typically results in an increase in afterload and renal glomerular perfusion pressure, with preservation of CO. Despite the potential for renal vasoconstriction, as a result of its effects on mean arterial pressure, norepinephrine is associated with an increase in urine output and creatinine clearance in hypotensive, and particularly septic, patients. A primary concern is to ensure adequate volume resuscitation prior to utilization due to risk of severe tissue damage from excessive vasoconstriction on the hypovolemic patient.

Isoproterenol

Isoproterenol is a synthetic catecholamine with potent β-adrenergic effects. From a cardiovascular standpoint, both cardiac and peripheral effects are significant. Stimulation of cardiac β_1-receptors prompts an increase in contractility, heart rate, and conduction velocity. The chronotropic response, however, may predominate. These activities, in conjunction with peripheral vasodilation, generate significant increases in CO and pulse pressure. Isoproterenol greatly increases myocardial oxygen demand and limits coronary filling due to tachycardia. As a result, indications for isoproterenol are limited to patients with hemodynamically significant bradyarrhythmias while preparations are made for electrical pacing.

Phenylephrine

Phenylephrine is a pure α-agonist and is an effective agent for increasing peripheral vascular resistance and arterial blood pressure. Although it has no direct effect on the myocardium, the increase in afterload increases left ventricular work and oxygen demand and may cause a decrease in SV and CO. It is often used as a first-line agent in patients with neurogenic shock, but its use is otherwise generally restricted to patients who remain hypotensive when the dosage of agents such as dopamine or norepinephrine cannot be increased due to excessive tachycardia.

Vasopressin

Vasopressin acts directly on V_1 receptors in vascular smooth muscle to cause vasoconstriction and increases the reactivity of vascular smooth muscle to catecholamines. Release of endogenous vasopressin is a normal physiologic response to shock. After septic or prolonged hemorrhagic shock, circulating vasopressin levels are decreased, possibly due to depletion of hypophyseal secretory stores. This relative deficiency may play a role in causing refractory hypotension. Vasopressin has minimal effects on normotensive patients, but in patients with septic shock, it is effective in increasing SVR and mean arterial pressure. Vasopressin does not have inotropic properties but has potent splanchnic and coronary vasoconstrictors. It has been associated with decreased CO due to myocardial ischemia and increased afterload and may worsen metabolic acidosis in patients in shock by causing splanchnic ischemia. As a result, early use of vasopressin at only physiologic

concentrations to minimize associated other pressor use may be indicated in the event that other pressor agents are unable to achieve optimal perfusion.[90]

Amrinone and Milrinone

Amrinone and milrinone are noncatecholamine inotropes with cardiovascular effects similar to dobutamine, but with minimal chronotropic activity. As steroid-like phosphodiesterase antagonists, they increase smooth muscle cyclic adenosine monophosphate (cAMP) and alter calcium metabolism. Cardiac contractility, SV, heart rate, and CO are increased, while a concomitant reduction in afterload offsets cardiac workload. The increase in cardiac performance with minimal demands on myocardial oxygen consumption offers some utility in the treatment of cardiogenic shock or as a potential alternative to dobutamine infusion. Both agents have a relatively long half-life of nearly 3 hours and should therefore be used with caution in patients at risk of developing hypotension, a major risk in the critically ill patient.

Vasodilators

Vasodilators are used as a means to augment cardiac function through optimization of preload and afterload, both of which reduce demands on the myocardium. The failing ventricle responds to afterload reduction with significant increases in SV. The reason for this is that the compromised myocardium is working past the plateau and on the down slope of the Starling curve. As a result, afterload reduction with vasodilator agents may allow CO to increase, resulting in improved oxygen delivery.

Nitroprusside

Nitroprusside is a balanced but potent arterial and venous smooth muscle vasodilator. It causes a reduction in afterload that increases CO and has a less prominent venodilatory effect that reduces pulmonary venous pressure and preload. Hypotension may limit its use, particularly in the presence of contractility deficits or inadequate preload. Infusions (>3 μg/kg/min) continued for greater than 48 hours require monitoring of serum thiocyanate levels and arterial pH to detect complications of cyanide toxicity.

Nitroglycerin

Nitroglycerin is primarily a venous smooth muscle vasodilator, with less significant arterial vasodilation effects than nitroprusside. Thus, although nitroprusside predominantly decreases afterload, nitroglycerin predominantly increases venous capacitance. It is an effective treatment for acute myocardial ischemia because it reduces excessive preload and ventricular end-diastolic pressure, thereby diminishing myocardial oxygen demand.

Miscellaneous Therapeutics

Corticosteroids

In septic shock, ACTH resistance may diminish the normal cortisol response. Also, peripheral tissue resistance to corticosteroids may develop through proinflammatory-induced downregulation of normal corticosteroid receptors. Utilizing low or physiologic doses (<300 mg/day) of hydrocortisone for a longer duration (>5 days) of treatment have demonstrated a beneficial impact on mortality, particularly in septic patients.[91] Currently, routine use of ACTH stimulation tests is not advocated since they provide little more than prognostic information.[92] Given that hypoadrenal shock complicates various shock states, routine use by some experts is considered appropriate. However, this should only be based on patients who have achieved adequate intravascular volume but remain in shock despite high vasopressor administration. Thus use of corticosteroids at only physiologic doses with immediate tapering once hemodynamics have improved should be used with caution.[93]

Metabolites and Electrolytes

Severe shock is frequently associated with hypocalcemia. Severe hypocalcemia that causes cardiac dysfunction or electrical instability should be rapidly treated. Calcium chloride rapidly corrects calcium deficits, whereas calcium gluconate must be degraded in the liver to release calcium ion, resulting in slower correction of deficits but less risk of tissue reaction. In the absence of evidence of cardiac dysfunction, attempts to restore plasma calcium to normal during shock are not warranted. Ischemia results in

decreased cell membrane ATP and failure of the membrane calcium pump. Thus, reduced serum calcium levels during severe shock are probably due to movement of ionized calcium into the cells. Increased cytosolic calcium causes release of lysosomal enzymes and activation of phospholipases, protein kinases, and proteases that cause membrane damage and cytoskeletal destruction. Administration of exogenous calcium may merely worsen this uncontrolled intracellular calcium influx, whereas effective resuscitation will usually restore circulating calcium levels to normal.

Many shock resuscitation protocols emphasize correction of metabolic acidosis with fluids and inotropes until the pH begins to normalize. When interpreting an acid–base disorder, the presence of an anion gap is supportive evidence of lactic acidosis. However, a non–anion gap acidosis with worsening base deficit frequently occurs when normal saline is administered in large volumes. Efforts to correct a non–anion gap acidosis with additional fluids that may no longer be needed will only increase the risk of fluid overload.

Future Therapies

When initiating therapy for shock, the clinician does not know whether therapy has been started early, when salvage is still possible, or late, after irreversible changes have occurred within the cell and death is inevitable. Failure to respond to fluids, inotropes, and vasopressors with restoration of normal oxygen consumption and aerobic metabolism probably represents a defect in cellular and subcellular function in critical organ systems. There are many active areas of investigation that reflect the progression of our understanding of shock that have been outlined in this chapter and that have begun to move the field beyond the basics of fluid resuscitation and hemodynamic monitoring.

Efforts to control ischemia–reperfusion injury include controlled reperfusion with carbon monoxide or other compounds to reduce oxidative stress. Induced hypothermia may interrupt generation of harmful byproducts of ischemia and enable restoration of circulation and repair of structural injuries in a cellular environment where hypoxia is no longer critical. Additional biomarkers, such as procalcitonin, may allow earlier diagnosis and treatment of sepsis and shock.[79] New biosensors using near-infrared light

may enable transcutaneous identification of critical limitations of blood flow and enable clinicians to more accurately target areas of regional hypoperfusion.[94] A search for agents that optimize circulation in the microvascular system by preventing activation of the endothelium may enable resuscitative efforts to restore oxygen to cells as needed to maintain normal respiration and provide critical nutrients.[94] Ultimately, further understanding of functional genomics may enable clinicians to target transcription and translational events triggered by shock and thus alter outcome.

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10

Critical Care

William C. Chiu and Samuel A. Tisherman

Key Points

1 In 1957 Peter Safar from the Baltimore City Hospital Department of Anesthesiology (later from the University of Pittsburgh School of Medicine) first reported on his new technique of mouth-to-mouth respiration using an artificial airway, leading to the development of cardiopulmonary resuscitation (CPR). In 1958, the first "Intensive Care Unit" (ICU) was established at the Baltimore City Hospital, to provide optimal medical and nursing care to all critically ill patients.

2 A recent systematic review and practice management guideline evaluated the use of focused echocardiography (ECHO) and pulse waveform analysis in patients with shock. The results were variable regarding the benefits of either modality in predicting fluid responsiveness, reduction in organ failure or complications, or mortality. However, the recommendations were that, in appropriate subpopulations and with adequate training in the technology, ECHO and pulse waveform analysis protocols can be associated with favorable outcomes.

3 In the recent Berlin definition of acute respiratory distress syndrome (ARDS), the ARDS spectrum is classified by the PaO_2/FiO_2 (P/F) ratio as mild (201 to 300), moderate (101 to 200), or severe ($\leq$100). Conventional ventilatory strategies incorporate a low-stretch philosophy. Evidence-based adjunctive strategies include prone positioning, airway pressure release ventilation, inhaled prostacyclins, and extracorporeal support.

4 Venous thromboembolism (VTE) is a significant problem in surgical ICU patients and chemical prophylaxis has been demonstrated to beneficially impact outcome. Low–molecular-weight heparin (LMWH) is more efficacious than unfractionated heparin in those at the highest risk in this population, if the risk of bleeding can be mitigated. Since LMWH is primarily eliminated by the kidneys, LMWH should be avoided in those with renal dysfunction. Increasing the prophylactic dose of LMWH may be appropriate in morbidly obese patients. Laboratory monitoring of anti-Xa activity should be considered when using LMWH in patients with renal impairment or obesity.

5 A conservative transfusion trigger (7 g/dL hemoglobin) may be appropriate in most surgical ICU patients, including those with gastrointestinal bleeding, neurotrauma, cardiac disease, and sepsis.

6 ICU patients should undergo routine assessment and adequate support of their nutritional status to preserve lean body mass, maintain immune

function, and avert metabolic complications. Enteral nutrition is strongly preferred over parenteral nutrition. There is little evidence for benefit of specialized formulas, either for immunonutrition or for specific organ failure support. Prophylaxis against stress-related mucosal disease is indicated for patients who will require mechanical ventilation for more than 48 hours or have a coagulopathy. Either proton pump inhibitors or histamine-2 antagonists can be used.

7 Acute kidney injury (AKI) is a common complication in the ICU and is associated with worse outcomes. Rapid restoration of normal hemodynamics and treatment of sepsis, as well as avoidance of nephrotoxic agents, are the best preventative measures. Both continuous and intermittent dialysis play an important role with severe AKI.

8 Successful management of sepsis requires rapid identification, appropriate cultures, early antibiotics, fluid resuscitation, and hemodynamic support with goals of normalizing perfusion. Catheter-associated infections are often preventable with proper maintenance and removal as soon as possible.

9 Delirium is common in critically ill patients and is associated with increased length of stay, increased post-intensive care syndrome, and, possibly, mortality. The causes are multifactorial. Trying to maintain normal day/night cycles can help. There are no drugs that directly improve delirium. Pharmacologic therapy is mainly useful for managing patients with hyperactive delirium with the main goal of preventing harm. Drugs that can aggravate the delirium, such as anticholinergics or benzodiazepines, should be avoided.

INTRODUCTION

The history of intensive care dates back to the 1854 Crimean War with Florence Nightingale, the founder of professional nursing.[1] Nightingale was known to have separated the most severely injured soldiers into close proximity to the nursing station to provide more intensive care. During the 1952 poliomyelitis epidemic in Denmark, Bjorn Ibsen advanced the concept of artificial respiration outside the operating room in a special department at the University of Copenhagen.[2] The majority of severe polio patients treated with the standard iron lung negative pressure respirator tanks were still dying. The new strategy employed was that patients with paralysis and respiratory failure underwent tracheotomy and manual

intermittent positive pressure ventilation performed by medical students at bedside in six-hour shifts.

1 In 1957 Peter Safar from the Baltimore City Hospital Department of Anesthesiology (later from the University of Pittsburgh School of Medicine) first reported on his new technique of mouth-to-mouth respiration using an artificial airway, leading to the development of cardiopulmonary resuscitation (CPR).[3] In 1958, the first "Intensive Care Unit" (ICU) was established at the Baltimore City Hospital, to provide optimal medical and nursing care to all critically ill patients.[4] This ICU maintained early emphasis on airway, ventilation, and resuscitation. Also in 1958, cardiologists Max Harry Weil and Herbert Shubin created the Shock Ward at the Los Angeles County General Hospital of the University of Southern California. This unit had early emphasis on acute circulatory failure and hemodynamics, employing new continuous monitoring techniques and physiologic measurements to manage patients with life-threatening critical illness. This evolving concept of multidisciplinary patient care with medicine, anesthesiology, surgery, nursing, and various collaborators would come to be known as the modern day ICU.[5]

Surgical ICUs and their patients share many features with those in medical ICUs. Patients admitted to the ICU make up a large proportion of hospital cost and resources, estimated to be roughly 1% of gross domestic product. More importantly, both surgical and medical ICUs continue to find themselves understaffed. The supply of critical care practitioners is inadequate and the demand is extensive, largely from aging patients with complex comorbidities undergoing complicated procedures. There are approximately 3,000 Board-certified surgical intensivists with less than 200 completing training annually, most of whom do not practice critical care exclusively. In the United States, these surgical intensivists serve largely in surgical specialty units of academic medical centers that account for approximately 10% to 15% of the nearly 6,500 ICUs with roughly 100,000 beds and 5 million admissions annually. The largest growing demographic in hospitals and ICUs is the group over 65 years of age, now accounting for over half of all admissions.[6]

HEMODYNAMIC MONITORING

Oxygen Transport

The transport of oxygen to the microcirculation and tissues is mediated by four general parameters: (1) arterial oxygen content (CaO_2), (2) the rate of oxygen delivery (DO_2) to tissues, (3) the rate of oxygen uptake from tissues, and (4) the fraction of oxygen in blood that is extracted by tissues. Oxygen delivery, the rate at

which oxygen is transported to the microcirculation, is the product of cardiac output and CaO_2 and is normally about 1,000 mL/min. Oxygen delivery falls in instances of cardiac failure, hypovolemia, anemia, but less so due to poor oxygenation. Oxygen consumption (VO_2), the rate at which oxygen is removed from the blood by the microcirculation, is the product of cardiac output and the arteriovenous O_2 difference and is normally 250 mL/min in an average adult. The oxygen extraction (OE) ratio or the ratio of VO_2 to DO_2 is normally about 25%. The myocardium has the body's highest extraction ratio at approximately 75%. Oxygen consumption remains constant over a wide range of DO_2 by changes in OE. For example, in situations of decreased DO_2 such as hemorrhagic or cardiogenic shock, VO_2 can be maintained by increasing extraction ratio. This mechanism may be altered in critically ill patients who show marked increases in VO_2 under the influence of stress hormones and catecholamines.

To evaluate the balance between systemic DO_2 and VO_2, the oxygen saturation of hemoglobin in mixed venous blood can be assessed. Mixed venous blood is obtained from the pulmonary artery using a pulmonary artery catheter (PAC) and reflects the final destination of circulating blood from all tissue beds prior to reoxygenation in the lung. Mixed venous oxygen saturation (SvO_2) may be used as a measure of tissue oxygenation, and is expressed as $1 - VO_2/DO_2$, with normal values of 60% to 80% that can be continuously displayed with an oximetric PAC. Reductions in SvO_2 reflect a mismatch between DO_2 and VO_2, commonly from a reduction in DO_2 and/or an elevation in VO_2 (**Table 10.1**).

More recently, central venous blood obtained from a central venous catheter in the superior vena cava (SVC) has been a more practical source for measurement of venous saturation. The normal values of central venous oxygen saturation ($ScvO_2$) are 65% to 85%, slightly shifted up compared to SvO_2. While large studies have revealed discordant results demonstrating the utility of monitoring $ScvO_2$, for common practice we recommend that $ScvO_2$ may be used as a helpful adjunct, but not as the only endpoint of resuscitation.

Volume Assessment

Assessment of volume status and cardiac function in the critically ill patient is evolving. Traditional static measures of volume assessment using central venous catheters and PACs are being replaced in many settings by dynamic or functional measures afforded by technologies such as pulse waveform analysis and focused

echocardiogram (ECHO). Similarly, indirect measurement of cardiac function by PACs is being succeeded by pulse waveform analysis and systolic and diastolic evaluation of left and right global and regional function using ECHO.

Table 10.1 Normal Hemodynamic Parameters

Parameter	Equation	Normal Range	Units
Oxygen delivery	$DO_2 = CO \times CaO_2 \times 10$	950–1,150	mL/min
Arterial oxygen content	$CaO_2 = SaO_2 \times 0.0138 \times Hgb + 0.003 \times PaO_2$	17–20	mL/dL
Oxygen consumption	$VO_2 = CO \times (CaO_2 - CvO_2) \times 10$	200–250	mL/min
Oxygen extraction ratio	$OE = VO_2/DO_2 \times 100$	22–30	%
Mixed venous oxygen saturation	$SvO_2 = (1 - VO_2/DO_2) \times 100$	60–80	%
Cardiac output	$CO = HR \times SV/1000$	4–8	L/min
Stroke volume	$SV = CO/HR \times 1000$	60–100	mL/beat
Stroke volume variation	$SVV = (SV_{max} - SV_{min})/SV_{mean} \times 100$	10–15	%

DO_2, oxygen delivery; CO, cardiac output; CaO_2, arterial oxygen content; SaO_2, oxygen saturation; PaO_2, partial pressure of oxygen in arterial blood; VO_2, oxygen consumption; CvO_2, central venous oxygen content; OE, oxygen extraction; SvO_2, mixed venous oxygen saturation; HR, heart rate; SV, stroke volume; SVV, stroke volume variation.

2 A recent systematic review and practice management guideline evaluated the use of ECHO and pulse waveform analysis in patients with shock. The results were

variable regarding the benefits of either modality in predicting fluid responsiveness, reduction in organ failure or complications, or mortality. However, the recommendations were that in appropriate subpopulations, and with adequate training in the technology, ECHO and pulse waveform analysis protocols can be associated with favorable outcomes.[7]

Fluid Responsiveness

The concept of volume status using static measures has evolved to "volume responsiveness" using dynamic or functional measures to assess whether a fluid bolus will improve the stroke volume (SV) and cardiac performance of a critically ill patient. Static measures such as central venous pressure (CVP) and pulmonary artery occlusion pressure (PAOP) can give inferential data of cardiac filling pressures at a single time-point, which then extrapolates to cardiac preload (end-diastolic volume) and volume status of the patient. However, these pressures can be altered depending on cardiopulmonary physiology, do not always correlate with Frank–Starling principles, and give no indication of whether the patient will respond to a bolus of infused fluid.

Measurements of CVP and PAOP are made at end-expiration when the pleural pressure is closest to atmospheric pressure. Normal venous waveform components include the "a" wave (corresponding to right atrial contraction), the "c" wave (tricuspid valve closure and isovolumic right ventricular contraction), and the "v" wave (ventricular ejection driving venous filling of the atrium) (**Fig. 10.1**). Clinically, the high point of the "a" wave is the atrial pressure at maximum contraction, where atrial pressure is greater than ventricular diastolic pressure. Here, the right atrium is contracted and the tricuspid valve is open, which is synonymous with right ventricular end-diastolic pressure, making the ventricle, atrium, and vena cava interconnected.

The use of CVP to guide resuscitation has not been demonstrated to be beneficial in many large clinical series. A large meta-analysis revealed a very poor relationship between CVP and blood volume.[8] Additionally, several large recent trials of sepsis resuscitation demonstrated that resuscitation targeted to CVP endpoints did not improve outcome.[9,10]

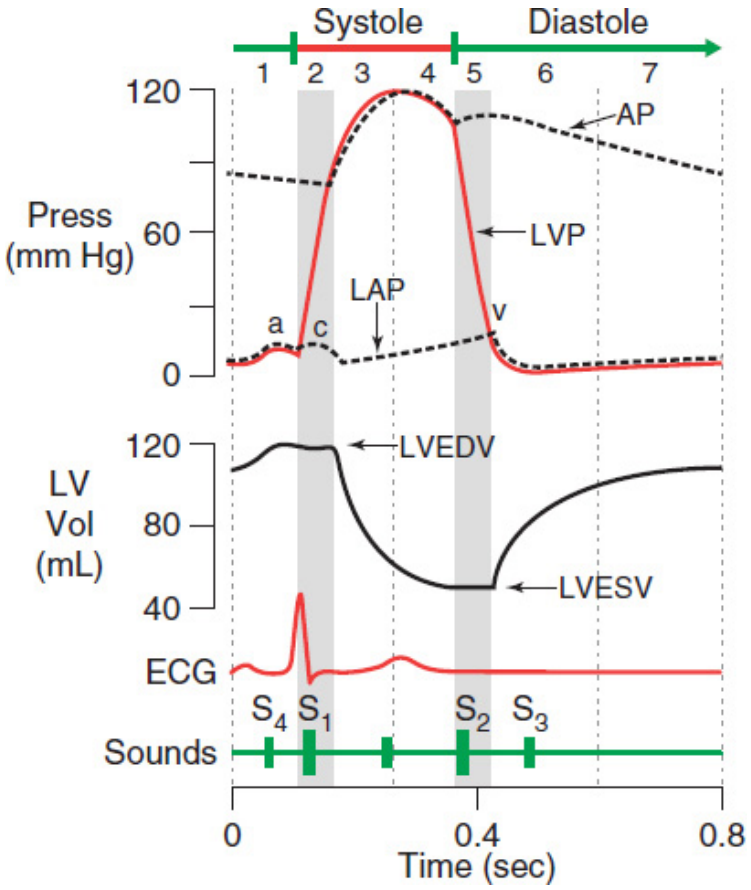

Figure 10.1 Normal venous waveform with ECG (a, c, and v waves).

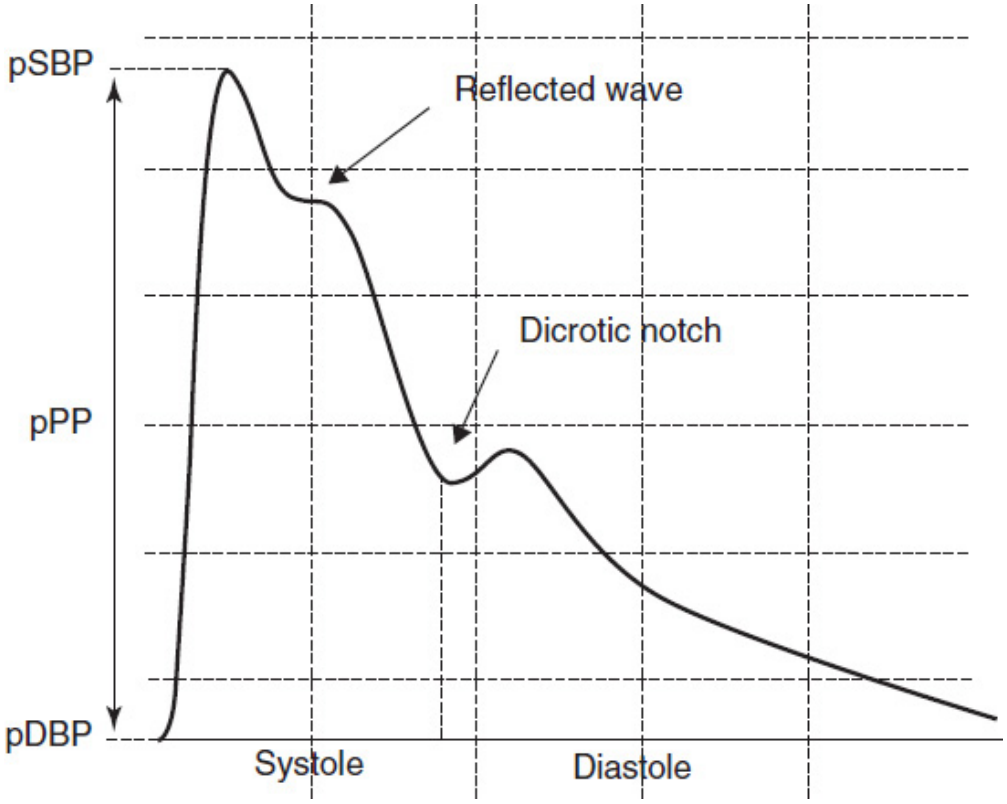

Figure 10.2 Arterial pressure waveform. Area under systole curve is used to calculate stroke volume. pSBP, peripheral systolic blood pressure; pPP, peripheral pulse pressure; pDBP, peripheral diastolic blood pressure.

PAC-based volume assessment employs the principle that a single column of fluid forms from the pulmonary artery to the left ventricle during diastole. For a given left ventricular end-diastolic pressure (LVEDP) and compliance, left ventricular end-diastolic volume (LVEDV) can be estimated. Based on the Frank–Starling principle, the force of ventricular contraction is proportional to muscle stretch and LVEDV. As PAOP estimates LVEDV for a given cardiac output, preload may be determined. Numerous physiologic changes may alter the relationship between PAOP and LVEDV, including pulmonary veno-occlusive disease, pulmonary hypertension, ARDS, increased intrathoracic pressure, valvular disease, and altered cardiac compliance. Finally, large clinical trials have failed to demonstrate a benefit to outcome for those resuscitated to a PAOP endpoint.[11]

Dynamic and functional assessment of volume responsiveness includes those on both the arterial and venous side of the heart. Normally, the inspiratory increase in pleural pressure during positive pressure breathing reduces right ventricular preload and stroke volume, manifested on the arterial side within a few beats. Left ventricular SV diminution is maximal during expiration. These normal physiologic

changes during the mechanically supported respiratory cycle are augmented with hypovolemia that is volume responsive.

Pulse waveform analysis is minimally invasive and uses a proprietary algorithm analysis of the arterial pressure waveform. The area under the curve corresponding to systole (i.e., before the dicrotic notch) is used to calculate SV (**Fig. 10.2**). Computer calculation is made of the maximal and minimal amplitude of the curve. In general, a stroke volume variation (SVV) of greater than 13% to 15% reflects volume responsiveness, whereas values below this threshold imply that the patient is beyond the upper inflection point of the Frank–Starling curve and will not benefit from further volume loading. There are instances where it is possible to misinterpret these values. For example, high vasopressor burden or lack of arterial compliance may alter blood flow and arterial wave morphology. However, clinical applications of SVV as a volume assessment tool have been promising.[12]

ECHO can provide arterial and venous volume assessment with both static and dynamic values. Many static measures can be rendered functional by performing measurements both before and after a passive leg raise, a maneuver that replicates volume loading. Passive leg raising measurements may be the only accurate methodology to approximate fluid responsiveness in spontaneously breathing patients. In these patients, a breath results in an increase in SV and systolic pressure. Static values include measurement of the diameter of the inferior vena cava (IVC) on the long axis view, or, in some series, the SVC or internal jugular vein (IJV) on the venous side or calculation of the velocity time integral (VTI) on the arterial side. Collapsibility of the IVC (or SVC/IJV) of at least 15% and as much as 50% during respiration predicts fluid responsiveness.[13] Right-sided heart failure may alter the size relationships of the central veins, thus providing an underestimate of fluid responsiveness using venous measurements.

In summary, ECHO, SVV, and passive leg raise are complementary tools to predict fluid responsiveness. Each technique has its own benefits and drawbacks, but in combination, depending upon local expertise, they can provide a multi-faceted approach. Repeated measures during resuscitation can allow the provider to further fine tune fluid management.

Cardiac Function

Assessment of cardiac function is best understood by recollection of the cardiac pressure–volume curve depicting the cardiac cycle (**Fig. 10.3**). Starting at the top right at “A,” the aortic valve opens and blood is ejected into the outflow tract. At “B” systole ends as the aortic valve closes. A period of isovolumic relaxation occurs and ventricular pressure falls until the mitral valve opens at “C,” the start of

diastole. Diastole ends as the mitral valve closes at “D” and then there is a period of isovolumic contraction with both valves closed until the cycle repeats. Note that the distance across the box represents SV, the amount of blood ejected per heartbeat, which is expressed in mL and determined by preload, afterload, and contractility. The product of SV and heart rate is CO. Ejection fraction (EF), a more valid estimate of cardiac function, is the proportion of preload or EDV ejected per beat or SV/EDV.

PACs determine cardiac output by thermodilution. The thermodilution technique measures temperature changes sensed by a thermistor at the distal end of the catheter after a cold saline injection is performed through the proximal port. Based on the modified Stewart–Hamilton equation, which constructs a plot of temperature change against time, measurements of cardiac output can be obtained. The thermodilution technique assumes that complete mixing of the blood occurs, that there is constant blood flow in the heart, and that there is no loss in concentration of the indicator between the point of injection and the distal balloon tip. Pulse contour analysis can also be used to measure stroke volume and cardiac output. Using PAC thermodilution as the gold standard, accuracy is acceptable.

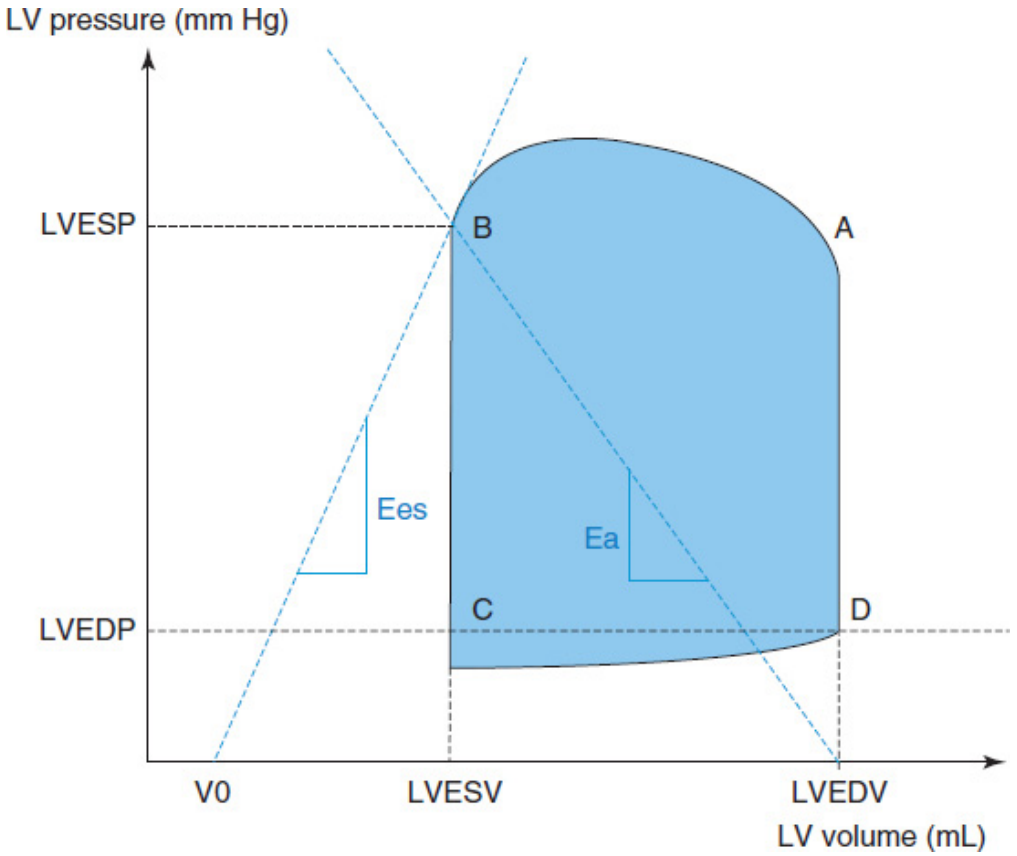

Figure 10.3 Left ventricular pressure–volume curve. Ees, LV elastance; Ea, arterial elastance; ESV, end-systolic volume; EDV, end-diastolic volume; ESP, end-systolic pressure; EDP, end-diastolic pressure; LV, left ventricle. *A:* aortic valve opens; *B:* aortic valve closes; *C:* mitral valve opens; *D:* mitral valve closes.

ECHO does not suffer from many of the shortcomings of CVP, PAC, or arterial line assessment of cardiac function, such as static measurement and requiring an invasive catheter. ECHO can determine left and right ventricular function, assess wall motion abnormalities, valve defects, pericardial fluid, and provide real-time information on effectiveness of inotropic and vasopressor therapy. ECHO can provide information about heart function in a qualitative or quantitative fashion, can be used to assess left and right heart morphology, dynamics, and size, can determine the difference in EF and SV, and can perform quantitative estimates of pulmonary artery and right ventricular pressure. Shock states may be due to impaired EF or contractility, or due to diminished volume status and SV.

ECHO can also discern right heart dysfunction, common in surgical ICU patients, by examining size, morphology and function of the right ventricle. Underfilling of the left heart, typically treated by volume loading, requires attention to inotropic support in the case of right heart failure. Finally, unique to ECHO is the ability to assess for diastolic dysfunction as occurs with diastolic heart failure, sepsis, tamponade, and

increased pleural pressure (as with pneumothorax, abdominal compartment syndrome, and massive pleural effusions). ECHO can be readily repeated as frequently as needed based upon the clinical situation.[14]

CARDIAC ARREST AND DYSRHYTHMIAS

Dysrhythmias are common in both cardiac and noncardiac surgical ICU patients. The most life-threatening dysrhythmias can be treated by following current American Heart Association Advanced Cardiac Life Support (ACLS) guidelines.[15] For patients who become pulseless in the ICU, rapid restoration of the circulation employing basic life support (BLS) is vital. The most important features of the current BLS guidelines include the recognition that CPR, when indicated, be delivered by pushing hard and fast with complete recoil at a rate of at least 100 compressions/min to a depth of 2 inches in adults. CPR providers should deliver no more than 2 minutes of chest compressions each (or five cycles of compressions) until a personnel switch is made. In adults, if 2 providers are present, the ratio of 30 compressions to 2 breaths is maintained until respirations can be controlled by intubation and controlled ventilation.

The rapid use of a defibrillator is key to improving postarrest survival. Cardiac arrest from a rhythm other than ventricular fibrillation, such as from bradycardia progressing to asystole or pulseless electrical activity (PEA), portends a poor prognosis, often as the result of acidosis or profound hypoxia incidental to sepsis and multiple organ failure. Another important feature of the current BLS and ACLS guidelines that may impact surgical ICU patients is the recognition of the need for postcardiac arrest care. This certainly includes fluid resuscitation and administration of vasopressors and inotropes as needed. However, there may also be a need to interrogate via coronary angiography and treat for acute coronary syndrome if anticoagulation can be tolerated and for consideration of postarrest targeted temperature management (goal of 33° to 36°C for 24 hours) to preserve neurologic function. Although targeted temperature management protocols were established to address out of hospital cardiac arrest with coma, there has been increasing use of the modality for hospitalized patients as well. Current guidelines also address new technology with biphasic electrical sources that deliver shocks for dysrhythmias with a pulse and defibrillation in those with ventricular fibrillation. Another important component of the recommendations is the use of end-tidal CO_2 monitoring to ensure adequacy of CPR quality.

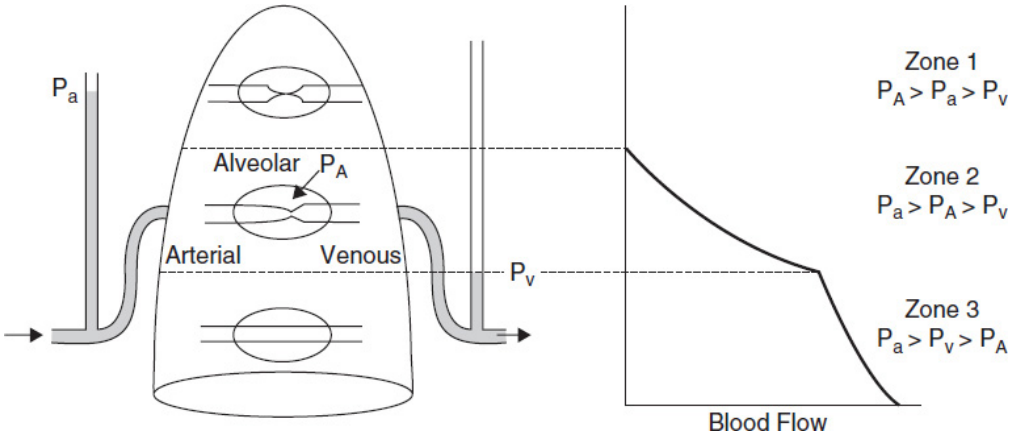

Figure 10.4 West lung zones. **Zone 1:** Not observed in healthy lung. Alveolar pressure exceeds pulmonary blood vessel pressure leading to alveolar dead space. **Zone 2:** Located approximately 3 cm above heart. Pulmonary vessel pressure exceeds alveolar pressure in a pulsatile fashion and allows pulmonary blood flow and alveolar distention. **Zone 3:** Majority of healthy lungs with continuous blood flow and oxygenation. P_A, Alveolar Pressure; P_a, arterial pressure; P_V, venous pressure.

Three dysrhythmias produce pulselessness: ventricular fibrillation, PEA, and asystole. Only ventricular fibrillation is responsive to defibrillation which is with 120 to 200 J using a biphasic device as per manufacturer's recommendations. PEA and asystole are treated by administration of epinephrine (1 mg every 3 to 5 minutes) and/or vasopressin (40 U one-time dose). Pulseless ventricular tachycardia is treated like ventricular fibrillation with additional shocks given after five cycles of CPR (2 minutes). In addition, epinephrine and vasopressin are administered as CPR continues. Continued pulseless ventricular tachycardia and fibrillation can be treated with amiodarone (300 mg with a second dose of 150 mg if refractory) or lidocaine (1.0 to 1.5 mg/kg).

PULMONARY GAS EXCHANGE

Oxygenation

Normal lung function and gas exchange require patent alveoli and pulmonary capillaries. Once red blood cells become saturated with oxygen, additional oxygen dissolves into the plasma and the measured partial pressure of oxygen (PO_2) is 100 mm Hg with an oxygen saturation (SaO_2) of 100%. Since a small portion of oxygenated blood is diverted away from the pulmonary circulation (via bronchial vessels), a normal PaO_2 is 90 mm Hg with 98% saturation. Insufficient blood oxygenation is termed hypoxemia. This is to be differentiated from hypoxia, which is

abnormally low oxygen content in a tissue or organ. The alveolar to arterial (A-a) oxygen gradient is a common measure of oxygenation ("A" denotes alveolar and "a" denotes arterial oxygenation).

Perturbations causing hypoxia and hypoxemia may be the result of ventilation/perfusion (V/Q) mismatch, impaired diffusion, or shunt. Hypoventilation, a result of neuromuscular dysfunction and impaired diffusion (occurring with pulmonary edema or interstitial lung disease) can be treated effectively by exogenous administration of oxygen. The A-a gradient is normal in hypoxemia due to pure hypoventilation and increased in V/Q mismatch. V/Q mismatch, the most frequent cause of hypoxemia in the ICU, occurs with decreased airflow to the alveoli in relation to the amount of pulmonary capillary blood flow. In the normal lung, there is V/Q mismatch because perfusion and ventilation are heterogeneous. Both ventilation and perfusion are greater in the bases than in the apices. However, the difference between apical and basilar ventilation is less than the difference between apical and basilar perfusion. Therefore, the V/Q ratio is higher in the apices than in the bases. In the diseased lung, V/Q mismatch increases because heterogeneity of both ventilation and perfusion worsen resulting in hypoxemia. Common causes of hypoxemia due to V/Q mismatch include obstructive lung diseases, pulmonary vascular diseases, and interstitial diseases. Shunting occurs when there is adequate ventilation of the alveoli but decreased pulmonary capillary blood flow. Hypoxia due to shunting with venous admixture as with severely depressed cardiac output or anemia cannot be overcome by administration of oxygen (**Fig. 10.4**).

Ventilation

Ventilation refers to the exchange of air from the lungs and alveoli. The rate at which alveolar ventilation occurs determines the amount of carbon dioxide (CO_2) excretion, a readily diffusible substance. The amount of CO_2 produced and requiring elimination is related to the respiratory quotient (RQ). RQ is the ratio of CO_2 produced to O_2 consumed and is normally 0.8, depending on the diet. Chemoreceptors in the medulla are responsive to pH changes and when patients become acidemic they hyperventilate to decrease $PaCO_2$ to maintain normal pH. End-tidal CO_2 may be lower than $PaCO_2$ if substantial lung is ventilated but not perfused (dead space).

VENTILATOR MODES

One of the initial steps in evaluating a patient with respiratory failure is to confirm a patent and protected airway. The ICU team must determine if the patient has an acute issue causing the respiratory failure that can be treated without mechanical ventilation. Through the use of physical examination, bedside ultrasound and radiography, the ICU team may diagnose a pneumothorax or acute pulmonary edema that can be treated without intubation. If the patient has acute respiratory failure without an easily treatable process, intubation and mechanical ventilation may be safest. When setting up the mechanical ventilator there are several options and modalities from which to select.

Mechanical ventilation may improve oxygenation and ventilation by attempting to improve V/Q mismatch and decreasing the amount of shunt. Current recommendations are for low tidal volume (Vt) settings of 6 to 8 mL/kg for the prevention of barotrauma in surgical ICU patients.[16] Respiratory rate (RR) is typically set at 12 to 16 breaths/min. RR is altered to achieve an optimal $PaCO_2$ or end-tidal CO_2. Positive end-expiratory pressure (PEEP) is applied to prevent significant alveolar collapse (atelectotrauma) during expiration and is particularly important in low lung volume ventilation strategies. PEEP is typically started at 5 cm H_2O but can be titrated up to improve oxygenation. The initial setting for patients with respiratory failure is an FiO_2 of 1.0. After initial check of ABG or O_2 saturation the FiO_2 is weaned down to maintain a minimal PaO_2 of >60 mm Hg and O_2 saturation of >90% with goals of FiO_2 <0.4 to prevent O_2 toxicity.

Pulmonary Mechanics

Pulmonary mechanics can be displayed graphically and include scalars and loops. Scalars are plots against time—either flow, pressure, or volume. Several loops are helpful clinically and include the pressure–volume and flow–volume loops. Each graphic can be important in demonstrating a physiologic abnormality. The flow–time scalar is helpful for identifying air trapping or auto-PEEP (**Fig. 10.5**). This can result in barotrauma or hemodynamic instability. Measures to decrease auto-PEEP include decreasing tidal volume, respiratory rate, inspiratory time, or increasing flow rate. The pressure–time scalar allows the practitioner to view and calculate compliance (**Fig. 10.6**). Elevations in peak airway pressure may occur as a result of bronchospasm, mucus plugging, a pneumothorax or kinked endotracheal tube or a sharp decrease may represent an airway leak or disconnection. The volume–time scalar allows one to identify an airway leak as well (**Fig. 10.7**).

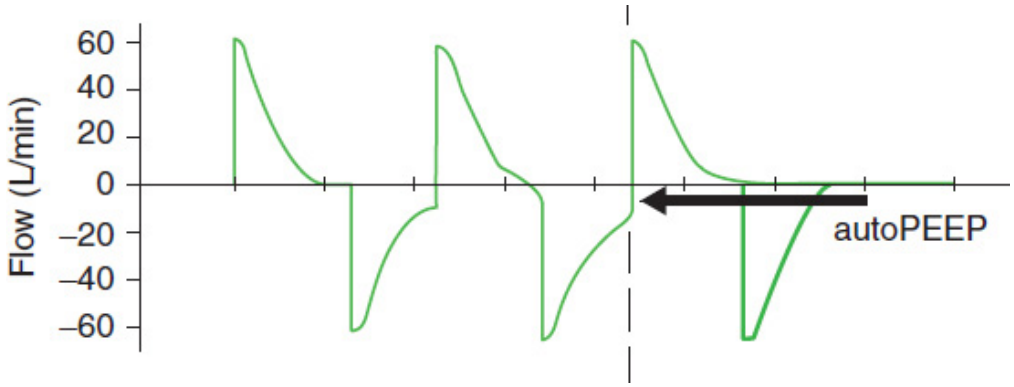

Figure 10.5 Flow–time scalar showing autoPEEP.

Ventilators often display all three scalars simultaneously. A spontaneously breathing patient is identified by the negative deflection in the pressure–time scalar at breath initiation (**Fig. 10.8**). Distinct ventilator modes have unique methods of cycling, triggering, and limitations of breaths. In volume-controlled ventilation, breaths are volume-cycled, time-triggered, and flow-limited (**Fig. 10.9**). In pressure-controlled ventilation, breaths are time-cycled, time-triggered, and pressure-limited. Note the distinct difference in the flow and pressure-time scalars compared to CMV (**Fig. 10.10**). Pressure supported breaths are flow-cycled, patient-triggered, and pressure-limited (**Fig. 10.11**). Pressure- and volume-controlled ventilation can be set in an assist control (AC) mode or synchronized intermittent mandatory ventilation (SIMV) mode. With either mode, the patient receives a minimum number of breaths delivered per minute whether with pressure or volume. In the AC mode, if the patient triggers additional breaths, the full pressure or volume is delivered, whereas these breaths are unassisted in the SIMV mode. Patients who are critically ill may require AC for full support but these patients may be weaned to a PSV mode to prevent respiratory muscle atrophy.[17]

ACUTE RESPIRATORY FAILURE

Diagnosis

3 Past consensus definitions of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI) categorized them by acute onset hypoxemia, bilateral infiltrates on chest radiography, and absence of cardiac etiology.[18] ALI and ARDS were differentiated by the degree of hypoxia, with ALI typified by a ratio of PaO_2/FiO_2 (P/F) $\leq$ 300 and ARDS with P/F $\leq$ 200. The newer Berlin definition makes an attempt at describing timing of ARDS relative to a known insult. Most importantly, ALI is now part of the ARDS spectrum that is classified as mild,

moderate, or severe if the PaO_2/FiO_2 ratio is between 200 and 300, between 100 and 200, and less than 100, respectively (**Table 10.2**).[19] Also, patients must be on at least 5 cm H_2O PEEP. Further, this gradation of disease is consistent with therapy, wherein less acute patients might be successfully treated with noninvasive ventilation, moderately ill patients with higher PEEP and possibly neuromuscular blockade, and severely ill patients possibly requiring prone positioning therapy and extracorporeal support.

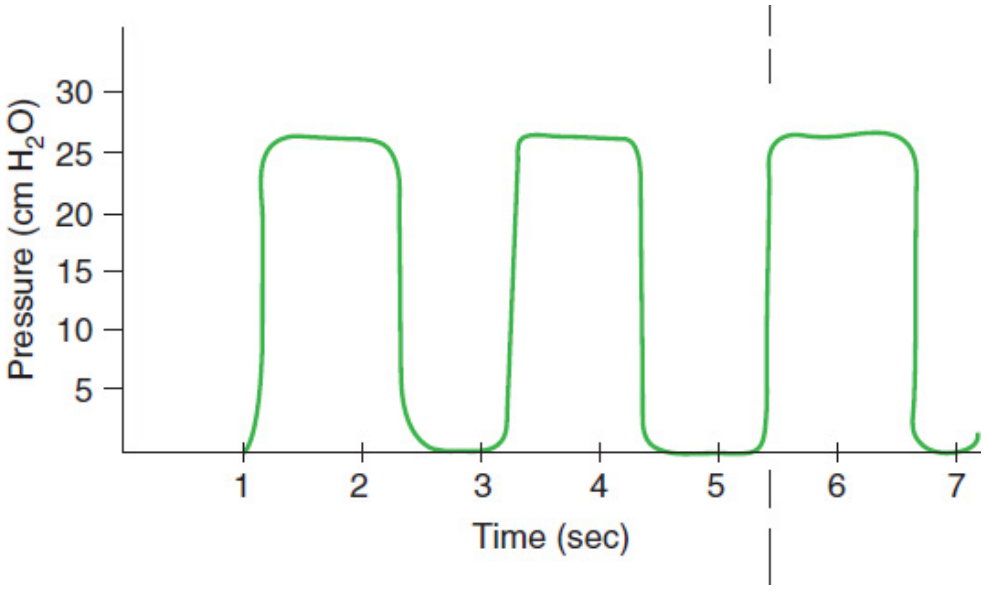

Figure 10.6 Pressure–time scalar.

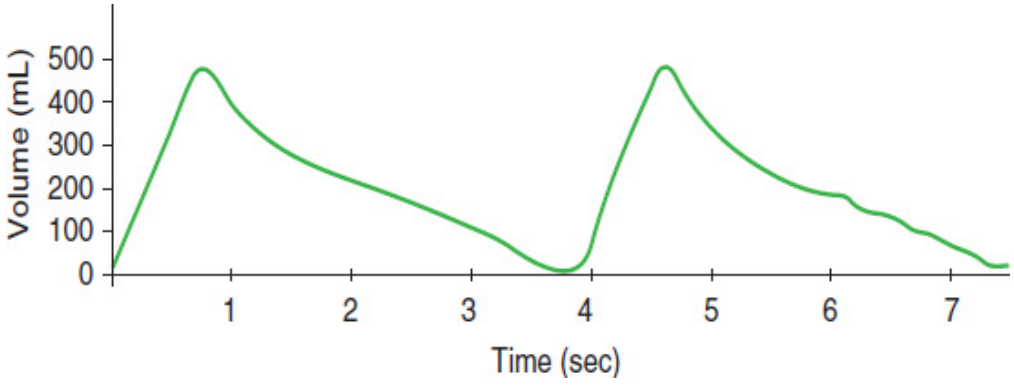

Figure 10.7 Volume–time scalar.

Ventilator Management

Conventional Modes

The standard of care of volume-controlled ventilation with low tidal volume was set forth as a result of an early study from the NIH ARDS Network. Patients ventilated at 6 mL/kg had better outcome than those who received 12 mL/kg. Thus, the standard of care for ventilating ARDS patients became the use of low tidal volumes, or low stretch therapy to diminish the incidence of ventilator-associated barotrauma.[20]

Adjunctive Therapies

High PEEP

Ideally, to prevent atelectasis and avoid overdistension, PEEP is titrated to the safe window between the lower and upper inflection points of the pressure–volume curve (**Fig. 10.12**). The precise PEEP level to optimize outcome from ARDS, particularly in the face of low stretch ventilation, has been the subject of several trials. The Assessment of Low Tidal Volume and Elevated End-Expiratory Pressure to Obviate Lung Injury (ALVEOLI) trial did not demonstrate a benefit to adding high PEEP to those ventilated with lower tidal volumes.[21] Two other trials (LOVS and EXPRESS) reached similar conclusions.[22,23] A systematic review and meta-analysis showed no statistically significant difference in hospital mortality overall but worse mortality in those with severe established ARDS treated with high PEEP.[24]

Table 10.2 ARDS: Comparison of AECC and Berlin Definitions

PaO_2/FiO_2 (P/F)	AECC Definition (Old)	Berlin Definition (New)
201–300	ALI	Mild ARDS
101–200	ARDS	Moderate ARDS
≤100		Severe ARDS

ARDS, acute respiratory distress syndrome; AECC, American-European Consensus Conference; PaO_2, partial pressure of oxygen in arterial blood; FiO_2, fraction of inspired oxygen; ALI, acute lung injury.

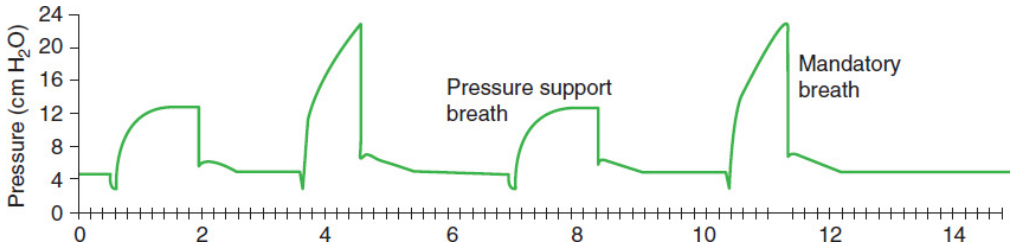

Figure 10.8 Pressure–time scalar with alternating ventilator-assisted breaths and spontaneous breaths.

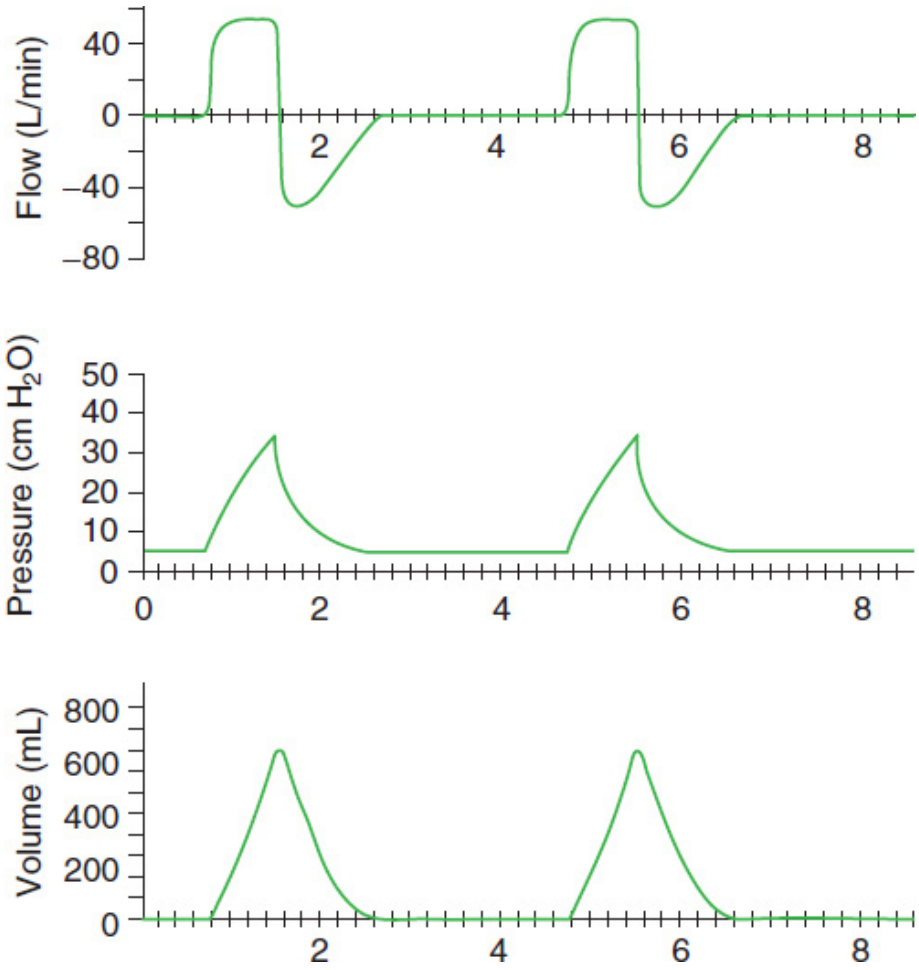

Figure 10.9 Controlled mandatory ventilation. Breaths are volume-cycled, time-triggered, and flow-limited.

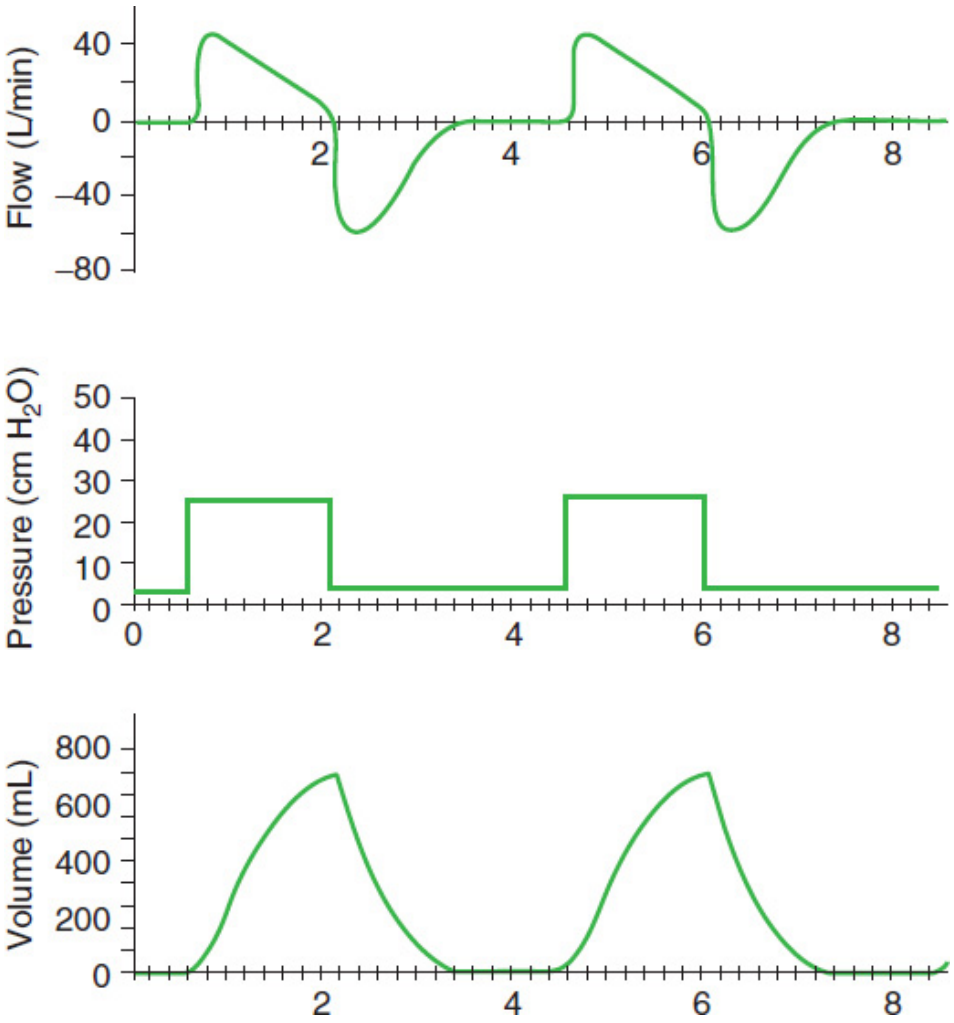

Figure 10.10 Pressure controlled ventilation: Breaths are time-cycled, time-triggered, and pressure-limited.

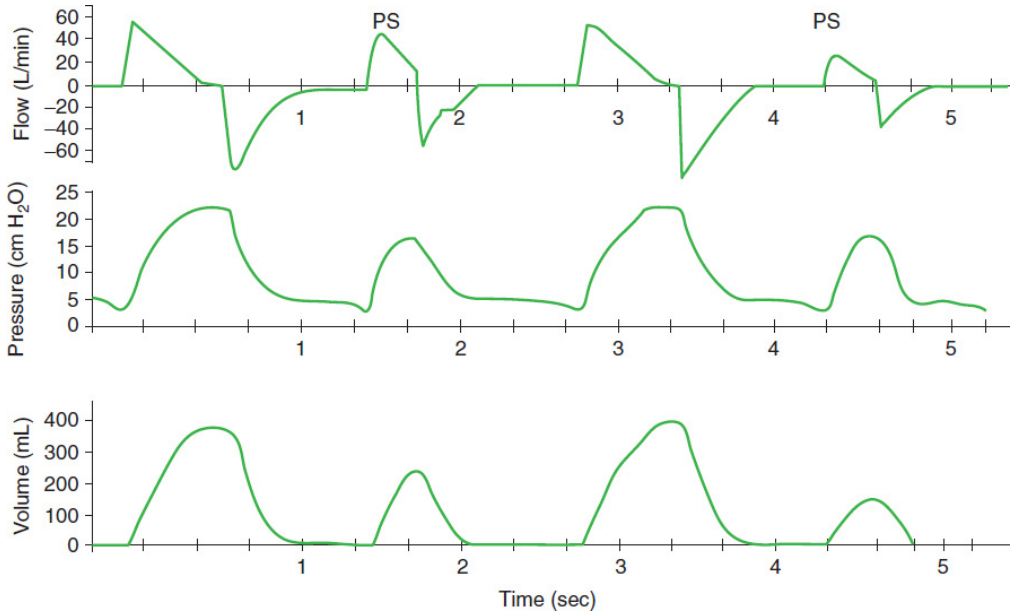

Figure 10.11 Pressure support (PS). Breaths are flow-cycled, patient-triggered, and pressure-limited. Pressure support breaths are second and fourth breaths.

High-Frequency Ventilation

These modes include high-frequency jet and oscillatory ventilation. Both utilize ultrafast subtidal ventilation and can be employed for rescue or treatment of bronchopleural fistulae. In general, heavy sedation and/or paralysis are required. The ventilator decouples oxygenation and ventilation such that unique settings are used to manipulate either one. The ventilatory circuit is heavy and cumbersome in this mode and secretion clearance is problematic. Importantly, two large trials failed to show improvement in ARDS patients, with one demonstrating an increased mortality in the high-frequency group.[25,26]

Airway Pressure Release Ventilation (APRV)

APRV takes advantage of spontaneous breathing with CPAP and an ultra-brief timed pressure release, generating a very high inspiratory to expiratory (I:E ratio). The extremely short phase time of pressure release maintains intrinsic PEEP to prevent atelectasis. There are increasing studies in the literature that demonstrate that APRV is at least equivalent to low stretch ventilation in terms of safety and outcome.[27,28] As APRV may be better tolerated than low tidal volume ventilation, some would say this provides an advantage. There is also some suggestion that routine use of APRV may decrease the incidence of, and mortality from ARDS.[29]

Inhaled Nitric Oxide and Prostacyclin

Inhaled nitric oxide (iNO) relaxes smooth muscle for selective vasodilation of the pulmonary vasculature without systemic effect. It improves oxygenation and lowers

pulmonary artery pressures. Five of the early meta-analyses showed improved oxygenation without a mortality benefit, with three of them demonstrating increased renal failure.[30] A more recent meta-analysis failed to show a mortality advantage for iNO use for ARDS.[31] Inhaled prostacyclins such as epoprostenol can also lower pulmonary artery pressures and improve oxygenation. A 2010 Cochrane review demonstrated no safety or outcome differences between iNO and epoprostenol. Although neither agent improves mortality, it seems reasonable to employ prostacyclin in ARDS patients with concomitant pulmonary hypertension.[32]

Positional Therapy

Prone positioning therapy can be used in conjunction with many other therapies previously described. It can be accomplished on a conventional ICU bed or one specially equipped to provide this therapy. Either way, extreme caution must be taken to avoid tube and line dislodgement and development of pressure-related skin complications. The ideal amount of time to keep a patient in the prone position is of debate. A recent large multicenter study in ICU patients demonstrated a significant improvement in mortality in ARDS patients treated with prone positioning therapy. This multicenter, prospective, randomized, controlled trial was from the French Proning Severe ARDS Patients (PROSEVA) study investigators.[33] They concluded that in patients with ARDS and severe hypoxemia, early application of prolonged (16-hours) prone-positioning sessions significantly decreased mortality. Similarly, a systematic review and meta-analysis reinforced the mortality benefit of nearly 25% by prone positioning therapy for ARDS.[34]

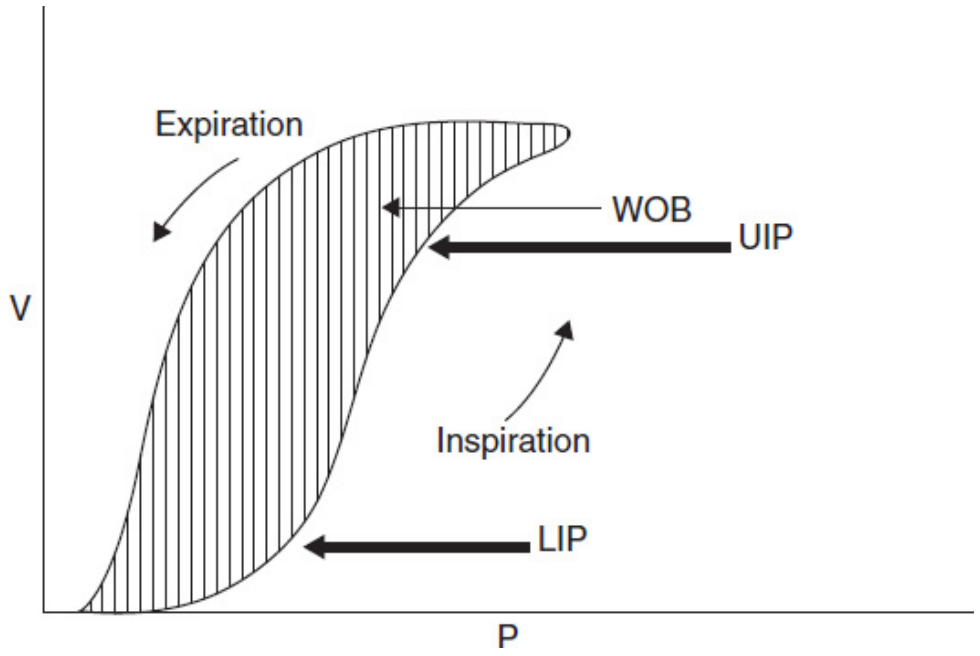

Figure 10.12 Pressure–volume curve with added PEEP. V, volume; P, pressure; LIP, lower inflection point; UIP, upper inflection point. Ideal PEEP is set between LIP and UIP.

Fluid Management

In ARDS, fluid management strategies should maintain the concept of providing sufficient circulating volume, but avoiding excessive extravascular lung water. A large trial conducted by the ARDSnet group Fluid and Catheter Treatment Trial (FACTT) demonstrated that ARDS patients have better outcome if managed with a conservative fluid strategy.[11] These findings must be reconciled with extensive data supporting improved outcome in septic patients who received more robust fluid resuscitation.[35,36] Another controversial topic concerns the utility and timing of diuretics in ARDS patients. Diuretics may improve lung compliance, oxygenation, and possibly ventilator duration, but there is little evidence for a survival benefit.

Rescue Therapies

Extracorporeal Support

Extracorporeal membrane oxygenation (ECMO) was thought to provide a beneficial effect to those patients in the European Conventional Ventilation versus ECMO for Severe Adult Respiratory Failure (CESAR) trial.[37] However, it was apparent on further analysis that patients with severe ARDS benefit most from transfer to a center that had ECMO capabilities, whether or not the therapy was actually used. Data from recent viral pneumonia epidemics are similarly confusing. Regardless of the effect on mortality, it is apparent that ECMO may be thought of as a rescue effort to improve oxygenation. Current technology involving smaller access catheters, more

portable oxygenators and venovenous deployment has made ECMO far less morbid than initial experience with it decades ago with prior mortality rates in excess of 50%.

Ventilator-Associated Events

Ventilator-associated pneumonia (VAP) is the most common life-threatening healthcare-associated infection.[38] VAP is associated with increased ICU and hospital length of stay and costs, and may often be preventable. Nonetheless, it can be extraordinarily difficult to define, particularly in injured patients who may be febrile and have pulmonary infiltrates for reasons other than pneumonia. Further, if attempts are made to diagnose the entity predominantly by microbiologic criteria (using bronchoalveolar lavage to culture $>10^4$ organisms), then the incidence of VAP may be overstated. Thus, the CDC has worked with various critical care societies to define the surveillance definition of ventilator-associated events (VAE) which are publicly reportable and include probable and possible VAP, which are not reportable. Briefly, VAE require patients to have a baseline period of more than 2 calendar days on the ventilator followed by a sustained decrement in oxygenation. Note there are no longer radiographic criteria for VAE or VAP. An infection-related VAE requires a change in temperature or white blood cell count and the initiation of a new antibiotic that is continued for 4 days. The differentiation between possible and probable VAP involves positive cultures as previously prescribed.[39]

Liberation from Ventilation

It is now apparent that the need for ventilation can be approached in a more bimodal, on–off approach, rather than the concept of sequential "weaning" of ventilator support. Thus, current practice is to complete daily spontaneous breathing trials (SBTs) to assess patients' readiness for liberation from ventilation. Of course, these trials should not be conducted in patients with hypoxia or hemodynamic instability. SBTs may be accomplished using CPAP with or without low PSV (<10 mm Hg), the latter to enable ventilatory monitoring of work of breathing and respiratory effort. If patients develop tachypnea, tachycardia, hypoxia, hypercapnia, and/or use accessory muscles during the SBT they are not ready to be extubated. Typically, the parameter that predicts extubation success most accurately is the rapid shallow breathing index (RSBI) or the respiratory frequency divided by the tidal volume with a level of less than 105 most predictive of success.[40]

Further, the requirement for airway support, as might be expected in those with burns, head injury, or anasarca must be considered separately from the requirement

for ventilatory support. Checking for a cuff leak, although conceptually of benefit in identifying patients with airway edema, may not be an accurate metric of those with a stable airway. Trials in the medical literature suggest that a short course of steroids may benefit some to diminish airway edema; these have not been replicated in surgical patients.[41] Finally, some patients, such as those with COPD, may benefit from extubation to noninvasive modes of ventilation such as bilevel positive airway pressure (BiPaP) or CPAP. Additionally, the use of high-flow nasal cannula oxygen, typically delivered at 40 L/min or greater may prevent reintubation.[42]

VENOUS THROMBOEMBOLISM PROPHYLAXIS

The surgical ICU patient is a particular target for venous thromboembolism (VTE) prophylaxis and has unique features rendering prophylaxis more challenging than it may be in a ward patient. VTE is a common cause of preventable morbidity and mortality in critical care patients. A large amount of VTE complications occur following surgery and injury.[43,44] Further, the risk of bleeding in the multitraumatized, immobile, and/or postoperative patient may be heightened in the ICU patient. Finally, safe administration of a chemoprophylactic agent must take into account drug metabolism that may be altered with renal or hepatic failure seen in ICU patients.

Incidence

The risk for developing asymptomatic lower extremity deep venous thrombosis (DVT) depends on the assessment of general risk factors and the type of surgical patient. The incidence can vary from less than 10% (in mobile patients undergoing brief, minor surgery) to over 80% (in those with spinal cord injury or elderly hip fracture patients) in the absence of prophylaxis. However, the true incidence may be unknown. It has become clear that upper extremity DVT is more common than previously appreciated and may result in pulmonary embolism at a higher rate than thought in the past,[45] thus dramatically affecting VTE rates. The incidence of fatal pulmonary embolism in surgical patients ranges from less than 1% in most undergoing elective general surgery to as high as 5% to 8% in those receiving operations for hip fractures.[46]

Risk Factor Scoring

Surgical ICU patients are at increased risk of VTE via Virchow's triad of stasis, vessel wall injury, and hypercoagulability. Acquired risk factors in the surgical critical care patients are a consequence of surgery, trauma, immobilization, obesity, malignancy, advanced age, and invasive monitoring devices. The American College of Chest Physicians (ACCP) 2012 guidelines[47] stratify surgical patients into four risk categories: very low, low, moderate, and high. The most widely used tool to assist in classification is the Caprini score (**Tables 10.3A** and **B**).[48]

Approaches to Prevention of VTE

Screening

One prevention strategy involves the early detection of subclinical venous thrombosis by regular screening tests. These tests include Duplex ultrasonography scans and laboratory assays such as evaluation of D-dimer. As most ICU patients will fall into moderate and high-risk categories for VTE (in whom D-dimer assays are universally elevated), there is virtually no role for utilizing D-dimer acquisition for diagnostic purposes. Further, the safety of early administration of chemoprophylactics is now being proven in even the highest-risk patients (e.g., neurotrauma).[49]

Mechanical Devices

Mechanical devices for thromboprophylaxis include graduated compression stockings and intermittent pneumatic compression devices. The use of mechanical devices alone, without chemical prophylaxis, is only considered for surgical ICU patients at the lowest risk for VTE, or for those patients with a contraindication to a chemoprophylaxis agent. Intermittent compression devices may afford additional protection from VTE in those in high-risk groups if used in concert with chemical agents.[50]

Chemical

UFH and LMWH

4 Few studies have performed a direct comparison of these agents for VTE prophylaxis in surgical ICU patients. A study of injured patients completed by Geerts and published in 1996 demonstrated that use of LMWH resulted in a significantly lower incidence of VTE (31% vs. 44%).[51] This likely drove the 2009 ACCP recommendation that moderate- and high-risk ICU patients should preferentially receive LMWH for prophylaxis. However, in the interim, Dr. Geerts and colleagues

performed a multicenter, RCT (PROTECT) that did not demonstrate a difference in the development of DVT or proximal DVT in those who received LMWH in the form of dalteparin compared to those administered twice-daily UFH.[52] There was no difference in bleeding rate, but a higher incidence of PE was noted in the UFH patients. This study, undoubtedly, drove the 2012 ACCP recommendation that UFH or LMWH can be used interchangeably.[47] However, it is vital to mention that the authors excluded injured, orthopedic, and neurosurgical patients from this study. Geerts himself provides guidelines suggesting that ICU patients at high risk for VTE including injured and major surgery patients should receive LMWH preferentially (**Table 10.4**). UFH should be reserved for moderate-risk ICU patients. High-risk patients at risk for bleeding should receive mechanical prophylaxis until the risk for bleeding is abrogated, and then LMWH should be initiated.[53] Literature suggests that this may be substantially earlier than we might have thought in the past.[54]

Since LMWH is primarily eliminated by the kidneys, LMWH should be avoided in those with renal dysfunction. Increasing the prophylactic dose of LMWH may be appropriate in morbid obesity (body mass index ≥ 40 kg/m^2). Laboratory monitoring of anti-activated factor X (anti-Xa) activity should be considered when using LMWH in patients with renal impairment or obesity.[55]

Factor Xa Inhibitors

Fondaparinux is a synthetic injectable indirect factor Xa inhibitor and has been studied extensively in the orthopedic and general surgery populations. In both these populations, it may be more efficacious than LMWH without an increase in bleeding risk.[47] How this extrapolates to the ICU population is unknown; however, it may be helpful in those with heparin-induced thrombocytopenia.

Table 10.3A Caprini Risk Assessment for Venous Thromboembolism (VTE) in Surgical Patients

1 Point	2 Points	3 Points	5 Points
41–60 yrs old	61–74 yrs old	>75 yrs old	Hip, pelvis, or leg fracture
BMI >25 kg/m^2	Arthroscopic surgery	PMH of VTE	Elective arthroplasty
Minor surgery	Major open surgery	FH of VTE	Stroke (<1 mo)
Swollen legs	Laparoscopic surgery	Factor V Leiden	Spinal cord injury (<1 mo)
Varicose veins	Malignancy	Prothrombin 20210 A	
Pregnancy/Postpartum	Bed rest >72 hrs	Lupus anticoagulant	
PMH of spontaneous abortion	Immobilizing cast	Anticardiolipin antibodies	
Oral contraceptives/hormone therapy	Central venous access	Elevated serum homocysteine	
Pneumonia (<1 mo)		HIT	
Sepsis (<1 mo)		Other thrombophilia	
Abnormal pulmonary function			
Acute MI			
CHF (<1 mo)			
PMH of inflammatory bowel disease			
Medicine patient on bed rest			

BMI, body mass index; PMH, past medical history; MI, myocardial infarction; CHF, congestive heart failure; FH, family history; HIT, heparin-induced thrombocytopenia.

There is even less experience using oral direct factor Xa inhibitors (rivaroxaban and apixaban) and direct thrombin II inhibitors (dabigatran) in the ICU. These agents may be less than helpful because of a long half-life. Nonetheless, we should appreciate that all three agents had a lower rate of significant bleeding such as intracranial hemorrhage in outpatients who were being treated for atrial fibrillation. Rivaroxaban is metabolized renally and apixaban both hepatically and renally. Due to similar concerns of time and ability to reverse, the use of warfarin may be limited in the ICU.

Table 10.3B Caprini VTE Percentage Risk Based on Score

Risk	Score	Estimated VTE Percentage Risk without Prophylaxis
Very low	0	<0.5%
Low	1–2	1.5%
Moderate	3–4	3%
High	>5	6%

From Caprini JA. Risk assessment as a guide to thrombosis prophylaxis. *Curr Opin Pulm Med* 2010;16:448–452, with permission.

TRANSFUSION

5 Transfusion of packed red blood cells to promote oxygen delivery is common in surgical ICU patients (**Table 10.5**). Nearly 85% of those who remain in the SICU after a week and over 40% overall will be transfused, many of whom are not actively bleeding.[56] It was common practice a decade or so ago to prescribe a transfusion for ICU patients whose hemoglobin levels fell below 10 g/dL with at least two units being administered. However, packed red blood cell transfusion may not dramatically improve oxygen delivery, particularly in situations where the oxygen dissociation curve has been shifted to the left, as with decreased 2,3-diphosphoglycerate concentrations (**Table 10.6**). In addition, in many patient populations, transfusion of packed red blood cells has been associated with increased infections and organ failure. The Transfusion Requirements in Critical

Care (TRICC) trial published in 1999 provided data to question the universal practice of red blood cell transfusion.[57] This multi-institutional trial of patients in Canadian ICUs was designed as a noninferiority trial comparing a restrictive transfusion strategy, aimed at maintaining a hemoglobin level greater than 7 to 9 g/dL, to a liberal one, targeting a level of 10 to 12. Hebert and colleagues demonstrated no difference in mortality between the groups. Although patients with significant cardiac history were excluded a priori, nearly 300 were studied, and there was no outcome difference in this group either.[58]

Table 10.4 VTE Prophylaxis in the ICU

ICU Patient Population	Thromboprophylaxis
Moderate VTE risk	(LMWH [40 mg QD] or LDUH [5,000 units TID]) + IPC
High VTE risk	LMWH (40 mg QD) + IPC
Trauma	LMWH (30 mg BID) + IPC
High bleeding risk	IPC until bleeding risk decreases
Renal impairment	LDUH (5,000 units TID) + IPC
Morbid obesity	LMWH increased dose + anti-Xa monitoring

VTE, venous thromboembolism; ICU, intensive care unit; LMWH, low–molecular-weight heparin; QD, daily; LDUH, low-dose unfractionated heparin; TID, thrice daily; IPC, intermittent pneumatic compression; BID, twice daily; anti-Xa, anti-activated factor X.

Table 10.5 Indications for RBC Transfusion in the General Critically Ill Patient

- RBC transfusion is indicated for patients with evidence of hemorrhagic shock.
- RBC transfusion may be indicated for patients with evidence of acute hemorrhage and hemodynamic instability.
- A "restrictive" strategy (transfuse when Hb <7 g/dL) is as effective as a "liberal" strategy (transfuse when Hb <10 g/dL) in critically ill patients with hemodynamically stable anemia, except possibly in patients with acute myocardial ischemia.
- The use of only Hb level as a "trigger" for transfusion should be avoided.
- In the absence of acute hemorrhage, RBC transfusion should be given as single units.
- RBC transfusion should not be considered as an absolute method to improve tissue oxygen consumption.

Adapted from Napolitano LM, Kurek S, Luchette FA, et al. American College of Critical Care Medicine of the Society of Critical Care Medicine and the Eastern Association for the Surgery of Trauma Practice Management Workgroup. Clinical practice guideline: Red blood cell transfusion in adult trauma and critical care. *Crit Care Med* 2009;37(12):3124–3157.

Despite widespread dissemination of this landmark article, transfusion practice did not rapidly change in many surgical ICUs, and there is still a minority viewpoint that older, cardiac, actively bleeding, neurosurgical, and septic patients should be excluded from restrictive transfusion practices. However, subsequent studies have further questioned this dogma. A large propensity matched study analyzed the effect of transfusion on ICU patients who were not actively bleeding. It revealed that nontransfused patients (including those with a significant cardiac history) had a lower hospital mortality and incidence of infection and acute kidney injury (AKI).[59] The RELIEVE trial was a multicenter randomized controlled trial of ventilated ICU patients over the age of 55, including one-third with ischemic cardiac disease. Those in the restrictive group received almost a quarter fewer transfusions and had over a 30% lower mortality rate.[60] A meta-analysis of the effect of blood transfusion during myocardial infarction noted that the therapy was associated with a relative risk of 2.91 for mortality and 2.04 for a subsequent MI with a number to treat of 8.[61] Further, a British propensity-matched study of cardiac surgery patients revealed odds ratios of 3.8 and 3.5, respectively, for infection and ischemia after transfusion and ratios of 6.69 and 1.32, respectively, for 30-day and 1-year mortality in transfused patients.[62]

Table 10.6 Factors Altering the Oxygen Dissociation Curve

Left Shift	Right Shift
Decreased temperature	Increased temperature
Decreased 2,3-DPG	Increased 2,3-DPG
Increased pH	Decreased pH
High altitude, carbon monoxide	

Oxygen dissociation curve describes how our blood carries and releases oxygen. Right shift represents a decreased affinity for oxygen by hemoglobin favoring to the ability to release oxygen to tissues in need. Left shift represents increased affinity by hemoglobin for oxygen.

2,3-DPG, 2,3-diphosphoglycerate.

This risk of transfusion in cardiac surgery patients is apparent even with administration of small-volume (i.e., one or two units of packed red blood cells) transfusions.[63] A large, randomized controlled trial of cardiac surgery patients over the age of 18 undergoing a bypass or valve replacement revealed no change in 30-day all-cause mortality or morbidity utilizing a transfusion trigger of 8 versus 10 g/dL of hemoglobin.[64] Further, a large single center study randomized those with severe acute upper gastrointestinal bleeding—almost 75% variceal—to a transfusion target of 7 versus 9 g/dL of hemoglobin. Nearly half of those in the restrictive group did not receive a transfusion and the mean time to endoscopy was 6 hours. This study reinforced the findings of a previous observation study that a liberal transfusion target in active upper gastrointestinal bleeding doubled the risk of rebleeding and increased mortality by 28%, presumably by promoting "popping the clot."[65] In a randomized clinical trial of patients with traumatic brain injury, a hemoglobin target of 10 compared to 7 g/dL was associated with no improvement in neurologic outcome at 6 months but a higher incidence of adverse events including thromboembolism.[66]

METABOLISM AND NUTRITION

Critically ill patients are at significant risk for developing severe malnutrition because the stress response to critical illness, surgery, and/or trauma significantly increases metabolic demands. The result is worse outcomes, including inability to wean from mechanical ventilation, inability to heal wounds (surgical or hospital acquired pressure injuries), and increased risk of nosocomial infections.

Starvation in a noncritically ill person leads to rapid depletion of hepatic glycogen stores as the brain and cellular components of blood require glucose. Once glycogen stores are depleted, gluconeogenesis from protein breakdown and, later, fat oxidation is required. Adaptation to more prolonged starvation includes shifting neuronal metabolism to free fatty acids, ketones, and glycerol, as well as a decrease in overall metabolic demands. These adaptations are quite limited in critically ill patients. Stress hormones, including cortisol and catecholamines, further drive protein catabolism.

Severely ill patients may develop the Persistent Inflammation, Immunosuppression, and Catabolism Syndrome (PICS), a combination of the Systemic Inflammatory Response Syndrome (SIRS) and the Compensatory Anti-Inflammatory Response Syndrome (CARS). These patients remained chronically critically ill. There is no specific test for this syndrome or any specific treatment. It seems logical; however, that providing aggressive nutritional support in addition to organ system support is the best approach.[67] The overall goals for nutritional support include preservation of lean body mass, wound healing, and immune function.[68]

Table 10.7 NUTRIC Score Table

Variable	Range	Points
Age (years)	<50	0
	50–<75	1
	≥75	2
APACHE II	<15	0
	15–<20	1
	20–28	2
	≥28	3
SOFA	<6	0
	6–<10	1
	≥10	2
Number of comorbidities	0–1	0
	≥2	1
Days from hospital to ICU admission	0–<1	0
	≥1	1
IL-6	0–<400	0
	≥400	1

APACHE, Acute Physiologic Assessment and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, intensive care unit; IL, interleukin.

Metabolic Requirements and Assessment

6 Assessment of nutritional status and risk for severe malnutrition begins with a careful history and physical examination. Key information includes diet, recent weight loss, the severity of critical illness, and the nature of any surgical procedures or trauma. Various scoring systems for nutritional risk have been developed. One commonly used score is the NUTRIC score (**Table 10.7**), which takes into account age, illness severity using the Acute Physiologic and Chronic Health Evaluation (APACHE), Sequential Organ Failure Assessment (SOFA), comorbidities, days in the hospital prior to ICU admission, and interleukin-6 level (if available).[69]

Because of the severely catabolic state of critically ill patients, meeting protein requirements are critical. Though it's possible to measure nitrogen balance by comparing nitrogen input via nutritional support with urinary urea nitrogen in 24 hours, this is cumbersome and does not clearly improve outcomes. Generally,

providing 1.2 to 2.5 g/kg/d of protein is sufficient.[68] The highest requirements are for patients with major surgical procedures, multitrauma, and burns. Measurement of serum proteins, such as prealbumin, transferrin, and retinol-binding protein, may demonstrate trends in nutritional status, but the utility is questionable, particularly since these proteins are acute phase reactants.

Meeting patients' caloric requirements is also important for improving outcomes, though hypocaloric feeding within the first several days of ICU admission does not seem to be harmful. Several equations, including Harris–Benedict and the Mifflin St. Jeor, have been used to calculate resting energy expenditure (REE). These equations take into account height, weight, age, and gender.

Indirect calorimetry, by measuring oxygen consumption (VO_2) and carbon dioxide production (VCO_2) and calculating the respiratory quotient ($RQ = VCO_2/VO_2$), can also be used, but the measurement is complicated. Intubated patients must be on a steady FiO_2 that is ≤80% and PEEP of ≤10 torr, without a cuff leak. REE is then calculated using the Weir formula ($1.44 \times [3.94\ VO_2 + 1.11\ VCO_2]$).[70] Like nitrogen balance, indirect calorimetry does not clearly impact outcomes.

In general, critically ill patients should receive 25 to 30 kcal/kg/d.[68] It's worth considering that hypothermia, coma, stable quadriplegia, barbiturates, sedatives, anesthesia, and muscle relaxants can decrease metabolic needs, while fever, sepsis, stress, shivering, and seizures can increase the needs.

The best way to estimate energy requirements in obese patients is unclear. A high-protein, hypocaloric strategy is favored in order to reduce fat mass, improve insulin sensitivity, and preserve lean body mass. One suggestion is to utilize 11 to 14 kcal/kg actual body weight per day in patients with body mass index (BMI) of 30 to 50 and 22 to 25 kcal/kg ideal body weight per day for patients with BMI >50. Obese patients should receive 2.0 to 2.5 g/kg ideal body weight per day of protein.

Nutritional Support

Macronutrients include carbohydrates, fat, and protein. Carbohydrates provide 3.4 kcal/g and have the highest RQ of 1.0. While a higher RQ from administration of a large amount of carbohydrates, compared to fats, may mildly increase the need for CO_2 removal via the lungs, the bigger issue can be overfeeding as overfeeding leads to increased glycogenesis and lipogenesis, which have an RQ higher than 1. Thus, overfeeding may impact the ability to wean a patient from mechanical ventilation.

Fat provides 9.0 kcal/g with an RQ of 0.7. Free fatty acid deficiency can cause anemia, thrombocytopenia, respiratory distress, and rash, but this deficiency is easily prevented. Fatty acids exist in two varieties, omega-3 and omega-6. Omega-3

fatty acids are derived from linolenic acid, found in fatty fish such as salmon, and are less pathogenic than omega-6 fatty acids derived from linoleic acid. It has been difficult, however, to demonstrate a benefit of using formulas such as SMOF (soybean oil, medium chain triglycerides, olive oil, and fish oil) designed to decrease the SIRS response to critical illness and trauma.[71]

Protein delivers 4.0 kcal/g with an RQ of 0.8. Essential amino acids cannot be synthesized endogenously and must be provided in the diet.

Current nutritional formulas contain sufficient trace elements and vitamins to make deficiency of these micronutrients in ICU patients extremely rare. These formulas generally include vitamin K, which is worth keeping in mind if anticoagulation using vitamin K antagonists is anticipated.

Routes of Nutritional Support

Enteral nutrition is preferred over parenteral nutrition as it preserves the gut mucosa and is associated with fewer complications and costs. Standard formulas have a calorie density of 1 kcal/mL. More concentrated formulas may provide more nutrition with less fluid volume. Standard enteral formulas are polymeric. For patients who have malabsorption with resultant diarrhea and/or fail to tolerate standard formulas, use of an elemental diet, which includes the basic building blocks of the energy substrates, for example, proteins as free amino acids, fats as medium chain triglycerides, and carbohydrates as oligosaccharides, may be beneficial. Formulas with high osmolarity may also cause diarrhea with tube feeds. Decreasing the osmolarity or adding bulking agents can help.

There are several complications related to enteral nutrition in the ICU. The most significant of which is aspiration. The risk for aspiration can be decreased by maintaining head-of-bed elevation at 30 to 45 degrees or greater. Though monitoring gastric residuals has been standard, the benefit of such monitoring has been questioned, at least in patients who have not undergone abdominal procedures. In general, there is no difference in aspiration risk between gastric versus postpyloric feedings.[72] When patients don't tolerate gastric feedings, use of prokinetic agents or placement of a postpyloric feeding tube may help.

Placement of transnasal feeding tubes can result in intrapulmonary or even transpulmonary placement. Having a dedicated team with a protocol for tube placement can minimize these risks.[73] Surgically placed tubes in the stomach or jejunum can become dislodged, leading to intra-abdominal leak and peritonitis.

For patients who have an artificial airway in place and may need to undergo multiple, nonabdominal operations, continuing tube feedings up to, and possibly during, the operation is safe.

When provision of enteral nutrition is not possible, parenteral nutrition may be indicated. Parenteral nutrition requires the insertion of a central line, adding risks for mechanical complications and infection. Some complications related to parenteral nutrition, such as cholestasis, can be decreased by the provision of at least a small amount of enteral feedings to maintain the trophic effects of gut hormones on the liver and prevent biliary stasis.

Timing of Nutritional Support

Nutritional support should be initiated within 24 to 48 hours of ICU admission following adequate resuscitation. Initiating enteral nutrition while the patient remains in shock can lead to bowel ischemia. On the other hand, patients who are relatively stable on low doses of vasoactive agents may tolerate feedings quite well. Having an open abdomen is not an absolute contraindication to enteral feedings, depending upon the status of the bowel.[74] The use of prone positioning for the management of the ARDS is also not an absolute contraindication.[75]

Enteral feeding does not need to immediately provide full nutritional support. Ideally, nutritional goals should be met within 5 to 7 days. If it is anticipated that the patient will not be able to tolerate enteral feedings for at least seven days, parenteral nutrition may be indicated. In addition, if the patient already has evidence of severe malnutrition at the time of admission, there may be benefit in earlier parenteral nutritional support.[68]

Patients often don't actually receive the amount of enteral nutritional support that is ordered. Tube feedings get held for many reasons, including procedures, baths, and ventilator weaning trials. One approach to make up for this decrease in support has focused on volume-based feeding. If the patient falls behind, the nurse can increase the feeding rate for a period of time to make up for the difference. Another approach to achieving feeding goals quickly is to start with a semi-elemental feeding formula that is readily absorbed, combined with the volume-based feeding approach and liberal use of prokinetic medications.[76]

Organ Specific Nutritional Support

A variety of formulas have been developed to potentially improve outcomes of specific organ dysfunction. Recognizing that a higher RQ is associated with increased CO_2 production, enteral formulas have been developed that are high in fat and low in carbohydrates. Use of such formulas has not improved weaning from mechanical ventilation or improved survival. Formulas with large quantities of antioxidants have also been tested in patients with the ALI without success.

For patients with AKI, the goals have been to decrease fluid volume, potassium load, and urea production. Provision of formulas high in essential amino acids to decrease urea has not decreased the need for dialysis. In general, minimizing protein intake to decrease urea production is counterproductive because these patients are so catabolic.

For patients with hepatic dysfunction, aromatic amino acids can cross the blood–brain barrier and worsen encephalopathy. Formulas that are high in branched chain amino acids but low in aromatic amino acids do not seem to have benefit, however.

In patients with acute pancreatitis, enteral nutrition, if tolerated, may decrease length of stay, improve resolution of SIRS, and decrease infection rate.[77] Enteral nutrition does not stimulate exocrine pancreatic secretion as much as was once thought. Parenteral nutrition should be reserved for patients who clearly do not tolerate enteral feedings.

Immunonutrition

A number of additives to nutritional formulas could improve immune function and thereby decrease the risk for infection and, perhaps, mortality. Immune modulating formulas containing arginine, glutamine, nucleotides, and omega-3 fatty acids did seem to improve some aspects of immune function, but did not clearly improve outcomes.[78] It seems that there may be marginal benefit for these formulas in patients who have undergone major surgery or trauma, but not in nonsurgical patients. Glutamine, which can be used as a substrate for gut metabolism could improve gut barrier function and thereby decrease translocation and infection, also lacks clear benefit.

Stress-Related Mucosal Disease

Endoscopic evidence of upper gastrointestinal bleeding from stress-related mucosal disease (SRMD) is common, even shortly after admission, in high-acuity ICU patients. The pathophysiology is thought due to be impaired mucosal protection, mostly related to blood flow, and not acid hypersecretion or *Helicobacter pylori* infection. Overt bleeding, that is, coffee ground upper intestinal aspirates or hemoccult-positive stool, is not uncommon in the ICU. Clinically significant bleeding resulting in the need for a blood transfusion and/or hemodynamic instability is much less common, with or without pharmacologic prophylaxis. The strongest risk factors for SRMD in the ICU are the need for more than 48 hours of mechanical ventilation and the presence of coagulopathy. It seems prudent that pharmacologic prophylaxis of SRMD be limited to those with one of these two risk factors. There

may, however, be a role to avoid pharmacologic agents even in the highest-risk patients, particularly if they are being enterally fed.[79] If pharmacologic prophylaxis is prescribed, proton pump inhibitors may be equivalent to histamine-2 receptor antagonists in terms of risk for gastrointestinal bleeding, mortality, prolonged length of stay, pneumonia, or *Clostridium difficile* colitis.[80]

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) complicates at least 5% and as many as 30% of all surgical ICU admissions with a mortality of over 50%, though it's not clear how much the AKI contributes to mortality or is more of a marker of illness severity.

Etiology

The causes of AKI are typically divided into prerenal, intrinsic renal, and postrenal. Prerenal causes relate to renal blood flow and may include hypovolemia, shock, and low cardiac output. Heart failure can also impair renal function by significantly increasing the pressure in renal veins and, thereby, impeding renal blood flow. Sometimes, the renal dysfunction, as manifest by low urine output, is the first sign of an underlying problem. Initially, the kidney is able to maintain perfusion by selectively dilating the afferent arteriole and vasoconstricting the efferent arteriole of the juxtaglomerular apparatus. As hypotension persists and the renin–angiotensin system is activated, systemic vasoconstriction occurs and cortical hypoperfusion occurs.

Renal parenchymal causes of AKI are the most common. Differentiating prerenal from renal AKI is not always obvious. Serum and urinary studies can help (**Table 10.8**). Postrenal causes can be detected with ultrasound or CT of the kidneys. More extensive testing is usually unnecessary, but may be needed in unusual cases.[81]

Table 10.8 Workup for Acute Kidney Injury

Diagnostic Study	Prerenal	Acute Tubular Necrosis
Urinalysis	Normal	Casts and epithelial cells
Serum BUN:creatinine	20:1	Normal
Urine osmolality	>500 mOsm/kg	<350–450 mOsm/kg
FENa	<1%	>2%

BUN, blood urea nitrogen; FENa, fractional excretion of sodium.

The most common cause of intrinsic renal AKI is acute tubular necrosis (ATN), though other causes, such as acute interstitial nephritis can occur. ATN is often caused by ischemia (initially a prerenal cause) or nephrotoxic agents. Medications that may cause ATN include aminoglycosides, cephalosporins, amphotericin, and cisplatin. Iodinated contrast-induced nephropathy is uncommon and, in fact, its existence has been debated.[82] Age, pre-existing kidney disease, diabetes, and vascular disease have been touted as risk factors. If iodinated contrast is clearly necessary, the best approach to prevention is administration of intravenous fluids before contrast administration. N-acetyl cysteine, bicarbonate, and prophylactic dialysis, before or after the contrast load, are not beneficial. Though gadolinium does not seem to be as directly toxic to the kidneys as iodinated contrast, it may cause nephrogenic systemic fibrosis in patients with pre-existing renal dysfunction. It, too, should be used with caution in patients with renal dysfunction.

Large amounts of pigments, such as myoglobin or hemoglobin, can cause AKI. Hemoglobin pigment rarely causes ATN in surgical ICU patients, except perhaps after a severe transfusion reaction. Myoglobinuria as a consequence of rhabdomyolysis is far more common, particularly after severe trauma, compartment syndrome, electrical burns, seizures, or coma with prolonged immobilization.[83] Myoglobinuria should be suspected in patients with dark urine and a positive urine dipstick without red cells on microscopy. Patients with a serum myoglobin level exceeding 10,000 ng/mL or a creatinine phosophokinase (CPK) greater than 20,000 IU/L are at risk for pigment nephropathy. Myoglobin is both a potent vasoconstrictor and a direct tubular toxin when converted to ferrihemate in an acid environment. However, alkalinization of the urine (with administration of sodium bicarbonate) has not been proven to be more effective than volume administration and forced diuresis to achieve a urine output of 2 mL/kg/hr. There is also no evidence that early initiation of dialysis improves outcomes, even if myoglobin levels decrease. Controlling the source of rhabdomyolysis is also critical.

Table 10.9 Acute Kidney Injury Severity Scores

Stage	RIFLE	AKIN	KDIGO	Urine output
1	Risk = SCr ↑ ≥1.5 or GFR ↓ >25% × baseline	SCr ↑ ≥0.3 mg/dL or 1.5–2 × baseline	SCr ↑ ≥0.3 mg/dL or 1.5–1.9 × baseline	<0.5 mL/kg/hr for 6–12 hrs
2	Injury = SCr ↑ ≥2 or GFR ↓ >50% × baseline	SCr ↑ 2–3 × baseline	SCr ↑ 2.0–2.9 × baseline	<0.5 mL/kg/hr for >12 hrs
3	Failure = SCr ↑ ≥3 or GFR ↓ >75% × baseline, or SCr >4 mg/dL with an acute ↑ >0.5 mg/dL	SCr ↑ >3 × baseline, or SCr ≥4.0 mg/dL with an acute ↑ >0.5 mg/dL, or on RRT	SCr ↑ ≥3 × baseline or SCr ≥4.0 mg/dL or initiation of RRT	<0.3 mL/kg/hr for ≥24 hrs or anuria for ≥12 hrs
4	Loss = Complete loss of kidney function >4 wks			
5	ESRD >3 mo			

RIFLE, risk, injury, failure, loss, end-stage renal disease (ESRD); AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcomes; SCr, serum creatinine; GFR, glomerular filtration rate; RRT, renal replacement therapy.

The best approaches to prevention of AKI include early resuscitation to restore renal blood flow, which should include appropriate volume expansion, vasopressors and inotropes, and avoidance of nephrotoxic agents.[84] There is little evidence that colloids are better than crystalloids. Hydroxyethyl starch preparations should be avoided, however, as they are nephrotoxic through tubular obstruction. There is no role for the use of low-dose dopamine or fenoldopam for protection against AKI or improvement of diuresis.

Postrenal AKI is caused by obstruction, usually from urinary retention, rarely from bilateral ureteral obstruction or unilateral ureteral obstruction in a patient with one functioning kidney. Evaluation may include placement of a urinary catheter, if one is not already present and patent, and renal ultrasound.

Severity

There has been interest in developing markers for early development of AKI with the thought that earlier detection could lead to earlier intervention and improved outcomes. Markers involved in cell cycle arrest during the early phase of renal cell injury include insulin-like growth factor–binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases 2 (TIMP-2). The NephroCheck point of care device can measure these markers. Neutrophil gelatinase–associated lipocalin (NGAL) is also produced after ischemic or toxic insults to the kidney. So far, however, measurement of these markers has not led to improved outcomes in terms of need for renal replacement therapy (RRT) or mortality.[85]

Several grading systems for AKI are based upon serum creatinine and urine output (**Table 10.9**). These include the Risk to Injury to Failure to Loss to End-stage kidney disease (RIFLE), as defined by the Acute Dialysis Quality Initiative (ADQI), Acute

Kidney Injury Network (AKIN) criteria, and Kidney Disease Improving Global Outcomes (KDIGO) work group criteria.[86,87] None of these systems are better or worse than the others at predicting outcome from AKI.

Treatment of Acute Kidney Injury

7 The most important issues in the management of patients with AKI are: (1) Minimizing any further injury to the kidney through adequate resuscitation and avoidance of nephrotoxic agents. (2) Adjusting the dosing regimens for medications that are excreted by the kidneys. Consultation with a critical care pharmacist can be invaluable. (3) Management of the physiologic effects of AKI, including electrolyte disturbances, acid–base disorders, and hypervolemia. Hyperkalemia is the most immediately life-threatening electrolyte disturbance. The absolute level of potassium may not be as important as the presence of changes on electrocardiography, such as peaked T waves or prolonged QRS. Depending upon severity, medical management can include the administration of calcium to stabilize the myocardium, administration of insulin and glucose, bicarbonate, and/or an inhaled beta-agonist to drive potassium intra-cellularly, or administration of polystyrene sulfonates to bind potassium in the gastrointestinal tract. Ultimately, dialysis (RRT) may be needed.

RRT is often required for patients who develop severe AKI.[88] The urgent indications for RRT include severe, refractory acidosis (e.g., pH <7.1 without respiratory acidosis), electrolyte abnormalities (particularly hyperkalemia), intoxication with agents that can be dialyzed, hypervolemia, and uremia, as manifested by pericarditis or encephalopathy. The latter can be difficult to separate from other causes of altered mental status in the ICU. Platelet dysfunction is also associated with AKI, particularly in face of a BUN in excess of 100 mg/dL. The administration of desmopressin (DDAVP) or analogues help temporarily.

Timing of RRT has remained controversial. Though some studies have suggested benefit from early initiation, others have suggested that waiting for a clear indication as outlined above is reasonable.[89]

Once a decision is made to initiate RRT, the next question is whether or not to utilize intermittent hemodialysis (IHD) or continuous RRT (CRRT). In general, the latter is preferred in patients with hemodynamic instability, but the benefit of this approach is unclear. Studies of using high-flux CRRT or specialized adsorbers to remove cytokines or endotoxin have not demonstrated benefit.[90]

LIVER DYSFUNCTION

In addition to acute liver failure (ALF), complications of chronic liver disease that may result in ICU admission include variceal hemorrhage, encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome. In addition, liver disease, as a comorbid condition, can have a significant impact upon patients who present with other disease processes.

Variceal Bleeding

The management of a patient with potential variceal bleeding should proceed like that for any other patient with an upper GI bleed. If necessary, the patient may need to be intubated to prevent aspiration. At the same time, fluid resuscitation, including transfusion of packed red blood cells, should be initiated. To minimize the effect of acid on the varices and potentially treat concomitant peptic ulcer disease, high-dose proton pump inhibitor therapy should be started. Administration of octreotide, a synthetic analogue of somatostatin, can decrease portal pressure and decrease bleeding. Vasopressin also reduces portal pressure but may cause myocardial ischemia and is less specific than octreotide.

Definitive control of hemorrhage usually requires endoscopic intervention, either with banding or sclerotherapy.[91] Complications include perforation, ulceration, and delayed stricture. In the face of massive, uncontrolled bleeding, balloon tamponade, using the Sengstaken–Blakemore or Minnesota tube, can temporarily control hemorrhage to allow time for adequate resuscitation. Complications of balloon tamponade include aspiration and esophageal ischemia or perforation. If other interventions fail, a portosystemic shunt, such as the transjugular intrahepatic portal-systemic shunt (TIPS) or surgical shunt, can be performed to reduce the pressure in the varices.

Patients with variceal bleeding are also at risk for worsening encephalopathy or infection, particularly spontaneous bacterial peritonitis (SBP). Prophylactic antibiotics are often administered.

The effects of liver disease on the clotting system are complex.[92] Not only are key coagulation factors synthesized in the liver, but so are anticoagulant proteins, such as protein C and protein S. Patients may have an elevated international normalized ratio but are actually hypercoagulable. Monitoring thromboelastography may be the best way to understand the patient's coagulation status and, thereby, titrate the use of fresh frozen plasma or cryoprecipitate. Patients with liver disease are also often thrombocytopenic. Platelet transfusions may be indicated.

Hepatic Encephalopathy

Hepatic encephalopathy may be precipitated by gastrointestinal hemorrhage or infection.[93] The diagnosis may be difficult because of other causes of an altered mental status such as hypoglycemia, hypoxemia, uremia, and medications. Hepatic encephalopathy results from increased blood ammonia and aromatic amino acid levels from nitrogenous substances within the gut lumen resulting in increased stimulation of γ-aminobutyric acid (GABA) receptors. Ammonia levels, however, do not correlate well with the severity of encephalopathy. In addition to controlling precipitating factors, management includes pharmacologically reducing the production and/or absorption of ammonia from the gut. The mainstay of therapy is lactulose, which acts to acidify the colon, trapping nonabsorbable ammonium in the gut lumen and causing diarrhea, eliminating nitrogen from the body. Reduction of urease-producing gut flora with antibiotics, such as neomycin or rifaximin, may also help relieve severe encephalopathy.

Ascites and Spontaneous Bacterial Peritonitis

Severe ascites may result in respiratory distress and, rarely, the development of abdominal compartment syndrome. Paracentesis is a temporizing measure for refractory ascites. SBP can occur in any patient with ascites. Common clinical manifestations include fever, abdominal pain and unexplained encephalopathy. Paracentesis is the appropriate diagnostic test for SBP. Finding greater than 250 neutrophils/mL suggests SBP, with or without a positive culture. Treatment is based on the organism sensitivity if the culture is positive, but empiric therapy with fluoroquinolones or third-generation cephalosporins is reasonable.

Hepatorenal Syndrome

Portal hypertension can lead to splanchnic vasodilation and reduced renal blood flow leading to decreased effective circulatory volume and activation of the renin–angiotensin system leading to worsening renal function, the hepatorenal syndrome.[94] Infection or bleeding can cause a rapid decline in renal function. Medical management focuses on improving renal blood flow with midodrine as a vasoconstrictor and octreotide to inhibit vasodilation. Patients with severe hepatorenal syndrome may require RRT, but the most definitive therapy is liver transplantation.

Liver Failure

Liver transplantation is the most effective treatment for chronic liver failure. The prognostic model for end-stage liver disease (MELD) score predicts liver-related mortality based on a formula involving the serum creatinine, serum bilirubin, and INR. The MELD score is used to allocate donor livers to the most appropriate patient.

ALF in patients with previously normal liver function or previously compensated liver disease is defined by a rapid decline in liver synthetic function combined with encephalopathy not attributable to another cause.[95] Supportive management focuses on respiratory failure, hypotension, coagulopathy, gastrointestinal bleeding, renal failure, sepsis, and encephalopathy. As the primary cause of death in ALF is cerebral edema, aggressive management of elevated ICP, whether or not invasive intracranial pressure monitoring is employed, is indicated. In rare circumstances, extracorporeal liver support systems, such as Molecular Adsorbent Recirculating System,[96] can bridge patients to recovery or transplantation.

ENDOCRINE ISSUES

Glucose Control

Hyperglycemia is common in critically ill patients due to elevated cortisol, growth hormone, and catecholamine levels, leading to increased hepatic gluconeogenesis and insulin resistance, and, ultimately, poor clinical outcomes.[97] Complications of hyperglycemia include an increased risk of infection and worse outcomes in patients with acute neurologic disorders such as stroke or traumatic brain injury. Though intensive insulin therapy, maintaining glucose levels of 80 to 110 mg/dL, demonstrated benefit in medical or cardiac surgery patients, subsequent studies did not demonstrate the same benefit, perhaps because of an increased rate of hypoglycemia. There is also evidence that glucose variability, in addition to absolute values, is associated with worse outcomes. Current guidelines recommend moderate blood glucose control of 144 to 180 mg/dL for critically ill patients to avoid both marked hyperglycemia and iatrogenic hypoglycemia.

Adrenal Insufficiency

The presence or absence of adrenal insufficiency in critically ill patients has been controversial for years. Absolute adrenal insufficiency is extremely rare, but relative adrenal insufficiency, also known as critical illness-related corticosteroid insufficiency, manifested by hypotension and fever (and rarely with electrolyte

abnormalities), may be more common in ICU patients and may be associated with worse outcomes.[98]

In the ICU, however, patients may have total levels of cortisol that are normal, but they may not respond appropriately to the stress of critical illness and lack the typical diurnal variation of cortisol seen in normal volunteers. In the past, relative adrenal insufficiency was defined by a cortisol level of less than 11 to 25 mcg/dL and/or failure to raise the level by more than 9 mcg/dL after stimulation by high-dose (250 mcg) ACTH. However, there is much debate as to what cortisol level is appropriate in septic shock, what constitutes an adequate response to ACTH stimulation and what dose of ACTH should be used. Current consensus is that ACTH stimulation tests are not helpful for determining which patients may benefit from steroid administration. Steroid administration in septic shock has undergone several randomized trials. One large, multicenter trial of hydrocortisone compared to placebo did not demonstrate benefit.[99] In contrast, two studies that included fludrocortisone in addition to hydrocortisone did demonstrate a mortality benefit.[100,101] The current Surviving Sepsis Campaign guidelines recommend adding hydrocortisone at a dose of 200 mg/d for patients with refractory shock despite adequate fluid resuscitation and vasopressors without doing any ACTH stimulation tests.[102] The steroids can be rapidly tapered off when the pressor requirement resolves.

Another controversial question regarding adrenal insufficiency is the potential effect of the induction agent etomidate, which is a reversible inhibitor of 11-beta-hydroxylase, and thus may cause transient adrenal insufficiency. Etomidate is frequently utilized for intubations in critically ill patients because it has little directly detrimental hemodynamic effects. Studies have not definitively demonstrated worse outcome between patients intubated using etomidate versus other induction agents such as ketamine.[103]

Critically ill patients who were on therapeutic steroids prior to their current illness are at risk for developing true adrenal insufficiency if the steroids are abruptly stopped or the relative dosing decreased. The stress dose of steroids currently recommended for refractory septic shock may actually be less than the equivalent baseline dose of steroid prior to admission.

Thyroid Abnormalities

New onset of clinically important thyroid abnormalities in ICU patients is extremely rare. Nonthyroidal illness, previously called euthyroid sick syndrome, seems to be more of a laboratory finding marked by high reverse T_3 levels and total T_3, normal

or low free T_4 and thyroid-stimulating hormone levels. The actual clinical significance is questionable. No treatment is required.

True hypothyroidism in the ICU is very rare. Consequently, there is little utility in testing thyroid function in chronically critically ill patients without a specific indication. Although the half-life of commonly administered thyroid medications is long, it is possible that critically ill patients with pre-existing hypothyroidism could develop severe hypothyroidism without supplementation in the ICU. Patients with severe hypothyroidism develop hypothermia, bradycardia, and obtundation with low serum sodium and glucose levels. The treatment includes supportive care and administration of thyroxine and hydrocortisone.

Thyroid storm can occur in patients with Graves disease or toxic nodular goiters who become stressed by infection, pregnancy, trauma, or surgery.[104] Supportive management includes monitoring hemodynamics and arrhythmias, cooling, and hydration. Beta-adrenergic antagonists, for example, propranolol, can ameliorate many of the physiologic effects of thyroid storm. Propylthiouracil (PTU) or methimazole is administered to inhibit the release of T_4. PTU also blocks the conversion of T_4 to T_3. Thereafter, iodine as saturated solution of potassium iodide (SSKI) or Lugol solution is given after PTU or methimazole have been administered to inhibit T_4 release. Glucocorticoids may also be indicated.

INFECTIOUS DISEASE ISSUES

Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Sepsis-induced organ dysfunction may be occult; unrecognized infection should be considered as the cause of new-onset organ dysfunction. In addition, specific infections may result in local organ dysfunction, for example, acute respiratory failure from pneumonia.

The working definition of sepsis has evolved over the years. The most recent, Sepsis-3, definition states that sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection.[105] In other words, it's the patient's immune response to the infection that leads to the organ failure. Operationally, a patient can be diagnosed with sepsis in the presence of a suspected infection and either an increase by at least 2 in the SOFA score or at least 2 of 3 quick SOFA criteria (respiratory rate of ≥22/min, altered mentation, systolic blood pressure ≤100 mm Hg). Septic shock is defined as vasopressor requirement to maintain mean arterial pressure (MAP) of at least 65 mm Hg and serum lactate level >2 mmol/L in the absence of hypovolemia.

Sepsis Guidelines

8 The management of patients with sepsis and septic shock has continued to evolve over the years. The comprehensive Surviving Sepsis Campaign (SSC) guidelines for management cover resuscitation, antibiotic coverage and source control, as well as many aspects of organ-specific supportive care.[102] The initial resuscitation of the patient with sepsis focuses on rapid restoration of normal hemodynamics and normalization of lactate level, termed early goal directed therapy. When compared to standard care in 2001, this approach significantly improved mortality.[106] More recent studies of relatively similar hemodynamic goals did not demonstrate significant differences in outcome.[9,10,107] It's worth pointing out, however, that the current control groups did as well as the treatment group in the original study, suggesting that the current standard of care already achieves early goal directed therapy, though specific goals continue to evolve.[108,109]

The SSC guideline for initial fluid resuscitation includes the administration of 30 mL/kg intravenous crystalloid in every patient who is hypotensive or has a lactate of at least 4 mmol/L. Additional fluids should be given as needed. There is no indication for the use of albumin unless the patient requires substantial crystalloids. Starches should not be administered. There is no indication for blood transfusion unless the patient's hemoglobin is <7 g/dL. The goal MAP is 65 mm Hg. If this is not achieved with the initial fluid bolus, initiation of a vasopressor, for example, norepinephrine, is indicated. Second-line agents include vasopressin and epinephrine. Dobutamine or epinephrine is also helpful if myocardial dysfunction is identified. The response to these interventions should be reassessed by lactate levels, $ScvO_2$, ECHO, passive leg raising, and/or focused physical examination.

If hemodynamic stability is not restored with adequate fluid resuscitation and vasopressor therapy, intravenous hydrocortisone at a dose of 200 mg/d delivered by bolus dosing or continuous infusion should be considered. The hydrocortisone can be tapered off once the patient is off vasoactive agents. There is no indication for performing the ACTH stimulation test.

Administration of antimicrobials should be initiated as soon as possible, with a goal of within 1 hour after recognition of sepsis or septic shock. Appropriate cultures should be obtained prior to starting antimicrobial therapy as long as doing so does not delay the start of antimicrobials. The initial empiric regimen should have activity against all likely pathogens. This regimen should be deescalated as soon as possible once cultures and sensitivities are known. The duration of antimicrobial therapy should generally be 7 to 10 days. Longer courses are appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus*, some fungal and viral infections, or immunologic deficiencies. Procalcitonin

levels may be utilized to shorten the course of antimicrobials or discontinue antimicrobials when there is limited evidence of sepsis.

For patients with surgical infections that require drainage, debridement, device removal, or definitive control (e.g., resection), a target of source control within 6 to 12 hours is sufficient in most cases. Adequate hemodynamic resuscitation is important prior to the administration of a general anesthetic.

The SSC has encouraged the use of bundles of care (**Table 10.10**). Within the first 3 hours of sepsis recognition, one should measure a lactate level, obtain blood cultures prior to administration of antibiotics, administer broad-spectrum antibiotics (though now this should be within 1 hour), and administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L in all patients, regardless of previous heart or renal failure. Earlier completion of this bundle, particularly the early antibiotics, can improve survival.[110] Within 6 hours, one should initiate vasopressors if hypotensive after a fluid bolus, reassess volume status and tissue perfusion, and reassess lactate level. Lactate may not be the best endpoint for resuscitation. Mixed venous O_2 saturation may be useful. Repeated assessment of capillary refill in a standardized fashion may be just as good.[111]

Table 10.10 Sepsis Bundles

To Be Completed within 3 hrs	To Be Completed within 6 hrs
Measure lactate level	Apply vasopressors for hypotension after that does not respond to initial fluid resuscitation
Obtain blood cultures	Reassess volume status and tissue perfusion
Administer broad spectrum antibiotics	Remeasure lactate if initial lactate elevated
Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L	

Hospital Acquired Infections

Central line-associated blood stream infections (CLABSI) can be an important cause of morbidity, resource utilization, and even attributable mortality in ICU patients.[112] The Center for Disease Control defines a CLABSI as a positive blood culture in a patient who has a central line in place within 2 calendar days of the culture and no

identifiable secondary sources of bacteremia. Typically, the management includes appropriate antimicrobial therapy and removal of the line. If more clinical proof is needed because of the potential risks and challenges related to catheter removal, quantitative blood cultures or differential time to positivity can be compared between paired cultures drawn from the line and peripherally. Blood drawn from an infected line should have a higher quantity of organisms that should also become positive more quickly than blood drawn peripherally.

Preventative measures, including use of an antimicrobial coated catheter (minocycline/rifampin or chlorhexidine/silver sulfadiazine), maximal sterile barrier precautions (handwashing, sterile gloves, large drape, sterile gown, mask, and cap) during insertion, use of a chlorhexidine-impregnated dressings, meticulous care of the insertion site, and rapid removal of catheters that are no longer needed, have significantly decreased the rate of CLABSI. The best site for line placement has been debated for years. Though it has been thought that subclavian has the least risk for infection, there may be reasons for choosing a separate site because of the risk for pneumothorax or venous stricture in a patient who may require long-term dialysis access. The internal jugular or femoral sites may be reasonable choices.

Catheter-associated urinary tract infections (CAUTI) are a common cause of bacteremia, leading to significant morbidity, but rarely mortality, in ICU patients. Maintenance of sterility during insertion and careful attention to care of the catheter following insertion are helpful. The most important strategy is assessing the need for the catheter on a daily basis and removing it when appropriate.

NEUROLOGIC ISSUES

Analgesia and Sedation

Surgical patients who require intensive care need appropriate levels of analgesia. Pain management in the ICU can be challenging because patients may not be able to describe or quantify their pain. Numerical pain scales or visual analog scales are commonly used, but these require subjective input from the patient. Behavioral scales, which assess the patient's pain based upon behaviors, may be more objective. Narcotics are frequently prescribed, either enterally or intravenously. The minimum dose of narcotic to achieve an acceptable level of pain should be utilized. Dosing should balance analgesia with the potential for mental status changes, respiratory depression, hypotension, prolonged need for mechanical ventilation, and constipation. Nonnarcotic alternatives, such as acetaminophen, no-steroidal anti-

inflammatories, regional blocks, lidocaine patches, and environmental modifications, should be utilized as much as possible.

Sedation is often used for patients on mechanical ventilation. As with analgesics, the minimum dose required to achieve the desired effect should be utilized. Short-acting agents, such as propofol or dexmedetomidine, are used as a continuous infusion. There are a number of sedation scales available. Regardless of which one is used, the goal is usually to have a calm, but responsive patient. Daily interruption or at least titration of the infusion is an important way to prevent over sedation. Deeper levels of sedation may be required in some circumstances, such as difficulty with ventilation requiring high airway pressures, intracranial hypertension, or an open abdomen.

Delirium

9 Delirium, defined as a state of altered or fluctuating mental status and inattention, plus disordered thinking or altered level of consciousness, is very common in critically ill patients. Delirium may be further classified as hypoactive (lethargic) or hyperactive (agitated). Common causes for delirium include patient factors (e.g., alcoholism, endocrine disorders), acute illness (e.g., sepsis [sometimes occult], stroke, head trauma), complications of acute illnesses (e.g., hypoxemia, hypoglycemia, hypovolemia, electrolyte abnormalities), and iatrogenic factors (e.g., medications). Lack of sleep and loss of the usual day/night cycles contribute substantially to delirium. Trying to maintain normal day/night cycles by keeping the patient active during the day and turning off lights, minimizing disturbance at night, and assisting sleep with mild medication, such as melatonin, can help.

The workup for a patient with delirium should focus on ruling out reversible causes. Any focal findings should be evaluated with a CT of the head. Without focal findings, a CT scan is likely to be unrevealing, but may still be indicated. If the patient remains unarousable, an electroencephalogram should be considered for ruling out nonconvulsive status epilepticus before assuming the issue is hypoactive delirium.

Management is mostly supportive. There are no drugs that directly improve delirium. Pharmacologic therapy is mainly useful for managing patients with hyperactive delirium with the main goals of preventing harm, for example, from an unplanned extubation, and promoting sleep.[113] Drugs that can aggravate the delirium, such as anticholinergics or benzodiazepines, should be avoided. Antipsychotics, such as haloperidol, which can be administered intravenously, are helpful in the acute situation. For ongoing issues, the atypical antipsychotics, such as risperidone, olanzapine, and quetiapine, can be very effective. The risk of arrhythmias related to

prolonged QTc with these agents seems to be small, but still worth monitoring. Dexmedetomidine infusion is also very effective in the acute situation, but its use may be limited by bradycardia, hypotension, or cost.

Delirium is associated with increased length of stay and, possibly, mortality. In addition, delirium can increase the risk for development of the postintensive care syndrome, which may include impairments of memory and concentration, judgment, and even posttraumatic stress disorder.[114]

ORGANIZATIONAL STRUCTURE OF CRITICAL CARE

Though critical care can be provided anywhere, the ICU provides an environment that allows close monitoring and care by experienced physicians, nurses, respiratory therapists, pharmacists, and other ancillary staff. Current ICUs have the following common features: (1) a designated geographical space, (2) specialized monitoring and therapeutic capabilities, (3) resources to provide continuous care, and (4) appropriate staffing. ICU nurse to patient ratios vary from 1:3 to 2:1 depending on patient acuity and therapeutic needs that may be addressed with a scoring system such as the therapeutic intervention severity score (TISS). Dedicated pharmacists, dieticians, physical therapists, and advanced practice providers improve process of care compliance and patient outcomes. Diagnostic and therapeutic capabilities may include invasive and minimally invasive cardiac monitoring, basic and rescue modes of ventilation and adjuncts, extracorporeal circulatory support, dialysis and hepatic support, and neurologic monitoring.

There is controversy, particularly in adult surgical ICUs, as to how superspecialized they should be (e.g., trauma, visceral transplant, cardiac surgery, noncardiac thoracic surgery, neuro). Practically, this is an issue of institutional volume and expertise as there is little data to support superspecialization in surgical units. Some of these decisions are based around the use of specific technology, such as intra-aortic balloon pumps or ECMO in a cardiac surgery ICU or intracranial pressure monitoring in a neuro ICU.

Traditionally there are two types of ICU organizational structures: open and closed formats. In an open ICU, the patients are admitted under the supervision and care of the primary medical or surgical team, which is responsible for decision-making, order entry, and communication with the staff and family. They have the option of consulting other services, perhaps including an intensivist service. This team also continues to care for patients in other areas of the hospital, providing

continuity, but decreasing their focus on care of the most acutely ill and injured in the ICU.

Within a closed ICU, the patient's care is transferred to an intensivist whose only responsibility is to take care of patients within the ICU. Of course, hybrid models exist. Some units have a mandatory intensivist consult. In some units, both the surgical team and the critical care team can write orders or share other responsibilities.

A multidisciplinary team led by an intensivist can function in either closed or open structures. A high-intensity staffing model (with an intensivist-led team or mandatory intensivist consultation) can improve adherence to national guidelines, shorten ICU stay, decrease costs and improve outcomes.[115] A ratio of one intensivist to a maximum of 14 patients should be maintained to ensure timely completion of rounds, staff satisfaction, and provision of high-quality patient care and education of trainees.[116] Extending this model to 24/7 attending intensivist coverage does not seem to improve outcomes, at least in large academic medical centers.[117] There may be a benefit in units with a lower-intensity staffing model during the day. Good communication between members of the healthcare team and patients/families, processes for performance improvement, development of protocols, and institutional support are critical for good outcomes.[118]

The role of telemedicine in the ICU environment continues to evolve. Clinicians, including physicians and advanced practice providers, have developed the skills necessary to be able to closely monitor critically-ill patients from a distance and work closely with the healthcare providers at the patient's bedside. The technology for compliance with the Health Insurance Portability and Accountability Act continues to improve. Also, the requirements for third-party pay or reimbursement have been defined. Use of telemedicine has been associated with decreased mortality, length of stay, patient safety, and, possible fewer malpractice claims.[119] The responses from trainees working with the telemedicine intensivist have generally been positive.

Table 10.11 Organ Failure Scores

Multiple Organ Dysfunction Syndrome Score

Organ System	0	1	2	3	4
Respiratory (PO_2/FiO_2)	>300	226–300	151–225	76–150	<75
Renal (Serum Creatinine) [μmol/L]	<100	101–200	201–350	351–500	>500
Hepatic (Serum Bilirubin) [μmol/L]	≤20	21–60	61–120	121–240	>240
Cardiovascular (Pressure Adjusted Heart Rate) (HRxCVP/MAP)	≤10	10.1–15	15.1–20	20.1–30	>30
Hematologic (Platelet) [$mL \times 10^3$]	>120	81–120	51–80	21–50	≤20
Neurologic (Glasgow Coma Scale)	15	13–14	10–12	7–9	≤6

Sequential Organ Failure Assessment Score

Organ System	0	1	2	3	4
Respiratory (PO_2/FiO_2)	>400	400–300	299–200	200–100 + mechanical ventilation	<100 + mechanical ventilation
Renal (Serum Creatinine) [mg/dL]	<1.2	≥1.2–≤2	≥2–≤3.5	≥3.5–≤5	≥5 or Dialysis
Hepatic (Serum Bilirubin) [mg/dL]	<1.2	≥1.2–≤2	≥2–≤6	≥6–≤12	≥12
Cardiovascular (MAP or vasopressor required)	≥70	<70	dopamine ≤5 μg/kg/min or dobutamine (any dose)	dopamine ≤5 μg/kg/min OR epinephrine ≤0.1 μg/kg/min norepinephrine ≤0.1 μg/kg/min	dopamine >15 μg/kg/min OR epinephrine >0.1 μg/kg/min norepinephrine >0.1 μg/kg/min
Hematologic (Platelet) [$mL \times 10^3$]	>150	100–150	50–99	49–20	≤20
Neurologic (Glasgow Coma Scale)	15	13–14	10–12	6–9	<5

Denver

Organ System	0	1	2	3	4
Respiratory (PO_2/FiO_2) [mm Hg]	>250	250–175	175–100	<100	
Renal (Serum Creatinine) [mg/dL]	<1.6	≥1.6–≤2.1	≥2.11–≤4.2	>4.2	
Hepatic (Serum Bilirubin) [mg/dL]	<2	≥2–≤4	>4–≤8	>8	
Cardiovascular (inotrope required)	None	1 inotrope, small dose	1 inotrope, moderate dose, or >1 inotrope, small dose	1 inotrope, large dose, or >2 inotropes, moderate dose	

Evidence-Based Care

National and international organizations have developed numerous evidence-based guidelines for various aspects of ICU care. Good examples of comprehensive guidelines are those developed by the SSC, discussed above. Recommended bundles of care that accompany guidelines provide actionable items that can be addressed routinely during patient care. Such guidelines and bundles lend themselves to the development of multidisciplinary, multi-professional, institutional protocols and clinical practice guidelines. The electronic health record can often help with order sets or electronic prompts to improve compliance. The use of a daily goals checklist in the ICU enables practitioners to ensure that important components of care are addressed. Discussing the goals assures that all members of the critical care team understand the game plan.[120]

The ABCDEF bundle developed by the ICU Liberation ABCDEF Initiative includes ***A***ssess, prevent, and manage pain; ***B***oth spontaneous awakening and breathing trials; ***C***hoice of Analgesia and Sedation; ***D***elirium assess, prevent, and manage; ***E***arly Mobility and Exercise; ***F***amily engagement/empowerment. Implementation of this bundle is associated with decreased mortality, mechanical ventilation use, coma, delirium, need for restraints, and ICU readmissions, and improved post-ICU discharge disposition.[121]

Severity of Illness

Several ICU scoring systems have been developed to provide a framework to describe patients' severity of illness for the routine evaluation of ICU performance and quality improvement initiatives. They have been designed more for evaluation of an ICU cohort and less for prognostication in an individual case. The most robust prognostication systems compare observed and risk-adjusted hospital mortality for critically ill patient groups derived from analysis of large data sets, based mainly on early physiologic derangements. Other systems have been developed to quantify organ dysfunction in a longitudinal fashion.

The most frequently used severity of illness scores in an adult ICU used to prognosticate hospital mortality are Acute Physiology and Chronic Health Evaluation (APACHE), the Mortality Probability Model (MPM), and the Simplified Acute Physiology Score (SAPS) with higher scores portending increased hospital mortality. Some versions of these systems can be calculated manually, while others require inputting data into a proprietary software program, which can be embedded in the electronic health record.[122] The ideal scoring system should be valid, reliable, calibrated, discriminating, and simple. The future of ICU prognostication may well

involve interpretation of "big data" that relies less on traditional data acquisition and storage and more on linear or logistic regression modeling.

Several organ failure scores for initial and/or serial assessments exist as well for use in clinical trials or quality assessment (**Table 10.11**). The Sequential Organ Failure Assessment and Marshall Multiple Organ Dysfunction Score consider variables in six categories (respiratory, cardiovascular, hematologic, central nervous system, renal, and hepatic). The Denver score excludes the hematologic and neurologic components.[123]

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11

Fluids, Electrolytes, and Acid–Base Balance

Bellal Joseph and Michael F. Ditillo

Key Points

1 The human body is conceptualized as being composed of two primary fluid compartments: extracellular fluid (ECF) and intracellular fluid (ICF). The two compartments are separated by cellular membranes.

2 The ECF can be further divided into smaller compartments: transcellular fluid, plasma, interstitial fluid, and bone/connective tissue fluid. Blood is a composite compartment containing both ECF (plasma) and ICF (red cell volume).

3 Sodium and potassium are the dominant cations of the ECF and ICF, respectively.

4 Extracellular tonicity is under tight regulation by osmoreceptors found in the hypothalamus. As sodium accounts for the majority of ECF tonicity, these receptors function essentially as ECF monitors.

5 Effective circulating volume is sensed by volume receptors (capacitance vessels, atria, hepatic, and central nervous system [CNS]) and pressure receptors (aortic arch, carotid, and intrarenal) that alter sodium and water balance mediated by renin–angiotensin, aldosterone, atrial natriuretic peptide (ANP), dopamine, and renal prostaglandins.

6 Water losses are composed of both sensible (i.e., measurable) losses via urine, stool, and sweat and insensible (i.e., immeasurable) via evaporative loss from the skin, respiratory tract, or open abdomen.

7 Goals of fluid therapy are to normalize body fluid compartment volumes and electrolyte concentrations. This can be achieved with crystalloid (preferable) or colloid infusion to correct deficits and/or match ongoing and expected losses.

8 The major electrolytes (Na^+, K^+, Ca^{2+}, Mg^{2+}, Cl^-, HCO_3^-, and HPO_4^{2-}) should be monitored and replaced, when possible, with respect to the pathophysiology of various disease states.

9 Acid–base balance is carefully buffered within very narrow limits. Acid–base disturbances are frequently mixed, involving combined

respiratory and metabolic derangements.

INTRODUCTION

In this chapter, the normal physiologic mechanisms of fluid and electrolyte homeostasis, inclusive of acid–base physiology, are reviewed. This will be the starting point for a discussion of fluid and electrolyte pathophysiology and the management of specific clinical situations. With a thorough understanding of disease- and injury-related alterations from normal fluid volume and electrolyte physiology, one can effectively care for all surgical and critically ill patients.

BODY FLUIDS

Total Body Water and Body Fluid Compartments

Total body water (TBW) is defined as the total amount of water contained within the body. The relationship between TBW and body weight varies according to the percentage of body fat.[1] The average TBW in adult men is 60% of total body weight and 55% in adult women. In infants, water makes up approximately 75% to 80% of body weight. This figure decreases to approximately 65% by 1 year of age and continues to decrease slowly throughout life, primarily related to decreases in lean body mass and an increase in adipose tissue.[1]

1 TBW is principally distributed into the intracellular and extracellular compartments which are in dynamic equilibrium (**Table 11.1**). ICF makes up approximately two-thirds of the TBW, and the remaining one-third is composed of ECF.[2]

2 The ECF compartment is subdivided into the interstitial and intravascular spaces. Interstitial water volume can be calculated as ECF–intravascular space volume and constitutes approximately 25% of TBW. The

intravascular space accounts for 25% of the ECF and contains the plasma volume, which is approximately 8% of the TBW.

Composition of Body Fluids

3 Sodium and potassium are the dominant cations in the body. As mentioned above, sodium is restricted primarily to the ECF. Sodium content in an average adult is approximately 60 mEq/kg. Approximately 25% is confined to bone and is nonexchangeable. Of the exchangeable fraction, approximately 85% is in the ECF. Potassium, calcium, and magnesium make up the remainder, smaller fraction, of the cations present in the ECF (**Table 11.2**).

In the ICF, potassium is the dominant cation. Total body potassium is normally approximately 42 mEq/kg, and most of this potassium is intracellular and freely exchangeable.

The Gibbs–Donnan equilibrium describes the relationship between charged particles in a solution that are unevenly distributed across a semipermeable membrane.[4] This special type of equilibrium exists between the ICF and ECF because of the high concentration of protein and nondiffusible phosphates in the cell. ECF cations are in electrochemical balance with chloride, bicarbonate, phosphate, and sulfate anions, although chloride is the major contributor to this balance. In addition, anionic proteins contribute to ion balance in plasma but not in interstitial fluid, which is essentially an ultrafiltrate of plasma that normally contains little protein. As a result, the content of both cations and anions in interstitial fluid is slightly higher than in plasma (**Table 11.2**).

Table 11.1 Body Fluid Compartments

	Body Weight (%)	Total Body Water (%)
Total	60	100
Intracellular	40	67
Extracellular	20	33
Intravascular	5	8
Interstitial	15	25
Transcellular	2	4

Interstitial fluid, in comparison, contains little protein. These impermeable intracellular negative charges tend to favor diffusion of permeable anions into the ECF. The concentration of protein is higher on the blood side of the capillary than on the interstitial fluid side. Thus, the concentrations of diffusible ions are not necessarily equal across these membranes because of the presence of these complex anions.

Osmotic Activity of Body Fluids

The concentration of solutes in the fluid compartments depends on the osmotic activity generated by the ion species contained in each compartment. When two solutions are separated by a semipermeable membrane, water moves across the membrane to equalize the concentration of osmotically active particles to which the membrane is impermeable. The maintenance of osmotic equilibrium across a semipermeable membrane is based primarily on the number of solute particles rather than on the molar concentration of the solution on each side of the membrane due to the flow of water.

The unit of measurement of osmotically active particles is the osmole (Osm) or milliosmole (mOsm) rather than the conventional units of solute concentration such as milliequivalents per liter (mEq/L). In solution, osmolarity (mOsm/L) and osmolality (mOsm/kg water) define the osmotic activity of particles. When 1 mol of NaCl dissociates in water to Na^+ and

Cl^-, it produces 2 Osm. The measured osmolality of a solution may not equal the calculated osmolality if the ions do not totally dissociate.

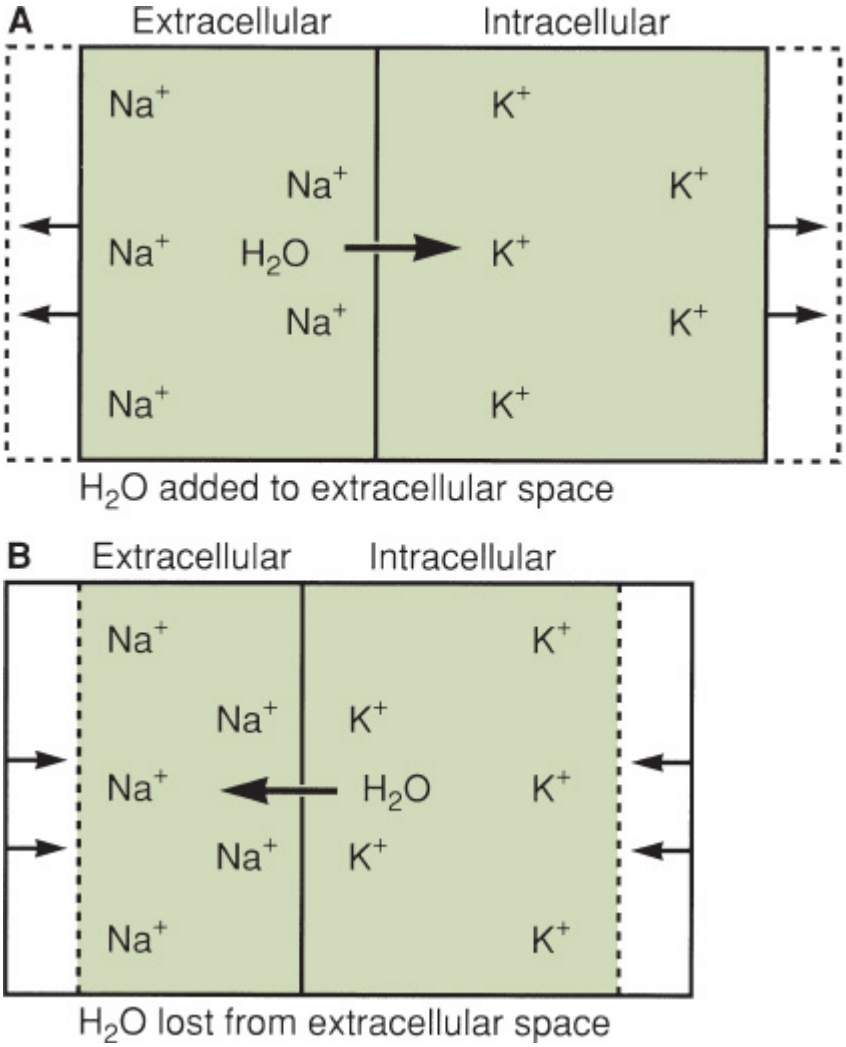


Figure 11.1 **A:** The equilibration of water from the extracellular to the intracellular space after the addition of free water to the extracellular fluid compartment. Osmolality transiently decreases in the extracellular compartment, causing water to move across the cell membranes into the intracellular space. **B:** Similar shifts after free water loss from the extracellular compartment. Water moves from the intracellular space to the extracellular space in response to the osmolal gradient that is established.

Cells are bounded by a semipermeable membrane. Adding free water to the fluid surrounding a cell causes water to move across the cell membrane to equalize the osmolality differential between the intracellular and extracellular compartments. On a larger scale, adding free water to the ECF

of the body causes an immediate expansion of the extracellular space, followed by a redistribution of water into the intracellular compartment (**Fig. 11.1A**). Conversely, loss of free water from the extracellular space ultimately leads to a shift of water from the intracellular to the extracellular space (**Fig. 11.1B**).

Table 11.2 Electrolyte Concentrations of Intracellular and Extracellular Fluid Compartments

	Extracellular Fluid (mEq/L)		
	Plasma	**Interstitial**	**Intracellular Fluid (mEq/L)**
Cations			
Na^+	140	146	12
K^+	4	4	150
Ca^{2+}	5	3	10^{-7}
Mg^{2+}	2	1	7
Anions			
Cl^-	103	114	3
HCO_3^-	24	27	10
SO_4^{2-}	1	1	—
HPO_4^{3-}	2	2	116
Protein	16	5	40
Organic anions	5	5	—

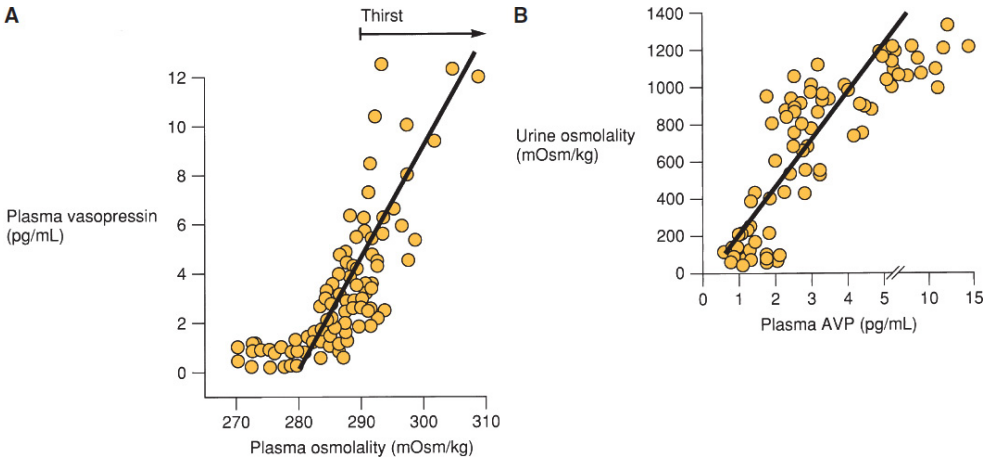


Figure 11.2 The relation of plasma antidiuretic hormone (arginine vasopressin [AVP]) secretion to plasma (**A**) and urine (**B**) osmolality in healthy adults in varying states of water balance. (Reproduced with permission from Robertson GL, Berl T. Water metabolism. In: Brenner BM, Rector FC Jr, eds. *The Kidney*. Philadelphia, PA: WB Saunders; 1986:392.)

Colloid Oncotic Pressure (Colloid Osmotic Pressure)

Plasma proteins are confined primarily to the intravascular space and contribute to the osmotic pressure developed between the plasma and the interstitial fluid. Normal plasma protein levels of 7 g/dL contribute approximately 0.8 mOsm/L.

Osmoregulation

Osmolality of body fluids stays fairly constant at approximately 4 285 to 295 mOsm/L as the result of tightly regulated water balance. Osmoreceptor cells in the paraventricular and supraoptic nuclei of the hypothalamus exert central control over the thirst mechanism and antidiuretic hormone (ADH) secretion from the posterior pituitary.[5] In the presence of excess free water, ECF osmolality falls toward 280 mOsm/kg H_2O, thirst is inhibited, and ADH levels decline. In the absence of ADH, the permeability of renal collecting tubules to water is decreased, causing free water reabsorption to decrease and excretion to increase. Urine osmolality (U_{osm}) can decline to 50 mOsm/kg H_2O (**Fig. 11.2**). As excess free water is eliminated, P_{osm} begins to

rise. Conversely, free water depletion causes an increase in P_{osm}. As P_{osm} approaches 295 mOsm/kg H_2O, thirst is stimulated as is ADH secretion. As ADH levels rise to approximately 5 pg/mL, the renal collecting tubules become maximally permeable to water. Water is reabsorbed from the collecting ducts in response to the concentration gradient developed in the renal medullary interstitium. Thus, the final concentration of urine depends on both the permeability of the collecting ducts (controlled by ADH secretion) and the concentration of the medullary interstitium.[5] Maximal U_{osm} may approach 1,200 mOsm/kg H_2O. The net effect of these mechanisms is to promptly return high or low P_{osm} to normal. The high sensitivity of the osmoreceptors and the responsiveness of the ADH feedback system ensure that even small changes in P_{osm} result in marked alterations in urine concentration. This relation can be expressed as follows:

$$\text{Urine osmolality} = 95 \times \text{Plasma osmolality}$$

Thus, a 1-mOsm change in P_{osm} results in a 95-fold change in U_{osm}.

Angiotensin II and neural input from medullary baroreceptors can also influence ADH secretion and thirst, thus tying water balance to hemodynamic alterations. Relatively small changes in pressure have little effect on ADH secretion, but large decreases in pressure can cause tremendous increases in ADH release. Therefore, ADH release as a response to changes in serum osmolality is regulated by a very sensitive system (only small changes in serum osmolality outside its normal range lead to dramatic changes in ADH release), while the nonosmotic release of ADH occurs in the setting of profound hypotension for the purposes of preserving volume homeostasis with the subsequent effect of water retention regardless of serum osmolality (**Fig. 11.3**).

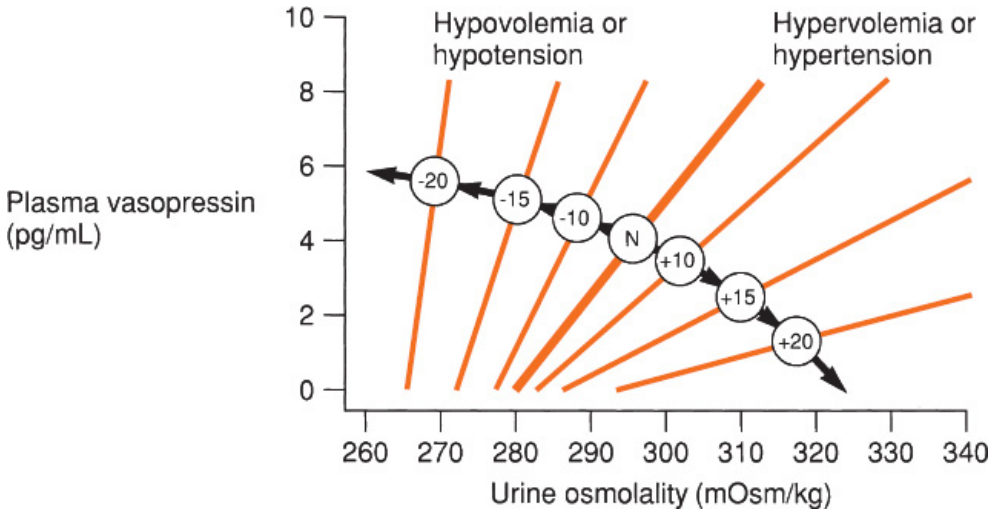


Figure 11.3 Effect of acute changes in blood volume or pressure on the osmoregulation of antidiuretic hormone (ADH; vasopressin). The heavy oblique line in the center represents the relation between plasma ADH and osmolality under normovolemic, normotensive conditions. The lines to the left and right show the shift in the relation when blood volume or blood pressure is acutely decreased or increased by the percentage indicated in the circles. (Reproduced with permission from Robertson GL. Physiology of ADH secretion. *Kidney Int* 1987;32(Suppl 21):520.)

Tonicity of Body Fluids

Tonicity refers to the effect of the particles on cell volume. (NB: O*smolality* defines the concentration of osmotically active particles in solution.) Permeable solutes can freely cross cell membranes, whereas impermeable solutes cannot. Although permeable solutes contribute to the osmolality of a solution, they have no effect on tonicity because they contribute neither to oncotic gradients across cell membranes nor to alterations in cell volume. Sodium is an example of an impermeable solute that affects both osmolality and tonicity. Urea and ethanol are permeable solutes that contribute to osmolality but have little effect on tonicity because they distribute equally across membranes.

Both impermeable and permeable solutes can contribute to *hyperosmolar* and *hypoosmolar* states. However, hypoosmolar states are always accompanied by hypotonicity, whereas hyperosmolar states are not always associated with hypertonicity. There may be marked hyperosmolality without hypertonicity with elevation of blood urea nitrogen (BUN) levels because urea is a freely permeable molecule. In contrast, elevated levels of plasma

glucose in diabetic patients are associated with hyperosmolarity and associated hypertonicity. Insulin increases the transport of glucose across cell membranes, rendering these osmoles *ineffective* and reducing hypertonicity. Plasma hyperglycemia is associated with the movement of intracellular water to the extracellular space. This causes expansion of ECF and plasma volume and a consequent decrease in the concentration of plasma sodium. The osmotic diuresis caused by the elevated glucose level tends to normalize the serum sodium if adequate hydration is maintained.

Plasma osmolality (P_{osm}) is an excellent measure of total body osmolality. Osmolality differentials between fluid compartments are only transient because fluid shifts maintain isosmotic conditions. Sodium is the predominant extracellular cation; thus, estimates of P_{osm} can be made by simply doubling the serum sodium concentration (serum $[Na^+]$):

$$P_{osm}\ (mOsm/L) = 2 \times \text{serum } [Na^+]$$

Because glucose and BUN may make significant contributions to P_{osm} in certain disease states, this formula is modified for glucose and for BUN:

$$P_{osm}\ (mOsm/L) = 2 \times \text{Serum } [Na^+] - \text{Glucose}/18 - \text{BUN}/2.8$$

Discrepancies of greater than 15 mOsm/L between calculated P_{osm} and P_{osm} measured in the clinical laboratory may be the result of the presence of other osmotically active particles, such as mannitol, ethanol, or ethylene glycol, or of a reduced fraction of plasma water secondary to high levels of myeloma proteins or hypertriglyceridemia.

FLUID BALANCE

Sodium Concentration and Water Balance

Abnormalities in serum sodium are usually indicative of abnormal TBW content. This is due to sodium being the primary extracellular cation. As potassium is the predominant intracellular cation, the serum $[Na^+]$

approximates the sum of the exchangeable total body sodium (Na^+_e) and total body exchangeable potassium (K^+_e) divided by TBW:

$$\text{Serum } [Na^+] = (Na^+_e + K^+_e)/\text{TBW}$$

Because the sum of total body solute content ($Na^+_e + K^+_e$) remains relatively stable over time, changes in TBW content is, therefore, inversely proportional to changes in the serum $[Na^+]$ (**Fig. 11.4**).

Volume Control

5 Changes in volume (i.e., hypovolemic/nonosmotic stimuli) are detected by both osmoreceptors and baroreceptors.[3] The osmoreceptors are responsible for the day-to-day fine-tuning of volume by responding to changes in tonicity, whereas the baroreceptors contribute relatively little to the control of fluid balance under normal conditions. As mentioned previously, large changes in circulating volume (10% to 20% blood volume loss) can modify the osmoregulation of ADH leading to nonosmotic stimulation of ADH release. Cardiac atrial baroreceptors control volume by means of sympathetic and parasympathetic neural mechanisms, whereas ANP released by atrial myocytes in response to atrial wall distention may influence sodium-linked volume control by inhibition of renal sodium reabsorption.[6–8]

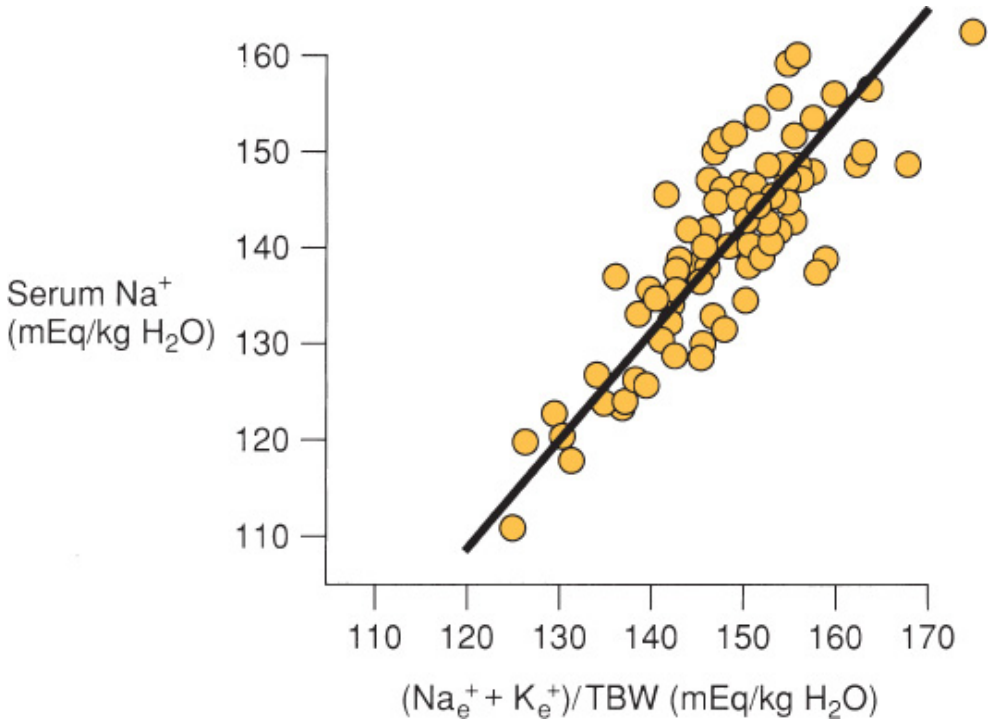


Figure 11.4 Relation between serum [Na^+] and the ratio of ($Na^+_e + K^+_e$) to total body water (TBW). (Reproduced with permission from Edelman IS, Liebman J, O'Meara MP, et al. Interrelationships between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium and total body water. *J Clin Invest* 1958;37:1236–1256.)

Osmoreceptors

Specialized cells in the anterolateral region of the hypothalamus that respond to changes in extracellular tonicity are known as *osmoreceptors*. It is believed that the activity of ion channels in the cell membrane, aquaporins, and changes in cell volume contribute to the function of these receptors. Osmoreceptors can respond to changes in tonicity as small as a few percent. For example, these cells shrink response to increase in plasma tonicity triggering the release of ADH and/or the sensation of thirst.

Baroreceptor Modulation of Volume Control

Effective circulating volume describes that portion of the extracellular volume that perfuses the organs of the body and is sensed by baroreceptors. The effective circulating volume normally corresponds to the intravascular volume.

Changes in the effective circulating volume are sensed by volume receptors in the intrathoracic capacitance vessels and atria, pressure receptors of the aortic arch and carotid arteries, intrarenal baroreceptors, and hepatic and cerebrospinal volume receptors.[8] These stretch receptors respond to changes in pressure and circulating volume and, through a complex system of neural and hormonal actions, alter sodium and water balance in the kidneys. Hormonal effects are mediated by the renin–angiotensin system, aldosterone, ANP, dopamine, and renal prostaglandins.

Hormonal Mediators of Volume Control

Renin–Angiotensin System

Renin is a proteolytic enzyme that is released from the juxtaglomerular cells of afferent arterioles in the kidney in response to several stimuli. These include changes in arterial pressure, changes in sodium chloride delivery to the macula densa of the distal convoluted tubule, increases in β-adrenergic activity, and increases in cellular cyclic adenosine monophosphate.

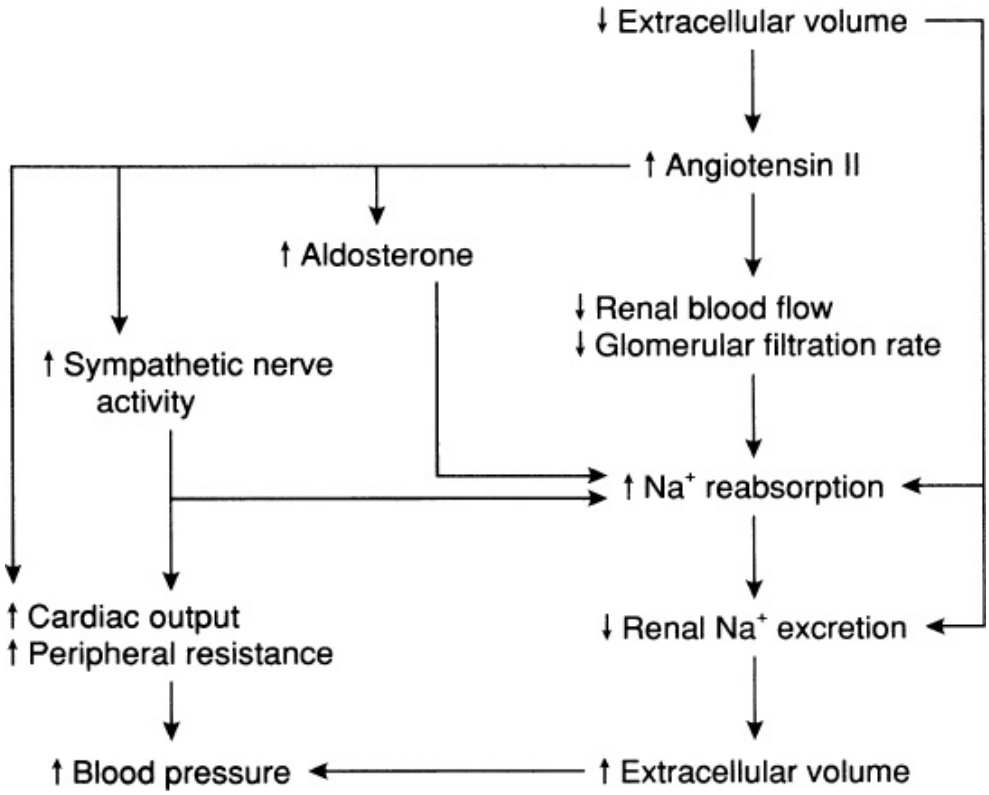


Figure 11.5 Multiple effects of increased angiotensin II release in response to the stimulus of decreased extracellular volume.

Renin cleaves angiotensin I from circulating angiotensinogen, produced by the liver. Angiotensin I is cleaved to the octapeptide angiotensin II by angiotensin-converting enzyme (ACE), which is produced by pulmonary vascular endothelial cells. The multiplicity of actions of angiotensin II is depicted in **Figure 11.5**.

Aldosterone

Aldosterone is a mineralocorticoid produced in the *zona glomerulosa* of the adrenal cortex. Aldosterone increases renal tubular reabsorption of sodium. Aldosterone acts directly on the distal tubule cells by modifying gene expression and stabilizing the epithelial Na^+ channel in the open state and by increasing the number of channels in the apical membrane of these cells.[5] By increasing protein production in these tubular cells, aldosterone induces an influx of sodium, which causes an increase in cellular Na^+-K^+-adenosine triphosphatase activity. The net result is increased sodium reabsorption and the obligate loss of potassium via the renal outer medullary potassium (ROMK) channel. Although the primary regulator of aldosterone secretion is angiotensin II, aldosterone release is also stimulated by increased potassium levels, adrenocorticotropic hormone, endothelins, and prostaglandins.[9]

Atrial and Renal Natriuretic Peptides

ANP is synthesized and released by atrial myocytes in response to atrial wall distention.[7,8] There is evidence that ANP has a direct inhibitory effect on renal sodium reabsorption. Although pharmacologic doses of ANP can cause changes in both renal blood flow and glomerular filtration rate (GFR), physiologic levels do not appear to have any major effect on these parameters. Other active fragments of the ANP prohormone have been found to have natriuretic activity. The best described is urodilatin, also known as *renal natriuretic* peptide.

Renal Prostaglandins

Renal prostaglandins (PG) appear to play a role in volume control, although under normal physiologic conditions, this role may be minimal.

PGE_2 and PGI_2 appear to be the predominant prostaglandins produced in the kidney. PGE_2 increases sodium excretion in the absence of changes in GFR. PGI_2 is a vasodilator, and its effects on renal vascular resistance

increase both renal blood flow and GFR. PGI_2 production is augmented by increases in angiotensin, catecholamines, and sympathetic tone. The administration of nonsteroidal anti-inflammatory agents, which inhibit cyclooxygenase, to patients with conditions known to cause renal dysfunction (e.g., cirrhosis) can precipitate renal failure, presumably because of loss of the protective effects of the renal prostaglandins.

Endothelins

Endothelins are peptide vasoconstrictors that are involved in volume and pressure regulation.[9] Endothelin is produced and released by endothelial and other cells to act on adjacent smooth muscle cells. In addition to increasing peripheral resistance, endothelin infusion has a direct inotropic effect on the myocardium.

Endothelin increases ANP secretion, activates ACE, and inhibits renin release by the juxtaglomerular apparatus. At low doses, endothelin-1 produces natriuresis and diuresis. Endothelin also modulates the biosynthesis of aldosterone, thereby inhibiting water reabsorption through aldosterone-controlled mechanisms. Vasopressin-mediated water reabsorption is also inhibited.[10]

Nitric Oxide

Nitric oxide is a short-lived free radical produced from L-arginine by nitric oxide synthases.[10] Nitric oxide is produced in renal smooth muscle cells, mesangial cells, tubules, and endothelial cells and participates in the regulation of renal hemodynamics and renal handling of water and electrolytes. Nitric oxide contributes to tubuloglomerular feedback, which modulates the delivery and reabsorption of sodium and chloride in the renal tubules. Nitric oxide also regulates renin release by the juxtaglomerular apparatus and mediates the effects of angiotensin on tubular reabsorption.[10]

Normal Water and Electrolyte Exchange

Surgical patients are prone to fluid and electrolyte abnormalities. It is important to recognize that disease states, trauma, and stress-related abnormalities—especially those caused by a surgical procedure—alter many of the body's fundamental homeostatic mechanisms. It is therefore important

to understand normal fluid and electrolyte balance to avoid additional iatrogenic perturbations of these mechanisms.

NORMAL WATER EXCHANGE

6 Water losses are both sensible (measurable) and insensible (unmeasurable). Measurable losses include urinary and intestinal. **Table 11.3** summarizes the normal sensible and insensible losses encountered in a 24-hour period. The volumes of these losses may vary considerably especially in disease states. Under normal conditions, the minimal amount of water needed to excrete normal metabolic waste products is approximately 300 to 500 mL/day.

Table 11.3 Water Losses in a 60- to 80-kg Man

	Average Daily Volume (mL)	Minimal Daily Volume (mL)
Sensible losses		
Urinary	800–1,500	300
Intestinal	0–250	0
Sweat	0	0
Insensible losses		
Lungs and skin	600–900	600–900

Adapted from Shires GT, Canizaro PC. Fluid and electrolyte management of the surgical patient. In: Sabiston DC, ed. *Textbook of Surgery*. Philadelphia, PA: WB Saunders; 1986:77, with permission.

The GI tract has a net secretory action down to the level of the jejunum. After that, the resorptive capacity of the remainder of the small and large bowel acts to keep further water loss to a minimum. Fecal water loss is usually trivial: ~150 mL/day. In disease conditions like bowel obstruction, severe diarrhea, and enterocutaneous fistulas, GI losses of water and electrolytes can be significant causing secondary pathophysiologic conditions.

Sweating and diaphoresis are active processes involving the secretion of a hypotonic mixture of electrolytes and water.

These aforementioned conditions are distinct from the immeasurable, evaporative loss of water from the skin under normal conditions (**Table 11.3**). Evaporative skin losses are increased with an increase in body surface area (especially infants and small children), patient temperature, and the relative humidity of the environment. Overall, normal insensible water losses average approximately 8 to 12 mL/kg/day. Insensible water loss increases 10% for each degree of body temperature above 37.2°C (99°F). Patients who are on respirators or who breathe air that is 100% humidified have no respiratory losses and may gain free water.

FLUID AND ELECTROLYTE THERAPY

Parenteral Solutions

Crystalloids

7 The most widely used parenteral solutions are composed most commonly of sodium and chloride. They are collectively referred to as *crystalloids* (based on the solid, room temperature form of the primary ingredient sodium chloride). Crystalloids are inexpensive and highly effective for fluid maintenance and rapid volume replacement. They also have excellent safety profiles.[11–15] The most commonly used crystalloid solutions available for parenteral administration are found in **Table 11.4**. Selection of the appropriate fluid requires assessment of the patient's maintenance fluid needs, existing fluid deficits, and anticipated ongoing fluid losses.

Isotonic saline (0.9% sodium chloride or *normal saline*) contains 154 mEq of both sodium and chloride. Although this solution can be useful in patients with hyponatremia or hypochloremia, the excess of both sodium and chloride can lead to acid–base disturbances. For example, infusion of large volumes of 0.9% saline can lead to a hyperchloremic metabolic acidosis.

Table 11.4 Electrolyte Content of Commonly Used Intravenous Crystalloid Solutions

	Electrolyte (mEq/L)					
Solution	Na^+	K^+	Ca^{2+}	Mg^{2+}	Cl^-	...
0.9% NaCl	154	—	—	—	154	—
0.45% NaCl	77	—	—	—	77	—
0.33% NaCl	56	—	—	—	56	—
0.2% NaCl	34	—	—	—	34	—
Lactated Ringer	130	4	4	—	109	28
3.0% NaCl	513	—	—	—	513	—
5.0% NaCl	855	—	—	—	855	—

Lactated Ringer solution is a buffered solution composed of the conjugate-base lactate. The solution has a lower sodium and chloride content (130 mEq/L) and adds a very small amount of potassium and calcium (4 mEq/L each). It is ideal for the replacement of acute fluid losses where serum electrolyte concentrations are initially normal. Normal renal function usually ensures that any extra free water from this solution is excreted. Hyponatremia can occur with extended use of lactated Ringer solution. Furthermore, the presence of potassium in lactated Ringer solution has been a concern when used in patients with acute kidney injury, although more recent data have suggested that normal saline (with no potassium in solution) may actually be more likely to cause hyperkalemia in this population due to metabolic acidosis-induced cellular shifts of potassium from the cell. Although the lactate anion in lactated Ringer solution is metabolized to bicarbonate in the liver, this does not appear to contribute to acidosis in normal hepatic function.[16] Studies suggest that the usage of chloride-restrictive intravenous fluids such as lactated Ringer solution was associated with a significant

decrease in the incidence of acute kidney injury and the need for renal replacement therapy.[17]

For maintenance fluid therapy especially prior to an operation with *nil per os* status or following correction of any existing deficits, less concentrated saline solutions are more appropriate to replace ongoing fluid losses (e.g., nasogastric tube losses). The specific crystalloid selected is best determined by calculated requirements. These fluids are hypoosmotic and hypotonic with respect to plasma. In theory, rapid infusion of very hypotonic solutions can result in red blood cell lysis. For this reason, 5% dextrose (50 g of dextrose per liter) has traditionally been added to these solutions to increase tonicity. The addition of dextrose is beneficial in pediatric patients who are unable to adequately control glucose homeostasis due to immature livers. A 5% dextrose solution represents 200 kcal/L of solution.

Hypertonic saline solutions (HTSs) (3% NaCl, 5% NaCl, 7.5% and 23% NaCl) are used as resuscitation fluids or for sodium delivery.[16,18,19] HTS appears to increase intravascular volume more quickly than isotonic solutions. It is believed that the osmotic gradient produced redistributes fluids leading to plasma volume expansion (up to fourfold). This, in turn, may decrease the total resuscitation volume requirement. When HTS is used for resuscitation of patients with severe sepsis, it has been shown to result in improvements in oxygen transport, cardiac output, and pulmonary capillary wedge pressure.[16]

The osmotic effect of HTS may benefit patients with acute severe brain injury.[19] By reducing the water content of the brain, HTS can help to control intracerebral pressure. In addition, HTS has immunomodulatory effects, which are well documented.[20] HTS reduces the systemic inflammatory response syndrome and may attenuate multiple organ dysfunction syndrome. HTSs are not without adverse effects, however. Patients are at risk for electrolyte abnormalities such as hypernatremia, hyperchloremia, and consequent metabolic acidosis.

Colloids

Colloids are composed of large molecules (e.g., albumin) that have a greater tendency to stay in the intravascular space. Their effectiveness at enhancing the plasma volume relative to crystalloid fluids is debatable. Colloid

solutions offer the potential benefits of promoting fluid retention in the intravascular space and reducing excess interstitial fluid (edema). Colloids are typically confined to the intravascular space resulting in transient plasma volume expansion. However, abnormal capillary membrane permeability (sepsis, hemorrhagic shock) allows the extravasation of colloids into the interstitial space worsening edema tissue oxygenation.[21,22] The CRISTAL trial (crystalloids vs. colloids) found no overall difference in survival when comparing crystalloids administration to colloids infusion.[23]

Albumin

Albumin is the primary protein in plasma responsible for oncotic pressure. Exogenous human albumin is derived from human plasma. It is available in a 5% (50 g/L) and a 25% solution (250 g/L) in isotonic saline. These act by increasing plasma oncotic pressures and theoretically slowing or even reversing movement of water into the interstitial space. Albumin has an approximate intravascular half-life of 4 hours in conditions of normal physiologic capillary permeability.

Hetastarch

Hydroxyethyl starches (HES) are synthetic colloids derived from hydrolyzed amylopectin. HES is slightly more effective than 5% albumin as a colloid—it has a higher colloid oncotic pressure than 5% albumin.

Hetastarch has been used as a resuscitative solution with variable results. Coagulopathy and bleeding complications have been widely reported.[24–26] HES administration prompted a prospective study, with results published in 2012.[27,28] The results of these trials prompted the FDA, the Pharmacovigilance Risk Assessment Committee, the European equivalent of the FDA, to suspend marketing authorization of all HES products and issued warnings to its use.[29,30] The Surviving Sepsis Campaign recommends against HES administration in septic patients.[31]

Dextrans

Dextrans are glucose polymers. Their use involves risks of anaphylaxis, hyperglycemia, renal dysfunction and failure, coagulopathy, and increased

thrombosis. The use of dextran solutions is no longer favored given a higher relative risk of mortality compared to HESs.[32]

Gelatins

Gelatin solutions produced from bovine collagen are effective as plasma volume expanders. These are currently only available outside the United States and were used in similar clinical settings to HES, with similar clinical results.[33] Adverse effects include: renal impairment, allergic reactions, and anaphylaxis.[34]

Artificial Oxygen Carriers

Non–red blood cell hemoglobin-based oxygen-carrying solutions (e.g., PolyHeme, Northfield Laboratories, Inc.)[35] are made from polymerized human hemoglobin. PolyHeme's originally was used in military trauma situations with massive blood loss when fresh whole blood is not readily available. On May 9, 2009, Northfield Laboratories, Inc. shut down operations after it failed to secure a biologic license application for PolyHeme from the FDA.

GOALS OF FLUID AND ELECTROLYTE THERAPY

Maintenance Fluid Therapy

Maintenance fluid volume requirements can be calculated based on body weight (**Table 11.5**). A 10-kg child requires 100 mL/kg/day or 1,000 mL/day. A 70-kg man requires 1,000 mL/day for the first 10 kg (100 mL/kg × 10 kg), plus 500 mL/day for the second 10 kg (50 mL/kg × 10 kg), plus 1,000 mL/day for the last 50 kg (20 mL/kg × 50 kg), for a total daily water requirement of 2,500 mL/day. In patients who may be intolerant of hypervolemia (i.e., cardiac disease, elderly patients), the requirement per kilogram over 20 kg is decreased to 15 mL/kg/day.

Maintenance Electrolyte Therapy

One to 2 mEq/kg/day of sodium is required, with any administered excess managed by urinary sodium excretion. Potassium requirements are approximately 0.5 to 1 mEq/kg/day. If sodium is replaced at 2 mEq/kg/day and potassium is replaced at 1 mEq/kg/day, a 70-kg patient requires 2,500 mL of water containing 140 mEq of sodium and 70 mEq of potassium. Each liter of parenteral solution would contain 56 mEq of sodium and 28 mEq of potassium. The solution that best fits this patient's daily maintenance requirements is 0.33% saline solution (56 mEq/L Na^+). Potassium chloride can be added to each liter of solution (20 to 30 mEq/L), with appropriate adjustments for the patient's electrolyte and renal functional status.

Table 11.5 Calculation of Maintenance Fluid Requirements

Body Weight	Fluid Requirement[a]	
For 0–10 kg	Give 100 mL/kg/day	A
For the next 10–20 kg	Give an additional 50 mL/kg/day	B
For weight >20 kg[b]	Give 20 mL/kg/day	C

[a]Maintenance fluid requirements = A + B + C.

[b]For elderly patients or patients with cardiac disease, this amount should be reduced to 15 mL/kg/day.

Additional Electrolyte Therapy

Short-term maintenance therapy generally does not require addition of calcium, phosphate, or magnesium. In patients with acute and/or chronic disorders, patients who experience significant volume shifts, or patients who require long-term parenteral fluid therapy, these electrolytes should be measured and corrected by the most practical, physiologically natural route. In general, the enteral route is preferred given normal physiology. If the enteral route is unavailable, these additional electrolytes are administered in parenteral nutrition solutions along with trace elements, vitamins, and appropriate caloric sources. Corrections and allotment must be made for disease states that may alter the need or absence of electrolytes (e.g., potassium in renal failure patients) in replacement solutions.

CORRECTION OF VOLUME ABNORMALITIES

Volume Deficits

Hypovolemia is common among surgical and trauma patients due to direct blood loss or other fluids. Large volumes of fluid can be sequestered in extravascular spaces (third-space losses) because of inflammation, sepsis, or shock-related endothelial injury and increased endothelial permeability.[36] Examples of disorders that cause third-space losses include bowel obstruction with edema of the bowel wall and transudation of fluid into the bowel lumen, pancreatitis (especially with retroperitoneal fluid extravasation) and extensive tissue destruction in trauma. With the resolution of the pathologic condition and normalization of microvascular permeability, these fluid losses abate. Sequestered extravascular fluid returns—albeit at variable rates—to the intravascular space.

Volume deficits can manifest either acutely or over time. Chronic volume deficits may manifest with decreased skin turgor, sunken eyes, oliguria, weight loss, hypothermia, tachycardia, and orthostatic hypotension. In addition, serum BUN and creatinine values may be elevated, with a high BUN/creatinine ratio (above 15:1). The absolute hematocrit level has been shown to be a poor predictor of intravascular volume status.

Acute volume losses usually manifest by an increase in heart rate and eventually hypotension and decreased urine output. Fluid resuscitation for hypovolemia is initiated with an isotonic solution (normal saline, lactated Ringer solution). Urine flow in critically ill patients is monitored with an indwelling Foley catheter with a goal of at least 0.5 mL/kg/hr output. In addition, a thorough history and physical examination will help determine the origins of the volume deficits, specifically addressing underlying causes and resultant losses.

Volume Excess

Volume excess may occur with significant resuscitative fluid, blood product administration, or excessive parenteral volume administration. Volume overload will occur if adjustments to fluid therapy are not made as the clinical status of the patient changes. Possible manifestations of volume

overload are weight gain, truncal and peripheral edema, and pulmonary congestion. Intravascular volume excess is treated by a combination of volume restriction and diuresis.

REPLACEMENT OF ONGOING FLUID LOSSES

Ongoing losses from stomas, fistulae, open body compartments (e.g., abdomen, chest) and all tubes (e.g., nasogastric) and drains—are recorded during the course of care. Once the net "ins and outs" have been calculated, any existing volume deficits should be replaced with fluid replacement. The electrolyte content of these fluids can be estimated or measured and used to guide the choice of replacement fluid type (**Table 11.6**).

Intraoperative Fluid Therapy

Fluid losses during operative procedures result from evaporative losses in open wounds, blood loss, and extravascular, third-space sequestration. Relative operative blood loss can frequently be measured. Evaporative losses as well as shifts of intravascular fluid to the extravascular space are difficult to measure but should be anticipated. Intraoperative replacement with crystalloid solutions is usually accomplished at rates of 500 to 1,000 mL/hr as this is roughly equivalent to the hourly insensible loss rate during open celiotomy cases. The choice of intraoperative fluid is dependent on many factors. Administration of buffered solutions (e.g., Ringer lactate solution) is as efficacious and safe as nonbuffered, saline-based fluids and may prevent postoperative hyperchloremic metabolic acidosis. Close monitoring of blood pressure, blood loss, urine output, and invasive monitoring techniques aids the surgeon and anesthesiologist in gauging fluid shifts and potential problems associated with intraoperative volume depletion.

Table 11.6 Electrolyte Concentrations in Gastrointestinal Secretions

	Electrolyte (mEq/L)					
Secretion	Na^+	K^+	Cl^-	...	H^+	Rate (mL/day)
Salivary	50	20	40	30	—	100–1,000
Gastric						
Basal	100	10	140	—	30	1,000
Stimulated	30	10	140	—	100	4,200
Bile	140	5	100	—	—	500–1,000
Pancreatic	140	5	75	—	—	1,000
Duodenum	140	5	80	—	—	100–2,000
Ileum	140	5	70	—	—	100–2,000
Colon	60	70	15	—	—	—

Postoperative Fluid Therapy and Monitoring

Routine monitoring of intraoperative and postoperative fluid status consists of serial vital signs (e.g., blood pressure and heart rate), measurements of all tubes, lines, and drains (e.g., urine output) and inclusive of all intravenous and enteral drips. The net gains (all inputs) minus the losses allow daily and length-of-stay volume assessments to be made. Daily weight should also be recorded and compared to the patient's starting or "dry" weight prior to their surgery, if possible. In the postsurgical patient, rapid fluctuations in weight are generally related to changes in TBW. In the absence of any extenuating circumstances (e.g., renal dialysis, kidney transplantation), adequate fluid is usually given to maintain a urine output of greater than 0.5 mL/kg/hr in adult patients.

Urine specific gravity can also be measured and serves as an indicator of both volume status and renal ability to concentrate and dilute the urine. A urine specific gravity of greater than 1.010 to 1.012 indicates that the urine is being concentrated (relative to plasma), and a urine specific gravity of less than 1.010 indicates that dilute urine is being produced.

Renal failure in the postoperative period may be accompanied by low urine volume (oliguric renal failure, <0.5 mL/kg/hr, or <500 mL/day). Additionally, normal or high urine volumes (nonoliguric or high-output renal failure) may also indicate renal dysfunction. Measuring the fractional excretion of sodium compared to creatinine (i.e., FeNa) can help delineate the potential etiology of renal dysfunction by discerning prerenal states (FeNa usually <1%) from acute tubular necrosis (FeNa usually >2%).

$$FeNa = (Urine_{Na})(Serum_{Creat})/(Urine_{Creat})(Serum_{Na})$$

Central venous pressures (CVPs) have also been extensively used to gauge fluid status and responsiveness. Normal CVP may range from 5 to 12 mm Hg. Higher pressures usually indicate volume overload or cardiac failure, whereas pressures below this range indicate intravascular volume depletion. However, the use of CVP measurements alone has been shown to be highly variable and inaccurate in assessing intravascular volume and venous return.

More recently, assessments of fluid status, responsiveness, and overall tissue perfusion are being accomplished by the use of (1) bedside echocardiography (e.g., transthoracic) to measure function through ventricular filling and ejection, (2) ultrasound of the vena caval diameter, and (3) peripheral arterial pulse-volume variability calculations. The latter measures the stroke volume variability (SVV) during the ventilatory cycle via a peripherally placed arterial line. SVV is the calculated percentage of the difference between the maximal and minimal stroke volumes (SVs) divided by the mean SV. This is usually calculated over a time period between 20 and 30 seconds.[37] Use of the SVV has been shown to be a reliable indicator of fluid responsiveness.

The efficacy of these techniques may be altered in abnormal right and/or left ventricular compliance, increased intrathoracic pressure (via elevated levels of positive end expiratory pressure and intraabdominal pressure), valvular heart disease (e.g., mitral stenosis) and cardiac dysrhythmias (e.g.,

atrial fibrillation). In order to solve any serious questions of volume status, the gold standard technique remains pulmonary artery catheterization in the critically ill patient.

Table 11.7 Electrolyte Concentrations in Plasma and Intracellular Compartments

	Normal Ranges	
Solute (mEq/L)	**Plasma**	**Intracellular**
Na^+	135–145	10–15
K^+	3.5–5.0	120–150
Ca^{++}	2.5 (8.5–10.5 mg/dL)	$0.0001–10^{-7}$
Mg^{++}	1.3–1.9	7
Cl^-	98–110	3–20
HCO_3	22–28	10–15
pH	7.37–7.43	7.0–7.2
Osmolarity	280–290	280–290

ELECTROLYTES

8 An electrolyte is defined as a substance that ionizes when dissolved in an appropriate solvent, the most common example being water.

In order to maintain homeostasis, the human body has a complex yet stable arrangement of electrolytes in different concentrations in the intracellular and extracellular environments (**Table 11.7**). In clinical practice, only measurements of serum values (extracellular space excluding the interstitial space) are performed and used to infer disruptions of homeostasis, which cause organ damage. For instance, with hyperkalemia, the serum concentration itself does not directly cause injury. It initiates depolarization

leading to impairment of cardiac conduction resulting in an end pathway of ventricular fibrillation or asystole.

Given that serum derangements can only be discovered if lab evaluation or symptoms are present, it is important to try to anticipate potentially life-threatening electrolyte abnormalities. This is especially important in surgical patients in whom the loss of electrolyte-rich GI fluids occurs and can cause predictable serum derangements (**Table 11.8**).

Table 11.8 Electrolyte Concentrations in Gastrointestinal Secretions

Secretion	Na^+	K^+	Cl^-	H^+	Rate (mL/day)
Salivary	50	20	40	—	100–1,000
Gastric					
Basal	100	10	140	30	1,000
Stimulated	30	10	140	100	4,200
Bile	140	5	100	—	500–1,000
Pancreatic	140	5	75	—	1,000
Duodenum	140	5	80	—	100–2,000
Ileum	140	5	70	—	100–2,000
Colon	60	70	15	—	—

Where Sodium Goes, Water Follows

There is a distinct correlation between sodium and fluid status. This relationship can help establish both the etiology and treatment of various derangements. For example, when thinking about hyponatremia, it is clinically important to assess the patient's volume status as well as check laboratory studies. These include serum sodium, serum osmolality, and urine electrolytes. Other values such as serum glucose, serum protein, and serum

lipids may also help to differentiate hyponatremia from pseudohyponatremia.[38,39]

Pseudohyponatremia

Marked elevations in serum lipid or protein result in a reduction in the fraction of serum that is water/sodium and thus causes a "dilutional" hyponatremia. Examples include hyperlipidemia, hyperproteinemia (e.g., multiple myeloma), hyperglycemia, and mannitol administration. In the case of hyperglycemia, the serum sodium concentration should fall 1.6 mEq/L for every 100 mg/dL rise in serum glucose concentration.

Hyponatremia

The most common pathophysiology is retention of water, which most commonly stems from oral intake or iatrogenic use of intravenous hypotonic fluids. The kidney has an enormous ability to dilute urine, however, in most surgical/trauma patients who experience hyponatremia, there is an inability to suppress ADH, as it is normally elevated during a stress response. In this case, the sodium rarely falls below 130 mEq/L because the hyponatremia itself, as well as volume expansion, decreases the effects of ADH on the renal collecting tubules.

In significant cases (i.e., serum sodium <130 mEq/L) it is helpful to take a more systematic approach. This entails assessing serum and urine osmolality as well as urine sodium (**Algorithm 11.1**).

Symptoms of hyponatremia occur in multiple organ systems including the CNS, GI, and musculoskeletal (**Table 11.9**). In acute hyponatremia, symptoms often start when serum sodium is less than 130 mEq/L; whereas in chronic hyponatremia symptoms typically do not occur until serum sodium is less than 120 mEq/L.

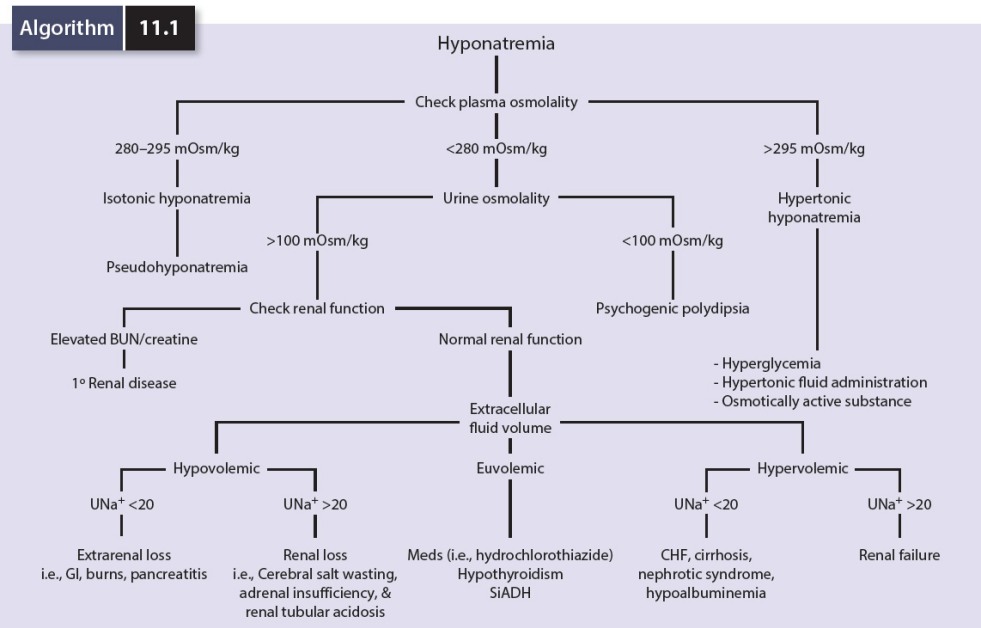
Treatment

Treatment depends on the patient's volume status. Hypovolemic patients are treated by rehydration with isotonic saline, with caution not to correct serum sodium faster than 0.5 mEq/L/hr and less than 10 mEq/L over 24 hours. If correction is faster than this rate the patient may develop *central pontine myelinolysis*. This can lead to "locked in" syndrome, which consists of

quadriplegia, dysarthria, and dysphagia. In order to best prevent this rare, yet highly morbid complication, use of the following calculation is recommended:

Table 11.9 Causes of Hypernatremia

Volume Status	Cause
Low	Free water loss Insensible—skin, respiratory Gastrointestinal loss Excessive hyperosmotic peritoneal dialysis Renal: diuretics, diabetes insipidus, nonoliguric renal failure
Normal	Same as "Low" volume status but with improper correction
High	Free water loss Increased mineralocorticoids—hyperaldosteronism, hypercortisolism Iatrogenic Excessive sodium administration



Algorithm 11.1 Hyponatremia.

$$Na^+ \text{ required (in mEq)} = (\text{Desired } Na^+ - \text{Actual } Na^+) \times \text{TBW}$$

$$\text{TBW} = 0.6 \times \text{Weight (kg)}$$

Rapid correction with 3% or higher-concentration solutions should be avoided unless significant CNS symptoms such as coma or seizures are present and should be done using the calculation above to prevent overcorrection. A reasonable initial dose in an emergent situation would be 100 mL of 3% saline given as a bolus; this can be repeated in 10-minute intervals with definite need for follow-up laboratory evaluation to prevent overly rapid correction.

Cerebral Salt Wasting and Syndrome of Inappropriate Antidiuretic Hormone

Cerebral salt wasting (CSW) and syndrome of inappropriate antidiuretic hormone (SIADH) are both seen in the setting of CNS disease, which is especially pertinent to trauma patients. CSW is much rarer and typically occurs within the first 10 days of CNS insult/injury. The pathophysiology is likely related to impaired sodium reabsorption leading to volume depletion, followed by increased ADH release causing hyponatremia from water retention. Laboratory findings are nearly identical among CSW and SIADH.

Both have elevated urine osmolality compared to serum. However, CSW is associated with ECF depletion and thus hypotension and/or elevated hematocrit, whereas SIADH patients are often net positive in fluid balance. Given the volume status associated with CSW the treatment is usually isotonic fluids which will suppress the release of ADH. On the contrary if isotonic fluid is given for SIADH it can actually worsen the hyponatremia. Other options to treat CSW include salt tablets and if needed fludrocortisone.

The initial treatment for SIADH is often fluid restriction of <800 mL/day. For more significant cases the use of oral salt tablets or 3% hypertonic saline is recommended. Finally, vasopressin receptor antagonists such as Conivaptan (IV) and Tolvaptan (PO) can be used; however, these do carry risks such as hepatotoxicity and can rapidly overcorrect serum sodium levels. Furthermore, they are fairly expensive in the United States and hence should only be used in select cases.[38,40]

Hypernatremia

Although a less common problem in surgical patients, hypernatremia has a variety of etiologies which, like hyponatremia can be categorized based on the patient's volume status (**Table 11.9**). The most common scenario is excessive free water loss associated with hypovolemia.

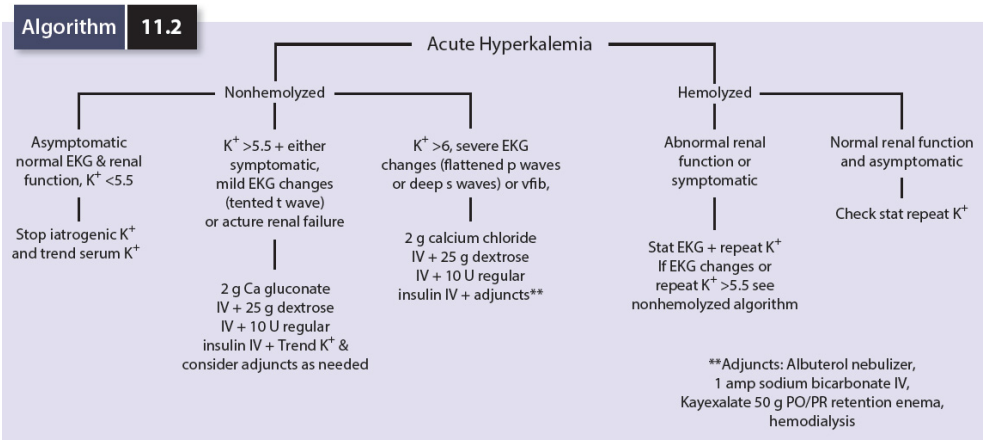
Symptoms of hypernatremia typically do not develop until serum sodium exceeds 160 mEq/L or serum osmolality is higher than 320 to 330 mOsm/kg. Acute hypernatremia can cause symptoms at lower levels than chronic hypernatremia. The majority of symptoms experienced are CNS related with early signs being irritability, restlessness, and spasms. Later symptoms include ataxia and seizures.

The treatment of hypernatremia, like hyponatremia should not occur too rapidly, otherwise complications can ensue. A rate >0.7 mEq/L is considered dangerous as it can lead to cerebral edema and brainstem herniation. The most judicious way to correct hypernatremia involves calculating the free water deficit to obtain a desired sodium level.

$$\text{Water requirement} = (\text{Desired change in } Na^+ \times \text{TBW})/\text{Desired } Na^+$$

$$\text{TBW} = 0.6 \times \text{Weight (kg)}$$

A caveat to this equation is that it does not take into account ongoing free water losses such as urinary or GI loss. Further calculations can be done to quantify urine losses if this is a major concern.



Algorithm 11.2 Acute hyperkalemia.

Potassium

Potassium is the most abundant intracellular cation with a normal intracellular concentration of 150 mEq/L as opposed to an extracellular level ranging from 3.5 to 5 mEq/L. This large gradient produces a strong membrane potential especially in cardiac, skeletal, and smooth muscles. The overall potassium balance is determined by potassium intake and renal/extrarenal excretion. Renal excretion accounts for 90% of excreted potassium. Thus, renal failure leads to hyperkalemia. Humoral factors such as aldosterone, vasopressin, and β-agonists stimulate renal excretion of potassium. Intracellular shifting is another strong causative agent for extracellular potassium change. For instance, insulin and alkalosis both cause K^+ to shift intracellular, one for glycolysis, the other in exchange for H^+ as a buffer. Conversely, acidosis causes K^+ to shift extracellular in exchange for H^+, again to buffer serum pH.

Hyperkalemia

Renal insufficiency is the leading cause of hyperkalemia in surgical patients. Potassium-rich intravenous fluids, especially blood transfusions can also lead to hyperkalemia. Disease processes associated with cellular injury such

as crush injuries, reperfusion syndrome, tumor lysis syndrome, and burns are all potential causes of hyperkalemia. Additionally, medications such as succinylcholine and ACE inhibitors can worsen existing hyperkalemia.

Regardless of the etiology, the common pathway for clinical manifestations is dysfunctional membrane depolarization, the most lethal scenario effecting cardiac membrane depolarization. On an electrocardiogram (EKG) this can be seen in the mildest form with peaked T waves, in a more severe state with flattened P waves, prolongation of the QRS, or deep S waves. The final pathway can yield ventricular fibrillation with or without cardiac arrest.

The initial medication of choice for hyperkalemia is intravenous calcium for membrane stabilization, which lasts approximately 30 to 60 minutes. Subsequent therapy can include insulin coadministered with dextrose, β_2-agonist, and sodium bicarbonate, which are designed to shift extracellular potassium into the intracellular space. Resin-binding agents such as Kayexalate act to decrease potassium absorption and thus are more important in the management of chronic hyperkalemia.[41,42] Loop diuretics can assist by promoting renal potassium excretion, but should only be used if the patient is not hypovolemic. A last resort in situations of complete renal failure or critical levels of potassium is hemodialysis. The treatment utilized depends upon the laboratory value, but more importantly the clinical scenario and EKG findings (**Algorithm 11.2**).

Hypokalemia

Similar to hyperkalemia, manifestations of hypokalemia result from the disturbance in the gradient between intracellular and extracellular potassium. The reference level of 3.5 mEq/L is often cited as the lowermost level of normal serum potassium. Below this level minor disturbances including intestinal ileus, premature ventricular complexes, and nonfatal arrhythmias can occur. Severe cardiac and muscle manifestations often do not occur until levels fall below 2.5 mEq/L. Findings at this dangerous level include significant muscle weakness and major EKG changes. Possible changes include prolonged QT, flattened T waves, ST depression, prominent U waves, and most dangerously ventricular arrhythmias.

Initial treatment consideration must include elucidation of possible etiologies (**Table 11.10**); certain etiologies are especially important, as without correction of the underlying cause, the hypokalemia itself may not be correctable. Examples of this include hypomagnesemia, acute alkalosis, hyperaldosteronism, and mucus secreting villous adenoma. The mainstay of initial treatment for hypokalemia is enteral or intravenous potassium replacement. If the patient is symptomatic, then the replacement or at least a portion of it should be given intravenously to achieve a more rapid effect. Limiting the rate of intravenous potassium infusion is necessary to prevent caustic injury to veins. Maximal recommended rates include 10 to 20 mEq/hr via a peripheral IV or up to 40 mEq/hr via central access.

Table 11.10 Causes of Hypokalemia

Major Causes of Hypokalemia
Vomiting/diarrhea
Diuretics (i.e., loop diuretic)
Catecholamines (endogenous or exogenous)
Renal tubular acidosis
Refeeding syndrome
Insulin
Hypomagnesemia
Acute alkalosis

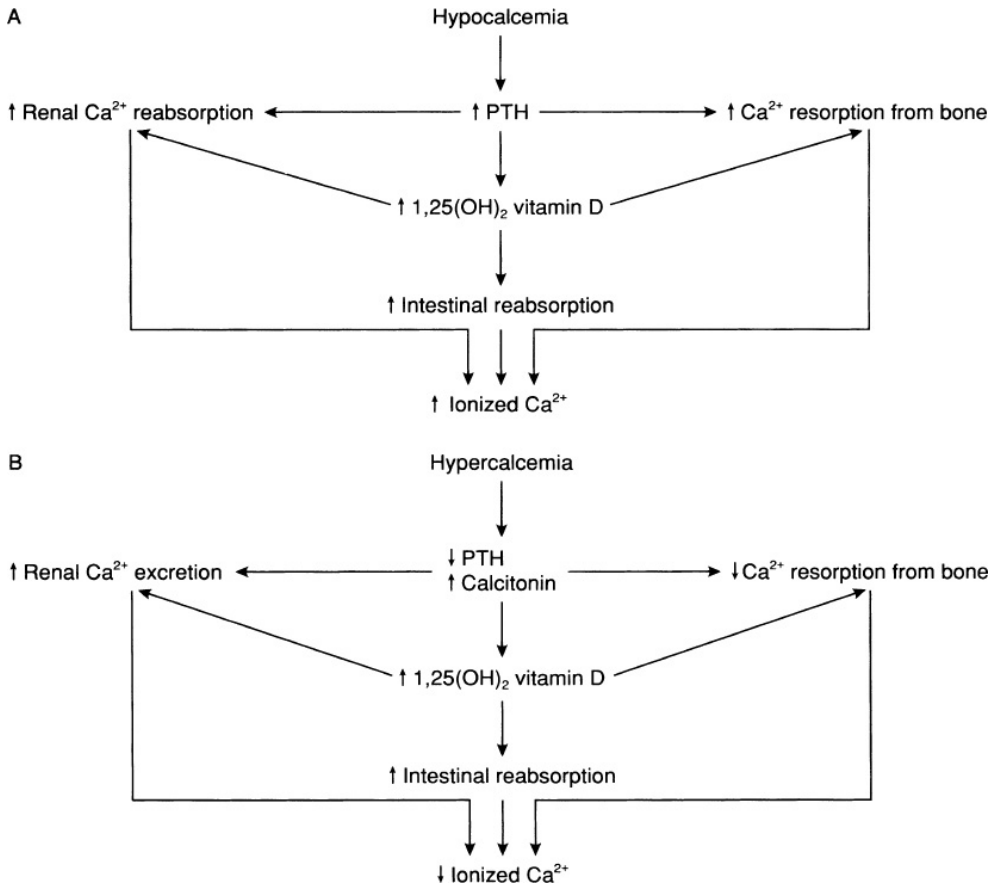


Figure 11.6 Effects of hypocalcemia (**A**) and hypercalcemia (**B**) on the mediators of calcium homeostasis. PTH, parathyroid hormone.

Calcium

Calcium (Ca^{2+}) is essential for human life. Calcium participates in numerous processes including cardiac membrane depolarization, muscle contraction, enzymatic reactions, coagulation, and formation of bone/teeth. Approximately 99% of total body calcium is located in bone. Ionized calcium, which makes up approximately 45% of total calcium, is responsible for most of the physiologic actions of calcium in the body. Normal serum concentration of ionized calcium is approximately 4.5 mg/dL and this level is tightly regulated. Both pH and plasma protein level can affect the proportion of calcium in the ionized state. A change in albumin concentration of 1 g/dL changes protein-bound calcium by 0.8 mg/dL in the same direction. The fundamentals of the regulation of calcium homeostasis are depicted in **Figures 11.6** and **11.7**.

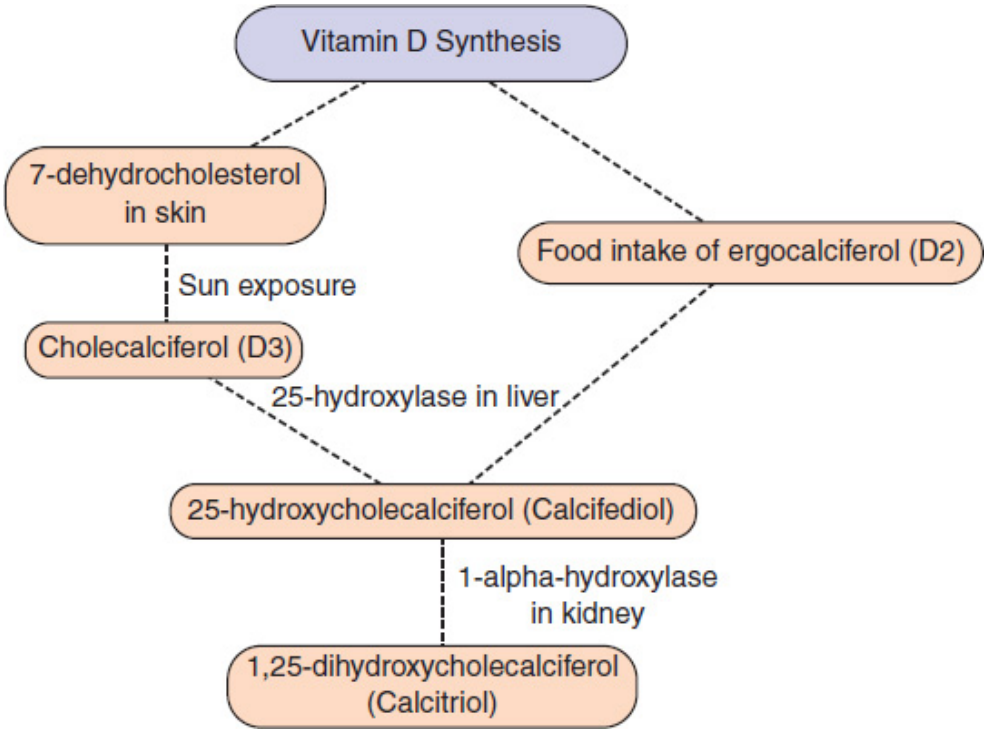


Figure 11.7 Vitamin D synthesis.

Hypercalcemia

The most common causes of hypercalcemia are hyperparathyroidism and malignancy (**Table 11.11**).[43,44]

Primary hyperparathyroidism occurs when one or more parathyroid glands inappropriately produce increased amounts of PTH. Parathyroid adenomas are responsible for ~85% of cases. Chief cell hyperplasia accounts for an additional 15% of cases, while parathyroid cancer is the cause in less than 1% of cases of primary hyperparathyroidism.

Table 11.11 Other Causes of Hypercalcemia

PTH mediated	Lithium Familial hypocalciuric hypercalcemia (FHH)
Cancer	PTHrp-mediated breast, lung, renal cancer Bone metastases Multiple myeloma
Calcitriol mediated	End-stage renal disease Sarcoid/granulomatous Lymphoma (ectopic 1,25 vit D) Milk alkali syndrome Exogenous vitamin D
Other causes	Vitamin A toxicity Thyrotoxicosis Paget disease Adrenal insufficiency Medications (i.e., Thiazide)

Table 11.12 Differential Diagnosis of Hypercalcemia

Cause	Ca^+	Phos	PTH	24-h UCa
Primary PTH	Increased	Decreased	Elevated/normal	Elevated
Secondary PTH	Low or normal (can be high w/ prolonged disease)	High	Elevated	N/A
FHH	Increased	Normal	Elevated/normal	Decreased
PTHrp mediated	Increased	Decreased	Decreased	Elevated
Tertiary PTH	Increased	Decreased	Very Elevated	Elevated

PTHrp, parathyroid hormone-related peptide; UCa, urine Ca^+.

Secondary hyperparathyroidism occurs when there is elevated PTH due to another organ system, namely renal failure. This occurs because of poor

renal excretion of phosphate and decreased intestinal absorption of calcium secondary to impaired renal hydroxylation of vitamin D.

Tertiary hyperparathyroidism is parathyroid hyperplasia with autonomous PTH production. Most commonly, patients who had renal failure with secondary hyperplasia then undergo renal transplant and still have hypercalcemia. This occurs in up to 30% of patients with prerenal transplantation hyperparathyroidism (**Table 11.12**).

Regardless of cause, hypercalcemia has characteristic clinical manifestations that affect various organ systems. Classically taught as "stones, moans, and psychiatric undertones," meaning renal, abdominal/GI, and neuropsychiatric manifestations (**Table 11.13**). The earliest symptoms are usually neuromuscular and mild GI symptoms. Cardiac and renal complications typically occur later in disease progression.

Treatment

Serum calcium concentration >14 mg/dL requires prompt treatment. If combined with hyperphosphatemia, this situation is even more concerning due to the potential for metastatic calcification. Initial treatment should include aggressive hydration with 0.9% normal saline with 20 mEq/L potassium with a goal of hydration to promote a urine output greater than 200 mL/hr. Once the patient is adequately hydrated a trial of furosemide can be performed as long as a positive fluid balance is maintained, and potassium and magnesium are adequately replaced. Other adjuncts include calcitonin (especially for inhibition of bone resorption), bisphosphonates (especially to treat malignancy), and in patients with renal failure the use of low-calcium dialysate. Patients with hematologic malignancies and granulomatous disease can be considered for treatment with steroids. Lastly, for those with hyperparathyroidism, parathyroidectomy of some form is clearly indicated, with operation type dependent upon whether the etiology is adenoma or hyperplasia. In medically refractory secondary or tertiary hyperparathyroidism, total parathyroidectomy with parathyroid autotransplantation or sub-total parathyroidectomy should be considered.[46]

Table 11.13 Signs and Symptoms of Hypercalcemia	
Constitution symptoms	Weakness, fatigue, anorexia
CNS	Drowsiness, lethargy, altered mental status, stupor, coma
Cardiac	Short QT interval
Renal	Nephrolithiasis, polyuria, renal failure, nephrogenic diabetes insipidus, nephrocalcinosis
GI	Constipation, abdominal pain, pancreatitis
Ophthalmologic	Calcium deposits in cornea

Hypocalcemia

There are many causes of hypocalcemia (**Table 11.14**). Other factors can affect the serum calcium level as mentioned previously, namely pH and albumin. In critically ill patients the incidence of hypocalcemia can be up to 85%. From a surgical perspective the most common causes are postsurgical, including hungry bone syndrome and loss of calcium from circulation.

Postsurgical hypocalcemia can occur in any neck surgery, although the incidence is higher with parathyroidectomy. In non-neck surgery hypocalcemia can occur because of hypoalbuminemia; this does not affect ionized calcium levels. Other postsurgical causes of hypocalcemia include atrophy of the remaining parathyroid glands (i.e., after removal of a large parathyroid adenoma), venous congestion, devascularization or *hungry bone syndrome*. Transient hypoparathyroidism is seen in up to 20% of thyroid cancer surgery; this is permanent in 1% or less of cases.

Table 11.14 Causes of Hypocalcemia	
Low PTH (hypoparathyroidism)	Postsurgical (thyroidectomy, parathyroidectomy, radical neck dissection, hungry bone syndrome) Autoimmune Infiltration of the parathyroid gland (granulomatous, iron overload, metastases) Radiation-induced destruction parathyroid glands HIV infection
High PTH (secondary hyperparathyroidism in response to hypocalcemia)	Vitamin D deficiency Pseudohypoparathyroidism Hypomagnesemia Renal disease Loss of calcium in circulation (i.e., hyperphosphatemia, tumor lysis, acute pancreatitis, osteoblastic metastases, acute respiratory alkalosis, sepsis)
Drugs	Bisphosphonate, calcitonin, phenytoin, foscarnet, calcium chelators

Other surgery-related etiologies include pancreatitis, small bowel fistula, renal failure, massive transfusion of blood, and severe hypomagnesemia. Pancreatitis-induced hypocalcemia occurs due to calcium precipitation in peripancreatic tissue. Small bowel fistula can lead to hypocalcemia by loss of calcium-rich effluent and vitamin D deficiency from malnutrition. Renal failure hypocalcemia is due to deficiency in 1,25-dihydroxyvitamin D and hyperphosphatemia. Massive transfusion hypocalcemia does not affect total

calcium but decreases ionized calcium as a result of citrate binding to ionized calcium.

Symptoms typically do not occur until calcium levels are below 8 mg/dL. Chronic symptoms include cataracts, dental changes, and extrapyramidal disorders. Symptoms of acute hypocalcemia are tetany, papilledema, and seizures. Tetany is defined as repetitive discharges after a single stimulus. Tetany usually does not occur until ionized calcium is less than 4.3 mg/dL or serum total calcium is less than 7.0 mg/dL. Alkalosis also plays a strong role in the development of tetany, even beyond its association with hypocalcemia, as tetany is rarely seen in renal failure patients despite low calcium levels. This is likely due to the protective effect of concurrent metabolic acidosis. The earliest symptoms of hypocalcemia are perioral and acral paresthesias. Motor symptoms such as *Trousseau sign* (induction of carpopedal spasm by inflation of sphygmomanometer above systolic pressure for 3 minutes) and *Chvostek sign* (tap facial nerve and ipsilateral facial muscles twitch) occur later. Of note, Chvostek sign is seen in up to 10% of normal patients. The last findings to occur are cardiac, in the form of ST segment prolongation (**Table 11.15**).[45]

Asymptomatic hypocalcemia needs no treatment as it is most commonly attributed to hypoalbuminemia with normal ionized calcium. Symptomatic hypocalcemia is best treated with intravenous infusion of calcium gluconate or calcium chloride. Calcium chloride is faster acting as it does not require hepatic metabolism to dissociate into an active form, hence is usually the drug of choice if severely symptomatic. A study during the anhepatic stage of liver transplantation found equally rapid increase in calcium after administration of calcium chloride and gluconate.[46] Calcium chloride carries a higher risk of irritation of veins and tissue damage should extravasation occur; hence calcium gluconate should be the drug of choice except in emergent situations. In order to minimize caustic damage to veins, any form of calcium should be administered at a rate not to exceed 1.5 mEq/min. If prolonged calcium replacement is needed it is recommended to check vitamin D levels and replace any deficiency with calcitriol, in addition to giving an oral form of calcium such as calcium carbonate, calcium citrate, or calcium lactate.

Table 11.15 Clinical Manifestations of Hypocalcemia	
Acute	Neuromuscular Paresthesia (initially perioral) Seizures Tetany (i.e., Trousseau/Chvostek sign) Pulmonary Laryngospasm, bronchospasm Cardiac Prolonged QT, hypotension, heart failure, arrhythmias Ocular Papilledema
Chronic	Abnormal dentition Extrapyramidal signs Ectopic calcification Subcapsular cataracts

Magnesium

Half of the total body magnesium is confined to bone. Most of the remaining magnesium is intracellular, with less than 1% of total body magnesium found extracellular. Magnesium is primarily absorbed in the small intestine and is influenced by 1,25-dihydroxyvitamin D3. The other source of magnesium is bone.

Hypermagnesemia

Outside of renal failure, hypermagnesemia is rare, as the kidneys have a strong ability to excrete large amounts of magnesium. Instances do occur with severe burns, crush injuries, or other causes of rhabdomyolysis but usually in the setting of renal insufficiency. Symptoms of hypermagnesemia include loss of deep tendon reflexes at levels greater than 8 mg/dL. Once levels are greater than 12 mg/dL paralysis can occur. Cardiac arrest can occur if levels exceed 18 mg/dL. The mainstay of treatment is intravenous calcium to

antagonize the effect of magnesium, volume expansion or loop diuretic depending on volume status, correction of acid–base disturbances and if needed, hemodialysis.

Hypomagnesemia

Kidneys are also able to conserve magnesium quite well with about 40% reabsorption in the proximal tubule. Most instances of hypomagnesemia occur with chronic malnutrition, prolonged intravenous fluid replacement without magnesium, and loop diuretics. Other causes include pancreatitis and diabetic ketoacidosis (DKA). Magnesium functions as a cofactor for many neuromuscular functions, thus deficiency can lead to muscle fasciculation or tetany. The treatment depends on the severity, which includes taking into account symptoms and magnesium level. For instance, if serum magnesium level is less than 1 mEq/L or if the patient is hemodynamically unstable or is in a torsade de pointes arrhythmia then immediate infusion of intravenous magnesium sulfate is indicated. The maximum recommended rate would be 150 mg/min excluding the above emergent situations where it can be given as IV push or over 5 minutes for torsade de pointes. If the patient has chronic or mild hypomagnesemia, oral doses of magnesium should be used, with options including magnesium oxide, magnesium chloride, and magnesium hydroxide (milk of magnesia) depending on side-effect profiles. It should be noted that doses greater than 80 mEq/day can become cathartic.

ACID–BASE

An acid is defined as a chemical that can donate a hydrogen ion (H^+), for example, HCl and H_2CO_3. A base is a chemical that can accept an H^+, for example, OH^- and HCO_3^-. Bases are commonly anions, but neutral substances can also function as bases (e.g., ammonia and creatinine). Some chemicals do not fit the classic definition of an acid, although they retain acidic properties when dissociated in water. For example, when $CaCl_2$ is dissolved in water, the Ca^{2+} accepts OH^- to form $Ca(OH)_2$.

The concentration of hydrogen ions [H^+] determines the acidity of a solution. The pH is the negative logarithm of [H^+] expressed in moles per

liter (mol/L). The concentration of H^+ in biologic systems is in the range of nanomoles (10^{-9} mol) per liter (nmol/L). The degree to which an acid dissociates determines its strength.

The *Henderson–Hasselbalch* equation describes pH as a measure of acidity in a biologic system.

$$pH = pK_a + \log_{10} ([A^-]/[HA])$$

pK_a = Negative log of the acid dissociation constant

A^- = Conjugate base

HA = Acid–base pair

Table 11.16 HCO_3^- and PCO_2 Derangements in Primary and Secondary Acid–Base Disturbances

		Primary		Secondary	
Disorder	pH	HCO_3^-	PCO_2	HCO_3^-	PCO_2
Metabolic acidosis	↓	↓			↓
Metabolic alkalosis	↑	↑			↑
Respiratory acidosis	↓		↑	↑	
Respiratory alkalosis	↑		↓	↓	

Buffer Systems

Buffers are chemicals in solution that tend to minimize changes in pH that would otherwise occur after the addition of acid or alkali. For instance, if a strong base is added to a weak acid, the base is neutralized:

$$NaOH - H_2CO_3 \rightarrow NaHCO_3 + H_2O$$

One type of buffer is a mixture of a weak acid and its salt. The presence of such buffer systems in the body is crucial in minimizing changes in pH, which can be deleterious to cell function.

The principal intracellular buffers are organic phosphates, bicarbonate, and peptides. In addition, hemoglobin functions as a significant buffer in red blood cells. The major extracellular buffer is bicarbonate. An approximation of the total body buffer capacity is 15 mEq/kg. More than half of the total body alkaline buffer content is located outside the ECF and may in large part reside in bone.[50] The buffer pair carbonic acid/bicarbonate (H_2CO_3/HCO_3^-) is the primary buffer system of the body.

From a chemical point of view, the ideal buffer should have a pKa that allows normal physiologic pH. The H_2CO_3/HCO_3^- buffer system has a pKa of only 6.1, which is not the normal body pH. That said, this buffer system is efficient because of the presence of large amounts of bicarbonate, the conversion of its acid H_2CO_3 to CO_2 that is rapidly excreted through the lungs, and an inexhaustible supply of CO_2 from metabolism.

Acid–Base Disturbances

9 There are four primary acid–base disturbances, each of which are related to changes in either $[HCO_3^-]$ or PCO_2. These are categorized as metabolic and/or respiratory (**Table 11.16**). A metabolic acidosis is a decrease in pH as a result of a relative decrease in $[HCO_3^-]$, whereas a metabolic alkalosis is an increase in pH caused by a relative increase in $[HCO_3^-]$. A respiratory acidosis is a decrease in pH secondary to a relative increase in PCO_2, and a respiratory alkalosis is an increase in pH caused by a relative decrease in PCO_2. In each of these disorders, compensatory changes occur to minimize changes in the relative ratio of $[HCO_3^-]$ to PCO_2 and thereby blunt the effect of the primary disturbance on pH (**Table 11.17**).[47,48]

Metabolic Acidosis

Anion Gap

The difference in the measured serum cations and anions yields the anion gap. This can be utilized to identify the etiology of a metabolic acidosis. The most common equation used in practice is as follows:

$$\text{Anion gap} = [Na^+] - ([Cl^-] + [HCO_3])$$

The normal value of serum anion gap is approximately 3 to 10; however, each laboratory should establish its own normal. If one includes potassium in the equation then the normal value should be increased by about 4 mEq/L. The differential for an elevated anion gap acidosis includes: lactic acidosis, salicylate poisoning, acute or chronic kidney disease, chronic acetaminophen ingestion, ketoacidosis (i.e., diabetic), and acute or chronic kidney disease. A common mnemonic used to address etiologies is the acronym: MUDPILES: methanol, uremia, diabetic ketoacidosis, propylene glycol, isoniazid, lactic acidosis, ethylene glycol, and salicylates.

Mechanisms of Metabolic Acidosis

Four mechanisms result in a decrease in extracellular bicarbonate concentration and metabolic acidosis:

1. Dilutional acidosis. Rapid infusion of an alkali-free solution results in dilution of the bicarbonate concentration.
2. Increased acid generation (e.g., lactic acidosis, ketoacidosis, salicylate poisoning).
3. Diminished renal acid excretion (e.g., renal failure or type I renal tubular acidosis [RTA]).
4. Decreased body bicarbonate content (e.g., severe diarrhea, fistula, type II RTA).

Table 11.17 Compensatory Mechanisms

Disorder	Compensation	Time
Metabolic acidosis	PCO_2 = serum HCO_3^- + 15 PCO_2 = 1.5 × serum HCO_3^- + 8 ± 2	12–24 h
Metabolic alkalosis	0.7 mm Hg PCO_2 per 1 mEq/L HCO_3^-	12–24 h
Acute respiratory alkalosis	2 mEq/L HCO_3^- per 10 mm Hg PCO_2	<3 days
Chronic respiratory alkalosis	4–5 mEq/L HCO_3^- per 10 mm Hg PCO_2	3–5 days
Acute respiratory acidosis	1 mEq/L HCO_3^- per 10 mm Hg PCO_2	<3 days
Chronic respiratory acidosis	~4 mEq/L HCO_3^- per 10 mm Hg PCO_2	3–5 days

The most common example of a dilutional acidosis is large resuscitation with normal saline, which causes a hyperchloremic acidosis. Clinically significant metabolic acidosis in surgical patients is most commonly related to net loss of bicarbonate. One means of classification would be renal acidosis versus extrarenal acidosis. Renal acidosis is not as readily compensated because the kidney's ability to regulate acid/base is compromised. Extrarenal acidosis can be further subdivided into increased acid production (e.g., lactic acidosis in shock) or increase bicarbonate loss (e.g., fistula).

Nonrenal Loss of Bicarbonate

Diarrhea, intestinal or pancreatic fistulas, and burns can cause metabolic acidosis secondary to loss of bicarbonate. Urinary diversion with segments of GI tract (ureterosigmoidostomy and ureteroileostomy) can result in loss of bicarbonate with reabsorption of NH_4Cl from the urine. The potential for fistulas to result in metabolic acidosis depends on the concentration of bicarbonate in the fluid and the rate of external drainage. For instance, metabolic acidosis is less common with biliary fistulas than pancreatic fistulas.

Ketoacidosis

Ketoacids are produced from the beta oxidation of fatty acids with subsequent formation of acetoacetate and β-hydroxybutyrate. During prolonged starvation, production of ketoacid increases to modest levels. In DKA, the ketoacid production is excessive because of insulin deficiency, which drives ketoacid production. The resulting osmotic glucose diuresis causes increased renal excretion of sodium, potassium, and water. Despite total body potassium depletion, serum potassium concentration is often increased in DKA secondary to metabolic acidosis, renal insufficiency, insulin deficiency, and hyperosmolality. These pathophysiologic changes result in the typical clinical presentation, which includes dehydration, polyuria, polydipsia, hyperglycemia, hyperventilation, and metabolic acidosis with an increased anion gap.

Lactic Acidosis

Lactic acid is one of the most common causes of metabolic acidosis.[49] Lactic acidosis commonly occurs in patients with sepsis[50] and hemorrhagic shock.[51] Its levels have been shown be highly predictive of outcomes in shock states.[51] In the setting of hypoxia, the cellular dependence on anaerobic metabolic pathways increases generating lactic acid. This process is directly correlated with the total oxygen debt, degree of hypoperfusion, and the severity of shock.[49] Lactic acidosis must be addressed by optimizing tissue perfusion with volume resuscitation. Upon restoring adequate perfusion, the lactic acid is rapidly metabolized by the liver and cleared from circulation normalizing the serum pH level.

Renal Acidosis

The most common renal-associated acidosis in surgical patients is that of acute or chronic renal failure. One of the kidney's many important functions is to excrete acid. When GFR decreases so does the ability to excrete acid, thus causing a metabolic acidosis.

The impaired ability of the kidney to excrete acid may be secondary to a decrease in the number of functioning nephrons and is termed RTA. Type I (distal) RTA is most commonly caused by autoimmune diseases (e.g., Sjögren disease or rheumatoid arthritis) and hypercalciuria in adults. Distal RTA leads to impaired distal acidification.

Type II (proximal) RTA is caused by a reduction in proximal bicarbonate reabsorption—the most common cause in adults being monoclonal gammopathies or medications such as carbonic anhydrase inhibitors.

Clinical Features of Acute Metabolic Acidosis

The major cardiovascular effects of acute metabolic acidosis are peripheral arteriolar dilatation, decreased cardiac contractility, and central venous constriction. These can lead to cardiovascular collapse and pulmonary edema. In addition, metabolic acidosis can increase oxygen delivery by shifting the oxygen–hemoglobin dissociation curve to the right.

Renal Compensation

The kidney is extremely sensitive to changes in serum bicarbonate concentration and responds by increasing net acid excretion primarily in the form of ammonia excretion. Maximal renal compensation requires 2 to 4 days. In addition, the maximal amount of ammonia excreted during acidosis depends on factors such as glutamine delivery, GFR, and the type of anion that accompanies the acid.

Respiratory Compensation

A decrease in blood pH causes an immediate stimulus to hyperventilate. Although effective in promptly raising blood pH, early ventilatory compensation is only partial. Full respiratory compensation can occur in 12 to 24 hours. The magnitude of the decrease in PCO_2 in response to a given

degree of metabolic acidosis can be used to determine whether the metabolic acidosis is complicated by coexisting respiratory acidosis or respiratory alkalosis. There are multiple equations that can describe this relationship:

$$\text{Arterial } PCO_2 = \text{Serum } HCO_3^- + 15$$

$$\text{Arterial } PCO_2 = 1.5 \times \text{Serum } HCO_3^- + 8 \pm 2 \text{ (Winter equation)}$$

The PCO_2 can fall no lower than 8 to 12 mm Hg in response to a severe metabolic acidosis and this compensation can only be maintained for a limited period due to respiratory muscle fatigue.

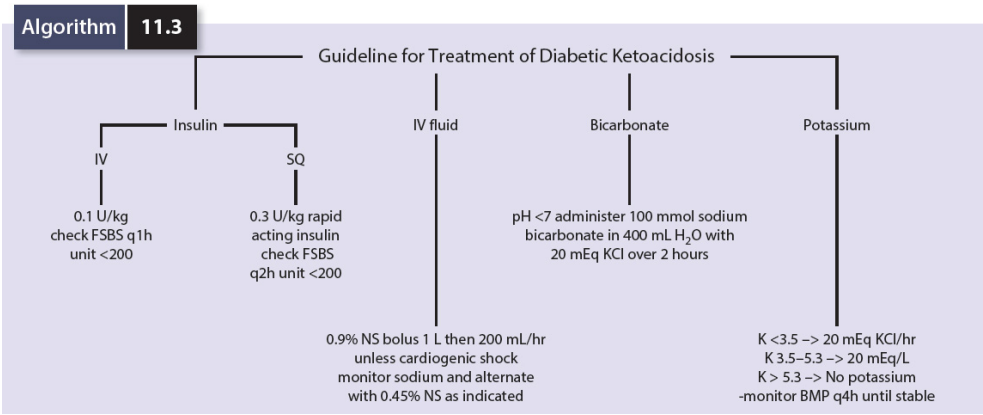
Treatment of Acute Metabolic Acidosis

Volume resuscitation alone may be enough to correct this acidosis. Attempts to correct acidosis with exogenous bicarbonate without addressing inadequate tissue perfusion will be unsuccessful. Furthermore, exogenous administration of bicarbonate may cause a superimposed respiratory alkalosis and a deleterious left shift of the oxygen–hemoglobin dissociation curve, by not allowing reversal of 2,3-diphosphoglycerate depletion, hence resulting in tissue hypoxia (**Algorithm 11.3**).

Metabolic Alkalosis

Sustained metabolic alkalosis occurs only if extracellular bicarbonate concentration is increased and renal excretion of excess bicarbonate is inhibited. Extracellular bicarbonate concentration increases can occur through several mechanisms. In surgical patients, loss of HCl is a frequent cause of metabolic alkalosis, most commonly due to vomiting or nasogastric drainage in the presence of gastric outlet obstruction. External loss of gastric acid results in a net gain in bicarbonate (generated by equimolar gastric secretion of HCl), which causes alkalosis. Although the kidney can excrete excess bicarbonate, this must be accompanied by excretion of sodium. Renal excretion of sodium is limited in the presence of the volume depletion that occurs with external losses of gastric secretion. As volume depletion progresses, sodium is conserved in exchange for hydrogen, and urine will

become acidic, even in the presence of severe metabolic alkalosis. This phenomenon is referred to as *paradoxical aciduria.*



Algorithm 11.3 Guidelines for the treatment of diabetic ketoacidosis.

Increased extracellular bicarbonate concentration can occur with administration of either bicarbonate or precursors of bicarbonate, such as lactate, citrate, or calcium carbonate, or as a result of increased renal production of bicarbonate. Conditions in which acid excretion exceeds endogenous acid production and in which the renal threshold for bicarbonate reabsorption is increased can result in metabolic alkalosis. Such conditions include moderate potassium depletion, excess mineralocorticoids, and high PCO_2.

Hypokalemia and cellular exchange of potassium for hydrogen can also lead to metabolic alkalosis. Hypokalemia results in enhanced proximal tubular bicarbonate reabsorption and distal tubular acid excretion. When potassium leaves the cell, it is exchanged for either sodium or hydrogen to maintain electrical neutrality. Loss of potassium from the body then results in a net gain in bicarbonate in the ECF.

Maintenance of elevated extracellular bicarbonate concentration can occur by a number of mechanisms. Volume contraction leads to decrease in renal blood flow and GFR thus reducing the filtered load of bicarbonate. This, in addition to increased proximal tubular reabsorption of bicarbonate, maintains high extracellular concentrations of bicarbonate. High PCO_2 causes an increase in renal threshold for bicarbonate secondary to decreased intracellular pH of the renal tubular cell. The net result is increased bicarbonate reabsorption.

Diuretics can cause or exacerbate metabolic alkalosis by both causing rapid contraction of intravascular volume and increasing renal excretion of acid. Chloride deficiency is another common factor that maintains an alkalotic state. In some instances of metabolic alkalosis, urinary excretion of chloride is markedly reduced. Reversal of metabolic alkalosis in these cases can be readily achieved by administration of chloride-containing solutions. Metabolic alkalosis can be categorically divided into chloride-responsive and chloride-resistant types.

Clinical Features

Clinical signs of metabolic alkalosis may not be prominent because the condition usually develops slowly. If acute, CNS manifestations of confusion, obtundation, stupor, and coma may be present as well as tetany or neuromuscular irritability.

Respiratory Compensation

Respiratory compensation for metabolic alkalosis should raise the PCO_2 by 0.7 mm Hg for every 1 mEq/L elevation in serum HCO_3^-. Typically the arterial PCO_2 does not go above 55 mm Hg. Among the four major acid–base disorders, this compensatory mechanism is the least effective.

Treatment

Correction of the underlying cause is the mainstay of treatment in this disorder. In general, correction of potassium depletion and volume depletion corrects the metabolic alkalosis. Renal excretion of bicarbonate cannot occur in the face of persistent volume depletion. Volume depletion should be corrected with chloride-containing solutions. In patients without intravascular volume deficits, renal excretion of bicarbonate can be enhanced by administration of the diuretic, carbonic anhydrase inhibitor acetazolamide. In extremely rare circumstances where renal excretion of bicarbonate cannot be increased because of underlying renal insufficiency or if the metabolic alkalosis is severe, acid may be administered to titrate in opposition the excess extracellular bicarbonate. Acids that can be used include ammonium chloride, arginine hydrochloride, lysine hydrochloride, or

dilute hydrochloric acid (0.1N). Partial correction of the alkalosis is the initial goal and a specialist should be involved prior to instituting this care. In the face of frank renal failure, dialysis may be necessary to remove excess bicarbonate.

Respiratory Alkalosis

Respiratory alkalosis is defined as increased extracellular pH secondary to decreased PCO_2 with hyperventilation. Hyperventilation and the ensuing fall in PCO_2 may be secondary to hypoxia, reflex stimulation from decreased pulmonary compliance, drugs, mechanical ventilation, or other causes.

Hypoxia stimulates ventilation through peripheral chemoreceptors in the carotid and aortic bodies. Decrease in arterial partial pressure of oxygen (pO_2), rather than in oxygen content, is the main stimulus. Acute drops in arterial pO_2 result in sustained hyperventilation only when the PCO_2 decreases below 60 mm Hg. Although hyperventilation occurs with even slight degrees of hypoxia, the resulting increase in brain pH suppresses the stimulus for hyperventilation unless severe hypoxia is present. In contrast, chronic hypoxia results in hyperventilation even with mildly decreased PCO_2 because brain pH is lowered by metabolic compensation. The two most common causes of hypoxia resulting in respiratory alkalosis are pulmonary disease and exposure to high altitudes.

Clinical Features

Chronic respiratory alkalosis is usually asymptomatic because compensatory mechanisms are successful in maintaining pH close to normal. Acute respiratory alkalosis may cause sensations of breathlessness, dizziness, and nervousness and can result in circumoral and extremity paresthesias, altered levels of consciousness, and tetany. These signs are related to decreased cerebral blood flow secondary to the decreased PCO_2 and decreased ionized calcium concentration secondary to the increased blood pH.

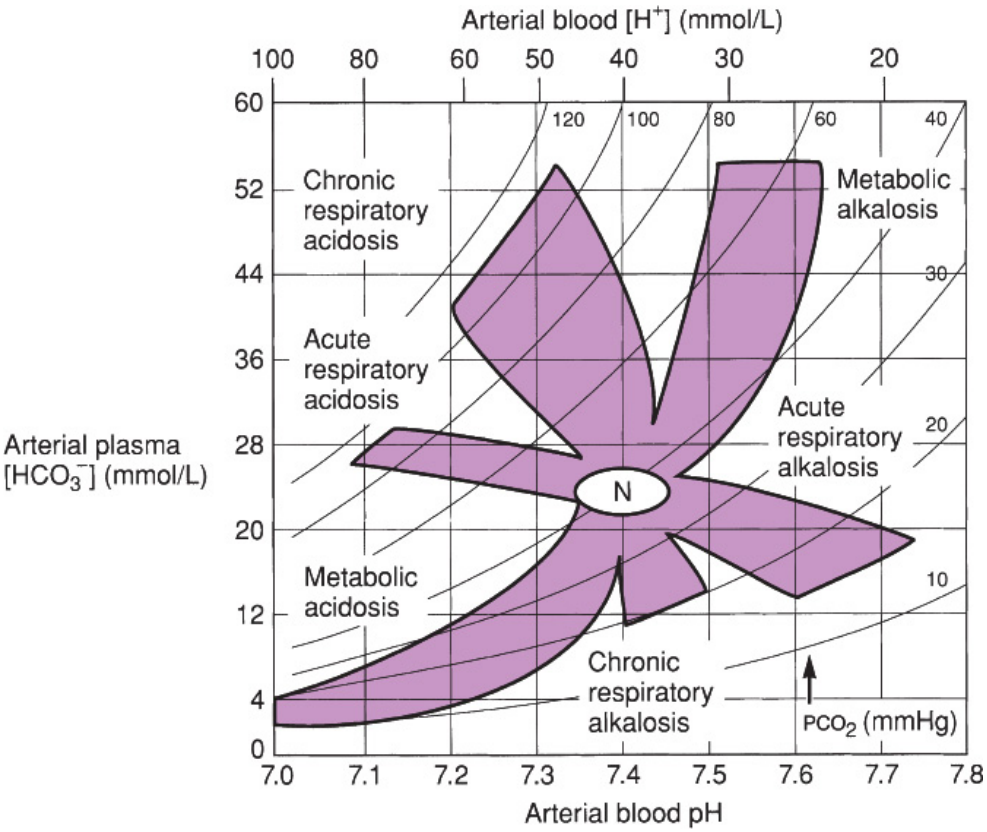


Figure 11.8 Acid–base nomogram. Shown are the 95% confidence limits of the normal respiratory and metabolic compensations for primary acid–base disturbances. (Reproduced with permission from Cogan MG, Rector FC Jr. Acid–base disturbances. In: Brenner BM, Rector FC Jr, eds. *The Kidney*. Philadelphia, PA: WB Saunders; 1986:473.)

Compensatory Mechanisms

Tissue buffering is the initial response to a decrease in PCO_2. Red blood cells provide one-third of the buffering. Consumption of bicarbonate results from cellular liberation of H^+. The magnitude of tissue buffering is weak compared with renal compensation. This is accomplished not by increasing bicarbonate excretion but by decreasing net acid excretion, namely ammonia. Acute compensation is not as strong as chronic compensation, which takes at least 3 days to occur.

Acute compensation: Decrease serum HCO_3^- by 2 mEq/L per 10 mm Hg reduction in PCO_2

Chronic compensation: Decrease serum HCO_3^- by 4 to 5 mEq/L per 10 mm Hg reduction in PCO_2

Treatment

The underlying stimulus for the hyperventilation should be addressed. The cause of hypoxemia should be determined and corrected. In acute symptomatic respiratory alkalosis, rebreathing or breathing 5% CO_2 temporarily relieves symptoms. If the condition is secondary to mechanical ventilation, decreasing tidal volume or respiratory rate should result in resolution of respiratory alkalosis.

Respiratory Acidosis

Respiratory acidosis is defined by a decrease in extracellular pH from a primary increase in PCO_2, due to inadequate ventilation. Causes of hypoventilation include CNS depression, impaired pulmonary mechanics, airway obstruction, and chronic obstructive pulmonary disease (COPD). In addition, inappropriate ventilator settings may result in respiratory acidosis in patients on mechanical ventilation.

Clinical Features

The magnitude of clinical manifestations depends on the chronicity and rate of development of respiratory acidosis. Acute increases result in cerebral acidosis, manifested by drowsiness, restlessness, and tremor, as well as stupor or coma in more severe cases. Cerebral vasodilation occurs in response to acidosis, resulting in increased cerebral blood flow. This may, in turn, result in increased intracranial blood pressure, headache, and papilledema. Systemic acidosis results in peripheral vasodilatation, depressed cardiac contractility, and insensitivity to catecholamines.

Compensatory Mechanisms

Increased pCO_2 results in increased H_2CO_3, which dissociates into H^+ and HCO_3^-. Cellular exchange of Na^+ and K^+ for H^+ allows the reaction to continue in this direction with increased extracellular bicarbonate. This tissue buffering is accomplished within minutes. Persistently elevated PCO_2 also stimulates increased renal acid excretion, primarily the chloride salt of

ammonia, and results in increased renal generation of HCO_3^-. Full renal compensation occurs over 3 to 5 days.

Acute compensation: 1 mEq/L HCO_3^- per 10 mm Hg PCO_2

Chronic compensation: ~4 mEq/L for every 10 mm Hg PCO_2

Treatment

Treatment should be directed to the underlying cause of hypoventilation. Endotracheal intubation to achieve adequate ventilation is paramount to the treatment of acute respiratory acidosis of any cause. In select cases of respiratory acidosis, namely patients with COPD, noninvasive positive pressure ventilation (i.e., CPAP/BiPAP) has proven effective. However, patients must be able to protect their airway and have no major concern for aspiration (i.e., not appropriate in the setting of a bowel obstruction). Furthermore, there must be close follow-up to ensure the acidosis is resolving.

The treatment of chronic, compensated respiratory acidosis may be complicated by the accompanying hypoxemia. In chronic hypercapnia, the central chemoreceptors may be insensitive, and the accompanying hypoxemia may supply the main respiratory drive through stimulation of peripheral chemoreceptors. In such patients, complete correction of the hypoxemia may further suppress respiration and worsen the respiratory acidosis. In addition, PCO_2 should not be normalized rapidly. Equilibration of cerebral bicarbonate concentration lags behind systemic changes. Thus, even if PCO_2 is normal, cellular and cerebral metabolic alkalosis may develop.

Mixed Acid–Base Disorders

Combinations of two or more of the four primary acid–base disorders may occur and should be suspected when blood pH approaches normal despite abnormal PCO_2 and [HCO_3^-], or when compensatory changes appear to be either excessive or inadequate (**Fig. 11.8**).

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12

Burns: Medical, Surgical, Critical Care and Reconstruction of the Burn Patient

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Key Points

1. Most chemical injuries should be treated with dilution of the chemical rather than neutralization.
2. Frostbite outcomes are improved if patients with threatened extremities are treated with tPA within 24 hours of injury.
3. Resuscitation is of crucial importance for burn patient outcome and physicians must be aware when to begin resuscitation (>20% total body surface area [TBSA]) and to monitor the patient response to avoid overresuscitation.
4. Early excision and grafting within 72 hours of the injury remains a pillar of burn care.
5. Order of burn coverage can affect patient outcome and can help prevent the patient from needing a tracheostomy.
6. New technologies have a role to play in scar rehabilitation, improving quality and pain associated with these scars.

INTRODUCTION

Burn injuries represent a major source of trauma, subsequent scarring and debilitation throughout the world. Improved worker safety programs, fire prevention efforts, and fire detection systems have significantly decreased the prevalence of major burn injuries. Burn survival has also been impacted by improvements in surgical critical care in areas such as lung protective ventilation, blood glucose control, and antibiotic stewardship. Overall, survival after burn injuries remains high, leading to a need for improved reconstructive treatment options for burn survivors.

EPIDEMIOLOGY

According to the Centers for Disease Control and Prevention (CDC), approximately 489,000 people received medical treatment for burns in the

United States in 2017.[1] Overall, more than 67% of reported cases had burn sizes <10% total body surface area (TBSA).[2] Men account for 67% and women account for 33% of reported injuries. Men make up the majority of burns in every age group except for those aged >80 years. Of those injured, 59% are Caucasian, 21% are African American, and 11% are Hispanic. The cause of these burn injuries vary with 41% from fire or flame burns, 35% from scald burns, 10% from contact burns, and 7% from electrical and chemical burns. Approximately 13% of these injuries are work related. The majority of all burn injuries happen at home. In 2018, there were 40,000 hospital admissions and 3,655 deaths from fire and smoke inhalation.[3] Of the patients who died, 74% of the deaths resulted from home fires, an increase of 3% from 2017. An estimated 13% of deaths were due to highway vehicle fires.

As in other trauma populations, children are affected to a greater degree. Children under 16 years of age comprise 26% of total burns, and adults 20 to 59 years make up 55% of burns. Older adults >60 years represent 15% of cases, but 37% of deaths from burns. Fire/flame is the most common etiology of injury for adults, whereas children under the age of 5 years typically suffer from scald burns caused by spilling of hot liquids. With improved surgical critical care and understanding of burn injury physiology, over 96% of burn patients survive.

Children

Burns are the fifth leading cause of unintentional nonfatal injury in infants and the third leading cause of fatal injury for newborns to children 9 years of age. Scald burns caused by hot liquids are the most common cause of pediatric burns and occur most often in the home.[2,4,5] The number of burns decreases from age 9 until adolescence and increases again after the age of 15, presumably due to greater exposure to hazards, experimentation, risk-taking, and employment.[6] Intentional burns account for around 10% of all cases of child abuse.[7] Scalds from hot bath immersion are the most frequent cause of these cases. Other common etiologies of intentional burns include contact with heated objects including cigarettes, irons, and heated kitchen utensils.

Adults

Flame burns are the most common cause of burns in adults and the elderly. Cigarette ignition of upholstered furniture or bedding account for 47% of fires and alcohol appears to be a significant contributor.[8]

Older Adults

The burn-related mortality rate increases greatly for adults aged 60 years or older. The mortality rate for a burn >20% TBSA is 15% for adults 60 years and older.[2] Individuals over the age of 65 comprise 12% of all burn unit admissions. The average age of those admitted is 76 ± 7 years.[9] The most frequent cause of burns that led to death in elderly women is clothing ignition during cooking.[10] Elderly burn patients treated for scald burns had relatively small burns (<13% of TBSA) but high mortality rates (30%).[11–13] Overall, burns are the fourth leading cause of mortality among the elderly population. Those aged 80 years and older have an overall mortality rate of 20% from burn injury. The mortality rate for a burn >20% TBSA is >60% for those aged 80 or older.

Race and Ethnicity

Differences exist in the susceptibility to burns by race and ethnicity. Burns are the leading cause of injury-related death in Black children between the ages of 1 and 9 and the rates are 2.7 times higher than in White, Hispanic, and Asian/Pacific Islander children.[14] In the pediatric population, for children under the age of 16 who sustain burns, non-White children exceed white children in each age group.[2] Likewise, in adults, the rate of burns in Black Americans aged 35 to 39 years was 221 per 100,000 Blacks, which is remarkably higher than the 135 per 100,000 Whites with burns in the same age group. The emergency room visit rate for burns from 1993 to 2004 in the United States was 62% greater among Black Americans (340 per 100,000 Black Americans) than White Americans (210 per 100,000 White Americans).[15] The age-adjusted death rate from burns of all causes in the United States in 2018 was highest in Blacks (1.6 per 100,000) and lowest in

Asians (0.3 per 100,000), with Native Americans (1.1 per 100,000), and Whites (1.1 per 100,000) falling in between this range.[6]

Socioeconomic Status

Socioeconomic status (SES) factors such as low household income, crowded household living conditions, and unemployment also increase the risk of burns. Children in the lowest SES groups requiring hospitalization for treatment in U.S. burn centers is twice the proportion of all children in the general population.[3] Furthermore, the incidence of house fires was eight times greater in low-income families compared to high incomes.[16] The higher incidence of house fires has been attributed to the frequent absence of functioning smoke detectors.[16]

ETIOLOGY

Numerous modalities, including fire or flame, scalds, contact, electrical conduction, and chemicals can produce burns. Between 2008 and 2017, 41% of burns were produced by fire or flame, 35% by scald, 10% by contact, and 7% by electricity and chemicals.[2]

Burns are caused by contact of heat, cold, or chemicals with the cutaneous surface of the skin. The depth of the burn injury is proportional to the temperature and duration of exposure. Burn depth is also dependent on the body region due to differences in skin thickness and blood flow.

Scald burns are most commonly caused by water in the community. Once the water temperature exceeds 156°F, only 1 second is needed for a full-thickness burn injury. The difference in contact time underlines the importance of making sure that hot water heaters are set at a low enough temperature to minimize childhood bath and shower scald injuries (120°F). It takes 3 minutes for a burn to occur from 120°F whereas it takes only 1 second for a burn to occur from 156°F water.

Though water scalds do not always cause full-thickness injury due to the variation in temperature, grease burns almost uniformly cause a deep partial- or full-thickness burn. Grease is usually 400°F and thus even minimal exposure will cause significant thermal injury. Tar and asphalt also exceed

400° to 500°F making them a high burn injury risk for industrial workers. Water and grease injury sites should be cleansed with aqueous solutions. Tar, however, requires a petroleum-based solution to remove it from the burn wound.

Flame Burns

Thermal injuries, caused by fire or flames, are the most common burn etiology reported over the past decade.[2] These injuries usually occur as a result of flammable liquids, motor vehicle crashes, cooking fires, or if bedding/clothes ignite. Flame injuries are associated with the highest risk of death and complications compared to all other burn etiologies. When evaluating thermal injuries, it is important to consider the possibility of smoke inhalation as its presence significantly impacts the morbidity and mortality of patients with flame burns. Inhalation injury occurs in 17% of patients with flame burns. The presence of smoke inhalation in burn patients is associated with an overall mortality rate of 24%, compared to the mortality rate of 4% in those patients without smoke inhalation.

Contact Injuries

Contact burns occur as the result of direct contact with hot surfaces and material, most frequently glass, metal, or plastic. The depth of the injury depends on the heat of the material and the length of contact. Frequent sites of injury include the palms of the hands as people, especially toddlers, will often fall with outstretched hands. Other commonly seen contact injuries are due to hot metal devices such as space heaters, curling irons, motorcycle exhaust systems, and vaping devices.

Electrical Burns

Electrical injuries occur more frequently in adults than children, since most result from occupational exposure. Patients who have high-voltage electrical injuries, defined as greater than 1,000 V, are at elevated risk of spine fracture injury due to tetany and require complete immobilization until vertebral injury is ruled out. Providers must also evaluate patients with high-voltage

injuries for cardiac damage. Direct muscle injury from current flow may cause gross myoglobinuria, requiring more aggressive fluid resuscitation.[17] Patients with gross myoglobinuria often require fasciotomy of affected limbs and a severe electrical injury often requires monitoring in the intensive care unit. Bone has the highest conductance and electricity flows along the skeleton causing significant muscle necrosis adjacent to the bone. TBSA involved is not necessarily associated with prognosis and it does not quantify damage to deep tissues in electrical injuries.

Thermal injuries occur as electricity can generate temperatures over 100°C. Electroporation occurs as electrical force drives water into lipid membrane causing cell rupture. Tissue resistance in decreasing order includes bone, fat, tendon, skin, muscle, vessel, and nerve. Bone heats to a high temperature and burns surrounding structures such as muscle, leading to muscle swelling and compartment syndrome which are common in high-voltage electrical injuries.

Electrical exposure can cause significant injuries to other organ systems. Arrhythmias are common at the scene (any voltage) or in the hospital (high voltage ≥1,000). Heart rhythm should be monitored continuously for at least 24 hours if cardiac injury is suspected at the scene or if a high-voltage injury has occurred. Ventricular fibrillation and asystole are the most common and advanced cardiac life support should be instituted immediately. Coronary artery spasm and myocardial injury and infarction have also been described. A normal cardiac rhythm on admission, however, means dysrhythmia is unlikely and thus 24-hour monitoring is not needed.[18] Additionally, injury to solid organs, acute bowel perforation, and gallstones after myoglobinuria have been described. Myoglobinuria from other causes require increased fluid administration; however, burn resuscitation usually provides adequate fluid. Given that electrical injury only patients often do not exceed 20% TBSA, fluid for high-voltage injuries should be given to maintain urine output of 75 to 100 cc/hr. Cataracts are also a long-term adverse effect of electrical injury necessitating an ophthalmology evaluation and follow-up.

When taking the patient to the operating room for debridement and grafting of electrical injuries, the physician should perform serial debridements and allow the tissue to completely declare itself which takes longer than a typical flame scald or flame burn. These injuries will often evolve with progressive muscle necrosis over time, thus early grafting (within the first week) often

fails to fully close the burn wound. These injuries have similarities to crush injuries and thus multiple trips to the operating room for debridement should not be viewed as a failure.

1 Chemical Burns

General Approach to Chemical Burn Treatment

Health care providers should use personal protective equipment—always considering that the chemicals are still present and must be neutralized or temporized. With few exceptions (see below), all chemical burns should be copiously irrigated with water. Water dilutes but does not neutralize the chemical and cools the injured area. Neutralization of the chemical is generally contraindicated because neutralization may induce a hyperthermic reaction leading to further thermal injuries. Water irrigation, however, is contraindicated or ineffective following exposure to elemental sodium, potassium, and lithium (precipitates an explosion). Dry lime should be brushed off, not irrigated. Phenol is water insoluble and should be wiped from the skin with polyethylene glycol–soaked sponges.

Types of Chemical Burns

Alkali causes liquefaction necrosis and protein denaturation and is found in oven and drain-cleaning products, fertilizers, and industrial cleaners. Alkali injuries extend deeper into tissues following exposure and are especially disruptive to eyes. **Acids** cause damage to tissue via coagulation necrosis and protein precipitation. Acid burns tend to be self-limited secondary to pain as the patient will quickly react to the offending agent. **Organic compounds (**phenol and petroleum**)** cause damage due to fat-solvent action (cell membrane–solvent action) and systematic absorption with toxic effects on the liver and kidneys. These agents also can cause significant erythema in the surrounding areas that can be mistaken for cellulitis.

Specific Types of Chemical Burns

Hydrofluoric acid is a potent and corrosive acid used for rust removal, glass etching, and to clean semiconductors. It is a weak acid but the fluoride ion is

toxic as it leaches calcium from cells. Hydrofluoric acid causes severe pain and local necrosis and should be treated with copious water irrigation. The fluoride ion is neutralized with topical calcium gel (one ampule of calcium gluconate in 100-g lubricating jelly). If symptoms persist, intra-arterial calcium infusion (10-mL calcium gluconate diluted in 80 mL of saline, infused over 4 hours) and/or subeschar injection of dilute (10%) calcium gluconate solution should be administered. Fluoride ion binds free serum calcium and thus it is crucial to make sure to check the serum calcium and replace with IV calcium as needed.

Phenol is commonly used in disinfectants and chemical solvents; it is an acidic alcohol with poor water solubility. Phenol causes protein disruption and denaturation resulting in coagulation necrosis. Systemically, phenol can cause cardiac arrhythmias and liver toxicity. Thus patients should have cardiac and liver function monitored. Additional adverse effects include renal injury and demyelination. Given phenol's anesthetic effect, pain is not a reliable indicator of injury. Treatment is copious water irrigation and cleansing with 30% polyethylene glycol or ethyl alcohol.

Tar is used in the paving and roofing industry and can be heated to 260°C (~500°F) prior to application. Tar causes thermal injury and then solidifies as it cools, often becoming enmeshed with hair and skin. Patients with tar injuries should be cooled with copious water irrigation to stop the burning process. Tar removers promote micelle formation to break the tar–skin bond. Sterile surfactant mixture (De-Solv-it or Shur-Clens) allows tar to be wiped away quickly. Wet dressings using polysorbate (Tween 80) or Neomycin cream for 6 hours prior to tar removal can also be effective.

White phosphorus is used to manufacture military explosives, fireworks, and methamphetamine. Obvious particles should be brushed off. Skin should be irrigated with a 1% to 3% copper sulfate solution. Copper sulfate stains the particles black for identification. Copper sulfate will also prevent ignition when particles are submerged in water. After copper sulfate irrigation, the exposed area should be placed in a water bath and the white phosphorous removed.

Anhydrous ammonia is an alkali used in fertilizer. Skin exposure is treated with irrigation and local wound care. Exposure is associated with rapid airway edema, pulmonary edema, and pneumonia. It is important to consider early intubation for airway protection in these cases.

Methamphetamine injuries have been on the rise. In addition to these compounds being highly flammable, exposure to methamphetamines causes tachycardia (greater than expected with a similar sized burn), hyperthermia, agitation, and paranoia. Any suspicion of chemical injury to the globe should be treated with prolonged irrigation with Morgan lenses. Eyelids may need to be forced open due to edema or spasm. Utilize topical ophthalmic analgesic and consult an ophthalmologist.

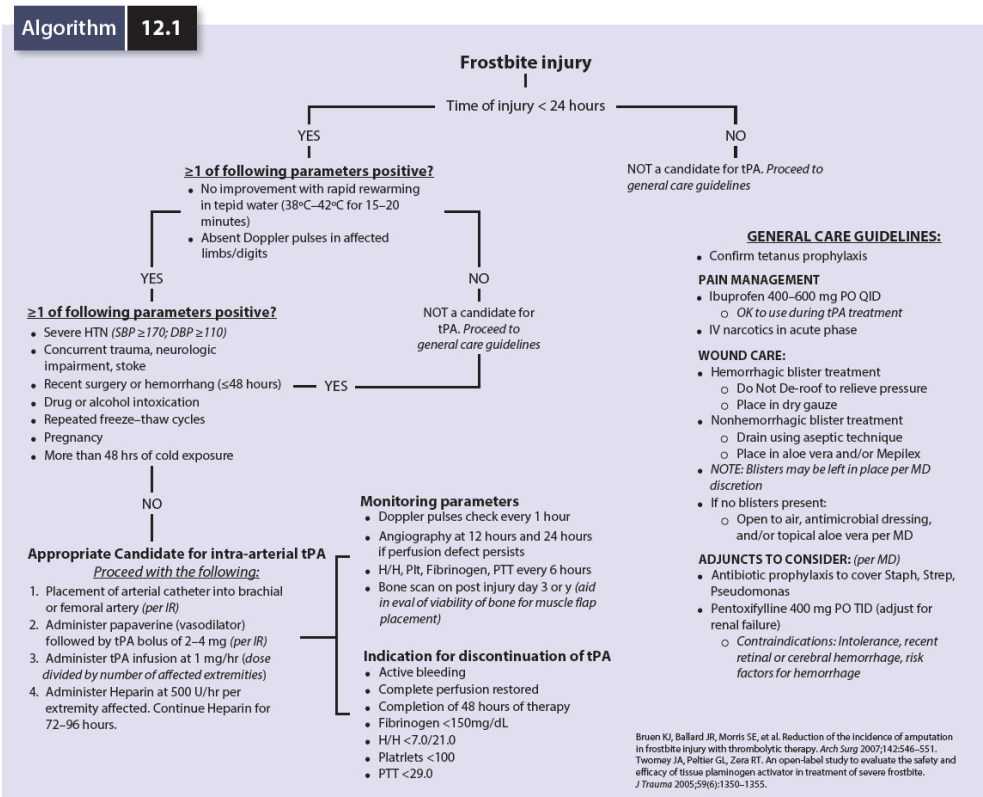
2 Frostbite

Frostbite injuries frequently result in severe ischemic damage of distal extremities. Frostbite classification is similar to that of burn injury (**Table 12.1**).

Historically, frostbite patients have been managed expectantly with long periods of observation followed by amputation of devitalized tissue. Recent advances with interventional radiology, thrombolytic therapy, and nuclear medicine have changed the treatment paradigm and protocol for these patients (**Algorithm 12.1**). Current treatment paradigms for patients with frostbite include rapid rewarming of affected area in 104° to 108°F water bath, not radiant heat as well as ibuprofen 400 mg, elevation of the limb, tetanus prophylaxis, and appropriate referral. If the patient has severe frostbite within the last 24 hours, the patient should be transferred to a center with interventional radiology expertise. Once they arrive, these patients should receive an arterial line (usually brachial or femoral) and intra-arterial tPA which treats the microvascular thrombosis.[19] Additionally, patients might benefit from nitroglycerin to treat the vasospasm. Patient should return to the interventional radiology suite after 12 hours to evaluate progress and potentially treat again. In general, tPA is stopped after 48 hours. After 5 to 7 days, a nuclear bone scan can help assess the extent of deeper tissue necrosis as the more superficial tissue will often appear worse than the actual extent of the injury.[20]

Table 12.1 Classification of Frostbite Injury

Degree	Depth	Clinical Characteristics
First	Very superficial	Central area of pallor; anesthesia of the skin surrounded by edema
Second	Superficial; no tissue loss	Large blisters containing clear fluid surrounded by edema and erythema. The blisters may form an eschar, but this later sloughs off, revealing healthy granulation tissue
Third	Deeper; tissue loss	Smaller blisters, hemorrhagic, more proximal. The skin forms a black eschar in one to several weeks
Fourth	Extends to muscle and bone	Mummification in 4–10 days



Algorithm 12.1 Protocol for frostbite injury.

PHYSIOLOGY OF BURNS

Burn Shock

Most patients with large burn or inhalation injuries will meet criteria for systemic inflammatory response syndrome (SIRS). Burn shock does not equate to septic shock in the acute setting as true sepsis from a burn injury with subsequent infection usually does not occur until after the first 48 to 72 hours.

Burn shock is unique in the degree of vascular permeability coupled with increased hydrostatic pressure.[21] This increased permeability is thought to result from the release of histamine from mast cells in burned skin following burn injury.[22] Histamine interferes with the venous tight junctions and thereby allows efflux of fluid and proteins causing intravascular hypovolemia despite total-volume hypervolemia.

Platelet activation products such as eicosanoids and serotonin also act to increase pulmonary vascular resistance and amplification of the vasoconstrictive effects of norepinephrine and angiotensin II.[23] In addition to the increased vascular leak, platelet-activating factor in addition to clotting factor dysregulation creates a hypercoagulable state with bleeding that resembles disseminated intravascular coagulation. This coagulation disorder is further amplified if patients become hypothermic during their resuscitation.[24] Thus, patient temperature monitoring and maintenance is crucial during resuscitation.

Changes in cardiac output are also seen in burn patients acutely as patients often have an increase in heart rate and systemic vascular resistance but hypovolemia. Though not defined as "cardiogenic shock," cardiac function is altered due to inflammatory mediators.[25–27] With appropriate burn resuscitation, cardiac output should return to normal levels within 24 to 72 hours.

Metabolic Response to Burn Injury

A physiologic response unique to burn injury is the extent of hypermetabolism. This hypermetabolism is characterized by increased body temperature, glycolysis, gluconeogenesis, proteolysis, lipolysis, and prolonged substrate cycling.[28,29] The degree of the hypermetabolic response is proportional to the size of burn injury and appears to plateau at 70% TBSA. Overall the basal level of glucose is elevated despite a high insulin state which can complicate outcomes and exacerbate muscle catabolism.

Lipolysis also occurs at a rate that is higher than normal due to abnormal substrate cycling. This results in an accumulation of triglycerides causing steatosis. Recent work to combat this peripheral lipolysis has had some success using propranolol.[30]

Proteolysis is increased in burn patients compared to nonburn patients. This is due to a combination of increased muscle breakdown and increased plasma protein production by the liver.

Catecholamines are also significantly elevated following a burn injury and are thought to play a role in the hypermetabolic response. Burn injuries also cause alterations in diurnal glucocorticoid levels leading to persistent hypercortisolemia.

There are three ways to influence hypermetabolism: nutrition, medication, and surgery as discussed in subsequent sections in the chapter.

Immunologic Response to Burn Injury

The immune system in burn patients demonstrates significant dysregulation that may explain their increased risk of infection. Serum levels of IgA, IgG, and IgM are decreased indicating decreased B-cell function. T-cell function or cell-mediated immunity is also impaired that is why prolonged homograft and xenograft take is seen. Interleukin 2 (IL-2) production is also decreased whereas IL-10 is increased. Similar to other types of nonthermal trauma, burn patients also have elevated tumor necrosis factor alpha and IL-6. With regard to the innate immune system, polymorphonuclear neutrophils have impaired chemotaxis as well as decreased oxygen consumption and impaired bactericidal capabilities.

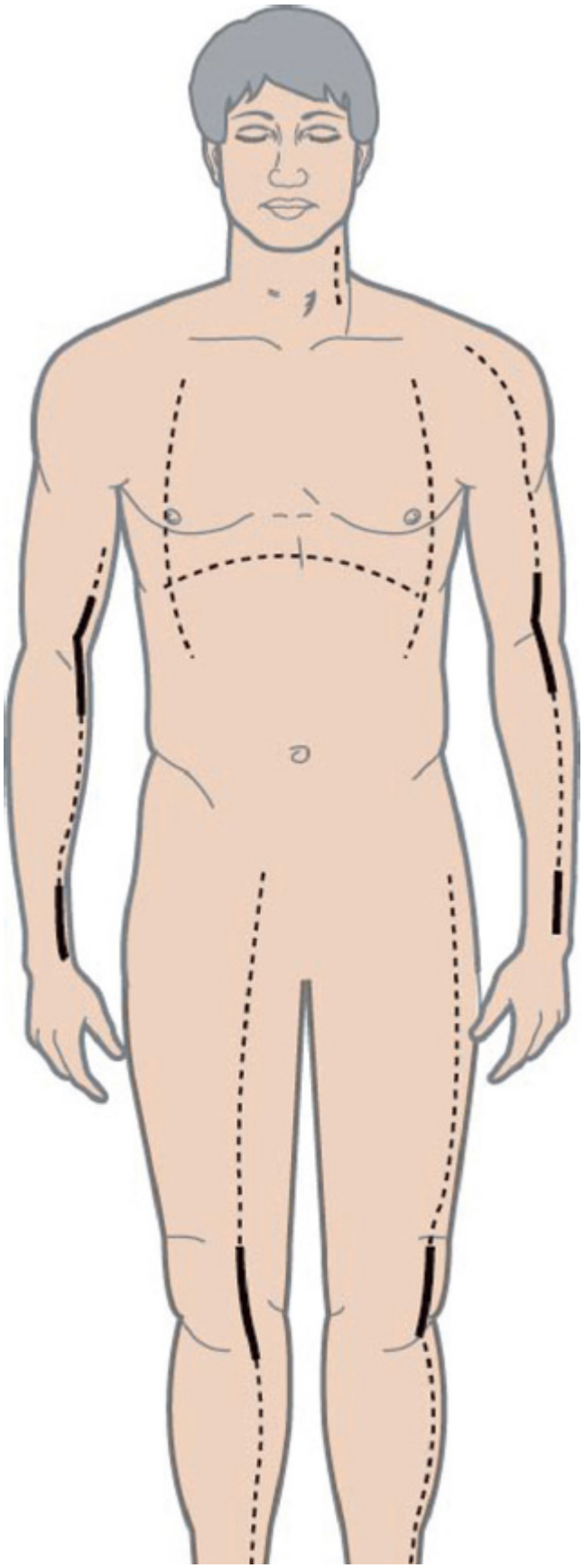
EMERGENCY CARE

The initial care in the field and emergency room is similar to that of any trauma patient. The airway should be stabilized, IV access should be obtained, concomitant life-threatening injuries should be ruled out, and escharotomies should be performed if there are any circumferential areas of full-thickness injury. Escharotomies should be placed on the lateral aspects of the extremities avoiding the sites of potential nerve and large vessel injury (**Fig. 12.1**). Escharotomies should be extended across the chest if there is full-thickness injuries and if difficulty ventilating arises. Abdominal escharotomies can also help with ventilation. Guidelines from the American College of Surgeons Advanced Trauma Life Support and the American Burn Association Advanced Burn Life Support programs have standardized the care of trauma patients and have improved overall patient outcomes. A complete history and physical examination should be performed with specific focus placed on the cause and timing of the injury, risk of smoke inhalation injury, concomitant injuries, and treatments including intravenous fluids received prior to patient arrival. The primary goal is to stabilize the patient, ensure standard injury assessment, and transfer to a burn center if

necessary. The American Burn Association (ABA) has published criteria to follow regarding when to transfer a patient to a verified burn center that is listed in **Table 12.2**.[31]

Table 12.2 American Burn Association Burn Center Referral Criteria

1. Over 10% total body surface area (TBSA) partial- or full-thickness burns
2. Burns that involve difficult anatomic sites such as the face, hands, feet, genitalia, perineum, or major joints
3. Full-thickness burns in any age group
4. Electrical burns, including lightning injury
5. Chemical burns
6. Inhalation injury
7. Burn injury in patients with pre-existing medical conditions that could complicate management, prolong recovery, or affect mortality
8. Any patient with burns and concomitant trauma. If, however, the coincident trauma is of greater risk to mortality, the patient should be stabilized prior to transfer. Physician's judgment will be necessary and should be in concert with the regional medical control plan and triage protocols
9. Burned children in hospitals without qualified personnel or equipment for the care of children
10. Burn injury in patients who will require special social, emotional, or rehabilitative intervention



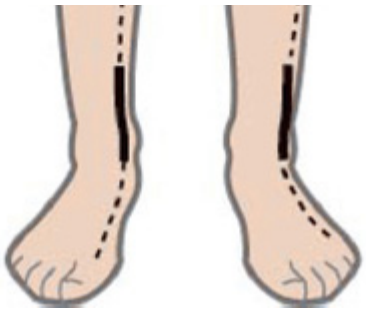


Figure 12.1 Incision lines for escharotomies. In general incisions should be kept on the lateral aspect of extremities to avoid damage to neurovascular structures.

Airway Assessment

Primary survey assessment should begin with evaluation of the airway. Inhalation injuries occur in approximately 10% of all burn patients, but are notably present in 70% of those who eventually die of their burn injury.[32] Thus, it is important to specifically note such findings as soon as the patient presents. Risk for inhalation injury can be first assessed by the history. In general, patients burned outside (not in an enclosed space) very rarely suffer inhalational injuries. If, however, the patient was in a burning home or a burning building, one's suspicions should be raised. Close physical examination should note facial burns, changes in voice, shortness of breath, singed nasal vibrissae, carbonaceous sputum, and intraoral swelling. If these findings are present and the patient appears to be in distress, oral intubation should be performed immediately by an experienced airway physician. In addition to a laryngoscope, the trauma team should have a video laryngoscope available and a surgeon present in case a surgical airway is required. If the patient is not in extremis and the level of inhalation injury is unknown, nasoendoscopy or bronchoscopy should be performed to directly visualize the airway and vocal cords. If significant swelling exists and the patient is expected to receive a large-volume intravenous fluid resuscitation, the airway should be immediately secured. If a patient is transferred with an endotracheal tube that the accepting physician feels is no longer needed, a spontaneous breathing trial should be performed followed by direct laryngoscopy to assess for cord swelling and assessment for a cuff leak should be performed before removing the endotracheal tube.

Oxygenation in a burned patient may be altered by carbon monoxide (CO) poisoning. Physical examination findings include red lips and altered mental status. Formal diagnosis should be based on history and evidence of carbon monoxide levels in the blood. Carbon monoxide binding is assessed by measuring the level of carboxyhemoglobin in a peripheral arterial blood gas sample. Symptoms of CO poisoning typically begin with headaches at levels around 10%, while CO in the blood becomes lethal at around 50% to 70%. The half-life of CO is normally 4 hours when breathing room air, however its half-life is shortened considerably with administration of supplemental oxygen. Treatment with 100% oxygen (FiO_2 100%) reduces the half-life of CO to 30 to 90 minutes. Hyperbaric oxygen treatment can reduce the half-life of CO to 15 to 23 minutes. However, if the patient has additional burn injuries or is unstable, the patient should not be placed in a hyperbaric chamber. Also, the time needed to transfer patients to hyperbaric facilities and the subsequent difficulty of resuscitating a critically ill patient in a closed chamber make hyperbaric oxygen an impractical option. Therefore, prompt and aggressive evaluation and maintenance of the airway is the most important initial step in management of a burn patient.

3 Fluid Resuscitation

It is important to have large-bore IV access with 16G or 18G peripheral IVs. Intravenous access catheters should preferentially be placed in nonburned areas of skin although this is not always possible. If the patient is going to require invasive hemodynamic monitoring, a central line should be placed under sterile conditions. Peripherally inserted central catheter (PICC) lines can be used in burn patients, however, their infection rate remains high. If a central line is used, this does not need to be changed out at a certain time point but rather should be monitored daily for signs of infection. Minimally invasive monitoring of cardiac output is helpful. Though several technologies exist including esophageal Dopplers, arterial waveform monitors, and thermodilution modalities, the trend of these values are more useful than the absolute value. Burn injury and soft tissue edema make noninvasive blood pressure measurement difficult and inaccurate, hence arterial line placement is frequently necessary.

The Parkland or Consensus Formula is most commonly used to estimate fluid requirements for the first 24 hours and should be used to guide initial fluid infusion rates. This is a start point and should not be construed as a dogmatic prescription of the total fluid volume to be given during the first day after injury. It is extremely important to note the original time of the injury is what is used in the calculation, not the time of initial presentation to care providers. Only partial- and full-thickness burns are totaled to calculate burned TBSA.

Consensus formula: First 24-hour requirement = 2–4 cc × %TBSA × weight (kg)

Half of this fluid volume is planned to be administered in the first 8 hours after burn injury and the second half is administered over the next 16 hours. For example, if a 70-kg patient with 20% TBSA burn sustained at 10 AM presents 2 hours later, the crystalloid fluid to be administered in the first 8 hours is calculated using the following formula: [(4 cc × 20% × 70kg)/2]/6 hours. Lactated Ringer's crystalloid solution is recommended as the first choice fluid to avoid complications associated with metabolic acidosis when using normal saline or abnormal fluid shifts with colloid fluids.[33] Currently the data do not support hypertonic saline, dextran, or albumin during the first 24 hours of resuscitation in standard clinical situations.[34,35] Studies, however, have suggested that limited albumin usage may play a role in reducing the rate of abdominal compartment syndrome when the patient requires substantially more fluid administration than estimated by the Parkland Formula (>1.5 times).[36–38] Additionally, D5LR is commonly used for maintenance fluids in children under 1 year of age to avoid hypoglycemia. After 24 hours, there are data to suggest that providing albumin reduces fluid requirement.

Once resuscitation is initiated, the patient's vital signs and urine output should be closely monitored and laboratory studies should be drawn frequently, since proper fluid resuscitation should be guided by overall clinical response and the trend of vital signs as well as several laboratory values (**Table 12.3**). Intravenous fluid infusion rate should be increased or decreased based on the response of the patient on an hourly basis with fluid administration titrated to maintain urine output goals of 0.5 to 1 mL/kg/hr in

adults and 1 to 1.5 mL/kg/hr in children. Blood pressure and heart rate should also be monitored, however, burn patients are often tachycardic regardless of the degree of resuscitation. Though the urine output is considered a "gold standard," it often lags behind and thus it may be necessary to increase fluid administration to compensate for increased urine output on occasion. In addition, close monitoring of the patient's laboratory parameters are necessary to determine the trend in organ perfusion (**Table 12.3**). Although any one of these values alone does not provide a sensitive marker of the patient status, trending these values during resuscitation can help direct resuscitation adjustments if the current fluid rate is causing a positive trend.

In the second 24 hours, all patients should receive crystalloid fluids that are sufficient to maintain urine output and parameters of perfusion including lactate, pulse volume variation, and cardiac output. This will often be at a maintenance rate plus adjustment for losses of fluid into the burn wound. Nutritional support should be started enterally within 24 hours. After 24 to 36 hours, fluids can be decreased by one-third as long as the patient continues to make adequate urine, and cut again for hours 36 to 48. Colloid can be given after initial crystalloid resuscitation (5% albumin at 0.3 to 0.5 mL/kg per %TBSA over 24 hours).

After 48 hours, fluids should be given to maintain urine output at 0.5 to 1 mL/kg body weight per hour. Insensible losses and hyperthermia are associated with hyperdynamic state and increased fluid requirements. Daily patient weights can be helpful to determine insensible fluid loss or retention.

Pediatric fluid resuscitation does have some differences with regard to fluid management. Due to the limited reserve in children under 20 kg, an additional glucose-based maintenance fluid is recommended based upon patient using D5-containing solutions. Additionally, their fluid requirements may be as high as 6 mL/kg per TBSA and their urine output should be 1.0 to 1.5 mL/kg/hr.[39] Since burn resuscitation should be considered in the setting of a 10% TBSA in children, transfer to a burn center is recommended.

Table 12.3 Burn Resuscitation Flowsheet

	First 8 hrs				Next 16 hrs				Post Burn Day 2			
Time Since Injury												
pH												
Bicarb												
CO_2												
BD												
Lactate												
CVP												
U/O												
Central Venous Sat.												
PiCCO #s												
SVV												
SVRi												
ELWi												
GEDi												

Pulmonary status is also an indicator of fluid status but in a delayed fashion. Complications such as pulmonary edema result from fluid overload and necessitate daily evaluation of oxygen requirements and ventilator settings.

Difficult to Resuscitate Patients

If the fluid resuscitation required during the first 24 hours is 1.5 times greater than initially estimated or >6 cc/kg/hr, the physician should reassess the clinical picture. If estimates predict these high levels of fluid will be given, clinicians should consider changing the crystalloid to colloid. Additionally, continuous renal replacement therapy (CRRT) should be considered for cases where excessive fluid is estimated and the patient has kidney injury.[40] Giving excessive crystalloid fluids and failure to use appropriate early resuscitation adjuncts is associated with significantly worse outcomes. Physicians often will give additional fluid due to low urine output not realizing that the kidney, like other organs during burn shock often lag behind the clinical picture. Specific complications associated with excessive resuscitation include compartment syndrome of both the extremities and the

abdomen. Signs of abdominal compartment syndrome include abdominal distention, decreased urine output, elevated ventilator pressures, and desaturations. Surgeons should have a low threshold to assess for this devastating complication in any patient requiring resuscitation above the Parkland formula. Diagnosis can be made both by observing clinical signs as well as by assessment of bladder pressure transduced through a Foley catheter. Pressures over 20 mm Hg are considered abnormal and pressures greater than 25 mm Hg with evidence of organ failure indicate the urgent need for intervention. Strategies to intervene should begin with decreasing the rate of fluid administration. If the patient has full-thickness burns on the abdomen or torso, escharotomies should be performed. The bed should be reclined and a chemical paralytic can be given to relax the musculature. If elevated bladder pressures remain despite these maneuvers, a decompressive laparotomy is often required. Some surgeons will attempt decompression with a suprapubic peritoneal drainage catheter; however, the morbidity of these procedures is significant in burn patients. Therefore, attempts should be made to minimize fluid overload with early vigilant monitoring of fluid administration.

When patients are difficult to resuscitate, additional monitoring devices can be used including monitors of cardiac output and cardiac index. Examples include esophageal Doppler, bedside echo, and a formal transthoracic echo. Serial echo examinations after providing a fluid bolus allow monitoring of cardiac filling, IVC variation, and wall motion changes.[41,42]

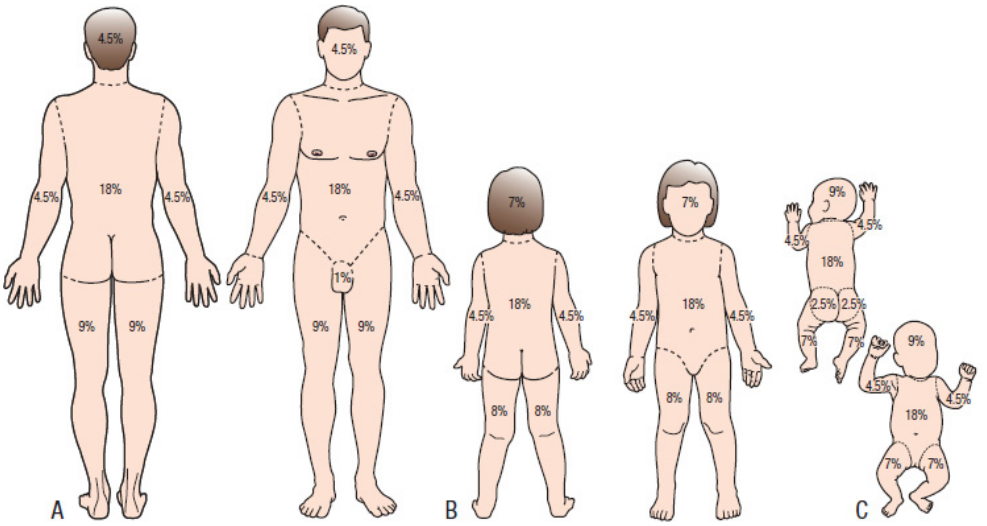
4 BURN SEVERITY

For full- and partial-thickness burns, identifying the extent of the burn injury is crucial. TBSA is useful to guide fluid resuscitation administration and defines the overall prognosis. Only partial- and full-thickness burns are totaled to calculate TBSA.

If small areas in various distributions are affected, it may be easier to use the patient as a ruler with one palm size (patient's) representing 1% TBSA. Another useful guide is the rule of 9s, where the adult body is partitioned into several areas that each constitutes 9% of the TBSA (**Fig. 12.2**). In children

and infants, the body surface area of the lower extremities constitutes a lower percentage while the head is higher. Careful estimation of TBSA is essential for proper early management of burn patients, as patients who have burns of more than 20% TBSA commonly require resuscitation.

Acute burn injuries require prompt intervention and serial examinations. On initial evaluation, it is important to recognize and treat constrictive circumferential burns that can lead to tissue ischemia and subsequent necrosis by limiting perfusion to the distal tissues.[32] All blisters and nonviable tissue must be debrided upon presentation. After the initial debridement, dressing changes are initiated while the patient is stabilized from a systemic standpoint. If patients suffer from full-thickness or deep partial-thickness injuries, debridement and grafting within 72 hours should be the standard of care.



rule of nines: (A) adult; (B) child; (C) infant

Figure 12.2 Rule of 9s used to estimate percent burns in adults and kids.

CRITICAL CARE OF THE BURN PATIENT

Hemodynamic Monitoring

Ideally, a critical care physician caring for a burn patient would be able to assess real-time responses to fluid administration through accurate cardiac output readings. Unfortunately, no such noninvasive devices to directly

assess cardiac output exist and those invasive devices that estimate cardiac output lack definitive studies supporting their use. Some centers use a pulse-induced contour cardiac output (PiCCO) device which provides a cardiac output based on temperature changes and use of the Fick equation; however, this requires a femoral arterial line and a large-bore internal jugular (IJ) or SVC catheter which introduces potential for complications. Some surgeons will use pulse volume variation (>25% being abnormal), however, this too lacks accuracy. Though goal-directed therapies with a pulmonary artery catheter, esophageal Doppler, TEE, or CVP monitor have demonstrated promising results in some critical care populations, their use in burn patients have been mixed.[43,44] Frequently, the output of monitors such as pulmonary artery catheters or CVP monitors fail to reflect the actual resuscitation of the patient.[46,47]

Ventilator Strategies

Treatment for Inhalational Injury

If inhalation injury is suspected, the patient should undergo urgent airway assessment and be placed on supplemental oxygen. Inhalation injury has three components that must be considered: (1) upper airway thermal injury which can cause swelling and obstruction, (2) carbon monoxide poisoning, and (3) lower airway chemical injury from toxic agents found in smoke. Upper airway thermal injury is treated by intubation of the airway and carbon monoxide poisoning is treated by 100% oxygen administration. Lower airway injury is diagnosed by evidence of soot or mucosal irritation on bronchoscopy. Airway mucosal injury from chemical pneumonitis leads to increased secretions while compromising the patient's ability to clear those secretions. This leads to increased risk of mucus plugging. Airway mucosal sloughing can also result in bleeding and clot formation that further obstruct airways. The use of aerosolized heparin, albuterol, and Mucomyst (HAM) following smoke inhalation to promote airway clearance is advocated in some centers, however, larger studies are needed to validate these treatments.[41,42,47–49]

Early endotracheal intubation and mechanical ventilator support is important in patients with inhalation injury or in large TBSA burns expected

to receive large-volume resuscitation. Ventilator management should follow ARDSnet protocol recommendations.[50,51] Recruitment maneuvers may be needed to improve oxygenation and/or ventilation. Permissive hypercapnia is preferred over large tidal volumes to avoid lung barotrauma. Limited studies have shown a potential role for high-frequency percussive ventilation in burn patients.[52]

Pulmonary infection in burn patients occurs in 30% to 50% of patients. Patients with three of the following five clinical criteria should be assessed for pneumonia with culture samples and placed on empiric antibiotic therapy: purulent sputum production, fever, elevated WBC, infiltrate on chest radiograph, and increasing supplemental oxygen requirements. If the patient has pneumonia and been in the hospital for over 48 hours, they should be treated for hospital-acquired pneumonia. Sputum or a bronchoalveolar lavage sample should be sent for aerobic, anaerobic, and quantitative cultures. Empiric antibiotics including coverage of Pseudomonas species and MRSA should be started until culture results become available.

Ventilator-Associated Pneumonia

Staphylococcus aureus and Streptococcus are common causes of early ventilator-associated pneumonia (VAP). *Pseudomonas aeruginosa* is the most common cause of late VAP. Normal diagnosis of pneumonia (fever, purulent sputum, or leukocytosis) is not helpful in burn patients since almost all patients are febrile, tachypneic, and have elevated white blood cell counts. The best diagnostic test is bronchoscopy-obtained bronchial alveolar lavage sample with quantification of the bacteria. Quantity of $>10^3$ CFU is considered positive for bronchoscopic specimen. ABA recommendations for length of VAP treatment are 8 days of antibiotic therapy for antibiotic-sensitive organisms and 15 days of therapy for multidrug-resistant organisms.[53] Consideration should be given to antifungal therapy (fluconazole [Diflucan]) if the patient does not respond to prolonged broad-spectrum antibiotics.

Electrolyte Abnormalities and Acute Renal Failure

The immediate effects of burn injury on kidney function are secondary to hypovolemia and circulating inflammatory mediators. The diuresis phase occurs at 48 to 72 hours after "third-space" fluid is reabsorbed. Hyponatremia is often seen due to large-volume resuscitation with hypotonic IV fluids and will usually self-correct. Open burn wounds or the use of topical silver nitrate can also cause hyponatremia. Renal hypoperfusion exacerbates hyponatremia by decreasing glomerular filtration. Hypernatremia may also occur due to insensible and evaporative water losses. Hypophosphatemia can result from dilution or refeeding syndrome. Hypocalcemia can result from use of silver nitrate.

Acute Kidney Injury

Risk factors include sepsis, large TBSA burns, organ failure, and antibiotic administration. Renal function is compromised by hypoperfusion, pharmacologic nephrotoxic insult, and sepsis which are all common following major burn injury. Physiologically there is a decrease in renal perfusion, glomerular filtration rate, and renal blood flow. Patients present with oliguria and decreased creatinine clearance. Early renal failure often results from hypovolemia-induced ischemic injury. However, overresuscitation can also compromise renal perfusion by causing abdominal compartment syndrome. Late renal failure occurs after fifth postburn day and is frequently caused by sepsis or nephrotoxic antibiotics. Continuous renal replacement therapy and pharmacologic treatments such as dopamine have not definitively been shown to improve outcomes. The initial care of acute renal failure patients should focus on reversing underlying causes and correcting any fluid and electrolyte imbalances.

Metabolic Response and Nutrition

The metabolism rate is significantly greater in burn patients than in other critically ill patients and leads to accelerated lean body mass wasting. Positive nitrogen balance is key to prevent skeletal muscle breakdown and highlights the importance of early nutritional support. The general composition of enteral feeding should include at least 60% calories from carbohydrates not exceeding 1,600 kcal/day, 12% to 15% from lipids and

essential fatty acids, and 20% to 25% from protein. Failure to meet large energy and protein requirements can impair wound healing and alter end-organ function. Even though adequate nutrition is crucial, overfeeding must be avoided. A randomized, double-blind, prospective study demonstrated that aggressive high-calorie feeding with enteral and parenteral nutrition was associated with increased mortality.[54] The daily caloric requirements can be calculated using the Curreri formula: [(25 kcal)(body weight (kg)] + [(40)(%TBSA burn)] 1 to 2 g/kg/day of protein for synthetic needs of the patient. Burn patients should receive less percentage of calorie requirements from fat than other ICU patients. The liver in a burn patient has less VLDL causing hepatic triglyceride elevation. Increased fat leads to increased complications including fatty liver, infection, hyperlipidemia, hypoxia, and mortality. Decreased gastrointestinal absorption and increased urinary losses can also lead to deficiencies in vitamin C, E, and zinc, iron, and selenium. Burn patients, like a subset of trauma and gastrointestinal surgery patients have been shown to benefit from glutamine supplementation.

Acute response to thermal injury is biphasic with the hypodynamic shock state at 24 to 72 hours and hyperdynamic catabolic state beginning on the fifth postburn day. Patients have supraphysiologic cardiac output, elevated body temperature, supranormal oxygen consumption, supranormal glucose consumption and altered glucose metabolism, increased and CO_2 production and accelerated tissue catabolism. This response is thought to be caused by excessive release of catabolic hormones including catecholamines, glucagon, and cortisol. There is a shift from anabolic–catabolic homeostasis to hypercatabolic state requiring increased substrates for energy including skeletal muscle which is broken down to maintain sufficient glucose amino acids. The resting metabolic rate is directly related to the severity of burn injury and a persistent hypermetabolic state is unsustainable. This hypermetabolism can be reduced by promptly treating sepsis as well as performing early excision and grafting of burn wounds. Recent studies have shown efficacy of a nonselective beta blocker such as propranolol which inhibits the effect of catecholamines and slows muscle catabolism. Herndon et al. demonstrated that propranolol in acute burns in the pediatric population improved net muscle synthesis and increased lean body mass.[55] Additionally, current standard of care includes providing pharmacologic agents such as

oxandrolone (testosterone analog given 0.1 mg/kg q12hr). Oxandrolone improves muscle synthetic activity, increases expression of muscle anabolic genes, and increases net muscle protein synthesis improving lean body mass composition and has been shown to reduce weight loss, improve donor-site wound healing and decreased hospital stay. Patients with burn injuries greater than 30% should receive oxandrolone for 6 months as the hypermetabolic state has been shown to persist following major burn injury. Despite being well tolerated, patients on oxandrolone should have their liver function tests monitored weekly. Human growth hormone and insulin-like growth factor have also been investigated but results have been indeterminate.

Glucose Control

Burn injury results in an increase in hepatic gluconeogenesis and impaired insulin-mediated glucose transport into skeletal and cardiac muscles and adipose tissue. Hypermetabolism seen in burn injury also leads to hyperglycemia and insulin resistance and thus glucose should be monitored in large burn injury patients. Currently, the data do not support strict glucose control (<110 mg/dL) but moderate blood glucose control is recommended (<180 mg/dL) and may decrease infectious complications.[56]

WOUND MANAGEMENT

There are a variety of burn wound dressing materials. Patient factors such as burn wound depth, condition, location of the burn, and comfort during dressing changes dictate the choice utilized.[33] Although the indications for systemic antibiotic therapy have not been clearly defined within the literature, use of antimicrobial dressings is recommended. Silver sulfadiazine (Silvadene) is a silver-containing cream that has broad-spectrum coverage against both gram-negative and gram-positive bacteria. Silvadene is commonly used on the skin of both partial- and full-thickness burn injuries. Its use is contraindicated in patients with sulfa allergies and over wounds near the eyes.[57] A self-limited leukopenia is commonly seen during the initial days of Silvadene treatment, but its use can be continued as leukocyte counts recover quickly without intervention. Mafenide acetate

(Sulfamylon) is an analogous agent that is used over cartilaginous areas such as the nose or ear due to increased tissue penetration compared to other dressing materials. Since topical Sulfamylon cream can be used without secondary dressing, it can be used for open burn wound therapy and regular examination of the burn wound surface. Both the cream and a 5% solution of Sulfamylon are equally effective.[58] Sulfamylon cream is useful for ear burns when there is risk of cartilage exposure. Sulfamylon may cause increased pain in the burn wound. In addition to the cream, Sulfamylon soaks can also be used for burn and postoperative dressings. Patients receiving large surface area Sulfamylon dressings should be monitored for complications such as hyperchloremic metabolic acidosis that can occur due to its mechanism of action as a carbonic anhydrase inhibitor.

Silver nitrate can also be used by soaking dressings in a 0.5% to 1.0% concentration solution and applied three to four times a day. These dressings offer several advantages over Sulfamylon soaks as they cover fungus in addition to bacteria and it is more cost effective. However, the use of silver nitrate in burn patients remains slightly controversial as nitrates are toxic to tissues and wound healing may be delayed by its use. The nitrates impair reepithelization and this effect is partially offset the benefits of silver in these compounds.[59] Furthermore, it can cause leaching of cations causing hyponatremia.

Bacitracin and Xeroform are additional examples of antimicrobial type dressing regimens and can be used after the first dressing takedown. While both can be used anywhere on the body, bacitracin is commonly used for facial burns. If grafts are placed in an area with surrounding cellulitis, soaks can be used during the first few days when the compressive dressing is still needed.

For patients who are at lower risk of infection based on the appearance of burn wounds, dressings may be changed with less frequency to achieve a balance between pain control and the need for wound coverage. Acticoat is one such option that is mainly used in partial-thickness burn injuries. This dressing consists of silver-impregnated sheets that have antimicrobial properties and can be changed less frequently, reducing pain and cost.[60] The nanocrystalline particles in Acticoat are able to reduce wound infection and promote wound healing compared to older silver products, including silver nitrate.[61] When using Acticoat, it is important to remember to moisten it with

water and not normal saline as sodium can inactivate the silver. There are other commercial products in addition to Acticoat that utilize the principle of nanocrystalline dressings. These dressings can be stuck on with mild adhesive (Mepilex), or wrapped or placed on like a glove (Silveron).

While dressing changes are sometimes used to optimize a wound before and after operative interventions, dressings also have the potential to completely heal a wound without the need for surgical intervention depending on the overall appearance of the burn and patient as a whole. Thus, a proper wound care team must not only include a critical care physician and surgeon, but it must also include a specialized wound care nurse to appropriately address this central modality of care for any burn patient.

Donor sites can be the most painful area for the patient and thus consistent donor-site care should be provided. Like other wounds, these wounds heal in a moist environment and though dry Xeroform can be used, this can be extremely painful for the patient. We prefer an adherent dressing that maintains wound moisture in addition to having an antimicrobial silver such as Mepilex.

OPERATIVE INTERVENTIONS

Excision and Grafting

After initial stabilization of the patient, which generally takes 24 to 48 hours, surgical intervention should occur as soon as possible since there are no benefits to delaying surgery when it is clear that a burn wound is of sufficient depth that it will not heal on its own.[62,63] Early excision of devitalized tissue appears to reduce the local and system effects of mediators released from burned tissue, thus reducing the progressive pathophysiologic derangements. It also removes dead skin which can serve as a nidus for wound infection. Tangential excision with a sharp blade on a guarded device removes necrotic tissue while preserving as much of the underlying viable tissue as possible. For large burn wounds, debridement should occur within 2 to 4 days of the initial injury. If there are insufficient donor sites to autograft all of the burn wounds, the debrided wound should be covered temporarily with allograft.[64]

Alternatively, the burn can be completely excised within the first several days after injury, and a temporary skin substitute can be used to close the wound remaining after available autologous skin has been harvested and grafted (**Fig. 12.3**). Sequential debridement and grafting is the backbone of burn care in those suffering from large TBSA burns. The use of allograft also allows the surgeon to assess the depth of the injury and the adequacy of their excision. If the homograft has good take, then it is likely an autograft will also take.

Figure 12.3 Full-thickness friction burn staged with Integra to allow for full declaration of the wound prior to grafting.

Figure 12.4 Grafting back of donor site with 4:1 split-thickness skin graft. (**Top**) Intraop placement of graft back. (**Bottom**) 4 weeks postop from graft back.

During tangential excision, tissue is debrided until healthy, bleeding tissue is reached. Grafting exists in many forms and decisions on coverage material and thickness of graft must be made in a strategic fashion to optimize functional and aesthetic outcomes. The gold standard is to use the patient's own tissue or autograft for reconstruction.

After a decision regarding the use of allograft versus autograft has been made, attention is turned to the size and thickness of the skin graft. Commonly, split-thickness skin grafts (STSGs) composed of the epidermis and a thin layer of dermis are utilized to minimize donor-site morbidity and optimize graft take. When delayed donor-site wound healing is expected such as in elderly patients and patients on chronic immunosuppressives, backgrafting back the donor site with 4:1 meshed grafts can accelerate healing (**Fig. 12.4**).

Thin grafts are more likely to succeed than thick grafts as it is easier to adhere and neovascularization to occur. There are certain areas, however, where split-thickness grafts should not be used since they cause greater secondary contracture and less color match over time as compared to full-thickness grafts. Areas of function, such as the hands and feet, lose a remarkable amount of utility if afflicted by scar contracture and may benefit from full-thickness grafts.[65] If split-thickness skin is used on the feet and hands, the grafts should be harvested on the thick side and meshing should be avoided if possible (**Fig. 12.5**). Similarly, aesthetically important areas, such as the face, are also more amenable to full-thickness skin grafting to optimize color match and minimize contracture over such areas.[66] If the cheeks or periorbital regions are involved, full-thickness skin grafts (FTSGs) should be placed prior to the development of ectropion which can be extremely difficult to treat. The abdomen can offer a site for large full-thickness harvest using an abdominoplasty incision (**Fig. 12.6**). Full-thickness grafts, nonetheless, are limited by increased donor-site morbidity due to the need to obtain both the epidermis and dermis from a region and also require closing the tissues primarily to avoid additional wounds. There is also more difficulty with successful and complete healing of the graft given that a more robust blood supply within the wound bed is necessary to optimize take of this thicker piece of tissue. Both full- and split-thickness grafts can be meshed to increase the surface area that may be covered. Meshing also allows for fluid egress, which minimizes the risk of fluid accumulation beneath the graft, a common cause of skin graft failure. Meshing should not be performed, however, over cosmetically sensitive areas given that the meshed pattern will be quite apparent even after complete healing has been achieved. Both types of skin grafts should be bolstered once placed to minimize shear, improve contact, and allow for imbibition and inosculation. **Table 12.4** summarizes the key steps involved in a burn excision.

Figure 12.5 Sheet grafting of full-thickness hand burns. In general meshed grafts should be avoided on the hands and across important joints to avoid scar contracture. (**Left**) Preop photo. (**Middle**) Intraop photo. (**Right**) 1-month postop photo.

Figure 12.6 Use of full-thickness skin graft to prevent facial ectropion. Full-thickness graft harvested from the abdomen. (**Left column**) Intraop photos. (**Middle figures**) Intraop donor-site photos. (**Right column**) Postop 2-week photo.

When burn injuries lead to large regions of exposed tendons, especially in the distal one-third of the lower extremity, free tissue transfer is often

required (**Fig. 12.7**). It is necessary to ensure that all dead tissue is debrided prior to coverage with a free flap to mitigate infection and flap failure. Additionally, if the patient is elderly or has vascular insufficiency, a preoperative CT angiogram should be obtained.

In larger burn wounds, patients may not have an adequate surface area available for donor sites. In such cases, allograft can be used instead for initial coverage. This homograft will serve as a temporary coverage and its take will ensure that the initial excision was performed at the correct depth. Allografts will eventually be rejected as the body recognizes the newly engrafted skin as foreign material after 10 to 13 days. The process is initiated by the placement of the allografts, which is associated with an inflammatory process, leading to the activation of the innate immune response. Donor dendritic cells migrate from the graft to the recipient's secondary lymphoid organs where they present donor antigens and elicit an adaptive immune response. This response results in activated effector T cells from the donor leaving the secondary lymphoid organs and infiltrating the graft where they mediate the rejection of the allograft.[67]

Additionally, if insufficient autograft exists even after temporary allograft, the surgeon should consider use of cultured epidermal autografts. Cultured epidermal autografts utilize the ability to grow keratinocytes in vitro to generate cohesive sheets of stratified epithelium, which maintains the characteristics of authentic epidermis. This technique was developed by Rheinwald and Green in 1975.[68] A 3- to 4-cm^2 sample is taken usually from the axilla or pubic area at the same time as initial debridement, and epidermal cells are isolated from the small skin biopsy and plated onto a layer of feeder cells that act as a supporting "feeder layer."[69] The feeder layer supports optimal clonal expansion of proliferative epithelial cells and promotes keratinocyte growth. Under optimal growth conditions, keratinocytes initiate growing colonies and after 3 to 4 weeks, the cultured epidermal autograft sheets are 8 to 10 cells thick.[70] These constructs require advanced planning as it takes at least 3 to 4 weeks to develop. Additionally, risks and benefits should be discussed with the family and patient as there is a high percentage of graft loss due to fragility. Furthermore, case reports of squamous cell cancer developing from cultured epidermal autograft sites do exist.

A newer technology known as the RECELL Autologous Cell Harvesting Device (or RECELL) is a point-of-care preparation and application of a suspension of noncultured, disaggregated, autologous skin cells. A 1 cm^2 of donor-site skin can be used to treat up to 80 cm^2 of excised burn.[71] It is used with widely meshed STSG (e.g., 6:1). Small trials have demonstrated noninferiority to STSG for small surface areas of mixed depth burn, however, the data are still lacking on effectiveness measures for this technology to be widely adopted.

Table 12.4 Pre- and Intraoperative Steps for a Burn Excision and Grafting Procedure

1. Preoperatively, it is helpful to correct hematologic and metabolic derangements given potential for large amount of blood loss.
2. The preoperative time-out should include a discussion of expected blood loss, the blood products available, and the transfusion triggers for the case.
3. In any burn over 20%, a preoperative blood type and crossmatch should be performed and PRBCs should be available in the operating room, and given appropriately, to avoid intraoperative acute blood loss anemia.
4. Arterial lines as well as large-bore IVs and often a central line should be in place before beginning the operation.
5. Techniques to decrease intraoperative blood loss include:
    a. The use of tourniquets on the extremities
    b. Use of topical spray thrombin and epinephrine-soaked Telfa pads placed immediately after excision followed by wrapping with Kerlix gauze soaked in a 1:1,000,000 epinephrine in saline solution
    c. In regions where circumferential wrapping cannot be performed, this epinephrine solution can be used as an injectable solution to perform dermatoclysis with an 18G spinal needle on the end of a 60 cc syringe or injection device
    d. This epinephrine injection solution is also used as a preharvest tumescent solution for donor sites, helping to create a flat surface on which to run the dermatome as well as decrease postharvest blood loss
    e. If working on an extremity, a good strategy is to start proximally and perform the excision followed by inflation of the tourniquet. Subsequently, the distal excision can be performed under tourniquet control
6. After achieving a healthy and well-vascularized wound bed, proceed with allografting or autografting.
7. If autografting is carried out, grafts can be excised in thicknesses ranging from 0.010 to 0.018 in. We typically use 0.012 in for standard grafts.
    a. Thinner grafts lead to faster donor-site healing, hence are helpful if there is a need to reharvest donor sites, or if the patient has thin skin

due to increased age or chronic immunosuppression.
   b. Thinner grafts increase the likelihood of skin graft take and decrease the risk of superficial epidermolysis of the graft, however, result in greater secondary contracture.
8. Grafts are meshed in 1:1 or 1:1.5 ratio to allow fluid egress.
9. Backgrafting: If backgrafting of the donor site is needed, the same area of graft harvested should be harvested next to the donor site then meshed 4:1 and placed over the entire donor site (**Fig 12.4**).

5 Order of Coverage

The first operations performed in large burn patients can often set the stage for if and how quickly a patient will recover. The first priority should be to excise all eschar and achieve coverage with autograft if available or with allograft if not available. In patients with large TBSA burns, it is crucial to get the back excised and covered first as delay of this step will make it difficult to have a patient stable enough to tolerate a prone position. Additional strategies to improve coverage of the back include the use of autograft meshed 3:1 covered with allograft meshed 2:1 and a secure bolster placed over top. This minimizes sheer and loss of the autograft. This early coverage of the back and avoidance of prone positioning may also mitigate the need to perform an early tracheostomy which in all other critical care patients has not proved beneficial. Once the posterior areas of the patient are excised and covered, then attention can be turned to the anterior regions and the extremities.

Extremity Treatment

Though the hands and feet are important to excise and cover early, these areas require the use of sheet or 1:1 meshed grafts. These areas should not delay the coverage of large areas such as the back which can use widely meshed grafts. More important, for the digits, is the use of early K-wire fixation in the intrinsic plus position in deep burns to the fingers. K-wires should be placed in the fingers to keep them in the intrinsic plus position: MC flexed at 70 to 90 degrees, wrist 20 to 30 degrees, IP joints in full

extension, and thumb kept abducted and slightly opposed. This will help prevent severe joint flexion contractures which can lead to the loss of digits if straightened in a delayed fashion.

Skin Alternatives

Integra is a newer alternative for temporary coverage and creation of a neodermis in a wound after debridement. Composed of bovine collagen and silicone film, this construct is designed to mimic the epidermis and dermis of the missing tissue.[64,72] Its structure allows for the growth of healthy granulation tissue into a wound bed to optimize the wound niche to promote greater and healthier take of the skin graft that will eventually be placed over the site of injury. This is especially important over areas of function, such as the hand, which has the potential for significant debilitation if scar or graft contracture occurs over the traumatized site. Integra is also important for areas that do not have enough viable or vascularized tissue to support a skin graft. Integra, however, often fails in burn patients due to infection and requires constant soaks with Sulfamylon. Additionally, clinicians should examine the Integra frequently and remove any areas of silicone under which there is concern for infection.

Porcine xenografts are an alternative to dressing changes alone in superficial partial-thickness burn wounds. In wounds that are likely to heal by themselves taking the patient to the operating room, performing a good debridement under anesthetic, and placement of xenograft to the burn wound can be beneficial (**Fig. 12.8**). The xenograft can minimize pain, improve wound healing, and deescalate the complexity of dressing changes. This benefit may be maximal in children or patients with tolerance to narcotic pain medications due to excessive pharmacologic supplementation before becoming injured.

PAIN CONTROL

Acute Pain

Burn injuries are among the most painful traumatic injuries sustained given their extensive nature. Thermal injury to the overlying epidermis leads to exposed nerve endings which are sensitive to stimulation. Thus, superficial partial-thickness burn injuries often cause the most pain to the patient. Deeper partial-thickness and full-thickness injuries may not cause as much pain to palpation; however, these regions are still painful due to the inflammatory response. Given the multifactorial nature of burn pain, elimination of pain in burn patients is not possible. Outcomes are often improved if a dedicated physician with expertise in pain management is part of the burn team. When establishing a pain regimen, the physician should focus on treating acute as well as chronic pain. A successful regimen often includes the use of short- to intermediate-acting narcotics to treat the acute pain as well as a long-acting narcotic such as methadone for the chronic pain.[73] Some patients will also benefit from gabapentin (Neurontin) to alleviate neurologic pain. Additional studies are underway to investigate the use of quetiapine (Seroquel) for patients with a large anxiety component associated with their pain. Balancing of narcotic dosing over time is essential to preserve their acute pain relief effect and to avoid situations in which tolerance renders all available agents and doses ineffective.

Figure 12.7 Use of free anterolateral thigh flap for reconstruction of lateral full-thickness ankle burn with exposed tendon. **A:** Wound bed. **B:** Free flap, intraoperative. **C:** Free flap, postoperative. **D:** Donor site. **E:** Healed donor site. **F:** Postoperative free flap appearance.

Chronic Pain and Substance Abuse

The burn patient population that is admitted with underlying substance abuse and alcohol dependency are a particular challenge for the burn team to successfully treat with regard to pain relief. In such circumstances, the team should have high vigilance for symptoms of drug or alcohol withdrawal. New studies are investigating prophylactic treatment with barbiturates to prevent alcohol withdrawal rather than currently used strategies which are largely reactionary and treat withdrawal after symptoms occur. Again the involvement of psychiatrist or pain specialist in the prescription of these drugs is beneficial. Methadone can also serve as helpful adjunct for patients with chronic pain at doses of 5 to 10 mg BID–TID given its decreased addictive potential to other narcotics.

INFECTIONS

Wound Infections

Burn wound sepsis is a severe sequelae of burn injuries caused by colonization of the damaged skin and soft tissues with infectious bacteria or fungi. The most common organisms are *Staphylococcus aureus, Streptococcus pneumoniae,* and *Pseudomonas aeruginosa*. Despite the morbidity of this complication, its incidence has decreased dramatically with the use of early excision and grafting and appropriate topical antibiotics therapy. If a burn wound infection is suspected, wound dressings should be taken down and a quantitative culture should be obtained. A bacterial count of greater than or equal to 10^5 colony-forming units bacteria/gram of tissue is considered a significant infection, though the data from which this number was derived dates back to the 1960s. General critical care infection protocols should be followed with burn wound debridement if the patient does not yet have skin grafts placed. If adequate excision was performed and the patient already has skin grafts placed, then antibiotic soaks or cream dressing changes and IV antibiotics will often help combat infection. Repeat quantitative cultures should be obtained every 3 to 4 days when treating a burn would infection to gauge progress and allow for escalation or deescalation of treatment.

Figure 12.8 Xenograft treatment of superficial partial-thickness burn to avoid use of STSG and to improve pain. (**Top, left**) Intraop photos of superficial partial-thickness burn. (**Top, right** and **bottom, left**) Placement of xenograft over burn using interrupted absorbable sutures. (**Bottom, right**) 1-month postop from xenograft placement.

Vascular Catheter–Related Infections

All central venous catheters should be placed using sterile technique and antibiotic impregnated catheters as these have proven efficacious in the general critical care population.[74] Additionally, central venous catheters should be placed in nonburned areas if possible. Routine changing of catheter after a specific time period has not been shown to improve outcomes. However, close attention should be paid to catheters in place for over 7 days, especially in burn areas if the patient is febrile and has signs of systemic infection. If a catheter-related infection is suspected, two peripheral blood cultures should be drawn. A culture specifically from the catheter does not improve diagnosis or outcomes. Despite the increased prevalence of the use of PICC lines, these lines have equal if not increased risk of infection than central venous lines.

Pneumonia

Along with the increased survival of burn patients comes the increased amount of time burn patients are on the mechanical ventilator. Increased incidence of pneumonia is seen with inhalation injuries and prolonged intubation and mechanical ventilation. As in other critical care populations, an emphasis should be placed on daily awakening and extubation/spontaneous breathing trials. Additionally, all patients on the ventilator should have their head of bed elevated greater than 30 degrees and daily chlorhexidine mouthwashes may be beneficial. If a pulmonary infection is suspected, a CXR should be performed and a quantitative culture specimen should be obtained from the bronchial tree. A quantitative result greater than 10^5 cfu/mL is considered positive and should be treated.

BURN RECONSTRUCTION

Optimizing Acute Treatment to Minimize the Need for Reconstruction

As in any plastic and reconstructive surgery case, meticulous planning and foresight is imperative. During the acute burn injury stages, emphasis should be placed on general coverage of burn wounds and large flaps and local tissue rearrangements should be delayed. However, if there is a high likelihood that the patient might need a flap or local tissue rearrangement in the future, the region of graft harvest should be carefully planned. For example, if a patient has a large neck burn or exposed lower extremity tendons or bone and an anterolateral thigh flap would help, then the thigh should be avoided as a donor site. Surgeons should consider the fact that a meshed skin graft will have an abnormal appearance once it heals as well as causing increased hypertrophic scarring. Donor sites should be harvested from inconspicuous locations in case a hypertrophic scar results. Other examples requiring acute reconstructive surgery include eyelid contracture with exposure keratitis and cervical contractures causing airway issues. Once acute grafts and donor sites have healed patients and physicians should focus on maximizing normal scar healing. Normal wound healing requires a balance in the hydration of the wound and water-based moisturizers should be encouraged. Silicone sheeting or other occlusive dressings can help in

early hydration of the wound.[75–77] Additionally, attempts should be made to minimize tension off of the scar with potential applications of new devices. Compression garments are also commonly used to decrease formation of hypertrophic scarring, though their efficacy is still debated.[78,79]

6 Hypertrophic Scarring

Thermal burn injures can cause tremendous morbidity, leaving the patient with not only cosmetic but also functional impairments. Hypertrophic scarring is a major complication after burn injury with a prevalence of 32% to 72%. Several risk factors have been identified that contribute to its development including the localization of the burn injury, burn depth, time to heal, and skin color.[80,81] While the precise mechanism by which hypertrophic scarring occurs remains unclear, strong and persistent expression of transforming growth factor beta (TGFβ), focal adhesion kinase-1 (FAK1), and its receptors have been associated with postburn hypertrophic scarring. Furthermore, a critical step in the healing process that is altered is the transition from granulation tissue into normal scarring. During this remodeling process, wound epithelization and scar collagen is formed but accompanied by a gradual decrease in cellularity due to apoptosis. However, early immature hypertrophic scars caused by burns are hypercellular and during the process of remodeling and maturing, fibroblast density do not resemble that of normal healing.[82] More specifically, apoptosis of myofibroblasts occur 12 days after injury in normal wound healing, but in hypertrophic scar tissue, the maximum apoptosis occurs much later at 19 to 30 months.[83] These events result in a significantly higher percentage of myofibroblast and the hypertrophy of the scar tissue following severe burn injuries.

One of the key pathologic factors that must be addressed in any hypertrophic scar is tension. A new concept of "scar rehabilitation" has emerged with the key idea being to improve the environment of the scar without actually excising the scar. The most important step in rehabilitating the scar is release of the tension. Rather than excising, the scar, this involves just releasing the area of greatest tension. Despite not removing any tissue, a large defect is often created once the tension is released. This defect can then be treated by adding new tissue such as an FTSG or a thick STSG.

Additional ways to relieve tension involve the use of tissue rearrangements such as a Z-plasty. A Z-plasty lengthens the scar at the expense of width alleviating tension along the central access of the hypertrophic scar. In general Z-plasty rearrangements are made with 60-degree angles to maximize tissue gain without causing excess tension on the donor-site closure. Alternative V-Y advancements are useful if there is healthy tissue surrounding the scar and can be advanced into the area of the contracture release. Both Z-plasties and V-Y advancements relieve the tension on the scar that help create the hypertrophic environment. By relieving this tension, the scars can heal in a more normal environment and often will do so without the raised erythematous characteristics initially present. The physiology of the Z-plasty is thought to result from improved collagen remodeling after relief of tension.[84,85] Z-plasties can be used to flatten a hypertrophic scar or elevate a depressed scar as long as the lateral limbs extend into normal tissue. The classic design of a Z-plasty has a central segment with limbs oriented at 60 degrees (although can be 30 to 90 degrees) with all three lines of equal length (**Fig. 12.9**). Widening the angle of the limbs increases percent gain in length along the central limb. Multiple Z-plasties can be designed in series to improve contracture release in large hypertrophic scars.

Although less well studied, postburn pruritus is another significant problem affecting almost 100% of pediatric and 87% adult patients and may persist for many years, resulting in a scratching/inflammation cycle leading to hypertrophic scarring. Treatment options are limited for postburn pruritus, commonly involving antihistamines and moisturization of the skin with only incomplete resolution of symptoms and thus significant deterioration in the quality of life.[86]

Current treatment strategies for hypertrophic scars include surgical manipulation, intralesional corticosteroid injections, cryotherapy, and laser therapy. Surgical manipulation to remove the excess skin remains the traditional treatment for hypertrophic scar. Recent studies investigating the role of fat grafting into scars have shown promise to further improve function and appearance.[87] Patients who have undergone fat transfer reported satisfactory results 6 months after the procedure, indicating considerable improvement in the features of the skin, skin texture, and thickness. Histologic examination demonstrated new collagen deposition, neovascularization, and dermal hyperplasia in regions treated with fat

grafting, which mimicked surrounding undamaged skin. Additionally, intralesional corticosteroids suppress the inflammatory process in wounds, diminish collagen synthesis, and enhance collagen degradation.[88] Conversely, cryotherapy induces vascular damage that leads to anoxia and ultimately tissue necrosis and has yielded marked improvement of hypertrophic scars.[89] However, its efficacy is limited to the management of small scars.

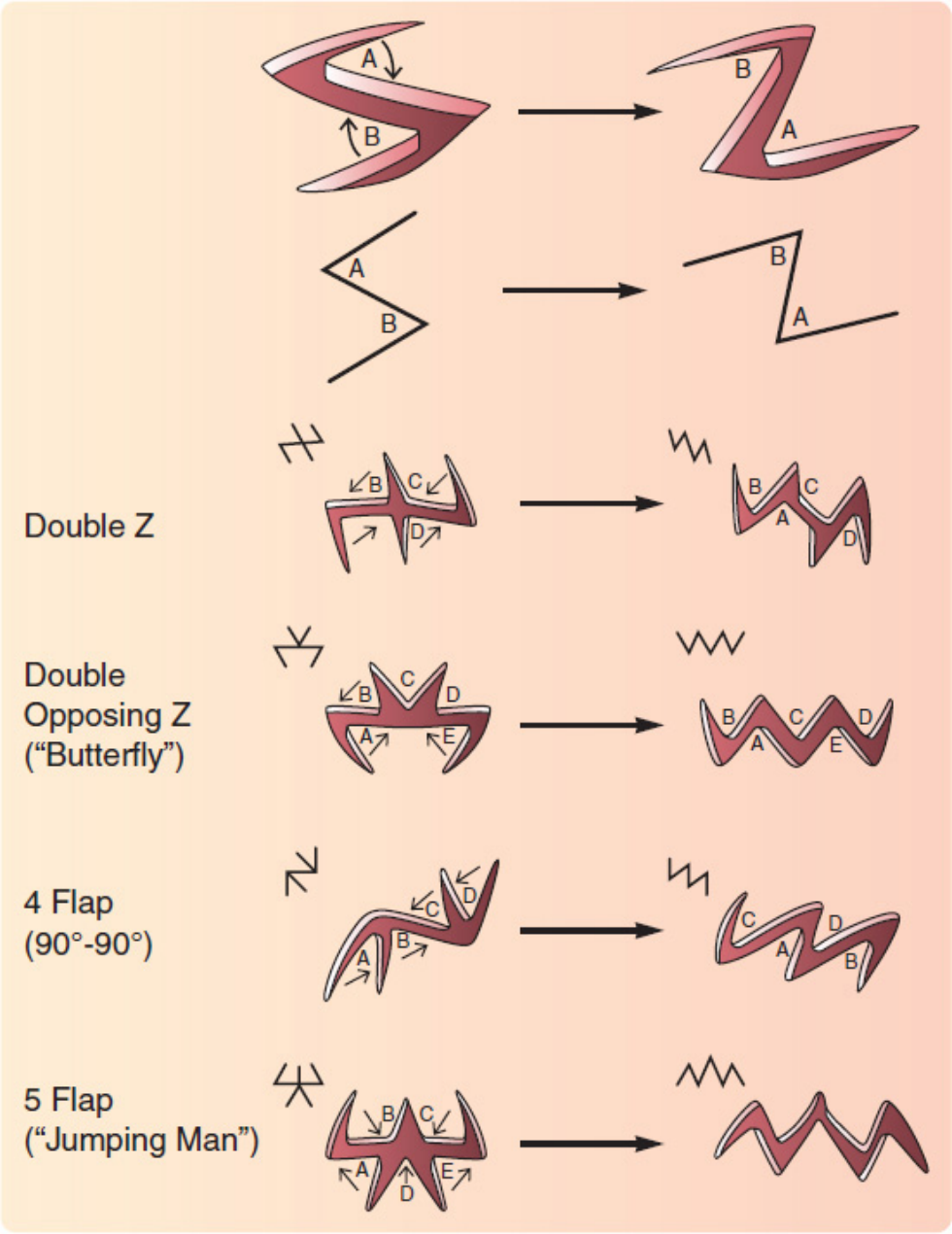


Figure 12.9 Z-plasty diagrams demonstrated tissue rearrangement used for hypertrophic burn scars.

Last, since the introduction of laser treatment in the mid-1980s, additional lasers with different wavelengths have been employed. Encouraging results have been obtained with the 585-nm wavelength pulsed dye laser (PDL), which has been recognized as an excellent therapeutic option for the treatment of younger hypertrophic scars.[90] PDL induces the dissociation of disulfide bonds in collagen fibers and leads to collagen fiber realignment, decreased fibroblast proliferation, and neocollagenesis. However, it is necessary for repeated treatments, generally between two and six treatments, for the optimal resolution. Shorter-pulse durations are generally more effective for scar improvement.[91] Unlike vascular malformations and hemangiomas, scars also tend to respond better to low or medium PDL fluences, about 4 to 7 J/cm^2, than to higher fluences.[92] Low, short-pulse duration PDL fluences induce local damage to the vascular endothelium followed by mural platelet thrombi, while high PDL fluences at longer-pulse durations tend to cause immediate intravascular coagulation with cessation of blood flow.[93] Side effects include erythema/purpura for 7 to 14 days, hyperpigmentation, and hypopigmentation. Though these lasers are effective in improving scar erythema, they do not have a substantial effect on the thickness or contour of hypertrophic scars. Controversy still exists about how much of this redness would subside if given adequate time compared to laser treatments.

Recently, research studies have demonstrated the benefit of fractional photothermolysis in the treatment of hypertrophic scarring. Though the exact mechanism is unknown, this concept uses a CO_2 laser (10,600 nm), which is an ablative laser that targets water in the underlying tissues. The laser creates columns of tissue destruction, which stimulates collagen production in adjacent uninjured columns of tissue. Only a portion of the epidermis and dermis is treated with columns of energy in order to create targeted areas of thermal damage (microthermal treatment zones, or MTZs). The untreated areas are a reservoir of collagen and promote tissue regrowth. Fractional lasers, as opposed to nonfractional lasers allow for greater penetration with decreased risk of scarring. This healing will take place outside of the acute inflammation period and thus allow for a more normal wound healing cascade than existed at the time of the initial excision and graft. The adjacent uninjured tissue allows for more rapid tissue regeneration from their follicles

and sweat glands. Ablative lasers have a greater potential depth of treatment compared to nonablative lasers (4.0 mm compared to 1.8 mm). Ablative lasers appear to be more effective for thicker scars and those associated with restriction. Overall, this creates a smoother appearance and allows meshed grafts to appear less obvious. Patients have described less tightness as well as decreased pruritus and improved overall appearance.[94–99]

Tissue Expansion

As a reconstructive technique, tissue expansion is versatile, reliable, and repeatable, and can be applied to many regions of the body. A tissue expander (TE) is an artificial filling device that is used to grow and expand local tissue to reconstruct an adjacent soft tissue defect. A silicone elastomer reservoir is placed beneath the donor tissue and slowly filled over time with saline, causing the overlying soft tissue envelope to stretch with a net increase in surface area per unit volume. Advantages to TE is that it allows the surgeon to reconstruct "like with like" using donor and recipient tissues that share similarities in color, thickness, texture, and hair-bearing patterns. Larger soft tissue defects that would usually require a local flap for reconstruction can be closed primarily using expanded local tissue, limiting donor-site morbidity. A robust angiogenic response is achieved histologically within the expanded local tissue resembling an incisional delay phenomenon. Predictable amounts of donor tissue can be gained through the expansion process. Disadvantages of tissue expansion include the need for multiple operations (at least two for placement and removal of the expander) and outpatient visits. Definitive reconstruction is delayed secondary to the expansion process. Specific complications related to the presence of foreign material can be as high as 30% (e.g., infection, exposure, or extrusion). This complication risk is even higher in the extremities and scalp.

Specific Anatomic Concerns

Neck contractures are the most common wound healing complication of burn injury. Functionally this can limit range of motion and oral competence. Surgical release of the scar contracture down to platysmal or subplatysmal

layer followed by coverage with large FTSG or thick STSG followed by aggressive range of motion 5 days after having patient in neck brace is an option for correction. If the contraction is severe, a free tissue transfer may be required after neck release. Postoperatively it is crucial to use compression garments for 6 to 18 months and neck bracing to keep neck extended to prevent contracture recurrence.

Ectropion is a common complication after periorbital burns. This deformity is caused by inadequate tissue therefore in addition to release the surgeon needs to replace tissue. If the ectropion is caused by an extrinsic contracture, scar release and provision of additional tissue are needed to prevent recurrence.

The axilla also represents a common area of contracture because it is difficult to maintain adequate positioning in the acute phase of burn wound healing. Anatomically the axilla can be divided into the anterior axillary fold, midaxillary line, and posterior axillary line. The shoulder should be kept 90 to 120 degrees abduction and 15 to 20 degrees flexion (60 to 80 degrees arm elevation). There are three grades of axillary contractures:

1A: Involves anterior axillary fold
1B: Involves posterior axillary fold
2: Involves both axillary folds
3: Involves both folds and axillary dome

Type 1 and 2 contractures can be treated with sequential release and thick STSGs or FTSGs. Type 3 contractures require local and distant flaps including parascapular and latissimus flaps. It is important to pay attention to where hair-bearing regions are transposed. Postoperative occupational therapy and splinting are necessary to prevent recurrence.

ASSOCIATED COMPLICATIONS OF BURN INJURIES

Muscle Catabolism and Wasting

Burn injury leads to significant changes in essential metabolic processes, which shift the physiologic homeostasis to a catabolic state, specifically resulting in the loss of lean body mass. The TBSA affected by the burn injury plays an important role, since reestablishing a functional skin barrier initially takes priority and requires a protein substrate, which is often provided by skeletal muscle.[100]

Muscle catabolism after burn injury is mediated by several factors including an increased energy requirement[101] and heightened inflammatory state involving the systemic release of stress hormones, catecholamines and glucocorticoids, which mediate the underlying metabolic derangements. Other factors include prolonged immobilization and the loss of a functional skin barrier, which leads to a disturbed thermoregulation requiring increased energy expenditure to maintain body temperature. The consequences can have devastating effects on the convalescence of the adult and especially pediatric burn patients, where an increased catabolic state can lead to delayed linear growth for up to 2 years after the injury.[102] The physiologic response of skeletal muscle to anabolic stimuli is altered in pediatric patients with amino acid infusion therapy failing to stimulate a net protein deposition in skeletal muscle of pediatric patients even 6 to 12 months post injury. This is most likely due to excessive protein breakdown.[103,104]

Some therapeutic approaches which have shown benefit in clinical trials include the blockage of beta-adrenergic receptors, resulting in attenuated catecholamine effect and improved net muscle protein balance.[105] Anabolic steroids, such as oxandrolone, and physical exercise have been shown to increase lean body mass in children who suffered from >40% TBSA burn injury.[106]

When the body is in a prolonged catabolic state due to the increase in caloric requirements, the patients must consume at least 2.5 to 3 g/kg/day of protein.[66] Nutritional shakes and high calorie foods are a necessity to optimize the conditions for wound healing. It is important to start nutrition as soon as possible, preferentially using the enteric route if possible.

Patients should also be referred to physical and occupational therapy. A therapeutic exercise program should be implemented to maintain normal range of motion, strength, and endurance. In order to counteract the catabolic effects of burn injuries, a program of active and active-assisted exercise is necessary. Depending on the severity of the burn and the patient's willingness

to tolerate the associated pain with exercise, passive range-of-motion exercises should be prescribed. In the event that full range of motion is not achievable, a program of stretching can be prescribed in its place. Furthermore, anesthesia can be used to assist these exercises, but should only be used in cases of patients who cannot tolerate the pain.

Range-of-motion exercises can also minimize skin contractures, as skin is a tissue that requires sustained mechanical stretch to facilitate lengthening of the underlying collagen and extracellular matrix compartments. Initial skin exercises should attempt to elongate the skin with repetitive low loads with differences in length. Following this initial precondition, a prolonged stretch is applied to maximize the skin laxity. Blanching is a clinical sign that capillary blood flow is impeded and is a good sign that the tissue has reached its maximum yield point. Strength exercise should follow as soon as the patient can tolerate it. Strength programs best suited for burn patients should include progressive resistive exercises. Fatigue and loss of endurance are major issues as a patient recovers. It is important to include endurance training and monitor cardiopulmonary response. Concurrently, patients should be encouraged to walk as ambulating patients have fewer lower extremity contractures, endurance problems, and venous thrombosis.

Heterotopic Ossification

Heterotopic ossification (HO) is the pathologic formation of bone in extraskeletal regions of soft tissue including muscle, joint spaces, and often encasing major nerves. This complication of burn injury causes significant pain, joint restriction, and contractures.[107] The incidence of HO is proportional to the severity of the injury with an increased incidence in severely burned patients. It may affect all areas of the body but is most frequently encountered in the elbow joint.[107,108] While the etiology of HO remains elusive, common risk factors that have been identified include upper extremity burns, large TBSA burns, young age, prolonged immobilization,[109] and a delay in time to wound closure.[110]

Early detection and diagnosis of heterotopic bone formation is critical in the clinical management of this complication, which oftentimes involves surgical resection. However, surgical intervention is associated with a high recurrence rate. Perioperative radiotherapy has been suggested as an adjunct

to surgical resection and has been shown to reduce the recurrence rate to some extent.[111]

Pharmacologic interventions have been shown to have some efficacy in limiting the severity of HO. Bisphosphonates and NSAIDs have been used for prophylaxis and treatment of HO with some success.[112,113] While there is no consensus on choice or timing of therapy, it has been proposed that bisphosphonates should be prescribed as soon as elevated alkaline phosphatase is noted or imaging studies establish the presence of HO. Other studies have shown that NSAIDs limit the severity of HO when delivered as a preventative therapy.

Majorlin Ulcer

Similar to chronic wounds from other etiologies, chronic untreated burn scars can lead to malignant degeneration. Squamous cell carcinoma is the most common type of malignancy observed, however, these malignancies are rare in an era of early excision and grafting. Malignancy requires wide excision with at least a 2-cm margin as well as sentinel lymph node biopsy. If the sentinel node is observed to be positive, a compete lymph node excision should be performed.

CLINICAL RESEARCH

Within the last decade, critical care, wound care treatment, and burn reconstruction research has advanced in both diagnosis and identification of efficacious therapies to improve the overall recovery process for burn victims.

Critical care research has focused on the delivery of appropriate resuscitation during the initial phase following the traumatic burn injury. Immediately following the trauma, burn patients experience severe shock due to concomitant inflammation leading to severe edema. Typical fluid resuscitation for burns has been crystalloid, though some centers use colloid as rescue therapy when patients exhibit increasing and greater than expected fluid requirements, known as “fluid creep.” A retrospective study assessing the use of crystalloid with colloid (5% albumin) supplementation in patients

with injury >20% TBSA demonstrated normalizing of resuscitation ratios (ratio of hourly intake in mL/kg/%TBSA/hr to hourly urine output in mL/kg/hr) with the addition of albumin.[38] Similar findings have also been reported in pediatric burn literature.[114] Our practice uses colloid supplementation after the first 24 hours in patients requiring higher than expected resuscitation to minimize fluid creep.

Transfusion strategy is also an area of investigation in burns, given that patients with major burns require large-volume transfusion during the acute treatment phase. The Transfusion Requirement in Burn Care Evaluation (TRIBE) trial compared a restrictive (hemoglobin goal 7 to 8 g/dL) versus a liberal (hemoglobin goal 10 to 11 g/dL) strategy for burns >20% TBSA.[115] The restrictive strategy halved blood product utilization. There was no difference in mortality, blood stream infection, or organ dysfunction with the restrictive strategy compared to the liberal strategy.

Autologous coverage burn excision sites in the setting of limited donor-site availability remains a challenge for large, full-thickness burns. As discussed in previous sections, cultured epithelial autografts have gained increased interest as an alternative for cutaneous coverage for patients with large burn wounds and small potential donor sites, however, there is yet a skin substitute to be developed that can function as well as an autograft. An active area of research is investigation of the effectiveness of new technologies such as RECELL. While small studies have demonstrated noninferiority to STSG for small burn wounds, the technology requires further investigation to prove effectiveness. There are currently trials ongoing to assess for the benefit of different wound dressings with RECELL technology, such as the BRACS trial, which is comparing silver dressings on mixed depth wounds with RECELL technology with and without Biobrane, a biosynthetic wound dressing.[116] Another trial is assessing the efficacy of negative pressure wound therapy in pediatric burns, the SONATA in C trial.[117] These studies will provide evidence-based guidelines for best practices in burn wound care.

BASIC SCIENCE AND TRANSLATIONAL SCIENCE RESEARCH

Basic science and translational science research in burn injuries have significantly advanced in the last 50 years and have focused on both understanding and treating the primary wound site as well as complications that arise from these traumatic burn injuries.

Wound healing can be described in three different stages: inflammation, proliferation, and remodeling phase. Hypertrophic scarring is an aberrant form of the normal wound healing process that does not extend beyond the original wound margins. Hypertrophic scar formation involves the constitutively active proliferative phase of wound healing, resulting in high vascularity and dense extracellular matrix deposition.[118] Histologic studies suggest that a robust inflammatory response, involving mast cells, macrophages, fibrocytes, and lymphocytes, may underlie the excessive fibrosis seen in hypertrophic scar formation.[119] The secretion of TGF-beta1, platelet-derived growth factors, and epidermal growth factor contribute to the inflammatory response and results in excessive inflammatory cell stimulation, fibroblast proliferation, adhesion, neovascularization, matrix production, and ultimately contraction.[120] As such, translational science research from the bench to the bedside focuses on new therapies targeted at quenching the inflammatory response, limiting fibrosis, and inhibiting angiogenesis to target the mediators of this scarring process.[121,122] Additional basic science research aimed at understanding the wound healing process and translational science research investigating new treatment options will continue to advance our understanding and treatment of burn-related injuries.

CONCLUSION

Burns are responsible for significant morbidity and mortality and are among the most complex and devastating of all traumatic injuries. Early proper diagnosis of burn depth and extent allows for the delivery of appropriate treatment ensures the best prognosis for burn patients. Early tangential excision and autografting remains the foundation of burn treatment. Diagnosis of secondary burn complications, such as joint contracture and heterotopic ossification, has advanced with new imaging tools. Nevertheless, the management of burn patients requires a team of physicians, nurses, critical care specialist, physical therapist, and counselor to provide optimal care to

patients and lessen the burden of the initial burn injury. Furthermore, novel clinical, basic science, and translational science research continues to improve our understanding of the pathophysiology of burn injuries. Elucidating the pathophysiology of both the primary wound and secondary complications will assist in the treatment during the critical period and following the initial trauma and prevent secondary burn complications.

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13

Anesthesiology and Pain Management

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Key Points

1 Anesthetics are generalized depressants of consciousness, pain, cardiopulmonary function, motor function, and recall.

2 To prevent movement and to facilitate the surgical exposure, neuromuscular blocking agents are generally used. These drugs are competitive or noncompetitive inhibitors of the neurotransmitter acetylcholine at the neuromuscular junction.

3 Residual neuromuscular blockade is a common and underappreciated phenomenon that impacts postoperative adverse events such as hypoxemia, pneumonia, reintubation, and prolonged recovery room stay. Sugammadex, a novel medication capable of reversing deep neuromuscular blockade, may revolutionize perioperative care for high-risk patients.

4 Opioids produce profound analgesia and respiratory depression. They have no amnesic properties, minimal direct myocardial depressive effects, and no muscle-relaxant properties.

5 Propofol is a lipid-soluble substituted isopropyl phenol that produces a rapid induction of anesthesia followed by awakening in 4 to 8 minutes after a single bolus. However, as the duration and dose of the maintenance infusion is increased, the time to return of consciousness is also significantly increased.

6 Although neuraxial techniques (spinal and epidural) may decrease pulmonary complications, they are associated with hemodynamic instability and are contraindicated in patients with severe flow-dependent cardiovascular diseases.

7 Peripheral nerve blockade can be used in lieu of general anesthesia as a primary anesthetic for surgery, or in conjunction with general anesthesia to serve as a postoperative pain management technique. Use of long-acting local anesthetics or placement of an indwelling continuous catheter provides long-term (16 hours to several days) pain relief.

8 The concept of airway management should be focused on not just endotracheal intubation, but also mask ventilation. Until the airway

can be secured via intubation, the patient must be supported through mask ventilation. The key elements of an airway examination are an assessment of obesity, mouth opening, neck flexion and extension, Mallampati oropharyngeal classification, presence of beard, and mandibular protrusion ability.

9 Laryngeal mask airways offer an alternative to endotracheal intubation for general anesthesia airway management in selected patients and procedures.

10 More than 8% of patients undergoing major noncardiac inpatient surgery will experience postoperative myocardial ischemia, elevating their risk of 30-day mortality. For symptomatic patients, benefits must be weighed against risk of initiating preoperative beta-blockers, alpha-blockers, and aspirin.

11 The appropriate duration to defer elective surgery after coronary stenting remains controversial, but recent guidelines from the American College of Cardiology/American Heart Association recommend 6 months for drug-eluting stents and 30 days for bare-metal stents. The role for antiplatelet therapy remains a major question, but data suggest that cessation of recommended antiplatelet therapy in the perioperative period may have significant coronary thrombotic risks without major improvement in bleeding adverse events.

12 The three goals of the preoperative evaluation are (a) to develop an anesthetic plan that considers the patient's medical condition, the requirements of the surgical procedure, and the patient's preferences; (b) to ensure that the patient's chronic disease is under appropriate medical therapy before an elective procedure; and (c) to gain rapport with and the confidence of the patient, answer any questions, and allay fears.

13 Patients receiving chronic pain or opioid addiction therapy with buprenorphine (Subutex, Suboxone) can be particularly challenging to manage in the postoperative period and should be immediately referred to their primary care physician and an anesthesiologist to

create a pain management plan prior to the day of surgery. Buprenorphine is mixed opioid agonist/antagonist that tightly binds at the μ-receptor and has a long and varied half-life (24 to 60 hours). It can inhibit the analgesic benefits of traditional opioids in the postoperative period, resulting in uncontrolled pain, decreased patient satisfaction, and the potential for adverse events due to the need for very high doses of opioids.

14 As positive-pressure ventilation impedes venous return within a closed thorax, decreases in systolic pressure associated with a respiratory pattern can be detected. In patients with sinus rhythm with stable cardiac contractility, the degree of systolic pressure variation (SPV) is inversely related to the intravascular volume status of the patient. The normal range of SPV is 5 to 10 mm Hg. Other measures such as pulse pressure variation (PPV) use similar physiologic assumptions to assess volume status.

15 Enhanced recovery programs incorporating preoperative optimization, standardized surgical and anesthesia protocols, and goal-directed therapy may improve patient outcomes and reduce costs.

16 Postoperative acute pain management may require a multimodal approach that incorporates opioids, peripheral nerve blockade, and nonopioid analgesics. Chronic pain patients can be particularly difficult to manage and may require preoperative optimization by an anesthesiologist.

INTRODUCTION

The goal of anesthesia is to enable the safe conduct of otherwise noxious procedures with maintenance of physiologic homeostasis while optimizing procedural conditions. The state of general anesthesia is a combination of hypnosis, amnesia, analgesia, and muscle relaxation, achieved by the administration of single or multiple anesthetic agents via inhalational or

intravenous routes. Historically, anesthesia was achieved by inhaling anesthetic vapors that produced each of these conditions in proportion to the concentration achieved in the central nervous system. Anesthesia can also be achieved by using a balance of multiple pharmacologic agents, each targeted to produce a specific effect—hypnotic/sedatives, analgesics, and neuromuscular blocking agents. As the concentration of hypnotic/sedative and analgesic agents increases, cardiovascular and respiratory functions may be progressively blunted; titration of these agents is necessary to optimize conditions for the surgery while maintaining cardiovascular stability.

Despite serious potential complications surgical anesthesia is administered with a high degree of safety 30 to 40 million times a year in the United States. The high degree of safety may be attributed to the efforts of thousands of surgeons and anesthesiologists who have advanced the art and science of their field.[1] Although modern surgical techniques, regional or neuraxial blockade procedures, and systemic analgesics have made it possible to ameliorate perioperative pain, significant challenges in postoperative pain management remain. Pain is not only unpleasant, but also can provoke a stress response leading to significant adverse effects.

ANESTHETIC AGENTS AND THEIR PHYSIOLOGIC EFFECTS

Inhalation Agents

1 Inhalational anesthetics produce dose-dependent depression of consciousness, pain, cardiopulmonary function, motor function, and recall. Comparative potency of inhalation agents is expressed as the minimum alveolar concentration (MAC), an empirically derived number defined as the expired percent concentration required to prevent movement on painful stimulation (incision) in half of experimental subjects. There is significant patient-to-patient variability independent of underlying comorbidities. Compounding this variability are the effects of age, weight, pre-existing heart disease, liver disease, and co-administered medications. **Table 13.1** lists the commonly used inhalation agents, their MACs and side effects. In general, all agents cause hypotension by myocardial depression and vasodilation. There

is also a generalized depression of cerebral function and cerebral metabolic rate for oxygen, although cerebral blood flow may increase because of cerebrovascular dilatation and a loss of flow-metabolism coupling. Renal blood flow and glomerular filtration rate are reduced by 20% to 50%. The body's regulation of core body temperature is lost, resulting in a redistribution of heat from the core to the periphery; the cold environment of the operating room and open body cavities make anesthetized patients extremely vulnerable to hypothermia (core body temperature <36°C).

Intravenous Sedatives/Hypnotics

Several commonly used intravenous sedative/hypnotic medications can also be used, by intravenous infusion, in lieu of an inhalational anesthetic to achieve maintenance of anesthesia. Unlike inhalational agents, currently, there is no ability to measure the patient's expired or blood concentration of these intravenous agents. As a result, the infusion rate is titrated to effect by observing patient movement (if muscle relaxants are not used concurrently) and hemodynamic responses to procedural stimuli. The sedative/hypnotic intravenous agents do not possess clinically useful muscle relaxant or analgesic properties and must be combined with other agents to deliver a "balanced" anesthetic. The most commonly used intravenous agent for maintenance of anesthesia is propofol, a lipid-soluble substituted isopropyl phenol that produces hypnosis and sedation through interactions with γ-aminobutyric acid (GABA), the primary inhibitory neurotransmitter of the central nervous system. When administered as a continuous infusion, propofol can achieve minimal levels of sedation, deep sedation, or general anesthesia. Additional details regarding the use and side effects of propofol are discussed later. Other classic agents such as benzodiazepines can also be used as maintenance infusions, but do not enable the rapid return to consciousness that propofol offers. The highly specific α_2-receptor agonist, dexmedetomidine, may also be used as an intravenous sedative/hypnotic and also has analgesic effects and does not produce significant respiratory depression. In the perioperative setting, it is currently limited to use as an adjunct to propofol and inhalational anesthetics for general anesthesia or as a sole agent during procedural sedation.

Muscle Relaxants

2 To prevent movement and to facilitate surgical exposure, neuromuscular blocking agents are generally used. These drugs are competitive or noncompetitive inhibitors of the neurotransmitter acetylcholine at the neuromuscular junction. The only noncompetitive inhibitor used clinically is succinylcholine. This drug rapidly binds to the nicotinic receptors and produces depolarization at the neuromuscular junction, clinically manifesting as fine-muscle fasciculations occurring 30 to 60 seconds after injection. Succinylcholine cannot be reversed, but has a short duration of action (<10 minutes) because it is quickly hydrolyzed in the plasma by cholinesterase. Because of rapid onset and short duration of action, succinylcholine is classically used to facilitate endotracheal intubation when it must be accomplished quickly, or when quickly regaining neuromuscular function is beneficial.

All other clinically useful muscle relaxants compete with endogenous acetylcholine at the neuromuscular junction, are termed *competitive inhibitors* and do not cause depolarization (nondepolarizing). The block produced is in direct proportion to the concentration of the agent relative to the concentration of acetylcholine. If the concentration ratio is low enough, competitive relaxants can be reversed by agents that block acetylcholine metabolism, an anticholinesterase (e.g., neostigmine). The neuromuscular blocking agent is still present, but motor function returns when acetylcholine concentration is high enough to overwhelm the blocking agent. Anticholinesterases hence exhibit a ceiling effect. There are systemic consequences to increasing the plasma concentration of acetylcholine. Acetylcholine is the predominant neurotransmitter in the preganglionic sympathetic and parasympathetic nervous systems and in the postganglionic parasympathetic nervous system. To counter the undesirable effects of systemic acetylcholine an anticholinergic drug (atropine or glycopyrrolate) must be given with the anticholinesterase. The common neuromuscular blocking drugs and their doses, durations, and side effects are listed in **Table 13.2**; common regimens of reversal agents are shown in **Table 13.3**.

Table 13.1 Common Inhalation Agents: Minimum Alveolar Concentrations and Effects

Agent	Minimum Alveolar Concentration (%)	Strengths	Weaknesses
Nitrous oxide	105	Analgesia Rapid uptake and elimination Less cardiac or respiratory depression	Sympathetic stimulation Expansion of closed air spaces Interference with vitamin B_{12} metabolism Limitation of inspired oxygen fraction
Isoflurane	1.15	Good muscle relaxation Stable cardiac rate and rhythm Usability in neurosurgery	Airway irritant, may cause coughing
Desflurane	6	Rapid induction and emergence	Airway irritant, may cause coughing High vapor pressure (Boiling point 23.5°C) requiring special

			pressurized vaporizer High cost
Sevoflurane	1.71	Rapid induction and emergence Less pungent, does not cause airway irritation	Moderate cost

3 Postoperative residual neuromuscular blockade is recognized as a common problem after routine administration of nondepolarizing muscle relaxants. The evaluation of depth of muscle relaxation is a subjective process based upon empirical pharmacokinetics or visual inspection of a patient's peripheral nerve response to external electrical stimulation. During peripheral nerve stimulator monitoring, two electrode patches are placed on the patient's skin along the course of a peripheral nerve which innervates an observable muscle group. Commonly used monitoring locations include the ulnar nerve, ophthalmic branch of the facial nerve, or the posterior tibial nerve. Electrodes are connected to a hand-held device which delivers four short transcutaneous bursts of electricity, ranging from 10 to 100 mA every 0.5 seconds, hence the term "train-of-four monitoring." A clinician visually inspects the response to each electrical stimulation. In a patient without any pharmacologic neuromuscular blockade, the strength of the fourth muscle response (or "twitch") matches that of the first. In the face of complete pharmacologic competitive inhibition of neuromuscular transmission, no muscular twitches are observed at all. At varying levels of neuromuscular blockade in between, the fourth, third, or second twitch may be absent. Due to competitive blocking of the neuromuscular junction nicotinic receptor, each successive stimulation results in a weaker response because sequentially fewer receptors are available for stimulation. The ratio between the strength of the fourth twitch and the first twitch is known as the train-of-four ratio. During normal neuromuscular transmission, the ratio is 1. Historically, a ratio of 0.7 was considered adequate muscular strength for

extubation. However, more recent literature suggests that a ratio between 0.7 and 0.9 still exposes the patient to significant risks of atelectasis, hypoxemia, aspiration, pneumonia, and possibly reintubation. In routine practice, a clinician is incapable of assessing a concept as precise or nuanced as train-of-four ratio. As a result, the number of twitches observed is typically reported, that is, 0/4, 1/4, 2/4, 3/4, 4/4. A patient with 3/4 or 4/4 twitches is capable of responding to cholinesterase inhibitors and return to normal function. A patient with 0/4, 1/4, or 2/4 is unlikely to adequately respond to cholinesterase inhibitors. Data from multiple centers have demonstrated that a significant proportion of patients demonstrated residual neuromuscular blockade of <0.9 in the recovery room despite reversal.

Table 13.2 Common Neuromuscular Blocking Drugs and Reversal Agents

Muscle Relaxant	Intubating Dose (mg/kg)	Infusion Dose (mg/kg/min)	Strengths	Weaknesses
Depolarizing				
Succinylcholine	1.0	100[a]	Fastest onset (30–60 s) Short duration[b] (5–10 min)	Associated with malignant hyperthermia, dysrhythmias, bradycardia, and hyperkalemia, especially in patients with burns or neurologic injury
Nondepolarizing				
Cisatracurium	0.2	0.1	Spontaneous degradation, not affected by renal or liver disease	Moderate cost
Vecuronium	0.1	1	No cardiovascular effects	
Rocuronium	0.8	10	Fast onset, no cardiovascular effects	

[a]This should not be used for longer than 1 hr.
[b]Duration is dramatically increased in patients with abnormal plasma pseudocholinesterase.

Table 13.3 Drugs for Antagonizing Nondepolarizing Neuromuscular Blockade[a]

Dose	Time to Peak Effect (min)	Dose	Use with	Comments
Anticholinesterases				
Edrophonium	1–2	0.5–1.0 mg/kg	Atropine	Very fast onset, not commonly used
Neostigmine	3–5	0.04–0.07 mg/kg	Glycopyrrolate	Most commonly used
Pyridostigmine	10–12	0.2–0.3 mg/kg	—	Not used clinically for neuromuscular reversal
Selective Relaxant Binding Agents				
Sugammadex	2–3	2–16 mg/kg	—	Primarily used for reversal of rocuronium and vecuronium

[a]For reliable results in reversing the effects of nondepolarizing muscle relaxants, administration of anticholinesterases is delayed until spontaneous recovery permits three to four twitch responses to a train-of-four stimulus. For patients with more profound blockade, larger amounts of anticholinesterases may be required, but doses of neostigmine higher than 0.14 mg/kg are unlikely to produce additional improvement.
CNS, central nervous system.
Adapted from Watling SM, Dasta JF. Prolonged paralysis in intensive care unit patients after the use of neuromuscular blocking agents: a review of the literature. *Crit Care Med* 1994;22:884.

The use of subjective train-of-four monitors is inferior to objective acceleromyography, a calibrated device used to accurately establish the "true" train-of-four ratio. Although clinically effective at eliminating the limitations of subjective train-of-four monitoring, its use remains limited because of the time necessary for set up, and an under-appreciation of the frequency of residual neuromuscular blockade. It has been promoted by patient safety experts, and is beginning to demonstrate increased penetration.

Muscles in the body are not equally sensitive to muscle relaxants. The diaphragm is most resistant to neuromuscular blockade, whereas the neck and pharyngeal muscles that support the airway are most sensitive. It is therefore possible for an intubated patient to exhibit adequate spontaneous ventilation and produce a large negative inspiratory pressure and yet develop complete airway obstruction when extubated.

A novel class of compounds known as *selective relaxant binding agents*—currently comprised of only one FDA-approved drug, sugammadex—may serve to revolutionize the practice of neuromuscular blockade and its reversal. Such compounds are able to rapidly reverse the effects of profound levels of muscle relaxation (0/4 twitches) created by steroidal nondepolarizing muscle relaxant agents rocuronium and vecuronium. These agents physically bind free muscle relaxant molecules within a cyclodextrin ring structure and decrease the concentration of free muscle relaxant allowing acetylcholine to function normally at the neuromuscular junction.

The cyclodextrin–muscle relaxant combination is eliminated via the kidney. The drug rapidly (<3 minutes) reverses profound muscle relaxation[2] without cholinergic side effects offering considerable advantage over the traditional approach. Sugammadex cannot reverse neuromuscular blockade achieved with benzylisoquinolinium muscle relaxants (atracurium, cisatracurium) given incompatibility in chemical structures.

Opioids (Narcotics) and Other Intravenous Analgesics

Narcotics and synthetic analogues belong to the class of drugs called *opioids*. The most commonly used drugs in this family are morphine, fentanyl, and hydromorphone. Since the mid-1980s, a series of synthetic opioids have been developed with fentanyl as the prototype. More recently developed synthetics (sufentanil, alfentanil, and remifentanil) are more potent and 4 of varying duration (**Table 13.4**). Opioids produce profound analgesia and respiratory depression. They have no amnesic properties, minimal direct myocardial depressive effects, and no muscle-relaxant properties. Opioids can produce significant hemodynamic effects indirectly by releasing histamine or blunting the patient's sympathetic vascular tone. Acutely injured patients may be hypovolemic and in pain, with high sympathetic tone and peripheral vascular resistance and can, therefore, experience dramatic drops in systemic blood pressure with minimal doses of opioids. Because of the lack of direct myocardial depression and the absence of histamine release with the synthetic opioids, they are frequently used as the primary anesthetic in combination with an amnesic agent and a muscle relaxant in patients with significant myocardial dysfunction.

All opioids can be reversed with naloxone. The duration of action of naloxone can be shorter than that of the opioid, and patients must be observed carefully for renarcotization after they have been treated with naloxone. Naloxone treatment has been associated with acute pulmonary edema and myocardial ischemia and should not be used electively to reverse the effects of a narcotic.

Propofol

Propofol is a lipid-soluble substituted isopropyl phenol that produces a rapid induction of anesthesia in 30 seconds followed by awakening in 4 to 8 minutes after a single bolus. Intravenous propofol can effectively produce total anesthesia (for less stimulating procedures), including amnesia, some 5 analgesia, and some degree of muscle relaxation. As the duration and dose of the maintenance infusion is increased, the time to return to consciousness is also significantly increased. This context-sensitive half-life of propofol must be incorporated into expectations of a "quick wake-up." Propofol has direct antiemetic properties and is a valid alternative to inhalational anesthetics in patients who have demonstrated a history of prolonged, refractory postoperative nausea and vomiting. It has an important role in intensive care units when used as a continuous infusion sedative. However, prolonged infusions have been associated with a lethal metabolic derangement known as propofol infusion syndrome, characterized by a profound metabolic acidosis and cardiovascular compromise.[3] Due to dose-dependent direct myocardial depression and peripheral vasodilation, propofol can produce significant hypotension when IV induction doses are administered. It also produces significant pain on injection in peripheral veins. Propofol is insoluble in aqueous solution and therefore presented dissolved in a lipid emulsion that has the associated risk of bacterial contamination. Once a vial of propofol is opened, it is not recommended that it be used after 6 hours.

Table 13.4 Analgesics

	Potency	Sedation Dose	Duration	Infusion Dose
Opioids				
Morphine	1	0.02–0.1 mg/kg IV	2–7 hrs	—
Fentanyl	100	0.5–1 mcg/kg IV	30–60 min	—
Sufentanil	1,000	Not recommended	—	—
Alfentanil	25	10–20 mg/kg IV	10–15 min	—
Remifentanil[a]	—	Not recommended	10 min	0.1–0.2 mg/kg/min
Other Analgesics and Anesthetics				
Propofol		0.1–0.5 mg/kg IV[b,c]		100–200 mcg/kg/min[b]
Ketamine		0.1–0.5 mg/kg IV[b] 1.0–2.0 mg/kg IM		1–2 mg/min (anesthetic dose) 500 mcg/kg (analgesic dose)
Dexmedetomidine		Not recommended		0.2–1.0 µg/kg/hr

[a]Will produce apnea.
[b]May produce apnea.
[c]Produces pain on injection that can be reduced by treatment with 20 mg of lidocaine IV.
IM, intramuscular; IV, intravenous.

Ketamine

Ketamine is a phencyclidine derivative that produces anesthesia characterized by dissociation between the thalamus and limbic systems. Induction of anesthesia is achieved within 60 seconds after IV injection of 1 to 2 mg/kg or within 2 to 4 minutes of intramuscular (IM) injection of 5 to 10 mg/kg. Patients appear to be in a cataleptic state in which their eyes remain open with a slow nystagmic gaze. The drug produces intense amnesia and analgesia but has been associated with unpleasant visual and auditory hallucinations that can progress to delirium. The incidence of these problems can be significantly reduced if benzodiazepines are co-administered. At low doses (0.1 to 0.2 mg/kg IV or 2 mg/kg IM), patients continue to spontaneously ventilate. At higher doses, ketamine acts as a respiratory depressant and produces complete apnea. Ketamine also has direct and indirect sympathetic nervous system stimulatory effects, which can be useful in hypovolemic patients or in patients likely to encounter bronchospasm. These effects are diminished or absent in patients who are catecholamine depleted. The

sympathetic stimulatory effect increases myocardial oxygen consumption and intracranial pressure, and ketamine is relatively contraindicated in patients with ischemic heart disease or space-occupying intracerebral lesions. Owing to its analgesic properties and relatively preserved ventilation, ketamine is frequently used as an IV analgesic during debridement procedures, at doses listed in **Table 13.4**. IM ketamine (1 to 2 mg/kg) is also very useful for sedating patients who are difficult to manage (e.g., combative or cognitively disabled patient), so IV access can be obtained. Ketamine's most frequent use is in subanesthetic doses as part of multimodal analgesic regimens hoping to minimize the use of opioids. For procedures requiring general anesthesia that may have significant postoperative opioid requirements, a preincision ketamine bolus dose with a low-dose intraoperative infusion may be associated with improved acute and chronic pain outcomes.[4]

Amnesics and Anxiolytics

Benzodiazepines are the primary class of agents used as amnesics and anxiolytics. The prototype drug, diazepam, has been mostly replaced by its water-soluble analog of shorter duration, midazolam. Lorazepam also belongs in this family of agents, but because it has a very long duration of action, it is not routinely used intraoperatively. Lorazepam has intensive care unit applications (**Table 13.5**). Benzodiazepines have no analgesic properties but can be used in combination with the short-acting opioid fentanyl to produce conscious sedation for minor procedures. Benzodiazepines can produce apnea and have synergistic adverse effects with narcotics. As with all anesthetics, benzodiazepines used as IV agents for sedation should be given in small incremental doses to achieve the desired effect. A reversal agent is also available for benzodiazepines (flumazenil). The recommended dosages of these drugs and the reversal agents appear in **Table 13.5**.

Local Anesthetics

Local anesthetics temporarily block nerve conduction by binding to neuronal sodium channels. As the concentration of the local anesthetic increases around the nerve, autonomic transmission will be blocked first, followed by sensory transmission, and then motor nerve transmission. These drugs can be

injected locally into tissue to produce a field block, around peripheral nerves to produce a specific dermatomal block, around nerve plexuses to produce a major conductive block, or into the subarachnoid or epidural space to produce extensive neuraxial blockade. All the methods have been used to assist in the provision of an alternative form of balanced anesthesia by supplementing analgesia and muscle relaxation.

Table 13.5 Anxiolytics and Amnesics (Benzodiazepines)

Name	Dose (mg)	Duration (hr)	Strengths	Weaknesses
Midazolam (Versed)	0.5–2 IV	0.5	Water soluble Short duration Good for sedation for short procedures	Acute respiratory depression
Diazepam (Valium)	5–10 IV	1	Intermediate duration	Irritation on IV injection Phlebitis Acute respiratory depression after IV overdose
Lorazepam (Ativan)	2–4 IV	6–8	Long duration	—
Benzodiazepine Reversal				
Flumazenil (Romazicon)	0.2 IV (0.2 mg repeated every 2–10 min until reversal is achieved) Maximum dose 1 mg	45–90 min	—	May produce seizures, panic, arrhythmias

IV, intravenous.

Adverse consequences associated with the use of local anesthetics fall into three categories: acute central nervous system toxicity due to excessive plasma concentration, hemodynamic and respiratory consequences due to excessive conduction block of the sympathetic or motor nerves, and allergic reactions. Whenever a local anesthetic is injected, there can be inadvertent intravascular injection or an overdose of the drug because of rapid uptake from the tissues. Overdose can produce seizures, as well as cardiovascular collapse from ensuing arrhythmias. Agents differ in duration of action (**Table 13.6**) which may be prolonged by the addition of epinephrine to the administered drug. Epinephrine works, for this purpose, by local vasoconstriction and hence delays the distribution of local anesthetic from tissues to the blood stream; it is not recommended for any anatomic site that may be subject to ischemia such as penis and digits.

When local anesthetics are administered for a spinal or epidural block, they produce a progressive blockade of the sympathetic nervous system,

which produces systemic vasodilation. Sympathetic nerves travel along the thoracolumbar region with the first four thoracic branches, including the cardiac sympathetic accelerators. A sympathetic blockade of this entire region produces a characteristic profound systemic vasodilatation and bradycardia. This condition is referred to as *total sympathectomy.* Affected patients are bradycardic, hypotensive, unconscious, and usually apneic. This disastrous situation is easily remedied if treated quickly with a vasopressor (phenylephrine or ephedrine) and atropine or small doses of epinephrine (increments of 10 μg for an adult). If not treated promptly, the situation proceeds to cardiac arrest. The required doses of epinephrine are higher than in a usual cardiac arrest because of the total sympathectomy.[5] Because the level of sympathetic block is two to six dermatomal levels higher than the sensory block, it is often 6 difficult to obtain a high spinal sensory level without approaching a total sympathectomy. For this reason, spinal or epidural techniques can present a prohibitively high risk in patients with severe flow-dependent cardiovascular disease.

Table 13.6 Local Anesthetics

	Maximum Single Dose (mg/kg)	Duration (hr)	Comments
Amides			
Lidocaine	4.5	1[a]	Fast onset
Ropivacaine	3	4–12[a]	Less cardiac toxicity than bupivacaine
Bupivacaine	3	4–12[a]	Exaggerated cardiotoxicity with IV injection Slow onset Long duration
Esters[b]			
2-Chloroprocaine	12	0.5–1[a]	Fast onset Lowest toxicity, rapid metabolism
Tetracaine	3	0.5–1	Slow onset

[a]Addition of 100 µg of epinephrine (0.1 mL of 1:1,000) lowers the toxicity and increases the duration of the local anesthetic.

[b]Metabolism to para-aminobenzoic acid may cause allergic reactions.

IV, intravenous.

Local anesthetics are chemically divided into two groups: esters and amides. The esters (2-chloroprocaine and tetracaine) produce metabolites that are related to *p*-aminobenzoic acid and have been associated with allergic reactions. Amides (e.g., lidocaine and bupivacaine) are rarely associated with allergic reactions. If an allergic reaction does occur, it is

most likely due to the preservative (methylparaben) used in multidose vials of lidocaine.

NEURAXIAL BLOCKADE

The two primary neuraxial techniques, a "single-shot" spinal and continuous epidural catheter, can be used for lower extremity and lower abdominal procedures. In the case of a spinal anesthetic—also known as a subarachnoid block—the intrathecal sac surrounding the cauda equina at vertebral interspace L2–L3 or below is located using a sterile, small-caliber needle (25 gauge typically). Once cerebrospinal fluid is observed in the hub of a needle, 1 to 3 mL of preservative-free local anesthetic (typically bupivacaine or lidocaine) is injected into the intrathecal space. The needle is then completely withdrawn. Blockade of sensory, motor, and sympathetic nerves occurs at the nerve roots. The spread of local anesthetic within the subarachnoid space is primarily determined by three factors: (a) the vertebral interspace accessed, (b) the density of the local anesthetic in relation to the density of cerebrospinal fluid (a concept known as *baricity*), and (c) the position of the patient during injection and immediately thereafter. In order to eliminate the risk of needle puncture of the spinal cord, subarachnoid blocks are only performed below L2–L3 in adults and L3–L4 in children. The local anesthetic solution may be combined with vasoconstrictors such as epinephrine or opioids such as fentanyl or morphine in order to increase the density or duration of the sensory blockade. Surgical anesthesia ranging from 1 to 2 hours can be achieved using a subarachnoid block. Because of concerns regarding permanent nerve damage, intrathecal catheters are typically not used.[6,7]

In the case of epidural techniques, the nerve roots are blocked outside the thecal sac in a potential space between the ligamentum flavum and dura mater. This space is accessed sterilely using a 19-gauge introducer needle and a loss of resistance technique. Once the space is identified, a 21-gauge catheter is inserted into the space via the introducer needle and the needle is removed leaving the catheter in place and redosing is therefore possible. Dilute local anesthetics combined with vasoconstrictors or opioids are the mainstay of epidural therapy. Epidural neuraxial techniques can be used for

surgical anesthesia, as an adjunct to general anesthesia, or for postoperative pain relief. Epidural catheters can be placed in the thoracic or lumbar regions because the intrathecal sac is not being accessed; associated dermatomal spread and analgesia is observed. Epidural techniques often fail to result in a dense sacral nerve root blockade making it a suboptimal choice for surgical anesthesia below the knee.

PERIPHERAL NERVE BLOCKADE

Peripheral nerve blockade (PNB) has been used for surgical anesthesia of the extremities since the days of intravenous regional anesthesia described by Bier in 1908. Upper extremity, lower extremity, and visceral peripheral nerves are targets. 7 Much like neuraxial blockade, PNB can be used to achieve intraoperative surgical anesthesia, intraoperative analgesia as an adjunct to general anesthesia, or for postoperative analgesia. Use of long-acting local anesthetics or placement of an indwelling continuous catheter provides long-term (16 hours to several days) pain relief. A specific preoperative planning discussion to match the planned surgical procedure to a feasible dermatomal distribution of blockade is essential. Even when blockade of a dermatomal distribution specific to a surgical procedure is feasible, a PNB may be contraindicated if a neurologic examination performed at or near the surgical site in the early postoperative period is necessary.

Because of the limited distribution of sympathetic blockade, PNB has a much smaller hemodynamic effect than general or neuraxial anesthesia. In addition, if general or neuraxial anesthesia can be supplemented by a PNB, the residual unwanted side effects of these anesthetics can be limited. However, PNB is not without side effects; the impact of phrenic nerve motor blockade associated with specific upper extremity blocks (common with interscalene and rare with supraclavicular) may have significant consequences for patients with underlying pulmonary disease.

Most anesthesiologists employ real-time ultrasound guidance of needle under direct visualization for the placement of PNB. Vascular structures and nerves are visualized in relation to a PNB needle in order to decrease the likelihood of intravascular or intraneural injection, increase the likelihood of

an efficacious block, and minimize the dose of local anesthetic required to achieve an efficacious block. Despite direct visualization using ultrasound, PNB in adults are typically performed in the awake state to minimize the risk of intraneural injection, which may be detected via patient complaint of significant pain upon injection. PNB can be extremely difficult or contraindicated in patients with challenging body habitus, local superficial infection, significant coagulopathy, or implants near the area to be visualized or injected.

While PNB targets named major peripheral nerves resulting in both motor and sensory blockade sufficient for surgical anesthesia, field blocks target small cutaneous sensory nerve fibers, used more commonly to achieve moderate sensory blockade for postoperative analgesia. These blocks typically do not achieve sensory blockade sufficient for surgical anesthesia and must be augmented by general anesthesia or deep sedation. Procedures such as transversus abdominis plane (TAP), adductor canal, intercostal nerve, and local infiltration enable postoperative analgesia.

SEDATION ANALGESIA FOR MINOR SURGICAL PROCEDURES

Sedation occurs on a continuum from minimal sedation (responds normally to verbal stimuli) to general anesthesia (unarousable). "Deep sedation" describes a drug-induced depression of consciousness from which a patient cannot easily be aroused but maintains the ability to respond purposefully to repeated or painful stimuli; since inadvertent progression to general anesthesia is a risk, providers are held to similar standards to those who provide anesthesia services by federal code. The term "monitored anesthesia care" (MAC) does not describe a level of sedation but is rather a specific anesthesia service in which an anesthesiologist participates. There are a variety of minor surgical procedures that can be accomplished safely and comfortably with anesthesia provided by infiltration of local anesthetics (most commonly 1% lidocaine or 0.25% bupivacaine) and minimal sedation/anxiolysis provided by IV agents. All IV benzodiazepines, narcotics, and other IV anesthetics produce apnea with substantial patient-to-

patient variation; small incremental doses are recommended to achieve a safe sedated state. Inadequate infiltration of local anesthetic cannot be compensated by increased doses of IV sedatives. Because of the potentially serious consequences of an apneic episode, The Joint Commission has required that all patients receiving sedation for minor surgical or medical procedures undergo the following as a minimum standard[8]:

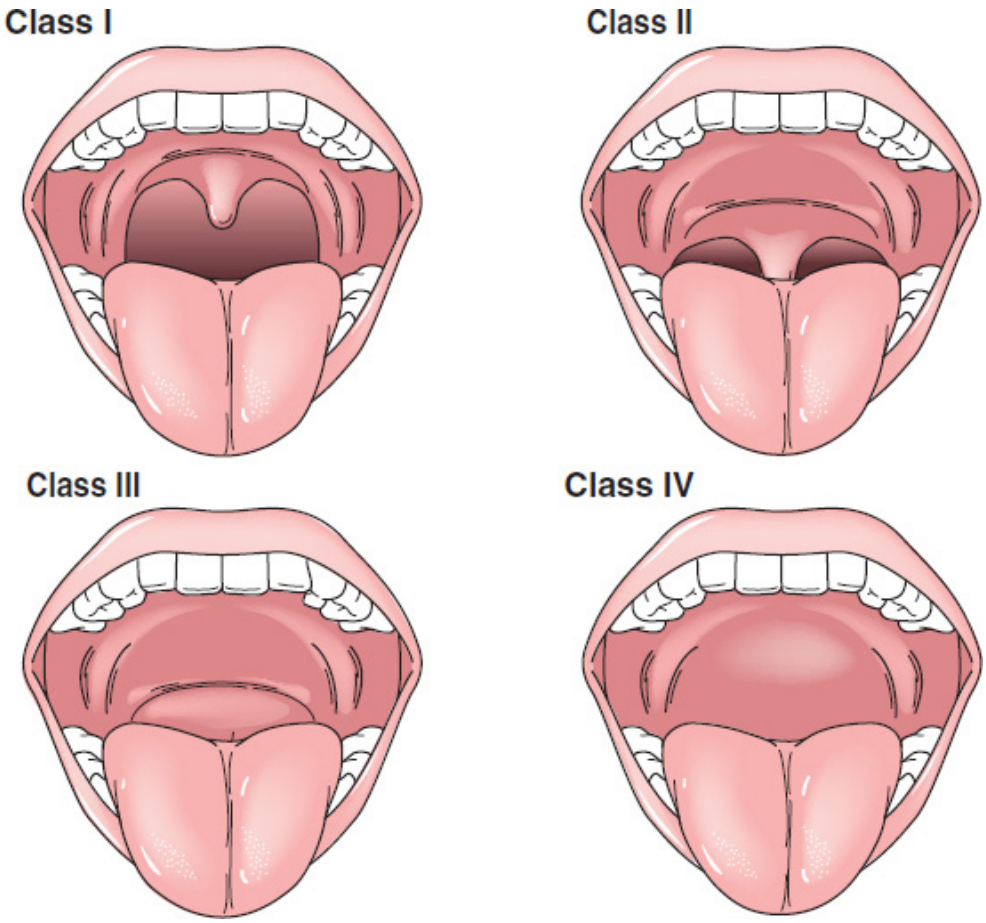


Figure 13.1 Classification of the patient's upper airway based on the size of the tongue and the pharyngeal structures visible on mouth opening. Class I, soft palate and anterior/posterior tonsillar pillars, and uvula visible; Class II, tonsillar pillars and part of uvula hidden by base of tongue; Class III, soft and hard palate visible; Class IV, soft palate not visible, only hard palate visible. (Redrawn from Stoelting RK, Miller RD. *Basics of Anesthesia*. 5th ed. New York: Churchill Livingston; 2007:146.)

1. A preprocedure evaluation including an airway examination (**Fig. 13.1**)
2. Appropriate monitoring: pulse oximetry as a minimum

3. Documentation of the patient's vital signs and arterial saturation as well as the dose and timing of sedatives provided during the procedure
4. Documentation of a recovery period and a return to a safe recovered state

The preprocedure evaluation should include current medications, coexisting disease, and a brief physical examination including an evaluation of the airway. The most common drug used to provide sedation is midazolam. This is a fast-onset, relatively short-acting benzodiazepine that can be easily titrated to produce a sedated yet cooperative arousable state. It is usually given to adults in incremental doses of 1 mg (0.01 mg/kg in children). Narcotics such as fentanyl even in small doses act synergistically with benzodiazepines to cause a more sedated state with a much higher incidence of apnea. To assess the effect of the drug, a validated sedation scale can be of value. The scale used at the University of Michigan is presented in **Table 13.7**.[9]

AIRWAY EVALUATION FOR THE NONANESTHESIOLOGIST

An essential skill for all clinicians is the assessment of a patient's airway to determine how difficult it may be to obtain control of the airway if a patient requires 8 ventilatory support. The concept of airway management should be focused on not just endotracheal intubation, but also mask ventilation. Until the airway can be secured via intubation, the patient must be supported through mask ventilation.[10] Supraglottic airway devices (laryngeal mask airways) are of additional consideration, used for both intraoperative airway management as well as a rescue technique for failed mask ventilation or failed intubation. Limitations to supraglottic airway devices, however, include a relative lack of protection from aspiration, as well as a limited ability to provide adequate positive-pressure ventilation in patients prone to airway obstruction 9 (e.g., morbidly obese, sleep apnea). The key elements of an airway examination are an assessment of obesity, mouth opening, neck flexion and extension, Mallampati oropharyngeal classification, presence of beard, and mandibular protrusion ability (**Table 13.8**).[11] There is no perfect combination of clinical tests to predict difficult intubation. However, the

presence of abnormalities in three or more of the aforementioned elements increases the likelihood of a difficult mask ventilation and/or difficult intubation by more than eight-fold.[11] In patients with multiple (three or more) airway abnormalities, the presence of a beard is an easily corrected characteristic. Assessment of oropharyngeal classification is performed by having patients open their mouth and maximally protrude the tongue without phonation. This Mallampati oropharyngeal assessment can be classified depending on whether the uvula can be completely seen (class 1), only partly seen (class 2), or not seen, with the hard and soft palate visible (class 3), or only the hard palate visible (class 4) (**Fig. 13.1**).[12]

Table 13.7 Sedation Scale

Sedation Scale	Description
0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant repeated physical stimulation
4	Unarousable

Table 13.8 Standard Airway Examination for Nonanesthesiologists

Exam Element	Concerning Findings
Body mass index (kg/m^2)	Body mass index ≥31
Mouth opening	Interincisor or intergingival distance <3 cm
Mallampati classification	Class III or IV (see **Fig. 13.1**)
Mandibular protrusion	Inability to protrude lower incisors to meet or extend past upper incisors
Neck anatomy	Radiation changes, or thick obese neck
Cervical spine mobility	Limited extension or possibly unstable cervical spine
Beard	Presence of full beard

RISKS ASSOCIATED WITH ANESTHESIA

With the advent of newer agents and monitoring techniques, it is estimated that the mortality rate directly attributable to anesthesia has decreased from about 1 in 10,000 patients in the 1950s to as low as 1 in 200,000 or less for healthy patients today.[13] When patients are placed in a condition in which they cannot breathe, there is always the possibility of a technical or judgmental error resulting in hypoxia and brain damage or death. It has been estimated that between 50% and 75% of anesthetic-caused deaths are due to human error and are preventable.

Efforts to improve outcome can be approached at three levels: (a) reduction of the incidence of rare but catastrophic anesthetic-related problems, (b) improvement of the care and experience of every patient undergoing anesthesia and surgery, and (c) improvement of the preparation and management of patients with pre-existing medical conditions that have

higher morbidity and mortality rates. Historically, the most common problems associated with adverse outcomes were related to the airway and included inadequate ventilation, unrecognized esophageal intubation, unrecognized extubation, and unrecognized disconnection from the ventilator. The incidence of these problems has been significantly reduced by including capnometry and pulse oximetry in addition to other noninvasive monitors, although a cause-and-effect relation has been difficult to prove. Standardized anesthesia machine checklists, anesthesiology training, pain management programs, and improved understanding of pre-existing comorbidities have also had positive impact.

Cardiovascular Diseases

Hypertension

Hypertension is the most common pre-existing medical disease in patients presenting for surgery and is a major risk factor for renal, cerebrovascular, peripheral vascular, and coronary artery diseases, as well as congestive heart failure (CHF). It is particularly associated with lipid disorders, diabetes, and obesity. It is these associated comorbidities that are most likely to lead to morbidity and mortality in the perioperative period. Hypertensive patients should be treated medically to render them normotensive before elective surgery. In general, antihypertension medications should be continued throughout the perioperative period. However, patients treated with angiotensin receptor blockers (ARBs), such as valsartan, candesartan, losartan, or angiotensin-converting enzyme inhibitors (ACE-Is), such as lisinopril, captopril, or ramipril, who are exposed to general anesthesia, are at risk for developing profound, refractory intraoperative hypotension. This ACE-I/ARB hypotension has been treated successfully with terlipressin, vasopressin, and methylene blue.[14–16] Most medical centers recommend withholding ACE-Is/ARBs the morning of surgery.[17,18] Patients on concomitant diuretic therapy are at greatest risk for intraoperative hypotension requiring treatment.[19,20]

The incidence of hypotension and myocardial ischemia intraoperatively is higher in untreated hypertensive patients than in adequately treated hypertensive patients if the preoperative diastolic pressure is 110 mm Hg or

higher.[21] Inadequately treated hypertensive patients undergoing carotid endarterectomies have an increased incidence of neurologic deficits, and those with a history of prior myocardial infarctions have an increased incidence of reinfarction. Patients commonly have an elevated blood pressure on admission to the hospital. Hypertensive patients can have exaggerated responses to painful stimuli and have a higher incidence of perioperative ischemia.

Coronary Artery Disease

Coronary artery disease or its risk factors are present in about 30% of patients who undergo major surgery each year.[22] It is the leading cause of death in the United States and continues to be a major cause of postoperative morbidity and mortality.[23] The goal of the preoperative cardiac evaluation is to identify patients who are at increased risk of perioperative cardiac morbidity and ensure that their chronic conditions are optimized. Although perioperative cardiac events are the leading cause of death following anesthesia and surgery, it has been difficult to define patient characteristics that accurately predict a high risk of adverse outcome.[24] It has been even more difficult to modify that risk effectively.[25] Preoperative CHF is clearly a significant risk factor, as is recent myocardial infarction or unstable angina (**Table 13.9**). Diabetes mellitus (DM), atherosclerotic vascular disease, and hypertension also appear to confer risk, although less than with CHF or unstable angina. Perioperative risk in patients with valvular heart disease varies with the severity of the disease as represented by CHF, pulmonary hypertension, and dysrhythmias. Dysrhythmias are also a concern in the presence of coronary artery disease. Age and stable angina remain controversial as predictors of perioperative risk, with equal numbers of supporting and refuting studies. The value of revascularization remains controversial as well. The ability to climb two flights of stairs without stopping or experiencing symptoms of angina or shortness of breath is considered a good practical test of cardiac reserve. Unfortunately, many patients with ischemic heart disease have concomitant pulmonary disease or other medical problems that limit their activity. A history of myocardial infarction is important information. Large retrospective studies have found that the incidence of reinfarction is related to the time elapsed since the

previous myocardial infarction.[26–28] The incidence of reinfarction appears to stabilize at about 6% (50-fold higher than patient without myocardial infarction) after 6 months. The highest rate of reinfarction occurs in the 0- to 3-month period. Mortality from reinfarction, for patients undergoing noncardiac surgery (**Table 13.10**), has been reported to be between 20% and 50% and usually occurs within the first 48 hours after surgery.

Table 13.9 Clinical Predictors of Increased Perioperative Cardiovascular Risk (Myocardial Infarction, Heart Failure, Death)

Major
Unstable coronary syndromes
Acute or recent MI[a] with evidence of important ischemic risk by clinical symptoms or noninvasive study
Unstable or severe[b] angina (Canadian class III or IV)[c]
Decompensated heart failure
Significant arrhythmias
High-grade atrioventricular block
Symptomatic ventricular arrhythmias in the presence of underlying heart disease
Supraventricular arrhythmias with uncontrolled ventricular rate
Severe valvular disease
Intermediate
Mild angina pectoris (Canadian class I or II)
Previous MI by history or pathologic Q waves
Compensated or prior heart failure
Diabetes mellitus (particularly insulin dependent)
Renal insufficiency
Minor
Advanced age
Abnormal ECG (left ventricular hypertrophy, left bundle-branch block, ST–T abnormalities)
Rhythm other than sinus (e.g., atrial fibrillation)
Low functional capacity (e.g., inability to climb one flight of stairs with a bag of groceries)
History of stroke
Uncontrolled systemic hypertension

[a]The American College of Cardiology National Database Library defines recent MI as >7 d but ≤1 mo (30 d); acute MI is within 7 d.

[b]May include "stable" angina in patients who are unusually sedentary.

[c]From Campeau L. Grading of angina pectoris. *Circulation* 1976;54:522.

ECG, electrocardiogram; MI, myocardial infarction.

Table 13.10 Cardiac Risk Stratification for Noncardiac Surgical Procedures

High (reported cardiac risk often >5%)[a]
Emergent major operations, particularly in the elderly
Aortic and other major vascular surgery
Peripheral vascular surgery
Anticipated prolonged surgical procedures associated with large fluid shifts and/or blood loss
Intermediate (reported cardiac risk generally <5%)
Carotid endarterectomy
Head and neck surgery
Intraperitoneal and intrathoracic surgery
Orthopedic surgery
Prostate surgery
Low[b] **(reported cardiac risk generally <1%)**
Endoscopic procedures
Superficial procedures
Cataract surgery
Breast surgery

[a]Combined incidence of cardiac death and nonfatal myocardial infarction.

[b]Do not generally require further preoperative cardiac testing.

Perioperative cardiac adverse event risk reduction has undergone significant changes over the past decade. Despite 10 these efforts, a large, international prospective study across 15,000 patients demonstrated that more than 8% of patients undergoing major inpatient surgery still experience postoperative myocardial ischemia.[29] These patients have significantly increased 30-day mortality, even though only 15% of perioperative ischemic episodes included typical cardiac symptoms. Previous retrospective studies demonstrating value to coronary revascularization spurred aggressive preoperative coronary artery disease identification and management. However, recent data have questioned the value of coronary revascularization among asymptomatic patients in not only the perioperative

period, but also in the general medical population.[30,31] The most recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines reserve preoperative coronary revascularization for patients demonstrating asymptomatic left main coronary artery disease, three-vessel disease, reduced ejection fraction, unstable angina, or acute myocardial infarction.[32] Furthermore, large retrospective and prospective studies have demonstrated that perioperative beta-blockade also bears significant risks that must be weighed against possible benefits.[33,34] As a result, the most recent ACC/AHA guidelines reserve the commencement of beta-blocker therapy for only high-risk patients that would warrant blockade independent of the surgical procedure.[32] Patients already on beta-blocker therapy should continue throughout the perioperative period.[32] The widespread use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, commonly known as statins, for cardiovascular disease and hyperlipidemia has introduced another medication into the surgical preoperative evaluation. Although prospective data establishing the value of instituting preoperative statin therapy are limited, there is general consensus that these medications should not be withdrawn.[35] A large randomized controlled trial evaluating the benefit of other promising agents—clonidine and aspirin—as perioperative optimization standards failed to demonstrate benefit.[36,37]

All patients in high-risk groups or with a history of ischemic heart disease must be evaluated and properly treated before elective surgery. All elective surgery should be delayed for 6 months after myocardial infarction. If this is not feasible, invasive monitoring should be considered in the perioperative period and intensive postoperative observation should continue for at least 48 hours. The intrusiveness of the surgical procedure also plays a part in the overall risk and need for preoperative workup of heart disease. The AHA has produced and updated an algorithm for the recommended preoperative workup (**Algorithm 13.1**).[32]

Percutaneous Coronary Intervention with Stenting

An increasing number of patients present for surgery following percutaneous coronary interventions via stenting (with or without drug-eluting coating). In-stent thrombosis is a feared complication with profound morbidity and mortality. Given the known proinflammatory and prothrombotic physiologic

state induced by acute illness, surgery, and anesthesia, coronary stents may be at elevated risk for thrombosis during the perioperative period. The risk of perioperative in-stent thrombosis is increased if noncardiac surgery is performed soon after percutaneous coronary 11 intervention.[38,39] The appropriate duration to defer elective surgery after coronary stenting remains controversial, but recent ACC/AHA guidelines recommend 6 months for drug-eluting stents and 30 days for bare-metal stents.[32] Data suggest that cessation of recommended antiplatelet therapy in the perioperative period may have significant coronary thrombotic risks without major reduction in bleeding.[38,39] The decision to stop antiplatelet therapy prior to recommended guidelines should be limited to specific procedures that demand a nearly bloodless surgical field or in procedures involving closed spaces incapable of tolerating minor bleeding (intracranial, minimally invasive spine surgery). The continuation of aspirin therapy throughout the perioperative period in patients with coronary artery stents should be the standard of care.[32]

Congestive Heart Failure

CHF has been described as the single most important factor predicting postoperative cardiac morbidity[40]; patients are less tolerant of the fluid shifts associated with surgery and the myocardial depression associated with the anesthetic. All elective procedures should be deferred until heart failure is medically optimized. If surgery cannot be deferred, aggressive management to enhance cardiac output is warranted. In contrast to isolated ischemic heart disease, CHF is more easily diagnosed by history, physical examination, and basic preoperative laboratory workup, electrocardiography (ECG), chest radiography, and echocardiography.

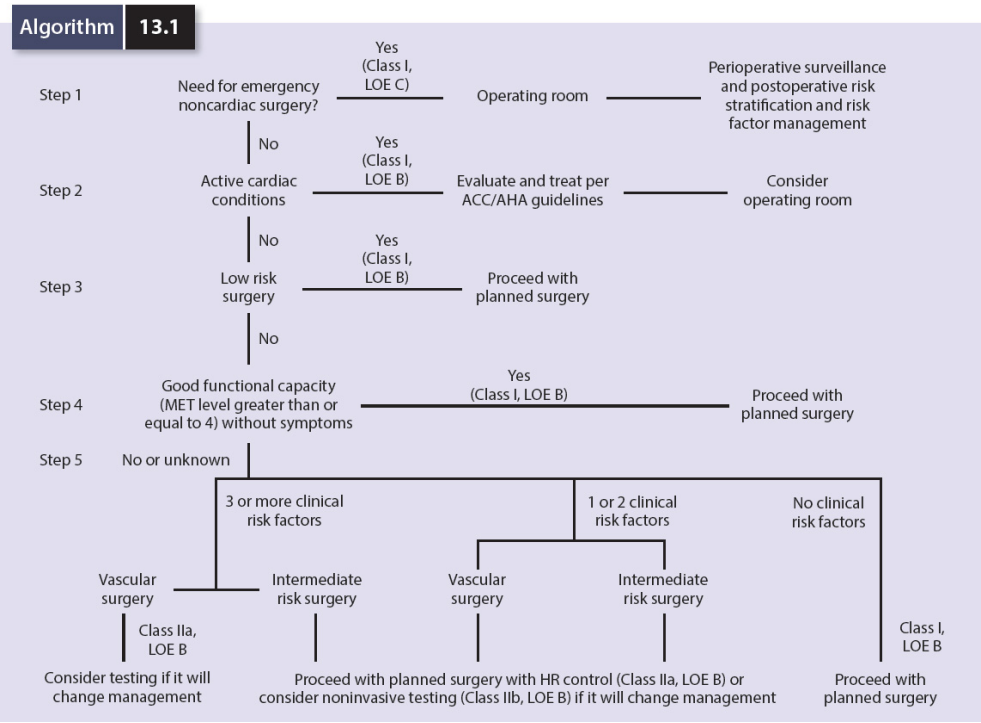
Pulmonary Disease

Recent data demonstrate that although cardiac complications have been the focus of surveillance and prevention, pulmonary and infectious complications may warrant similar attention.[41]

Pulmonary disease is classically divided into acute and chronic restrictive and obstructive disease. Restrictive disease is defined by processes that

reduce lung volumes; obstructive disease is characterized by reduced flow rates.

Obstructive diseases are present in patients with forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratios of less than 50%. Obstructive pulmonary disease can be either chronic or acute (asthma). Any reversible component of obstruction should be reversed before surgery. Patients are maintained on bronchodilator medications, and those with chronic secretions are appropriately hydrated and receive physiotherapy to mobilize secretions. Reactive bronchospasm can complicate anesthetic induction and the emergence; severe bronchospasm is a life-threatening. Administration of potent local (albuterol) and systemic (epinephrine) bronchodilators in a timely fashion is essential.



Algorithm 13.1 Decision aid for preoperative cardiac evaluation prior to noncardiac surgery. This decision tree for preoperative evaluation takes into account not only the patient's physical status but also the severity of the surgical procedure. ACC, American College of Cardiology; AHA, American Heart Association; LOE, level of evidence.

Regional or neuraxial techniques which allow airway manipulation to be avoided have particular advantage. However, for sensory and motor levels

of T6 and above, patients lose significant accessory motor function that can decrease expiratory reserve volume and the ability to cough and clear secretions. Any intubated patient with severe respiratory disease should be extubated with caution only when they meet adequate extubation criteria relative to preoperative test data. Patients undergoing upper abdominal surgery are at particular risk. Both vital capacity and functional residual capacity are reduced, reaching lowest levels in the first 24 hours postoperatively. Therapy should be directed toward restoring functional residual capacity to preoperative levels. Because of the potential adverse effects of systemic narcotics on respiratory drive, the use of epidural narcotics and local anesthetics for postoperative pain control is very popular. These techniques allow the patients to be extubated earlier and, in patients with intrathoracic and upper abdominal surgery; help restore pulmonary function toward baseline.[42]

Obesity

Obesity is defined as a body mass index (BMI) greater than or equal to 30 kg/m^2. The pathophysiologic changes associated with morbid obesity (BMI $\geq$40 kg/m^2) affect the respiratory, cardiovascular, and gastrointestinal systems. Patients develop external restrictive lung disease that reduces functional residual capacity and is exacerbated by supine positioning. Increased airway pressures required to maintain adequate ventilation in obese patients predispose this patient group to barotrauma, furthering their risk of pulmonary complications. Obese patients frequently desaturate at night and have a high incidence of sleep apnea. Because of increased blood volume and frequent desaturations, obese patients can develop pulmonary hypertension and right-sided heart failure. Obese individuals have a high incidence of coronary artery disease. Because of size alone, they have increased cardiovascular demands with limited cardiac reserve and exercise tolerance. Obese patients have a high incidence of hiatal hernia and gastroesophageal reflux, increasing the risk for aspiration on induction and emergence from anesthesia. Venous access, positioning and blood pressure measurement are often difficult.

The combined problems of aspiration risk, rapid desaturation caused by reduced functional residual capacity and increased oxygen demand, and

technical difficulties associated with intubation due to anatomic fat deposits make intubation a high-risk procedure. Awake intubation can be useful or necessitated. Patients should receive prophylactic administration of H_2-receptor antagonists and a nonparticulate antacid to improve the pH of gastric contents. To prevent aspiration on emergence, obese patients should be extubated when fully awake, preferably in the sitting position. Epidural analgesics for postoperative pain management allow earlier extubation and ambulation of these patients.[43]

Diabetes Mellitus

The incidence of DM is rising, particularly, type 2 DM in the elderly. This is a systemic disorder that has particular relevance for the anesthesiologist and surgeon because of its effect on the vascular, renal, nervous, and immune systems. Patients with DM should be investigated for the presence of concomitant coronary artery disease, peripheral vascular occlusive disease, renal failure, and autonomic and peripheral neuropathy. Problems with cardiovascular instability, fluid balance, and aspiration due to gastroparesis should be expected. In addition, these patients are more prone to infection and have problems with temperature control. The management of the diabetic state is important and complicated. Hypoglycemia during anesthesia is a feared complication because of challenges in prompt diagnosis. Oral hypoglycemic agents such as glipizide should be stopped prior to surgery and hyperglycemia treated with short-acting intravenous or subcutaneous insulin during the perioperative period. Insulin-dependent diabetics for same-day admission or outpatient surgery should take one-half of their usual morning dose of long-acting insulin. Additional insulin is directed according to frequent (every 1 to 2 hours) blood sugar monitoring. Although there are compelling data associating perioperative hyperglycemia with adverse postoperative events, there are no randomized controlled trials demonstrating improved outcomes with aggressive intraoperative hyperglycemia management.[44] Furthermore, complications from hypoglycemia are arguably greater than those from hyperglycemia, and are more likely as insulin therapy becomes more aggressive during the perioperative period.

Renal Insufficiency and Failure

Because the kidneys play a vital role in metabolic, synthetic, and fluid homeostasis, renal failure is associated with many effects on the cardiovascular, pulmonary, hematologic, gastrointestinal, and immune systems. Pre-existing renal insufficiency is a known risk factor for postoperative myocardial infarction and renal failure.[45,46] Optimizing fluid and metabolic status of a patient in end-stage renal disease is of vital importance. Elective surgery should be delayed until such optimization is performed. In emergent situations, the urgent need for hemodialysis should be considered to avoid life-threatening electrolyte and fluid derangements. Nearly 15% of patients undergoing general surgery procedures experience postoperative acute kidney injury, as defined by a 0.3 mg/dL increase in serum creatinine within seven postoperative days.[47] Risk factors for postoperative acute kidney injury in patients undergoing general surgery are listed in **Table 13.11** and should be considered during the patient consent.

Table 13.11 Predictors of Postoperative Acute Kidney Injury after General Surgery Procedures

Age ≥56 yrs
Male sex
Emergency surgery
Intraperitoneal procedures
Preoperative renal insufficiency (serum creatinine >1.2 mg/dL)
Ascites
Active congestive heart failure
Diabetes mellitus requiring oral hypoglycemic or insulin therapy
Hypertension requiring chronic medication

From Kheterpal S, Tremper K, Heung M, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery. *Anesthesiology* 2009;110:505–515.

Obstructive Sleep Apnea

With increasing obesity prevalence, obstructive sleep apnea (OSA) is emerging as a major comorbidity that has impact on postoperative outcomes and costs.[48] The physiologic changes on the upper airway, lungs, pulmonary circulation, heart, and brain are extensive and challenge immediate perioperative and postoperative management.[49] These patients are prone to airway collapse at induction and emergence, hypoxemia, delayed emergence, respiratory depression, and cardiovascular collapse.[50] Preliminary data demonstrate increased sensitivity to the effects of opiates as well.[51] Observational data demonstrate a relationship between OSA treatment and a reduction in postoperative complications.[52,53] The standard protocol for all preoperative evaluations should be the use of a locally accepted OSA screening tool (STOP-BANG questionnaire, Perioperative Sleep Apnea Prediction score, etc.) and ensuring postoperative access to continuous positive airway pressure therapy for patients currently prescribed such therapy as outpatients. Some undiagnosed or noncompliant patients may require initiation of therapy in the immediate postoperative period and the perioperative resources to fulfill clinical urgency are essential.

Risks Associated with Regional Techniques in Patients Being Treated with Anticoagulants

As the indications for anticoagulant therapy have increased, ranging from drug-eluting stents to atrial fibrillation and venous thromboembolism prophylaxis, the number of patients and types of anticoagulant therapy has continued to increase. In particular, low–molecular-weight heparin (LMWH) and oral direct factor Xa inhibitors are often part of a patient's pre- or postoperative therapy plan. The use of neuraxial or PNB in patients with preoperative anticoagulation requires careful planning and assessment of the risks and benefits of specific anesthetic techniques and withdrawal of anticoagulant therapy. LMWH raises specific concerns of epidural hematoma formation when neuraxial techniques are used. The American Society of Regional Anesthesia has published specific guidelines for central conduction block (spinal and epidural anesthesia) to try to minimize the incidence of this

devastating complication[54]: In general, LMWH therapy requires coordination of neuraxial administration at least 12 hours after the last dose. Coumadin, clopidogrel, and ticlopidine should be held for at least 5, 7, and 10 days prior to neuraxial techniques, respectively. The absence of any reversal agents or reliable diagnostic testing for oral direct Xa inhibitors requires a conservative approach of withdrawal of therapy and no data currently exist to establish a specific threshold. Data regarding risks for PNB are even more scarce and local protocols should be established and followed.

PREOPERATIVE EVALUATION

12 The three goals of the preoperative evaluation are (a) to develop an anesthetic plan that considers the patient's medical condition, the requirements of the surgical procedure, and the patient's preferences; (b) to ensure that any chronic disease is under appropriate control; and (c) to establish rapport answer questions, and allay fears.

Optimization of a patient's medical conditions (**Table 13.12**) is best performed by the primary care physician, with medical specialty consultation, if necessary. The following questions must be answered when evaluating a patient undergoing an elective surgical procedure: What must be included in the preoperative evaluation? Who should be involved in this process? When and where are all the steps in this process to be conducted? How should all the information be coordinated so that it is available to the appropriate personnel at the appropriate time? If the procedure is deemed a surgical emergency, the anesthesiologist is responsible for assessing the patient quickly, developing the appropriate anesthetic plan, and proceeding to the operating room as soon as possible. During such scenario, the anesthesiologist is not obligated to seek medical consultation to evaluate chronic medical problems.

Table 13.12 Hospital Mortality Rates in Relation to Age, Preoperative Disease, and Surgery

Preoperative Disease and Surgery	Age (yr) <50[a]	Age (yr) 50–69[a]	Age (yr) >70[a]
Chronic heart failure	0.1%/0.5%	0.4%/2%	0.8%/4%
Renal failure	0.2%/1%	0.9%/2%	2%/9%
Abdominal surgery	0.3%/2%	1%/6%	3%/12%
Chronic heart failure and renal failure	0.7%/3%	3%/13%	6%/24%
Chronic heart failure and abdominal surgery	0.9%/4%	4%/17%	7%/30%
Renal failure and abdominal surgery	2%/8%	2%/32%	16%/50%
Chronic heart failure, renal failure, and abdominal surgery	6%/26%	22%/60%	37%/76%

[a]Figures are for elective surgery (first number) and emergency surgery (second number).

From Pedersen T, Eliasen K, Henriksen E. A prospective study of mortality associated with anesthesia and surgery: risk indicators of mortality in hospitals. *Acta Anaesthesiol Scand* 1990;34:176, with permission.

The following steps must be completed before moving the patient into the operating room:

1. A comorbidity-focused history and physical examination
2. Appropriate laboratory studies and medical consultations
3. An anesthesiologist's preoperative evaluation with assignment of an American Society of Anesthesiologists (ASA) physical status
4. Discussion with the patient of the options and risks
5. Development and communication of the anesthetic plan to the patient and surgeon
6. Acute optimization of any pertinent medical conditions

The history and physical examination have repeatedly been shown to be the most valuable parts of the preoperative assessment. The anesthesiologist must review previous anesthetic problems experienced by the patient or blood relatives, the patient's exercise tolerance, and additional details regarding general medical conditions. This evaluation not only determines the laboratory tests that may be required but also allows for the assignment of ASA physical status (PS) (**Table 13.13**). The classification serves as a general measure of the patient's state of well-being, taking into account all problems the patient brings to the operating room, including systemic disturbances caused by the surgical illness. Although studies of anesthetic mortality show a correlation with the PS classification, this categorization does not describe the risk directly. The risk of any operation is determined not only by patient-related factors but also by procedure-specific ones. For patients with complex medical problems, it is frequently helpful to supplement the surgical history and physical examination with a recent assessment by the patient's primary physician in order to assess the patient's long-term health trajectory. There are no data demonstrating the value of routine preoperative medical consultation.[55]

Table 13.13 Physical Status Classification of the American Society of Anesthesiologists

Physical Status Classification	Description
PS-1	A normal, healthy patient
PS-2	A patient with mild systemic disease that results in no functional limitation *Examples:* Hypertension, diabetes mellitus, chronic bronchitis, morbid obesity, extremes of age
PS-3	A patient with severe systemic disease that results in functional limitation *Examples:* Poorly controlled hypertension, diabetes mellitus with vascular complications, angina pectoris, prior myocardial infarction, pulmonary disease that limits activity
PS-4	A patient with severe systemic disease that is a constant threat to life *Examples:* Congestive heart failure, unstable angina pectoris, advanced pulmonary, renal, or hepatic dysfunction
PS-5	A moribund patient who is not expected to survive without the operation *Examples:* Ruptured abdominal aneurysm, pulmonary embolus, head injury with increased intracranial pressure
PS-6	A declared brain-dead patient whose organs are being removed

	for donor purposes
Emergency operation (E)	Any patient in whom an emergency operation is required *Example:* An otherwise healthy 30-year-old woman who requires dilation and curettage for moderate but persistent vaginal bleeding (PS-1E)

Table 13.14 Simplified Strategy for Preoperative Testing

Estimated Energy Requirements for Various Activities

1 MET ↓ 4 METs	Can you take care of yourself? Eat, dress, or use the toilet? Walk indoors around the house? Walk a block or two on level ground at 2 to 3 mph or 3.2 to 4.8 km/hr? Do light work around the house like dusting or washing dishes?	4 METs ↓>10 METs	Climb a flight of stairs or walk up a hill? Walk on level ground at 4 mph or 6.4 km/hr? Run a short distance? Do heavy work around the house like scrubbing floors or lifting or moving heavy furniture? Participate in moderate recreational activities like golf, bowling, dancing, doubles tennis, or throwing a baseball or football? Participate in strenuous sports like swimming, singles tennis, football, basketball, or skiing?

MET, metabolic equivalent; mph, miles per hour.

The value of preoperative laboratory studies has undergone substantial reevaluation since the mid-1980s. The current thinking is that a laboratory test should not be ordered unless a change in the surgical or anesthetic plan is anticipated. The only preoperative screening test required at the University of Michigan, for instance, is an ECG within a year of the planned surgical procedure for men older than 50 years and women older than 60 years of age. For procedures with significant anticipated blood loss, a type and cross match is ordered, and a preoperative hematocrit is also required. All other tests should have an indication based on history and physical examination. A simple strategy to evaluate physical robustness is presented in **Table 13.14**. Electronic patient questionnaires have also been developed, allowing the appropriate laboratories to be selected based on the patient's response to questions.[56]

Discussions of the options of anesthetic techniques and anesthetic risks are best performed by the anesthesiologist who will provide the anesthetic. However, because of the logistical problems of scheduling, most institutions have developed preoperative anesthesia clinics to allow for a more efficient and timely patient assessment, to facilitate planning, and to avoid unnecessary same-day case cancellations.

The patient's medication regimen must be reviewed to ensure that appropriate medications are continued or discontinued in the days and hours leading up to an elective procedure. In general, diuretics and ACE-I/ARB's should not be taken the day of surgery. Several important classes of medications should be continued as per the patient's normal regimen: chronic pain therapy (including opioids), beta-blockers, statins, and proton pump inhibitors. The decision regarding anticoagulant therapy is complex and must consider the indication for therapy, the likelihood and impact of surgical bleeding, and the risk of perioperative thrombosis. Insulin and oral 13 hypoglycemic agents should be continued at a reduced dose. Patients receiving chronic pain or opioid addiction therapy with buprenorphine (Subutex, Suboxone) can be particularly challenging to manage in the postoperative period. Buprenorphine, a mixed opioid agonist/antagonist, tightly binds at the μ receptor and has a long and varied half-life (24 to 60 hours). Patients who continue treatment risk impaired analgesic benefits of traditional opioids and the potential for adverse events due to the need for very high doses of opioids,[57] while those that discontinue treatment risk

addiction relapse. A management protocol used at the University of Michigan is demonstrated in **Algorithm 13.2**.

The potential of a difficult intubation is of fundamental concern as should be evaluated as previously discussed (**Fig. 13.1** and **Table 13.8**). The requirement of an awake fiberoptic technique, takes planning and can cause delay without prior warning.

MONITORING THE SURGICAL PATIENT

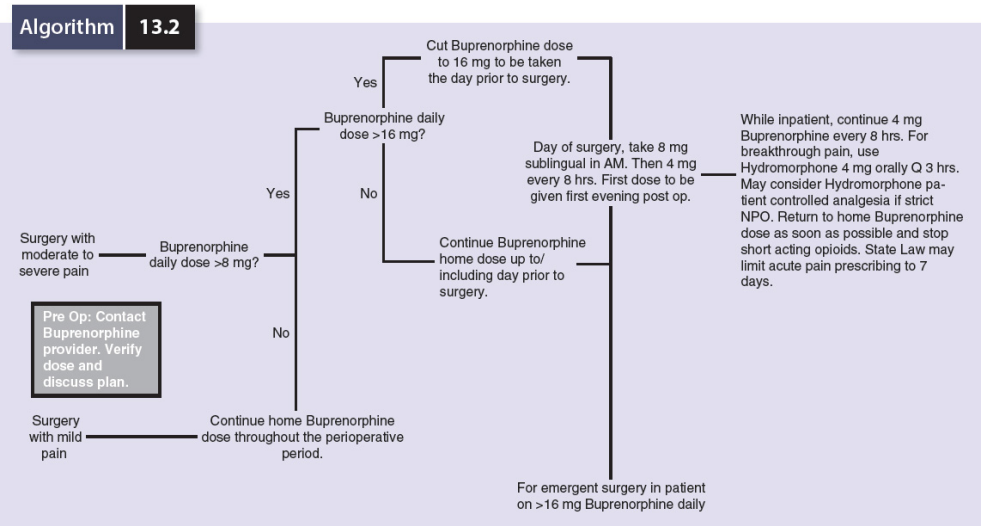
The routine use of an array of electronic monitors to provide continuous surveillance of physiologic status is well established. Because the art and science of anesthesiology involves titrating pharmacologic agents to produce desired physiologic effects, there must be a measured parameter to which drug dosages are titrated. Depending on the severity of pre-existing disease and the extent of the surgical procedure, invasive techniques can be used to provide comprehensive continuous data to guide the titration of fluid therapy and cardiovascular agents.

Monitors of Oxygenation

Pulse oximetry is perhaps the most significant advance in patient monitoring to date. This device continuously, noninvasively, and inexpensively provides arterial hemoglobin saturation (SaO_2) and peripheral pulse by measuring light absorption in a manner similar to that of a laboratory cooximeter. A laboratory cooximeter shines light through a cuvette filled with a blood sample. Each hemoglobin species absorbs light in direct proportion to its concentration (Beer–Lambert law). A cooximeter requires one wavelength of light for each hemoglobin species to be measured, that is, one wavelength for oxyhemoglobin and one for reduced hemoglobin. To measure other hemoglobins, such as carboxyhemoglobin or methemoglobin, the device requires four wavelengths of light.

The traditional pulse oximeter uses two wavelengths of light, one red and one infrared that shine through a tissue bed, usually a finger. Opposite the light sources is a photodiode that measures the transmitted light intensity. A large proportion of the light absorbed as it passes through the tissues is not

associated with arterial blood but with other components of the tissue, such as skin, muscle, bone, and venous blood. Therefore, the device analyzes only the pulsatile component of absorption and assumes that anything that pulses within the tissue bed is arterial blood, hence the name *pulse oximeter.* Actually, the pulse oximeter measures the ratio of the pulsatile component of red light absorbed to the pulsatile component of the infrared light absorbed. This ratio changes with SaO_2. The exact relation between this ratio and SaO_2 has been empirically determined from volunteer studies and is programmed into the electronics of the oximeter. If any artifacts occur in a pulsatile nature, they may be erroneously integrated into the equation, causing erroneous SaO_2 estimates.



Algorithm 13.2 Algorithm for managing a patient on chronic buprenorphine therapy. APS, acute pain service; ICU, intensive care unit; PCA, patient-controlled anesthesia; NSAIDs, nonsteroidal anti-inflammatory drugs.

Several things should be remembered when interpreting a pulse oximeter's output: (1) The device measures SaO_2 and not arterial oxygen tension (PaO_2). (2) The PaO_2 must drop below 80 mm Hg before any significant change in SaO_2 occurs. (3) As the PaO_2 drops below 60 mm Hg, the SaO_2 rapidly falls as the inflection point of the sigmoidal oxyhemoglobin dissociation curve is approached. (4) The pulse oximeter measures saturation and not arterial content or oxygen delivery to tissues.

Traditional pulse oximeters use only two wavelengths of light, and therefore, cannot detect the presence of carboxyhemoglobin or methemoglobin. Pulse oximeters that incorporate additional wavelengths of light and are capable of detecting carboxyhemoglobin and methemoglobin have been developed but are not widely used clinically.[58]

Ventilation Monitors

By definition, a patient is appropriately ventilated when arterial carbon dioxide tension ($PaCO_2$) is 40 mm Hg. Measuring the respiratory rate can document only the presence of ventilation, not its adequacy. Capnography, or end-tidal CO_2 monitoring, is the visual display of the CO_2 concentration at the airway. To understand the utility of capnography, one must understand dead-space (DS) components and how they affect CO_2 removal from the body.[59] DS is defined as the portion of the tidal volume (V_T) that does not participate in gas exchange.

$$V_T = DS + V_A$$

The alveolar volume (V_A) is the volume of the inspired gas that reaches well-perfused alveoli. The remainder of the V_T, which equals the DS, can be divided into three subcomponents: apparatus dead space (DS_{ap}), anatomic dead space (DS_{an}), and alveolar dead space (DS_{al}). At the end of inspiration, the respiratory apparatus (e.g., endotracheal tube) is filled with inspired gas that should not contain CO_2. Similarly, all the anatomic airways (trachea, bronchi, and all conducting airways down to the alveoli) should be filled with inspired gas and should therefore contain no CO_2. In this model, there are two types of alveoli: those that are well perfused and those that are not perfused. The alveolar gas should completely equilibrate with the arterial blood and contain CO_2 at the same tension as the arterial blood; ideally, $PaCO_2$ should equal 40 mm Hg. As the patient expires, the CO_2 detected at the patient's mouth first reflects the DS_{ap} gas having no CO_2 followed by the DS_{an} gas, again with no CO_2 and finally the alveolar gases, containing both DS and well-perfused alveolar gas. When mixed alveolar gas reaches the

airway, it produces a rapid rise in the CO_2 concentration to a level somewhere between the concentration in the alveolar gas (40 mm Hg) and the DS_{al} (0 mm Hg), depending on each component's proportion of volume. For example, if half of the alveoli are DS_{al} and $PaCO_2$ equals 40 mm Hg, then the plateau value of the capnogram should be 20 mm Hg, implying that half of the alveoli are not being perfused. With inspiration, the CO_2 value again drops to 0 until another expiration, and a square wave appears again as the alveolar gas is detected at the mouth. With each breath, there should be a square wave, the height of which approaches the $PaCO_2$ value as the amount of the DS_{al} gas approaches 0.

In a healthy young adult, there is no significant DS_{al} gas, and the end-tidal CO_2 value equals the $PaCO_2$. Therefore, the difference between these values indicates the proportion of DS_{al} in the patient. The presence of a capnogram itself implies that there is metabolism (the production of CO_2), circulation (blood flow to the lungs), and ventilation (respiratory rate and an intact ventilator circuit).

Providing this information on a breath-to-breath basis, the continuous capnogram is extremely useful in many critical situations. It can be used as a surveillance monitor of both the respiratory circuit and the cardiovascular system. Any acute decrease in cardiac output will decrease blood flow to the lungs and increase the DS_{al}, causing an acute drop in end-tidal CO_2. The only acute catastrophic cardiopulmonary problem that will not be detected by the capnometer is arterial desaturation. Therefore, the combination of the capnometer and the pulse oximeter creates a dynamic beat-to-beat and breath-to-breath surveillance of metabolism, circulation, ventilation, and oxygenation.

Circulation Monitors

Hemodynamic stability can be monitored by a variety of methods, the most basic of which is systemic arterial blood pressure. Intermittent, noninvasive measurement of systemic blood pressure with an oscillometric blood pressure cuff is the standard in the operating room, and its accuracy equals that of clinical measurements by auscultation. Blood pressure cuffs can be

cycled as quickly as once per minute, but when used for an extended duration, they should be cycled no more than once every 3 to 5 minutes. When tighter control or observation is required in patients with significant comorbidities or large swings in hemodynamics due to surgical circumstances, invasive arterial monitoring is recommended. Pressure measurements provided by invasive and noninvasive techniques, usually coincide closely. A continuous invasive arterial tracing can also be used to assess the adequacy of fluid resuscitation by following the systolic pressure variation (SPV) with positive-pressure ventilation. 14 As positive-pressure ventilation impedes venous return within a closed thorax, decreases in systolic pressure associated with a respiratory pattern can be detected. In patients with sinus rhythm with stable cardiac contractility, the degree of SPV is inversely related to the intravascular volume status of the patient. The normal range of SPV is 5 to 10 mm Hg. A systolic pressure decrease of greater than 10 mm Hg during positive-pressure ventilation implies inadequate preload and the need for more aggressive fluid resuscitation.

In this context, central venous access may be reserved for patients and procedures with the potential for large, rapid volume resuscitation requirements or expected need for potent vasoactive medication. Transesophageal echocardiography (TEE) is now commonly used to quickly assess systolic and diastolic function as well as valvular dysfunction. Increasing familiarity in the use of TEE by noncardiac anesthesiologists may result in the pulmonary artery catheter being reserved for very specific patients demonstrating the need for pulmonary artery pressure monitoring or continuous cardiac output trending.

Finally, a wave of noninvasive continuous cardiac output monitors has gained the attention of surgeons and anesthesiologists alike. These monitors, promising the realization of goal-directed therapy, use indirect means to assess the missing aspect of blood pressure-focused hemodynamic management—stroke volume. Thoracic electrical bioimpedance, pulse wave transit time, peripheral pulse contour analysis, volume clamp, and other methods of estimating stroke volume have been in existence for decades, but have seen a recent rise in interest as variation in intraoperative fluid management may impact surgical outcomes. However, conflicting studies in real-world critically ill patients have failed to establish an outcome benefit.[60] Despite the absence of compelling clinical data, many enhanced

recovery protocols have begun including some type of noninvasive cardiac output monitoring to guide fluid therapy.[61] It is unclear whether these monitoring devices offer superior guidance to sound clinical judgment administered by a vigilant anesthesiologist.

"Awareness" and Level of Consciousness Monitors

When delivering a general anesthetic, one of the major imperatives is to achieve and maintain a loss of consciousness. Normally, this is achieved through careful observation of vital signs (heart rate, blood pressure), physical examination signs (movement in a patient without neuromuscular blockade), and delivery of inhalational or intravenous agents at doses consistent with a loss of consciousness. However, this "science" is inexact and must account for patient age, comorbidities, chronic medications, surgical stimulus, and patient-to-patient variability. As a result, patients may rarely experience "awareness under anesthesia"—a state characterized not only by consciousness but also by recall of intraoperative events. The lay press and public have increased their scrutiny of this perioperative event.

First, appropriate expectations and effective communication of the anesthetic are required. Literature has demonstrated that patients undergoing regional anesthesia are as likely to report unpleasant "awareness" as patients undergoing a general anesthetic.[62] This is despite the reality that loss of consciousness is only a goal of general anesthesia.

Second, several level of consciousness monitors have been developed in hopes of providing the anesthesiologist with additional objective data to guide their assessment and actions. The current generation of monitors generally uses electroencephalographic (EEG) analysis to provide the clinician with an assessment of the relative "depth" of anesthesia achieved. Several commercially available monitors such as the bispectral index (BIS) from Aspect Medical Systems and Entropy from General Electric Healthcare are in common clinical use. Data evaluating the value of these EEG-based monitors in reducing awareness are conflicting.[63,64] As a result, the ASA has not adopted awareness monitors as a standard of care and leaves the decision to use such monitoring technology to each provider, patient, and

situation.[65] The largest, trials have failed to demonstrate a measurable reduction in awareness.[66,67]

COMMON PROBLEMS IN THE POSTOPERATIVE PERIOD

Postanesthesia care units are required in any setting where surgical procedures are conducted. The increased scope of surgery and the invasive technology used to monitor sicker patients has increased the service at and training required to operate these facilities. In 2014, the ASA revised the Standards for Postanesthesia Care (**Table 13.15**).

The scoring systems used to assess the postoperative patient direct attention to the primary areas of concern. The postanesthesia recovery score is an attempt to evaluate postanesthesia patient status (**Table 13.16**).[68] This basic information should be incorporated in a record that provides clear documentation of postoperative events. Documentation should also include details of postoperative outpatient care, with a note indicating postoperative telephone contact made to elucidate problems. Problems should receive appropriate follow-up, and written postoperative discharge instructions should be provided for the patient.

Almost ¼ of patients experience a complication within the postanesthesia care unit. Nausea, vomiting, and the need for airway support constitute 70% of these (**Fig. 13.2**).[69] The need to maintain airway support is by far the most common respiratory complication. The duration of the procedure, ASA classification and type of procedure appear to be important determinants. Hypothermia is also noteworthy, slowing drug metabolism, delaying recovery and is associated with prolonged postoperative postanesthesia care unit stay.

Among cardiovascular complications in the postoperative period, none is more important or more difficult to diagnose than myocardial ischemia. The association of perioperative myocardial ischemia with cardiac morbidity has been clearly documented.[26] Diagnosis is complicated by the fact that only 10% to 30% of patients suffering documented myocardial infarction have pain and that postoperative ECG T-wave changes are often nonspecific.[70]

Instead, one must seek secondary indications of ongoing ischemia or such as hypotension, arrhythmias, elevated filling pressures, or postoperative oliguria. Arrhythmias are common and are significant primarily because of the association with myocardial ischemia or hypoxemia.

Nausea and vomiting are rarely unifactorial and cause considerable discomfort. Opioids are responsible for stimulating the emesis center in a significant cohort of patients. These patients may provide a clear history of opioid sensitivity and anesthetic and analgesic regimens may be tailored to limit exposure. In general, however, there is little evidence to favor one anesthetic or anesthetic technique over another, although propofol appears to have an antiemetic effect. Nitrous oxide, often considered causative, does not appear to increase the incidence of nausea. It is not unusual for an antiemetic agent to be included preoperatively or as part of the anesthetic technique, especially in patients with a positive history or those deemed to be at risk, such as menstruating young women undergoing laparoscopy. Standard usage includes phenothiazines, butyrophenones, $5HT_3$ antagonists, and steroids. A multimodal approach that avoids redosing of a given medication class is most beneficial.[71] Despite decades of research, classic medications such as droperidol remain a mainstay of therapy. The FDA recently added a black-box warning to droperidol due to concerns of QT prolongation, but such concerns have not been validated when compared to other perioperative medications.[72,73]

Table 13.15 Standards for Postanesthesia Care

Standards		Criteria to be Fulfilled
Standard I[a]	All patients who have received general, regional, or monitored anesthesia care shall receive appropriate postanesthesia management.	1. A PACU or an area that provides equivalent postanesthesia care shall be available to receive patients after anesthesia care. All patients who receive anesthesia care shall be admitted to the PACU or its equivalent *except* by specific order of the anesthesiologist responsible for the patient's care. 2. The medical aspects of care in the PACU shall be governed by policies and procedures that have been reviewed and approved by the department of anesthesiology. 3. The design, equipment, and staffing of the PACU shall meet requirements of the facility's accrediting and licensing bodies.
Standard II	A patient transported to the PACU shall be accompanied by a member of the anesthesia care team who is knowledgeable about the	

	patient's condition. The patient shall be continually evaluated and treated during transport with monitoring and support appropriate to the patient's condition.	
Standard III	On arrival in the PACU, the patient shall be re-evaluated and a verbal report provided to the responsible PACU nurse by the member of the anesthesia care team who accompanies the patient.	1. The patient's status on arrival in the PACU shall be documented. 2. Information concerning the preoperative condition and the surgical/anesthetic course shall be transmitted to the PACU nurse. 3. The member of the anesthesia care team shall remain in the PACU until the PACU nurse accepts responsibility for the nursing care of the patient.
Standard IV	The patient's condition shall be evaluated continually in the PACU.	1. The patient shall be observed and monitored by the methods appropriate to the patient's medical condition. Particular attention shall be given to monitoring oxygenation, ventilation, circulation, and temperature. During recovery from all

anesthetics, a quantitative method of assessing oxygenation such as pulse oximetry shall be employed in the initial phase of recovery. This is not intended for application during the recovery of the obstetric patient in whom regional anesthesia was used for labor and vaginal delivery.

2. An accurate written report of the PACU period shall be maintained. Use of an appropriate PACU scoring system is encouraged for each patient on admission, at appropriate intervals prior to discharge, and at the time of discharge.
3. General medical supervision and coordination of patient care in the PACU should be the responsibility of an anesthesiologist.
4. There shall be a policy to ensure the availability in the facility of a physician capable of managing complications and providing

		cardiopulmonary resuscitation for patients in the PACU.
Standard V	A physician is responsible for discharging the patient from the PACU.	1. When discharge criteria are used, they must be approved by the department of anesthesiology and the medical staff. They may vary depending on whether the patient is discharged to a hospital room, to the ICU, to a short stay unit, or home. 2. In the absence of the physician responsible for the discharge, the PACU nurse shall determine that the patient meets the discharge criteria. The name of the physician accepting responsibility for discharge shall be noted on the record.

[a]For nursing care issues, refer to Standards of Postanesthesia Nursing Practice, published by the American Society of Postanesthesia Nurses.

ICU, intensive care unit; PACU, postanesthesia care unit.

Based on American Society of Anesthesiologists (ASA)'s *Standards for Postanesthesia Care.* A copy of the full text can be obtained from ASA, 1061 American Lane, Schaumburg, IL 60173. https://www.asahq.org/standards-and-guidelines/standards-for-postanesthesia-care.

Table 13.16 Postanesthesia Recovery Score

Parameter	Score[a]
Activity	
Voluntary movement of all limbs to command	2
Voluntary movement of two extremities to command	1
Unable to move	0
Respiration	
Breathes deeply and coughs	2
Dyspnea, hypoventilation	1
Apneic	0
Circulation	
Blood pressure equals 80% of preanesthetic level	2
Blood pressure equals 50%–80% of preanesthetic level	1
Blood pressure equals <50% of preanesthetic level	0
Consciousness	
Fully awake	2
Arousable	1
Unresponsive	0
Color	
Pink	2
Pale, blotchy	1
Cyanotic	0

[a]Patients should score at least 7 before discharge from the postanesthesia care unit.

The most common cause of delayed emergence is the residual effects of anesthesia. The differential diagnosis is best approached by ruling out physiologic, pharmacologic, and neurologic cases, in this order (**Table 13.17**). There should be little confusion about the implication of muscle relaxants because physical indications of ventilatory distress, combined with the readings of the blockade monitor are diagnostic. Where appropriate, opioids can be reversed using titrated doses of naloxone. Flumazenil can be used for reversal of benzodiazepines.

ENHANCED RECOVERY PROTOCOLS

15 With the increasing adoption of minimally invasive surgical techniques and a realization that postoperative complications may be impacted by intraoperative management, nearly every surgical subspecialty establish efforts towards enhanced recovery protocols. These comprehensive care management plans dictate the preoperative preparation, intraoperative management, surgical technique, and postoperative management. While a consistent decrease in length of stay, complications, and costs have been observed across the many trials assessed in many surgical specialties, there are very few consistent protocols.[74,75] The process of collaboration and standardization may be the most important element.

POSTOPERATIVE ACUTE PAIN MANAGEMENT

Postoperative pain is an inevitable consequence of surgery. Its severity is site dependent (**Table 13.18**), but the magnitude of the pain experienced by individual patients after similar surgical procedures is influenced by a multitude of factors. Variation in patient experience has been clearly demonstrated by several authors and is reflected in deficiencies in postoperative pain control.[76]

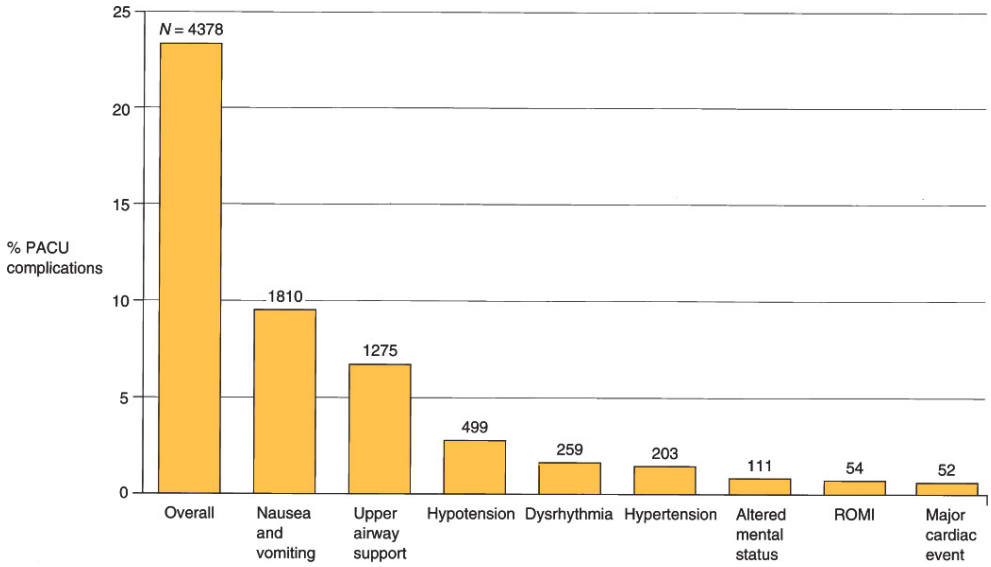


Figure 13.2 Major postanesthesia care unit complications by percentage of occurrence and number of patients experiencing each complication. Nausea and vomiting were the most frequently observed complications. ROMI, rule out myocardial infarction. (Reproduced with permission from Hines R, Barash PG, Watrous G, et al. Complications occurring in the postanesthesia care unit: a survey. *Anesth Analg* 1992;74:505.)

Table 13.17 Differential Diagnosis of Delayed Emergence
Metabolic Abnormalities
Hypoxia
Hypercarbia
Hypoglycemia
Hypotension
Hypothermia
Hyponatremia
Drug Effects
Muscle relaxants
Opioids
Barbiturates
Benzodiazepines
Ketamine
Anticholinergics
Inhalational anesthetics
Neurologic Injury
Ischemia
Mass lesions
Seizure disorders

In 1965, the crucial role of nociceptive C fiber feedback behavior and its modulation by cells in the substantia gelatinosa of the dorsal horn was recognized.[77] Repetitive stimulation of these fibers by cellular mediators, such as kinins and catecholamines, promotes neural excitation, prolongs repetitive firing, and lowers the threshold to further excitation. As a result, C fibers do not show fatigue, and the stage is set for continuous pain. Counterirritation of large afferent activity has been shown empirically to have beneficial effects. The gate-control theory provides an explanation for the inhibition of C fiber–mediated pain. Serotonergic and enkephalinergic descending inhibitory pathways modulate activity in the dorsal horn before information is relayed to the somatosensory cortex through the spinothalamic tract. The common observation that pain is worse at night, when less sensory

information is processed, and that it decreases with daytime activity is an example of how this complex neural system functions.

Superficial somatic pain is well localized and has a protective function. Superficial somatic pain is readily treated by common analgesic techniques. Deep somatic pain may not be well localized; may have some protective function, as in joint immobilization; and is fairly responsive to a variety of analgesics. Visceral pain, served almost entirely by C fiber activity, is poorly localized, often referred, and difficult to treat. In major operations, all modes can be activated, compounding the clinical challenge of providing adequate pain management. These clinical observations direct the focus of postoperative pain management to the treatment of somatic pain by attacking the nociceptor and the subsequent transmission of the painful impulse by the nerve fiber. The use of nonsteroidal anti-inflammatory drugs with or without the injection of local anesthetics into the wound is very effective. If done preemptively at the time of surgery, this approach can significantly benefit the patient's postoperative experience. Examples of nerve blocks for various procedures are shown in **Figure 13.3**.

Including potent opioids in the treatment of deep pain, both somatic and visceral, has been routine. However, the responses to standard regimens have been notoriously unreliable, from inadequate pain relief to narcosis, with complications at both ends of the scale. It was not until the 1980s that variations in response were linked to variable serum concentrations of analgesic drugs. Interpatient variation in serum levels to any standard dose can be fivefold, and interpatient therapeutic concentrations can vary on a similar scale. When factored together, there is the potential for a 25-fold variation in patient response to a standard drug prescription. Each patient has an individual therapeutic window. The clinical implications are enormous.

Table 13.18 Percentage of Patients Who Require Analgesic Injections

Operation	No Analgesic Needed (%)	Three or More Analgesic Injections (%)
Minor chest wall	82	0
Inguinal hernia	52	0
Appendectomy	25	10
Lower abdominal surgery	18	40
Upper abdominal surgery	10	45–65

In 1968, investigators demonstrated the virtue of small IV doses given on demand. As a result, the patient experienced greater pain relief, yet used the same or less total narcotic (**Figure 13.4**). Although there was significant patient variation, the demand from any individual patient, though cyclic, was constant. Patient-controlled analgesia (PCA) and the technologic and administrative systems to provide it have developed to a point of some sophistication, requiring servicing and a support structure with its own set of problems (**Table 13.19**). PCA administration requires a receptive environment, education of all personnel, and adequate patient instruction. PCA has received widespread acceptance by patients, nursing staff, and physicians because it provides more prompt and painless analgesia that more closely matches the patient's need over time. PCA is as safe as conventional IM medication. Morphine is the most commonly used drug, and an example of orders is shown in **Table 13.20**.

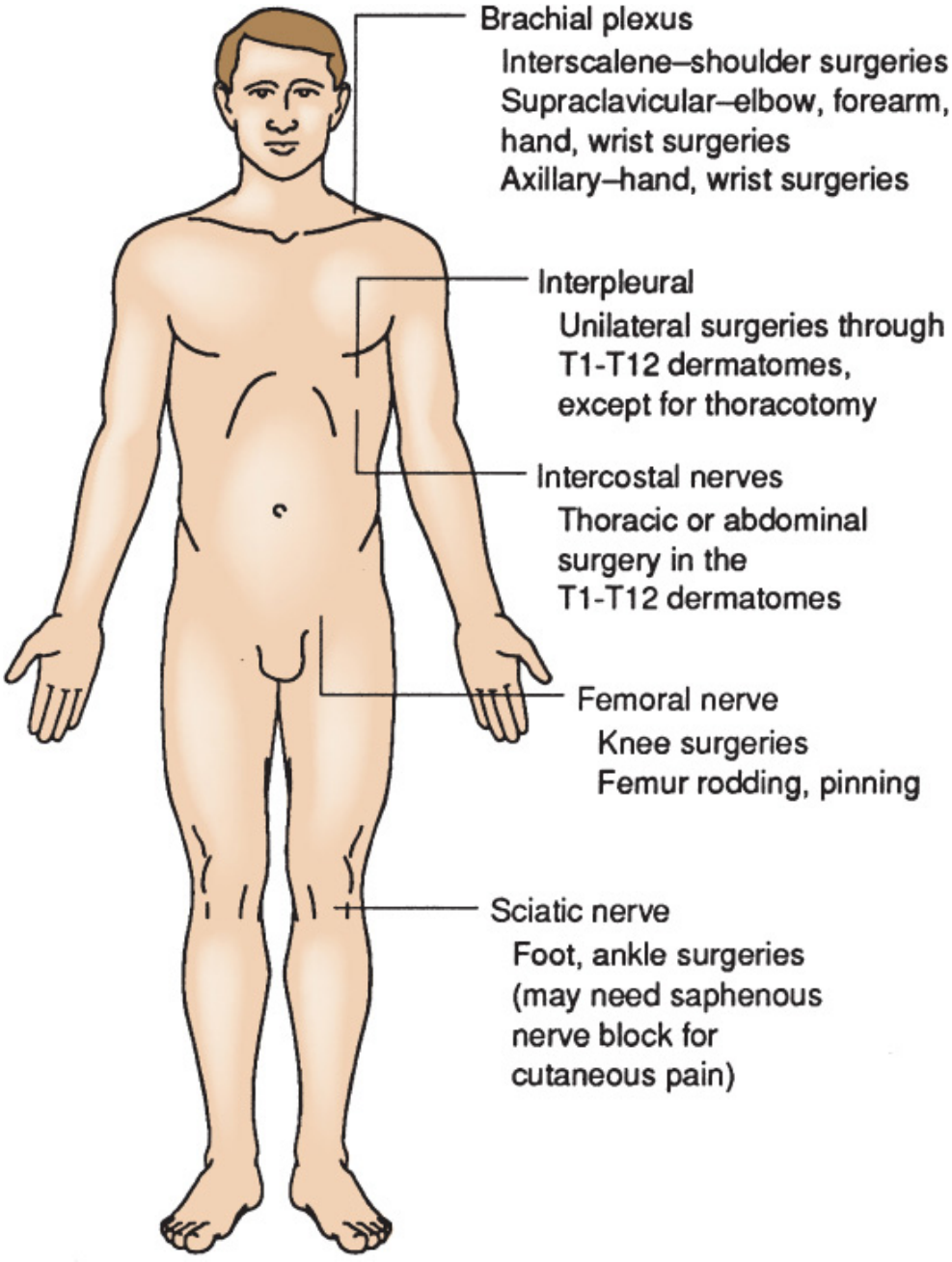


Figure 13.3 Surgical procedures in which peripheral nerve blockade can provide postoperative pain relief.

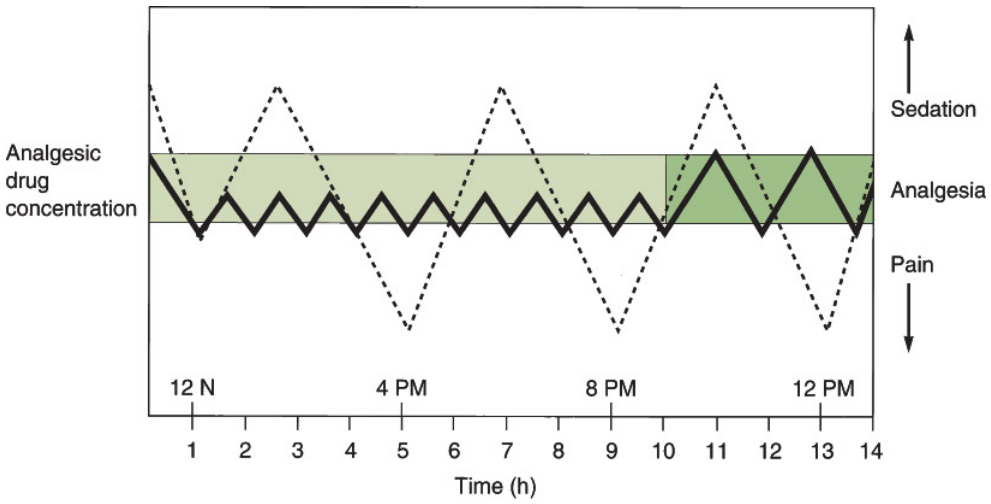


Figure 13.4 Theoretical relation among dosing interval, analgesic drug concentration, and clinical effects when comparing a patient-controlled analgesia system (*solid line*) to conventional intramuscular therapy (*dashed line*). (Reproduced with permission from White PF. Patient-controlled analgesia: a new approach to the management of postoperative pain. *Semin Anesth* 1985;4:261.)

Transdermal narcotic delivery is receiving attention and may become available for postoperative pain. The method is both practical and inexpensive and aims to maintain continuous delivery and constant blood levels. Fentanyl has been the drug of choice and has been well received by patients. The method appears to be safe, but there is a significant lag time between application and the attainment of therapeutic blood levels.

The discovery of endorphins in the 1970s and recognition of their importance in modulating pain at spinal sites led to the supposition that it would be possible to selectively apply opioids directly to receptors. This led to the development of epidural opiate analgesia, in which opioids are applied directly to the receptors at spinal sites. The goal of epidural analgesia is to obtain maximal analgesia while minimizing systemic side effects. For severe acute postoperative pain caused by major surgery, epidural analgesia has proved to be a superior modality for pain control. In high-risk cases, there is evidence that it has an overall beneficial effect on morbidity.[43]

Table 13.19 Problems That Can Occur during Patient-Controlled Analgesia (PCA) Therapy

Operator Errors
1. Misprogramming PCA device
2. Failure to clamp or unclamp tubing
3. Improperly loading syringe or cartridge
4. Inability to respond to safety alarms
5. Misplacing PCA pump key
Patient Errors
1. Failure to understand PCA therapy
2. Misunderstanding PCA pump device
3. Intentional analgesic abuse
Mechanical Errors
1. Failure to deliver on demand
2. Defective one-way valve at Y-connector
3. Faulty alarm system
4. Device malfunctions

The effective use of this sophisticated modality requires education and the establishment of protocols with rigorous attention to detail. The potential for respiratory depression demands adherence to monitoring standards. Morphine and fentanyl, often in combination with a dilute local anesthetic solution, are most often prescribed (**Table 13.21**).

A comprehensive postoperative pain management service demands resources and must use the physical and pharmacologic modalities available while recognizing the significant subjective component of any individual's pain. The ability to recognize the impact of acute pain or an underlying chronic pain disorder requires experience and the active involvement of nursing staff and surgeons is essential.

16 Postoperative acute pain management may require a multimodal approach that incorporates opioids, PNB, and nonopioid analgesics. Chronic pain patients can be particularly difficult to manage and may require preoperative optimization and opiate tapering. These patients require very

large doses of IV analgesics and need to be maintained orally. The best way to evaluate an appropriate starting dose is to convert the preoperative opioid regimen to an IV morphine equivalent, then add what would be required to treat the acute surgical pain. The use of nonopioid and nonpharmacologic treatments is essential in the management of acute postoperative pain in this patient population. PNB, aggressive use of acetaminophen and nonsteroidal anti-inflammatory agents, and novel agents such as dexmedetomidine may be necessary to minimize the adverse effects associated with uncontrolled postoperative pain. The relationship between the administration of opiates during the intraoperative and immediate postoperative phase of care with the "opiate crisis" remains to be fully determined.

Table 13.20 Example of Orders for Patient-Controlled Analgesia (PCA)

1. Patient is to be initiated on PCA with standard monitoring protocol		
2. Drug selection	Morphine 1 mg/mL	Hydromorphone 0.2 mg/mL
3. Loading initial dose (start PRN for pain) Maximum total loading dose	2–5 mg 10 mg	0.2–0.5 mg 1 mg
4. Pump setting PCA dose Lockout interval 4-hr limit	1–2 mg 6–10 min 30–45 mg	0.1–0.2 mg 6–10 min 4–5 mg

University of Michigan Hospitals online order form Acute Pain Service, Patient Controlled Analgesia Standard Orders.

Table 13.21 Opioid Protocols in Epidural Opiate Analgesia

	Morphine[a]	Fentanyl[b]
Length of onset	Longer (30–60 min)	Shorter (15–30 min)
Duration	Longer (6–24 hrs for single bolus)	Shorter (1–2 hrs for single bolus)
Cephalad spread and side effects	More prone	Less prone
Indication	Favored for lumbar administration after abdominal surgery	Favored for thoracic administration after chest surgery
Dose	Typically 3–5 mg, q6–8h	Typically 50–75 mg/hr (±dilute bupivacaine)

[a]Hydrophilic: slow in, slow out.

[b]Lipophilic: fast in, fast out.

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14

Preoperative Risk Assessment

Pauline K. Park

Key Points

1 Preoperative risk assessment is critical to informing patients of the risk and benefits of surgical interventions.

2 The development of postoperative complications drives patient mortality and higher healthcare costs.

3 Consideration of patient-centered outcomes may appropriately determine that non-curative surgical intervention may be counter to the patient's true desires.

4 Interventions aimed at prevention and early recognition of complications may lower surgical risk.

5 National Surgical Quality Improvement Programs from the Veterans' Administration and the American College of Surgeons have examined large datasets in a data-driven approach to more finely characterize risk for outcomes of mortality and complications.

6 Identification of patients at risk permits quality assurance monitoring and offers the opportunity to improve care with individual and system level interventions.

7 Specific comorbidities affect both the conduct of surgery and the outcome in ways that can be anticipated and addressed.

INTRODUCTION

1 The goal of preoperative assessment is to evaluate an individual's risk for postoperative adverse events to balance against the benefits of proceeding with surgery. It forms the basis of the contract between the patient and the surgeon; by synthesizing clinically available data, we can stratify and attempt to modify risk to maximize benefit and prioritize patient-centered goals of care.

Early landmark work in cardiac preoperative evaluation by Goldman[1] demonstrated that high-risk surgical patients could be identified through careful assessment of clinical history, physical examination, and laboratory data. This has been extended by further observations in specific types of

surgery and in subgroups of patients with particular disease states. Patient-level analyses using "big data" approaches have informed development of targeted interventions aimed at reducing the risk of a given procedure for a given patient. Additional work in systems of care and patient safety has also reduced patient morbidity and mortality.[2,3] Thus, preoperative evaluation has evolved to include not only prediction of risk but also implementation of proactive interventions during the perioperative period at both the individual patient and system levels.[4] Inclusion of patient values and desired outcomes completes the course of informed decision making.

This chapter will review the relevance of risk determination, clinical aspects of preoperative evaluation, guidelines for specific disease-related conditions and future directions for prevention of complications and intervention should they occur. All of these should be considered in the context of selecting the best approach for each of our patients.

SURGICAL MORTALITY, COMPLICATIONS, AND PATIENT-CENTERED OUTCOMES

Mortality rates following surgery have continued to improve with innovations in surgical technique and advances in overall quality of medical care. Since the 1950s, large reductions in intraoperative mortality have been accomplished through initiatives championing safer operating room protocols, continuous monitoring, and error reduction. By incorporating high-reliability processes into operating room routines, the overall mortality risk attributable to a general anesthetic has been reduced from 25 to 50 per million in the 1970s and 1980s to 1 to 5 per million.[5]

From the surgical standpoint, population-based mortality varies sharply with the extent of the procedure and patient age.[6] Overall surgical mortality in an American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP®) sample from 2013 showed overall unadjusted 30-day mortality of 1.06%.[7] Substantial interhospital variation in outcomes exists and underscores the possibility for additional opportunities for improvement.

2 The search for further improvement in surgical mortality has focused on reducing the incidence of postoperative complications. The 10 most common perioperative complications seen in the Patient Safety in Surgery study included infectious, pulmonary, cardiac, renal, and venous thrombotic events (**Table 14.1**).[8] Surgical complications are strongly related to mortality,[9–11] with the ability to rescue from postoperative complications an important factor in determining eventual outcome.[12] Postoperative complications are associated with increased healthcare costs and resource utilization.[13] They are the most common reason for hospital readmission[14] and a substantial number of complications are identified after discharge (**Table 14.2**).[15]

3 The direct impact of postoperative complications on an *individual* patient's quality of life should be considered. A surgical admission may represent a turning point in the overall trajectory of a patient's life; in 2008, one-third of Medicare decedents underwent a surgical procedure during their last 12 months of life.[16] The preoperative discussion should address the patient's understanding of the potential impact of surgical care and include expected quality-of-life outcomes. It is important to integrate patient-centered goals of care into treatment recommendations; an operation that does not prolong meaningful quality of life may be counter to the patient's expectations of surgical care.

Table 14.1 Surgical Complications: Comparison of the 10 Most Frequent Perioperative Complications between Private Sector and VA Hospitals in **the Patient Safety in Surgery Study**

14 Private Sector Hospitals (n = 54,585)		128 VA Hospitals (n = 130,258)	
Perioperative Complication	**%**	**Perioperative Complication**	**%**
1. Superficial wound infection	3.6	1. Superficial wound infection	3.1
2. Failure to wean from ventilator for >48 hrs	2.9	2. Pneumonia	2.5
3. Urinary tract infection	2.8	3. Failure to wean from ventilator for >48 hrs	2.5
4. Pneumonia	2.2	4. Reintubation	2.0
5. Systemic sepsis	2.1	5. Urinary tract infection	2.0
6. Reintubation	1.8	6. Deep wound infection	1.6
7. Deep wound infection	1.2	7. Systemic sepsis	1.6
8. Wound dehiscence	1.1	8. Wound dehiscence	1.2
9. Acute renal failure	0.7	9. Cardiac arrest	0.9
10. Deep vein thrombophlebitis	0.7	10. Myocardial infarction	0.6

Adapted from Khuri SF, Henderson WG, Daley J, et al. Successful implementation of the Department of Veterans Affairs' National Surgical Quality Improvement Program in the private sector: the Patient Safety in Surgery study. *Ann Surg* 2008;248(2):329–336.

RISK STRATIFICATION

4 The goal of risk stratification is to identify patients at risk for adverse 5 outcomes and to target high-risk groups for potential interv 6 ention to reduce that risk. To date, the largest organized surgical efforts have evolved through the ACS NSQIP. In 1991, the Department of Veterans Affairs (VA) system implemented the NSQIP paradigm which collects demographic information, baseline physiologic status, medical comorbidities, laboratory values, and surgical operative characteristics to model the risk of postoperative morbidity and mortality (**Table 14.3A**,**B**). Ongoing system-level analysis evaluates and benchmarks performance between institutions using observed/expected (O/E) ratios for specified outcomes, and allows for linkage of outcomes to process and structure of care.[17] Ten years after the start of NSQIP data collection, the 30-day mortality of major surgery in the VA system decreased by 27% and the 30-day morbidity decreased by 45%.[17] Success in data-driven VA process improvement initiatives has led to validation and adoption in academic and community centers.[17]

Table 14.2 Common Reasons for Unplanned Surgical Readmissions

Surgical procedure–related infection, fever
GI complication, ileus, obstruction
Failure to thrive, dehydration, malnutrition
Pulmonary complications
Venous thromboembolism
Pain

Continued data collection and benchmarking have been sponsored by the American College of Surgeons (ACS) under the ACS NSQIP program. Reports have been utilized as catalysts for institutional-level change, with substantial improvements seen with targeted quality improvement efforts.[18] Following implementation, 66% of ACS NSQIP hospitals saw reduced

mortality and 82% saw reduction in complications. The annual benefit for a hospital enrolling in ACS NSQIP has been estimated at 250 to 500 fewer complications and 12 to 36 fewer deaths.[19] Observed improvements in outcomes appear to be sustained, with the magnitude of quality improvement increasing over time.[20] Of note, improvements in risk-adjusted outcomes at ACS NSQIP hospitals were not found to differ significantly from those concurrently seen in matched non-NSQIP hospitals, suggesting that while feedback and reporting may be critical to implementing process change, they are not by themselves required to drive improvement.[21,22]

Table 14.3A Logistic Regression Models for Prediction of 30-Day Operative Mortality Using Preoperative Variables

Variable	Odds Ratio
ASA Class 4 or 5 vs. 1 or 2	8.1
ASA Class 3 vs. 1 or 2	3.5
Serum albumin (per gram)	0.62
Emergency operation	2.6
Age (per year)	1
Platelet count <150,000	1.9
Disseminated cancer	2.9
Dyspnea at rest vs. none	1.6
Dyspnea with minimal exertion vs. None	1.3
DNR	3.9
BUN >40 mg/dL	1.3
Work RVU (per unit)	1.02

Derived from private sector hospitals, n = 54,450 patients.

ASA Class, American Society of Anesthesiologists Physical Status Classification; BUN, blood urea nitrogen; DNR, do not resuscitate; RVU, relative value unit; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count K/cmm. Khuri SF, Henderson WG, Daley J, et al. Successful implementation of the Department of Veterans Affairs' National Surgical Quality Improvement Program in the private sector: the Patient Safety in Surgery study. *Ann Surg* 2008;248(2):329–336.

Table 14.3B Logistic Regression Models for Prediction of 30-Day Operative Morbidity Using Preoperative Variables

Variable	Odds Ratio
ASA Class 4 or 5 vs. 1 or 2	2.1
ASA Class 3 vs. 1 or 2	1.6
Albumin (per gram)	0.73
Work RVU (per unit)	1.05
Emergency operation	1.7
Dyspnea at rest vs. none	1.7
Dyspnea with minimal exertion vs. none	1.2
Wound infection	1.6
Patient on ventilator prior to surgery	1.9
Bleeding disorder	1.5
WBC > 11,000/mL^3	1.2
Age (per year)	1.01

Derived from private sector hospitals, n = 54,450 patients.

ASA Class, American Society of Anesthesiologists Physical Status Classification; BUN, blood urea nitrogen; DNR, do not resuscitate; RVU, relative value unit; COPD, chronic obstructive pulmonary disease; WBC, white blood cell count K/cmm.

Khuri SF, Henderson WG, Daley J, et al. Successful implementation of the Department of Veterans Affairs' National Surgical Quality Improvement Program in the private sector: the Patient Safety in Surgery study. *Ann Surg* 2008;248(2):329–336.

Risk Calculators

Algorithm-based risk stratification based on large datasets is now available through the internet and on mobile devices. In 2011, a cardiac risk calculator based on NSQIP variables compared favorably to performance of the

Revised Cardiac Risk Index (RCRI).[23] In 2013, the ACS released an online decision support tool including a perioperative risk calculator built on the NSQIP database, now including data from 4.3 million operations (www.riskcalculator.facs.org). The calculator incorporates 21 variables from the original VA NSQIP data collection and has excellent predictive performance for mortality, morbidity, and six specific complications.[24] In 2019, the option to view geriatric outcomes was added for patients greater than 65 years of age. Potential criticisms of the model include dependence on American Society of Anesthesiology (ASA) Physical Status classification, imprecise definition of functional outcomes and lack of validation outside of an NSQIP cohort,[25] however the ability to rapidly provide individualized patient risk estimation is an important advance. **Figure 14.1A,B** demonstrates an example of risk determination for a patient undergoing elective colon surgery, entering specific clinical variables and reporting specific complications in an individualized fashion.

GENERAL CONCEPTS OF PREOPERATIVE EVALUATION

7 The setting for preoperative evaluation varies with the surgical procedure and with patient circumstances. Coordinated preoperative care at a dedicated facility has led to improved efficiency for outpatient elective surgery,[26] however rapid changes in telehealth practices begun during the COVID-19 pandemic[27] will likely shape practice in the future.

Patient education remains a key aspect of the initial preoperative visit. Preoperative teaching has been shown to improve patient satisfaction and increase cooperation with postoperative recommendations.[28] The wealth of information available on the internet has enabled patients to be better educated, stronger consumers and has empowered many to participate more actively in their care. Prior to the first office visit, many will have researched their disease process, surgical procedure as well as the scorecards of the hospital and surgeon. Forward-thinking surgeons can leverage this engagement to increase the value of the face-to-face

appointment by providing online teaching materials ahead of the actual office visit.

Initial evaluation includes a standard medical history and complete physical examination. The presence of allergies, current medications, chronic illnesses related and unrelated to the surgical condition, prior procedures as well as staging and acuity of disease all contribute to the risk and benefit determinations.

Routine preoperative laboratory testing is no longer recommended for low-risk surgery. The majority of preoperative laboratory tests are rarely indicated and are of limited value.[29] It has been demonstrated that, even when abnormal, preoperative testing often does not lead to change in perioperative management or adverse postoperative outcomes.[30] Despite this, preoperative testing continues to be overused in both low-risk[31] and hospital settings.[32]

Selective laboratory testing has potential value in certain elective cases, as well as in remote telemedicine evaluations[33] and as part of risk assessment in elderly patients.[34] In all cases, testing should be based on clinical likelihood of finding and acting on abnormal results. Adjunctive cardiopulmonary evaluation should be performed selectively (see Cardiovascular and Pulmonary sections).

Anesthesia

For otherwise healthy patients, selective, rather than routine, evaluation by an anesthesiologist is recommended. Use of a screening questionnaire identifying high-risk conditions (history of prior or familial anesthetic difficulty, difficult airway/limited neck motion, decreased exercise tolerance, stroke, thyroid cardiac, asthma, liver and renal disease) has been validated as a trigger for formal anesthesia consult.[35,36]

The ASA Physical Status classification (**Table 14.4**) addresses the overall physical status of the patient, exclusive of specific surgical considerations. Despite its relative imprecision and inconsistent application, ASA class remains strongly associated with other predictors of surgical outcomes[37] and continues as a standard adjunct during preoperative evaluation.

The choice of anesthetic approach (local, monitored anesthesia care/sedation, neuraxial, and general) varies based on the indicated

procedure as well as patient considerations, with general anesthesia carrying a higher risk for pulmonary complications.[38] General anesthesia–related reduction in FRC may persist for up to 2 weeks postoperatively, with endotracheal intubation, inhalational anesthetic, and neuromuscular blockade all potentially contributing to pulmonary dysfunction. Shorter-acting neuromuscular blocking agents may minimize periprocedural weakness and promote better recovery from general anesthesia.

Epidural anesthesia combined with general anesthesia can reduce intraoperative shunting and preemptively address postoperative pain.[39] Meta-analysis of 141 randomized controlled trials suggests that the use of neuraxial blockade (spinal or regional anesthesia) in surgery is associated with overall mortality reduction and decreased complications, notably the incidence of postoperative pneumonia and respiratory failure,[40] however it is not possible to ascertain if these findings were due to salutary effects of regional blockade or reduction in use of general anesthesia.[40]

ACS NSQIP® | Surgical Risk Calculator

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Inspiring Quality: Highest Standards, Better Outcomes

Home | About | FAQ | ACS Website | ACS NSQIP Website

Enter Patient and Surgical Information

Procedure 44140 - Colectomy, partial; with anastomosis — Clear

Begin by entering the procedure name or CPT code. One or more procedures will appear below the procedure box. You will need to click on the desired procedure to properly select it. You may also search using two words (or two partial words) by placing a "+" in between, for example: "cholecystectomy + cholangiography"

Reset All Selections

Are there other potential appropriate treatment options? ☐ Other Surgical Options ☐ Other Nonoperative options ☐ None

Please enter as much of the following information as you can to receive the best risk estimates.
A rough estimate will still be generated if you cannot provide all of the information below.

Age Group: Under 65 years
Sex: Female
Functional Status: Independent
Emergency Case: No
ASA Class: Healthy patient
Steroid use for chronic condition: No
Ascites within 30 days prior to surgery: No
Systemic Sepsis within 48 hours prior to surgery: None
Ventilator Dependent: No
Disseminated Cancer: No

Diabetes: Insulin
Hypertension requiring medication: No
Congestive Heart Failure in 30 days prior to surgery: No
Dyspnea: No
Current Smoker within 1 Year: No
History of Severe COPD: No
Dialysis: No
Acute Renal Failure: No
BMI Calculation:
Height: 65 in / 165 cm
Weight: 150 lb / 68 kg

Step 2 of 4

Back | Continue

A

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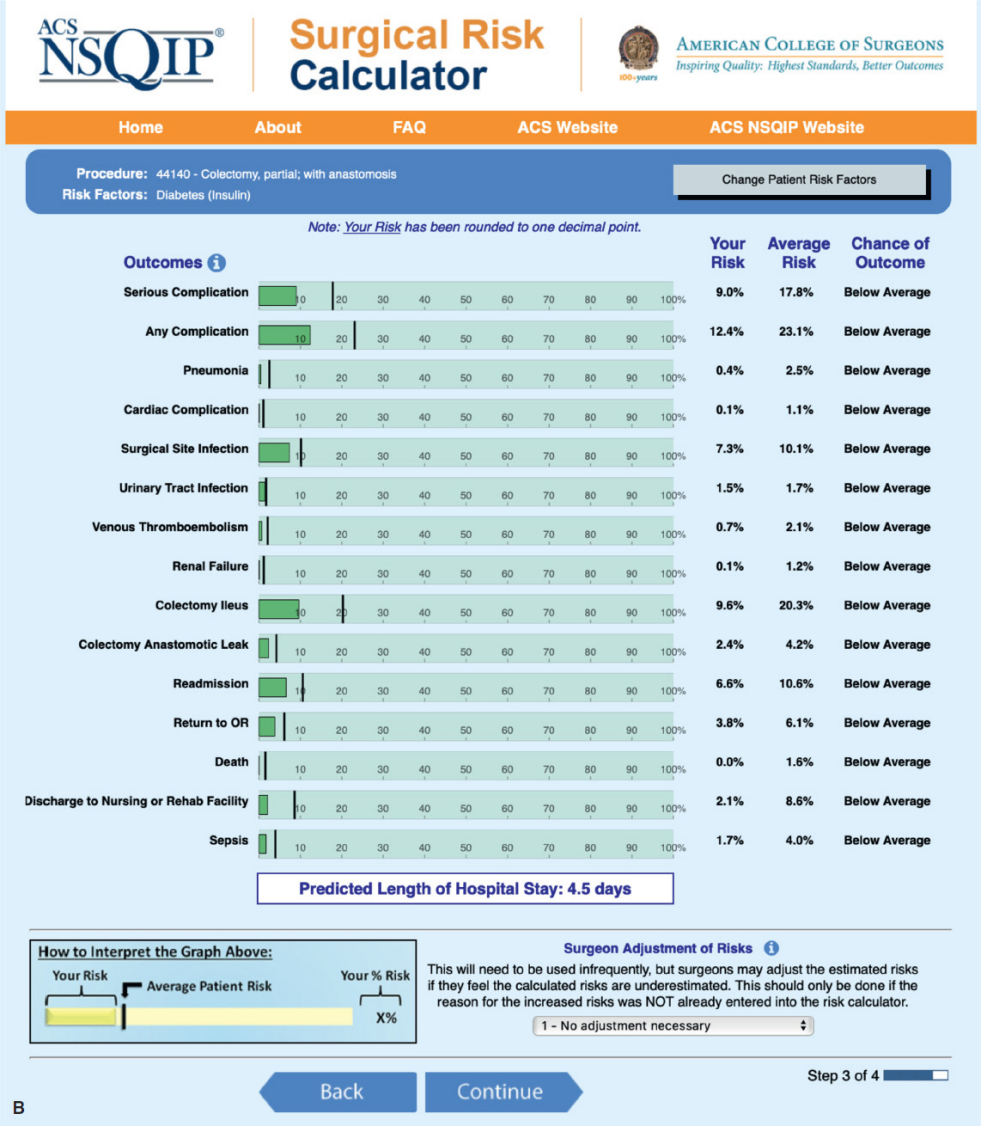


Figure 14.1 **A, B:** Risk stratification: ACS NSQIP risk calculator. (From www.riskcalculator.facs.org, American College of Surgeons.)

Surgical Procedure

Each surgical procedure carries its own set of specific risks. Procedures involving the thoracic or abdominal cavity, neurosurgery, head and neck, or vascular system carry higher risk[41] than those limited to the extremities or subcutaneous tissue. Procedural duration, often associated with complexity and extent of resection, is also associated with increased risk.[38] The extent of surgical exposure has also been correlated with physiologic impact with thoracotomy and upper abdominal incisions associated with most marked

changes in postoperative functional residual capacity. Minimally invasive approaches have, in general, been associated with lower hospital length of stay, earlier return to function, reduced postoperative pain and patient satisfaction. For vascular surgery, endovascular approaches reduce risk of pulmonary complications compared with open surgery.[42]

The urgency of the procedure affects risk assessment (**Table 14.5**).[25] **Emergency surgery** carries the additional challenges of life- or limb-threatening condition without the opportunity for medical optimization. The underlying processes are often catastrophic, with increased risk of infection, hemorrhage, and uncorrected physiologic derangement adding to the risk of postoperative complications[43] and mortality.[41] In ACS NSQIP, unadjusted 30-day mortality was 0.4% for elective procedures, 2.3% for urgent procedures, and 3.7% for emergency procedures.[7]

Table 14.4 American Society of Anesthesiologists (ASA) Physical Status Classification

ASA PS Classification	Definition	Adult Examples, Including, but not Limited to:
ASA I	A normal healthy patient	Healthy, nonsmoking, no or minimal alcohol use
ASA II	A patient with mild systemic disease	Mild diseases only without substantive functional limitations. Current smoker, social alcohol drinker, pregnancy, obesity (30 < BMI < 40), well-controlled DM/HTN, mild lung disease
ASA III	A patient with severe systemic disease	Substantive functional limitations; one or more moderate to severe diseases. Poorly controlled DM or HTN, COPD, morbid obesity (BMI ≥40), active hepatitis, alcohol dependence or abuse, implanted pacemaker, moderate reduction of ejection fraction, ESRD undergoing regularly scheduled dialysis, history (>3

		mo) of MI, CVA, TIA or CAD/stents
ASA IV	A patient with severe systemic disease that is a constant threat to life	Recent (<3 mo), MI, CVA, TIA or CAD/stents, ongoing cardiac ischemia or severe valve dysfunction, severe reduction of ejection fraction, shock, sepsis, DIC, ARD, or ESRD not undergoing regularly scheduled dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured abdominal/thoracic aneurysm, massive trauma, intracranial bleed with mass effect, ischemic bowel in the face of significant cardiac pathology or multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Adapted from the ASA Relative Value Guide®.

The addition of "E" denotes Emergency surgery: (An emergency is defined as existing when delay in treatment of the patient would lead to a significant increase in the threat to life or body part.)

These definitions appear in each annual edition of the ASA Relative Value Guide. There is no additional information that will help you further define these categories.

Last amended by the ASA House of Delegates on December 13, 2020 (original approval: October 15, 2014).

Disparities

Disparities in surgical outcomes persist based on racial and socioeconomic considerations.[44] The relative rates of postoperative complications, including respiratory failure, bleeding, infection, and physiologic, and metabolic derangements are generally increased for minority patients over Caucasian patients.[45] The causes are multifactorial and, likely chronic and acute healthcare resource availability, as well as patient-related factors, play a role. In a survey of the U.S. Nationwide Inpatient Sample involving over three million oncologic procedures performed between 1999 and 2009, African American, but not Hispanic patients had higher rates of vascular, wound, GI, and infectious complications when compared to white patients.[46] Variations in outcomes suggest that unexploited opportunities likely exist to reduce the existing disparities. Cultural and economic barriers to surgical care may not be readily visible to the surgeon and should be intentionally considered.

Age

Patients are living longer and with more substantial comorbidities. The world's population of people 60 years of age and older has doubled since 1980 and is forecast to reach two billion by 2050.[47] Demand for surgical services continues to increase faster than the rate of population growth; in 2006, surgery on elderly patients accounted for 35% of inpatient and 32% of outpatient surgical procedures.[48]

Table 14.5 Procedural Urgency

Category	Characteristics	Time Frame	Example
Emergency	Immediate threat to life or limb	Typically in <6 hrs	Acute traumatic hemorrhagic shock
Urgent	Threat to life or limb	6–24 hrs	Small bowel obstruction
Time-Sensitive	Sufficient time for evaluation and management changes which may significantly alter outcome	1–6 wks	Oncologic surgery
Elective	Condition permits delay	Up to a year	Aesthetic surgery

Adapted from Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;130(24):2215–2245.

Normal aging reduces the ability to maintain homeostatic response in the face of acute physiologic stress[49] such as surgery. In a series of over a million Medicare patients, operative mortality for patients 80 years of age and older was observed to be more than twice that for patients 65 to 69 years of age.[6] Compared with patients less than 60 years of age, the risk of postoperative pulmonary complication was doubled for patients between the ages of 60 and 69 and tripled for patients aged 70 to 79.[50] In addition, an initial infectious or pulmonary complication is associated with significantly higher-risk–adjusted failure-to-rescue rates in elderly patients when compared with younger patients.[51] Attending to both prevention and early

recognition of complications potentially will have the greatest impact on these outcomes in the elderly population.

Table 14.6 Preoperative Evaluation of the Geriatric Patient

Domain	Evaluation	Potential Intervention
Cognitive impairment and dementia	Cognitive screen: Mini-Cog, family interview	If screens positive, further evaluation by PCP, geriatrician, or mental health specialist
Decision-making capacity	The patient can: clearly indicate treatment choice understand relevant information acknowledge condition, treatment options, and likely outcomes engage in rational discussion about treatment options	If altered, discuss surrogacy for medical decision making
Depression	Depression screen: PHQ2	If screens positive, further evaluation by PCP, geriatrician, or mental health specialist
Risk for postoperative delirium	Risk assessment	In at-risk patients avoid benzodiazepines and antihistamines when appropriate
Alcohol and substance abuse	Modified CAGE questionnaire	If procedure can be delayed, consider referral to substance abuse specialist

		Perioperative daily MVI and thiamine
Cardiac evaluation	ACC/AHA algorithm (**Algorithm 14.1**)	If positive, consider strategies to reduce risk
Risk for pulmonary complications	NSQIP predictors (**Table 14.11**)	If positive, consider strategies to reduce risk
Functional status, mobility, and fall risk	Timed Up and Go test	If abnormal
Frailty scoring	Frailty score	If abnormal
Nutritional status	BMI <18.5 kg/m^3 Serum albumin 3.0 g/dL without renal or hepatic dysfunction Unintentional weight lost >10–15% in past 12 mo	If feasible, full nutritional assessment by dietician with perioperative nutritional planning
Medication management	Review medication list	Avoid polypharmacy
Counseling regarding: advance directive and surrogate decision making the patient's treatment goals the patient's expectations of surgery		

the patient's family and social support system		
Appropriate preoperative diagnostic testing	Selective preoperative testing	Normal laboratory values obtained up to 4 mo preoperatively can be used safely as long as nonsubstantial interval change in clinical status has occurred

Adapted from Chow WB, Rosenthal RA, Merkow RP, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J Am Coll Surg* 2012;215(4):453–466.

The ACS and American Geriatrics Society (AGS) have published a best practices guideline for the Optimal Preoperative Assessment of the Geriatric Surgical Patient.[48] The guidelines highlight 13 geriatric-specific domains to identify and address during the preoperative period (**Table 14.6**). Few of these domains are covered in detail during traditional preoperative surgical evaluation and further integration into routine practice is needed. In 2016, an additional best practices guideline for perioperative management was added.[52] Interdisciplinary, geriatric-focused preoperative and perioperative care has been demonstrated to decrease complications, shorten hospitalization, increase discharge home and reduce readmissions.[53]

While surgical risk increases with advancing age, chronologic age alone should not be considered a contraindication to surgery in otherwise healthy patients. The association of age with other factors such as decreased functional status, increased number of comorbidities, and more complex pharmacologic history[54] renders simple conclusions unfeasible. For example, in the RCRI model for cardiac mortality, other risk factors become more significant than age alone,[55] while in cases of advanced age, adding age to the RCRI model improves its utility for prediction.[56]

Medical Comorbidity

Hypertension, coronary artery disease, diabetes, and COPD are the most frequently seen comorbidities in patients over the age of 70.[54] More than 50% of these patients suffer from at least one infirmity and 30% suffer from two or more.[54] Adaptation to multiple chronic illnesses and treatments may combine to create altered physiologic response to surgery. For example, a patient with hypertension that is well controlled with diuretics and β-blockade may be chronically volume depleted and unable to mount cardiovascular response to further blood loss in surgery.

Obesity/Obstructive Sleep Apnea

The prevalence of adult obesity is increasing in the United States, with one-third of adults in 2009–2010 considered to be obese (body mass index [BMI] ≥30 kg/m^2).[57] Paradoxically, in nonbariatric general surgery, a J-shaped relationship of lower mortality has been reported in overweight and moderately obese patients.[58]

The American Society of Anesthesiologists updated guidelines for perioperative management of patients with obstructive sleep apnea in 2014.[59] In this report, the prevalence of sleep-disordered breathing was 9% in women and 24% in men. Patients often present without formal polysomnographic confirmation of the diagnosis. Increases in perioperative risk are noted to occur in proportion to the severity of sleep apnea.[60] Sleep apnea should be suspected in patients with history of apparent airway obstruction during sleep, BMI >35 kg/m^2, large neck circumference, craniofacial abnormalities, snoring, frequent arousals from sleep, and unexplained daytime somnolence or fatigue. A trial of preoperative continuous positive airway pressure (CPAP) may be attempted to improve nighttime airway obstruction, particularly if OSA is severe. Other potential interventions include the use of mandibular advancement devices, oral appliances and preoperative weight loss, however evidence was judged to be insufficient to make formal recommendations.

Intraoperative considerations include choice of anesthetic technique, airway management, patient positioning, and patient monitoring. For appropriate procedures, regional anesthesia may be preferred over general anesthesia and continuous monitoring should be employed because of the

potential for airway obstruction. Patients at risk for obstructive sleep apnea may have associated difficult airway and require special attention during induction and emergence from anesthesia. Sedation and neuromuscular blockade should be carefully monitored and fully reversed prior to extubation. Postoperative analgesia should be carefully titrated, using any appropriate modalities to minimize opioid requirements. Supine positioning should be avoided and upright, sitting, lateral or prone positioning may be considered. When not contraindicated by the surgical procedure, patients who use CPAP or noninvasive positive pressure ventilation (NIPPV) preoperatively should have these continued postoperatively. It is important to titrate support based on their usual home settings and patients may bring their home machines to use perioperatively. Continuous, rather than intermittent pulse oximetry, combined with direct observation, is recommended for as long as the patient remains at risk for postoperative respiratory depression.

Anemia

Anemia is independently associated with mortality in noncardiac surgery,[61] yet it is not clear that correction of anemia will alter mortality. Several randomized trials examining transfusion strategies in relatively stable patients failed to demonstrate mortality benefit with higher transfusion triggers in the ICU,[62] cardiac,[63] and orthopedic surgery[64] settings. At present, recommendations for perioperative transfusion are general, with consideration for higher thresholds given to patients who are symptomatic with chest pain, hypotension or fatigue, those with known cardiac ischemia or those receiving massive transfusion for hemorrhagic shock. Current evidence does not support aggressive preoperative transfusion in patients with sickle cell disease.[65] Systematic review of trials evaluating the use of human recombinant erythropoietin combined with iron supplementation in anemic patients prior to noncardiac surgery suggests that these agents successfully reduce the need for RBC transfusion and at higher doses, can increase preoperative hemoglobin, but mean number of units of PRBC transfused, risk of adverse events, hospital length of stay, or 30-day mortality are not clearly reduced.[66]

Preoperative Functional Status

The importance of preoperative functional status has been recognized for years. Self-reported exercise intolerance (to walking four blocks or two flights of steps) is independently associated with higher risk of perioperative cardiovascular, myocardial ischemia, and neurologic events after elective major noncardiac surgery.[67] The relationship is inversely related to the total number of blocks that could be walked or flights of stairs that could be climbed. Functional ability can be quantified in terms of metabolic equivalents (METs), with 1 MET defined as the amount of oxygen consumed while sitting at rest and equal to 3.5 mL O_2 uptake/kg/min.[68] Functional status can be categorized as excellent, >10 METs; good, 7 to 10 METs; moderate, 4 to 6 METs; and poor, <4 METs. Risk is increased if unable to perform at a level of 4 METs (**Table 14.7**).[25] The ACS recommends a four-question survey of activities of daily living (ADLs) as a screen to identify unsuspected functional compromise in geriatric patients (**Table 14.8A**).[69]

Systematic reviews of the ability to influence postoperative outcomes by improving preoperative physical status ("prehabilitation") are limited, but suggest that inspiratory muscle training, aerobic exercise, and/or resistance training may decrease postoperative complications following abdominal and cardiac surgery.[70,71]

Table 14.7 METs Equivalents

METs Level	Example
>10 METs	Strenuous sports (swimming, skiing, singles tennis)
>4 METs	Climbing flight of stairs Walking up a hill Walking 4 mph on level ground
<4 METs	Slow ballroom dancing Golfing with a cart Playing a musical instrument Walking at 2–3 mph
1 MET	Eating, dressing, toileting

Adapted from Fleisher LA, Fleischmann KE, Auerbach AD, et al. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;130(24):2215–2245.

Table 14.8A Short Simple Screen for Functional Assessment

Ask the patient the following questions: 1. Can you get out of bed or chair yourself? 2. Can you dress and bathe yourself? 3. Can you make your own meals? 4. Can you do your own shopping?
If NO to any of these questions, more in-depth evaluation should be performed, including full screening of activities of daily living and instrumental activities of daily living.
Deficits should be documented and may prompt perioperative interventions (i.e., referral to occupational therapy and/or physical therapy) and proactive discharge planning.

Adapted from Chow WB, Rosenthal RA, Merkow RP, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J Am Coll Surg* 2012;215(4):453–466.

Frailty

Separate from comorbidity, elderly patients may suffer from frailty and sarcopenia.[72] In the Medicare population, additional mortality has been related to frailty[73] and the relationship has been documented in a broad population, including patients undergoing ambulatory general surgery,[74] gastric surgery,[75] gynecologic oncology,[76] and cardiac surgery,[77] as well as in patients requiring unplanned admission following elective ambulatory surgery.[78] CT-based morphomic quantitation of trunk muscle volume is associated with decreases in functional performance on ADLs and independent activities as measured by the Vulnerable Elder Survey[79] as well as poorer outcomes in liver transplantation[80] and aortic surgery.[81] An operational frailty score (**Table 14.8B**) has been validated in elderly surgical patients and is associated with higher incidence of postoperative adverse events, increased length of hospital stay, and higher likelihood of discharge to a skilled or assisted-living facility.[82]

Direction of Care

One of the most important discussions between a surgeon and patient is the understanding of the patient's desires regarding direction of care. There is little question of aggressive interventions for a healthy patient expecting rapid return to their preoperative level of function after elective surgery. Nevertheless, patients with severe underlying comorbidity or limited life expectancy should have the opportunity to direct overall goals of their care. Approaches that incorporate principles of geriatric and palliative care can be used to frame surgical care for these patients in the context of time-limited trials[83,84] or best case/worst case framework.[85] In this fashion, treatment decisions can be matched to the individual patient's overall priorities and goals.

Table 14.8B Frailty Scoring (Operational Definition)

Criteria	Definition
Shrinkage	Unintentional weight loss ≥10 lb past year
Weakness	Decreased grip strength
Exhaustion	Self-reported poor energy and endurance
Low physical activity	Low weekly energy expenditure
Slowness	Slow walking
The patient receives 1 point for each criterion met: 0–1 Not frail 2–3 Intermediate frail (prefrail) 4–5 Frail	

Adapted from Chow WB, Rosenthal RA, Merkow RP, et al. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. *J Am Coll Surg* 2012;215(4):453–466.

MEDICATION MANAGEMENT

Medication management in the perioperative period is subject to general guidelines of practice. The pharmacokinetics of drug administration, distribution, metabolism, and excretion may all be affected by surgery. Major GI procedures limit oral intake and may require alternate routes of administration. Patients receiving volume resuscitation may have increased drug volume of distribution. Fluctuations in hepatic and renal function and addition of multiple new medications may alter drug metabolism and excretion. New drug interactions may lead to increased toxicity; appropriate monitoring by drug levels may improve drug management.

A careful medication history includes prescription and nonprescription medications, nutritional and herbal supplements. Patients may be taking over-the-counter herbal supplements with substantial physiologic effects[86] but may not perceive these as being relevant to the conduct of their surgery. In one series, more than 70% of patients failed to disclose herbal medicine use during routine preoperative assessment.[87] Herbal supplements are presently not subject to FDA regulation; contents may vary substantially from manufacturer to manufacturer and frank adulteration has been documented.[88] Variations in supplement content may make a 7-day holding period prudent.[89]

In the absence of clear evidence-based guidelines for perioperative medication management, a general approach is to continue drugs that would cause withdrawal within the perioperative period, and to discontinue unnecessary drugs or those with potential for adverse events, restarting them as soon as the patient condition permits (**Table 14.9**).[89] Medications that are generally continued include β-blockers, clonidine, statins, and selective serotonin reuptake inhibitors (SSRIs). Medications that can be discontinued include diuretics, metformin and, possibly, angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). Additional specific management of cardiac medications and dual antiplatelet therapy in the setting of cardiac stent placement is detailed in the Cardiovascular section.

Management of anticoagulation is of critical importance to surgeons and the indication for anticoagulation should be weighed against the risk of procedural bleeding. Agents should be held for the minimum interval felt safe after invasive procedure.

Patients on chronic long-acting anticoagulation who are undergoing elective operation generally can use preoperative bridging with unfractionated or low–molecular-weight heparin prior to surgery.[90] In the recent PAUSE trial, patients with atrial fibrillation who had direct oral anticoagulant interruption for elective surgery, a perioperative strategy without bridging or coagulation function testing was associated with low rates of major bleeding or thromboembolic complications.[91]

In the emergent setting, the American College of Chest Physicians (ACCP) has published guidelines covering reversal of vitamin K competitors based on urgency of procedure and risk of life-threatening hemorrhage.[92] Reversal of newer direct thrombin inhibitors is now feasible with targeted monoclonal antibodies. In addition, dabigatran may be removed with dialysis, however rivaroxaban and apixaban are highly protein bound and unlikely to be removed with this modality.

Table 14.9 Common Medications Which May Require Special Perioperative Management

Anticoagulants	▪ May require reversal in acute situations ▪ May bridge therapy with unfractionated or LMW heparin
Aspirin or dipyridamole	▪ In setting of PCI and prior drug-eluting stent, see **Algorithm 14.2** ▪ Withhold 7 d prior to surgery with increased bleeding risk ▪ May continue in select procedures
Thienopyridine P2Y12 inhibitors (i.e., clopidogrel, ticlopidine)	▪ In setting of PCI and prior drug-eluting stent, see **Algorithm 14.2** ▪ Withhold 7 d prior to surgery with increased bleeding risk
Glycoprotein IIb/IIIa inhibitors	▪ In setting of PCI and prior drug-eluting stent, see **Algorithm 14.2** ▪ Withhold at least 12 hrs prior to surgery, although antiplatelet effect may persist for longer
NSAIDs	▪ Withhold prior to surgery with risk of renal complications
β-Blockers	▪ Continue in patients already receiving drug, including day of surgery ▪ Do not begin new therapy in preoperative setting
Statins	▪ Continue in patients already receiving drug, including day of surgery ▪ Consider initiating in patients undergoing vascular surgery
Calcium channel blockers, nitrates, most antiarrhythmics	▪ Continue in patients already receiving drug, including day of surgery
Angiotensin-converting	▪ Risk of intraoperative hypotension and

enzyme inhibitors, angiotensin receptor blockers	renal risk, hold day of surgery
Diuretics	▪ Renal risk, potential for hyperkalemia with potassium sparing diuretics, hold day of surgery
Metformin	▪ Risk of lactic acidosis, withhold at least 2 d prior to surgery
Insulin	▪ Adjust dose prior to surgery
Lithium	▪ Potential prolongation of neuromuscular blockade, sedative action, cardiac arrhythmia ▪ Withhold at least 1 d prior to surgery
Monoamine oxidase inhibitors	▪ Potential anesthetic interactions ▪ Proceed with MAO-safe anesthetic or hold for 2 wks
Selective serotonin release inhibitors	▪ Potential bleeding complications ▪ Discontinue for 3 wks preoperatively in conjunction with psychiatry evaluation
Buprenorphine/naloxone	▪ Preoperative weaning in conjunction with the prescribing physician ▪ Postoperative pain management may require pain/addiction specialist consultation
HIV drugs	▪ Minimize interruptions in antiretroviral therapy ▪ Prophylaxis may vary based on immune status
Steroids, immunosuppressives	▪ Stress dose steroids indicated only if evidence of abnormal hypothalamic–pituitary–adrenal axis

	▪ May be advisable to discontinue or reduce dose in presence of active infection
Oral contraceptives, conjugated estrogen	▪ Increase hypercoagulable state ▪ Consider holding 4 wks prior to surgery; if not feasible, ensure adequate DVT prophylaxis
Over-the-counter herbal medications	▪ Consider holding 7 d prior to surgery

In large series, perioperative aspirin administration was associated with an increased risk of postoperative hemorrhage,[93] however a recent meta-analysis concluded that aspirin should not be stopped in the perioperative period unless bleeding risk outweighed thrombotic risk of holding the drug.[94]

Perioperative glucose control reduces mortality, hospital length of stay, and deep wound infections in cardiac surgery.[95] An adjusted dose of short-acting insulin is administered perioperatively, with intravenous insulin infusion intraoperatively if needed. The oral hypoglycemic, metformin, is associated with lactic acidosis and should be held prior to surgery.

Psychiatric medications should be managed based on concern for precipitating withdrawal. Abrupt withdrawal of SSRIs may lead to nausea, vomiting, lethargy, with symptoms seen more quickly in drugs with shorter half-life.[96] The use of SSRIs may increase the risk of bleeding, particularly when used in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs).[89] Benzodiazepines may be continued perioperatively. Older agents, including tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs), may precipitate hypertensive crisis in conjunction with indirect sympathomimetics.

Patients receiving daily maintenance buprenorphine will not have sufficient surgical analgesia from usual postoperative opioid dosing regimens. Preoperative consultation with their prescriber and with the anesthesiology pain service is recommended prior to surgery. Alternative strategies, including the use of regional anesthesia, nonsteroidal and nonnarcotic regimens may facilitate postoperative management.

Immunosuppressant mediations may be reduced or discontinued prior to surgery, depending on the extent and the presence of associated infection, although a systematic review of immunomodulators in patients with inflammatory bowel disease has suggested no clear increased risk of total or infectious complications with azathioprine, cyclosporine, or infliximab.[97] Steroid use carries a dose-dependent relationship with increased risk of postoperative complications, both infectious and overall.[98] Meta-analysis of randomized controlled trials suggests that perioperative stress dose steroids are not required unless there is dysfunction of the hypothalamic–pituitary–adrenal axis.[99] Anti-VEGF inhibitors are associated with increased risk of GI perforation and delayed wound healing and their use is not recommended for 28 days before or after surgery or until surgical wounds are healed.

SPECIFIC ORGAN SYSTEM GUIDELINES

Cardiovascular

Prediction of cardiac adverse events following noncardiac surgery was pioneered in the 1970s[1] and risk stratification is most refined in this area.

Risk Stratification

The current RCRI (**Table 14.10**)[55] is based on risk of surgery, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, preoperative insulin–requiring diabetes mellitus, and preoperative renal insufficiency and can be used to identify patients at higher risk for major cardiac complications (MI, pulmonary edema, ventricular fibrillation, primary cardiac arrest, complete heart block). The RCRI has been validated as a predictor of increased risk, and pooled estimates of external validation studies over the past 15 years show higher-risk estimates than the original RCRI.[100] Disappointingly, targeted interventions in high-risk groups have yet to show benefit in risk reduction. Active angina, recent myocardial infarction, signs of left ventricular dysfunction, such as dyspnea or worsening heart failure, syncope, significant arrhythmias, and severe valvular disease should also prompt further preoperative evaluation.

The American College of Cardiology (ACC) and the American Heart Association (AHA) issued joint recommendations for perioperative cardiovascular evaluation and management for noncardiac surgery in 2014.[25] The guideline covers preoperative evaluation, risk assessment, perioperative management, and postpercutaneous coronary intervention (PCI) recommendations. Outcomes are defined in terms of a composite major adverse cardiac event (MACE), which includes death or myocardial infarction (MI). Low-risk procedures are defined as carrying a predicted MACE risk of <1%, and elevated-risk procedures carrying a MACE risk of ≥1%.

Stable patients undergoing low-risk surgery and those with good exercise tolerance rarely need further cardiac evaluation. For those at higher risk, cardiology evaluation is recommended. In urgent or emergent situations where surgical intervention must proceed prior to any meaningful management changes, delay for cardiac evaluation will not be of benefit and care is focused on prompt recognition and treatment of any perioperative events. In this paradigm, decision making for higher-risk patients can be simplified to (1) initial determination if the procedure can be delayed to permit additional evaluation and management which could significantly alter the outcome and (2) further risk stratification and intervention if the patient condition permits. The overall ACC/AHA algorithm is reproduced in **Algorithm 14.1** and specific recommendations are summarized below.

Table 14.10 Revised Cardiac Risk Index

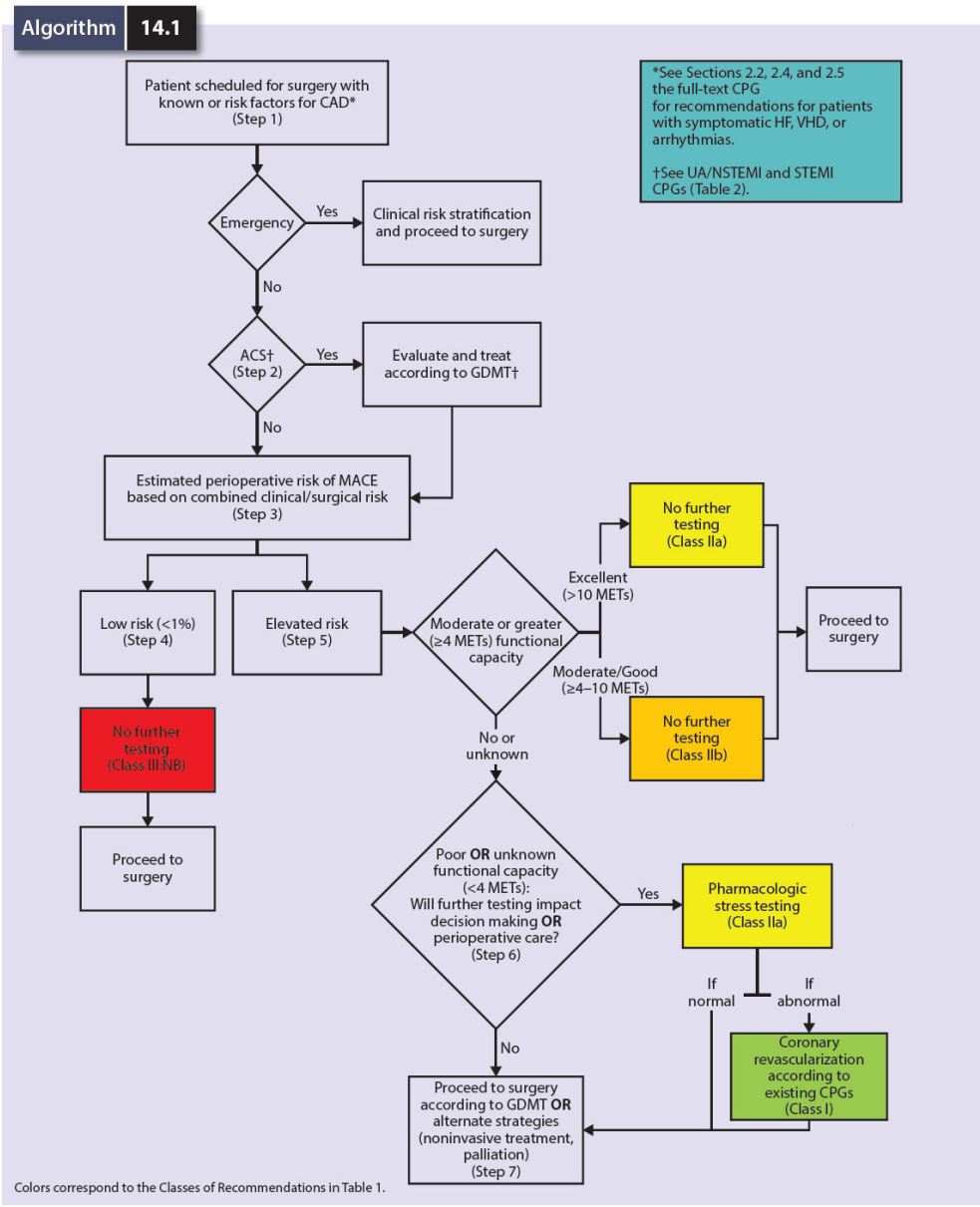
Revised Cardiac Risk Index Criteria	
High-Risk Surgery ▪ Intraperitoneal ▪ Intrathoracic ▪ Suprainguinal vascular	
History of Ischemic Heart Disease ▪ History of myocardial infarction ▪ History of or current angina ▪ Use of sublingual nitrate therapy ▪ History of positive exercise test ▪ Pathologic Q waves on electrocardiogram	
History of Congestive Heart Failure ▪ Pulmonary edema, bilateral rales, or S3 gallop ▪ Paroxysmal nocturnal dyspnea ▪ CXR showing pulmonary vascular redistribution	
History of Cerebrovascular Disease ▪ History of transient ischemic attack ▪ History of cerebrovascular accident	
Diabetes Mellitus Requiring Insulin Therapy Chronic renal insufficiency, defined as a baseline creatinine level of at least 2.0 mg/dL (177 μmol/L)	
Patient receives 1 point for any finding within the 6 major categories	
Points	**Risk of Major Cardiac Event (%)**
0	3.9
1	6.0
2	10.1
3–6	15.0

Adapted from Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100(10):1043–1049.

Pre-Existing Cardiac Disease

The presence of underlying coronary artery disease is associated with postoperative MACE following noncardiac surgery. Following an acute MI, the rate of subsequent postoperative ischemia and MI decreases as the time interval to surgery increases. The risk of perioperative stroke was also increased with surgery occurring within 6 months of MI.[101] In the absence of myocardial revascularization, noncardiac surgery should be delayed for 60 days or more after acute MI. Coronary artery bypass grafting (CABG) solely to reduce perioperative risk is not recommended and should be performed only if the procedure would otherwise be indicated.

The presence of heart failure is a strong predictor of perioperative cardiac morbidity and mortality. The stability of heart failure is likely to affect outcomes, with decompensated, symptomatic heart failure identified on physical examination carrying higher risk. Preservation of left ventricular ejection fraction is an independent predictor for patients undergoing elevated-risk surgery[102] and patients with an LVEF ≤29% were identified as having higher risk in vascular surgery.[103]



Algorithm 14.1 Stepwise approach to perioperative cardiac assessment for CAD. Abbreviations: ACS, acute coronary syndrome; GDMT, Guideline-directed medical therapy; MACE, major adverse cardiovascular events; METs, metabolic equivalents; CPGs, clinical practice guidelines. (Data from Fleisher LA, et al. *Circulation* 2014;130[24]:2215–2245.)

Patients with clinically suspected valvular heart disease should have review of echocardiography evaluation performed within 1 year prior to surgery or have repeat study if there has been a significant change in status or physical evaluation. Concomitant evaluation for ischemic disease should be

considered. If valvular intervention is clinically indicated, intervention prior to noncardiac surgery may reduce perioperative risk.[104]

Postoperative arrhythmias are common and are often triggered by the stress of surgery. Patients with heart block, implanted pacemakers, or automatic implantable cardioverter defibrillators (AICDs) are best served by effective communication between surgery, anesthesiology, and cardiology to optimize perioperative device management.

Although not included in most cardiac risk scoring, pulmonary hypertension is associated with increased complications[105] and patients may benefit from referral to a center with expertise for further evaluation. In a single institution study evaluating adult patients with pulmonary hypertension undergoing anesthesia, specific risk factors were identified as associated with short-term morbidity (history of pulmonary embolism, NYHA functional class ≥2, elevated-risk surgery, anesthesia >3 hours) and postoperative mortality (pulmonary embolism, right axis deviation on EKG, RV hypertrophy or RVSP:systolic blood pressure >0.66, intraoperative vasopressor and anesthesia when nitrous oxide was not used).[106]

Adult patients with congenital heart disease, when possible, should undergo preoperative evaluation in a regional center specializing in congenital cardiology.[107]

Preoperative Testing (Algorithm 14.1)

EKG should be considered for patients undergoing elevated-risk surgery. It should also be considered in patients with a history of CHD, significant arrhythmia, peripheral arterial disease, cerebrovascular disease or significant structural heart disease, unless they are undergoing low-risk surgery.

More extensive evaluation, including exercise stress testing, assessment of left ventricular function or coronary angiography is performed selectively after initial risk stratification and determination of exercise tolerance. Exercise stress testing is not recommended for patients undergoing low-risk surgery or patients able to tolerate >10 METs; patients with elevated RCRI risk, but able to tolerate >4 METs; and patients with elevated RCRI risk, unable to tolerate <4 METs, but for whom cardiac evaluation will not change management. In patients with elevated RCRI risk or unable to tolerate <4

METs in whom the opportunity exists to improve cardiac management, stress exercise testing can be useful.[25]

Management of Antiplatelet Therapy Following Percutaneous Coronary Intervention (Algorithm 14.2)

Recommendations following PCIs center not only on the cardiac risk, but also the risk of discontinuing dual antiplatelet therapy. Premature discontinuation of antiplatelet agents increases the risk for early and late stent thrombosis and this must be weighed against the relative risk of surgical bleeding. Dual antiplatelet therapy should not be interrupted for the initial 4 to 6 weeks after PCI. Elective surgery should be delayed at least 14 days after balloon angioplasty, 30 days after bare-metal stent implantation if antiplatelet agents are to be discontinued, and 365 days after drug-eluting stent (DES) implantation, if feasible. Elective surgery may considered earlier (180 days) following DES implantation if risk of surgical delay outweighs risk of stent thrombosis.

Management in all other situations should be determined by consensus of the surgeon, anesthesiologist, cardiologist, and patient. In patients undergoing emergent surgical procedures that mandate discontinuation of P2Y12 platelet receptor inhibitors, aspirin should be continued if possible and the P2Y12 platelet receptor inhibitor resumed as soon as possible following surgery.[25]

Other Cardiac Medication Management

Patients on chronic β-blockade should continue treatment during the perioperative period. Prior recommendations for initiating β-blockade in patients without cardiac risk factors have been removed after meta-analysis indicated increased mortality.[108] In patients with intermediate or high risk for myocardial ischemia, that is, three or more risk factors on RCRI, new initiation of β-blockers can be considered preoperatively but enough time should be allowed to assure stability before surgery. Statin therapy should be continued perioperatively and new initiation can be considered for vascular[109] or elevated-risk patients' clinical indications. α-2 Blockade with clonidine should not be administered for prevention of cardiac events.[110] Aspirin, while it has a role in acute coronary syndrome and following PCI, is not indicated solely for prevention of perioperative cardiac events.[93] No

benefit has been identified for perioperative nitroglycerine and routine use is not recommended.

Pulmonary

Pulmonary complications following surgery are among the most frequent and costly postoperative events and lead to similar increases in morbidity, mortality, and length of stay as cardiac complications.[38] In particular, the development of pulmonary complications in the elderly may predict long-term mortality after surgery.[111] Age-related diminution of pulmonary function is associated with postoperative complications[38] and increasing age is an independent risk factor for postoperative pulmonary complications.[50] Other factors associated with increased risk of postoperative pulmonary complications are summarized in **Table 14.11**.

Risk Stratification

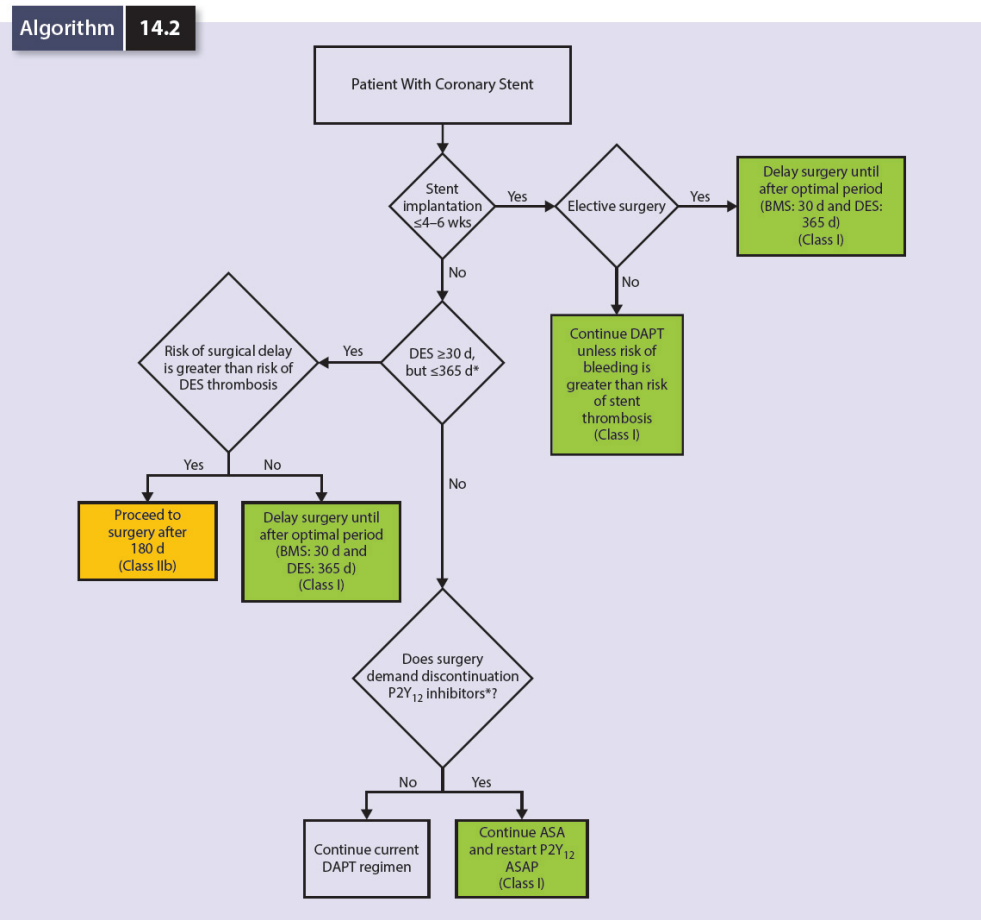
The 2006 American College of Physicians guideline for preoperative pulmonary evaluation includes evaluation of patient-related, operative, and laboratory risk factors associated with increased risk of postoperative pulmonary complications.[50] Chronic lung disease was the most frequently identified risk factor; other patient-related factors include ASA class greater than II, increasing age, congestive heart failure, functional dependence, restrictive lung disease, and uncontrolled reactive airway disease. Operative risk factors include surgical site, duration, choice of anesthetic, emergency procedures, and low serum albumin. Other pulmonary risk stratification scales also identified elevated BUN, dyspnea at rest, or low levels of activity[112]; low preoperative arterial oxygen saturation, acute respiratory infection during the previous month, age, preoperative anemia, upper abdominal or intrathoracic surgery, surgical duration of at least 2 hours, emergency surgery[113]; and age, smoking status, airflow limitation, ASA class, hypoalbuminemia, emergency surgery, and nonlaparoscopic abdominal/cardiac and AAA repair[114] as risk factors for pulmonary complications. In Europe, the ARISCAT Score for pulmonary complications has been validated to predict three levels of postoperative pulmonary

complications, though performance differed between different regions (**Table 14.12**).[115]

Table 14.11 Risk for Pulmonary Complications in Noncardiac Surgery

Risk Assessment for Pulmonary Complications in Noncardiothoracic Surgery
Patient-Related Factors
Age >60
ASA class II, or greater
Chronic obstructive pulmonary disease
Functional dependence
Congestive heart failure
Dyspnea at rest or minimal exertion
Operative Factors
Prolonged surgery (>3 hrs)
Abdominal surgery
Thoracic surgery
Neurosurgery
Head and neck surgery
Vascular surgery
Emergency surgery
Use of general anesthesia
Laboratory Values
Serum albumin <3.5 g/dL
BUN >40 mg/dL

Modified from Qaseem A, Snow V, Fitterman N, et al. Risk assessment for and strategies to reduce perioperative pulmonary complications for patients undergoing noncardiothoracic surgery: a guideline from the American College of Physicians. *Ann Intern Med* 2006;144(8):575–580 and Khuri SF, Henderson WG, Daley J, et al. Successful implementation of the Department of Veterans Affairs' National Surgical Quality Improvement Program in the private sector: the Patient Safety in Surgery study. *Ann Surg* 2008;248(2):329–336.



Algorithm 14.2 Proposed algorithm for antiplatelet management in patients with PCI and noncardiac surgery. Abbreviations: BMS, bare metal stent; DES, drug eluting stent; DAPT, dual antiplatelet therapy; ASA, aspirin; P2Y12, P2Y12 inhibitor; ASAP, as soon as possible. (Data from Fleisher LA, et al. *Circulation* 2014;130[24]:2215–2245.)

Preoperative Evaluation

Symptomatic dyspnea is a strong predictor of pulmonary complications and should be investigated further as it may signal underlying cardiopulmonary or neuromuscular dysfunction. Chronic cough or sputum production, particularly in the setting of chronic obstructive lung disease, cigarette smoking, or occupational exposures should trigger consideration of possible associated infection. Systemic diseases may have associated pulmonary compromise. A history of restrictive chest wall disease or neuromuscular disorders may signal impaired ventilatory reserve and may impart additional risk. Physical examination findings of abnormal auscultation, scoliosis, chest wall deformity, and accessory muscle use may denote decreased functional

capacity. While a history of asthma has not been confirmed to be independently associated with postoperative pulmonary complications, patients with poor control are at increased risk.[116]

Table 14.12 ARISCAT Score for Postoperative Pulmonary Complications

Risk Factor	Points	
Age		
≤50	0	
51–80	3	
>80	16	
Preoperative SpO_2		
≥96%	0	
91–95%	8	
≤90%	24	
Respiratory infection[a] in past month		
No	0	
Yes	17	
Hemoglobin ≤10 g/dL		
No	0	
Yes	11	
Surgical Incision		
Peripheral	0	
Upper abdominal	15	
Intrathoracic	24	
Duration of Surgery		
<2 hrs	0	
2–3 hrs	16	
>3 hrs	22	
ARISCAT Score	**Risk Group**	**Risk of In-Hospital Postoperative Pulmonary Complications (%)**
<26	Low	1.6
26–44	Intermediate	13.3
≥45	High	42.1

[a]Either upper or lower (i.e., URI, bronchitis, pneumonia), with fever and antibiotic treatment.

Complications were defined as a composite including respiratory failure, respiratory infection, pleural effusion, atelectasis on chest x-ray, pneumothorax, bronchospasm treated with bronchodilators, and aspiration pneumonitis.

Adapted from Canet J, Gallart L, Gomar C, et al. Prediction of postoperative pulmonary complications in a population-based surgical cohort. *Anesthesiology* 2010;113(6):1338–1350.

An early international study of over 1,000 patients identified with perioperative SARS-CoV-2 infection showed high overall 30-day mortality (23.8%), with pulmonary complications occurring in half of the patients and implicated in over 80% of deaths.[117] Independent risk factors for mortality included male sex, age ≥70, malignancy, ASA 3 to 5, and major and emergency surgery. Pending further data, higher thresholds for surgical intervention were recommended, with nonoperative therapy or postponement of nonurgent procedures considered when feasible.

Routine chest radiography, pulmonary function tests, and arterial blood gases are not indicated for extrathoracic surgery,[50] but may be considered in evaluation for resectional and nonresectional thoracic surgery and in patients with symptoms and undiagnosed chronic lung disease. Dyspnea on exertion should be evaluated with pulmonary function tests and chest radiography. If a cardiac etiology is suspected by history or physical examination, echocardiography can be considered. Abnormal chest radiography suggesting diffuse parenchymal disease should be investigated further. Preoperative albumin and BUN are associated with increased complications and should be obtained as part of evaluation in patients with at least one other identified risk factor.[50] Identification of patient, operative, or laboratory risks should prompt further investigation.

Cigarette smoking is directly toxic to respiratory epithelium, is associated with chronic lung disease, and is associated with increased chance of major morbidity (surgical site infection, pneumonia, shock, unplanned intubation) and mortality.[118] Benefits of smoking cessation likely increase with increased interval between stopping and surgery. Meta-analyses suggest that the effects of cigarette smoking on the tissue microenvironment and inflammatory cellular functions may be reversed within 4 weeks[119] and that smokers who quit more than 4 weeks before surgery have lowered risk of perioperative respiratory and wound complications.[120] Reports of increased airway

reactivity during these initial weeks following smoking cessation raise concerns regarding proceeding with surgery during this period,[121,122] although more recent studies suggest no increase in complications for shorter intervals.[120,123] A general recommendation is that for maximum benefit, smoking should be discontinued 6 to 8 weeks preoperatively, but that stopping for any duration before surgery is beneficial.

Additionally, surgery may represent an opportunity for a teachable moment for the patient's health. In a longitudinal study, patients undergoing major surgery doubled the chance of quitting.[124] A recent Cochrane review suggested that brief and intensive interventions reduced perioperative smoking, and that more intensive structured smoking cessation interventions, including weekly preoperative counseling and nicotine replacement therapy, may be used to extend perioperative smoking cessation to long-term success.[125]

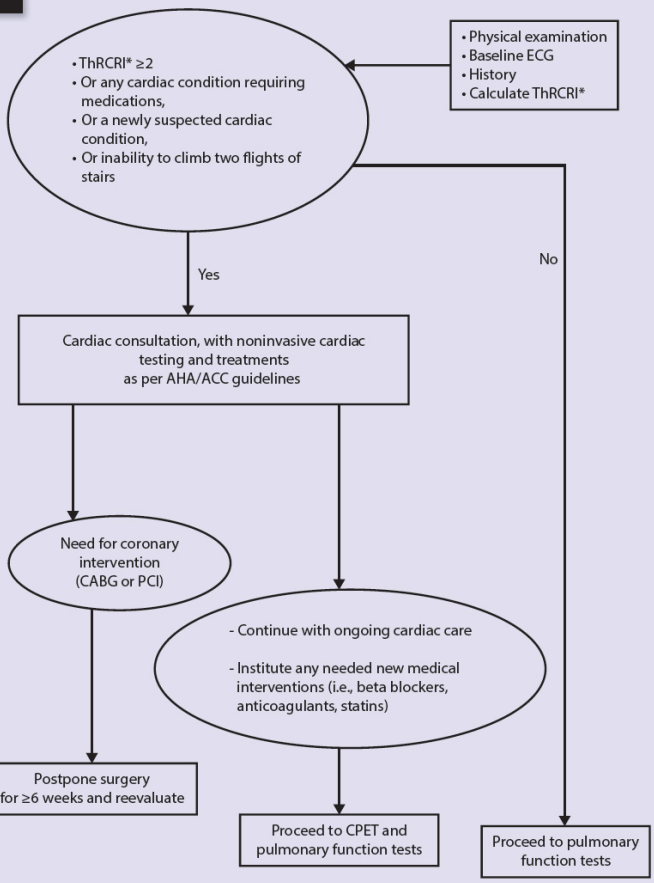
Pulmonary complications may be reduced by optimizing status of patients with pre-existing lung disease, lung expansion maneuvers, and smoking cessation. Patients with chronic lung disease should be optimized prior to elective surgery with longer-acting controller medications. Aerosolized β_2-adrenergic receptor agonists, inhaled anticholinergics, and inhaled and systemic corticosteroids may be used to improve pulmonary function.[50] Preoperative management of poorly controlled asthma includes eliminating wheezing, cough or dyspnea, and targeting peak expiratory flows >80% of predicted or the patient's personal best.[126] Elective surgery should be delayed for signs of acute infection, including increased secretions or change in character of sputum.

Lung expansion maneuvers reduce postoperative reductions in FRC by augmenting alveolar recruitment. Common modalities, including incentive spirometry, deep-breathing exercises, and CPAP, have been demonstrated to improve postoperative pulmonary outcomes.[50,127] Concentrating education during preoperative sessions may increase patient compliance and enhance improvements in high-risk patients.[128,129]

Preoperative Evaluation Prior to Lung Cancer Resection (Algorithm 14.3)

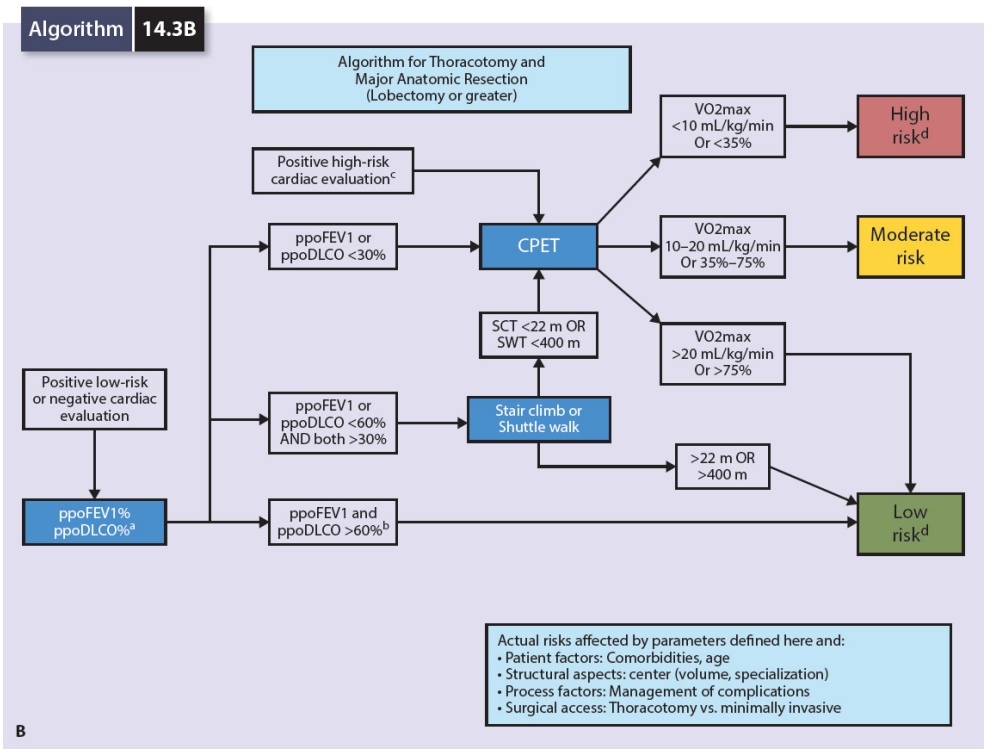
Considerations for patients undergoing surgical treatment of lung cancer balance the intent for curative resection with concern for residual function and long-term disability following surgery. As conditions promoting the development of lung cancer, that is, cigarette smoking and occupational exposures, are also associated with intrinsic reductions in pulmonary function, the guidelines rely on physiologic testing to estimate perioperative risk as well as the effect on postoperative lung function.

Algorithm 14.3A



*** ThRCRI (*Thoracic revised Cardiac Risk Index*)**
- Pneumonectomy: 1.5 points
- Previous ischemic heart disease: 1.5 points
- Previous stroke or TIA: 1.5 points
- Creatinine >2 mg/dL: 1 point

A



Algorithm 14.3 **A**: Physiologic evaluation prior to lung resection. Abbreviations: ThRCRI, Thoracic revised Cardiac Risk Index; ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass graft surgery; CPET, cardiopulmonary exercise test; PCI, percutaneous coronary intervention; TIA, transient ischemic attack. **B**: ppoFEV1 or ppoDLCO cutoff value of 60% predicted values has been chosen based on indirect evidences and expert consensus opinion. Definition of risk. Low risk: The expected risk of mortality is below 1%. Major anatomic resections can be safely performed in this group. Moderate risk: Morbidity and mortality rates may vary according to the values of split lung functions, exercise tolerance, and extent of resection. Risks and benefits of the operation should be thoroughly discussed with the patient. High risk: The risk of mortality after standard major anatomic resections may be higher than 10%. Considerable risk of severe cardiopulmonary morbidity and residual functional loss is expected. Patients should be counseled about alternative surgical (minor resections or minimally invasive surgery) or nonsurgical options. For pneumonectomy candidates, we suggest to use Q scan to calculate predicted postoperative values (ppo) of FEV1 or DLCO (ppo values = preoperative values × (1 − fraction of total perfusion for the resected lung), where the preoperative values are taken as the best measured postbronchodilator values. For lobectomy patients, segmental counting is indicated to calculate predicted postoperative values of FEV1 or DLCO (ppo values = preoperative values × (1 − y/z), where the preoperative values are taken as the best measured postbronchodilator value and the number of functional or unobstructed lung segments to be removed is y and the total number functional segments is z. Abbreviations: ppoDLCO, predicted postoperative diffusing capacity for carbon monoxide; ppoDLCO%, percent predicted postoperative diffusing capacity or carbon monoxide; ppoFEV1, predicted

postoperative FEV1; ppoFEV1%, percent predicted postoperative FEV1; SCT, stair climb test; SWT, shuttle walk test; VO_2 max, maximal oxygen consumption; mL/kg/min, milliliters per kilogram per minute; m, meters; CPET, cardiopulmonary exercise testing. (Adapted from Brunelli A, Kim AW, Berger KI, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143[5 Suppl]:e166S–e190S.)

In 2013, the ACCP updated clinical practice guidelines for physiologic evaluation of the patient with lung cancer being considered for resectional surgery.[130] Multidisciplinary evaluation was stressed as essential for counseling, particularly in patients with borderline function. Age alone was felt to be insufficient grounds to deny lung resection surgery. Cardiology evaluation was recommended for patients with major factors for increased perioperative cardiac risk and a modified Thoracic revised cardiac risk index (ThRCRI) incorporating need for pneumonectomy, prior ischemic heart disease, stroke or TIA, and creatinine >2 mg/dL has been validated.[131] Measurement of preoperative FEV1 and diffusing capacity for carbon monoxide (D_{LCO}) and calculation of predicted postoperative values are recommended for patients undergoing lung resection surgery. Further evaluation with low technology exercise test (stair climb or shuttle walk test) or formal cardiopulmonary exercise testing with measurement of maximal oxygen consumption (VO_{2max}) is recommended based on the initial results. In patients with borderline assessments, counseling regarding nonstandard surgery and nonoperative treatment options is recommended.

Postoperative atrial fibrillation occurs in up to 19% of patients following lung cancer resection with incidence peaking on the second postoperative day.[132] Greater risk is present for men >55 years of age and in the presence of a resting heart rate >72 beats/min. Close attention should be paid to volume and electrolyte status.

Hepatic

Postoperative risk in liver disease is related to the severity of underlying liver disease and the extent of the surgical procedure.[133] Patients are living longer with chronic liver disease and they may present as relatively

asymptomatic with normal liver function tests even with substantial degree of hepatic dysfunction. In addition, occult chronic liver disease with silent cirrhosis may be present. Nonalcoholic steatohepatitis (NASH) affects 2% to 5% of Americans, primarily middle-aged, overweight, or obese patients. In a series of patients undergoing bariatric surgery, 6% were found to have unsuspected cirrhosis in the setting of fatty liver.[134]

The presence of cirrhosis is associated with high risk of complications and death; delayed hepatic decompensation can follow routine surgery. Intra-abdominal[135,136] and cardiac surgery[137] have been associated with high mortality rates in cirrhotics. In one series, patients with cirrhosis undergoing surgery had a 30-day mortality of 11.6% and an overall complication rate of 30%.[138] The most frequent complication was pneumonia, with other complications including bleeding, hepatic decompensation, sepsis, and renal failure. Formal hepatic resection in cirrhosis carries a high mortality rate which is elevated in patients with postresectional liver failure.[139] Umbilical hernia may be aggravated in the presence of uncontrolled ascites and nonoperative management may be warranted.

Table 14.13 Modified Child–Turcotte–Pugh Score

	Score		
	1 Point	2 Points	3 Points
Total serum bilirubin (μmol/dL)	<3.4	3.4–5.0	>5.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
International normalized ratio	<1.7	1.7–2.2	>2.2
Ascites	None	Controlled with medication	Treatment refractory
Encephalopathy	None	Grade I–II or controlled with medication	Grade III–IV or treatment refractory

	Sum total points for each component:	
	Total Points	Surgical Mortality (%)
Class A	5–6	10
Class B	7–9	30
Class C	10–15	80

Adapted from Child CG, Turcotte JG. Surgery and portal hypertension. *Major Probl Clin Surg* 1964;1:1–85 and Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60(8):646–649.

While the liver is usually protected from ischemia due to dual portal and systemic blood flow, in disease states, alterations in splanchnic and

autonomic vascular regulation increase vulnerability to hypoperfusion and ischemic injury. Avoidance of shock states is imperative for at-risk patients.

Patients with portal hypertension are at risk for bleeding from visceral and retroperitoneal varices; meticulous hemostasis is necessary and may prolong expected operative times. Perioperative management includes optimization of liver function, including management of portal hypertension, cholestasis and coagulopathy, and avoidance of further hepatic injury secondary to drugs, inhalation agents, hypoperfusion, and ischemia. Surgical procedures with anticipated right heart failure may worsen hepatic congestion and thus may be contraindicated. Peripheral shunting and vasodilation complicate management of acute volume shifts. β-blockade and octreotide may be of use in reducing splanchnic hypertension; the role of preoperative TIPS is unclear.

Risk Stratification

Overall surgical risk in cirrhotic patients appears to correlate with established scoring systems. Risk stratification extrapolates scoring based on studies in cirrhotic patients undergoing portal decompression (modified Child–Turcotte–Pugh [CTP]) score (**Table 14.13**)[140,141] and survival models for patients with end-stage liver disease (model for end-stage liver disease, MELD score, **Table 14.14**).[142–144] MELD and CTP scores both may correlate with postoperative mortality and are useful to guide preoperative counseling.[145–147] A calculator version of a modified MELD score incorporating age and ASA score is available at www.mayoclinc.org/meld/mayomodel9.html.

Historically, surgery in Child class A patients carries a mortality of 10%, Child class B, 30% and Child class C, 76% to 82%.[148,149] The rate of postoperative complications including liver failure, encephalopathy, bleeding infection, renal failure, hypoxia, and intractable ascites also increases with class. Poorer outcomes are associated with anemia, ascites, the presence of encephalopathy, hypoalbuminemia, hypoxia, malnutrition, concomitant infection, preoperative upper GI bleeding, intraoperative hypotension, associated renal failure or COPD, and emergency, cardiac, hepatic resection, or abdominal procedures.[133,138] In general, mortality rates for patients undergoing emergency surgery and patients with portal hypertension are higher.

Table 14.14 Model End-Stage Liver Disease Score (MELD) and Surgical Mortality

MELD score = $(9.57 \times \log_e[\text{creatinine mg/dL}]) + (3.78 \times \log_e[\text{bilirubin mg/dL}]) + (11.20 \times \log_e[\text{international normalized ratio}]) + 6.43$

Minimum laboratory value is 1.0 (for laboratory values <1.0, use value of 1.0)

Maximum creatinine is 4.0 (for creatinine >4.0, use value of 4.0)

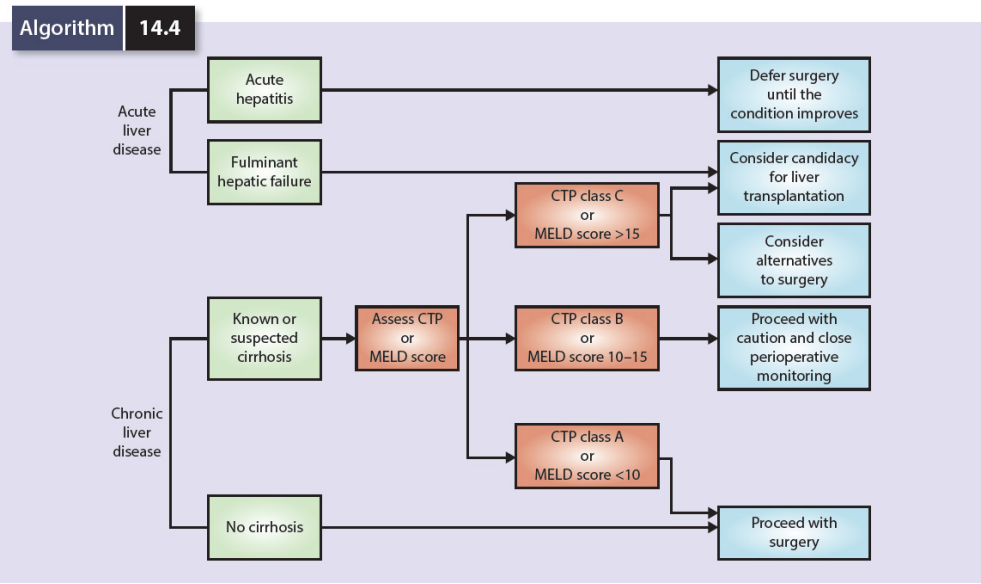
If patient has had dialysis twice within the previous week, use value of 4.0

Round final score to nearest whole number

Maximum score is 40

MELD		Postoperative Mortality					
Score	(n)	7 d	30 d	90 d	1 yr	5 yrs	10 yrs
0–7	351	1.9	5.7	9.7	19.2	50.7	72.6
8–11	257	3.3	10.3	17.7	28.9	58.5	78.1
12–15	106	7.7	25.4	32.3	45.0	69.5	87.3
16–20	35	14.6	44.0	55.8	70.5	94.1	94.1
21–25	13	23.0	53.8	66.7	84.6	92.3	100
≥26	10	30.0	90.0	90.0	100	100	100

Adapted from Northup PG, Wanamaker RC, Lee VD, et al. Model for end-stage liver disease (MELD) predicts nontransplant surgical mortality in patients with cirrhosis. *Ann Surg* 2005;242(2):244–251 and Teh SH, Nagorney DM, Stevens SR, et al. Risk factors for mortality after surgery in patients with cirrhosis. *Gastroenterology* 2007;132(4):1261–1269.



Algorithm 14.4 Proposed algorithm for preoperative evaluation of patients with liver disease. (Adapted from Hanje AJ, Patel T. Preoperative evaluation of patients with liver disease. *Nat Clin Pract Gastroenterol Hepatol* 2007;4[5]:266–276.)

Preoperative Evaluation (Algorithm 14.4)

History and physical examination may reveal unsuspected liver disease. History of prior hepatitis, cirrhosis, hepatic decompensation, prior anesthetic toxicity, biliary disease, hereditary metabolic disorders, bleeding, or prior alcohol or substance abuse should be sought. Physical examination may reveal stigmata of portal hypertension including hepatomegaly, splenomegaly, ascites, abdominal wall varices, asterixis, and palmar erythema. Thrombocytopenia secondary to splenic sequestration may be an early sign of previously undiagnosed portal hypertension. If liver disease is suspected during routine preoperative evaluation, elective surgery should be deferred for further workup.[150]

Acute conditions for which elective surgery is contraindicated include acute liver failure, acute viral hepatitis, alcoholic hepatitis, liver disease with associated acute renal failure, cardiomyopathy, hypoxemia, or severe coagulopathy.[133] Hepatic recovery may occur following an initial insult and elective surgery should be deferred for a period of several weeks to optimize the patient's condition. For acute alcoholic hepatitis, abstinence from alcohol for 12 weeks before elective surgery has been recommended.

For patients with known chronic liver disease and cirrhosis, surgical morbidity and mortality correlates with the degree of hepatic dysfunction. Patients with compensated chronic liver disease generally tolerate most surgery well, however patients with decompensated cirrhosis may have substantial perioperative risk proportional to the degree of hepatic dysfunction. A suggested preoperative evaluation for hepatic disease is presented in **Algorithm 14.4**.[151] A preoperative checklist for patients with portal hypertension has been published.[152]

Patients with a history of alcohol abuse may undergo acute withdrawal immediately prior to or following surgery. Signs of autonomic instability, agitation, and delirium should be managed symptomatically with β-blockade, clonidine, and benzodiazepines. Protocolized symptom–triggered regimens are associated with lower total medication dose compared to standing regimens.[153] DT prophylaxis with round-the-clock medication is not indicated outside of high-risk cases or a history of prior DTs. Empiric thiamine, folate, and multivitamin replacement should be considered.

Renal

Renal dysfunction is frequent after surgery and there is increasing recognition that new renal failure manifested by even small, transient increases in serum creatinine during the postoperative period is associated with later mortality.[154] Small increases in creatinine, as little as 0.3 mg/kg, may increase risk.[155] In a noncardiac general surgical population, the incidence of postoperative renal failure may be as high as 1%.[156] Therefore, preoperative evaluation should be based not only on determining current status of chronic or acute renal disease, but also the potential for further deterioration.

Risk Stratification

The strongest risk factor for development of postoperative acute kidney injury is the presence of pre-existing chronic renal disease.[157] The development of postoperative renal failure is in turn strongly associated with increased mortality.[154,156,158] A single episode of AKI as defined by RIFLE criteria is associated with long-term mortality in proportion with the severity of injury. Preoperative risk scores have been developed, primarily in cardiac

surgery[159,160] populations and are based on baseline renal function, and the presence of associated medical comorbidity. In a large noncardiac surgery series,[161] anemia (hemoglobin <12.0 g/dL) and decrease in postoperative hemoglobin greater than 1.1 g/dL were associated with higher risk for renal failure. Using a large intraoperative dataset, risk factors for the development of acute kidney injury in noncardiac surgical patients were identified and used to model an Acute Kidney Injury Risk Index scoring system (**Table 14.15**).[156] Biomarker-based and physiologic time series data are being investigated for development of prediction models using machine learning computational approaches.[162]

Table 14.15 General Surgery Acute Kidney Injury Risk Index Classification System

	Derivation Cohort, *n* = 57,080			Validation Cohort, *n* = 18,872		
Preoperative Risk Class	Total Patients, *n*	AKI Incidence % (*n*)	Hazard Ratio (95% Confidence Interval)	Total Patients, *n*	AKI Incidence % (*n*)	Hazard Ratio (95% Confidence Interval)
Class I (0–2 risk factors)	31,500	0.2 (66)		10,301	0.2 (25)	
Class II (3 risk factors)	12,570	0.8 (104)	4.0 (2.0–5.4)	4,218	0.6 (32)	3.1 (1.0–5.3)
Class III (4 risk factors)	7,033	1.6 (144)	6.8 (0.0–11.5)	2,025	2.0 (53)	8.5 (5.3–13.7)
Class IV (5 risk factors)	3,015	3.3 (118)	10.1 (11.0–21.5)	1,244	3.6 (45)	15.4 (0.4–25.2)
Class V (6+ risk factors	1,450	8.0 (120)	40.3 (34.2–62.0)	484	9.5 (40)	40.2 (26.3–70.9)
	Patient receives 1 point for each risk factor:					
	Age ≥56 yrs					
	Male sex					
	Active congestive heart failure					
	Ascites					
	Hypertension					
	Emergency surgery					
	Intraperitoneal surgery					
	Renal insufficiency, preoperative serum creatinine >1.2 mg/dL					
	Diabetes mellitus, on oral or insulin therapy					

From Kheterpal S, Tremper KK, Heung M, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology* 2009;110(3):505–515.

Preoperative Evaluation

The presence of underlying renal disease should be suspected based on history. Chronic renal disease in the adult population is not uncommon, with an estimated prevalence at 13%.[163] Common systemic conditions such as hypertension, diabetes mellitus, and arteriosclerosis may lead to end-organ damage. Renal impairment must be considered in the context of the presence of associated systemic disease. A history of prior renal injury should be sought.

Determination of renal function is based on the glomerular filtration rate (GFR), estimated by equations such as the Cockcroft–Gault equation.[164] As the GFR is reduced to <30% of baseline, electrolyte, volume, and red cell homeostasis are altered. Medication excretion will be decreased and drug dosing should be titrated by levels to minimize toxicity.

Prevention of Acute Kidney Injury

Strategies for prevention of postoperative renal failure include stabilization of homeostatic imbalances, maintenance of adequate renal perfusion, avoidance of intraoperative hypotension, and judicious use of nephrotoxic agents, including aminoglycosides, ACE inhibitors, intravenous contrast agents, and NSAIDs. In patients with known chronic renal disease, careful evaluation of electrolyte abnormalities, anemia, and intravascular volume should be performed.

The mainstay of prevention strategies is to assure adequate renal perfusion by avoiding hypotension from hypovolemia. Despite extensive clinical testing, no pharmacologic intervention has been found to successfully improve postoperative renal outcomes. Preoperative statin,[165] prophylactic or therapeutic acetylcysteine,[166] ANP,[167] insulin-like growth factor,[168] tight glycemic control, fenoldopam,[169] clonidine, and antiplatelet drugs[155] have all failed to show efficacy.

Renal replacement therapy is indicated emergently for correction of acidosis, symptomatic hyperkalemia, severe volume overload, or uremic pericarditis. Dialysis may be undertaken preoperatively to optimize volume and electrolyte status prior to surgery. Once GFR falls below 5 to 10 mL/min, hemodialysis is usually indicated for clearance. Continuous venovenous hemodialysis may permit volume removal in the hemodynamically unstable patient. Consideration should be given to the

location of temporary dialysis access; subclavian and upper extremity access should be avoided in patients who may eventually go on to require permanent dialysis access.

ADDITIONAL CONSIDERATIONS, FUTURE DIRECTIONS

Considerable progress has been made in refining preoperative risk assessment, however the majority of the risk factors identified to date have been nonmodifiable (i.e., age, need for emergent surgery, type of surgery required). As electronic health data collection becomes more prevalent and facile, new predictors of surgical risk that permit targeted interventions may be uncovered and present opportunities for study.

In the meantime, the preoperative visit should continue to function as an opportunity to initiate perioperative care for patients identified as high-risk. Process of care practices with broad proven benefit can be protocolized as part of routine presurgical orders. Studies evaluating early "prehabilitation" or "training for surgery" for patients with functional deficits are in progress. Advances in preoperative assessment combined with proactive preoperative and perioperative interventions will enable the best outcomes for surgical patients.

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15

Measuring the Quality of Surgical Care: Surgeons, Hospitals and Systems

Andrew M. Ibrahim and Justin B. Dimick

Key Points

1. Quality measures fall into three categories: structure, process, and outcomes. Healthcare structure refers to fixed attributes of the system in which patients receive care. Process of care measures are the clinical details of care provided to patients. Outcome measures reflect the end result of care, from a clinical perspective or as judged by the patient.
2. No quality measure is perfect. Clinical leaders, patient advocates, payers, and policy makers will have to make decisions about when imperfect measures are good enough to act upon. A measure should be implemented only with the expectation that acting on it will result in net improvement in health quality.
3. It is important to ensure a good match between the performance measure and the primary goal of measurement. The right measure depends on whether the underlying goal is (a) quality improvement —raising the level of performance for all providers or (b) optimizing delivery—directing patients to providers and hospitals best aligned to their needs.
4. For quality improvement purposes, a good performance measure must be actionable. Measurable improvements in the given process should translate to clinically meaningful improvements in patient outcomes.
5. With optimizing delivery, a good measure will steer patients to the best providers without limiting access.
6. One of the biggest limitations of surgical quality measurement is the statistical "noise" from the small sample sizes at most hospitals. This problem makes it difficult to isolate the quality signal from the background statistical noise. Multiple statistical techniques (e.g., reliability adjustment), directly addresses this problem. This technique, based on hierarchical modeling, quantifies and subtracts statistical noise from the measurement process.
7. While the structure, process, and outcomes framework to evaluate surgical quality has traditionally focused on surgeons and hospitals,

an emerging area of study now includes healthcare systems. As hospitals have merged into larger networks they have an opportunity to optimize their accumulated assets to deliver high quality surgical care. Metrics in this growing space center around access (e.g., distance traveled, wait time for appointment), appropriate referral (e.g., centralizing high-risk operations), and resource stewardship (e.g., appropriate decentralization of ambulatory operations).

INTRODUCTION

With growing recognition that the quality of surgical care varies widely, good measures of performance are in high demand. Patients and their families need accurate information to help them choose the safest hospitals for surgery.[1] Employers and payers need reliable measures for their value-based purchasing programs.[2] Motivated in part by these external pressures, clinical leaders need better measures to guide their quality improvement efforts.[3]

Despite a broadening array of measures, there remains considerable uncertainty about which measures are most useful.[4,5] Current measures are remarkably heterogeneous, encompassing different elements of healthcare structure, process, and outcomes. With the proliferation of value-based purchasing which requires a global assessment of quality that has significant implications on reimbursement, growing attention has been placed on evaluating the performance measures themselves.[6] Although each of these measurement approaches has strengths, each is also associated with conceptual, methodologic, and/or practical problems (**Table 15.1**).

This chapter provides an overview of existing quality indicators followed by a review of the main strengths and limitations of each type of measure: structure, process, outcomes. For common limitations, the chapter outlines established statistical techniques now applied routinely in measuring surgical quality. The chapter then closes with how these measurement tools are moving from evaluating surgeons and hospitals toward the performance of across an entire healthcare system.

OVERVIEW OF CURRENT MEASURES

An ever-broadening array of performance measures has been developed for assessing surgical quality. Over the past few years, the National Quality Forum (NQF) has emerged as the leading organization endorsing quality measures. While the NQF is the central organization for evaluating candidate measures, many other organizations continue to create their own quality indicators. For example, the Centers for Medicare & Medicaid Services (CMS) Surgical Care Improvement Program (SCIP), which includes process measures related to prevention of surgical site infections, postoperative cardiac events, venous thromboembolism, and respiratory complications, are routinely collected and publicly reported on the Hospital Compare website for most U.S. hospitals. The Agency for Healthcare Research and Quality (AHRQ) has focused on quality measures that can be used with administrative data. For example, the AHRQ maintains and distributes state and national administrative data as part of their Healthcare Cost and Utilization Project (HCUP).

Table 15.1 Examples, Strengths, and Limitations of Different Approaches to Measuring Surgical Performance

	Examples	Strengths	Limitations
Structure	Hospital or surgeon volume Surgeon specialty training	Inexpensive and readily available Strong relationship to important outcomes	Not actionable for quality improvement Not good at discriminating individual provider performance
Process	Appropriate selection, timing, and duration of antibiotic prophylaxis Use of internal mammary artery for coronary artery bypass grafting	Actionable as targets for improvement Everybody can achieve 100% compliance	Most known processes relate to secondary outcomes High-leverage processes are unknown for most procedures
Outcome	Risk-adjusted mortality Risk-adjusted morbidity	Seen as the bottom line of patient care Buy-in from providers	Sample sizes too small at individual hospitals

Most recently, U.S. News and World Report announced that it will explore the new measures—structure, process, and outcomes—that apply not to just to surgeons or hospitals, but instead entire healthcare systems.[7] We will discuss possible candidates for system levels measures later in this chapter.

TRADITIONAL QUALITY MEASURES

1 Quality measures fall into three categories: structure, process, and outcomes.

Structure

Healthcare structure refers to fixed attributes of the system in which patients receive care. Many structural measures describe hospital-level attributes, such as the resources or staff coordination and organization (e.g., nurse-to-patient ratios, hospital teaching status). Other structural measures reflect attributes of individual physicians (e.g., subspecialty board certification, procedure volume).

Strengths

Structural measures of quality have several attractive features. First, they are strongly related to patient outcomes. For example, with esophagectomy and pancreatic resection, operative mortality rates at high-volume hospitals are often 10% lower, in absolute terms, than low-volume centers.[8,9] In some instances, structural measures such as procedure volume are more predictive of subsequent hospital performance than any known processes of care or even direct mortality measures.

Perhaps the most important advantage of structural variables is the ease with which they can be assessed. Many can be determined using readily available sources, such as administrative billing data. Although some structural measures require surveying hospitals or providers, such data are much less expensive to collect than measures requiring detailed patient-level information.

Limitations

Perhaps the greatest limitation of structural measures is that they are not readily actionable. For example, a small hospital cannot readily make itself a high-volume center. Thus, while selected structural measures may be useful for selective referral initiatives, they have limited value for quality improvement purposes. Structural measures are also limited in their ability to

discriminate the performance of individual providers. For example, in aggregate, high-volume hospitals have much lower mortality rates than lower-volume centers for pancreatic resection.[8,9] However, some individual high-volume hospitals may have high mortality rates, and some low-volume hospitals may have low mortality rates.[10] Although the true performance of individual hospitals is difficult to confirm empirically (for sample size reasons), this lack of discrimination is one reason structural measures are often viewed as "unfair" by many providers.

Process of Care

Process of care measures are the clinical details of care provided to patients. Although they historically have applied mostly to medical care, their popularity in surgery is growing rapidly. Perhaps the best example of the trend toward using process measures is the CMS's SCIP. As previously mentioned, this quality measurement initiative focuses exclusively on processes related to prevention of surgical site infections, postoperative cardiac events, venous thromboembolism, and respiratory complications.

Strengths

Since processes of care reflect the care actually delivered by physicians, they have face validity and enjoy greater buy-in from providers. They are also directly actionable and provide good substrate for quality improvement activities. Although risk adjustment may be important for outcomes, it is not required for many process measures. For example, the appropriate prophylaxis against postoperative venous thromboembolism is a widely used process measure. Since virtually all patients undergoing open abdominal surgery should be offered some form of prophylaxis, there is little need to collect detailed clinical data for risk adjustment.

Limitations

The biggest limitation of process measures is the lack of correlation between processes of care and important outcomes.[4] There is a growing body of empirical data showing very little correlation between processes of care and important outcomes.[11–13] Most data come from literature on medical

diagnoses, such as acute myocardial infarction. For example, The Joint Commission and CMS process measures for acute myocardial infarction explained only 6% of the observed variation in risk-adjusted mortality for acute myocardial infarction.[12]

Emerging evidence demonstrates a similar relationship for surgical process measures, especially for SCIP measures, with no measurable relationship between these widely collected process measures and important outcomes.[13]

There are several reasons why existing process measures explain very little of the variation in important surgical outcomes. First, most process measures currently used in surgery relate to secondary outcomes. While none would dismiss the value of prophylactic antibiotics in reducing risks of superficial wound infection, this process is not related to the most important adverse events of major surgery, including death.

Second, process measures in surgery often relate to complications that are very rare. For example, there is consensus that venous thromboembolism prophylaxis is necessary and important. The SCIP measures, endorsed by the NQF, include the use of appropriate venous thrombosis prophylaxis. However, pulmonary embolism is very uncommon, and improving adherence to these processes will, therefore, not avert many deaths. Until we understand which processes of care account for those adverse events leading to death and severe disability, process measures will have limited usefulness in surgical quality measurement.[4,11–14]

Outcomes

Outcome measures reflect the end result of care, from a clinical perspective or as judged by the patient. Although mortality is by far the most commonly used measure in surgery, other outcomes that could be used as quality indicators include complications, hospital readmission, and a variety of patient-centered measures of quality of life or satisfaction. For example, a recent evaluation of Medicare revealed a significant drop in hospital readmissions among surgical patients after payment incentives were announced. While some readmissions after surgery may in fact be good and represent high-quality care, the significant drop suggested there were also avoidable readmissions that were prevented.[15]

Strengths

There are at least two key advantages of outcome measures. First, outcome measures have obvious face validity, and thus are likely to get the greatest "buy-in" from hospitals and surgeons. Surgeon enthusiasm for adopting objective measurement of quality and joining quality collaboratives centered on outcomes clearly underline this point. Second, the act of simply measuring outcomes may lead to better performance—the so-called Hawthorne effect. For example, surgical morbidity and mortality rates in VA hospitals have fallen dramatically since implementation of systematic measurement two decades ago.[16] No doubt many surgical leaders at individual hospitals made specific organizational or process improvements after they began receiving feedback on their hospitals' performance. However, it is very unlikely that even a full inventory of these specific changes would explain such broad-based and substantial improvements in morbidity and mortality rates.

Limitations

Hospital- or surgeon-specific outcome measures are severely constrained by small sample sizes. For the large majority of surgical procedures, very few hospitals (or surgeons) have sufficient adverse events (numerators) and cases (denominators) for meaningful, procedure-specific measures of morbidity or mortality. For example, data from the Nationwide Inpatient Sample to study seven procedures for which mortality rates have been advocated as quality indicators by the AHRQ.[17] For six of the seven procedures, a very small proportion of U.S. hospitals had adequate caseloads to rule out a mortality rate twice the national average (**Fig. 15.1**). Although identifying poor-quality outliers is an important function of outcome measurement, focusing on this goal alone significantly underestimates problems with small sample sizes. Discriminating among individual hospitals with intermediate levels of performance is even more difficult.

Another significant limitation of outcome assessment is the expense of data collection. Reporting outcomes requires the costly collection of detailed clinical data for risk adjustment. For example, it costs over $100,000 annually for a private sector hospital to participate in the ACS-NSQIP. Because of the expense of data collection, the ACS-NSQIP currently collects data on only a sample of patients undergoing surgery at each hospital.

Although this sampling strategy decreases the cost of data collection, it exacerbates the problem of small sample size with individual procedures.

CHOOSING THE RIGHT MEASURE

2 No quality measure is perfect. Clinical leaders, patient advocates, payers, and policy makers will have to make decisions about when imperfect measures are good enough to act upon. A measure should be implemented only with the expectation that acting on it will result in net improvement in health quality. Thus, the direct benefits of implementing a particular measure cannot be outweighed by the indirect harms. Unfortunately, these benefits and harms are often difficult to measure and heavily influenced by the specific context and who—patients, payers, or providers—is doing the accounting. For this reason, there is no simple answer for where to "set the bar."

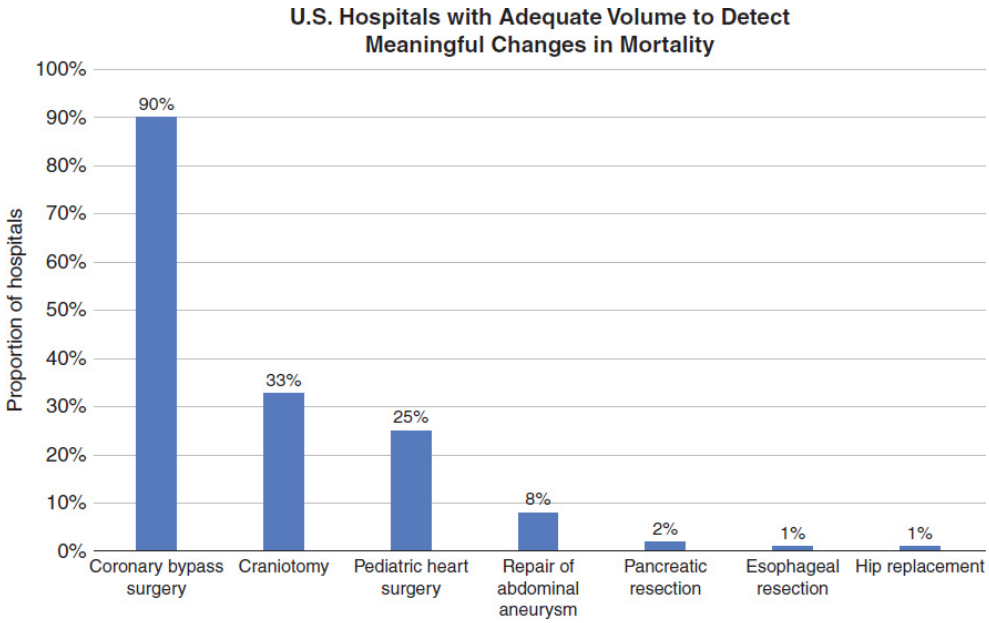

Figure 15.1 Big problems with small samples: the proportion of hospitals in the United States with sufficient caseloads (sample size) to reliably use mortality rates to measure quality.

3 It is important to ensure a good match between the performance measure and the primary goal of measurement. The right measure depends on whether the underlying goal is (a) quality improvement—raising the performance of all providers or (b) selective referral—directing patients to

higher-quality hospitals and/or providers. Although many pay-for-performance initiatives have both goals, one often predominates. For example, the ultimate objective of the CMS's pay-for-performance initiative with prophylactic antibiotics is improving quality at all hospitals (quality improvement). Conversely, the Leapfrog Group's efforts in surgery are primarily aimed at getting patients to hospitals likely to have the best outcomes (selective referral).

4 For quality improvement purposes, a good performance measure must be actionable. Measurable improvements in the given process should translate to clinically meaningful improvements in patient outcomes. Although quality improvement activities are rarely "harmful," their major downsides relate to their opportunity cost. Initiatives hinged on bad measures divert resources (e.g., time and focus of physicians and other staff) away from more productive activities.

5 With selective referral, a good measure will steer patients to better hospitals or physicians. As a basic litmus test, a measure based on prior performance should reliably identify providers likely to have superior performance now and in the future. At the same time, an ideal measure would not incentivize perverse behaviors (e.g., surgeons doing unnecessary procedures to meet a specific volume standard) or negatively affect other domains of quality (e.g., patient autonomy, access, and satisfaction).

Many believe that a good performance measure must discriminate performance at the individual level. From the provider perspective in particular, a "fair" measure must reliably reflect the performance of individual hospitals or physicians. Unfortunately, as described earlier, small caseloads (and sometimes case mix variation) conspire against this objective for most procedures. Patients, however, should value information that improves their odds of good outcomes on average. Many measures meet this latter interest while failing on the former (e.g., hospital volume standards). There may be no simple solution to resolving the basic tension implied by performance measures that are unfair to providers yet informative for patients. However, it underscores the importance of being clear about both the primary purpose (quality improvement or selective referral) and whose interests are receiving top priority (provider or patient).

IMPROVING OUR ABILITY TO MEASURE

Over the last two decades significant progress has been made in the science of quality measurement for surgical outcomes. One 6 of the biggest limitations of surgical quality measurement is the statistical "noise" from the small sample sizes at most hospitals. This problem makes it difficult to isolate the quality signal from the background statistical noise. In other words, it is often hard to know whether hospitals or surgeons have poor performance because they provide low-quality care or because they were unlucky. For obvious reasons, labeling surgeons and hospitals correctly is extremely important.

An emerging technique, reliability adjustment, directly addresses the problem of statistical noise.[18,19] This technique, based on hierarchical modeling, quantifies and subtracts statistical noise from the measurement process. Essentially, it "shrinks" providers' performance back toward average unless they deviate to such an extreme that it is safe to assume they are truly different. In this way, it gives providers the benefit of doubt. **Figure 15.2** shows the risk-adjusted mortality rates for pancreatic resection in Medicare patients before and after reliability adjustment. Prior to reliability adjustment, the mortality rates varied from 0% to 100%. After reliability adjustment, the mortality rates only vary from 2% to 22%, yielding a range of performance that is clinically more realistic. Reliability adjustment is gaining popularity outside surgery (e.g., ambulatory care) and is becoming widely recognized as a valid tool for improving the accuracy of quality measurement.[18–20]

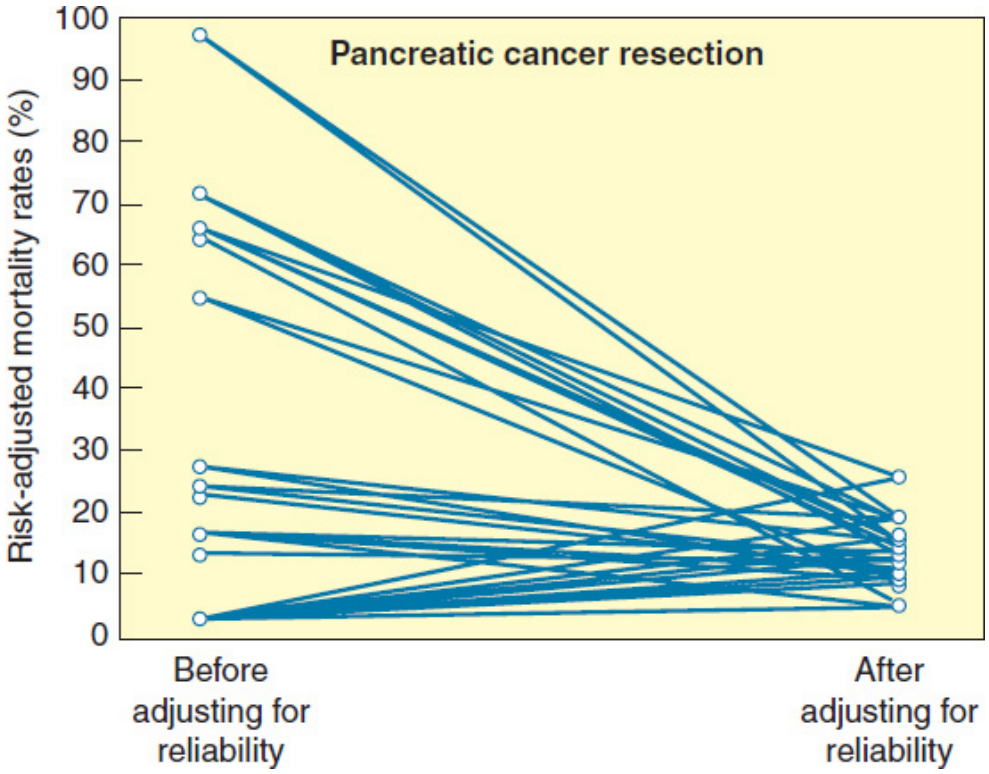

Figure 15.2 Variation in hospital mortality rates before and after adjusting for reliability. Twenty randomly sampled hospitals are shown. (Sourced from National Medicare Claims Data.)

EMERGING NEED TO MEASURE AND IMPROVE SURGICAL CARE ACROSS HEALTHCARE SYSTEMS

7 While previous measures of surgical quality have focused on individual surgeons and hospitals (as discussed above), increasing attention is now being focused on healthcare systems. Since passage of the Affordable Care Act in 2010, the rate of hospital mergers as doubled.[21] As a result, the majority of hospitals now belong to a larger system. The interest in measuring quality of surgical care at the systems level can be understood through a recent study of 16 healthcare systems. Together, these 16 systems comprise 87 hospitals. When measuring key quality measures after surgery at the hospital level (e.g., failure to reassure, complications), there is just as much variation within healthcare systems as there is across them.[22] In other

words, hospitals now belonging to the same system vary widely in their outcomes.

There are multiple reasons why measuring quality at the healthcare system level has appeal. First, doing so reflects the day-to-day reality of healthcare leadership who now assume responsibility for care delivery across multiple sites. Second, payers and policy makers have increasingly explored and adopted systems level metrics as a novel way to incentivize quality. Third, patients now increasingly recognize the trusted brand of a healthcare system and assume uniform quality across multiple sites of care. Taken together, systems level metrics reflect an optimism that the parts together can function at a higher quality than when they were alone by taking advantage of shared resources and expertise.

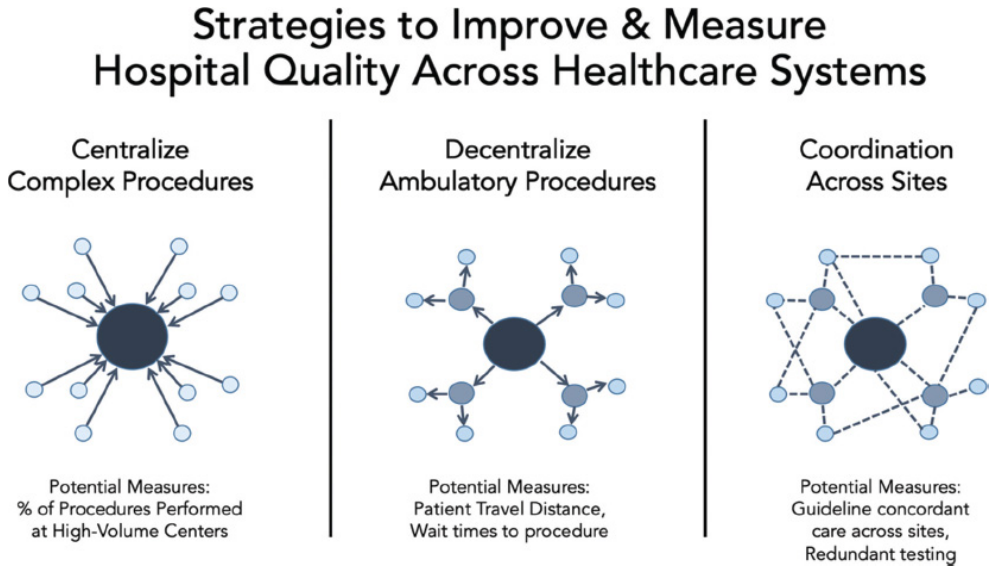

Figure 15.3 Measuring and improving systems delivery of surgical care.

At present, there are no widely agreed upon measures to evaluate surgical quality across healthcare systems. We propose three possible domains that build on previous quality measures and apply them toward measuring healthcare system (**Fig. 15.3**).

Centralize Complex Procedures. Multiple surgical procedures, particularly those are high risk, have known volume-outcome relationships. With the creation of new hospital networks, it has become fertile ground for in-network regionalization.[23] The percent of patients undergoing high-risk procedures at a high-volume center could be an important systems metric.

More importantly, the clinical outcomes (e.g., mortality) should also be measured.

Decentralize Ambulatory Procedures. With accumulated assets of a newly formed networks, hospital systems can be provided at multiple sites. For common procedures that are low risk, these can be performed at multiple sites that have lower overhead and are located closer to patients. In doing so, healthcare systems can improve access for patients and also decrease the cost of the procedure. Measures to assess this level of systems delivery could include patient travel time and procedure expenses.

Delivery Coordination. As patients will likely move across multiple sites within a healthcare system, there will need to be ways to measure how well their care is coordinated. Possible measures may include patient wait times or redundant tests and imaging.

When measuring quality, it is important to keep in mind the ultimate goal: improving the quality and efficiency of surgical care. Quality measures are only useful if they inform improvement efforts. Future refinements in measurement should therefore aim to meet the diverse needs of the improvement efforts of patients, payers, and providers. In this chapter, the three dominant approaches for improving surgical quality were discussed: selective referral, process compliance, and outcome measurement. These three policy approaches roughly mirror the three types of quality measures (structure, process, and outcomes), providing real-world examples of how various stakeholders weigh the pros and cons of quality indicators, and ultimately choose an assessment approach by matching the measure to the purpose.

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16

Improving Surgical Quality

Kristan L. Staudenmayer

Key Points

1. The foundation for quality metrics in healthcare was established by Donabedian in 1966 when he proposed using the framework of structure, process, and outcome to evaluate quality.
2. There are strengths and limitations to all structure, process, and outcome metrics.
3. Balancing measures are important to ensure possible unintended consequences from quality improvement efforts are identified and addressed.
4. Current quality improvement efforts focus on peer review and and a focus on culture.
5. Payers and regulators are attempting to improve quality by shifting payment incentives from fee-for-service to value-based models.

INTRODUCTION

Efforts to improve quality have been increasing ever since the landmark publication by the Institute of Medicine in 2000, “To Err is Human,” raised

the alarm bells on the state of quality in healthcare in the United States.[1] The report estimated that 44,000 to 98,000 lives were lost in hospitals every year as a result of medical errors, and that costs from medical errors were estimated to be as high as $29 billion. Despite efforts to improve quality, issues remain and new dimensions to these issues have been identified. For example, it is well recognized that the burden of poor quality is not spread evenly across the United States, and disparities based on factors such as race and socioeconomic status exist. It is clear that quality needs to remain a priority focus for the U.S. healthcare system.

Ensuring the delivery of quality healthcare involves obtaining a good medical education, practicing evidence-based medicine, and having a strong grounding in biomedical ethics. Within surgery, quality improvement takes on additional dimensions. Surgery is, by its nature, invasive and involves technical components. Every point in the surgical planning and delivery process can impact the quality of care a patient receives. These characteristics have historically made surgeons highly attuned to the importance of and need for quality measurement and improvement. As a result, surgeons have often been in the lead with regard to quality improvement. For example, registry-based quality improvement programs hosted by surgical organizations such as the Society for Thoracic Surgeons and the American College of Surgeons are well-established efforts that have been shown to improve quality on a national scale.

Going forward, surgeons need to continue to lead quality improvement. To do so requires a solid understanding of necessary quality improvement components, which will be discussed in this chapter. The first concept addresses quality metrics. W. Edwards Deming, a leader in quality improvement, had said “if you can’t measure it, you can’t manage it.” It is easy to conceptualize how this could apply in other industries, such as automobile manufacturing. In medicine, it is more challenging but just as important. The second is an overview of strategies that are currently being used by providers to improve surgical quality. The third includes a summarization of current regulations and incentives by payers that are aimed at quality improvement.

QUALITY METRICS

1 The foundation for quality metrics in healthcare was established by Donabedian in 1966 when he proposed using the framework of structure, process, and outcome to evaluate quality.[2] There have been modifications to this framework since, but this construct continues to guide quality efforts today. For example, process metrics are endorsed by the National Quality Forum, structural metrics are used in surgical quality programs to verify and accredit centers of excellence, and outcome metrics are promoted by various organizations such as Medicare (**Table 16.1**).

The first category of metrics, structural metrics, consist of characteristics possessed by a hospital or a provider that are associated with desired outcomes. These metrics area attractive for quality improvement as they are relatively easy to measure. One of the most commonly recognized structural metrics is surgical volume. The volume–outcome relationship was recognized as early as 1979.[3] In 2002, Birkmeyer et al. confirmed the existence of a volume–outcome relationship for selected surgical procedures,[4] and others have validated these findings. The reasons for this relationship have been found to be wide ranging, including such factors as institutional experience with diseases and others such as technical skills. Other structural measures include closed intensive care units, nurse–patient ratios, Level 1 trauma center designation to name a few.

While structural metrics are conceptually appealing and relatively easy to measure, their usefulness in improving quality is less clear. For example, with regard to surgical volume, the relationship between volume and outcomes appears to be sensitive to many factors. For example, the relationship between volume and outcomes is not always linear and varies for different procedures. For abdominal aneurysm repair, there are diminishing returns in outcomes as the number of surgeries increases, whereas for cardiac valve replacement, there is a reliable linear association between volume and outcomes maintained across the range of volume.[5] There are also other factors that can modify the relationship between volumes and outcome, such as the surgeon's specialization.[5,6] In addition to the complex relationships between structural metrics and outcomes is the fact that structural metrics might have limited pragmatic usefulness. In the case of surgical volume, surgeons and hospitals do not necessarily have the ability to

change volume to the scale required to achieve quality for a selected procedure. In summary, while structural metrics such as volume–outcome metrics are attractive for their simplicity, using them is complicated by the fact that important quality-driving factors are overlooked and implementation of policy to change these factors can have negative unintended consequences.

Table 16.1 Process Metrics

	Process	Structure	Outcomes
Example	Checklists	Surgical Volume	30-Day Mortality
Pros	Easy to measure Based on known process–outcome relationships	Easy to measure Based on known structure–outcome relationships	Directly measures outcomes that are desired
Cons	Policies that employ these metrics not universally successful	Policies that employ these metrics not universally successful Might not reflect factors amenable to change	Hard to measure and analyze No single measures for all patients, conditions, or procedures

Another category of quality metrics consists of process measures. Process measures are similarly easy to measure but have the added benefit of helping to identify possible quality improvement solutions. One example of a process measure is the now-retired Surgical Care Improvement Project (SCIP), a collaborative between the Centers for Disease Control (CDC) and the Centers for Medicare and Medicaid Services (CMS) initiated in 2005. The purpose was to improve surgical quality by reducing surgical site infections. SCIP process measures included the timely delivery of appropriate

antibiotics and other factors known to be associated with infection (e.g., hyperglycemia, hypothermia). Encouraging compliance with these process metrics was attractive on many fronts. The recommendations had biologic plausibility, were evidence based, and compliance could be easily measured. However, process measures such as SCIP also have limitations. For example, compliance with the SCIP guidelines was found to not result in improved outcomes and the program was retired in 2015.[7] While multiple reasons for SCIP's failure have been cited, chief among them is that the development of wound infections is complex. This complexity could not be easily translated into what were overly simplistic process measures.

The third type of quality improvement metrics consists of outcome metrics. In contrast to structural and process metrics, outcome metrics are the most proximate measure to what matters to patients. Another benefit to outcome metrics that make them attractive for quality improvement is that they are simple to understand (e.g., mortality, length of stay, infection). In contrast to structural and process metrics, however, outcome metrics present other pragmatic challenges. Most importantly, outcome metrics can be difficult to analyze. Risk adjustment is critically important and successful risk adjustment can be limited by the availability of variables that affect that outcome, such as social determinants of health. Results are also sensitive to adequate statistical techniques. For example, outcomes must be reliability adjusted to account for inaccurate assumptions that might result from differences in sample size.

Despite these limitations, outcome metrics have remained attractive and new classes of outcome metrics are being explored. Patient Reported Outcome Measures (PROMs) and patient experience metrics (e.g., the Hospital Consumer Assessment of Healthcare Providers and Systems, or HCAHPSs) are increasingly used for quality reporting. Another newer outcome metrics that is unique to surgery is "failure to rescue" (FTR). FTR is defined as the number of patients who die after developing a surgical complication. Outcome metrics continue to evolve with the hope that improved data capture and statistical technique will ensure higher-quality metrics.

2 Structure, process, and outcome metrics all have their strengths and limitations. As a result, it is important to include on the list a fourth category of quality improvement metrics—balancing measures. Balancing measures

are not quality mea 3 sures per se, but instead are measures of unintended consequences that might result as a consequence of a quality improvement effort. For example, if there is a desire to decrease the use of an expensive medication that has bioequivalency to a generic, it should not drive the use of another expensive medication.

QUALITY IMPROVEMENT PROCESSES

Outcome Based

The field of quality improvement in healthcare continues to grow. Surgeons have historically led and innovated in this space, 4 particularly for those that have used outcome metrics. Peer review has served as the cornerstone of these quality efforts. While peer review has always been a part of surgical culture, surgeons continue to improve on the process. More recently, this has involved formalizing peer review within surgical departments to ensure fair and transparent processes. These efforts are often coupled with other activities, such as the establishment of a Surgical Quality Council within a surgical department. The American College of Surgeons has recently published a guide that describes the role of such a council, as well as how such a structure fits into the broad array of surgical quality.[8]

An extension of the historic peer review process is a locoregional collaborative where surgeons compare outcomes and best practices in a geographic region. The leading example for this is the Michigan Surgical Quality Collaborative (MSQC). The MSQC is a collaborative of over 2,000 surgeons and 70 Michigan hospitals that share data and best practice. This collaborative has been shown to both reduce complications and save substantial costs.[9]

Surgical quality improvement efforts have also extended the peer review concept to a national level by engagement in collaborative peer networks. Collaborative networks allow for an organization to benchmark its outcomes against those of peer institutions. Examples of these networks include the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP). Such programs allow participants to track their

progress through the regular issuance of reports, and to identify best practice by learning from others in the network.

Culture and Quality

More recently has been the recognition that organizational culture can have a strong influence on quality. This has been described as a "culture of safety." The concept did not originate within healthcare, but in other industries where it was recognized that there were organizations that consistently minimized adverse events. These companies were deemed to be "high-reliability" organizations. High-reliability companies achieved success through commitment at every level toward promoting a culture of safety. Components of such a culture involves ones where communication founded on mutual trust, where the importance of safety is recognized at all levels of the organization, and where there is confidence that measures undertaken to improve outcomes will be successful. This is in contrast to a culture that seeks to place blame on individuals and/or groups for bad outcomes. These concepts are now being applied to the challenges with improving quality in healthcare. Healthcare organizations have made resources available for those interested in improving the culture of safety including the Agency for Healthcare Research and Quality (AHRQ),[10] the Institute for Healthcare Improvement,[11] and The Joint Commission.[12]

QUALITY IMPROVEMENT POLICY AND REGULATION—THE MOVE TOWARD VALUE

Healthcare is one of the most heavily regulated industries with multiple layers of quality-ensuring policies and regulations. 5 These range from individual physician board certification and licensing, to hospital accreditation by The Joint Commission, and quality-based reimbursement models. Many of these mechanisms are under continuous evolution and exist in various stages of maturity. Of these, the most notable in recent history has been the shift from fee-for-service (FFS) toward value-based reimbursement. Collectively these are called value-based purchasing (VBP) models. The

notion behind VBP is that incentives in a pure fee-for-service payment structure encourage poor quality—incursion of a complication will result in more payments to a provider rather than less. Shifting the burden of risk onto the provider financially aligns the interests of payers and providers. These reimbursement strategies are being employed by both private and public payers, and the CMS plan to transition completely from FFS to VBP models.

An example of a VBP program is the CMS Hospital-Acquired Condition (HAC) Reduction Program. The program began to reduce payments to hospitals for a list of conditions that were deemed preventable in 2008. The success of the program is still largely argued. The reason for this is due to challenges inherent to the use of outcome metrics—appropriate risk adjustment and avoidance of bias. There is no universal agreement that the HAC methodology is sufficient to produce fair results and therefore that it is able to accomplish its intended goals.

Another VBP model is the concept of an Accountable Care Organization (ACO). The ACO is a provider or a collaborative of providers who work together to ensure that the patients cared for by the entity remain healthy. This is achieved through aligning incentives via capitated payments for each covered life. If an ACO can keep patients out of the hospital or from receiving costly care, they receive a greater margin. While the alignment of incentives is an attractive mechanism to ensure high-performing providers are rewarded for delivering quality care, it is not clear that these arrangements work. Initial results from the 2014 CMS ACO implementation did not show financial savings. Furthermore, with regard to surgery and ACOs, surgery has not been prioritized as a target area for improvement. Surgical-specific VBP have largely been focused on specific procedures such as hip replacement surgery or coronary artery bypass surgery.

New VBP-based programs continue to be developed and existing programs evolve. No dominant model has yet been determined. That said, it is reasonable to expect that the concept of reimbursement based on value rather than services rendered is one that will continue to drive quality improvement efforts from payers in the foreseeable future.

SUMMARY

There are opportunities to improve the quality of surgical care at every level from the individual provider to policymakers. Surgeons have led in the quality improvement space and there is a need for them to continue to do so. Peer review processes and benchmarking remain a cornerstone of these efforts. It is important that surgeons continue to strive to make these even more effective tools than they are today. Furthermore, policymakers and payers require guidance by those with experience caring for surgical patients and improving quality at home as they make the change to value-based strategies. The need for continued surgical quality leadership is clear.

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Global Surgery

Tiffany E. Chao, Jahnavi K. Srinivasan, and Sherry M. Wren

GLOBAL SURGERY DEFINED

The provision of comprehensive perioperative care in a resource-lacking environment, typically a low-income country, is often termed "global surgery." The working definition for global surgery is rooted in the Koplan et al.[1] broader characterization of global health as "an area of study, research, practice, and advocacy that seeks to improve health outcomes and achieve health equity for all people who require surgical care, with a special emphasis on underserved populations and populations in crisis."[2] Critical to this definition is an emphasis on systemic problems that contribute to overall poorer determinants of societal health. Thus, care is not necessarily centered only in low- and middle-income countries (LMICs) but rather where there is the greatest inequity. Although surgery has long been minimized in the greater global health discourse, the rising burden of noncommunicable diseases (NCDs) has led to the increasing recognition of the important role of surgery in global health.[3]

HISTORY

Before 1990, "global public health" and "tropical medicine" focused mostly on communicable diseases, namely, malaria, tuberculosis, and HIV. These diseases were highlighted mainly due to their prevalence and

transmissibility, the cost-effectiveness of their treatments, and strong advocacy by public health efforts. Surgical pathologies were not traditionally included in "global health" for a number of reasons, including their noncommunicability, underestimations of the surgical disease burden, beliefs that surgery was not a cost-effective intervention, and a high level of investments required to develop infrastructure and human resources. Because of this, public support and political will to address these issues were limited.

A diverse group of conditions comprise surgical burden of disease, including, but not limited to, obstetric care, trauma/injury, intra-abdominal emergencies, cancer care, correctable congenital anomalies, hernias, cardiovascular disease, and head and neck pathology such as dentistry, cleft palate, and cataracts.[4] Over the past three decades, the prevalence of NCDs has increased around the world, now outpacing communicable diseases and accounting for 70% of the estimated annual deaths worldwide[5] (**Fig. 17.1**).

Global health researchers identified this shift, and a number of notable publications began to highlight the role surgery can play in global health. It was once estimated that 11% of the global burden of disease is surgical disease, although better recent estimates are closer to 29% to 32%.[6,7] Reports on the total volume of global surgery performed in 2008 highlighted the role surgery could play in global health.[8] Safety initiatives such as the World Health Organization's (WHO) Surgical Safety Checklist or efforts to increase pulse oximetry in operating rooms identified areas in which quality could be improved.[9,10] Surgical capacity in various resource-limited settings was evaluated using a variety of tools, including the WHO Situational Analysis Tool, the Harvard Humanitarian Initiative's surgical capacity assessment tool, and the Surgeons OverSeas' (SOS) Personnel, Infrastructure, Procedures, Equipment and Supplies (PIPES) survey. Data about cost-effectiveness underscored an economic argument for providing surgical care.[11]

In 2013, the Lancet Commission on Global Surgery was formed to discuss the role of surgery as a fundamental component of public health. During the opening meeting of the Commission, President of the World Bank, Jim Kim, declared that "surgery is an indivisible, indispensable part of health care and of progress towards universal health coverage."[12] 2015 was a "banner year" in global surgery, with the publications of the Commission's findings,

Disease Control Priorities Third Edition (DCP3) Volume 1 *Essential Surgery*, and the adoption of World Health Assembly (WHA) resolution 68.15—"Strengthening emergency and essential surgical care and anesthesia as a component of universal health coverage."[13] This progress reflects the work done by professional societies, nongovernmental health organizations, government agencies, and academic institutions to study the scope of the problem and subsequently garner economic support and implement initiatives to improve the delivery of surgical care worldwide.

CHALLENGES OF PROVIDING SURGICAL CARE

Many barriers have been identified that pose difficulties in providing safe and well-distributed surgical care globally. One issue is the degree of government investment in health infrastructure. Many hospitals and health facilities in LMICs lack basic equipment needed to provide surgical care, or if the equipment exists, they do not have the proper maintenance capability. In particular, operating rooms, equipment, and consumables need to be available, as well as sterility of the materials and an adequate supply chain for maintenance of this infrastructure. Laboratory and pathology testing and radiologic investigations are also important to determine the need for surgical intervention.

From a human resources standpoint, a competent surgical and anesthesia provider must be present, as well as a trained perioperative team that includes intraoperative and perioperative care managers. The surgical care capacity in LMICs is highly correlated with the availability of surgeons and a perioperative workforce, and the issues with development, recruitment, training, and retention are major hindrances to having an adequate workforce. It is often the case that providers may complete training in their residential area and elect to immigrate to a different region of their country or another country altogether due to a combination of higher salaries, more resources, and other benefits. These workforce issues are particularly dramatic in surgery, due to the lengthy and intensive training required to become a surgical provider, typically at least 4 years of postgraduate training,

compared to general practitioners who may require just 1 year of training. Surgically trained providers are therefore both highly desirable and difficult to replace. Task shifting of surgical care to medical officers or nonphysician clinicians has been a common strategy in many nations to address the lack of sufficient surgeons. Depending on the country, as many as 90% of obstetric surgeries, 38.5% of general surgery procedures, and 43% of nonobstetric laparotomies are performed by both nonsurgeons and nonphysicians.[14]

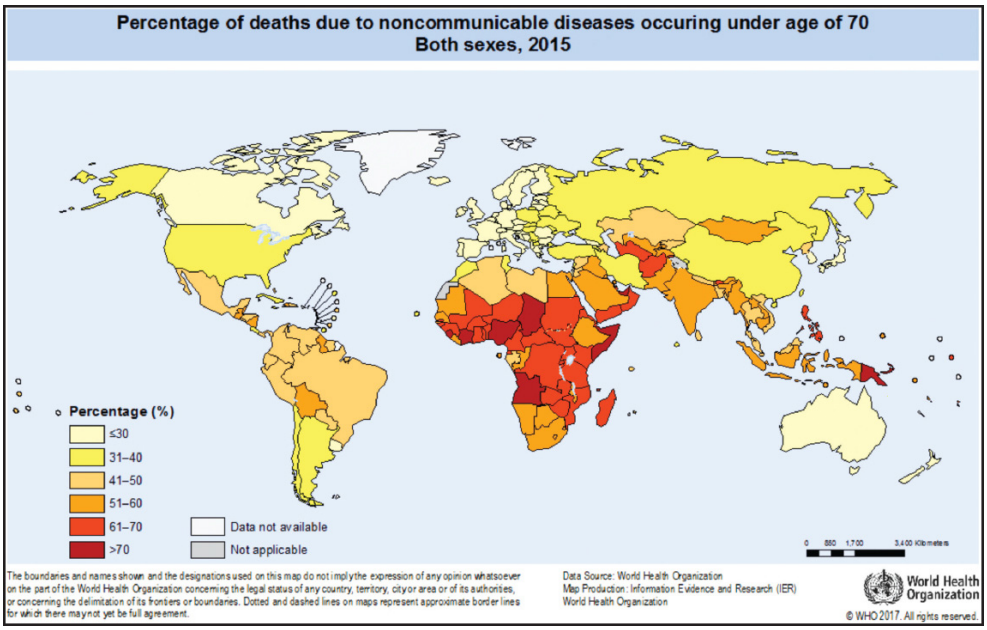

Figure 17.1 Percentage of deaths due to noncommunicable diseases occuring under age of 70. (Reprinted with permission from the World Health Organization.)

From a systems perspective, another limitation in surgical care is the lack of prehospital and emergency services systems coordination, which often creates delays in transportation, hindering appropriate and timely care delivery. In-hospital system limitations pose challenges in patient safety monitoring and quality care improvement. Some political and environmental barriers also exist, such as corruption and mismanagement of health care funds, lack of policies and advocacy, and inaccessibility of referral facilities.

EPIDEMIOLOGY

The WHO Initiative for Emergency and Essential Surgical Care defines necessary surgical care as "interventions that are critical for specific conditions in preventing premature death and disability."[15] These essential services are widely acknowledged to encompass surgical, obstetric, and anesthetic provision. There have been a number of methods used to estimate the prevalence of surgically treatable conditions. Population cluster-based surveys with and without physical examinations have demonstrated a prevalence of 11% of surgically treated conditions and that 25% of deaths are potentially avoidable if care could be accessed.[16,17] The Lancet Commission on Global Surgery reports in 2015 have become the most common cited definitions and statistics for the field. Their model created a framework using variables such as the proportion of serious injuries transported by ambulance, use of pulse oximetry, and the amount of out-of-pocket costs.[18] This framework emphasizes that various barriers to surgical care exist: Can the patient get to a hospital in a timely fashion? Once there, is surgical provision available? If yes, is the surgical provision safe? Once performed, will the patient be free of catastrophic health expenditures? It is estimated that currently 5 billion people worldwide lack full access using this definition[19] (**Table 17.1**).

Striking disparities in surgical access exist between high- and low-resource countries. Over a third of the world's population lives in LMICs, but their populace only receives 3% to 6% of the estimated 234 to 313 million procedures performed annually worldwide.[19,20] It should also be noted that surgical provision does not only refer to operations; there are many disease states, such as management of nonoperative head trauma or wound care, that require surgical expertise but never result in operative intervention.[21] A 2015 survey of global health providers throughout North America, sub-Saharan Africa, and Southeast Asia estimated that 32.9% of worldwide deaths were attributable to surgical pathology.[7] In 2011, WHO global health estimates more specifically calculated that annually about 270,000 women died of pregnancy-related complications and 5 million from injuries.[21] Sixty-five percent of cancers require some form of surgical intervention as part of their treatment paradigm, 25% of disabilities are treatable with some type of surgical intervention, and an estimated 2 million lives can be saved in LMICs by scaling up trauma care.[22]

Table 17.1 Core Indicators for Monitoring Universal Access to Safe, Affordable Surgical and Anaesthesia Care When Needed[a]

Indicator	Definition	Rationale	Data Sources	Responsible Entity	Comments	Target
Group 1: Preparedness for Surgical and Anesthesia Care						
Access to timely essential surgery	Proportion of the population that can access, within 2 hr a facility that can do cesarean delivery, laparotomy, and treatment of open fracture (Bellwether procedures)	All people should have timely access to emergency surgical services. Bellwether procedure performance predicts accomplishment of many other essential surgical procedures; 2 hr is a threshold of death from complications	Facility records and population demographics	Ministry of Health	Informs policy and planning regarding location of services in relation to population density, transport systems, and facility service delivery	A minimum of 80% coverage of essential surgical and anesthesia services per country by 2030
Specialist surgical workforce density	Number of specialist surgical, anesthetic, and obstetric physicians who are working per 100,000 population	The availability and accessibility of human resources for health are crucial components of surgical and anesthesia care delivery	Facility records and data from training and licensing bodies	Ministry of Health, Ministry of Education	Informs workforce, training, and retention strategies	100% of countries with at least 20 surgical, anesthetic, and obstetric physicians per 100,000 population by 2030
Group 2: Delivery of Surgical and Anesthesia Care						
Surgical volume	Procedures done in an operating theater per 100,000 population per year	The number of surgical procedures done per year is an indicator of met need	Facility records	Facility, Ministry of Health	Informs policy and planning regarding met and unmet needs for surgical care	80% of countries by 2020 and 100% of countries by 2030 tracking surgical volume; 5,000 procedures per 100,000 population by 2030
Perioperative mortality rate (POMR)	All-cause death rate prior to discharge among patients who have undergone a procedure in an operating theater, divided by the total number of procedure, presented as a percentage	Surgical and anesthesia safety is an integral component of care delivery; perioperative morality encompasses deaths in the operating theater and in the hospital after the procedure	Facility records and death registries	Facility, Ministry of Health	Informs policy and planning regarding surgical and anesthesia safety, as well as surgical volume when the number of procedures is the denominator	80% of countries by 2020 and 100% of countries by 2030 tracking perioperative mortality; in 2020, assess global data and set national targets for 2030
Group 3: Impact of Surgical and Anesthesia Care						
Protection against impoverishing expenditure[b]	Proportion of households protected against impoverishment from direct out-of-pocket payments for surgical and anesthesia care	Billions of people each year are at risk of financial ruin from accessing surgical services; this is a surgery-specific version of a World Bank universal health coverage target	Household surveys, facility records	Ministry of Finance, World Bank, WHO, USAID	Informs policy about payment systems, insurance coverage, and balance of public and private services	100% protection against impoverishment from out-of-pocket payments for surgical and anesthesia care by 2030
Protection against catastrophic expenditure[c]	Proportion of households project against catastrophic expenditure from direct out-of-pocket payments for surgical and anesthesia care	Billions of people each year are at risk of financial ruin from accessing surgical services; this is a surgery-specific version of a World Bank universal health coverage target	Household surveys, facility records	Ministry of Finance, World Bank, WHO, USAID	Informs policy about payment systems, insurance coverage, and balance of public and private services	100% protection against catastrophic expenditure from out-of-pocket payments for surgical and anesthesia cure by 2030

[a]Access, workforce, volume, and perioperative mortality indicators should be reported annually. Financial protection indicators should be reported alongside the World Bank and WHO measures of financial risk protection for universal health coverage. These indicators provide the most information when used and interpreted together; single indicator provides an adequate representation of surgical and anesthesia care when analyzed independently. Equity stratifiers are listed in report's discussion.
[b]Impoverishing expenditure is defined as being pushed into poverty or being pushed further into poverty by out-of-pocket payments.
[c]Catastrophic expenditure is defined as direct out-of-pocket payments of >40% of households income net of subsistence needs.
USAID, U.S. Agency for International Development; WHO, World Health Organization.
Reprinted with permission from the Lancet Commission on Global Surgery.

COST-EFFECTIVENESS

While the human resources and infrastructure required for surgical care require significant investment, studies have demonstrated that basic surgical services can, in fact, be remarkably cost-effective. The disability-adjusted life-year (DALY) is a metric that serves to quantify morbidly and mortality from conditions, as well as the cost-effectiveness of interventions. In simple terms, a DALY is considered one lost year of *healthy life*. An estimated 77.2 million DALYs could be annually averted by scaling up basic surgical care in LMICs.[4] In 2013, a systematic review and analysis of individual studies that assessed cost-effectiveness of surgical procedures demonstrated that the median cost-effectiveness ratios of cleft lip/palate repair ($47.74/DALY), general surgery ($82.32/DALY), hydrocephalus surgery ($108.74/DALY), and ophthalmic surgery ($136/DALY) are comparable to that of the BCG

vaccine ($51.86 to $220.39/DALY).[11] In addition, median incremental cost-effectiveness ratios (ICERs) of cesarean sections ($315.12/DALY) and orthopedic surgery ($381.15/DALY) are significantly less than those of medical treatment of ischemic heart disease ($500.41 to 706.54/DALY) and HIV treatment with multidrug antiretroviral therapy ($453.74 to $648.20/DALY). Data demonstrating cost-effectiveness of U.S. $5.07/DALY for cataract repair in Nepal, U.S. $7.38/DALY for circumcisions in Mozambique, and U.S. $10.93/DALY for general and obstetric surgery implementation in Bangladesh suggest that these low-cost operations are comparable even to the U.S. $9.07/DALY cost of the Expanded Program on Immunization (EPI) with tuberculosis, diphtheria, pertussis, tetanus, polio, and measles vaccinations. Notably, in contrast to infectious or chronic diseases, which may require ongoing or recurrent treatment, surgery is often curative. Additionally, surgical conditions frequently affect the young working population and therefore correcting these conditions results in greater reductions in death and long-term disability.

SCALING UP SURGICAL CAPACITY

Workforce Shortages

Appropriate and early recruitment, education, and retention are crucial to increasing workforce density and building surgical capacity worldwide. It is estimated that an additional 1.27 million surgeons are needed globally to meet the goal of 20 to 40 surgeons per 100,000 population recommended in order to meet surgical need worldwide. While it has been estimated that training this number of physicians over 15 years would cost $45 billion, this number is small relative to the estimated losses in gross domestic product (GDP) that would occur over the same time from not treating the top five surgical conditions affecting 90% of the world's population—estimated to be $20.7 trillion.[19] Making this investment is economical, lifesaving, and beneficial to society, as healthy and more productive people can enter the workforce.

Not only well-trained surgical and anesthesia providers are in short supply but also this workforce is unevenly distributed across the globe. For

example, the WHO Global Health Observatory notes the African, Eastern Mediterranean, and Southeast Asia regions host only 17% of the world's licensed surgeons but account for 47% of the global population.[23] The Observatory also estimates there is a mere one licensed anesthesiologist per 1 million population in the WHO Africa and Southeast Asian regions. A regional study of five countries in East Africa demonstrated that there were only 237 anesthesiologists in that region for a population of 142.9 million people, providing an average workforce density of 0.13 anesthesiologists per 100,000 population.[24] Further contributing to the problem is the tendency for licensed health care providers to congregate and provide services in urban areas, leaving wide gaps for care delivery in the rural areas. Engagement of women into the surgical workforce is critical, without which the deficit in surgeons will not be solved. For example, women make up less than 10% of the surgical workforce in Africa (9%) as well as Japan (6%), which affects access to surgical care.[25,26]

Training and Education Models

Postgraduate Surgical Training Programs

To address physician shortages, many countries have developed postgraduate surgical training programs. A review of 64 articles describing surgical residency training programs in 34 LMICs and six regions performed in 2016 demonstrates there is much variability between programs.[27] Local curricular requirements fit the local context. For example, the general surgery curriculum from the College of Surgeons of East, Central, and Southern Africa (COSESCA), a 14-country consortium for education and certification, lists OB-GYN procedures (caesarean section, dilatation and curettage, oophorectomy, salpingectomy, hysterectomy, vesicovaginal fistula repair) as well as orthopedics (fracture reduction and treatment with external and internal fixation) as part of the required curriculum. Training challenges exist because there are not enough surgical trainers for the increasing number of medical school graduates in many countries. Postgraduate general surgery programs range in duration from 2.5 to 7 years after completing an undergraduate program ranging from 3 to 8 years. The curricula are not standardized across countries, with a variety of didactic and practical

experiences at rural and district hospitals. Testing is conducted at differing intervals throughout the training with a mix of oral, written, and clinical examinations. Nevertheless, the development of regional organizations, such as the West African College of Surgeons (WACS), COSECSA, and the Pan-African Academy of Christian Surgeons (PAACS), has provided structure in terms of standardizing final examinations, consolidating resources, and unifying curriculum content and are excellent organizations for North American surgical programs to collaborate with.

In general, programs in low-resource settings face many challenges—clinical responsibility versus educational time conflicts, financial and resource limitations, and early independence with limited supervision due to the constraints of the supervising surgeons. Conflicts also can arise when Ministries of Health govern physician positions and hospital salary allowances while Ministries of Education provide oversight to graduate and postgraduate education. Program development and successful implementation may require planning across sectors that do not historically work together. Through coordinated efforts, a region or country's investment into a tailored and structured surgical education training curriculum can improve workforce density, build capacity, and decrease morbidity and mortality from surgical conditions in the short and long terms.

Train the Trainer

Other training models such as the "train-the-trainer" program work to complement postgraduate training programs and build capacity in subspecialty surgical care. Those programs generally consist of experienced and/or specialized surgeons providing intensive workshops to surgeons in areas with few specialists in order to train them to perform specific procedures and to develop local centers of referral. For instance, IVUmed, a pediatric urology medical and surgical education program, works to pair physicians and nurses in low-resource settings.[28] They create peer-to-peer interface through interactive workshops, live case demonstrations, and resource provision with the end goal of establishing a self-sustaining educational program. A mobile training project for endoscopic third ventriculostomy (ETV) procedures led to a subsequent program to develop neurosurgery as a permanent specialty in Kenya and Zanzibar.[29]

Short-term pediatric training programs have not only increased specific surgical procedure numbers but also promoted the development of regional specialty care and training centers.[30,31] This model maintains care locally, builds mentoring relationships, and establishes the infrastructure to train future residents.

Academic Partnerships and Collaborations

Another method of improving surgical training capacity and enhancing resources is forming academic partnerships between high-income and low- to middle-income countries. These are generally longitudinal, multiyear commitments established at an institutional level with an overarching commitment to improving educational programs, building research capacity, enhancing clinical care, and promoting infrastructure strengthening. Collaborations can be multidisciplinary or specialty-focused and can be formed with universities, nongovernmental organizations, and academic associations.[31,32] Most importantly, the goals and responsibilities must be driven by local priorities and mutual respect. An initial needs assessment can evaluate existing strengths and weaknesses, available human and physical resources, and infrastructure capability and identify the most frequent surgical pathologies and procedures performed. This evaluation can then guide curriculum development appropriate to the local or regional environment in partnership with the local program, with frequent feedback from stakeholders. Ideally, exchange will be bidirectional, with local trainees and health care providers receiving access to expertise and resources not previously accessible and external professionals will learn about local pathologies and innovative, low-resource techniques to enhance patient care. Some of the major benefits of a long-term institutional-level partnership include building trust and relationships over time, opening access to numerous disciplines and specialists, and developing common goals and mutually beneficial programs over time. U.S. programs need to be cautious about trying to send trainees to participate in “medical tourism” or experiences that are more about bragging than embedding and working with the local partners in a way that is mutually beneficial.

Virtual and Simulation-Based Education

Simulation-based education is another supplement to any training program and an important way to build expertise and capacity. Simulation is a valuable tool for skill acquisition and improvement in general surgery, providing a safe and low-risk environment for trainees and surgeons learning new skills. Procedures and skills can be taught in person or virtually depending on mentor availability and then repeated as often as needed until proficiency and comfort are achieved. Webinars, virtual lectures, and e-curricula can also be a good way to improve local education programs when teaching surgeons are stretched thin. These techniques have led to improvements in knowledge and confidence, allowed for flexible scheduling, and can provide an ample library with little to no space.[33,34] While costly access and limitations to Internet availability can be barriers, the world of telecommunication and telemedicine is rapidly expanding and is a very viable option for improving surgical proficiency in a safe, reliable setting at a local level.[35]

Task Sharing

Task sharing or task shifting is another model that has been employed in some LMICs to solve the workforce density shortages. Task sharing involves training nonsurgeons or nonphysicians in specific surgical procedures. Some examples are training medical assistants and clinical officers in providing anesthesia, performing cesarean deliveries, and placing external fixators on fractures.[36,37] This practice has been particularly successful in areas with a shortage of physicians, which is often the case in LMICs. Moreover, as technology advances, virtual supervision is becoming more prevalent and possible. Organizations such as CapaCare work to increase the level of skilled health staff at district hospitals to perform lifesaving surgical and obstetrical procedures in areas where there are no surgeons.

LOGISTICS AND SPECIAL CONSIDERATIONS

Whether entering another country for a clinical, research, or education-based experience, there is quite a bit of advanced planning that should be considered in order to make sure time in country is safe and appropriate. Obtaining visas, applying for medical licensure in the country of interest,

organizing travel and evacuation insurance, signing up for the U.S. State Department's Smart Travelers Enrollment Program (STEP), and visiting a travel clinic for the appropriate vaccinations and/or malaria prophylaxis are some important issues to consider. Being aware of the current political climate, and anticipating any blockades, violence, or social unrest (particularly around election times), is important.

Another recommendation to help ensure the safety of all team members prior to travel is to provide or endorse a cultural competency course specific to the country or region of the program. Understanding current and historical ethnic conflicts, warring factions, cultural hierarchies, customs, language and greetings, social norms, gender relations, and appropriate dress codes can help ensure team members do not unknowingly put themselves in an uncomfortable or harmful situation. Ethical issues should be anticipated, and team members should agree in advance about what types of medical care they feel comfortable and safe performing. In the end, at no point should the safety of the visiting team, local partners, or patients being treated be jeopardized for the purpose of the program, so a cautious and reasonable approach is recommended. The Berman Institute of Ethics free online ethics course http://ethicsandglobalhealth.org/ is an excellent resource for trainees to complete before going to another setting.

Research

When conducting research, it is critical to involve local collaborators including partner clinicians, hospital administrators, university researchers, the Ministry of Health, or all of the aforementioned in the development of research questions and in study design. There may be a misalignment of incentives when it comes to research; it is important to assess existing research projects, current clinical weaknesses, and stakeholder-identified future research directions to ensure the research addresses local needs and not solely the academic curiosity of the visiting team. Advance investigation should be made to determine if a local Institutional Review Board or Ethics Committee exists at the hospital, municipal, or national level where you will be working. Understanding the policies and authorization process, which may include manual delivery of paper copies of the research protocol or signed letters of authorization, with an effort to receive approval prior to the study

start date, is the most appropriate and ethical way to conduct research with international partners. Moreover, conversations with in-country partners should be conducted to inform study design and avoid barriers or challenges that have been faced by other local or international researchers prior to your arrival. Troubleshooting as many issues as possible in the planning phase can make the transition to implementation a smoother process. Increasingly, surgical journals are setting expectations about authorship when manuscripts are being submitted with data from LMICs. For example, the *World Journal of Surgery* expressly states that manuscripts must include one or more local coauthors who live and work in the country where the data have been collected.

Humanitarian Surgery Considerations

There are surgeons who are interested in working in humanitarian settings. These are typically in either conflict or disaster zones. It is critical to make sure that the surgeon has sufficient training and experience to work in these environments because of significant resource limitation, wide scope of procedures, and security concerns. The care provided after the 2010 Haiti earthquake exposed the inadequate training and coordination of emergency medical personnel, which resulted in care that was described as "medically shameful."[38] Best practice would be to work with designated humanitarian organizations such as *Médecins Sans Frontières* (MSF, also known as Doctors Without Borders), Samaritan's Purse, and the International Committee of the Red Cross. Providing care in these settings requires surgeons to have functional knowledge of the unique rules and ethics that govern the decisions for caring for injured people regardless of their combatant status in volatile and unpredictable settings. Surgeons must have a basic understanding of the Geneva Conventions and sections of International Humanitarian Law.[39]

Another important consideration of a program that includes humanitarian surgery as a component is affirming that surgical providers are appropriately trained in the operations they will be performing. Board-certified general surgeons in the United States may not have the skill set to match the broader range of pathology treated during humanitarian outreach programs. A study comparing MSF procedure logs to U.S. general surgery resident case logs

only noted overlap for 44% of procedures—the majority of which were general surgery operations such as herniorrhaphies and bowel resections.[40] However, MSF surgeons recorded 46.8% of cases to be obstetrics and gynecology and 21.2% to be orthopedics—specialties in which general surgery residents have very little exposure during traditional residency tracks. To address these inconsistencies and give residents more exposure to specific procedures such as caesarian sections, hysterectomies, amputations, long bone fixations, and suprapubic tube placements, some programs provide global and rural surgery residency tracks or fellowships or humanitarian skill workshops.[41] Providing surgeons with the appropriate clinical skills for the environment they are entering is essential for safe and suitable patient care as well as better incorporation into the local hospital and workforce.

GETTING INVOLVED

At every level of training and throughout the surgical career, there are ways to get involved in global surgery activities. In this section, opportunities are broken down by training level and activity type.

Students

Two international networking organizations exist specifically for students: InciSioN (incisionetwork.org) and their U.S. affiliate the Global Surgery Student Alliance (GSSA—www.globalsurgerystudents.org). The mission of these organizations is to engage students early in sustainable global surgery projects and to create a worldwide network of peer-to-peer partnerships and foster student–faculty mentor relationships. They have a number of international chapters with active social media presence to facilitate local and multinational collaboration. Moreover, their websites highlight resources, ways to get involved, and events, including an annual symposiums and regional conferences. Engaging undergraduate and medical students early will instill drive, passion, and the academic skill set to keep them ethically engaged in global surgery or global health throughout their careers.

Residents and Fellows

Over the last 10 years, academic opportunities in global surgery have increased significantly for resident surgeons. In terms of networking, the Global Surgery Working Group within the American College of Surgeons Resident and Associate Members Society (ACS-RAS) meets quarterly to bimonthly each year. The group has hosted webinars and hangouts on global surgery topics, and member work has been featured in the *RAS Newsletter*. A Communities message board provides members a way to connect on similar projects and share resources. Future directions for the working group include enacting an international residency training needs assessment and an RAS-COSECSA trainee co-mentorship program.

Many general surgery programs across the United States have developed global and rural surgery training opportunities, varying from 4- to 6-week international rotations to 1- to 2-year research fellowships to integrated track positions. A study from 2015 determined that 42 of 239 (16%) general surgery program websites had information about international surgical opportunities, and this number has only increased.[42] Several programs have written about their experiences with international surgery partnerships and the attendant benefits and challenges of responding to local needs, forming long-term partnerships, building capacity, promoting research, and providing guidance for other programs.[43–45] The University of Colorado Humanitarian Surgical Skills Workshop is held annually for residents to acquire subspecialty skills that are useful in low-resource environments.

Postgraduate Surgeons

There are also hands-on workshops that are geared specifically toward developing a humanitarian surgical skill set. The International Humanitarian Aids Skills Course hosted by the Stanford Center for Continuing Education occurs annually every February. The course spans 1.5 days with didactic and practical sessions. The hands-on portion with cadaveric or realistic models provides exposure to procedures such as orthopedic fixation, basic flaps, burns grafting, craniotomies, caesarian sections, and emergency gynecologic management. Participants can hone clinical skills in a safe, simulated setting. There is a Global Health Competencies and Cognitive Skills precourse offered at the American College of Surgeons Clinical Congress, with a simulation skills course offered every 3 years.

For the licensed general or specialty surgeon, the types of activities and the level of possible involvement vary broadly. As a general overview, two organizations have created world maps with pins highlighting clinical and research opportunities for surgeons, subspecialists, and trainees to collaborate internationally—the Association for Academic Global Surgery (https://www.academicglobalsurgery.org/maps) and Intersurgeons (https://intersurgeon.org). The interactive maps can be utilized to promote individual work, solicit clinical or academic partners, or locate particular needs in your region of interest.

Another option for identifying academic or clinical international work is through international or national academic societies, which are numerous and beyond the scope of this chapter. Some examples include the American College of Surgeons' Operation Giving Back, the Global Initiative in Children's Surgery, Global Affairs Committee of the Association for Academic Surgery (AAS), the Society for University Surgeons (SUS) Global Academic Committee, and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) Global Affairs Committee. The Royal College of Surgeons' Global Affairs Committee, the International Society of Surgery (ISS), and the Society of Asian Academic Surgeons (SAAS). COSECSA, WACS, and PAACS are some examples of well-known, multinational organizations that organize surgeons and surgical training in sub-Saharan Africa. Membership in these societies and involvement on the committees can provide access to educational and clinical opportunities, research support, and access to far-reaching networks with opportunities for bidirectional exchange and collaboration.

There are a number of well-known short- or long-term clinical opportunities to work internationally. MSF is a politically independent humanitarian organization that responds to crisis situations across the world and often partners with other organizations that are listed on its website (https://www.msf-me.org/other-organisations-working-field). Other groups that may accept volunteer surgeons or perioperative workforce include International Committee of the Red Cross, International Medical Corps, Médecins Du Monde, Samaritan's Purse, and Mercy Ships. There are other organizations, such as Operation Smile, Healing the Children, Touching Hands, Team Heart, and Mission Urology, which focus on specific pathologies. Some considerations when deciding which organization to

partner with are the organization's track record, longitudinal presence, philosophy or religious background, and the time and financial commitment required.

CONCLUSION

Global surgery is rapidly evolving and represents a growing interest for surgeons and trainees. There are many opportunities for those interested in forming collaborative partnerships in service, research, and education. To build sustained and successful engagements, it is important to ensure that individuals working overseas have had proper clinical and ethics training, relevant clinical experiences, and an understanding of research logistics and they are working in sync with the local collaborator.

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18

Patient Safety

Kiran Gupta and Elizabeth C. Wick

Key Points

1. Safety events are usually rare occurrence but when examined in aggregate may reveal themes.
2. "Measuring" how safe an hospital is in the traditional sense is difficult.
3. Most safety events occur as a result of poorly defined systems as opposed to an error on the part of an individual.
4. Developing a culture of safety is a long term commitment that requires close collaboration and alignment between hospital leadership, management and frontline staff.
5. Root cause analyses are the most common approach for evaluating serious safety events in a hospital.

INTRODUCTION TO PATIENT SAFETY

In 1999, the National Academy of Medicine (NAM, formerly called the Institute of Medicine) published *To Err is Human: Building a Safer Health System,* which highlighted the large number of Americans dying every year

from medical errors and has been largely credited with catalyzing the modern patient safety movement.[1] Before *To Err is Human*, it was largely believed that errors in medicine resulted from "bad apples," but the report elucidated how mistakes in health care frequently result from poor system design. Many began to draw analogies to and learn from other high stakes industries such as aviation, pointing out how broad system reform that prioritized safety had led to better outcomes in other fields. This shift in thinking launched sweeping efforts to improve the 1 safety of the health care delivery system in the United States, prompting important changes in measurement of safety, event reporting, culture, training, regulation, and technology. While much progress has been made over the last two decades, significant opportunity remains to improve safety, particularly in complex procedural areas like operating rooms. To be effective in helping to transform surgical culture and ensuring safe care for patients, it is critical that all surgeons have a working knowledge of patient safety as well as a general awareness of the principles of improvement.

ADVERSE EVENTS AND ERRORS

After *To Err is Human*, numerous studies were published further supporting the pervasiveness of mistakes and associated adverse outcomes for patients across all health care settings including surgery. It is important to understand that in health care, adverse patient outcomes can result both from underlying disease processes and from medical care received. The latter are typically referred to as adverse events, or medical harm which is defined by the Institute for Healthcare Improvement as: "unintended physical injury resulting from or contributed to by medical care (including the absence of indicated medical treatment) that requires additional monitoring, treatment, or hospitalization, or that results in death."[2] Adverse events can be further subdivided into those that are thought not to be preventable, resulting from appropriate medical care without 3 any error, and those that are preventable, resulting from errors on the part of an individual or a poorly functioning system, or a combination of both. In health care, an error or mistake is defined as "an act of commission (doing something wrong) or omission (failing to do the right thing) that leads to an undesirable outcome

or significant potential for such an outcome."[3] Not all errors or mistakes lead to adverse outcomes for patients and one that does not may be referred to as a "near miss." Within the field of patient safety, the focus has shifted from measuring and reducing errors to measuring and reducing the totality of preventable adverse events or preventable harm. It is important to acknowledge that what is defined as preventable harm may continue to evolve over time. For example, central line–associated blood stream infections (CLABSIs) were once thought not to be preventable and now it is well established that with proper techniques and protocols in place, CLABSI rates can be driven close to zero.[4]

While medical errors can occur across all health care settings, there are some forms of harm that are unique to the perioperative area (**Table 18.1**). Some of the errors that receive the most attention include patients undergoing surgery on the wrong limb, retention of foreign objects after the patient leaves the operating room and mislabeling of critical specimens. As the science of safety has advanced, systems have been put in place to try to prevent these events such as marking of the planned surgical site and side prior to the patient going back to the operating room (wrong-site surgery), using radio frequency identification or digital counting to account for all surgical laparotomy pads (retained foreign objects) and implementing team debriefings (mislabeled surgical specimens). But, despite these interventions, events still occur. In this chapter, we provide a brief background on patient safety; summarize the role of culture, teamwork, and communication in improving safety; and highlight the importance of working toward zero preventable harms in surgical patients.

MEASUREMENT CHALLENGES

2 Despite advances in the field of patient safety over the last two decades, measuring safety remains an ongoing challenge and some have aptly stated that "what you see depends on how you look."[5] Health care organizations often choose to measure safety in numerous ways. Many have established voluntary event–reporting systems in which employees can share information about errors, mistakes, and near misses. Commonly referred to as "incident-reporting systems," these databases contain information only about what

frontline health care workers choose to report. A high rate of reported incidents could either reflect a strong safety culture and comfort with sharing concerns, or reflect true safety problems. It can be hard to tell whether fluctuation in the rate of reported incidents reflects changes in the culture of reporting or true changes in safety. In addition, different types of health care providers might note different concerns and because nurses file incident reports far more frequently than physicians, these reporting systems might not adequately reflect physicians' safety concerns.[6] Despite their inherent flaws, incident-reporting systems are one major way that health care systems keep track of concerning events and trends.

Table 18.1 National Quality Forum Never Events

1. Surgical or Invasive Procedure Events
   1A. Surgery or other invasive procedure performed on the wrong site (updated)
   Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
   1B. Surgery or other invasive procedure performed on the wrong patient (updated)
   Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
   1C. Wrong surgical or other invasive procedure performed on a patient (updated)
   Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
   1D. Unintended retention of a foreign object in a patient after surgery or other invasive procedure (updated)
   Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
   1E. Intraoperative or immediately postoperative/postprocedure death in an ASA Class 1 patient (updated)
   Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices

2. Product or Device Events
   2A. Patient death or serious injury associated with the use of contaminated drugs, devices, or biologics provided by the health care setting (updated)
   Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities
   2B. Patient death or serious injury associated with the use or function of a device in patient care, in which the device is used or functions other than as intended (updated)

Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

2C. Patient death or serious injury associated with intravascular air embolism that occurs while being cared for in a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, long-term care/skilled nursing facilities

3. Patient Protection Events

3A. Discharge or release of a patient/resident of any age, who is unable to make decisions, to other than an authorized person (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

3B. Patient death or serious injury associated with patient elopement (disappearance) (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

3C. Patient suicide, attempted suicide, or self-harm that results in serious injury, while being cared for in a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

4. Care Management Events

4A. Patient death or serious injury associated with a medication error (e.g., errors involving the wrong drug, wrong dose, wrong patient, wrong time, wrong rate, wrong preparation, or wrong route of administration) (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

4B. Patient death or serious injury associated with unsafe administration of blood products (updated)

Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

4C. Maternal death or serious injury associated with labor or delivery in a low-risk pregnancy while being cared for in a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers

4D. Death or serious injury of a neonate associated with labor or delivery in a low-risk pregnancy (new)
Applicable in: hospitals, outpatient/office-based surgery centers

4E. Patient death or serious injury associated with a fall while being cared for in a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

4F. Any stage 3, stage 4, and unstageable pressure ulcers acquired after admission/presentation to a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, long-term care/skilled nursing facilities

4G. Artificial insemination with the wrong donor sperm or wrong egg (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices

4H. Patient death or serious injury resulting from the irretrievable loss of an irreplaceable biologic specimen (new)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

4I. Patient death or serious injury resulting from failure to follow up or communicate laboratory, pathology, or radiology test results (new)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

5. Environmental Events

5A. Patient or staff death or serious injury associated with an electric shock in the course of a patient care process in a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

5B. Any incident in which systems designated for oxygen or other gas to be delivered to a patient contains no gas, the wrong gas, or are contaminated by toxic substances (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

5C. Patient or staff death or serious injury associated with a burn incurred from any source in the course of a patient care process in a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

5D. Patient death or serious injury associated with the use of physical restraints or bedrails while being cared for in a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

6. Radiologic Events

6A. Death or serious injury of a patient or staff associated with the introduction of a metallic object into the MRI area (new)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices

7. Potential Criminal Events

7A. Any instance of care ordered by or provided by someone impersonating a physician, nurse, pharmacist, or other licensed health care provider (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term

care/skilled nursing facilities

7B. Abduction of a patient/resident of any age (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

7C. Sexual abuse/assault on a patient or staff member within or on the grounds of a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

7D. Death or serious injury of a patient or staff member resulting from a physical assault (i.e., battery) that occurs within or on the grounds of a health care setting (updated)
Applicable in: hospitals, outpatient/office-based surgery centers, ambulatory practice settings/office-based practices, long-term care/skilled nursing facilities

Using administrative date, the Agency for Healthcare Research and Quality (AHRQ) developed patient safety indicators (PSIs) as triggers to identify safety issues.[7] Over time and not without controversy, PSIs have been incorporated into public-reporting and pay-for-performance programs.[8,9] However, reliance on administrative data may not always adequately capture true safety concerns. Other approaches including retrospective chart review, trigger tools and hospital standardized mortality ratios all pose challenges as well.[10–12] In reality, organizations use a variety of approaches to measure safety and identify harm; incident reporting, administrative data, publicly reported measures, retrospective chart review, trigger tools, and even patient-reported concerns are those most frequently utilized.

SYSTEMS THINKING

A key shift in patient safety has been the realization that adverse events often occur because of poorly designed or poorly functioning systems, rather than because of the actions of a single individual. Historically, the approach was

to place blame for a bad outcome on a particular individual caring for a patient. In the past, medical errors were thought to reflect incompetence and as a result, clinicians frequently tried to keep them undercover, preventing organizations from learning from these events and promoting a lack of transparency. While there has been a significant shift away from blame in the last decade, there is still significant opportunity to integrate appropriate analysis of the health care system into discussions regarding adverse events.

The adoption of such "systems" thinking in health care—the idea that humans are human and as such will inevitably make mistakes and that systems need to be designed to be resilient, mitigating the possibility of error or identifying risk before harm results—has transformed the ability to realize safety. Systems thinking often involves redesigning systems using a combination of frontline provider input, human factors principles, systems engineering, and health information technology to significantly decrease the risk of adverse events and harm. James Reason's "Swiss cheese model" is frequently referred to when discussing how a series of defects in a system can align to cause inadvertent harm and worth becoming familiar with.[13]

Health care is considered a high-risk industry with a high error rate, but other high-risk industries, such as nuclear power and commercial aviation, have managed to achieve and maintain an impeccably low error rate.[13] Much of the credit for the safety record in these areas can be attributed to the culture, characterized by individual responsibility and accountability, attention to detail, professionalism, transparency, and respect for all team members. It is the culture in these industries that facilitates high-quality communication under high-risk, high-stress conditions. As health care's views on patient safety have matured, improvement efforts have largely shifted from remediating individual providers to buttressing the "system" by simplifying processes and building in the use of tools such as checklists and read-backs that facilitate redundancy and standardized approaches where possible.[14]

DISTINCTION BETWEEN QUALITY AND SAFETY

Although the lines can be blurred at times, there is a distinction between quality and safety. In 2001, NAM published another well-known report, *Crossing the Quality Chasm*, in which it defined six aims for achieving a high-quality health care system: safe, effective, patient-centered, timely, efficient, and equitable.[15] Within this framework, safety is defined in a way as one aspect of high-quality care. When analyzing events, safety and quality problems may both be present.

CREATING A CULTURE OF SAFETY

4 Culture is to an organization what personality is to an individual—a difficult to precisely define, yet unifying set of characteristics and attributes that provide meaning and direction.[16] Organizations with effective safety cultures share a constant commitment to safety as a top-level priority that permeates the entire organization—from the frontlines (learners, technicians, clerks, nurses, anesthesia providers, surgeons, sterile processing staff) to the leadership (perioperative executives, chief operating officers, clinical department leadership). Organizations that are able to align and promote an effective culture of safety in the surgical areas are generally characterized the following qualities[17]:

1. Recognize the high-risk, error-prone nature of surgery and perioperative services.
2. They have fostered a nonpunitive environment where individuals are able to report errors or close calls without fear of punishment or retaliation; sometimes called a "Just Culture."
3. They develop forums and expectation for collaboration across disciplines and ranks to seek solutions to vulnerabilities and identified safety breeches.
4. They express a willingness to direct organizational resources (project management, dedicated nonclinical time for key personnel, health information resources, etc.) to address safety concerns.

It is important to acknowledge that traditional surgical culture stands at odds to some of the core principles of a culture of safety. The operating room has historically been a hierarchal environment where the surgeon was considered to be the "captain of the ship." The emphasis was solely focused

on executing the surgeon's orders and requests and not on speaking up if there were concerns or even valuing collective input. Furthermore, surgeons have been hesitant to discuss errors as mistakes have been equated with incompetence. Discussions of errors have usually taken place only among peers in morbidity and mortality forums. Surgeons also tend to minimize the effects of stress on their ability to make decisions.[18] Establishing clarity of roles as well as a culture that promotes raising concerns are key steps on the journey toward optimal safety culture in the operating room; hierarchy can prevent nurses and other operating room staff from pointing out potential errors or mistakes made by the team resulting in potentially preventable adverse events. It is important to note that although progress in perioperative areas has been slower than in others, fear of speaking up is not limited to the operating room. The culture of medicine in general strongly values professional autonomy, which frequently promotes individualism over cooperation, often to the detriment of patient care.[19] Although often viewed as important, safety culture is seldom promoted from an organizational priority to an organizational value. Organizations often do not feel the need to devote resources to overhauling their patient safety systems to achieve optimal culture as long as they perceive their existing processes to be adequate. It is a common refrain to hear that hospital-based patient safety teams are underresourced and are not able to convene essential groups or provide the necessary follow-up and systems-level changes after a safety event—key steps required to accelerate the journey to realizing strong culture of safety and to becoming a high reliability organization.[20]

MEASURING SAFETY CULTURE

It is important to establish a unifying culture of patient safety throughout an organization because culture evolves at multiple levels: within health care systems, hospitals, departments, and units. Efforts to foster cultural change within an organization with regard to patient safety have been limited in the past by the inability to measure the impact of any given intervention. However, studies have shown that surveys determining what is important and what attitudes and behaviors are rewarded, supported, expected, and accepted, with regard to patient safety are associated with error reduction

behaviors in aviation and with decreased rates of CLABSIs.[4] The Safety Attitudes Questionnaire (SAQ) and the Survey on Patient Safety Culture (SOPS) are validated survey instruments that can be used to measure culture in a health care setting.[21] The SOPS has been adapted for multiple settings including ambulatory surgery centers, outpatient practices, nursing homes, and pharmacies. More recently, additional optional questions have been developed around health information technology and value. The Joint Commission encourages all hospitals to measure safety culture every 18 months to 2 years.

Although perceptions of safety culture domains can differ as a function of one's role in the OR (i.e., technician, surgeon, nurse, anesthesia provider, environmental services worker, clerk), perceptions of the overall climate has been shown to be relatively consistent across OR providers in a given hospital.[22] Using a survey, hospitals can compare culture between different types of health care workers within a work area as well as culture between work areas throughout the institution. Scores can be compared to those of other participating institutions to have a sense to how the hospital compares to other similar sized hospitals. Importantly, in addition to simply awareness, the survey and scores can be used to evaluate the effectiveness of safety interventions by comparing the survey safety climate scores post implementation to baseline scores.

Teamwork and Communication

According to The Joint Commission, communication breakdown is one of the top three root causes of sentinel events such as a wrong-site surgery. Poor communication contributed to over 60% of sentinel events reported to the Joint Commission on Accreditation of Healthcare Organizations in 2011.[23] Good communication is an essential component of teamwork and is especially important in the OR, one of the most complex work environments in health care.

Within the realm of patient care, there are enormous amounts of information being exchanged between health care providers on a daily basis. Much of this information, if prioritized correctly, has the potential to prevent unintended medical errors and serious harm to patients. The importance of good communication in preventing medical error is undeniable; however, it

is difficult to achieve. The traditional surgical hierarchy can prevent OR personnel from sharing important patient data and expressing safety concerns. One perioperative field study showed a 30% rate of communication failure in the OR, with 36% of these breakdowns having a substantial impact on patient safety.[24]

MEASURING TEAMWORK

Research in commercial aviation has demonstrated a strong correlation between better teamwork and improved safety performance. Cockpit crew members' reluctance to question a captain's judgment was long ago identified as a root cause of aviation accidents. Good attitudes about teamwork are associated with error-reduction behaviors in aviation, improved patient outcomes in ICUs, and decreased nurse turnover in the OR.[22] It is also associated with higher job satisfaction ratings and less sick time taken from work.

Safety culture surveys can be used to measure teamwork and provide benchmarks for departments or hospitals seeking to measure and improve their teamwork climate.[25] The teamwork scores are responsive to interventions that aim to improve teamwork among operating teams, such as the implementation of crew resource management or team training, executive walk rounds, and preoperative briefing team discussions. The communication and collaboration sections of the surveys reflect OR caregiver views on teamwork and can be used to distinguish meaningful interventions from impractical and ineffective programs.

In a survey of operating room personnel across 60 hospitals, the SAQ identified substantial differences in the perception of teamwork in the OR depending on one's role.[26] Physicians frequently rated the teamwork of others as good, while nurses at the same institutions perceived teamwork as poor. These discrepancies can be attributed to differences in the communication skills that are valued by surgeons and nurses. For example, nurses describe good collaboration as having their input respected, while physicians describe good collaboration as having nurses who can anticipate their needs and follow instructions. Efforts to improve the communication that takes place between physicians and nurses can directly improve the

perception of teamwork and collaboration by the OR team. Empowering well-respected surgeons to promote principles of teamwork and communication can go a long way toward transforming attitudinal and behavioral changes in fellow physicians as well as other members of the surgical team. Surgeons are increasingly encouraging the respectful and timely voicing of concerns of OR personnel.

Ultimately, a strong safety culture and prioritization of teamwork and communication will help organizations chart new territory more nimbly and successfully. This was exemplified at our hospital in the era of COVID-19 in the operating rooms. All patients scheduled for elective surgery were required to undergo SARS-CoV-2 testing. In order to have testing results available to inform surgical decision making, patients were instructed to undergo testing 2 to 4 days prior to surgery. However, 100% compliance was hindered due to travel distance, lack of social support, shelter-in-place orders, as well as taxed testing resources.

On the third day of our preoperative universal testing protocol, one patient arrived without a SARS-Cov-2 test. He was asymptomatic and had been sheltering at home. Therefore, it was decided to proceed with surgery. A nasopharyngeal swab was obtained the evening after surgery. The following morning, a positive test result was reported. His complex case and hospitalization potentially exposed multiple health care workers to SARS-CoV-2 leading the team to conclude that the communication and teamwork pertaining to perioperative SARS-CoV-2 testing had failed. We could have improved preoperative communication about the need for testing or arranged for testing the night or morning before surgery. **Figure 18.1** illustrates the complex intersection between technical work like a SARS-CoV-2 testing protocol and the adaptive work, the culture, communication and teamwork in the workplace.

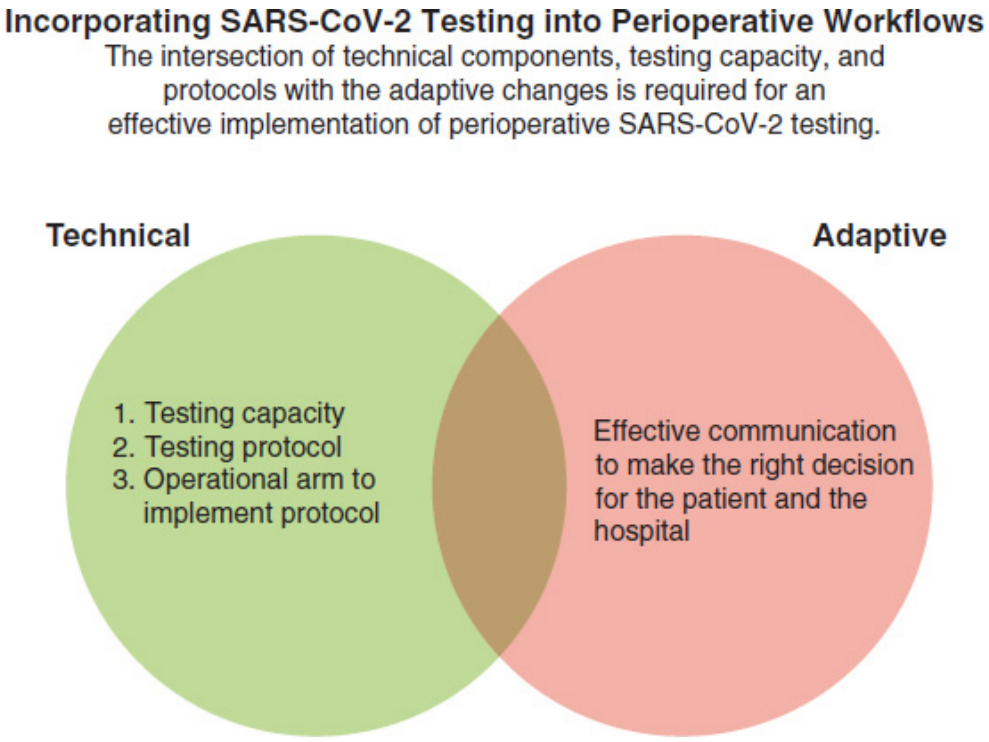

Figure 18.1 Intersections between technical and adaptive work. (Reprinted with permission from NEJM Catalyst [catalyst.nejm.org] © Massachusetts Medical Society.)

TOOLS FOR IMPROVING SAFETY CULTURE, TEAMWORK, AND COMMUNICATION

A hallmark of high reliability organizations is the frequent use of tools such as prompts, checks, standard operating protocols, and communication interventions such as team briefings and debriefings. These tools identify and mitigate hazards and allow an organization to complete tasks more efficiently. They also foster a culture of open communication and speaking up if a team member identifies a safety concern. Safety checks and standardized team discussions serve as prompts to help "engineer out" human error, providing quality assurance and improving information flow. They also can prevent errors related to omissions, which are more likely to occur when there is information overload, multiple steps in a process, repetitions in steps, planned departures from routine processes, and when there are other interruptions and distractions present while the process is being executed.

These same interventions have been shown to improve patient safety in ORs and ICUs.[20,27]

Preoperative briefings and checklists, when used appropriately, help to facilitate transfer of information between team members. A briefing, or checklist, is any preprocedure discussion of requirements, needs, and special issues of the procedure. Briefings are best when locally adapted to the specific needs of the specialty. They have been associated with an improved safety culture, including increased awareness of wrong-site/wrong-procedure errors, early reporting of equipment problems, reduced operational costs, and fewer unexpected delays. In one study, 30.9% of OR personnel reported a delay before the institution of OR briefings, and only 23.3% reported delays after briefings were instituted.[28,29] OR briefings are increasingly being used to ensure evidence-based measures, such as the appropriate administration of preoperative antibiotics and deep vein thrombosis (DVT) prophylaxis, are used. Briefings allow personnel to discuss potential problems, before they become a "near miss" or cause actual harm.

The World Health Organization (WHO) has developed a comprehensive perioperative checklist as a primary intervention of the "Safe Surgery Saves Lives" program—an effort to reduce surgical deaths across the globe.[30] The WHO checklist includes prompts to ensure that infection prevention measures are followed, potential airway complications are precluded (e.g., anesthesia has necessary equipment and assistance for a patient with a difficult airway), and the groundwork for effective surgical teamwork is established (e.g., proper introductions of all OR personnel). Aspects of The Joint Commission's preprocedure "Universal Protocol" (or "time-out") are also included in the checklist (e.g., checks to ensure operation performed on correct patient and correct site). The initial WHO checklist study was associated with significant reduction in mortality worldwide but follow-up studies evaluating the efficacy of the checklist in governmental programs have failed to reproduce the same impact on morbidity and mortality. It is now understood that the efficacy of checklists are largely dependent on the safety culture in which they are implemented.[29] Simply mandating use is unlikely to change the quality of care delivered but comprehensive interventions to improve safety culture and implement checklists will likely

result in meaningful improvement. It is important to adapt checklists to the local environment (**Fig. 18.2**).

Tools such as checklists, sign-outs, briefings, and debriefings improve communication between health care providers and create a safer patient environment. Although their use in health care is still highly variable, specialties that have incorporated them, such as intensive care and anesthesia, have made impressive strides in patient safety. Currently, communication breakdowns, information loss, frequent handoffs, multiple competing tasks, and high workload are considered "annoying but accepted features" of the perioperative environment. As physician attitudes toward error mitigation, stress reduction, and optimizing teamwork become more favorable, medicine will likely achieve many of the milestones in safety that high-reliability industries such as aviation already have.

The comprehensive unit based safety program (CUSP) is a tool that was initially designed for the intensive care unit, but has been translated to different clinical areas.[31] CUSP is an effective approach for improving both safety culture and clinical outcomes. Every clinical area that implements CUSP assembles a multidisciplinary team and follows five iterative steps: training on the science of safety, identifying patient safety hazards, partnering with senior executive, learning from defects and implement tools to improve teamwork, and improving communication. All teams include providers from relevant disciplines such as nurses, physicians, hospital infection control practitioners, technicians, advanced practice providers, resident physicians and clerks. This approach has been successfully used to reduce colorectal SSIs from 27% to 18% in a university-based setting.[31] It has been adapted to other perioperative settings across the country through a national implementation project in collaboration with the American College of Surgeons. Subsequently the approach has been used to disseminate enhanced recovery after surgery (ERAS) pathways across multiple service lines.

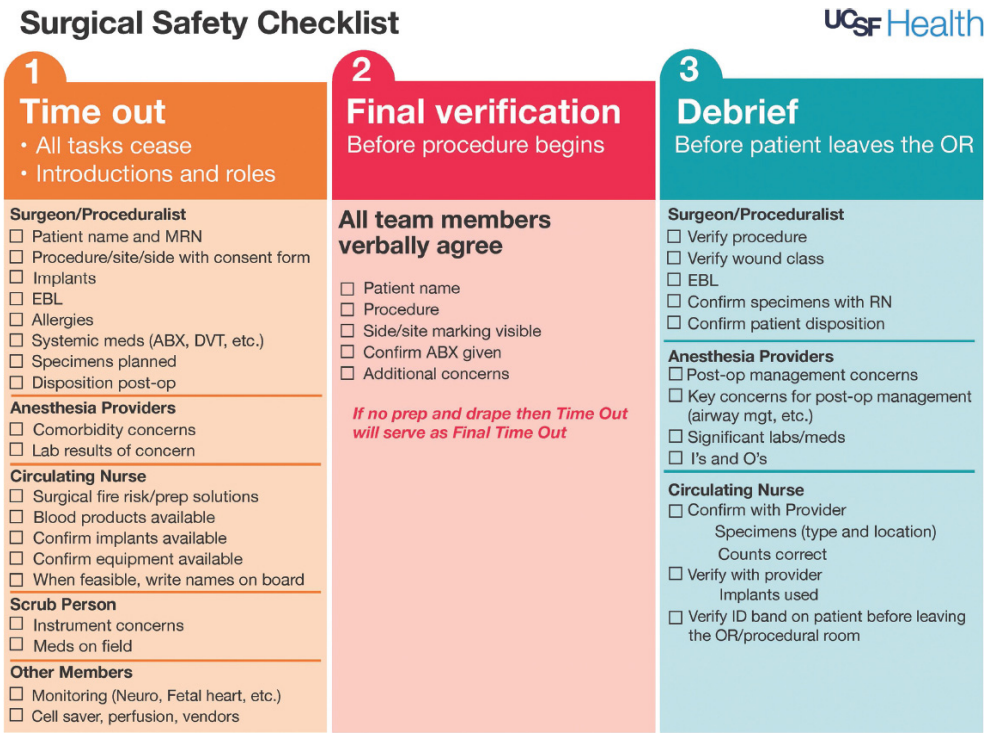

Figure 18.2 University of California, San Francisco perioperative briefing and debriefing checklist.

INVESTIGATING A SAFETY EVENT: ROOT CAUSE ANALYSIS

5 The approach to analyzing adverse events and mistakes has shifted from assigning blame to using frameworks that help elucidate contributing factors so that improvements can be put in place to make the system more resilient, thereby preventing similar harms or near misses from occurring in the future. Division and department morbidity and mortality conferences (M&Ms) have long provided a protected space in which clinicians from similar fields can openly discuss clinical decision making, including errors. The focus of the discussion can at times be very technical. However, M&Ms are not always the optimal forum for discussing cases in which broad systems-issues beyond the purview of a particular division or department may have played a role. Furthermore, M&Ms have traditionally been focused on surgeons and attendance by nonsurgeon personnel is usually restricted, further limiting both the scope and impact of the discussions. In addition, there are certain events

that occur, often referred to as sentinel events or never events, for which health care institutions are required by certain states and The Joint Commission to conduct thorough, detailed systematic reviews, often with the engagement of the appropriate hospital leadership. The process most commonly employed by health care organization for such systems-level analysis is referred to as root cause analysis (RCA).

The goals of the RCA process are two-fold: 1) to identify the systems factors that contributed to the adverse event, error or near miss and 2) to identify improvement opportunities to prevent similar events in the future. When conducting a RCA, it is important to consider:

- Selecting an experienced and skilled facilitator to lead the discussion
- Using structured tools to help identify possible contributing factors
- A multidisciplinary approach that engages a diversity of clinicians, staff, and hospital leadership with time for those involved in the case to share their perspective
- Development of action items for improvement to mitigate the risk of future harm and weighing the relative strength of those action items (e.g., educational intervention or policy change vs. a true systems fix)
- Implementing processes for accountability and sustainment of action items as well as dissemination of learnings from the discussion throughout the organization
- A framework that refers aspects of a case involving an individual's decision making to the appropriate peer review forum for further discussion so that the RCA can focus on systems issues
- Establishing appropriate support resources for staff and providers who may be particularly impacted by the case and for whom the discussion may also be hard.[14,32]

What a Surgeon Should Consider When Preparing to Attend an RCA?

- Debrief with your supervisor/division chief/department chair about the case and consider requesting that the case undergo M&Ms in advance of the RCA so that care management issues and decision making are well understood and expert surgical colleague input can be had.
- Consider using a structured approach such as the "5-Whys" or a fishbone diagram to help identify possible contributing factors to the system defects so that you are prepared to share your thoughts at the RCA.

- If the case was particularly impactful for other team members, it can be helpful to debrief with them prior to the RCA.
- If there are concerns about risk and disclosure, seek the advice of risk management at the time of the event to ensure appropriate documentation and discussion with the patient and family.
- Try to avoid placing blame on others during the discussion and speak openly about your concerns related to system issues and why you think things did not go as planned.
- Be sure to recommend inclusion of key people that might not be obvious based on record review.

ESTABLISHING A COMPREHENSIVE SAFETY PROGRAM

Historically, safety issues and concerns were managed in a fragmented manner within divisions and departments, at times falling under the purview of a single hospital leader such as the Chief Medical Officer. Many larger organizations have now developed robust infrastructure dedicated to managing safety at an institutional level. Safety programs are at times embedded within the broader quality efforts of the organization (e.g., under a Chief Quality Officer) and frequently engage closely with the risk management department.

Most comprehensive hospital safety programs employ a safety officer or manager to help oversee various aspects of the work which usually includes the following[14]:

- The incident-reporting system which for a large institution like ours can result in well over a thousand incidents a month that need to be investigated and addressed
- Addressing safety data from various sources including outcome data related to a variety of externally reported safety and quality measures (readmissions, mortality, PSIs, etc.)
- Addressing issues from cases referred from division and departmental review processes
- Safety culture survey and intervention efforts
- The Joint Commission survey related work

- Engaging relevant clinical and operational leadership in event review to motivate needed change
- Ensuring appropriate review of serious errors and sentinel events
- Establishing a high-level patient safety committee to discuss strategy and priorities related to safety
- Engaging frontline clinicians and clinical leaders in safety-related efforts

CONCLUSIONS

The fields of quality and safety have evolved tremendously in the past two decades. Much of the terminology is now commonplace and many frontline providers are routinely engaged in efforts related to quality and safety. Yet, there remains tremendous opportunity to improve culture and communication to ensure safe care for patients. As surgeons we must be dedicated to acquiring competency in the areas described above so that we can serve as leaders in advancing patient safety in our hospitals and operating rooms.

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Part Two Surgical Practice

Section A: TRAUMA

19

Trauma and Trauma Care: General Considerations

John W. Scott and Hasan B. Alam

Key Points

1. Injuries are the leading cause of death in young Americans and account for one out of every 10 deaths in the world.
2. The three most common mechanisms of injury-related deaths are motor vehicle collisions, firearms, and falls; however, fall-related deaths are rapidly rising, reflecting the aging population.
3. Bleeding is the number one cause of preventable deaths.
4. Early hemorrhage control is the major priority along with balanced resuscitation using an appropriate ratio of blood products.
5. The vast majority of trauma-related deaths are within the first few hours (<6 hours) after sustaining injuries.
6. Establishment of trauma systems that use evidence-based triage and treatment protocols saves lives.
7. Recent military conflicts have rapidly advanced trauma care in many domains, and these developments are now being transferred to the civilian trauma settings.

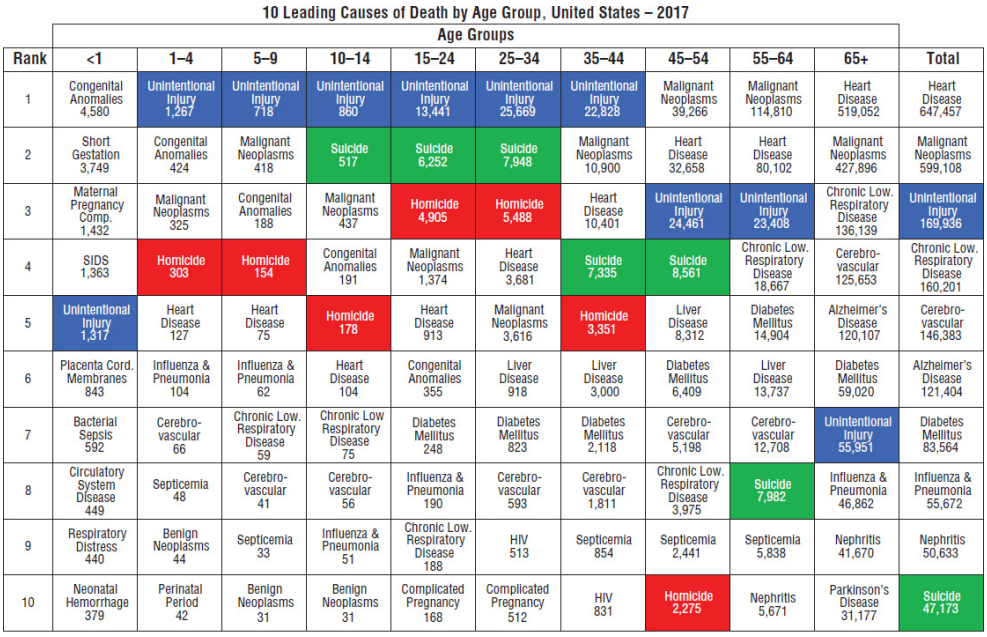
BURDEN OF DISEASE

Injuries and violence affect everyone, regardless of age, race, or economic status. According to the Centers for Disease Control and Prevention (CDC), National Center for Injury Prevention and Control, injuries account for over 243,000 deaths per year.[1] As opposed to cancers, cardiovascular diseases, and strokes, injuries disproportionally strike people in the prime of their lives.[1] Injury is the number one cause of death for Americans younger than 60 years.[1] In fact, 54% of all 1 deaths among people of 1 to 44 years of age in the United States are due to injuries, which are more than all noncommunicable diseases and infectious diseases combined.[1] **Figure 19.1** shows the top 10 causes of death in different age groups in the United States, whereas **Figure 19.2** shows the top 10 causes of injury-related deaths, highlighting the unintentional causes.[1] Excluding drug overdoses, the top three mechanisms of injury-related deaths in the United States are motor vehicle collisions 2 (MVCs), firearms, and falls—each of which account for just under 40,000 deaths annually (**Table 19.1**).[1] On the global scale, injuries account for over 10% of the entire global burden of disease.[2] Each year, almost 100 million people are injured and nearly 5 million people die from injuries—more deaths than from HIV/AIDS, malaria, and tuberculosis combined.[2]

Although striking, the mortality data do not tell the entire story. In 2017, there were approximately 30 million injured patients treated in emergency departments, and there are approximately 3 million hospitalizations for injuries.[3] The overwhelming majority of these patients survive, but they may face lifelong mental, physical, social, and financial challenges. These challenges may greatly impair a patient's functional status and limit their ability to return to school, work, or preinjury activity level. At the population level, the resultant economic toll on our society is staggering. In 2013, the total cost of injuries in the United States was estimated to be $671 billion.[4] The costs associated with fatal injuries were $214 billion, while nonfatal injuries accounted for over $457 billion.[4]

EVOLVING MECHANISMS OF INJURIES WITH CHANGING POPULATION DEMOGRAPHICS

Trauma represents a heterogeneous group of injury mechanisms that have a dynamic relationship with societal and demographic changes over time (**Fig. 19.3**). For example, better roads, safer cars, more frequent use of seat belts, and a reduction in drunk driving over the last few decades have resulted in a decrease in the MVC fatality rate despite a marked increase in the number of cars on the roads and overall miles driven (**Fig. 19.4**).[5–8] Conversely, falls—which are more common in older adults—are rapidly becoming a major health care issue due to increasing age of the population.[9] In the United States today, one in nine Americans is 65 years or older, which by 2050 will increase to one in five.[9] The fall-related death rates have been climbing since the early 1990s (**Fig. 19.5**) and are expected to increase even more dramatically over the next few decades. These patients also have many more comorbid problems, and the various age-related anatomic, physiologic, and immunologic changes make it especially challenging to care for them.[9,10] Firearm deaths also demonstrate the complex interplay of injury and society. The overall firearm death rate, including both homicide and suicide, decreased significantly from the mid-1970s through the mid-2000s.[11] This trend has mirrored the national trends in overall violent crimes, which have fallen significantly over the same time period.[12] However, over the past decade, firearm-related deaths are no longer decreasing. Gun suicide rates have been increasing since 2006, and gun homicide rates have been increasing since 2014 (**Fig. 19.6**).[11] Both of these trends are mostly concentrated among males. In 2017, there were 39,773 firearm-related deaths in the United States, 60% of which were suicides.[11] The crude and age-adjusted firearm-related death rates in 2017 were the highest recorded rates in the last 20 years.[11] Over the past few years, there is an increasing awareness that reducing firearm-related deaths will require a public health approach, as advocated for by the 2019 Medical Summit on Firearm Injury Prevention.[13]

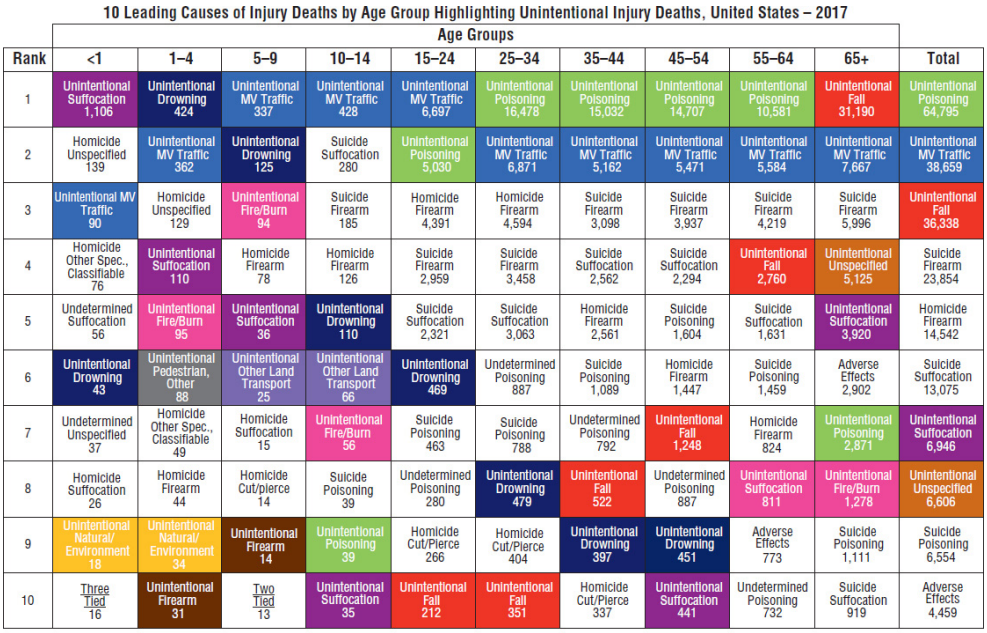


10 Leading Causes of Death by Age Group, United States – 2017

Rank	Age Groups <1	1–4	5–9	10–14	15–24	25–34	35–44	45–54	55–64	65+	Total
1	Congenital Anomalies 4,580	Unintentional Injury 1,267	Unintentional Injury 718	Unintentional Injury 860	Unintentional Injury 13,441	Unintentional Injury 25,669	Unintentional Injury 22,828	Malignant Neoplasms 39,266	Malignant Neoplasms 114,810	Heart Disease 519,052	Heart Disease 647,457
2	Short Gestation 3,749	Congenital Anomalies 424	Malignant Neoplasms 418	Suicide 517	Suicide 6,252	Suicide 7,948	Malignant Neoplasms 10,900	Heart Disease 32,658	Heart Disease 80,102	Malignant Neoplasms 427,896	Malignant Neoplasms 599,108
3	Maternal Pregnancy Comp. 1,432	Malignant Neoplasms 325	Congenital Anomalies 188	Malignant Neoplasms 437	Homicide 4,905	Homicide 5,488	Heart Disease 10,401	Unintentional Injury 24,461	Unintentional Injury 23,408	Chronic Low. Respiratory Disease 136,139	Unintentional Injury 169,936
4	SIDS 1,363	Homicide 303	Homicide 154	Congenital Anomalies 191	Malignant Neoplasms 1,374	Heart Disease 3,681	Suicide 7,335	Suicide 8,561	Chronic Low. Respiratory Disease 18,667	Cerebro-vascular 125,653	Chronic Low. Respiratory Disease 160,201
5	Unintentional Injury 1,317	Heart Disease 127	Heart Disease 75	Homicide 178	Heart Disease 913	Malignant Neoplasms 3,616	Homicide 3,351	Liver Disease 8,312	Diabetes Mellitus 14,904	Alzheimer's Disease 120,107	Cerebro-vascular 146,383
6	Placenta Cord. Membranes 843	Influenza & Pneumonia 104	Influenza & Pneumonia 62	Heart Disease 104	Congenital Anomalies 355	Liver Disease 918	Liver Disease 3,000	Diabetes Mellitus 6,409	Liver Disease 13,737	Diabetes Mellitus 59,020	Alzheimer's Disease 121,404
7	Bacterial Sepsis 592	Cerebro-vascular 66	Chronic Low. Respiratory Disease 59	Chronic Low Respiratory Disease 75	Diabetes Mellitus 248	Diabetes Mellitus 823	Diabetes Mellitus 2,118	Cerebro-vascular 5,198	Cerebro-vascular 12,708	Unintentional Injury 55,951	Diabetes Mellitus 83,564
8	Circulatory System Disease 449	Septicemia 48	Cerebro-vascular 41	Cerebro-vascular 56	Influenza & Pneumonia 190	Cerebro-vascular 593	Cerebro-vascular 1,811	Chronic Low. Respiratory Disease 3,975	Suicide 7,982	Influenza & Pneumonia 46,862	Influenza & Pneumonia 55,672
9	Respiratory Distress 440	Benign Neoplasms 44	Septicemia 33	Influenza & Pneumonia 51	Chronic Low. Respiratory Disease 188	HIV 513	Septicemia 854	Septicemia 2,441	Septicemia 5,838	Nephritis 41,670	Nephritis 50,633
10	Neonatal Hemorrhage 379	Perinatal Period 42	Benign Neoplasms 31	Benign Neoplasms 31	Complicated Pregnancy 168	Complicated Pregnancy 512	HIV 831	Homicide 2,275	Nephritis 5,671	Parkinson's Disease 31,177	Suicide 47,173

Data Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.

Figure 19.1 Ten leading causes of death by age group in the United States (2017). (From Centers for Disease Control and Prevention. Available at https://www.cdc.gov/injury/wisqars/LeadingCauses.html. Accessed December 31, 2019.)



10 Leading Causes of Injury Deaths by Age Group Highlighting Unintentional Injury Deaths, United States – 2017

Rank	Age Groups <1	1–4	5–9	10–14	15–24	25–34	35–44	45–54	55–64	65+	Total
1	Unintentional Suffocation 1,105	Unintentional Drowning 424	Unintentional MV Traffic 337	Unintentional MV Traffic 428	Unintentional MV Traffic 6,697	Unintentional Poisoning 16,478	Unintentional Poisoning 15,032	Unintentional Poisoning 14,707	Unintentional Poisoning 10,581	Unintentional Fall 31,190	Unintentional Poisoning 64,795
2	Homicide Unspecified 139	Unintentional MV Traffic 362	Unintentional Drowning 125	Suicide Suffocation 280	Unintentional Poisoning 5,030	Unintentional MV Traffic 6,871	Unintentional MV Traffic 5,162	Unintentional MV Traffic 5,471	Unintentional MV Traffic 5,584	Unintentional MV Traffic 7,667	Unintentional MV Traffic 38,659
3	Unintentional MV Traffic 90	Homicide Unspecified 129	Unintentional Fire/Burn 94	Suicide Firearm 185	Homicide Firearm 4,391	Homicide Firearm 4,594	Suicide Firearm 3,098	Suicide Firearm 3,937	Suicide Firearm 4,219	Suicide Firearm 5,996	Unintentional Fall 36,338
4	Homicide Other Spec., Classifiable 76	Unintentional Suffocation 110	Homicide Firearm 78	Homicide Firearm 126	Suicide Firearm 2,959	Suicide Firearm 3,458	Suicide Suffocation 2,562	Suicide Suffocation 2,294	Unintentional Fall 2,760	Unintentional Unspecified 5,125	Suicide Firearm 23,854
5	Undetermined Suffocation 56	Unintentional Fire/Burn 95	Unintentional Suffocation 36	Unintentional Drowning 110	Suicide Suffocation 2,321	Suicide Suffocation 3,063	Homicide Firearm 2,561	Suicide Poisoning 1,604	Suicide Suffocation 1,631	Unintentional Suffocation 3,920	Homicide Firearm 14,542
6	Unintentional Drowning 43	Unintentional Pedestrian, Other 88	Unintentional Other Land Transport 25	Unintentional Other Land Transport 66	Unintentional Drowning 469	Undetermined Poisoning 887	Suicide Poisoning 1,089	Homicide Firearm 1,447	Suicide Poisoning 1,459	Adverse Effects 2,902	Suicide Suffocation 13,075
7	Undetermined Unspecified 37	Homicide Other Spec., Classifiable 49	Homicide Suffocation 15	Unintentional Fire/Burn 56	Suicide Poisoning 463	Suicide Poisoning 788	Undetermined Poisoning 792	Unintentional Fall 1,248	Homicide Firearm 824	Unintentional Poisoning 2,871	Unintentional Suffocation 6,946
8	Homicide Suffocation 26	Homicide Firearm 44	Homicide Cut/pierce 14	Suicide Poisoning 39	Undetermined Poisoning 280	Unintentional Drowning 479	Unintentional Fall 522	Undetermined Poisoning 887	Unintentional Suffocation 811	Unintentional Fire/Burn 1,278	Unintentional Unspecified 6,606
9	Unintentional Natural/ Environment 18	Unintentional Natural/ Environment 34	Unintentional Firearm 14	Unintentional Poisoning 39	Homicide Cut/Pierce 266	Homicide Cut/Pierce 404	Unintentional Drowning 397	Unintentional Drowning 451	Adverse Effects 773	Suicide Poisoning 1,111	Suicide Poisoning 6,554
10	Three Tied 16	Unintentional Firearm 31	Two Tied 13	Unintentional Suffocation 35	Unintentional Fall 212	Unintentional Fall 351	Homicide Cut/Pierce 337	Unintentional Suffocation 441	Undetermined Poisoning 732	Suicide Suffocation 919	Adverse Effects 4,459

Data Source: National Center for Health Statistics (NCHS), National Vital Statistics System.
Produced by: National Center for Injury Prevention and Control, CDC using WISQARS™.

Figure 19.2 Ten leading causes of injury deaths by age group in the United States (2017), highlighting unintentional causes. (From Centers for Disease Control and Prevention. Available at https://www.cdc.gov/injury/wisqars/LeadingCauses.html. Accessed December 31, 2019.)

Table 19.1 Crude Death Rates by Mechanisms, All Ages (United States 2017)[a]

Mechanisms	Number of Deaths	Crude Death Rate (per 100,000 Population)
All Injury Mechanisms	**243,039**	**74.6**
Drug poisoning	70,237	21.6
Firearm	39,773	12.2
Motor vehicle, traffic	38,659	11.9
Fall	37,587	11.5
Suffocation	20,689	6.4
Nondrug poisoning	5,117	1.6
Drowning	4,508	1.4
Fire/Flame/Thermal	3,398	1.0
Cut/Pierce	2,758	0.9
Transport, all other	2,418	0.7
Pedestrian, pedal cyclist	1,315	0.4
Struck by/against	1,035	0.3
All other mechanisms	15,545	4.8

[a]Data obtained from the Centers for Disease Control and Prevention, Wide-ranging ONline Data for Epidemiologic Research (WONDER). Compressed mortality file. Available at https://wonder.cdc.gov/mortSQL.html. Accessed December 31, 2019.

BIOMECHANICS OF INJURY

At the most basic level, injuries are caused by energy transfer that results in deformation and damage of bodily tissues. In general, mechanisms of injury are categorized as penetrating (e.g., stab and gunshot wounds), blunt (e.g., falls and MVCs), or thermal (e.g., flame burns and electrocution). Penetrating trauma causes injury to the tissues that are in the path of the foreign body, whereas blunt trauma causes damage either through crush or by shear forces. Different types of energy transfer will result in different classically described patterns of injury. Understanding this link between the mechanisms of energy transfer and their associated patterns of injury will greatly aid the initial patient evaluation and subsequent management priorities in the prehospital setting, the trauma bay, the operating room, and the intensive care unit (ICU).

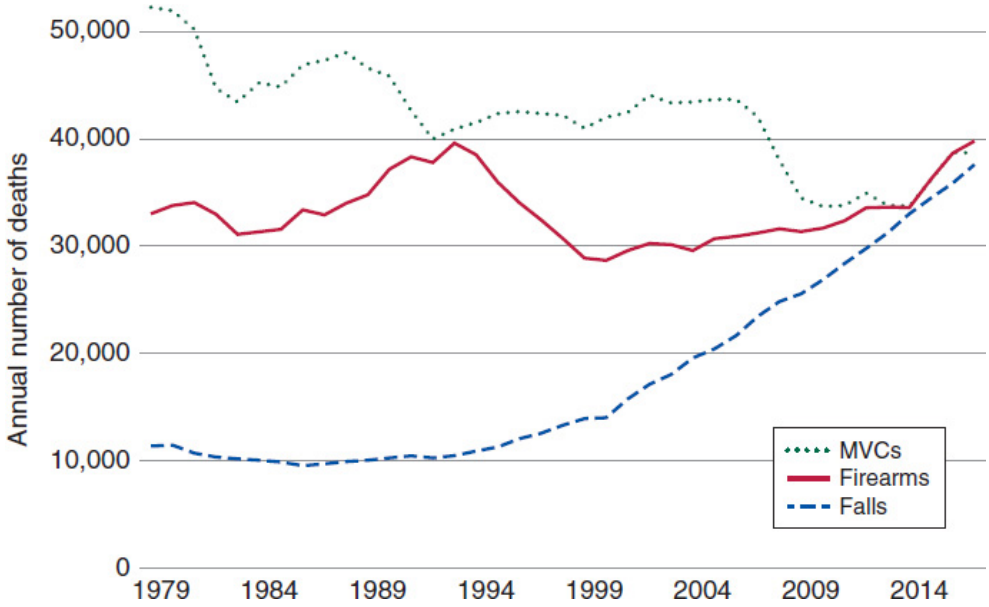


Figure 19.3 Top three causes of injury-related mortality over time in the United States. (From Centers for Disease Control and Prevention, Web-based Injury Statistics Query and Reporting System. Fatal injury data. Available at https://www.cdc.gov/injury/wisqars/fatal.html. Accessed December 31, 2019.)

Blunt trauma is best understood by applying the rules of kinetic energy transfer: KE = $(M \times V)/2$, where KE is kinetic energy, M is mass of the object, and V is velocity. Thus, a head-on collision between two large sport utility vehicles (approximately 6,000 lb each) traveling at 65 mph can

generate enormous amounts of forces. Various safety mechanisms in the modern vehicles direct this force away from the occupants of the vehicle, but the clinicians have a tendency to underappreciate the forces and the vectors involved in the collision. With frontal impact, the vehicle stops abruptly, and the occupants continue to move forward (if not belted) and either hit the steering wheel or slide under to hit their knees against the dashboard, resulting in classically described injury patterns (**Fig. 19.7**). In a rear impact, the kinetic injury generated depends upon the differences between the velocities of the two vehicles, and the occupant of the front vehicle abruptly accelerates forward, resulting in cervical spine hyperextension ("whiplash"). Lateral impact imparts rotational forces and often results in significant protrusion of the passenger compartment. In addition to limb trauma, this can result in major torso (chest, abdomen, and pelvis) injuries. The rotational forces are also more likely to cause torsion injury, where the mobile areas join relatively fixed structures (e.g., aortic laceration, cervical spinal ligamentous injuries). Rollover crashes are especially dangerous as the vehicle is impacted from various angles repeatedly during the process. The occupants of the vehicle are thrown around and may even be ejected from the vehicle. Ejection increases the chances of death by approximately 10-fold. Similarly, death of another occupant is considered a high-risk event, as it is a surrogate for the severity of impact or the complexity of the forces involved. The clinician also must specifically look for clinical evidence of energy transfer. For example, a "seat belt" sign across the abdomen must raise suspicion for energy transfer across the bowel, mesentery, pancreas, and the lumbar spine. Similarly, wedge fracture of L1 vertebra in this setting mandates ruling out a pancreatic injury as the pancreatic body drapes across the anterior aspect of L1. In fact, orthopedic injuries should be considered markers of kinetic energy transfer and make the clinicians proactively look for injuries to adjacent organs, nerves, vessels, and tendons (**Table 19.2**).

Penetrating injuries result in either lacerations or puncture wounds. Lacerations are usually straightforward, as the structures in the depth of the wound can be examined and injuries to critical organs ruled out by careful visual inspection. Conversely, low-energy puncture wounds (e.g., stab wounds) often present a greater challenge when it comes to ruling out occult injury to deeper structures. For example, a stab wound to the neck[14] can cause injuries to the airway, esophagus, blood vessels, thyroid gland, or

intrathoracic organs. In the absence of obvious vascular or aerodigestive tract injury, a complete workup may include a computerized tomographic (CT) scan to evaluate the blood vessels in the neck, laryngoscopy and bronchoscopy to evaluate for a missed airway injury, and both a video esophagoscopy and a confirmatory esophagram to rule out an occult esophageal injury. Stab wounds to the trunk may be characterized as involving the anterior abdominal wall, the back/flank, the thoracoabdominal area, or the chest.[15,16] Diagnostic and operative decision making is driven by the likelihood of underlying injury. For hemodynamically normal patients with stab wounds to the anterior abdominal wall, the decision to operate is based on evidence of intraperitoneal penetration.[15] Flank stab wounds may involve retroperitoneal structures that will not elicit peritonitis on examination and thus often require evaluation with a CT scan enhanced with intravenous (IV), oral, and rectal contrast.[15] Hemodynamically normal patients with stab wounds to the chest often mandate a placement of a chest tube and close evaluation of both initial and ongoing chest tube outputs.[16] In all three scenarios, a hemodynamically abnormal patient is assumed to have uncontrolled hemorrhage and should thus be immediately taken to the operating room for emergency exploration and prompt hemorrhage control.[14–16]

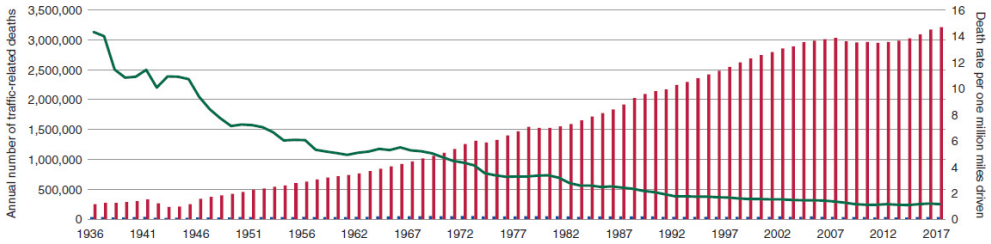


Figure 19.4 Motor vehicle–related fatalities over time in the United States. (From U.S. Department of Transportation, National Highway Traffic Safety Administration. Fatal motor vehicle crashes: overview. Available at https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/812826. Accessed December 31, 2019.)

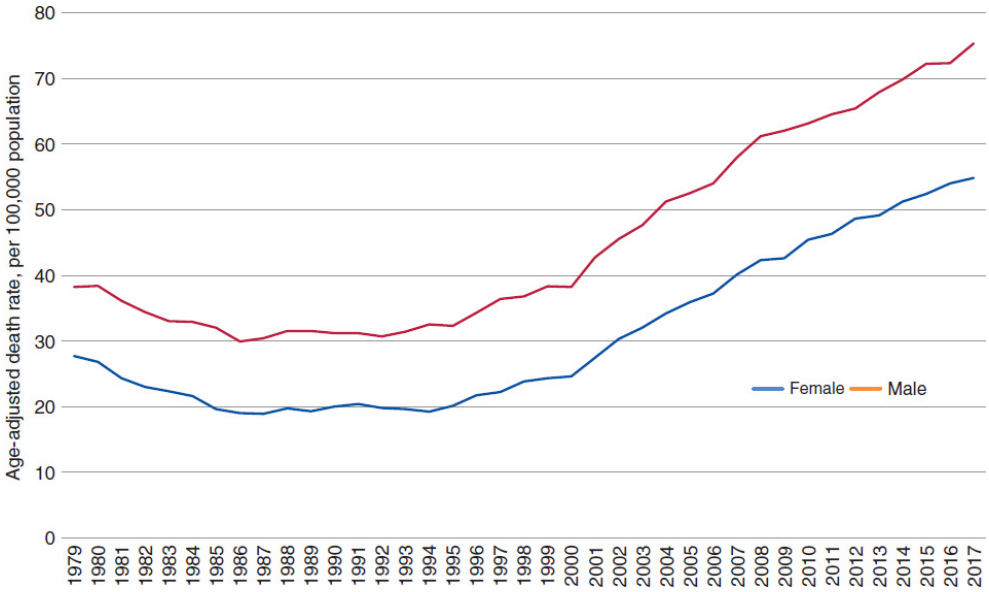


Figure 19.5 Age-adjusted death rates from unintentional falls for ages 65 years and older, by sex. The figure is a line graph showing the age-adjusted death rate for unintentional falls among males and females 65 years and older from 1979 to 2017. (From Centers for Disease Control and Prevention, Web-based Injury Statistics Query and Reporting System. Fatal injury data. Available at https://www.cdc.gov/injury/wisqars/fatal.html. Accessed December 31, 2019.)

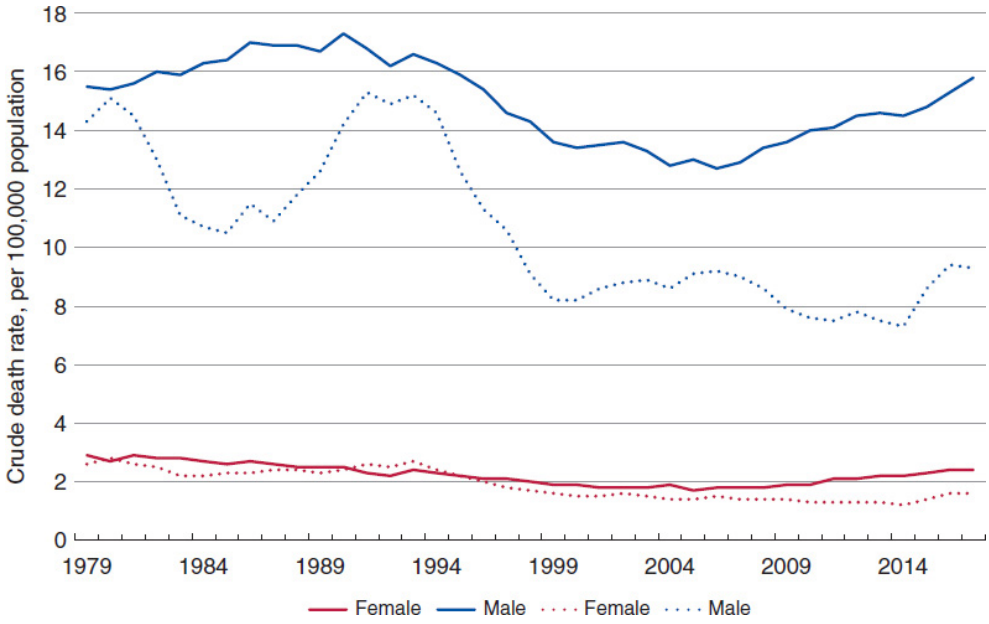


Figure 19.6 Gun-related crude death rates for ages 15 years and older, by sex. *Solid lines* represent gun suicide rates, and *dotted lines* represent gun homicide rates. Gun-related death rates fell dramatically from a peak in the early 1990s through the mid-2000s. Since 2013, however, gun-related death rates are now increasing. (From Centers for Disease Control and Prevention, Web-based Injury Statistics Query and Reporting System. Fatal injury data. Available at https://www.cdc.gov/injury/wisqars/fatal.html. Accessed December 31, 2019.)

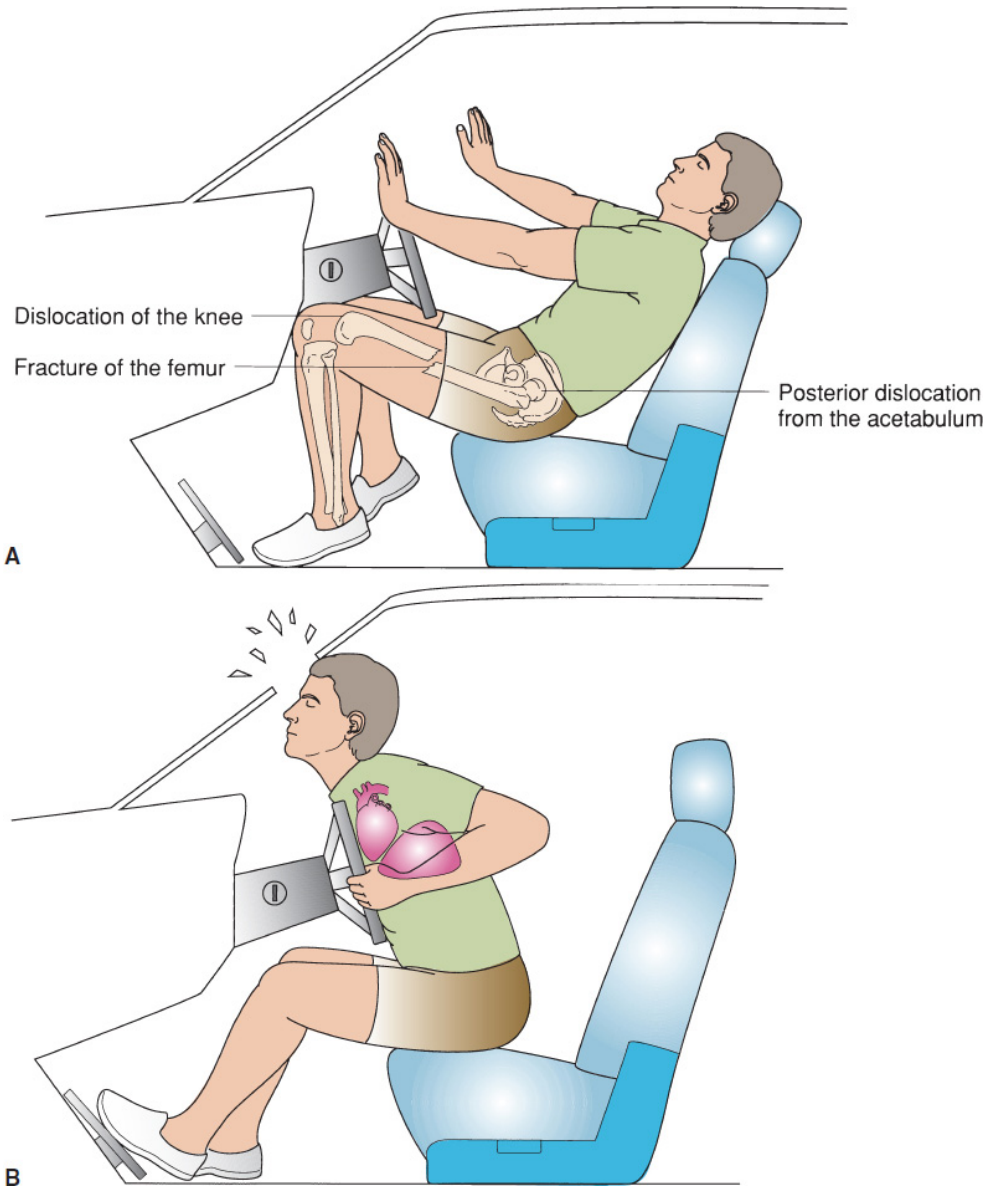


Figure 19.7 **A, B:** Frontal deceleration impact.

Bullet wounds differ from stab wounds not only in the fact that the bullets impart significant kinetic energy depending upon their velocity and weight (**Table 19.3**) but they can also cause "cavitation" effect. Cavitation occurs as tissues impacted by the bullet recoil and transmit the kinetic energy outward, creating a cavity due to the rapid acceleration and deceleration. This can injure organs/tissues that are adjacent to the bullet track even if not hit directly by the projectile. In addition to the kinetic energy, the actual area of injury is influenced by factors such as profile of the bullet, tumble (spin and yaw), and fragmentation. A jacketed bullet does not deform much, whereas a

hollow point bullet fragments, spreads, and deforms (increasing the area of damage). Similarly, tumbling of the bullet increases the area of energy exchange and much larger zone of damage. Generally, low-velocity (<1,200 ft/sec) or medium-velocity (1,200 to 2,000 ft/sec) firearms are more common in urban trauma, with high-velocity wounds seen typically in combat settings. The cavitation effect is significantly more pronounced in high-velocity injuries, and the kinetic energy differences translate into a much larger area of destruction, more devitalized tissues, and contamination (cavitation can pull in debris, clothes, etc., into the wound). Injuries to multiple organs and structures, even in different body cavities, are possible with bullet wounds. For example, a bullet injury to the anterior wall of the stomach can easily pass through the posterior wall, through the pancreas, duodenum, vena cava, and the kidney, depending upon the trajectory. While trying to determine the trajectory, it is important to *not* assume that the subject was in a "normal" anatomical position (standing straight front facing with arms by his or her side) when shot. Typically, victims assume a variety of odd positions in an effort to avoid getting hit. In addition, bullets do not necessarily travel in a linear track and can bend and bounce off in atypical directions. Thus, gunshot wound to the chest can easily result in injuries not only in the chest (ipsilateral or contralateral) but also in the abdomen, pelvis, or the neck depending upon the course of the projectile. It is also wrong to notice two holes and assume that they represent a through and through gunshot wound. It is equally likely to be two separate gunshot wounds, with both bullets still inside the body. As a general rule, the number of gunshot wounds and the number of retained bullets should add up to an even number; otherwise, you are missing either a hole or a bullet. Even in critically ill patients, quick x-rays of the chest/abdomen/pelvis, as a "bullet survey," can be very helpful before rushing to the operating room. This information can be critically important in planning the surgical approach and in deciding which body cavity to tackle in what sequence.[17]

Table 19.2 Patterns of Injury to the Head, Neck, Trunk, and Extremities Associated with Orthopedic Injuries

Diagnosed Injury	Associated Injury
Fracture—temporal, parietal bone	Epidural hematoma
Maxillofacial fracture	Cervical spine fracture
Sternal fracture	Cardiac contusion
First and second rib fracture	Descending thoracic aorta, intra-abdominal bleeding
Fractured scapula	Pulmonary contusion
Fractured ribs 8–12, right	Lacerated liver
Fractured ribs 8–12, left	Lacerated spleen
Fractured pelvis	Ruptured bladder, urethral transection
Fractured humerus	Radial nerve injury
Supracondylar humerus	Brachial artery injury fracture
Distal radius fracture	Median nerve compression
Supracondylar femur fracture	Popliteal artery thrombosis
Anterior dislocation shoulder	Axillary nerve injury
Posterior dislocation of hip	Sciatic nerve injury
Posterior dislocation of knee	Popliteal artery thrombosis

IMMEDIATE, EARLY, AND LATE DEATHS AFTER INJURY

Although life-threatening injuries result from a variety of blunt and penetrating mechanism, deaths tend to occur in a well-described temporal

pattern and due to only a few underlying causes. The classical trimodal distribution of trauma deaths was first described by Trunkey[18] in 1983, based on the patterns of posttraumatic deaths in several counties of Northern California. In that report, nearly half of the deaths occurred within minutes after injury due to disruption of major blood vessels, devastating central nervous system (CNS) injuries, or a combination. A smaller second peak, lasting a few hours, followed that first major peak in mortality (approximately 30% of the deaths) where depending upon the mechanism of trauma, ongoing hemorrhage and CNS injuries played an almost equal role. The third peak was noted days to weeks after injury due to infections, multiple-organ failure (MOF), and various late complications. An understanding of these patterns of death has led to significant advances in the arenas of injury prevention, trauma systems development, early hemorrhage control, balanced resuscitation, avoidance of trauma-associated coagulopathy (TAC), and improvements in surgical critical care.

Table 19.3 Muzzle Velocity, Kinetic Weight of Projectile, and Approximate Maximum Kinetic Energy of Frequently Used Firearms

Description (Caliber)	Projectile Weight (g)	Muzzle Velocity (ft/sec)	Kinetic Energy (ft/lb)
Pistols			
.22 Short	.29	.1,000	.72
.38 Special	.158	.870	.263
9-mm Luger	.125	.1,150	.440
.45	.250	.860	.410
.357 Magnum	.158	.1,430	.695
.44 Magnum	.240	.1,470	.1,150
Rifles			
.22 Long	.40	.1,150	.150
.56-mm M-16	.55	.3,200	.1,248
.30-30 Winchester	.170	.2,200	.1,830

"Immediate deaths" that occur within first few seconds to minutes after injury will only be avoided by altering the nature and severity of the energy transfer to the body or by prevention of the injury altogether. As mentioned earlier, improved roads, safer car design, increased seat belt use, and enforcement of speeding and drunk driving laws result in thousands of avertable deaths each year.[5–8] For MVCs that do occur, these same factors may reduce the energy transfer to the body and convert what would have been an instantly fatal injury into a survivable injury that can be attended to by modern trauma care. Based on a recent multi-institutional review of preventable trauma deaths by the Western Trauma Association,[19] 60% of preventable prehospital deaths were due to hemorrhage and 30% were due to

neurotrauma. As more patients survive the first few moments of injury and as prehospital transfer to definitive care improves, opportunities to reduce preventable deaths exist in the prehospital setting, the trauma bay, the operating room, and early intensive care.

"Early deaths," those occurring within the first 1 to 24 hours after injury, are overwhelming due to exsanguination and traumatic brain injury (TBI).[20–23] Of these two conditions, bleeding is clearly more treatable, 3 which makes it the number one cause of *preventable* deaths. If patients can survive these first few hours, modern data show that even among massively bleeding patients (without head injuries), mortality beyond the first 24 hours is only approximately 10%.[24] Although there is still a great deal of work to do in reducing preventable mortality among this patient population, tremendous advances in survival have been made among patients at risk of "early death" due to massive hemorrhage primarily due to reducing early exsanguination from hemorrhage and reducing TAC.

The most fundament way to prevent early death from exsanguination is definitive hemorrhage control. The location of hemorrhage dictates the most effective modality of definitive control. For example, most bleeding extremity wounds can be classified as compressible hemorrhage. Serious but survivable extremity injuries can lead to death by exsanguinating in a matter of minutes if not addressed. However, these life-threatening injuries can be temporized with direct pressure, the use of hemostatic gauze and topical agents, and tourniquets. Early containment of compressible hemorrhage is the basis of the "Stop the Bleed" course run by the American College of Surgeons-Committee on Trauma (ACS-COT), which teaches members of the public to act as first responders to prevent death secondary to compressible hemorrhage.[25] Noncompressible life-threatening hemorrhage in the chest, abdomen, retroperitoneum, or pelvis is a far greater challenge and requires definitive treatment in the operating room. Interventions such as a resuscitative thoracotomy or the emerging use of retrograde endovascular balloon occlusion of the aorta (REBOA) are only meant to reduce exsanguination long enough to enable definitive control of the source of intracavitary bleeding.

The reduction in early deaths among bleeding patients is also driven by prevention and correction of TAC. Appropriate resuscitation with whole blood, component blood therapy, IV fluids, and other medications that impact

the body's coagulation and fibrinolytic pathways is critically important before, during, and after obtaining definitive hemorrhage control.[26,27] Over the past few decades, valuable lessons have been learned from advances in military trauma care and Department of Defense–funded research, which have improved our ability to both treat and even prevent TAC. For example, shifting from salt-based solutions (crystalloids) to balanced resuscitation with blood components, or even whole blood, has led to less TAC and better outcomes.[28] Blood is a complex fluid that contains thousands of proteins, cells that carry oxygen to the tissues (red blood cells) and generate clot to stop bleeding (red blood cells and platelets), various clotting factors, buffers, enzymes, and hormones. As crystalloids lack all of these, their administration results in rapid dilution of cells, clotting factors, and proteins, which can worsen bleeding. 4 Thus, aggressive crystalloid resuscitation, especially in the absence of early hemorrhage control, is impractical, inadequate, and potentially harmful in many circumstances.[27–31]

Once in the operating room, early deaths are avoided by continued prioritization of hemorrhage control and avoidance of TAC. Although an in-depth description of operative decision making in trauma is outside of the scope of this introductory chapter, the basic principles of the trauma laparotomy include prepping and draping from chin to knees and from table to table, rapid entry into the abdominal cavity, early control of bleeding, temporary control of contamination, exploration of the entire intra-abdominal cavity, and finally either definitive repair of injured structures or a damage control operation with temporary abdominal closure. "Damage control laparotomy" refers to an abbreviated laparotomy focused on hemorrhage control and temporary control of contamination, followed by temporary abdominal closure, resuscitation in the ICU, and a return to the operating room for definitive management within 24 to 48 hours.[32,33] This serves to reduce the likelihood of entering the deadly "bloody vicious cycle" of uncontrolled acidosis, coagulopathy, and hypothermia[34] that will develop when the severely injured patient undergoes a prolonged operation. Common indications for a damage control operation are found in **Table 19.4**.

Finally, some of the most obvious gains in injury-related mortality reduction have occurred among the so-called "late deaths" occurring weeks to months after injury. In more contemporary studies, the trimodal distribution has now evolved into a predominately bimodal distribution, where 61% of

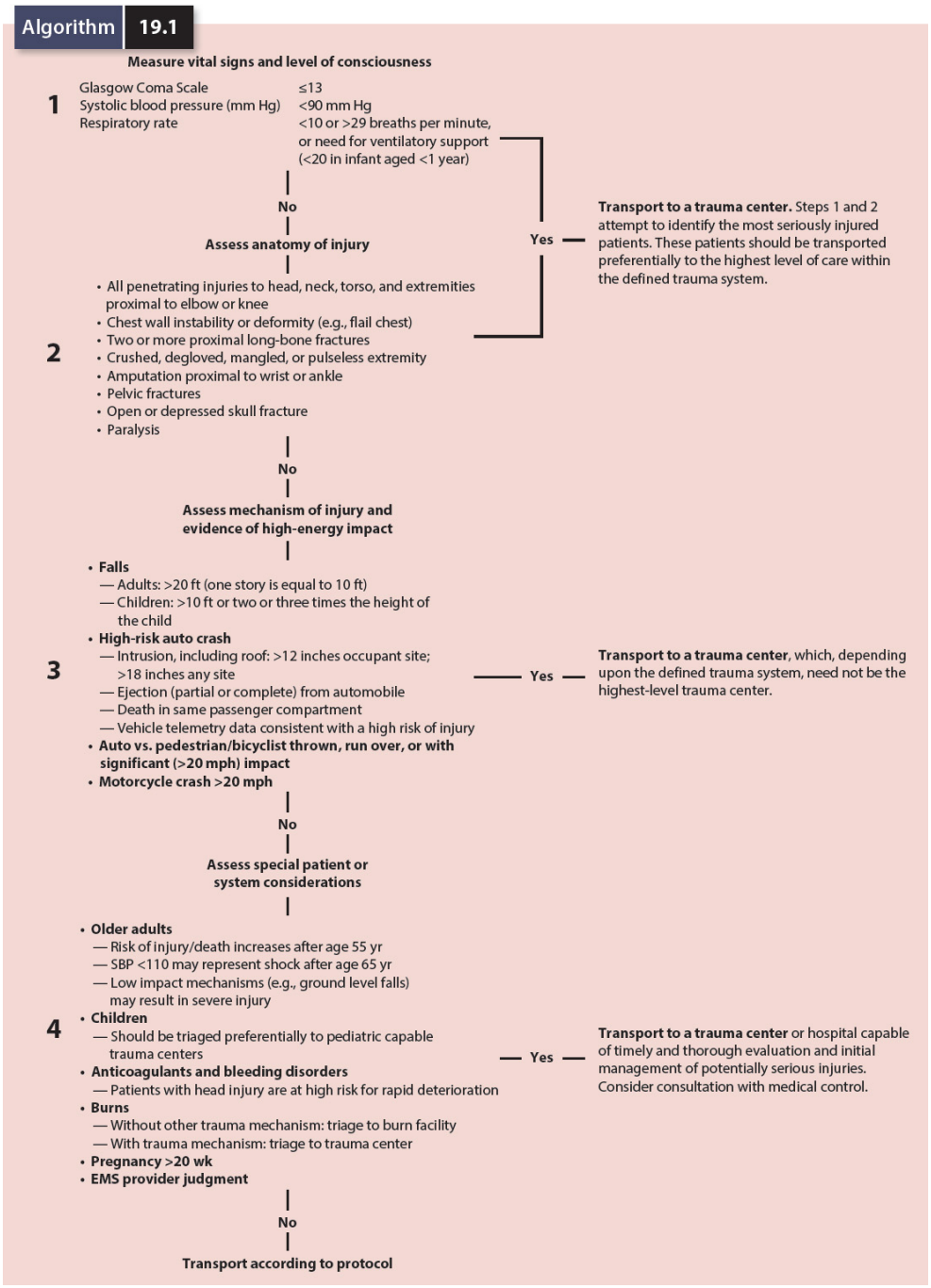
the deaths are immediate, 29% early, and only 10% are late.[35] Compared with the classical description, the percentage of immediate deaths remained unchanged and early deaths occurred much earlier (median 52 vs. 120 minutes). However, unlike the classical trimodal distribution, the late peak has markedly diminished, most likely due to significant improvements in surgical intensive care. Mortality rates for many of the reasons for late death are rapidly dropping with wider adoption of best care practices for managing critical care illnesses.[36–38] For example, due to more judicious resuscitation practices, severe respiratory failure after trauma has become a fairly rare occurrence.[39] Clearly, critical care is resource intensive and adds significantly to our health care costs, but it has "flattened" the third peak. In other words, not only the incidence of late complications has dropped but also our ability to "rescue" patients has markedly improved even if they develop the complications. This predominately bimodal distribution of trauma deaths was reiterated by a recent multinational trial of more than 5 20,000 patients,[40] which once again demonstrated that the majority of deaths (even in developing and underdeveloped countries) occur within a few hours after injuries, with <2.5% of the injured succumbing to MOF.

Table 19.4 List of Proposed Indications for Damage Control, Including Range of Values Reported in Various Articles

1. Core temperature <35°C (34°–35°C)
2. pH <7.20 (7.10–7.30)
3. Base deficit >14
4. Systolic blood pressure persistently <80 mm Hg (70–90 mm Hg)
5. Blood transfusion >10 units packed red blood cells
6. Estimated blood loss >4 L
7. Operating room fluid replacement >10 L
8. Associated life-threatening injuries in second anatomical location
9. Vascular injuries in inaccessible locations
10. Inability to close the abdomen due to visceral edema
11. Clinical evidence of coagulopathy (nonsurgical bleeding)

FIELD TRIAGE DECISIONS AND EARLY PRIORITIES

Broadly speaking, the trauma patients can be divided into three categories: patients with (a) rapidly fatal injuries, (b) potentially fatal injuries, and (3) all others. A key component of effective prehospital triage is to properly place the injured into these categories based on the available data (mechanism of injury, age of the patient, comorbid diseases, physiologic status, and injury patters) and then make a rapid decision about what type of facility is the most appropriate for the patient. The ACS-COT has developed detailed criteria for designating hospitals into different levels depending upon the resource availability, from the highest (level 1) to the lowest (level 4). These criteria can easily be found in the Resources for Optimal Care of the Injured Patient—2014.[41] Working with the CDC, the ACS-COT has also developed a guideline for the prehospital triage of the injured patients (**Algorithm 19.1**).[42] The document also contains very detailed guidelines about which patients should be transferred from lower-level to higher-level trauma centers (**Table 19.5**).[41] Appropriate and timely triage to the right facility saves lives. Results from the National Study on the Costs and Outcomes of Trauma were published in *The New England Journal of Medicine* (*NEJM*) in 2006 and demonstrated that 6 treatment at a level 1 trauma center, compared to treatment at a nontrauma center, was associated with a 20% lower odds of death—with even larger benefits among those with more severe injuries.[43]



Algorithm 19.1 2011 Guidelines for the field triage of the injured patients. (From Sasser SM, Hunt RC, Faul M, et al; Centers for Disease Control and Prevention. Guidelines for field triage of injured patients: recommendations of the National Expert Panel on Field Triage, 2011. *MMWR Recomm Rep* 2012;61(RR-1):1–20. Available at https://stacks.cdc.gov/view/cdc/23038/Share. Accessed December 31, 2019.)

Table 19.5 Criteria for Consideration of Transfer from Level 3 Centers to Level 1 or 2 Centers

1. Carotid or vertebral arterial injury
2. Torn thoracic aorta or great vessel
3. Cardiac rupture
4. Bilateral pulmonary contusion with PaO_2:FiO_2 ratio <200
5. Major abdominal vascular injury
6. Grade IV or V liver injuries requiring transfusion of >6 units of red blood cells in 6 hrs
7. Unstable pelvic fracture requiring transfusion of >6 units of red blood cells in 6 hrs
8. Fracture or dislocation with loss of distal pulses
9. Penetrating injuries or open fracture of the skull
10. Glasgow Coma Scale score of <14 or lateralizing
11. Spinal fracture or spinal cord deficit
12. Complex pelvis/acetabulum fractures
13. More than two unilateral rib fractures or bilateral rib fractures with pulmonary contusion (if no critical care consultation is available)
14. Significant torso injury with advanced comorbid disease (such as coronary artery disease, chronic obstructive pulmonary disease)

Data from American College of Surgeons, Committee on Trauma. Resources for Optimal Care of the Injured Patient 2014.

In concert with appropriate triage, the key priorities during the prehospital phase are the ABCs (airway, breathing, and circulation) of trauma care, with a major focus on hemorrhage control and appropriate resuscitation. In patients who are in hemorrhagic shock but are breathing and maintaining adequate airway/oxygenation, intubation and mechanical ventilation should be avoided (especially for short prehospital times) as administration of sedating drugs and an increase in the intrathoracic pressure (due to positive pressure ventilation) further decrease the preload, which could precipitate an arrest. Judicial administration of crystalloid fluids is acceptable, but aggressive fluid resuscitation in the absence of hemorrhage control can worsen outcomes. In a landmark 1994 study published in *NEJM*, hypotensive

patients with *penetrating injury to the torso* were randomized to routine fluid resuscitation or resuscitation was delayed until bleeding had been surgically controlled.[30] The results showed a survival advantage in the delayed resuscitation group (70% vs. 62%, $p = 0.04$). In fact, a systematic analysis of all the published data failed to find any support in favor of (or against) large-volume crystalloid resuscitation in bleeding trauma patients.[44] As these studies had focused on young patients with penetrating trauma, the question remains whether these findings can be generalized to the blunt trauma population. The blunt trauma patients are typically older, may have a higher incidence of coronary and carotid stenosis, and about 20% to 30% have associated TBI (which can worsen due to hypotension). Furthermore, as opposed to penetrating trauma, the sources of bleeding can be multiple and not always surgically correctable in the blunt trauma victims. Because of all these reasons, limited volume ("controlled") resuscitation rather than no resuscitation is logical in this population. This is also supported by an early pilot prospective randomized trial where 192 patients with an out-of-hospital systolic blood pressure (SBP) of 90 mm Hg or lower were randomized to receive controlled resuscitation (CR) or standard resuscitation (SR).[45] While the SR group received 2 L initially and additional fluid as needed to maintain an SBP of ≥110 mm Hg, the CR patients received 250 mL of fluid if they had no radial pulse or an SBP of <70 mm Hg, and additional 250-mL boluses were given only to maintain a radial pulse or an SBP of ≥70 mm Hg. This protocol was maintained until hemorrhage control or 2 hours after arrival in the hospital. The results showed that among the cohort of patients with blunt trauma, 24-hour mortality was 3% and 18% in the CR and SR groups, respectively, with an adjusted odds ratio of 0.17 (0.03 to 0.92).[45] At present, published data only support careful small-volume crystalloid resuscitation to keep the injured alive during transport and aggressive crystalloid resuscitation should be avoided. New data are now emerging regarding the role of prehospital administration of component blood products. In the Control of Major Bleeding After Trauma (COMBAT) trial, plasma-first resuscitation was not shown to have a survival benefit in a single-center randomized trial at a large urban trauma center.[46] In the multicenter, cluster-randomized Prehospital Air Medical Plasma (PAMPer) trial, 501 hypotensive patients requiring air medical transport were randomized to 2 units of thawed plasma or SR.[47] The group receiving plasma had a 24-hour

mortality of 23.2%, while the SR group had a mortality of 33.0% ($p = 0.03$). The plasma group also had a lower 30-day mortality rate and a shorter time to normal coagulation parameters ($p < 0.05$ for both). Notably, subsequent secondary analyses from two randomized prehospital plasma trials have demonstrated that the survival benefits of prehospital plasma are primarily in the blunt trauma patients and not evident in patients with penetrating injuries.[48] Also, the duration of the prehospital transport is a critical variable, and plasma resuscitation is associated with a survival benefit when transport times are longer than 20 minutes.[49] Further work in this area is ongoing.

While these advances are promising, for now, rapid transport to a specialized trauma center ("scoop and run") appears to be the most reasonable strategy in urban environments where the transport times are relatively short. In fact, a prospective comparison between Advanced Life Support (ALS) and Basic Life Support (BLS) transport[50] showed that patients transported by ALS units more often underwent prehospital interventions (97% vs. 17%; $p < 0.01$), including endotracheal intubation, needle thoracostomy, cervical collar, IV placement, and crystalloid resuscitation. While ALS ambulance on-scene time was significantly longer than that of BLS ($p < 0.01$) and had more prehospital interventions (1.8 ± 1.0 per ALS patient vs. 0.2 ± 0.5 per BLS patient; $p < 0.01$), 69.5% of ALS patients and 88.4% of BLS patients ($p < 0.01$) survived to hospital discharge. The message is clear—Less is more in the prehospital arena, and time to definitive care is the most critical variable. Other studies also support the argument that rapid transport to the trauma center is more important than prehospital interventions in urban victims of penetrating trauma.[51]

EARLY HOSPITAL CARE AND PRIORITIES

The Advanced Trauma Life Support (ATLS) program has put together a systematic, concise approach to the care of a trauma patient.[52] ATLS was developed by the ACS-COT and was first introduced in 1980 and is now taught in 60 countries across the world. The ATLS program provides

participants with a safe, reliable method for immediate management of the injured patient and the basic knowledge necessary to:

1. assess the patient's condition rapidly and accurately.
2. resuscitate and stabilize the patient according to priority.
3. determine if the patient's needs exceed a facility's capacity.
4. arrange appropriately for the patient's interhospital transfer (who, what, when, and how).
5. ensure that optimum care is provided and that the level of care does not deteriorate at any point during the evaluation, resuscitation, or transfer process.

The basic concepts of ATLS include a primary survey focusing on the ABCDE (airway, breathing, circulation, disability, and exposure) to identify and address the life-threatening issues, followed by a secondary survey to identify all the injuries. The specific treatments of various injuries have been addressed in the different chapters that follow. However, the key points to emphasize are that the two main killers during the early hospital period ("golden hour") are the same as those in the prehospital setting—*bleeding and TBI.* As treatments of TBI remain mostly supportive, bleeding remains the number one cause of *preventable* deaths during the first 6 hours following trauma. In a bleeding patient, the priorities are to identify and control the source of bleeding in the shortest possible period of time. Sometimes the bleeding source is obvious and can be controlled by direct compression (e.g., stab wound to the femoral artery in the groin), tourniquets (e.g., mangled extremity), or sutures (e.g., scalp laceration), but often it is inside a body cavity. Localization of the hemorrhage source is relatively easy for penetrating trauma that is limited to a specific body region but is notoriously difficult in the blunt polytrauma patients. In these patients, it helps to remember that a person can only lose significant volumes of blood in five locations: (1) pleural space, (2) intra-abdominal, (3) pelvis/retroperitoneal space, (4) soft tissues at the site of long bone fractures/sheer injuries, and (5) externally. With a quick examination and a chest x-ray, three of these possibilities can be easily ruled out, and the choice typically comes down to deciding between the abdomen and the pelvis. If the pelvic x-ray shows a significant pelvic fracture, then the possibility of pelvic bleeding source is significant, and a pelvic binder should be applied promptly (or pelvis

wrapped tightly with a sheet) for appropriate fracture patterns (e.g., suitable for open book fracture but potentially harmful for severe lateral compression). Focused assessment with sonography for trauma (FAST) can also be helpful in determining the source of hemorrhage. If it shows free fluid in the abdomen in a hypotensive patient, then emergent laparotomy for hemorrhage control is justified. While the reported false-negative rate in the literature has been reported to be as low as 2%,[53] others have reported a significant false-negative rate even in experienced hands.[54] Although diagnostic peritoneal lavage has largely been abandoned, a bedside diagnostic peritoneal aspiration (DPA) can be very helpful in these patients. Percutaneous DPA can be performed in 1 minute, and it has been shown to be accurate, safe, and superior to FAST for the diagnosis of abdominal blood as the source of hemodynamic instability in multitrauma patients.[55]

In addition to hemorrhage control, massive transfusion protocol (MTP) should be activated in patients who are actively bleeding to avoid development of TAC. Normal coagulation homeostasis depends on a delicate balance between clot formation and breakdown. Normally, trauma tilts the balance in favor of clot formation at the site of injuries to stop the bleeding. However, major injuries, excessive blood loss, prolonged tissue hypoperfusion, and TBI with disruption of the blood–brain barrier have all been shown to upset the normal coagulation homeostasis, resulting in TAC.[56,57] This can manifest as abnormal clot formation and/or excessive or rapid clot breakdown (fibrinolysis). Unless treated promptly, this coagulopathy leads to further bleeding, which sets up a vicious cycle resulting in the "lethal triad" of coagulopathy, acidosis, and hypothermia that is associated with an extremely high mortality.[34,58] An analysis of TAC suggests that depletion coagulopathy results in abnormalities of traditional coagulation parameters (international normalized ratio, partial thromboplastin time) and predicts mortality whereas fibrinolytic coagulopathy predicts infection, end-organ failure, and mortality, without a detectable difference in international normalized ratio or partial thromboplastin time.[59]

Damage control resuscitation (DCR) or hemostatic resuscitation has recently emerged as a potential solution for the prevention and reversal of TAC.[29,60,61] This approach advocates early hemorrhage control, permissive hypotension (until control of hemorrhage), avoidance of crystalloids, and

early use of blood components such as fresh frozen plasma (FFP) and platelets (in 1:1 or 1:2 ratios). A recent prospective randomized multi-institutional trial enrolled 680 patients with severe trauma and major bleeding to test two different blood component ratios.[24] In this study, early administration of plasma, platelets, and red blood cells in a 1:1:1 ratio compared with a 1:1:2 ratio did not result in significant differences in mortality at 24 hours or at 30 days. However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours.[24] It must be emphasized, however, that high-ratio protocols do not improve survival in patients who do not require massive transfusion (10 units of packed red blood cells [PRBCs] in 24 hours).[62] In fact, inappropriate infusion of plasma in patients who are not massively bleeding can worsen their outcomes.[63] So, while the exact ratio of PRBCs to FFP and platelets may be debatable, contemporary resuscitation practices have moved to early delivery of component therapy in the setting of massive bleeding, using standardized protocols (see later). Also, it should be emphasized that resuscitation is an adjunct to early hemorrhage control and not a substitute. In a bleeding patient, initiating DCR is a great idea, but the patient's eventual survival depends on the ability (or inability) to obtain rapid and reliable hemorrhage control. In addition, prevention and active reversal of hypothermia (e.g., use of fluid warmers, body warming devices) and correction of acidosis and hypocalcemia are critically important while resuscitation protocols are carried out.

We also know that development of a clot is just the initial part of the process, and rapid breakdown of the clot may be equally detrimental. It has been shown that development of fibrinolysis is a highly lethal event in severely injured patients,[64,65] and treatment with blood products alone is incapable of reversing this process. Despite ongoing debate about precise ratios of blood products,[66] there is general agreement that blood products should be administered in the form of an MTP to optimize the processes of care and to improve outcomes. Cotton et al.[67] tested the effectiveness of a trauma exsanguination protocol by comparing patients treated with the protocol (n = 94 over 18 months) to a cohort of similar patients admitted during the prior 18 months (n = 117). The study found that implementation of the protocol reduced 30-day mortality (51% vs. 66%, $p < 0.03$), decreased intraoperative crystalloid administration (4.9 L vs. 6.7 L, $p = 0.002$), and

reduced postoperative blood product use (2.8 vs. 8.7 units of PRBCs, $p < 0.001$; 1.7 vs. 7.9 units of FFP, $p < 0.001$; 0.9 vs. 5.7 units of platelets, $p < 0.001$). Dente et al.[68] conducted a similar study of an MTP (1:1:1 ratio of platelets, FFP, and PRBCs) by comparing matched patients during a 1-year period before and after the implementation of protocol (73 patients in the protocol group and 84 matched controls). Implementation of the protocol was found to reduce mortality in the first 24 hours (17% with MTP vs. 36% pre-MTP, $p = 0.008$) and at 30 days (34% vs. 55%, $p = 0.04$), with a more pronounced impact in the patients with blunt trauma.[68] This study also showed that MTP patients required fewer overall transfusions of PRBCs and FFP after the first 24 hours (2.7 vs. 9.3 units of PRBCs, $p < 0.0001$; 3 vs. 7.5 units of FFP, $p < 0.05$). The University of Michigan MTP is provided for reference (**Fig. 19.8**).[69] It should be emphasized that to be effective, these protocols should not only incorporate the best available evidence, which is constantly changing, but also reflect the resources and realities of the individual institutions.

LESSONS LEARNED FROM THE BATTLEFIELD

Every major war has catalyzed rapid advances in trauma care. As the medical systems grapple with the challenges of taking care of massive numbers of injured people (military and civilian), often in very austere settings, they quickly evolve, adapt, and improvise. Wars also prompt significant financial investment by the governments in research and development and attract some of the best minds to the field. Many of the things (various operative interventions, drugs, fluids, dressings, rapid transport systems, trauma teams, in-field care, and many more) that are taken for granted today in the civilian trauma centers can be traced back to the wars of the past. Interestingly, as the war medicine improves and evolves to take care of worse injuries, the war industry responds by developing more lethal weaponry. Thus, the percentage of injured who die in the battlefield (killed in action or KIA rate) has remained relatively static during the 20th century, hovering around 25% (**Table 19.6**). The current conflict is the first

time in modern warfare that the KIA rate has dropped down to 10%.[70,71] This dramatic drop is clearly multifactorial in etiology and reflects the focus on prevention strategies with widespread use of superior protective body armor and deployment of better-designed 7 military vehicles. In addition, the current ongoing conflicts have fundamentally altered how we take care of the injured, which has resulted in not only improved survival rates but also markedly superior functional outcomes. A brief list of the key advancements can be found in **Table 19.7**.

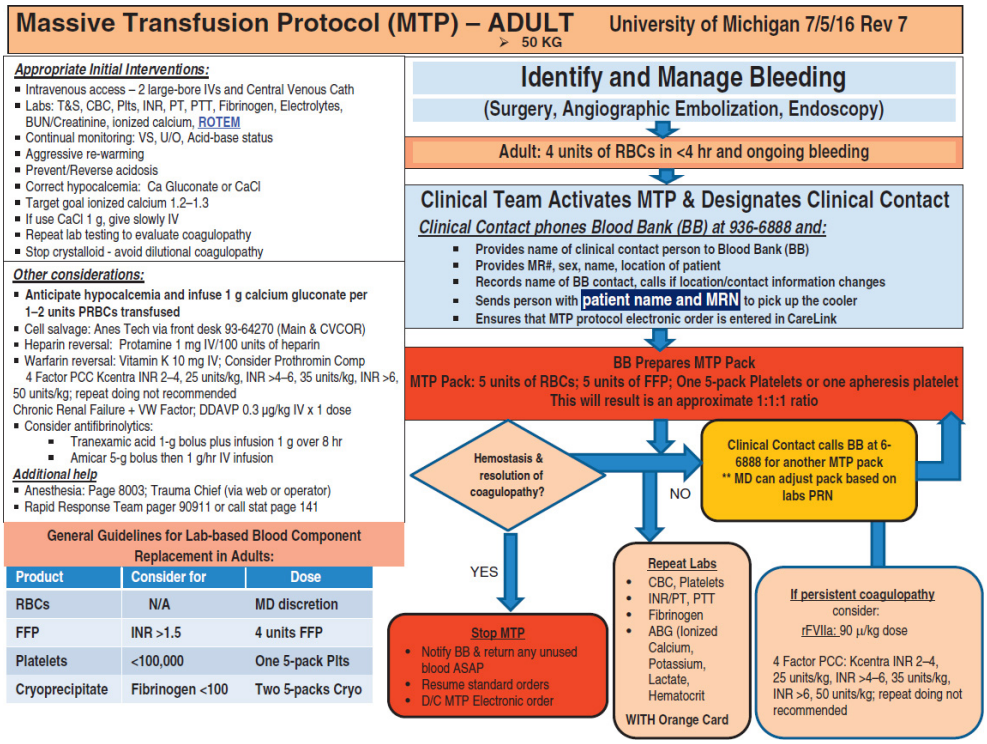


Figure 19.8 Massive transfusion protocol (MTP). BB, blood bank; BUN, serum urea nitrogen; CBC, complete blood count; Cryo, cryoprecipitate; FFP, fresh frozen plasma; INR, international normalized ratio; PCC, prothrombin complex concentrates; Plts, platelets; PRBCs, packed red blood cells; PT, prothrombin time; PTT, partial thromboplastin time; ROTEM, rotational thromboelastometry; rFVIIa, recombinant factor VIIa; T&S, type and screen; VS, vital signs; U/O, urine output; CVCOR, cardiovascular center operating room; DDAVP, desmopressin (1-desamino-8-D-arginine vasopressin); PRN, as needed (pro re nata); ABG, arterial blood gas; D/C, discontinue. (Reproduced with permission from the University of Michigan Hospitals and Health Centers. Massive transfusion protocol. https://www.pathology.med.umich.edu/static/apps/cms/ckfinder/userfiles/238/files/Massive%20Transfusion%20Protocol%202014Mar24.pdf. Accessed April 27, 2016.)

FUTURE DIRECTIONS

The future of trauma care will require novel advances at both the basic science level and the health systems level. Even with development of robust trauma systems, improvements in early hemorrhage control, a focus on balanced resuscitation, institution of MTPs, and adoption of standardized best practices in modern surgical critical care, an estimated one in five trauma deaths is still preventable. Many of these individuals have underlying injuries that are potentially survivable, but they die before getting definitive care. While resuscitation restores tissue perfusion, it does not have any specific prosurvival properties. By the time the injured gets to the hospital, nothing can be done to reverse the "irreversible shock." A much more exciting approach would be to improve the survival by administering specific pharmacologic agents in the field that could immediately upregulate prosurvival genes and proteins to create a *prosurvival phenotype*[107] or use strategies to induce a state of "suspended animation" to keep the organs preserved until the source of hemorrhage can be controlled.[108,109] In the not too distant future, early trauma resuscitation may be very different from what we currently practice due to advances in our understanding of the cellular response to injury. Promising, ongoing work suggests that one day we may see advances such as the development of specific prosurvival drugs that can be given in the prehospital setting to keep the injured alive long enough to get evacuated to higher levels of care; ability to temporarily "suspend" life using hypothermia or hibernation strategies for patients who have potentially survivable injuries, but need more time for surgery or transfer; individualized therapy with administration of specific pharmacologic agents based on the individual's cellular disturbances; and monitoring of response to therapy that goes beyond measurement of physiology and looks at the reversal of cellular disturbances.

Table 19.6 Lethality of War Wounds among U.S. Soldiers

	No. Wounded or Killed in Action	No. Killed in Action	Lethality of War Wounds (%)
Revolutionary War, 1775–1783	10,623	4,435	42
War of l812, l812–l815	6,765	2,260	33
Mexican War, 1846–1848	5,885	1,733	29
Civil War (Union Force), 1861–1865	422,295	140,414	33
Spanish–American War, 1898	2,047	385	19
World War I, 1917–1918	257,404	53,402	21
World War II, 1941–1945	963,403	291,557	30
Korean War, 1950–1953	137,025	33,741	25
Vietnam War, 1961–1973	200,727	47,424	24
Persian Gulf War, 1990–1991	614	147	24
Current conflicts,[a]	53,085	5,443	10

	2001–Jan 19, 2020

[a]Includes data reported publicly by the Department of Defense that are available at http://www.defense.gov/casualty.pdf. Accessed January 19, 2020. These data include the following military operations: Operation Iraqi Freedom, Operation New Dawn, Operation Enduring FREEDOM, Operation Enduring Freedom, Operation Inherent Resolve, and Operation Freedom's Sentinel.

From Gawande A. Casualties of war—military care for the wounded from Iraq and Afghanistan. *N Engl J Med* 2004;351:2471–2475; *U.S. Casualty Status*. Washington, DC: Department of Defense; 2004. https://www.defense.gov/casualty.pdf. Accessed January 19, 2020.

Table 19.7 Translating Lessons from Military Experience to Civilian Trauma Care

Domain of Trauma Care	Lessons from Military Experience	Translation to Civilian Trauma Care
Prevention	Improvements in body armor and armored transportation have resulted in changing injury patterns[72] and decreased case fatality rates.[73] Kevlar helmets have made otherwise lethal injuries now survivable, such that mild TBI was the most common injury from the Iraq war.[72] Mortality from direct chest trauma has fallen to 10%, with the most common injury being pulmonary contusion as opposed to lethal injury to vital organs in the chest.[73]	The Multi-Disciplinary Multi-Institutional Mortality Investigation in the Civilian Prehospital Environment (MIMIC) study is funded by the US Department of Defense and will help create reliable measures for prehospital time and distance to definitive care and also help determine which injured civilians who die before reaching the hospital had a potentially preventable cause of death.[74]
Management of Extremity Hemorrhage	Advanced hemostatic bandages were quickly developed, rigorously tested, and expeditiously deployed by the military.[75–79]	These same hemostatic dressings are now used widely for intracavitary hemorrhage control in the operating room.[80]

	Military experience demonstrated that survival rates improved markedly for casualties that had injuries suitable for tourniquets.[80]	Both advanced hemostatic dressings and windlass tourniquets are used widely by EMS first responders for temporary control of compressible or extremity hemorrhage. Increased tourniquet use in the civilian population has been associated with a survival benefit in patients with extremity vascular injuries.[81] The ACS-COT's "Stop the Bleed" course has trained over 1 million civilian first responders in the application of direct pressure, the use of advanced hemostatic dressings, and windlass tourniquets for compressible hemorrhage. Bleeding control kits are increasingly available in public places such as airports, stadiums,

		and schools, akin to automatic external defibrillators.[25]
Management of Junctional and Truncal Hemorrhage	Junctional injuries to the very proximal extremities are not amenable to windlass tourniquets, but the Combat Ready Clamp and the SAM Junctional Tourniquet have been developed and tested in the military setting.[82,83] Military and civilian collaboration has led to the development and refinement of the resuscitative endovascular balloon occlusion of the aorta (REBOA) device.[84–86] Military guidelines suggest a role for REBOA in the prehospital setting when used by advanced combat medical personnel with specialized training in an effort	Junctional tourniquet devices are now used for temporary hemorrhage control by prehospital EMS personnel and at trauma centers around the United States.[90] REBOA is now used in trauma centers throughout the United States. While there have been numerous series demonstrating promising results,[91,92] the most recent data to date suggest that further work is needed to properly define when and in which patient population REBOA offers benefit.[93] The Reducing Exsanguination Via In-Vivo Expandable Foam (REVIVE) trial started in late 2019 at five civilian

	to reduce death from noncompressible hemorrhage.[87,88] DARPA-funded research led to development of novel injectable foam to temporize pelvic hemorrhage.[89]	trauma centers in the United States.[94]
Damage Control Resuscitation and the Prevention and Treatment of Trauma-Associated Coagulopathy	Many DoD agencies, such as the Office of Naval Research (ONR), the US Army Medical Research and Material Command (MRMC), and Defense Advanced Research Projects Agency (DARPA), just to name a few, have been long-standing sponsors of resuscitation research. In the late 1990s and early 2000s, experts from three national consensus conferences agreed that aggressive resuscitation is deleterious, an "ideal" fluid is yet	The DoD-funded Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT) study was performed at 10 U.S. level 1 trauma centers and showed that higher ratios of plasma and platelets early in resuscitation was associated with lower mortality.[61] As a follow-up to the MATTERs trial, the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) trial took place in 40 countries and again

not available, and that low-volume resuscitation (hypertonic, colloid, or combination) is the most logical choice for the military needs.

Most current recommendations of the Tactical Combat Casualty Care (TCC) guidelines emphasize hypotensive resuscitation, avoidance of crystalloids, early blood product use, high ratios of plasma and platelets to RBCs, and administration of TXA when appropriate.[95]

The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs II) took place in a Role 3 Combat Surgical Hospital in southern Afghanistan and showed that the

showed that both all-cause mortality and death due to hemorrhage were lower in TXA-treated patients than in placebo.[40]

Massive Transfusion Protocols (MTPs) have been shown to save lives among bleeding patients[24,61] and are now standard of care at civilian trauma centers, and these are based on military data and DoD-funded research that prioritize avoidance of crystalloids, use of TXA in appropriate patients, and 1:1:1 ratio of RBCs, plasma, and platelets.

The U.S. Army Medical Research and Materiel Command funded the recent PAMPer trial, which demonstrated a survival benefit from prehospital

	addition of cryoprecipitate independently added to the benefits of TXA in the seriously injured in the battlefield.[96] However, this study also showed higher rates of VTE among soldiers receiving TXA.	administration of plasma in hypotensive blunt trauma patients requiring air medical transport.[47]
Rapid Evacuation and Long-Distance Transport	In 2009, the U.S. military mandated that the prehospital helicopter transport of critically injured combat casualties should be ≤60 min. Median transport time was cut into half, and follow-up data showed significant reductions in total casualty rate and case fatality rate, resulting in hundreds of lives saved.[97] Operation Iraqi Freedom and Operation Enduring Freedom provided new insight into the	The lessons learned regarding the safety, and the survival benefit, of long-distance transport for severely injured patients have important applications to civilians injured in rural areas, where they may be far from the nearest level 1 trauma center.

	rapid movement of critically injured casualties within hours of wounding. Review of the Critical Care Air Transport Team and Joint Theater Trauma Registry databases shows that for severely injured (mean ISS = 23.7) that were evacuated to the Landstuhl Regional Medical Center in Germany, the en route mortality rate was <0.02%.[98]	
Rehabilitation	Lower-extremity injuries account for 60% of all injuries to the U.S. troops in Iraq and Afghanistan, which are mostly due to explosive devices.[99] But unlike previous wars, temporary vascular shunts have been used more widely,[100,101] and early vascular reconstruction has	Complex extremity care in civilian trauma systems has learned a great deal from the more recent military experience with regard to both initial injury management and the needs of longer-term functional recovery.[106]

	being performed more frequently with excellent outcomes.[102,103]
Modern development and implementation of comprehensive rehabilitation strategies[104] and cutting-edge technology in prosthetic limbs[105] to treat the injured service members with complex lower-extremity trauma from combat have resulted in some of the best functional outcomes in the history of warfare.	

At the other end of the spectrum, there is significant work underway at health systems level to better understand which deaths are potentially preventable and how the current organization of trauma delivery systems can be further optimized. In the 2016 report by the National Academies of Science, Engineering, and Medicine (NASEM),[110] "A National Trauma Care System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths," the ACS-COT joined a broad coalition of trauma stakeholders including the National Highway Traffic Safety Administration (NHTSA), the U.S. Department of Defense, NASEM, and the National Institutes of Health to develop a national trauma action plan. The action plan identified existing gaps in our current trauma care systems including regional variation in emergency medical services (EMS) care, mismatch of level 1

and 2 trauma center location and population distribution, and inadequate funding for research to improve care of the injured patient. The NASEM report highlighted the need to develop a national trauma research plan, share innovation between the military and civilian sectors, engage the public through programs such a Stop the Bleed campaign, and empower trauma survivors and their families to be key advocates for advancing trauma care. Ultimately, it will take innovation at the basic science level, the clinical science level, and the health systems level to achieve the goal of "zero preventable deaths" in trauma.

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20

Prehospital and New Advances in Resuscitation

Jason L. Sperry and Christine M. Leeper

Key Points

1. Triage is an active process with the goal of transporting patient to most appropriate trauma center in the shortest time while avoiding over or under triage situations.
2. Prehospital assessment should follow ABCDE (Airway, Breathing, Circulation, Disability and Environment); providers should perform only necessary critical interventions while avoiding delays in transfer to definitive care.
3. Direct pressure and hemostatic dressings can be used for control of hemorrhage; however, large-volume extremity hemorrhage may need to be addressed with placement of a tourniquet.
4. Prehospital fluid resuscitation follows damage control principles of permissive hypotension and whole blood or balanced blood products if available while minimizing crystalloid.
5. Prehospital use of Resuscitative Endovascular Balloon Occlusion of Aorta (REBOA) is not recommended at this time, though its application in hospital settings in the United States and internationally is increasing.

INTRODUCTION

Trauma continues to be the leading cause of death for 1- to 44-year olds and has risen to the overall third leading cause of death for all age groups.[1] The care of the injured patient is a tightly integrated exercise combining the expertise of the prehospital care team and the trauma team once they arrive at the hospital. The likelihood of patient survival is vastly increased by timely transport and proper interventions on arrival to definitive care centers. The care of the injured patient begins immediately following injury. This may be rendered initially by nearby civilian bystanders or a variety of trained first responders. The main goal of a prehospital system is expedient assessment and care for the injured patient, then transportation to the most appropriate hospital for definitive care as quickly and safely as possible. At times the

most appropriate hospital may be the closest, and at others it may be more distant but with the capabilities more suitable to a particular patient. Most commonly, a phone call placed to a 9-1-1 dispatcher activates the emergency medical system (EMS) and quickly allocates resources to the location where help is needed.

PREHOSPITAL CARE

Personnel

Prehospital personnel are comprised of civilians, emergency medical technicians (EMTs), paramedics, firefighters, police, nurses, and less commonly physicians. The Hartford Consensus III placed nonmedical civilians on the forefront of hemorrhage control as a ready force of immediate responders; prompted by this call to action, more than one million civilians to date have received basic training in bleeding control principles to provide immediate care until first responders arrive.[2] There are multiple levels of EMTs whose capabilities can vary slightly by system. In general, the EMT-B or basic level has training capable of providing basic life support (BLS). BLS maneuvers include triage and transport, external hemorrhage control, administration of supplementary oxygen, spine immobilization, cardiopulmonary resuscitation, and application of an automated external defibrillator (AED). Prehospital advanced life support (ALS) was first employed as a "mobile intensive care unit" in 1967.[3] Paramedics require additional training, upward of 1,200 hours, and may administer ALS techniques. In addition to the maneuvers administered by BLS personnel, an ALS unit can typically provide cardiac drugs, pain control, blood pressure management, glucose control, needle decompression of tension pneumothoraxes, and anticonvulsant medication. There is much debate as to whether ALS is superior to BLS in the prehospital setting for injured patients. A recent meta-analysis concluded that ALS provides a survival advantage only to nontrauma patients.[4] However, there may be some benefit to the presence of ALS providers for injured patients who require advanced lifesaving maneuvers in the prehospital environment, even at the expense of prolonged scene time.[5] In certain U.S. cities, a physician medical director of

EMS is available at all times to advise to ground crews and dispatch centers. Some physicians may also respond in person to certain calls as needed. Their role includes providing quality control, education, and approval of drug administration outside of set protocols. Outside of the United States some countries have full-time physicians riding with ambulance crews at all time. While physician presence increases transport time, which may not be beneficial for trauma patients, there is evidence of an increase in survival in patients with acute myocardial infarction and respiratory distress.[6]

Triage

1 Triage is an active process that takes into account multiple factors with the goal of transporting the patient to the most appropriate trauma center in the shortest amount of time. The Centers for Disease Control and Prevention publish guidelines helping to facilitate proper triage of injured patients. These guidelines underwent their most recent update in 2011 and use physiologic, anatomic, and the mechanisms of the injury to guide the triage of the patient.[7] Changes specific to the 2011 update include lowering GCS for the physiologic criteria, broadening the definition of injuries in the anatomic criteria, and addressing the differences in older adult trauma patients relative to young trauma patients. The implementation of these guidelines is key to preventing both under- and overtriage of the acutely injured patient. Undertriage is the practice of sending an acutely injured patient to a lower tier in the trauma system that may lack resources to adequately care for that patient. This leads to prolongation to definitive care for injuries, multiple transfers to identify the correct level of care, and overall worse outcomes for the patient. Overtriage is transferring a patient to a highest-level trauma system when their injuries do not warrant that level of care. This allocates scarce resources to patients who ultimately do not need them, and as such may prevent those who need that resource appropriately from getting it and increases healthcare costs.[8] The development and validation of prehospital prediction models that could translate to user-friendly prehospital applications is an area of active investigation.

A special triage situation occurs when multiple patients are injured. A multicasualty event is where a hospital is able to manage the number of casualties with local resources. The majority of level 1 trauma centers are

able to take care of a small multicasualty event without significant strain on their work environment. A mass-casualty event exists when the numbers, severity, and diversity of injuries overwhelm the local medical resources. Mass-casualty events require coordination at the state and national level, and extensive practice at implementing triage criteria.

Scoop and Run versus Stay and Play

Traditionally, two paradigms that dictate the amount and type of care that patients receive in the prehospital setting are the "Scoop and Run" and the "Stay and Play." The overarching premise of the Scoop and Run technique is to get the injured patient to a facility that can provide definitive care in the shortest period of time. The proponents of this system cite the increasing amount of evidence that prehospital interventions are fraught with complications from both their intervention as well as the resultant delay in arriving at a trauma facility.[9] Stay and Play advocates feel that the early control of life-threatening injuries is considered of critical importance in the management of the injured patient, and initiating therapy for such injuries in the prehospital environment may improve patient survival.[10] The truth to which paradigm is best for the patient most likely lies somewhere in the middle of the two and depends on the resources available. In an urban setting with readily accessible trauma facilities it makes sense to extract the patient and get them to the closest center, performing limited, lifesaving interventions during transport. In a rural environment, where access to a hospital may be delayed by prolonged ground transport time or wait for helicopter transport arrival, it may be necessary to provide care on site allowing for stabilization of the patient's injuries.

SCENE ASSESSMENT AND MANAGEMENT

Airway

Once on scene, it is paramount for the prehospital provider to determine the status of the patient's airway quickly. Evaluating the patient's Glasgow Coma Scale (GCS), chest rise, extent and nature of injuries provides vital insight

into whether or not the patient is and will be able to maintain their airway. Supplemental 2 maneuvers such as suctioning, chin lift/jaw thrust, placement of oropharyngeal airways, and use of bag-mask devices can temporarily restore oxygenation in the acutely injured patient (**Table 20.1**). These maneuvers will usually maintain airway patency for the patient during their transport to definitive care; for those who are unable to do so, advanced airway maneuvers are key to securing a patent airway. Tracheal intubation provides a definitive airway with a cuffed endotracheal tube that will facilitate oxygenation, ventilation, and prevent aspiration. The skills required to successfully intubate are difficult to achieve and even more difficult to maintain, as this is a low frequency event often performed under challenging conditions.[11]

Table 20.1 Prehospital Assessments and Interventions

A	Chin lift/jaw thrust, oropharyngeal airway, nasopharyngeal airway
B	LMA, King tube, surgical airway, needle decompression, chest tube, capnography
C	Tourniquet, needle decompression, permissive hypotension, early blood products
D	C spine immobilization, backboard placement, splinting of extremity fractures
E	Clothing removal, exposure of wounds, warming devices

There is conflicting literature regarding field intubation, with the majority of studies suggesting that prehospital intubation does not improve survival and prolongs time to definitive care.[12,13] The only randomized controlled trial of prehospital intubation versus bag-mask ventilation occurred in 2000 with pediatric patients, which showed that the addition of out-of-hospital

intubation did not improve survival or neurologic outcomes.[14] A meta-analysis evaluating emergency intubation for the acutely ill did not show a benefit for trauma patients in the urban environment.[15] A retrospective review of prehospital intubation versus bag-mask ventilation by Stockinger and McSwain showed no survival advantage to intubation and an increased prehospital time.[11] Moreover, a pediatric cohort from a conflict region showed increased mortality with prehospital intubation after controlling for other factors associated with death.[16] One study that did show a mortality benefit was a retrospective review of blunt trauma patients with severe head injury, who had a statistically significant decrease in mortality when intubated in the field compared to those who were not.[9]

While the majority of situations in the prehospital setting do not require intubation, there are certain scenarios in which it may be prudent to secure an airway. For instance, patients who have evidence of extensive facial trauma with airway compromise and those patients who are apneic due to suspected cervical injury may be appropriate to be intubate in the prehospital setting. The reflexive intubation to "protect" the airway should be avoided, and further randomized studies are required to truly answer the question of who and when to intubate in the prehospital setting.

There are alternative measures to endotracheal intubation that can be taken for those who need to establish an airway: laryngeal mask, Combitube, and King airway all require less training and skill for insertion, though they have not been shown to increase survival. While video-assisted airway insertion devices are commonly utilized in the hospital setting for "difficult" airways and increasingly for standard airways as well, data regarding their use in the prehospital setting is limited. A randomized controlled trial of direct laryngoscopy versus video laryngoscopy in a prehospital cohort failed to show a difference in intubation success rate, tracheal intubation times, number of attempts, or difficulty. Notably, the number of technical problems with the equipment was increased in the video group.[17] As technology advances, the use of video-assisted airway devices may allow for more successful prehospital intubation, though whether this will translate to a survival benefit is unknown at this time.

A surgical cricothyroidotomy (CRIC) can provide an emergency airway in the hands of skilled practitioners. This maneuver requires much training and is utilized infrequently, mainly by personnel in austere environments or after

failed orotracheal intubation efforts. A retrospective review by the Israeli Defense Force showed a 93% success rate with CRIC for patients requiring an emergency airway[18]; a review of the Netherlands Hospital EMS database reported a comparable 94% success rate.[19] A retrospective review of the Department of Defense Trauma Registry reported that CRIC was an infrequent event in combat settings that did not confer a survival advantage over the less technically challenging supraglottic airway in a comparable comparison cohort.[20]

Breathing

Assessment of patient's breathing occurs concurrently with airway assessment. Evaluation of symmetric chest rise, obvious signs of chest trauma, and presence of bilateral breath sounds give the first responder an idea of the patient's status. The presence of a tension pneumothorax is a life-threatening event that may lead to obstructive shock, hemodynamic collapse, and potentially death. Signs of tension pneumothorax may include tracheal deviation, neck vein distention, and cyanosis. Prompt decompression of the thoracic cavity with a needle is necessary to reverse the tension effect. While the traditional landmark has been the midclavicular line, cadaver and computerized tomography evaluations had demonstrated more consistent evacuation of air using the anterior axillary, especially in females.[21] Further management with tube thoracostomy will be addressed once the patient arrives at their receiving facility. Large sucking chest wounds that permit the rapid equilibration of pleural and atmospheric pressure can be rapidly fatal. These wounds prevent the lung from expanding and preclude alveolar ventilation. These large wounds cause hemodynamic collapse rapidly unless an airway is obtained that allows for positive-pressure ventilation. The very rare smaller open sucking chest wounds are amenable to a three-sided dressing that allows for gas to exit from the chest wall defect but prevents gas from entering the chest wall. These can be fashioned in a field expedient manner and function as a temporizing action until definitive therapy with a chest tube can be achieved.

Mismanagement of ventilation in the intubated patient, specifically those with traumatic brain injury (TBI), can result in inadvertent harm. Intentional hyperventilation in the prehospital setting had been previously advocated and

is unfortunately still occasionally practiced. Current recommendations from the Brain Trauma Foundation[22] target normocapnea or $PaCO_2$ between 30 and 39 mm Hg, as overventilation causes acute vasospasm and an overall decrease in the cerebral blood flow in patients with a severe TBI. The resulting cerebral ischemia is one mechanism for secondary brain injury and increased mortality in patients with severe TBI.[23,24] Unintentional hyperventilation is also an issue given that many prehospital personnel ventilate patients via bag-valve devices connected to either a face mask or directly to an endotracheal tube; with bag volumes in excess of 1,200 mL, injudicious ventilation can easily result in hyperventilation. Some have advocated, therefore, for the use of end-tidal CO_2 ($ETCO_2$) monitoring by prehospital providers. The use of $ETCO_2$ as a means for measurement of exhaled CO_2 is the standard found in the operating room and emergency departments; however, its use in the prehospital setting was not commonplace 10 years ago. As technology has advanced, the ease of use and application of $ETCO_2$ monitoring has become more commonplace. $ETCO_2$ was first used as a way to confirm placement of endotracheal tubes in the prehospital setting using colorimetric CO_2 detector.[11] Esophageal intubation rates have been reported as high as 17% to 25% in emergency airway management of nonarrest patients.[25] The use of the colorimetric detector in conjunction with auscultation and symmetric chest rise make the likelihood of esophageal intubation near zero. Silvestri et al.[26] showed that there were no misplaced endotracheal tubes in patients who had continuous $ETCO_2$ monitoring (0/93) whereas 23.5% of misplaced (14/60) prehospital intubation did not use monitoring in the prehospital setting.

While their utility in confirming endotracheal intubation is more clear, $ETCO_2$ monitors are an imperfect device to guide ventilation in the setting of trauma. The relationship between $ETCO_2$ and arterial $PaCO_2$ is complex in the injured patient, as $ETCO_2$ is dependent on metabolism, expired CO_2, and pulmonary perfusion status. In one 2009 study, $ETCO_2$ in prehospital intubations did not correlate to arterial blood gas $PaCO_2$, with patients most likely being underventilated ($PaCO_2$ >40) 80% of the time and severely underventilated ($PaCO_2$ >50) 30% of the time.[27] Therefore, $ETCO_2$ in

injured patients may reflect poor perfusion status rather than hyperventilation and lead providers astray if interpreted in isolation.[23]

Circulation

Prehospital Control of Hemorrhage

3 Evaluation of circulatory status begins with initial evaluation of mental status and inspection for obvious signs of active hemorrhage. Direct pressure and hemostatic dressings can be used for control of hemorrhage; however, large-volume extremity hemorrhage may need to be addressed with placement of a tourniquet. Tourniquet use for injury has documentation as far back as 6 BC in Hindu texts for the treatment of a snakebite.[28] Recent experience in combat environments supports the extension of this historically military practice to the provision of civilian trauma care. In the Vietnam War, surgeons recognized that of the casualties killed in the war, 2,590 lives could have been saved with better prehospital hemorrhage control.[29] Analysis of the casualties of Operation Gothic Serpent, the 1993 battle fought between U.S. forces and the militias in Somalia, showed 7% of fatalities resulted from penetrating extremity trauma and that hemorrhage control in the form of tourniquet use should be more widely adopted.[28] The current conflict in Iraq and Afghanistan provided the strongest data supporting the use of prehospital tourniquets. A prospective study of casualties over a 7-month period in 2006 at a combat hospital in Baghdad showed tourniquet application with the absence of shock was strongly associated with survival, no amputations resulted solely from tourniquet use, and only four nerve palsies at the level of the tourniquet occurred all of which resolved without issue.[29]

Studies have detailed successful civilian application of this concept. Most recently, a multicenter retrospective review of all patients sustaining peripheral vascular injuries admitted to 11 level I trauma centers compared tourniquet and nontourniquet groups. Mortality was 5.2% in the nontourniquet group compared with 3.9% in the tourniquet group, with adjusted odds ratio of survival = 5.86 in tourniquet group. Delayed amputation rates were not significantly different between the two groups.[30] A systematic review in 2018 included eight trauma centers (n = 718) and one national database (n = 2,048) study reporting prehospital tourniquet use. The aggregate data

reported >90% effectiveness of tourniquet, 6% mortality rate, 5.4% amputation rate, 4% extremity compartment syndrome, 3.7% peripheral nerve dysfunction, and 4% wound infection.[31] The overall mortality and limb amputation rate was less than that seen in similar cohorts of military patients. Additional quality research in civilian trauma patient is required to support whether tourniquet use leads to increased survival and limb salvage. In addition to their use in adult combat and civilian trauma, CAT tourniquets have been shown to be effective in preschool and school-age children[32] and are recommended by the Pediatric Trauma Society in the prehospital setting and during the resuscitation of children suffering from exsanguinating hemorrhage from severe extremity trauma.[33]

A final, more fatal, type of hemorrhage is junctional hemorrhage, defined as bleeding from the pelvis, groin, perineum, axilla, and neck. These wounds are seen extensively in the current era of combat as the use of improvised explosive devices (IEDs) has increased. Holcomb et al. reviewed preventable causes of death in U.S. Special Forces Soldiers in 2007 and found that junctional or noncompressible trauma was implicated in 47% of deaths.[34] The junctional tourniquet has shown in healthy volunteers to occlude blood flow to the lower extremity,[35] and requires effectiveness and implementation data prior to widespread utilization in prehospital trauma protocols.

Resuscitation

Once the circulatory status of the patient has been addressed, sites of rapid compressible exsanguination identified and treated, the decision is made for intravenous access and possible use of intravenous fluid. Placement of peripheral intravenous or intraosseus access should be performed only if it does not delay the transport of the patient. In patients without evidence of hemorrhage or in prehospital settings where blood and blood products are not available, numerous choices of fluid are available. However, most fluid options are actually poor choices for resuscitation of injured patients. Normal saline (0.9% sodium chloride) has an average pH of 5.5, with a sodium and chloride concentration of 154 mEq/L. Normal saline is often preferred as a universal solution for prehospital settings as it is “compatible with blood,” contains no potassium, and is cheap to carry; with a low overall

cost and extended shelf life. Lactated Ringer, initially developed to support organs in the lab (because of calcium content) and later championed for treating cholera, has only a slightly better physiologic profile. Lactated Ringer gives the clinician a better average pH of 6.5, with lower sodium (130 mEq/L) and chloride content (109). The optimal fluid, however, is Plasmalyte/Normosol which has an average pH of 7.4 and an electrolyte content that resembles a normal metabolic profile (sodium—140 mEq/L, potassium—5.0 mEq/L, chloride—98 mEq/L, and magnesium—3.0 mEq/L). In addition to its superior profile, Plasmalyte is compatible with all blood products and has been shown in a randomized trial to result in improved acid–base status and less hyperchloremia at 24 hours postinjury.[36]

Prehospital Transfusion Protocols

Resuscitation practice is rapidly evolving based on the imperative that the prehospital setting is the ideal place to begin early resuscitation with blood products. Hemorrhage is the leading cause of preventable death in trauma, responsible for 33% to 56% of prehospital casualties. Trauma-induced coagulopathy is common in severely injured trauma patients, and contributes to morbidity and mortality. Severely injured patients are now receiving blood and blood product transfusion in the prehospital setting to facilitate early hemostatic resuscitation and prevention of coagulopathy complications.

Early studies focused on transfusion of packed red blood cells (RBCs) versus standard practice (crystalloid); the evidence overwhelmingly supports transfusion of RBCs for patients in hemorrhagic shock. Shackelford et al. described a cohort of military combat casualties with traumatic amputation or hemorrhagic shock. In comparing those who received blood product transfusion prehospital (RBCs, plasma, or both) to those who received delayed or no transfusion, patients who received early product transfusion had decreased 24-hour (adjusted HR = 0.26) and 30-day (adjusted HR = 0.39) mortality.[37] Brown et al. conducted a retrospective, case-controlled analysis of patients who received prehospital RBCs (n = 240) against those who did not (n = 480).[38] Those receiving prehospital transfusion had an increased likelihood of 24-hour survival, lower odds of shock, and lower overall 24-hour blood products transfused. A subsequent study from these investigators evaluated over 2,000 blunt trauma patients presenting to care

within 2 hours of injury,[39] comparing those who received RBCs in the prehospital setting (n = 3.5%) to those who did not. Those who received prehospital RBCs had a 95% reduction in the odds of 24-hour mortality, 64% reduction in 30-day mortality, and an 88% reduction in the incidence of trauma-induced coagulopathy. In a multicenter study of over 1,400 injured patients with evidence of shock, patients receiving prehospital RBCs had increased 24-hour and 30-day survival, as well as less coagulopathy on arrival in those patients receiving prehospital RBC transfusions.[40] Subsequently, the Houston group published their aeromedical experience comparing patients who received prehospital plasma and RBC (n = 137) versus those who received crystalloid (n = 1,540). Those who received products had improved acid–base status on hospital admission, decreased use of blood products over 24 hours, and reduced 6-hour mortality in the sickest cohort.[41] In another prehospital study comparing four different resuscitation groups (crystalloid only; PRBC; plasma; and PRBC + plasma), the group receiving plasma and PRBC had the greatest risk-adjusted 30-day mortality benefit.[42]

4 Further interest in prehospital plasma administration resulted in two concurrent trials: PAMPER and COMBAT. Sperry et al. enrolled 501 patients in a multicenter cluster-randomized trial comparing the administration of thawed plasma with standard-care resuscitation during air medical transport. Mortality at 30 days was significantly lower in the plasma group than in the standard-care group, as was median prothrombin time on arrival to the trauma center.[43] In the COMBAT trial, 125 eligible patients in the as-treated analysis dataset were compared, 65 receiving plasma and 60 receiving crystalloid. There was no difference in 28-day mortality, the lack of benefit posited to be due to short transport times and rapid presentation to high-volume, high-quality care centers[44]; a post hoc analysis of these combined datasets did show a significant mortality benefit when transport times were greater than 20 minutes.[45] Further research is focusing on the use of freeze-dried plasma (FDP) to increase the shelf-life in systems and locations where maintaining a supply of fresh frozen plasma is not practical. Early studies indicate that the use of FDP in military combat settings at the point of injury[46] and in prehospital civilian trauma systems[47,48] is feasible and acceptable.

Current transfusion practice emphasizes a balanced transfusion strategy with high ratios of plasma and platelets to packed RBCs that attempts to mimic or "reconstitute" whole blood composition. The foundation for this practice comes from the landmark PROPPR trial, which included patients who received blood transfusion prehospital and showed that more patients resuscitation in the 1:1:1 group versus 1:1:2 group achieved hemostasis and fewer experienced death due to exsanguination by 24 hours.[49] In the last decade, in keeping with the desire to transfuse in 1:1:1 ratios, the pendulum has swung back toward utilizing whole blood as opposed to reassembling it from its component part. Transfusion of cold-stored low titer group O whole blood (LTOWB) as the first resuscitative fluid is now the standard of care in over 70 civilian trauma centers and prehospital settings[50] in the United States. There are theoretical concerns regarding the safety of group O WB administered to non–group O recipients, as hemolysis might occur due to the anti-A and -B that are naturally occurring in all group O WB units. However, studies in both adult and pediatric trauma patients demonstrate an excellent safety profile and no increased risk of hemolysis among the non–group O recipients compared to the group O recipients of WB who are not susceptible to hemolysis following LTOWB transfusion.[51,52] Advantages to whole blood include higher hematocrit, greater platelet and factor concentrations, and less saline and additive solution compared to an equivalent volume of "reconstituted" whole blood (**Table 20.2**). Further, cold stored platelets (1° to 6°C) have better performance in in vitro coagulation testing as compared to room-temperature platelets.[53] Importantly, cold storage also permits a lengthy storage time, and facilitates the utilization of a platelet-containing blood product in prehospital settings where maintenance of conventional room-temperature platelets would not be feasible.[50] Further, LTOWB is a single product that can be transfused more efficiently than multiple component products, as evidenced by the significantly faster time to transfusion of at least one unit of RBCs, plasma, and platelets among pediatric trauma patients who received LTOWB versus conventional components (median = 15 minutes vs. 303 minutes, respectively).[51] In a single-center comparison of LTOWB versus component therapy in adult trauma patients, LTOWB was associated with a 53% reduction in post-ED blood product transfusion and twofold increase in likelihood of 28-day survival compared to component therapy after controlling for age, injury

severity, and prehospital physiology.[54] Patients receiving fewer transfusions are therefore exposed to fewer donors overall, decreasing the associated inherent risks. Further study is required to determine if whole blood transfusion will improve other patient outcomes.

Table 20.2 Components of Whole Blood versus Reconstituted Component Products

	Whole Blood	Components
	1 unit whole blood	1 unit red blood cells 1 unit plasma 1 pack platelets 1 unit cryoprecipitate
Product volume (mL)	570	675
Hematocrit (%)	38–50	29
Platelet count	150,000–400,000	88,000
Factor activity (%)	100	65
Fibrinogen (mg)	1,000	750

Permissive Hypotension

The concept of permissive hypotension involves keeping the blood pressure low enough to avoid exsanguination while maintaining perfusion of end organs.[55] It is an integral part of Damage Control Resuscitation protocols that dates back to World War I. The work of Walter Cannon and John Fraser while serving with the Harvard Medical Unit in France involved the observation that artificial elevations in blood pressure may overcome the clot preventing further hemorrhage, and the patient will lose sorely needed blood.[56] In 1994 Bickell et al. presented a randomized prospective control trial showing delayed fluid resuscitation in adults with penetrating torso injuries lead to greater survival and overall shorter hospital length of stay.[57] These results have been repeated in subsequent studies showing no benefit to targeting physiologic or supernormal blood pressures in either blunt or

penetrating trauma. A multicenter, randomized study[58] randomized hypotensive blunt trauma patients to receive small boluses of fluid (250 mL) if they had no radial pulse or a systolic blood pressure lower than 70 mm Hg or to receive a 2-L fluid bolus and additional fluid needed to maintain a systolic of 110 mm Hg or greater. The permissive hypotension group received 1 L less of fluid, had less deaths (5% vs. 15%) at 24 hours after admission, and among patients with blunt abdominal trauma 24-hour mortality was 3% versus 18%, all statistically significant. There was, however, no difference in mortality among patients with penetrating trauma. This data suggests that controlled resuscitation in the out-of-hospital setting may offer an early survival advantage to the blunt trauma patient.

This strategy of permissive hypotension remains controversial in patients with severe traumatic brain injury in light of well-described evidence on secondary brain injury and poor outcomes due to even a single episode of prehospital hypotension. Further confusion is generated for prehospital providers as recommendations for permissive hypotension in trauma literature on damage control resuscitation[59] directly contradict the Advanced Trauma Life Support guidelines that advocate for early administration of 2-L crystalloid bolus for those patients manifesting signs of shock. Additional studies are necessary to clarify this issue and at which level fluid administration may be paused; however, the general paradigm prehospital trauma providers should follow includes minimizing intravenous fluids, tolerating systolic blood pressures in the 90 mm Hg range, and not resuscitating to supernormal values with crystalloids. Importantly, children do not tolerate hypotension. They have the physiologic reserve to maintain normotension to the verge of circulatory collapse; hypotension therefore is a sign that a child is in extremis and should be treated with expedient fluid resuscitation, not observation.

CONTROVERSIES

Resuscitative Endovascular Balloon Occlusion of Aorta

5 Resuscitative endovascular balloon occlusion of aorta (REBOA) is a balloon placed via the femoral artery to occlude the aorta and prevent life-threatening hemorrhage. While the technology is new, the concept was described in the journal Surgery in 1954. While initially popularized as a substitute for resuscitative thoracotomy, it is probably best suited for temporizing pelvic hemorrhage (before the patient has lost pulses) as a bridge to embolization in interventional radiology, or as an adjunct in the operating room.[60] High-volume centers who utilize REBOA in a protocolized fashion report feasibility, faster time to aortic occlusion, fewer early deaths, and improved overall survival as compared with resuscitative thoracotomy (37.5% vs. 9.7%).[61,62] The Japanese have published a retrospective review of their experience with the safety and feasibility of REBOA for trauma in 2014.[63] Their data show that REBOA was feasible for trauma resuscitation, however, there was an increased risk of lower limb ischemia that occurred in 12.5% of their patients. While the majority of U.S. trauma centers do not perform REBOA placement, and those that do perform only a few each year (median = 6),[64] it is feasible that continued training in endovascular skills may lead to greater implementation of this skill.

Safety concerns with REBOA include the following: (1) Prolonged aortic occlusion may lead to spinal cord ischemia; (2) ischemia reperfusion injury can lead to acute kidney injury and multisystem organ failure; (3) femoral access complications (dissection, hematoma, pseudoaneurysm, etc.) may result in limb loss or need for complex vascular repair/reconstruction; (4) balloon rupture or overinflation can result in rupture or thrombosis of aorta or iliac vessels; (5) Prolonged attempts to complete the procedure, in particular in obtaining vascular access, can delay definitive hemorrhage control.[65] Measures to reduce the risks and maximize success of REBOA include adequate training and preparedness of a skilled multidisciplinary team, having the resources for urgent operative or catheter-based hemostasis following REBOA placement as soon as possible, using a smaller-diameter sheath devices (<8 Fr), limiting aortic occlusion time, and attentive assessment of lower extremity perfusion.[64]

There have been case reports of REBOA placement by physicians in prehospital settings outside of the United States. However, prehospital placement of REBOA is not recommended in the United States at this time due to lack of clear “safe” duration of aortic occlusion, difficulty defining

reliable and appropriate patient selection criteria, lack of safety data in prehospital settings, and potential to delay transport to definitive care.

LTOWB Rh-Positive Transfusion in Children and Women of Childbearing Potential

Concerns regarding the transfusion of Rh(D)-positive whole blood to Rh(D)-negative children and women of child-bearing potential (WCP) are sometimes raised as a barrier to the transfusion of whole blood to these populations in emergencies. The risk in this scenario is that a woman who is Rh(D) negative will be exposed to Rh(D)-positive RBCs in the transfusion of whole blood and could become alloimmunized to Rh antigen. If she goes on to carry a Rh(D)-positive fetus, maternal anti-D antibodies would cross the placenta, and bind and destroy fetal RBCs. This hemolytic disease of fetus and newborn (HDFN), if untreated, may cause death or significant developmental neurologic morbidity in the child.

One strategy to avoid this would be transfusion of Group O Rh(D)-negative whole blood, which is the practice in some pediatric protocols currently. However, this is an incredibly rare product and is not available in quantities sufficient to support all whole blood programs. Another strategy is recognizing that the risk of demise of a future fetus as a result of receiving Rh(D)-positive whole blood is 0.3% in adult women, and even lower in children due to decreased alloimmunization rates after exposure to Rh antigen.[66] This number is small compared to the lifesaving benefits of early blood product administration in a bleeding emergency. Further, with modern medicine, severe HDFN is much less common with timely diagnosis and treatment.

Rapid Sequence Intubation versus Non-RSI

While standard of care in the inpatient setting, the use of rapid sequence intubation (RSI) in the prehospital setting is debated among experts with published data to both support and refute the practice. The drugs that are used for RSI are highly variable and include combinations of the following: succinylcholine, rocuronium, vecuronium, midazolam, diazepam, lidocaine,

ketamine, and etomidate. Many argue that the complications that are associated with RSI, including the consequences of multiple failed intubation attempts, unnecessary exposure of patients to dangerous procedure, and complications of the medications do not value the implementation of RSI in the prehospital setting. A 2005 paper published on the use of RSI in the out-of-hospital setting was unable to predict which patients had severe TBI and over half the patients experienced a desaturation during the RSI procedure, while only one-quarter of they were hypoxic before RSI.[67] A further study from the United Kingdom showed an incidence of 18.3% for hypoxemia during prehospital RSI and 13% developed hypotension lower than pre-RSI blood pressures. This paper attributes its lower incidence of hypoxemia and hypotension to the fact that in the United Kingdom board–certified physicians preform all the prehospital RSI and intubations, while in the San Diego paper the entire procedure was carried out by EMTs. Using a propensity-adjusted model, investigators showed no statistical difference in mortality between prehospital intubations with and without RSI. Further randomized, prospective trials are necessary to prove a benefit to prehospital RSI.

CONCLUSION

Prehospital trauma care is a constantly evolving field. Much of our advances from recent military conflicts are being rapidly implemented in the civilian prehospital setting. Further research and developments are necessary to continue the previous success seen in saving the critically injured trauma patient.

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21

Head Injuries

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Key Points

1. Traumatic brain injury accounts for a significant mortality and morbidity worldwide.
2. Factors that worsen primary brain insult such as hypoxia and hypotension should be aggressively treated.
3. A noncontrast computed tomography (CT) is the preferred imaging modality in any trauma patient with suspected traumatic brain injury (TBI).
4. Management goals for treatment of severe TBI include ongoing resuscitation with priority for maintenance of airway, breathing, and circulation.
5. We recommend the use of invasive intracranial pressure (ICP) monitoring in all patients with severe TBI.
6. A tiered approach for the management of elevated ICP is recommended.
7. Prompt surgical intervention should be performed in patients with large mass lesions and with refractory medical management of elevated ICP.

INTRODUCTION

1 In 2013, it was estimated that about 973 million people sustained injuries that warranted health care and injury accounted for 4.8 million deaths.[1] It is estimated that about 16,000 people die from injuries every day. Eighty-five percent of all traumatic injuries occur in developing countries, and trauma is the leading cause of mortality in the 5 to 40 age group, worldwide. Even in high-income countries, unintentional injuries, self-inflected injuries and injuries related to interpersonal violence account for the majority of deaths in the 15 to 45 age group.[1] The additional burden of the sequelae from trauma with significant morbidities account for a very large part of the disability spectrum. There are major economic effects of trauma. In the United States, trauma accounts for a substantial burden. Estimates from the year 2005 suggest that mortality from unintentional injuries resulted in $1,374,873,000 in medical costs. The economic burden of disability for the same year is much higher at $82,942,825,000. Economic effects in developing countries are dramatic; India forfeits 3% of annual GDP to accidents. Additionally, major disability imparts tremendous societal and economic burdens.

Craniocerebral injuries account for the majority of deaths following trauma across the world including 30% of the deaths in the United States. Traumatic brain injury (TBI) is also the leading cause of death in the military setting. Additionally, they represent the leading cause for disability in the United States and the world. In the current chapter we will discuss the epidemiology, clinical assessment, treatment paradigms, and prognostic elements associated with head injuries and in particular TBI.

EPIDEMIOLOGY

Although TBI has traditionally been a disease of the young, its epidemiology is shifting toward an elderly population due to falls and the wider use of anticoagulation. The TBI-related hospitalization as a result of motor vehicle crashes in the younger population gradually declined till 2007. However, every day about 155 patients die in the United States from TBI.[2] This was accompanied by an increase in hospitalizations for TBI in elderly population as a result of falls. In fact, fall-related TBI in the elderly has

disproportionately increased by 54% in the last decade.[2] Patients in this category tend to do poorly due to additional comorbidities, anticoagulant therapy for other conditions and lesser neuroplasticity.

Additionally, there has been an increase in the incidence of intentional injuries that include self-inflicted and interpersonal violence. Data reported from the United Nations Office on Drugs and Crime (UNODC) suggest that while the incidence of homicide is decreasing in Asia and Europe, it is increasing in South America and Eastern and Southern Africa.[3] The proportion of TBI secondary to violence has proportionally risen accounting for 7% to 10% of TBI.[1] Self-harm is the second leading cause of death from injuries including TBI and the global trend suggests an uptick, particularly observed during the recent global economic downturn. Other risk factors that account for increased incidence of TBI include lower socioeconomic status, the use of alcohol and drugs, as well as the presence of neurologic and neuropsychiatric disorders.[4] In adolescents, sports-related injuries account for a substantial proportion of TBI.[5]

Though most of the clinical diagnostic and treatment paradigms are relevant for moderate and severe TBI, a notable inclusion would be the epidemiologic factors of mild TBI including concussion and persistent postconcussive states. It is estimated that between 70% and 90% of hospital admissions fall into the category of mild TBI (Glasgow Coma Scale [GCS] 13 to 15). This condition has gone through varying definitions. A recently concluded WHO task force has changed the guidelines to include confusion and disorientation instead of altered mental status in addition to the presence of focal signs, seizure, and intracranial lesion that do not require any surgical intervention. Moreover, the WHO definition allows for the GCS of 13 to 15 to be estimated at later time points beyond 30 minutes. Overall, mild TBI continues to be a problem with varying diagnostic elements and definitions. However, there has been an emerging body of evidence to indicate that neuropsychological evaluations and targeted interventions may help recovery from mild TBI.[6]

CLASSIFICATION

TBI is a heterogeneous disease. It can vary from physiologic disturbances in the brain to significant macroscopic anatomic alterations in the brain that lead to loss of brain function and sometimes death and disability. Though there are multiple ways to characterize the nature of this disease (etiology, pathology, severity, and prognosis), one must take into consideration the treating bedside clinician into account. For this reason, a scoring system that is simple, easy to estimate, and reproducible is likely to be of most help. Important other considerations include nature of trauma (e.g., blunt vs. penetrating injuries, blast injury) that may affect the type and severity of the pathologic insult on the brain. Finally, the importance of extracranial injuries in a multisystem trauma cannot be overemphasized. These injuries are present in about 35% of trauma patients[7] and additional systemic hypotension from blood loss and lactic acidosis combined with the presence of hypoxia have been identified as important potential reasons for deterioration of secondary brain injury.

Clinical Scoring System

Using the GCS, TBI has traditionally been classified using injury severity scores. This is the most commonly used across most emergency departments and ICU in the world. It includes three separate components: eye opening, motor score, and a verbal score (**Table 21.1**). A GCS of 13 to 15 is considered mild injury, 9 to 12 is considered moderate injury, and 8 or less is considered severe TBI. GCS is widely followed mainly because of its simplicity. However, it has also been recognized for its reproducibility and ability to prognosticate the severity of the injury. Because of these factors, GCS is recognized as the single most important assessment for an injured patient with suspected TBI. It has been universally adapted by the bedside clinicians, prehospital providers, and plans for specific training of the GCS have been provided by the brain trauma foundation. While it is considered a single score, the best way to provide the scores is by each of the separate components. As an example, a patient with a GCS of 8 is better described as E2V3M3. The primary reason behind this practice is that the motor score has been recognized as the single most important portion of the score in terms of severity and prognosis, particularly with severe TBI. The presence of an endotracheal tube obviates the verbal score. Other limiting factors for GCS

include medical sedation, neuromuscular paralysis, and intoxication with drugs and alcohol. These confounding issues are often particularly prominent in patients with a low GCS.[8] On the other hand, the eye opening and verbal responses appear to be more helpful in the characterization of mild TBI. GCS has also been applied to describe conscious states other than TBI and has found broad application in the ICUs for comparative assessment across time.

Table 21.1 Glasgow Coma Scale

Response	Score
Eye Opening	
No eye opening	1
To pain	2
To speech	3
Spontaneously	4
Best Verbal Response	
None	1
Incomprehensible sounds	2
Inappropriate words	3
Patient confused	4
Patient oriented	5
Best Motor Response	
None	1
Extensor response to painful stimulus	2
Flexion to painful stimulus	3
Withdraws from pain	4
Localizes to pain stimulus	5
Obeys commands	6

There exist other scoring systems. For example, the Full Outline of UnResponsiveness (FOUR) score has been developed mainly by including a brainstem examination.[9] However, this score is more complicated to perform

particularly by nonneurologists and therefore has not found broad applicability, like the GCS.

Neuroimaging Scales

A detailed discussion of the radiologic tools for diagnosis is described under the section of radiologic assessment. For all practical purpose, a computed tomography (CT) scan remains the cornerstone for early diagnosis and establishing guidelines for therapy in patients with TBI. Based on the CT assessments, two different scales are currently in use. The Marshall scale uses CT findings to classify injuries in six different categories based on the presence of cisterns, lesion, and midline shift (**Table 21.2**).[10] There are multiple studies which have shown a clear increase in mortality with increasing severity by the Marshall grading system. However, it does not describe traumatic subarachnoid hemorrhage, does not characterize the type of lesion (such as epidural/subdural), and does not characterize the extent of compression of the cisterns.

The Rotterdam scale is a more recent CT-based classification developed to overcome the limitations of the Marshall scale (**Table 21.3**). It includes the presence of subarachnoid hemorrhage (SAH), presence or absence of epidural lesion, and adds a category for compression of cisterns. Though it has shown promising early results,[11] its applicability remains subject to a broader validation.

PATHOPHYSIOLOGY OF TBI

The pathophysiology of brain injury is classified into primary and secondary brain injuries. The primary brain injury occurs at the time of impact and mainly involves disruption of the brain parenchyma along with the blood vessels. Secondary injury is mainly related to additional factors such as hypotension, hypoxia, effects of intracranial pressure (ICP) elevation, and other biochemical factors that have the ability to potentiate the primary structural damage. The major tenets of treatment of TBI are predicated on the fact that mitigation of the secondary insults has the potential to reduce the overall effect of the injury on the brain. While surgery may be needed for a

very small number of primary brain injuries, for the vast majority of patients, the identification, prevention, and treatment remain the mainstay for amelioration of secondary brain injury through appropriate neurologic critical care.

Table 21.2 Marshall Classification for Radiologic Assessment of TBI

Diffuse Injury I (no visible pathology) ▪ No visible intracranial pathology
Diffuse Injury II ▪ Midline shift of 0–5 mm ▪ Basal cisterns remain visible ▪ No high or mixed density lesions >25 cm^3
Diffuse Injury III (swelling) ▪ Midline shift of 0–5 mm ▪ Basal cisterns compressed or completely effaced ▪ No high or mixed density lesions >25 cm^3
Diffuse Injury IV (shift) ▪ Midline shift >5 mm ▪ No high or mixed density lesions >25 cm^3
Evacuated Mass Lesion V ▪ Any lesion evacuated surgically
Nonevacuated Mass Lesion VI ▪ High or mixed density lesions >25 cm^3 ▪ Not surgically evacuated

From Marshall LF, Marshall SB, Klauber MR, et al. The diagnosis of head injury requires a classification based on computed axial tomography. *J Neurotrauma* 1992;9 Suppl 1:S287–S292.

Primary Brain Injury

Mechanisms of direct trauma to the brain include direct impact, movement of the brain within the skull producing impact with the inner table (coup and

contrecoup injuries). As an example, direct frontal impact has the potential to produce frontal lobe injuries whereas the contrecoup mechanism could result in the injury to the occipital lobe. Other impact forces that cause primary brain injury are forces associated with rapid acceleration and deceleration, typically sustained in a high-speed motor vehicular accident or fall from a height. Penetrating bullet wounds with cavitational effects on the brain parenchyma are particularly devastating. Bullet wounds that are bihemispheric are associated with significant mortality and early herniation. Injury encountered around IED explosions mainly involves blast waves.[12,13] These waves have the potential to cause serious injury and presence of a helmet does not adequately protect the brain from acoustic injuries. Through these varied mechanisms, external energy transfer results in serious injuries to the brain parenchyma, white and gray matter neurons in addition to vascular injury, and disruption of the blood–brain barrier. One particular type of injury, diffuse axonal injury (DAI) is thought to be related to rotational forces inside the cranium resulting in disruption of the white matter often described as gray–white matter dysjunction.[14] Magnetic resonance imaging (MRI; in particular diffusion tensor imaging) is more sensitive than CT for detecting DAI.[15] Rotational and torsion injuries particularly at the site of the brain stem (fixed portion) can be devastating.

Table 21.3 Rotterdam Scale for Radiologic Assessment of TBI

Basal Cisterns ▪ 0: normal ▪ 1: compressed ▪ 2: absent
Midline Shift ▪ 0: no shift or ≤5 mm ▪ 1: shift >5 mm
Epidural Mass Lesion ▪ 0: present ▪ 1: absent
Intraventricular Blood or Traumatic SAH ▪ 0: absent ▪ 1: present

From Maas AI, Hukkelhoven CW, Marshall LF, et al. Prediction of outcome in traumatic brain injury with computed tomographic characteristics: A comparison between the computed tomographic classification and combinations of computed tomographic predictors. *Neurosurgery* 2005;57(6):1173–1182.

Cerebral contusions are the most commonly observed injury in TBI patients and occur as a result of direct impact as well as acceleration/deceleration injuries. They are most commonly seen in the basal frontal and temporal areas. Direct trauma-induced disruption of the blood vessels or the coalescence of cerebral contusions may result in an intraparenchymal hematoma. Vascular trauma may also result in the development of pseudo or true aneurysms of the cerebral vasculature with immediate or delayed consequences.

Extra-axial hematomas are defined as those occurring outside the substance of the brain and within the layers of the covering dura. They include epidural, subdural, and subarachnoid hemorrhage. A typical description of the kinematics of epidural hematoma is described as a glancing blow to the side of the head resulting in a temporal fracture and bleeding from the branches of the middle meningeal artery. They tend to be

lenticular in shape and considering there is no underlying brain parenchymal injury, have a very good prognosis with timely care.[11] On the other hand, subdural hematomas (SDHs) result from injury to the bridging veins of the cerebral cortex. They are particularly common in older patients who suffer minimal trauma and patients with cerebral atrophy with increased space between the brain and the dura. They are typically crescent shaped and are often associated with underlying cerebral injury. SAH can occur with disruption of pial vessels. They commonly occur in the sylvian fissures and interpeduncular cisterns. The distribution of posttraumatic SAH is different from SAH related to a ruptured cerebral aneurysm. The distribution pattern should lead the clinician to investigate the possibility of a ruptured aneurysm that result in loss of consciousness and subsequent motor vehicular crash. On the other hand, intraventricular hemorrhage occurs from injury to the subependymal veins, or by direct extension from adjacent intraparenchymal or subarachnoid hemorrhage.

Secondary Brain Injury

Though the cellular processes involved with secondary injury to the brain are complex and include mitochondrial dysfunction, neuronal apoptosis, and secondary ischemic insults, it is important to discuss the remediable causes that have been identified 2 to significantly impact the injured brain. Examples include hypotension and hypoxia (which decrease substrate delivery of oxygen and glucose to injured brain), fever and seizures (which may further increase metabolic demand), osmotic changes, increased ICP (ischemic insult), and hyperglycemia (immune modulation).[16]

However, a critical aspect of ameliorating secondary brain injury after TBI is the avoidance of secondary brain insults, which would otherwise be well tolerated but can exacerbate neuronal injury in cells made vulnerable by the initial TBI.

Hypotension

Systemic hypotension has long been recognized as a factor that determines the impact on the evolution of secondary brain injury and thereby affects mortality. In a meta-analysis, hypoxia (PaO_2 <60 mm Hg) and hypotension

(systolic blood pressure [BP] <90 mm Hg) were present in 50% and 30% of patients, respectively, and were associated with a higher likelihood of a poor outcome: hypoxia (odds ratio [OR] 2.14); hypotension (OR 2.67).[17] In a more recent study, using balanced controls of patients with severe TBI, a mean arterial pressure (MAP) of less than 65 mm Hg at presentation was associated with a fourfold increase in mortality.[18] In fact, a single episode of hypotension has been linked to adverse outcomes. Episodes of hypotension can be particularly devastating in patients with severe TBI and elevated ICP as discussed in the next section, the impact of maintaining the cerebral perfusion pressure (CPP) is one of the mainstays in the management of severe TBI. For all these reasons, appropriate resuscitation and maintenance of MAP over 65 remain the cornerstone of therapeutic strategies in TBI.

Hypoxia

It has been known for quite some time that neurons in particular are highly sensitive to hypoxia. Multisystem trauma patients are particularly prone to systemic hypoxia in view of high incidence of aspiration-induced lung injury, lung contusions, and rib fractures with associated atelectasis. Additionally, the therapeutic measures including crystalloid administration, blood transfusion, and particularly administration of FFP have been all linked to respiratory failure and ARDS. Moreover, patients particularly with severe TBI and associated reduction in the level of consciousness often are unable to protect their airway and thereby become candidates for endotracheal intubation and mechanical ventilation. Though these respiratory interventions are easily accomplished in a well-equipped and trained emergency department, such an undertaking in the field can be challenging. In a large study of moderate and severe TBI patients in the prehospital setting, the authors concluded that endotracheal intubation is an independent risk factor for increased mortality.[19] However, subsequent studies have established that the experience of the paramedics at the scene and intubations performed in the hospital settings can be achieved safely.[20,21] Additional work by different groups has identified as oxygen saturation less than 90% as an independent risk factor for mortality.[22] The current guidelines established by the BTF suggest maintenance of oxygenation as an important principle in the management of TBI.[23] As in any critical illness, the threshold of

administration of blood transfusion has been consistently lowered to hemoglobin of 7 g/dL. It is currently understood that critical illness is associated with deficits in oxygen uptake at the tissue level and merely raising the concentration of hemoglobin is not effective, considering the adverse effects of blood transfusion with immunologic alterations and cardiac overload.

Intracranial Hypertension and Cerebral Autoregulation

The Monroe–Kellie doctrine simply states that the total volume of contents remains constant within the skull that is rigid and nonexpansile. The contents of the cranial cavity include the brain, the vasculature, and the CSF. Therefore, the injured brain tissue and volume increase have to occur at the cost of reduction in other components, which typically involve compression of the venous reservoir and the CSF. However, once a threshold of displacement of the venous system and CSF is reached, the ICP begins to increase.

The CPP is clinically defined as the difference between MAP and the ICP. It is important to understand the concept of cerebral autoregulation. The precapillary venules have the regulatory ability to undergo vasoconstriction and dilatation. This response is mainly controlled by the MAP. Through autoregulation, the cerebral vasculature, particularly the venules maintains an adequate cerebral blood flow (CBF) across a wide range (50 to 150 mm Hg) of MAP (**Fig. 21.1**). There appears to be a direct correlation between the degree of brain injury and loss of autoregulation. Cerebral autoregulation is disrupted in approximately one-third of patients with severe TBI.[24,25] In these patients, a rise in MAP can lead to elevated ICP due to increased cerebral vasodilatation, thereby increasing the cerebral blood volume. In such patients with the loss of autoregulation, decreases in the MAP lead to hypoperfusion and therefore ischemia. A goal CPP of 60 to 70 mm Hg is recommended for all patients with moderate and severe TBI. However, every attempt should be made in addressing the factors leading to increased ICP prior to the institution of vasopressors to elevate the MAP. Numerous studies have shown that these strategies are associated with improved survival and favorable neurologic outcomes.[26] Though studies using a higher target of CPP

were associated with increased survival, a routine use of these maneuvers are not recommended based on higher incidence of ARDS.[27]

The effects of elevated ICP, particularly when persistent could lead to herniation of the brain. Herniation occurs across compartments with incomplete barriers. Typical sites of herniation include the transtentorial, across the falx cerebri, and through the foramen magnum. In addition to the compression of the brain, herniation compresses the cerebral vasculature leading to ischemic insults.

Hyperglycemia and Hypoglycemia

Over the last decade, there has been a raging controversy on the best management practice for glycemic control. While this is true for any critical illness including moderate and severe TBI, the pendulum seems to have shifted to a target blood glucose of 140 to 180. Intensive insulin therapy targeting a blood glucose of 80 to 110 is not regularly practiced as the benefits of tight glycemic control is offset by a higher incidence of hypoglycemia. Hypoglycemia can be particularly ominous in TBI patients as they have altered mental status and the symptoms may not be easily recognized. Both hyper- and hypoglycemia are associated with worsened outcome in severe TBI.[28,29] Hyperglycemia could lead to aggravation of secondary brain injury. Though the cellular mechanisms of hyperglycemia-induced cerebral injury are unclear, the possibilities include free radical generation with oxygen scavenging and alteration of the blood–brain barrier.

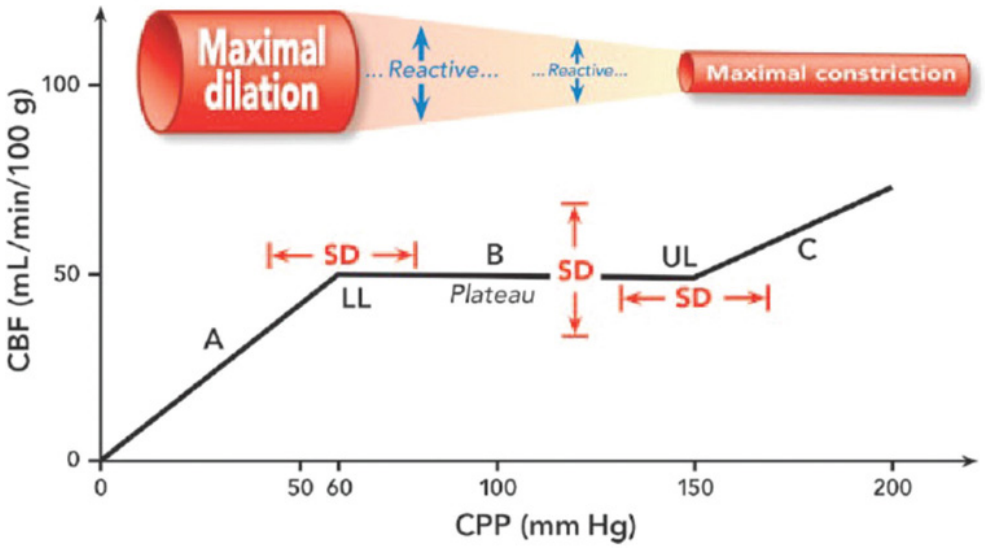

Figure 21.1 Cerebral autoregulation depicted in a graph with cerebral blood flow (CBF) in y axis and cerebral perfusion pressure (CPP) in x axis. Typically the autoregulation is maintained at CPP of 50 to 150 mm Hg. Cerebral vascular reactivity is additionally illustrated. (Adapted from Meng L, Gelb AW. Regulation of cerebral autoregulation by carbon dioxide. *Anesthesiology* 2015;122:196–205.)

Coagulopathy

Another potential reason for worsening of the primary insult is the effect of bleeding associated with coagulopathy. It is estimated that about one-third of patients with severe TBI develop a coagulopathy. The presence of coagulopathy, either from a primary neurologic injury or from blood loss and multivisceral trauma, are both associated with worsening of the neurologic outcomes and death.[30,31] It is equally important to recognize that patients with TBI with existing medical conditions placed on warfarin, aspirin, and antiplatelet agents have the potential of significant expansion of bleeding.

Other factors that have been shown to have the potential to increase brain injury include aggressive resuscitation with sodium free containing fluids and elevated intrathoracic and intra-abdominal pressure. Conditions such as fever and seizure activity that lead to increased metabolic demands on the brain add further insult to the injury as well.

Molecular and Cellular Mechanisms in TBI

The complexity of the brain combined with the heterogeneous nature of TBI makes it hard for one to characterize the precise nature of the biochemical

and cellular changes that occur in the brain following injury. It is well understood that neuroinflammation and neurodegeneration contribute significantly to the neurologic disability seen in patients with TBI. Though the acute traumatic event involves tissue and vascular disruption, it is important to recognize that there is abundant activation of glial cells, generation of inflammatory cytokines, and neutrophil recruitment. The microglia appear to be the major resident immune cell in the brain. Additional changes that have been documented acutely include alteration of calcium channels and sensors, apoptotic cell death, and generation of reactive oxygen species further increasing injury and inflammation. There is broad agreement about disruption of the blood–brain barrier that can lead to protein deposition in the extravascular space and this process can continue for prolonged periods of time. Persistent and chronic changes associated with microglial inflammation and posttraumatic neurodegeneration contribute to the long-term disability. Regardless of the better understanding of the pathophysiology of the brain, modulation of these processes has yet to translate into meaningful clinical therapeutic interventions.

CLINICAL ASSESSMENT

Assessment of a TBI patient in the emergency department should be run along the guidelines and principles established by the Advanced Trauma Life Support (ATLS). These are specific with respect to airway, breathing, and circulation, which take precedence over other areas enlisted under disability. Ongoing resuscitation along with securing large-bore IV lines, obtaining specific laboratory samples including an arterial blood gas and chest x-ray, are performed concurrently.

The importance of identification and treatment of associated injuries in a multisystem trauma patient cannot be overemphasized. Care must be taken to stop bleeding from external sources by application of direct pressure or a tourniquet. Identification of torso hemorrhage sources such as blunt injury to the spleen or pelvic fractures may require concurrent surgery or evaluation in a hybrid suite. Injuries that cause hypotension and hypoxia in patients with TBI have to be emergently addressed and additional secondary brain insults mitigated.

RADIOLOGIC ASSESSMENT

A noncontrast CT is the preferred imaging modality in any trauma patient with suspected TBI. This test should be done as soon as possible. The presence of hemodynamic instability can be an impediment with timely imaging by CT can. Focused assessment by sonography in trauma is a very valuable test in such situations. Combined with a chest x-ray, a negative FAST examination can provide guidance for further management in patients with suspected TBI in ruling out major thoracoabdominal hemorrhage as a cause of hypotension. A quick CT of the head and C-spine can be performed in such patients. On the other hand, a patient with hemodynamic instability with a positive FAST with blood in the abdomen with a GCS of 15 can be taken for an emergent laparotomy without any additional radiologic assessment of the head. The CT in addition could detect skull fractures, intracranial hematomas, and presence of cerebral edema. In addition to a GCS of ≤14, a full list of indications for obtaining CT scans and other radiologic techniques in patients with mild TBI is outlined in **Table 21.4**.

A follow-up repeat CT scanning should be performed with clinical deterioration. A repeat imaging in 6 hours is also indicated in patients with an extra-axial hematoma or intracerebral hematoma with a propensity to expand, such as seen in patients on anticoagulation. Additional CT scans may also be indicated in patients with a GCS <9,[32] particularly in patients where an awake examination cannot be safely performed. Evolution of CT findings is common and is likely to change the treatment strategy in a significant proportion of patients with severe TBI. In the absence of clinical deterioration contrast extravasation within the brain parenchyma may predict a higher risk of hemorrhage progression.[33]

The findings on the CT scan that carry the most ominous signs include cisternal compression with a midline shift of >5 mm. These signs are indicative of significant ICP elevation. Additional signs of elevated ICP that may require immediate intervention include severe cerebral edema and loss of gray–white matter junction. Epidural hematomas are typically distributed over the anterior and posterior portions of the temporoparietal area. They are lenticular in shape of mixed or high density depending on the age of presentation (**Fig. 21.2**). SDHs are crescentic lesions distributed over the convexity of the brain as they occur frequently from disruption of the bridging

cortical veins (Fig. 21.3). The incidence of underlying brain injury in the SDHs is much higher than with epidural hematomas. The underlying brain injury in these patients, and not the bleeding, correlates with neurologic outcomes and the degree of cerebral edema. Intracerebral hematomas are common following trauma and are seen as high-density lesions in the brain parenchyma (Fig. 21.4). Their distribution is related to the site of impact on the skull and has the potential to have a blossoming effect over time. Close observation and repeat imaging are considered as part of clinical guidelines in their management.

Table 21.4 Indications for Obtaining CT Scans in Mild TBI

High Risk for Neurosurgical Intervention
GCS less than 15 at 2 hrs after injury
Suspected open or depressed skull fracture
Any sign of basilar skull fracture (raccoon eyes, CSF otorrhea or rhinorrhea, hemotympanum)
Vomiting (more than 2 episodes)
Age more than 65 yrs
Use of anticoagulants
Moderate Risk of Brain Injury on CT
LOC for more than 5 min
Amnesia before impact (more than 30 min)
Dangerous mechanism (pedestrian vs. motor vehicle, fall more than 3 ft or 5 stairs)

From Steill IG, Wells GA, Vandemheen K, et al. Canadian CT head rule for minor head injury. *Lancet* 2001;357(9266):1391–1396.

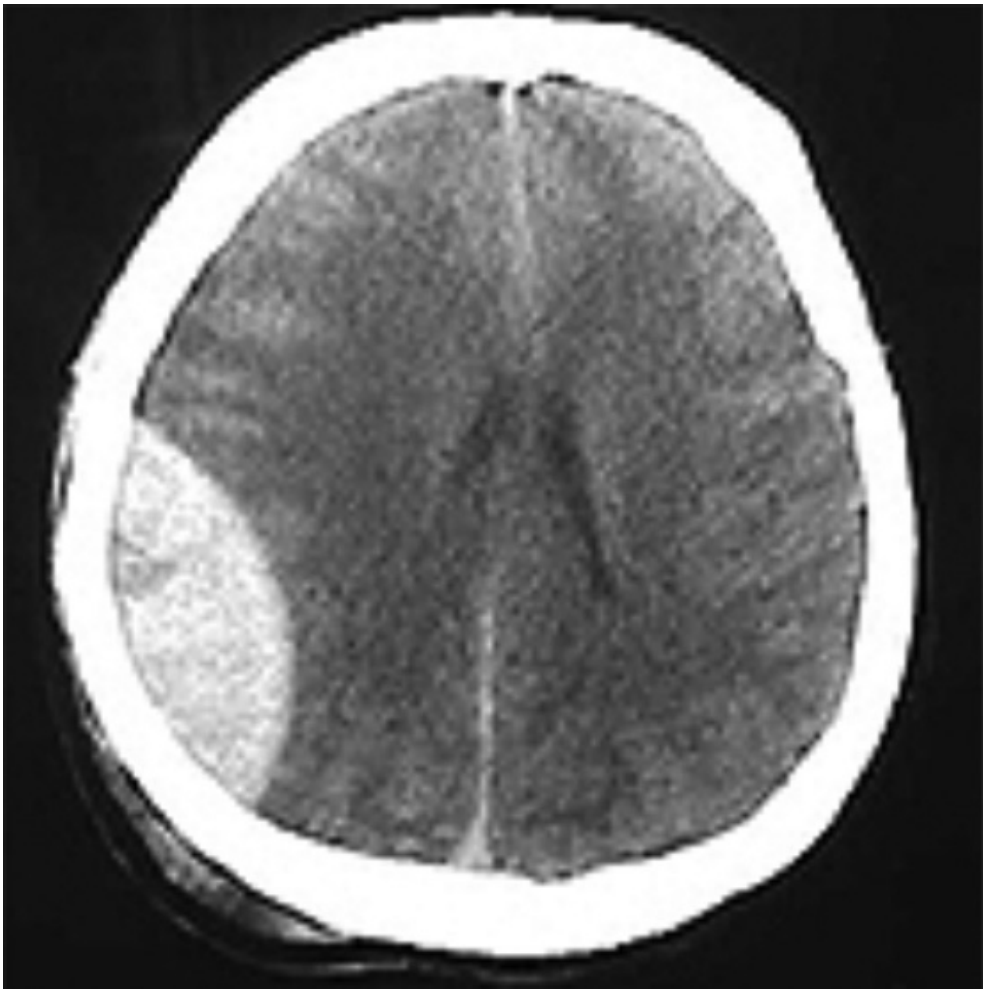

Figure 21.2 CT showing acute posttraumatic epidural hematoma.

Figure 21.3 CT showing acute left subdural hematoma with severe midline shift.

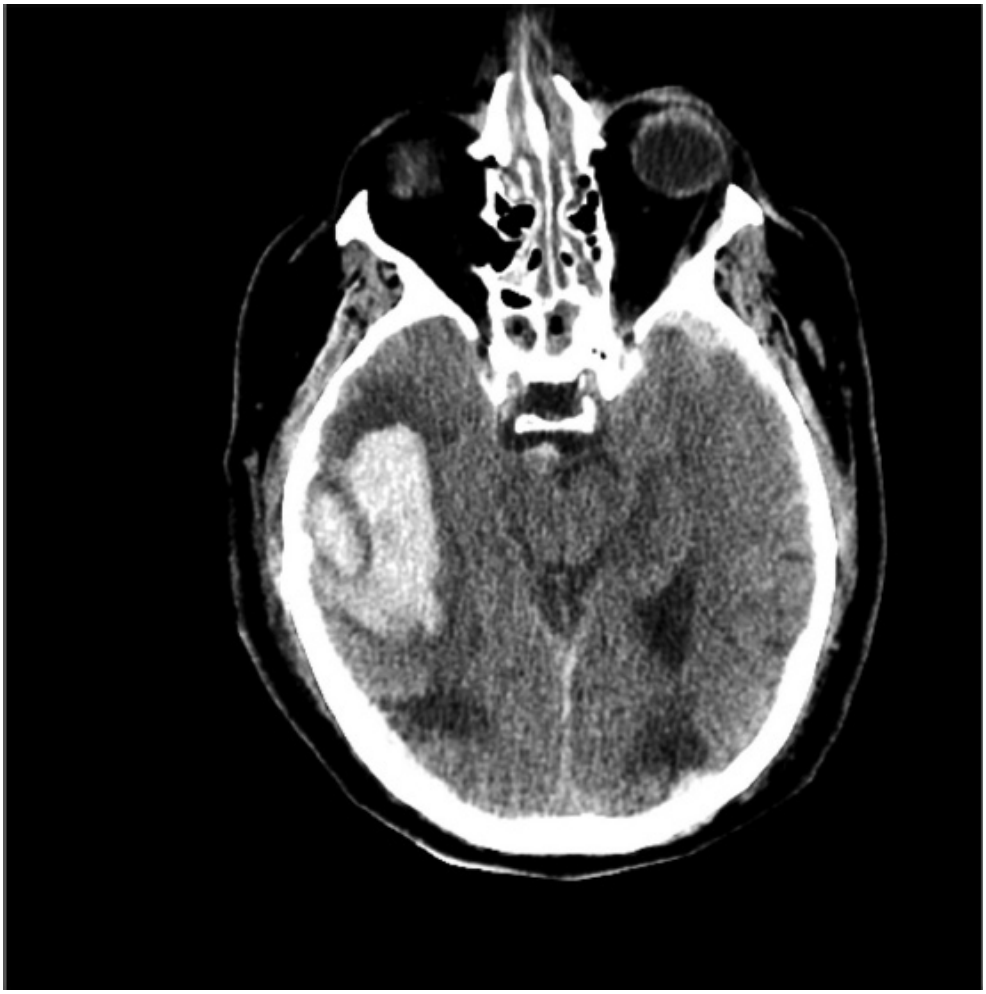

Figure 21.4 CT showing large right temporal contusion.

Subarachnoid hemorrhage appears as thin layer of blood on the surface of the parenchyma (**Fig. 21.5**). Careful study of the location of these hemorrhages helps differentiate posttraumatic SAH from ruptured intracranial aneurysms.

Other radiologic findings that help with the delineation of a therapeutic plan and prognostication in patients with TBI include the presence and degree of depressed skull fractures, extent of cerebral hematomas in addition to hemorrhagic contusions of the thalamus, basal ganglia, and the brain system.

3 Other radiologic tools such as MRI and diffusion tensor imaging[34] may be helpful in specific circumstances but not used frequently in the acute management of TBI. Studies involving nuclear medicine cisternography are

sometime indicated to delineate the site and presence of CSF rhinorrhea and otorrhea.

Figure 21.5 CT showing acute bifrontal traumatic subarachnoid hemorrhage.

MANAGEMENT OF BRAIN INJURIES

Broad Goals of Management

The key principles of management of a trauma patient remain the same, regardless of the specifics of injury. A major goal is to avoid the development of the "lethal triad" of hypothermia, acidosis, and coagulopathy. Additionally, the injured patient requires adequate oxygenation with

prioritization of injuries, reducing ongoing blood loss and treatment of hypotension.

Initial Resuscitation

Once airway, breathing, and circulation have been assessed and necessary interventions have been carried out to stabilize the patient, clinical assessment with GCS needs to be performed. Pupillary evaluation is of paramount importance. Handheld pupillometry is more commonly being used in the ICUs. They appear to be more reliable especially considering the poor interrater reliability of the qualitative pupillary examination. The pupilometer could be used to calculate the normalized neurological pupil index (NPi).[35,36] Pupillary dilation or loss of light reflex without significant changes either in the level of consciousness or other indicators of TBI should raise the possibility of local ocular injury or oculomotor dysfunction.

4 With TBI, early endotracheal intubation should be performed for all patients with a GCS <9.[23,37] Other reasons for emergent intubation include the inability of the patient to protect the airway (concurrent drugs/alcohol) and hypoxia due to other causes and inability to maintain SpO_2 >90% despite the use of supplemental oxygen. A notable inclusion is for patients who are identified as showing signs of clinical herniation or at risk for impending herniation. These signs include pupillary asymmetry, unilateral or bilateral fixed and dilated pupils, decorticate or decerebrate posturing, and the Cushing reflex of hypertension with bradycardia.[38]

The fluid of choice in early resuscitation involves a restrictive use of crystalloids including lactated Ringer's with a potential for correcting the metabolic acidosis from lactate accumulation. Additionally, balanced crystalloid solutions (e.g., lactated Ringer's and plasmalyte) have been associated with a reduced risk of acute kidney injury in critically ill patients. For patients with a dominant TBI, normal saline would be appropriate for its isotonicity. In TBI patients enrolled in SMART ICU study, no benefit was seen with the use of balanced fluids.[39] Electrolyte imbalances are common in patients with TBI and should be regularly assessed along with other laboratory parameters.

Current evidence indicates that rather than crystalloids, blood loss in trauma needs to be resuscitated with pRBC and component products. A ratio of 1:1:1 pRBC:FFP:platelets is the preferred mode of administration of blood products.[40,41] Most trauma centers follow the principles outlined in damage control resuscitation (**Table 21.5**).

There has been a resurgent role of thromboelastography or TEG in the management of bleeding trauma patient. For patients requiring massive transfusion, we suggest early TEG–based goal-directed resuscitation and management of fibrinolysis rather than treatment based on standard coagulation assays, when the technology is available.[42] However, the evidence for TEG is based on multiple clinical studies but without adequate randomization.

Table 21.5 Principles of Damage Control or Hemostatic Resuscitation

Damage Control or Hemostatic Resuscitation

- Prioritize hemorrhage control
- Permissive hypotension
- Avoid crystalloids
- Early component therapy (protocol driven)
- Adjuncts:
  - Correct hypothermia, acidosis, hypocalcemia
  - Antifibrinolytics

Neuromonitoring

ICP Monitoring

5 Elevated ICP is a strong predictor of subsequent neurologic deterioration in patients with severe TBI.[43] The primary rationale for ICP monitoring is therefore to detect potentially life threatening, but clinically occult, intracranial hypertension before clinical deterioration, cerebral herniation and death, or permanent neurologic injury occurs. Early detection of clinically occult intracranial hypertension permits the early initiation of ICP-targeted therapy. The previous edition of BTF guidelines for ICP monitoring

in TBI patients was broadly classified into the category of patients with a GCS ≤8 and an abnormal CT scan. However, the current guidelines recommend the use of invasive ICP monitoring in all patients with severe TBI, based on observational data that suggest reduction in short-term mortality with the use of ICP-targeted management.[26]

6 An external ventricular drain (EVD) connected to a transducer is considered the gold standard and cost-effective method of ICP monitoring. Additionally, an EVD can be used to treat elevated ICP with appropriate drainage of CSF. However, the presence of a midline shift and compressed ventricles (slit ventricles) make the placement technically challenging with a higher risk of bleeding. Intraparenchymal monitoring of ICP by placement of an intraparenchymal catheter is easier to perform and has a lower risk of hemorrhage and infection. An I7 CP goal ≤22 mm Hg is recommended for therapy as values above this level are associated with the increased probability of mortality and unfavorable neurologic outcomes.[44]

While monitoring of ICP has been considered the gold standard for management of severe TBI, a randomized study of patients with severe TBI (BEST TRIP) found no differences in outcomes where the management of the patients was subjected to a clinical and radiologic evaluation without ICP measurement.[45] The study was conducted in a low resource setting of Ecuador and Bolivia, where placement of ICP can be costly and associated with a higher risk of meningoencephalitis. The study also had a number of patients with delayed treatment and significant differences in the way the therapy was carried out in the two arms. Other studies[46,47] have, however, suggested that ICP monitoring is associated with an independent reduction in the inhospital mortality rates.

Pressure Reactivity Index

As indicated above, cerebral autoregulation is an important mechanism to preserve tissue perfusion, especially in patients with severe TBI and increased ICP. In an attempt at measuring the degree of cerebral autoregulation in individual patients, a few studies have evaluated the use of continuously monitored correlation coefficient between mean ICP and MAP. A direct correlation of ICP with MAP (pressure reactivity index [PRx] value = 1) would suggest that there is complete loss of autoregulation. On the other

hand, a lower PRx value such as 0.05 suggests the presence of cerebral autoregulation. In one study using this value, the investigators were able to predict survival and favorable outcome, respectively, in one study.[48] However, these measurements have not been routinely used in other centers.

Noninvasive ICP Monitoring

Optic nerve ultrasound (ONUS) is one of the best-evaluated noninvasive tools for the detection of intracranial hypertension, and is already in clinical use in several emergency departments and in settings where ICP monitoring is unavailable.[49–52] The optic nerve sheath (ONS) is a continuation of the dura and contains the subarachnoid space. An increase in ICP is transmitted through the subarachnoid space and results in distension of the retrobulbar ONS.[49–52] The optic nerve sheath diameter (ONSD) can be measured posterior to the globe using point-of-care ultrasound, and a threshold ONSD used to identify the presence of elevated ICP. Several studies have reported high accuracy of ONSD for the detection of elevated ICP.[49–52] However, the ONSD threshold to identify elevated ICP has varied greatly between studies. At present, this test is under investigation and based on the current understanding cannot be recommended as standard of care. Transcranial Doppler has also been evaluated for noninvasive ICP assessment, with mixed results.[53,54]

Role of Cerebral Oximetry and Microdialysis

Tissue oximetry has been investigated as a marker of tissue perfusion in many different types of vascular beds. Notable examples include sublingual, gastric, and cutaneous circulations. Measurement of brain tissue oxygen tension ($PbtO_2$) by placement of an oxygen electrode into the white matter is a similar technique that assesses tissue perfusion of the brain. While values above or equal to >20 $PbtO_2$ mm Hg are considered normal, persistent levels of $PbtO_2$ below 15 mm Hg are associated with worsened outcome.[23] A randomized clinical trial (BOOST-2) concluded that ICP and brain tissue oxygenation monitoring with a specific protocol reduced brain tissue hypoxia with more favorable outcomes than the ICP-only treatment arm.[55] Currently recruitment is being actively performed for a phase 3 trial (BOOST-3).

Cerebral microdialysis uses the minimally invasive approach to measure solute concentration in the brain. Similar to oximetry, an intraparenchymal probe is introduced. Typical measurement includes the products of anaerobic (lactate as an example) and aerobic oxidative phosphorylation (glucose, pyruvate, etc.).[56,57] Attempts are made to optimize therapeutic measures in response to a predominantly anaerobic and conversion to an aerobic state. These are currently in the investigational stages.

Medical Management of ICP Elevation

Basic principles of medical management of elevated ICP include elevating the head end of the bed and avoidance of factors such as increased intrathoracic pressure (such as PEEP) and intra-abdominal pressure (such as seen in abdominal compartment syndrome). These pressures are directly transmitted to the intracranial space.

Sedation and Analgesia

Effective analgesia is a critical first step in the management of intubated mechanically ventilated TBI patients. Additionally, patients with severe TBI do not have normal complaints or manifestations of pain. Fentanyl is the analgesic of choice because of short half-life and better hemodynamic profile compared with morphine and hydromorphone, which are the alternative choices. Though it may be reasonable to control the sedation with an effective use of analgesia alone, this approach in patients with elevated ICP is considered inadequate. Effective sedation lowers the ICP by lowering the metabolic demand, affecting the CBF and volume.[58] Propofol is the preferred agent for sedation in view of its very short half-life, reduction in ICP, and the ability to evaluate quickly with an awake neurologic examination with discontinuation.[59] Bradycardia and hypotension are common with propofol and this may require vasopressor infusion to maintain the CPP. For patients with severe TBI, with appropriate control of ICP, a Richmond Agitation-Sedation Scale (RASS) of 0 to 2 is preferred.[58] The routine use of neuromuscular paralysis in the control of ICP is not recommended and may actually prove harmful in the long run due to associated critical illness, polymyopathy and neuropathy.

Cerebrospinal Fluid Drainage

Drainage of CSF in patients with EVD is often the first intervention for lowering ICP following sedation and analgesia. The BTF guidelines recommend continuous CSF drainage for better control of ICP compared with intermittent drainage.[23] However, continuous drainage may lead to ventricular collapse and occlusion of the catheter, particularly with slit ventricles.

Osmotic Therapy

Osmotic therapy involves the administration of a hyperosmolar agent in an attempt to reduce the degree of cerebral edema by diffusion of water across the blood–brain barrier. It is generally recommended as the next step following sedation, analgesia, and ICP drainage in patients with refractory ICP. The most common agents used include mannitol and hypertonic saline. Mannitol is used as 0.25 to 1 g/kg body wt as the initial dose for osmotherapy. It can be administered every 4 to 6 hours. It is also known to be a free radical scavenger. However, with its use, no specific hyperosmolar treatment protocol has been shown to improve function outcome or mortality in clinical trials. Hypertonic saline is an effective hyperosmolar agent for the control of elevated ICP.[60,61] With continuous infusion, 3% NaCl may be titrated to an initial sodium goal of approximately 145 to 155 mEq/L. Hypertonic saline could cause extravasation injury when used through a peripheral line and a central line with higher flow is typically preferred. Hypertonic saline has several advantages over mannitol including lesser incidence of hypovolemia and hypotension.[60] However, repeated administration of hypertonic saline can cause serious metabolic abnormalities including hyperchloremia and nonanion gap metabolic acidosis. There is no convincing evidence to clearly state that one agent is better than the other. The effect of hyperosmolar therapy diminishes with time, as a compensatory increase in brain osmoles occurs within 24 hours.[62]

Seizure Prophylaxis

Seizure prophylaxis is generally recommended for all severe TBIs. The incidence of seizures following TBI has been widely reported as 15% to 30%[63] and typically peak in the first 2 weeks following the trauma. Though

the use of anticonvulsant has been shown to reduce the incidence of early seizures, there is no lasting effect identified on the incidence of long-term epilepsy.[64] In the early period following TBI, seizures constitute a well-identified etiology for aggravation of secondary brain insult by increasing the metabolic demand on the brain in addition to increasing CBF and ICP. About one-fourth of all patients with TBI also suffer nonconvulsive seizure activity, typically identified on 24-hour EEG monitoring.[63,65]

Most neurosurgical and trauma programs around the country have switched over from phenytoin to levetiracetam (Keppra) as the drug of choice. Phenytoin use over multiple years has been associated with worse functional outcomes especially in patients with SAH. However, in a head-to-head comparison, there was no difference in efficacy in controlling seizures between these two agents.[66]

Role of Tranexamic Acid

Over the last decade, it has been increasingly clear that pathogenic fibrinolysis following trauma and particularly TBI play an important role in ongoing bleeding, coagulopathy, and therefore increased mortality. Tranexamic acid (TXA) is the agent most used in clinical trials. The most definitive study, the CRASH-3 trial used a pragmatic approach in their study design that included multiple countries including many considered in the low- and middle-income group. The authors concluded that administration of TXA within 3 hours of injury is beneficial in TBI with GCS <13. This benefit translated into mortality improvement particularly when patients with bilateral dilated pupils were excluded from both the placebo and TXA groups.[67]

TXA is administered as 1 g IV infusion over 10 to 15 minutes followed by a gram administered every 8 hours for the first 24 hours in these patients.

Early Enteral Nutrition

Early enteral nutrition either through a nasogastric tube or postpyloric silastic tube is recommended for all patients with TBI. Though there was earlier study to indicate that earlier enteral nutrition is associated with lesser incidence of pneumonia and mortality,[68] a subsequent randomized study did

not show any difference in either pneumonia or mortality rates between early and delayed enteral nutrition.[69]

Others

Trauma including TBI is identified as a unique high-risk factor for the development of thromboembolism. We typically initiate early thromboprophylaxis with enoxaparin as 40 mg/day or 30 mg twice a day once it is established that a repeat CT scan does not show any progression of hemorrhage. This practice is based on a combination of data obtained from multiple clinical and observational studies analyzed in a meta-analysis that showed safety in patients with TBI.[70]

Febrile activity is a known cause of secondary brain injury with its propensity to increase cerebral metabolism, increases CBF and therefore ICP.[71] Therefore, control of fever is strongly recommended either with antipyretics or external and intravascular cooling devices. About 10% of patients also exhibit signs of paroxysmal sympathetic hyperactivity that include hyperdynamic circulatory response in addition to posturing and increased tone. Specific therapy includes hydration and nonselective beta blockade in addition to the exclusion of other diagnoses such as sepsis and pulmonary embolism.

Therapeutic Intensity Level and Management Parameters to Control ICP

In an attempt to understand the interpretation of ICP measurements without realization of the associated therapeutic maneuver undertaken, Maas and co-authors devised a therapeutic intensity level (TIL).[72] The TIL was charted for basic and moderate scales. The basic scale is outlined in **Table 21.6**. Subsequent study has validated the TIL scoring system of the management of ICP in the intensive care units by studying them at 4- and 24-hour time points. The authors concluded that the TIL scale is a reliable measurement instrument with a high degree of validity for assessing the TIL of ICP management in patients with TBI.

Management of Impending Cerebral Herniation

Patients admitted with a severe TBI should be subjected to 2 hourly neurologic assessments. This should include discontinuation of propofol and other sedatives. Neurologic signs of herniation include new-onset fixed and dilated pupils, decorticate or decerebrate posturing, or hypertension with bradycardia. Immediate maneuvers proved to be of benefit are listed in **Table 21.7**. These interventions include brief hyperventilation[73] and osmotherapy.[74,75] It is important to recognize that such interventions are often temporary and a repeat CT scan may be indicated to evaluate the need for additional surgical intervention.

SURGICAL APPROACH

Skull Fracture

Skull fractures are extremely variable in both their presentation and management. Closed linear convexity skull fractures without significant displacement can typically be managed conservatively without any specific restrictions or precautions. Conversely, open fractures with significant depression causing mass effect upon the brain parenchyma typically require washout and elevation of bony fragments. Skull base fractures require special care and evaluation. Clinically, skull base fractures may present with CSF rhinorrhea or otorrhea, raccoon eyes (bruising around the orbit), or Battle sign (bruising behind the ears). On imaging, fluid within the mastoid air cells or sphenoid sinus should raise concern for a skull base fracture. Pneumocephalus can also help identify fractures. Due to their proximity with the intracranial circulation, skull base fractures pose a risk for cerebrovascular injury such as dissection or pseudoaneurysm formation (**Fig. 21.6**). Fracture lines that are in close approximation to structures such as the carotid canal warrant further imaging with CT angiography. Skull base fractures also pose a risk for CSF leak, particularly with fractures in the frontal sinus, cribriform plate, or ethmoid/sphenoid sinuses. Surgical repair may be indicated in these cases. Surgical treatment entails cranialization of

the frontal sinus (removal of the posterior wall of the frontal sinus), stripping of the mucosa in the sinus, and pericranial flap placement along the anterior skull base. Abdominal fat may be harvested to pack the sinuses. In certain cases, endoscopic endonasal approaches may be appropriate rather than open craniotomy.

Table 21.6 Basic Scale for Therapeutic Intensity Level (TIL)

TIL 0—No Specific ICP-Directed Therapy
TIL 1—Basic ICU Care ▪ Sedation for ventilator/endotracheal tube tolerance ▪ Volume/Vasopressors for non-CNS cause (e.g., sepsis, myocardial injury) ▪ Head up positioning (ventilator bundle) ▪ Normocapnia ($PaCO_2$ ≥40 mm Hg)
TIL 2—Mild ▪ Higher levels of sedation ▪ Vasopressors/Volume for CPP support ▪ Low-dose osmotic therapy ▪ Mild hypocapnia ($PaCO_2$ 4.6–5.3 kPa; 35–40 mm Hg) ▪ CSF drainage <120 mL/day (<5 mL/hr)
TIL 3—Moderate ▪ Higher doses of osmotic therapy ▪ Moderate hypocapnia ($PaCO_2$ 4.0–4.5 kPa; 30–35 mm Hg) ▪ Mild hypothermia (>35°C) ▪ CSF drainage ≥120 mL/day (>5 mL/hr)
TIL 4—Extreme ▪ Profound hypocapnia ($PaCO_2$ <4.0 kPa; <30 mm Hg) ▪ Hypothermia <35°C ▪ Metabolic suppression for control of ICP ▪ Surgery for refractory ICP (decompression, lobectomy)

Table 21.7 Immediate Management of Impending Cerebral Herniation

Endotracheal intubation, if not already performed
Elevation of the HOB to 30–45 with the head in neutral position to promote venous drainage
Brief hyperventilation to a pCO_2 of approximately 30 mm Hg[72]
Osmotherapy with either mannitol 1–1.5 g/kg[73] or 23.4% hypertonic saline[74]
Higher mean arterial pressure (MAP), to approximately 80–100 mm Hg, to maintain an adequate cerebral perfusion pressure (CPP) with fluids ± vasopressors
Definitive surgical interventions when indicated

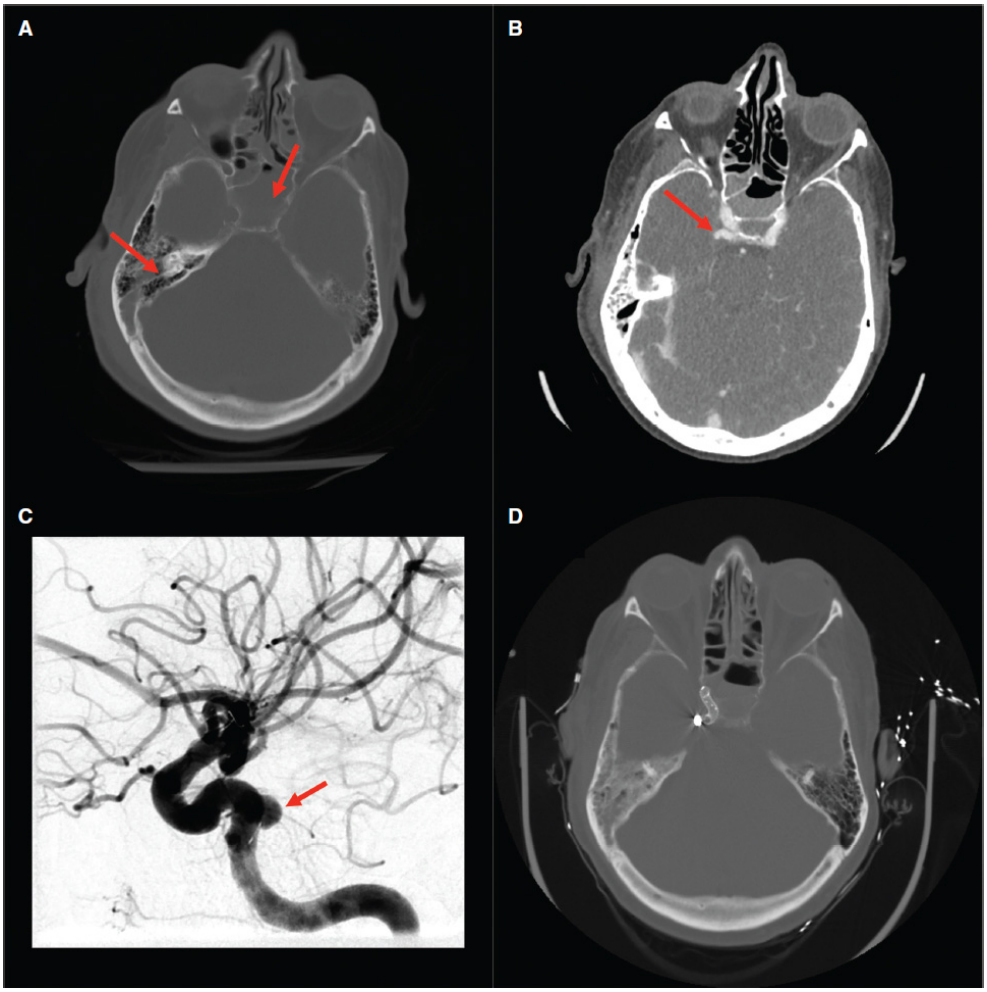

Figure 21.6 **A:** Initial CT showing fluid in the right mastoid air cells and sphenoid sinus (*red arrows*), raising suspicion for skull base fracture. **B:** CT angiography and (**C**) digital subtraction angiography showing a pseudoaneurysm (*red arrows*) of the right cavernous internal carotid artery. **D:** Stent-coil embolization of the pseudoaneurysm.

Epidural Hematoma

Epidural hematomas are typically thought to arise from laceration of the middle meningeal artery, causing arterial bleeding between the dura and skull. In many cases, there is a skull fracture in the pterion. Smaller epidural hematomas, particularly in other locations, can be due to dural lacerations and skull fractures. Hematomas that cross the midline may involve injury to the dural venous sinuses. Given the high pressure and high flow through the MMA, epidural hematomas can rapidly expand, leading to sudden coma and death. Classically, a "lucid interval" is described, where a patient is initially

neurologically intact, with subsequent rapid deterioration. Emergent surgical decompression is warranted for evacuation. A temporal craniotomy is usually sufficient to evacuate the hematoma and coagulate the torn MMA. If performed prior to a herniation syndrome, patient outcomes can be excellent.[76]

Subdural Hematoma

SDHs can present acutely after severe trauma or in a subacute fashion from minor trauma or even in the absence of a history of trauma. In acute severe TBI, an SDH causing significant midline shift (>5 mm) and neurologic deficits may warrant an emergent surgical evacuation. In certain circumstances, ICP monitoring may be pursued in lieu of immediate surgery. Surgery for acute SDH typically involves a large unilateral craniotomy in order to adequately evacuate the gelatinous clot. In many circumstances with elevated ICP, a craniectomy is pursued in order to ensure that the brain is sufficiently decompressed. A randomized trial is currently ongoing to evaluate differences between craniectomy and craniotomy in this population (RESCUE-ASDH).[77] As opposed to acute SDH, chronic or subacute SDH is a disorder of the elderly. As SDHs age, they tend to liquefy. Due to this, chronic or subacute SDH causing neurologic symptoms may be evacuated through burr holes or a small craniotomy (**Fig. 21.7**).

Parenchymal Contusions

Parenchymal contusions pose a difficult dilemma for management. They tend to occur in the basal frontal lobes or in the temporal lobes. Contusions typically “blossom” or enlarge over the course of several days. Therefore, contusions rarely require emergent surgery at initial presentation. However, due to their enlargement, coupled with a significant edematous reaction of the surrounding parenchyma, patients tend to deteriorate 3 to 7 days, post trauma. Close neurologic monitoring should be carried out during this time, and ICP monitoring may be warranted. Patients with temporal contusions are at particular risk for developing uncal herniation even in the absence of ICP elevations. Conversely, patients with bifrontal contusions may develop global ICP elevations. Decompressive craniectomy (DC) is warranted if

medical management is unsuccessful. For bifrontal contusions, a bifrontal craniectomy is typically performed. In the case of temporal contusions, a unilateral craniectomy is performed.

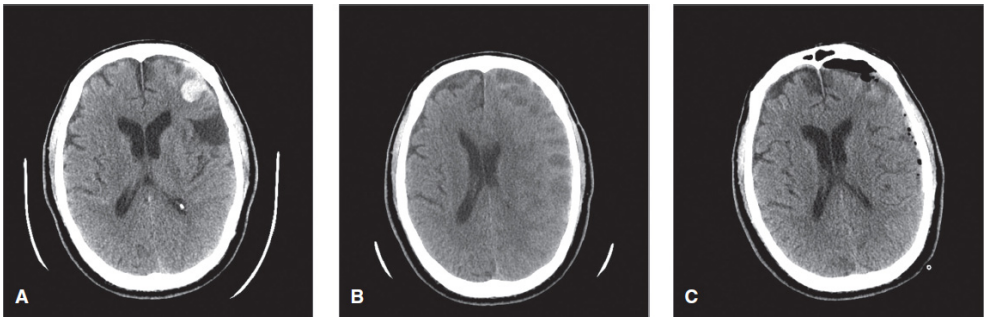

Figure 21.7 **A:** Initial CT showing a left frontal contusion with associated small subarachnoid and subdural hemorrhage. **B:** Follow-up CT at 2 months showing resolution of the contusion, but development of a large loculated subdural hemorrhage causing significant mass effect and midline shift. **C:** Postoperative CT showing evacuation of the hemorrhage with resolution of mass effect.

Diffuse Axonal Injury

DAI occurs due to shearing forces from blunt trauma affecting axons throughout the brain. It can be difficult to identify on CT, but can be seen readily on MRI. DAI can also occur concurrently with other traumatic intracranial pathology. DAI is typically a nonsurgical entity and is managed medically with ICP monitoring.

Penetrating Injuries to the Brain

Gunshot wounds (GSWs) comprise the vast majority of penetrating brain injuries. Most patients with GSWs to the head either die in the field or do not survive initial resuscitation. Physical examination and CT should be used to evaluate the path of the bullet. Bihemispheric injury, and particularly bithalamic injury, portends an extremely grim prognosis. However, if a patient is able to be stabilized hemodynamically and has evidence of brain function, emergent surgical treatment is necessary. Due to the cavitation injury by the bullet, patients develop rapid malignant cerebral edema (**Fig. 21.8**). Therefore, surgery should involve a large DC. Due to the significant risk of direct blood vessel injury, voluminous blood loss is typical and intraoperative death is a major concern. During decompression,

any concomitant hematomas should be evacuated. Similarly, devitalized scalp should be resected, and any air sinuses encountered should be exenterated. Bone and bullet fragments that are deep in the parenchyma should not be retrieved due to the risk of causing further injury.

Non–gunshot-penetrating trauma usually involves low-velocity objects such as knives, arrows, nails, etc. In these cases, preoperative CT angiography is helpful to identify if there is an injury to a major blood vessel. If the object is still embedded when the patient presents, it should not be removed until in surgery. In these cases, a craniectomy is typically necessary with careful extraction of the embedded object. If the object is not embedded, the patient may be managed similar to a closed head injury.

Role of Decompressive Craniectomy

DC continues to be a mainstay in the surgical treatment of severe TBI. The rationale for DC is that it is a rapid, reliable, and sustainable intervention to decrease ICP. It may be performed either immediately at the time of severe TBI (primary DC), or in a delayed fashion if nonsurgical methods for ICP control have failed (secondary DC). Nevertheless, the role and indications for craniectomy continue to be controversial. While control of ICP with DC is undeniable, there has not been definitive evidence that DC leads to improved clinical outcomes.[78]

There have been two major randomized trials evaluating secondary DC. The DECRA trial was first published in 2011.[79] In this study, 155 patients were randomized to bifrontal craniectomy versus standard of care nonsurgical treatments. The inclusion criteria were patients within 72 hours of injury with diffuse severe TBI who had intracranial hypertension. This was defined as ICP >20 mm Hg for over 15 minutes within a 1-hour time period, despite standard of care medical interventions. Surgical treatment was standardized to be a bifrontal craniectomy. Outcomes were measured with the GOS-E at 6-month follow-up. The results of the trial found that while DC led to a decrease in mortality, it also led to more patients in a vegetative state or with severe disability. DECRA was limited by significant flaws. The inclusion criteria ICP led to a median ICP *prior* to randomization of 18 to 22 mm Hg. In addition, only diffuse TBI was included. Finally, a

bifrontal craniectomy was used, which is atypical for practice, particularly in the United States, where hemicraniectomy is preferred.

RESCUEicp was published in 2016.[44] In this trial, 408 patients were again randomized to DC or standard nonsurgical management. Differing from DECRA, the investigators included any severe TBI with an abnormal CT. ICP for inclusion was >25 mm Hg for 1 to 12 hours despite nonsurgical methods. In addition, patients who underwent craniotomy for mass lesion earlier in their course remained eligible. The surgical approach for decompression was not standardized. Primary outcome was GOS-E at 6 months, while secondary outcomes were at 12 months. The results showed that DC again led to a significant improvement in survival with a similar increase in patients in vegetative state or with severe disability. However, at 12 months, surgical patients showed an increased rate of living independently when compared to the medical group. RESCUEicp benefitted from being a more “real-world” situation but was significantly limited by crossover (37.2% of the medical group eventually had a craniectomy).

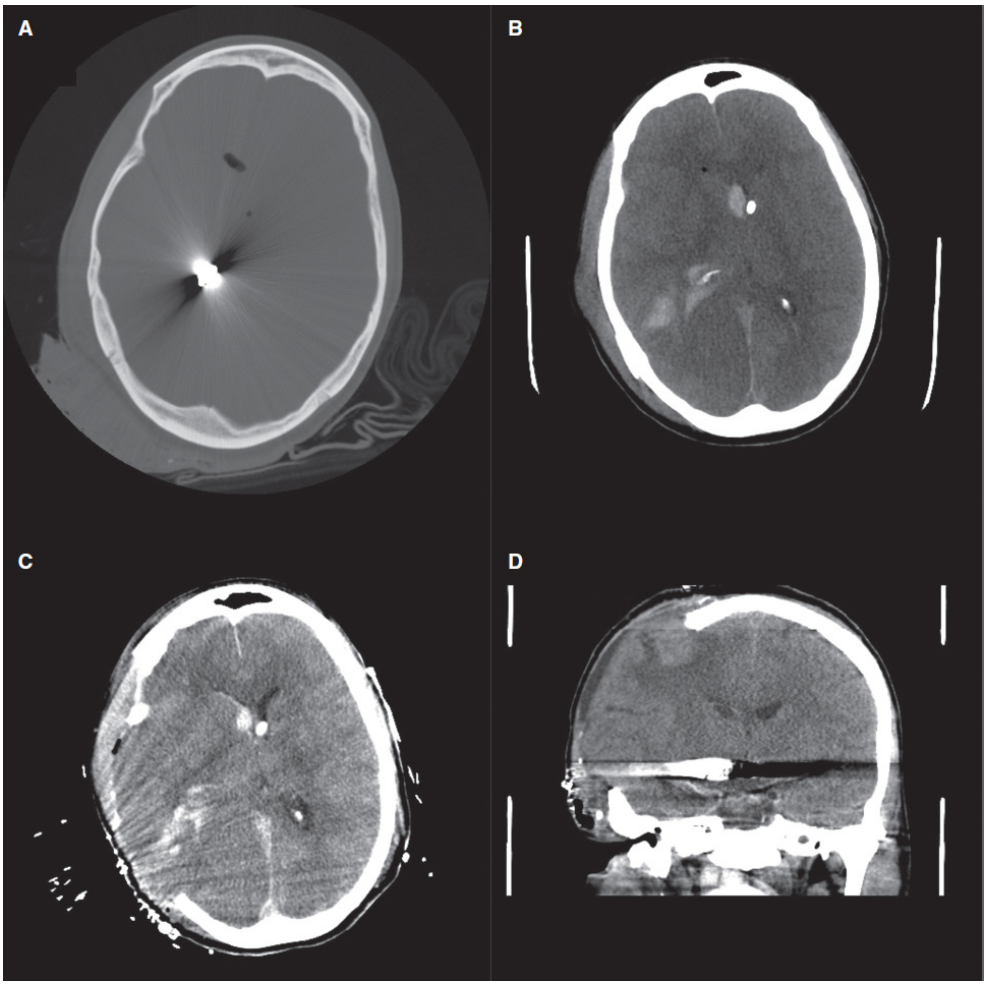

Figure 21.8 **A:** Initial CT showing intracranial bullet fragment. **B:** Development of progressive hemorrhage and mass effect. Ventriculostomy catheter can be seen on the left side. **C, D:** After right decompressive craniectomy, mass effect is relieved and brain parenchyma can be seen herniating through the craniectomy defect.

PROGNOSIS

Outcome from severe head injury is dependent on a range of factors (**Table 21.8**). It is important to remember that none of these factors in isolation are as important as a collective evaluation. While a few studies have utilized biomarkers such as serum and CSF levels of S-100β protein, neuron-specific enolase, and α-synuclein,[80] others are currently being investigated.

Clinical prediction models that incorporate known predictors of death and poor long-term functional outcome have been developed. The CRASH prediction model, which incorporates age, country, GCS, pupillary reactivity, the presence of extracranial injury, and CT findings to predict 2-week mortality and 6-month functional outcome, was developed using data from a large international multicenter clinical trial of glucocorticoids in TBI.[81] The IMPACT model, derived from 8,509 patients, uses age, GCS, pupillary reactivity, the occurrence of hypoxia and hypotension, the Marshall CT grade, presence of traumatic SAH, presence of epidural hematoma, glucose and hemoglobin levels to predict 6-month mortality and functional outcome.[82] These models are best applied to large cohorts, however, and should not be used to guide management decisions in individual patients or counsel families.

Table 21.8 Factors that Determine Prognosis in Patients with TBI

GCS at Presentation (Motor Score—Most Important Prognosticator)
CT—high-grade subarachnoid hemorrhage, cisternal effacement, midline shift
Pupillary function
Age—older age associated with poor prognosis
Presence of factors that cause secondary brain injury—hypotension, hypoxemia, and fever
Elevated intracranial pressure (ICP) and reduced cerebral perfusion pressure (CPP)
Associated coagulopathy
Diffuse axonal injury and brain stem injury

Overall patients with severe TBI (GCS ≤8) have an approximately 30% to 40% mortality. A sizable fraction of patients (1/3 to 2/3) with severe TBI will regain some independence.[83] Considering the degree of injury could be profound and each area of the brain has a different degree of ability to heal or exhibit varying degree of neuroplasticity, functional recovery may take up to a year to fully materialize.[84] It is also known that a small proportion (close to 10%) of patients with severe TBI may end up in a vegetative state.[85]

Among patients with more moderate TBI pretrauma, educational attainment is associated with increased odds of disability-free recovery.[86]

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22

Injury and Violence Prevention: A Public Health Approach

Joseph V. Sakran and Nicole Lunardi

Key Points

1 Injuries are preventable, and we should therefore avoid using the term "accident."

2 Injury prevention requires a multidisciplinary team, including education, health care, criminal justice, legislature, communications/media, business, and community organizations.

3 Violence is a public health problem.

4 Healthcare systems must engage the community in addressing the social determinants of health of disease, which contribute to structural violence in underserved communities.

5 Injury and violence prevention takes place on a continuum: before the injury occurs (primary prevention) or after the injury occurs by minimizing the mortality, likelihood of reoccurrence (secondary prevention), and reducing long-term morbidity (tertiary prevention).

6 Our medical organizations must commit to working together in order to provide constructive actions that reduce injury and death in communities across America.

7 Surgeons have a critical role in social movements and advocating for evidence-based solutions.

HISTORY OF INJURY PREVENTION

1 The field of injury prevention is young. Its roots trace back to occupational hazards in the first half of the 20th century. Injuries, at the time, were considered true accidents: random, unavoidable, or, even, acts of God. Thus, the notion of systematically preventing "accidents" was novel. The National Safety Council, created in 1913, distributed information related to industrial hazards. Simultaneously, thought leaders were studying national trends and analyzing the circumstances of workplace "accidents." Julian Harvey put forth the first framework of accident control in 1923, which became known as the "three Es": education, engineering, and enforcement.

Despite these advancements, many workplace injuries were still considered unavoidable accidents.[1,2]

Starting in the mid-20th century, the paradigm shifted toward developing evidence-based injury prevention. Federal agencies teamed up with local health departments to educate the public and implement prevention programs. Epidemiologists applied the principles used to describe disease to injuries: host demographics, causal agents, environments, seasonal/cyclical trends, distributions, and epidemic episodes.[3–5] By 1972, William Haddon Jr, the director of the National Highway Safety Bureau, proposed a framework to describe the interaction between causal factors regarding the host, agent, and environment before, during and after the injury. The Haddon Matrix allowed for strategic prevention efforts. He is credited as the father of modern injury epidemiology.[6]

In the same period, basic scientists were describing the mechanisms by which energy transfer (kinetic, electric, chemical, etc.) caused tissue damage for the first time.[7] These discoveries allowed for the production of safer products, like padded dashboards, air bags, and seat belts in cars. Product safety along with the development of the first regional trauma systems worked to decrease severity of injury and increase survival through prompt medical treatment.[1]

By the late 20th century, a robust group of stakeholders, including basic scientists, engineers, epidemiologists, healthcare workers, local, state and national health agencies, and nonprofit organizations were building a coalition to establish the science of injury prevention. Representing a true shift in understanding, the word "accident" was replaced with the word "injury" in International Statistical Classification (ICD) codes in 1979.[1,2] The trauma community has worked to shift daily terminology to reflect the firmly grounded principle that injuries are preventable. That is, avoiding the use of "motor vehicle accident" and shifting to "motor vehicle crash."

Advancements in the field were contemporaneous with the emergence of injury as a leading cause of death in the United States. In fact, injury has been in the top 15 causes of death of all Americans since 1965 (https://www.cdc.gov/injury/wisqars/LeadingCauses_images.html).[8] In 1966, the National Academy of Sciences landmark paper, "Accidental Death and Disability: The Neglected Disease of Modern Society," identified the need for improved care of the injured patient.[9] In 1985, the Department of

Transportation along with the National Academy of Sciences and Institute of Medicine drew attention to injury being responsible for more life years lost than cancer and heart disease, but having the smallest funding allocation with no central agency in "Injury in America."[10] That very year, the Centers for Disease Control and Prevention (CDC) Injury Control Pilot Program was created. It oversaw and funded multidisciplinary research centers and demonstration projects. The pilot program was found to be efficacious in a 1988 review. By 1990, the Injury Control Act was signed reauthorizing the CDC-based program.[2] These groundbreaking papers brought the burden and cost of injury into focus, which led to the development of injury prevention infrastructure.

Over the course of the century, the field of injury prevention was created with the overarching goal to reduce the morbidity, 2 mortality, and economic burden of injury. The field is, by definition, multidisciplinary, drawing on the expertise from basic scientists, engineers, epidemiologists, health systems and administrators, healthcare workers, educators, the private sector, and numerous others.

EPIDEMIOLOGY OF INJURY: DEFINING THE PROBLEM

The CDC's National Center for Injury Prevention and Control (NCIPC) collects and stores national injury data on the Web-based Injury Statistics Query and Reporting System (WISQARS: cdc.gov/injury/wisqars/index.html).[8] Made available for the first time in 2000, WISQARS includes the 1981–2018 data on fatal and nonfatal injury, leading causes of death and injury, violent deaths (homicides and suicides), years of potential life lost, and cost of injury. This data is compiled from sources, including the National Vistal Statistics System, National Electronic Injury Surveillance System—All Injury Program, the Pacific Institute for Research and Evaluation, and the National Violent Death Reporting System (NVDRS: cdc.gov/violenceprevention/datasources/nvdrs/index.html).[11] In 2002, the NVDRS started collecting homicide and suicide data from 6 states and has grown to include all 50 states, Puerto Rico, and Washington, DC by

2018. The NVDRS is unique in that it collects data from law enforcement, medical examiners, and death certificates regarding the violent incident (geography, weapon used), characteristics of the victim (mental and physical health problems, toxicology reports, substance abuse, financial problems), and the relationship between victim and suspect (nature of relationship, relationship problems, and intimate partner violence [IPV]).

Injury data can be studied from many different perspectives, with the two most common being by intent and mechanism. Intent, as captured by the ICD codes, falls into the following major categories: unintentional, suicide/self-harm, homicide/assault, and legal intervention. There is a small percentage of cases each year for which the intent is not determined (2.3% in 2018). Mechanism describes the way by which the injury occurred. Common mechanisms of injury include transportation (motor vehicle collision, pedestrian, cyclist), penetrating injury (firearm, cut/pierce), blunt injury (stuck, fall), drowning, suffocation, burns, and poisonings (drug, nondrug). For the purposes of a complete discussion, trends regarding both intent and mechanism will be explored.

Unintentional Injury

Unintentional injury has consistently been among the leading causes of death for Americans regardless of age, race/ethnicity, and sex, claiming 167,127 lives in 2018 alone. It was single leading cause of death for all Americans aged 1 to 44 between 2000 and 2018. The most common mechanisms of these deaths varied based on age: drowning (age 1 to 4), motor vehicle crashes (age 5 to 24), and poisonings (age 24 to 44). For every single fatality, there were 218 nonfatal unintended injuries in 2018.

From 2001–2018, 10,722 fatal and 309,289 nonfatal unintended injuries involved a firearm. While the age-adjusted rates of unintended firearm fatalities has been steadily decreasing (0.76 in 1981 to 0.14 deaths/100,000 population in 2018), the trend in nonfatal firearm injuries has been labile (**Fig. 22.1**).[8]

Suicide and Self-Harm

Overall, suicide is the 10th leading cause of death for all Americans with 48,344 deaths in 2018. Suicide rates are higher in men than women. Men are more likely to use a firearm, whereas women are likely to die from poison or suffocation. Greater than half of all suicide deaths are committed with a firearm (**Fig. 22.2**). Among American men, older White and younger American Indian men have higher suicide rates than Blacks or Asians (**Fig. 22.3**).[8] This racial and age disparity has been well documented.[12,13]

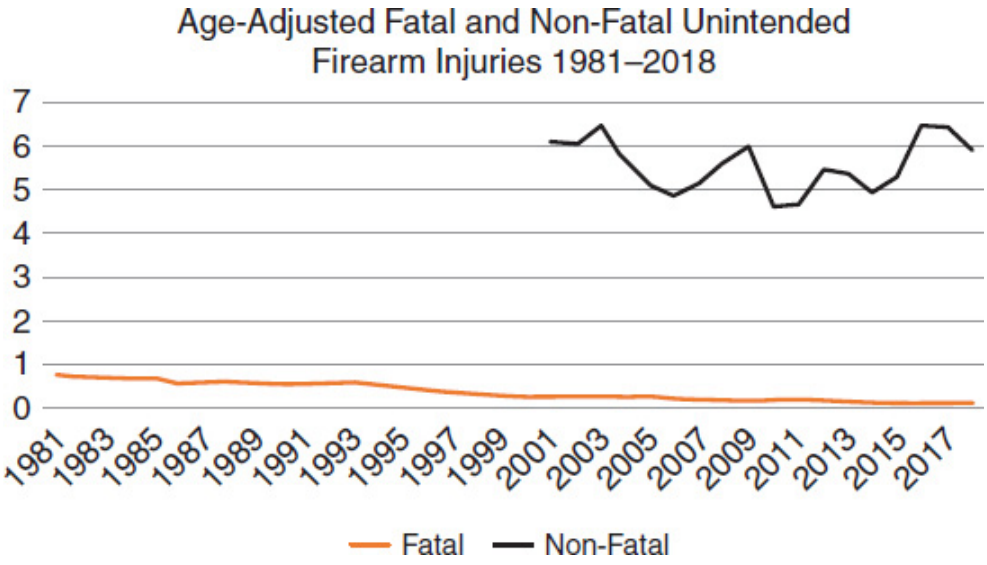

Figure 22.1 Age-adjusted fatal and non-fatal unintended firearm injuries per 100,000 persons. (Data sourced from WISQARS *Data from* National Center for Injury Prevention and Control. WISQARS [Web-based Injury Statistics Query and Reporting System], Injury Center, Centers for Disease Control and Prevention: Injury Prevention & Control Data and Statistic [WISQARS]. https://www.cdc.gov/injury/wisqars/index.html. Published March 30, 2020. Accessed June 15, 2020.)

Between 2001 and 2018, for every single suicide there were 11 self-harm injuries. These nonfatal injuries are more common among women (**Fig. 22.4**) and are most likely to involve poisoning or cutting. There are so few failed suicide attempts involving a firearm that the absolute number is not reported. Surviving a suicide attempt with a firearm is very unlikely given the high lethality of the weapon.[8]

Homicide and Assault

Homicides are less common than unintentional injury and suicides in the United States. The Major Cities Chief Association, representing 70 law enforcement agencies, identified that the homicide rate has been increasing in two-thirds of all major cities.[14,15] In 2018, there were 18,830 homicides. The majority of deaths were among males 15 to 44 years of age (**Fig. 22.5**). Racial and ethnic minorities' risk of death from homicide is significantly higher than non-Hispanic Whites. Young, Black males (aged 15 to 34), in particular, have the highest homicide rate (**Fig. 22.6A,B**). In fact, it is the leading cause of death in this population. Of all homicides between 1981 and 2018, 70% used a firearm. For every homicide death, there are 93 nonfatal assaults. Approximately 4% of nonfatal assaults involve a firearm.[8]

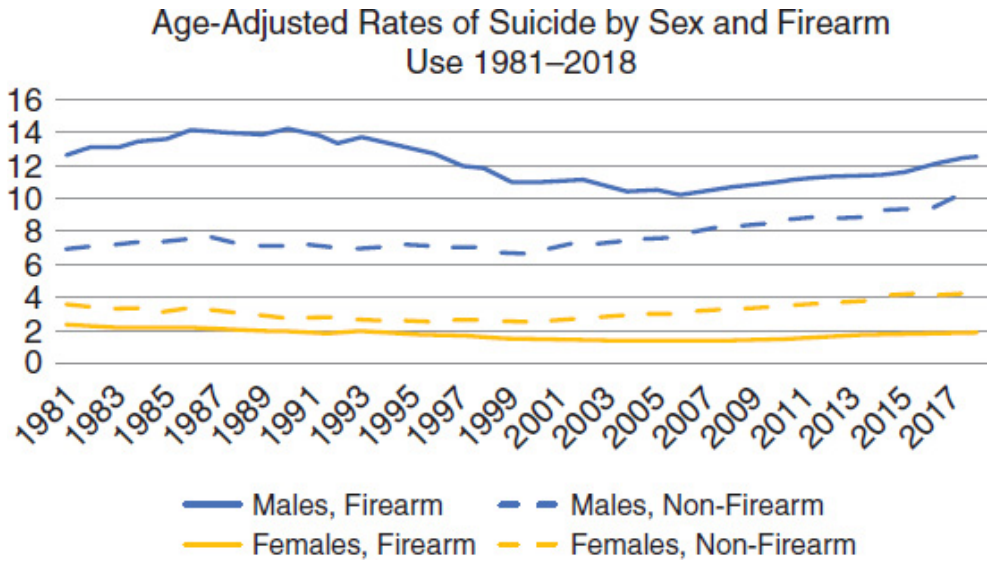

Figure 22.2 Age-adjusted rates of suicide per 100,000 people by sex, firearm use, and year. (Data sourced from WISQARS *Data from* National Center for Injury Prevention and Control. WISQARS [Web-based Injury Statistics Query and Reporting System], Injury Center, Centers for Disease Control and Prevention: Injury Prevention & Control Data and Statistic [WISQARS]. https://www.cdc.gov/injury/wisqars/index.html. Published March 30, 2020. Accessed June 15, 2020.)

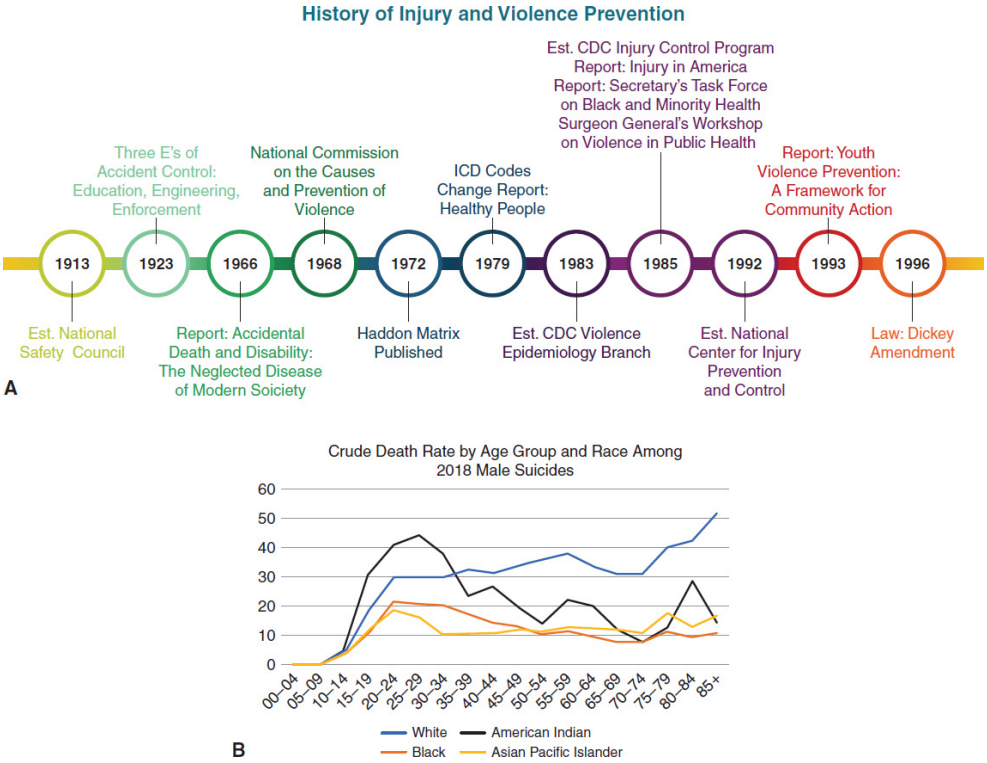

Figure 22.3 **A:** Landmark moments in the history of injury and violence prevention. **B:** Crude death rate per 100,000 people by age group and race among 2018 male suicides. (Data sourced from WISQARS *Data from* National Center for Injury Prevention and Control. WISQARS [Web-based Injury Statistics Query and Reporting System], Injury Center, Centers for Disease Control and Prevention: Injury Prevention & Control Data and Statistic [WISQARS]. https://www.cdc.gov/injury/wisqars/index.html. Published March 30, 2020. Accessed June 15, 2020.)

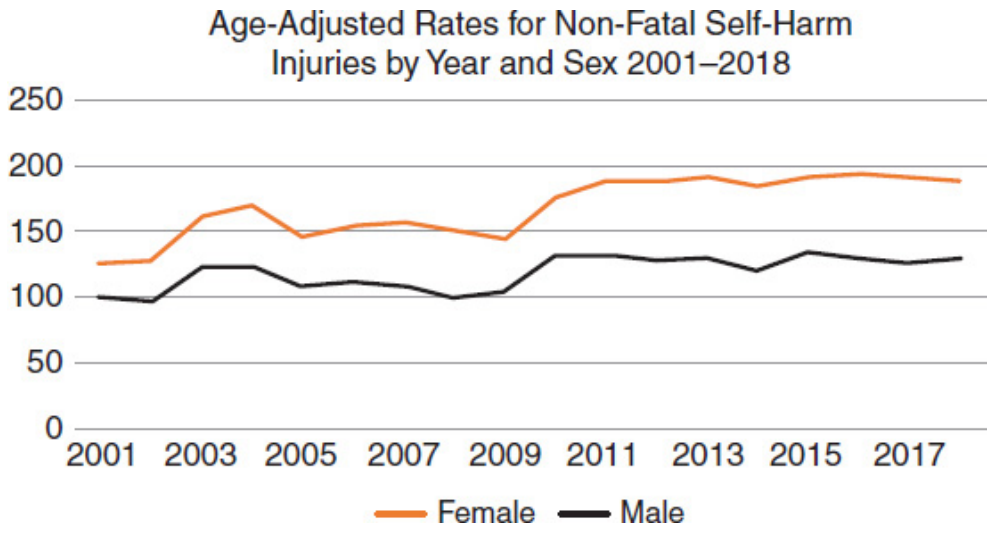

Figure 22.4 Age-adjusted rates for nonfatal self-harm injuries per 100,000 people by year and sex. (Data sourced from WISQARS *Data from* National Center for Injury Prevention and Control. WISQARS [Web-based Injury Statistics Query and Reporting System], Injury Center, Centers for Disease Control and Prevention: Injury Prevention & Control Data and Statistic [WISQARS]. https://www.cdc.gov/injury/wisqars/index.html. Published March 30, 2020. Accessed June 15, 2020.)

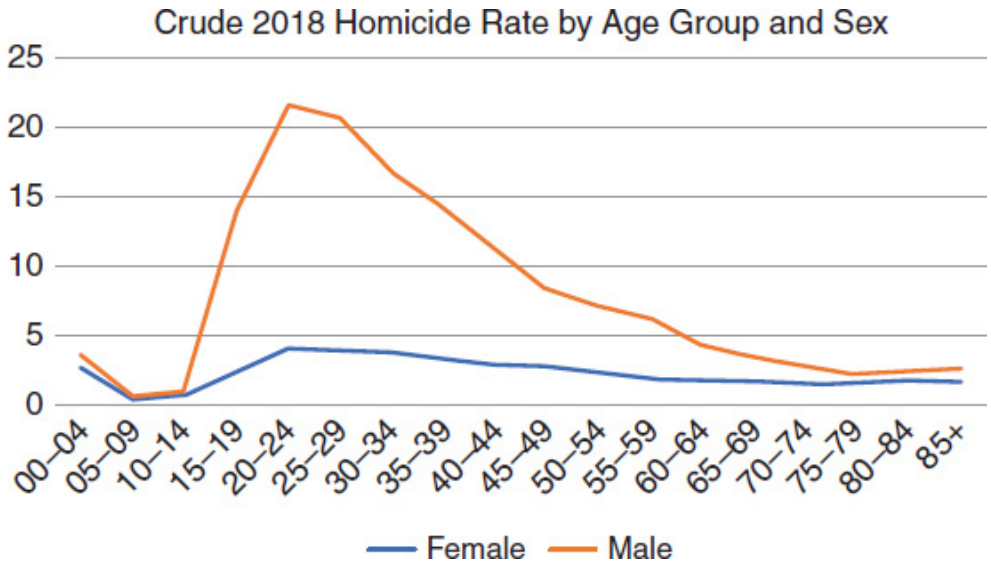

Figure 22.5 Crude 2018 homicide rates per 100,000 people by age group and sex. (Data sourced from WISQARS *Data from* National Center for Injury Prevention and Control. WISQARS [Web-based Injury Statistics Query and Reporting System], Injury Center, Centers for Disease Control and Prevention: Injury Prevention & Control Data and Statistic [WISQARS]. https://www.cdc.gov/injury/wisqars/index.html. Published March 30, 2020. Accessed June 15, 2020.)

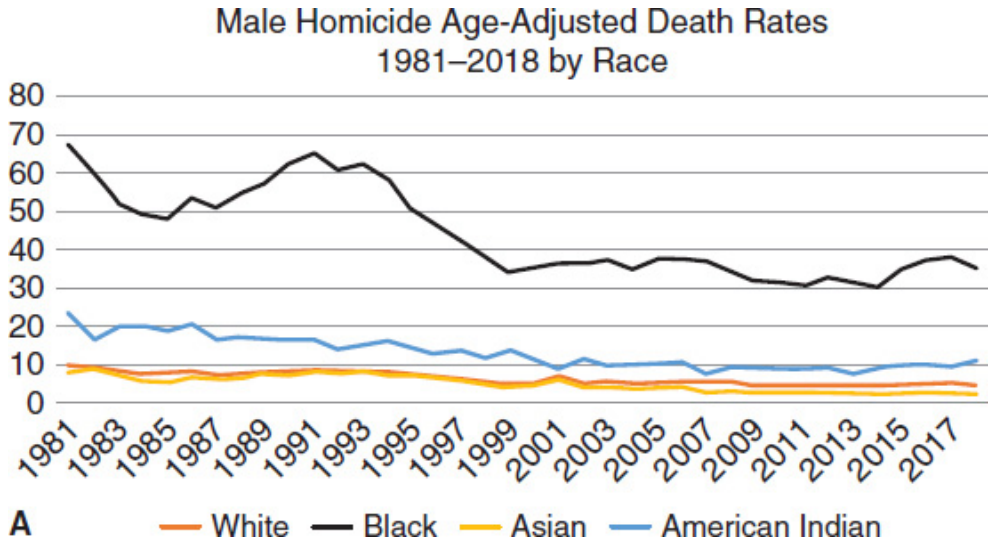

Figure 22.6A Male homicide age-adjusted death rates per 100,000 people by race in 1981–2018. (Data sourced from WISQARS *Data from* National Center for Injury Prevention and Control. WISQARS [Web-based Injury Statistics Query and Reporting System], Injury Center, Centers for Disease Control and Prevention: Injury Prevention & Control Data and Statistic [WISQARS]. https://www.cdc.gov/injury/wisqars/index.html. Published March 30, 2020. Accessed June 15, 2020.)

These acts of fatal and nonfatal violence occur daily between strangers, community members, partners, and families. Experiencing or, even, witnessing violence, in all of its forms, increases the risk of being a future victim or perpetrator of violence. Thus, to truly understand the pervasiveness of the problem is to understand the different permutations of interpersonal violence.

Mass Shootings

Mass shootings, as they are discussed here, include four or more shooting victims in a public setting. Between 1966 and May of 2019 there were 176 mass shooting incidents in 42 states and Washington, DC. These acts were committed by 183 shooters, 179 of which were male. Over 1,200 people were killed, with thousands more injured. Mass shootings have been more deadly and occurring more frequently, bringing the topic of gun violence into the public eye. Once occurring on average every 180 days (1966–1999), they now occur once every 47 days (2015–2019).[16,17]

Legal Intervention

Deaths or injury attributed to *legal intervention* are acts inflicted by on-duty law enforcement agents. Within the WISQARS database, there is no indication of legal circumstances of these events. In 2018, there were 618 fatalities and 85,075 nonfatal injuries.[8] There is data to suggest, however, that these incidents are vastly unreported, particularly if the injured individual is lower socioeconomic class or a minority.[18] The majority were young males. Ninety percent of deaths involved a firearm. Age-adjusted death rates were highest among Blacks (0.28) and American Indians (0.26) followed by Whites (0.14) and Asians (0.06). This disparity is consistent with studies that have shown officers are more likely to shoot a Black individual holding weapons faster and more often when compared to White individuals in the same circumstance.[18,19]

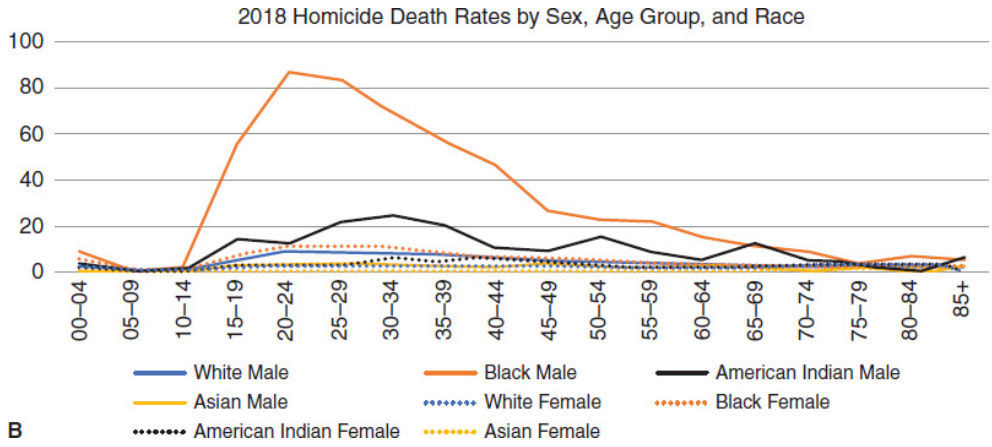

Figure 22.6B Homicide death rates per 100,000 people by sex, age group and race in 2018. (Data sourced from WISQARS *Data from* National Center for Injury Prevention and Control. WISQARS [Web-based Injury Statistics Query and Reporting System], Injury Center, Centers for Disease Control and Prevention: Injury Prevention & Control Data and Statistic [WISQARS]. https://www.cdc.gov/injury/wisqars/index.html. Published March 30, 2020. Accessed June 15, 2020.)

Intimate Partner Violence

Intimate partner violence (IPV) encompasses physical, sexual, emotional, and psychological violence between current or past spouses. In fact, 25% of women and 10% of men have experienced some form of IPV in their life

time. The majority of individuals experienced IPV for the first time before the age of 25. Fifteen percent of men and 21% of women have experienced severe physical violence from a partner. One in six homicides involve intimate partners. Half of all female homicide victims are killed by their spouse. It is estimated that the medical, legal, and lost productivity of IPV cost $3.6 trillion annually.[20]

Child Abuse

Child abuse is defined as physical, sexual, emotional abuse or neglect of a minor by a caregiver. In 2018, one in seven children were victims of child abuse or neglect. Survivors are at increased risk of future injury and violence. While rare, 1,800 children were killed as result of abuse in 2018.[21]

Firearm Injury

The public health burden of injuries has been well documented since the mid-20th century. Prevention initiatives have aimed to reduce the morbidity and mortality attributed to common vectors like motor vehicles, since the 1930s, and firearms, since the 1980s. Over the last 10 years, the age-adjusted death rates for firearm injury first equalized and has now surpassed that of motor vehicles (**Fig. 22.7**). As such, it is an unprecedented time in the history of the field of injury prevention. Firearms are among the top five mechanisms of injury deaths. In 2018, 39,740 deaths were caused by a firearm. The majority, 62%, were suicides. Thirty-five percent were homicides, 1% legal intervention, and 1% unintentional. There were over 900,000 years of productive life lost. Nonfatal and fatal firearm injuries resulted in $45 billion in medical costs and lost wages in 2010.[8]

Firearms play an intricate role in injury mortality in that they are a highly lethal, common vector within unintentional, suicide, homicide, and legal intervention injuries.[22] Contrary to what is depicted in popular media, the victims of gun injuries reflect the diversity of circumstances in which guns are used. This should come as no surprise to the surgical community. It is the older adult suicide attempt, the hunting injury, the child unintentionally wounded after finding and playing with a gun, the teenager shot during an altercation, the battered spouse, and the store patrons present during a mass

shooting—all of whom are rolled into the trauma bay with devastating injuries. Despite the heavily charged political debate about firearms in the United States, decreasing firearm-related deaths and disability should be approached as a public health priority with an emphasis on minimizing death and suffering through broadly based prevention efforts.

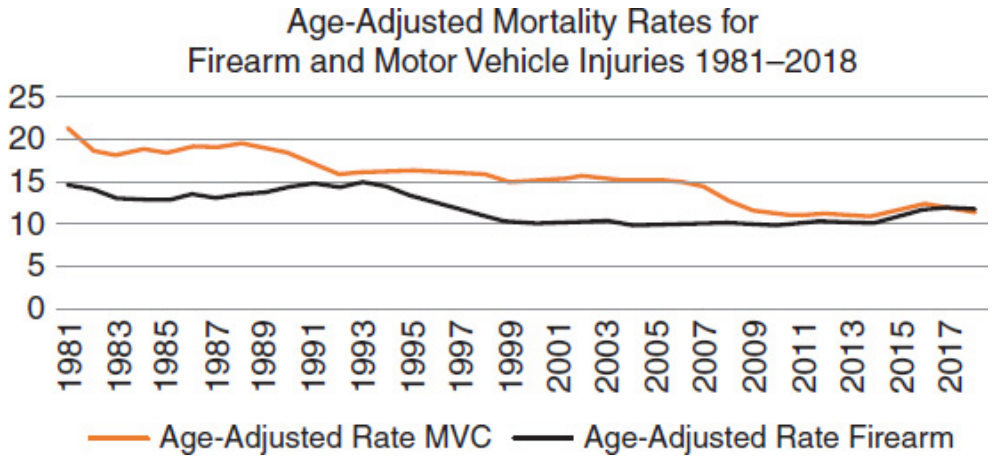

Figure 22.7 Age-adjusted mortality rates per 100,000 for firearm and motor vehicle injuries 1981–2018. (Data sourced from WISQARS *Data from* National Center for Injury Prevention and Control. WISQARS [Web-based Injury Statistics Query and Reporting System], Injury Center, Centers for Disease Control and Prevention: Injury Prevention & Control Data and Statistic [WISQARS]. https://www.cdc.gov/injury/wisqars/index.html. Published March 30, 2020. Accessed June 15, 2020.)

LANDMARK INJURY PREVENTION INITIATIVES

Workplace, motor vehicle, and childhood injuries have been the subject of injury prevention initiatives since the inception of the field. As such, these three areas are heavily represented in the field's landmark achievements.

The Occupational Health and Safety Act created the CDC's National Institute for Occupational Safety and Health in 1970 (NIOSH; https://www.cdc.gov/niosh/).[23] NIOSH aims to keep America's workforce safe through research, partnership, and program implementation covering topics from asbestos exposure to needlestick injury to machine safety. The OSHA blood-borne pathogen standards (1992) along with NIOSH

recommendations (1999) aimed to reduce the nearly 800,000 needlestick injuries each year. Interventions targeted safer sharps and sharp container design, universal precautions, worker education, free hepatitis B vaccinations, and postexposure evaluation and treatment.[24–30] These efforts have proven to be effective, with a decrease in total needlesticks to less than 400,000 by 2015.[31]

Nation-wide motor vehicle and road safety policies, programs, and behaviors have developed over the last century. Starting in the 1920s there was a call for national, uniform, enforced road safety laws, including speed limits, seat belts, child car seats, and maximum blood alcohol limits.[2,32–40] As a mechanism to ensure national adoption of these policies, a stipulation was made that any state that failed to pass these laws would not receive federal highway funding.[32] Widespread behavior change came about with both law enforcement (i.e., sobriety checkpoints) and public education campaigns (Mothers Against Drunk Driving, "Click it or ticket"). Seatbelt use, for example, increased from 11% in 1981 to 91% in 2019. Nearly 15,000 lives were saved by seat belt use in 2017 alone.[32,36,41] States have varying degrees of graduated drivers' license for new, young adult drivers.[42,43] Furthermore, over this time frame, cars have become safer.[34] Despite the 10-fold increase in number of miles driven per year in America between 1920 and 1990, the death rate per mile travelled has decreased by 90%.[32,44]

In addition to the widespread success in car seat use, there have been several other initiatives to mitigate childhood injuries in all settings.[45] The Child Safety Network of the Health Resources and Services Administration spearheads national and state wide efforts on diverse topics like poison control, sports safety, child abuse, and fall prevention (https://www.childrenssafetynetwork.org/).[46] Window guards, stair gates, bike helmets, energy-absorbing playground surfacing, and child supervision improvements have all been shown to successfully reduce falls.[47–55] One specific program example includes the "Children Can't Fly" campaign in New York City. This 1974 initiative required window guards in homes with children less than 10 years old. The result was a 96% decrease in falls from windows.[56] While work-place, motor-vehicle, and childhood injury prevention has developed over the last century, violent injury prevention came into the purview of the field much more recently.

Violence as Public Health Problem

3 Violence was considered purely a criminal justice issue until 1968. It was then that President Lyndon B. Johnson appointed the National Commission on the Causes and Prevention of Violence with the goal of identifying the social underpinnings of violent acts.[57] Thereafter, data was collected and analyzed regarding the morbidity, mortality, and healthcare cost of violent injuries. The Healthy People 1979 report was the first instance in which injury and violent behavior was described as a public health priority.[58] Subsequently, the 1980 Promoting Health/Preventing Disease Report outlined specific objectives for child abuse, homicides, suicides, privately owned guns, and data collection.[59] Violent injury has been identified as a priority in all subsequent Healthy People Reports (https://www.healthypeople.gov/).[60] The CDC then created the Violence Epidemiology Branch in 1983 and the Extramural Research Program for injury and violence in 1986. An infrastructure to treat violence as a public health issue was thereby created.

Two milestones occurred in 1985. The first was the Secretary's Task Force on Black and Minority Health Report which outlined the heavy contribution of violent firearm injury to health disparities among Blacks.[61] This disparity persists to this day. Second, Surgeon General C Everett Koop convened the first Surgeon General's Workshop on Violence in Public Health.[62] Other Surgeon Generals have followed his lead, understanding violence as a public health problem.[63] More recently, there have been calls for an annual Surgeon General's report to deepen understanding of firearm injury causes and effects.[64]

The precedent was set in the 1980s: violence, like other injuries, is a preventable, public health issue. The CDC received its first congressional appropriation for youth violence prevention in 1992, which led to the creation of the NCIPC (cdc.gov/injury/index.html).[65] School- and community-based programming was implemented, monitored, and evaluated. In 1993, the CDC published its findings in "Youth Violence Prevention: A Framework for Community Action" promoting programs that strengthened social, emotional, behavioral, and familial competencies.[66]

Similar to injury prevention, violence prevention called for multidisciplinary teams, including education, health care, criminal justice, legislature, communications/media, business, and community organizations.

The NCIPC ultimately expanded its prevention efforts beyond youth violence to include IPV, sexual violence, child maltreatment, elder maltreatment, and suicide.[2] By 2001, public health violence prevention initiatives were proven to be both efficacious and cost effective in the "Youth Violence: A Report of the Surgeon General."[67]

Federally funded injury and violence prevention research in the 1990s included gun violence. Initial studies identified having a firearm in the home was an independent risk factor of homicide. Unfortunately, firearms have not been a bipartisan topic. Controversy ensued. Through the National Rifle Association's strong lobby and, ultimately, the Representative Jay Dickey's 1996 Omnibus Appropriations Act, the CDC was banned from conducting research that may ultimately promote gun control. In 2012, this ban extended to the U.S. Department of Health and Human Services.[68] Attempts were made to repeal the ban of firearms research in both 2015 and 2017. Both failed. Firearm possession by private citizens remains a controversial, partisan topic of debate in the public arena.[69] However, recent data would suggest a majority of Americans actually agree on particular gun restrictions.[70] The goal of this chapter is to refocus the conversation on the health and well-being of the patients encountered in the trauma bay—in preventing injury, increasing survival, and improving long-term outcomes for the individual, communities, and the nation.

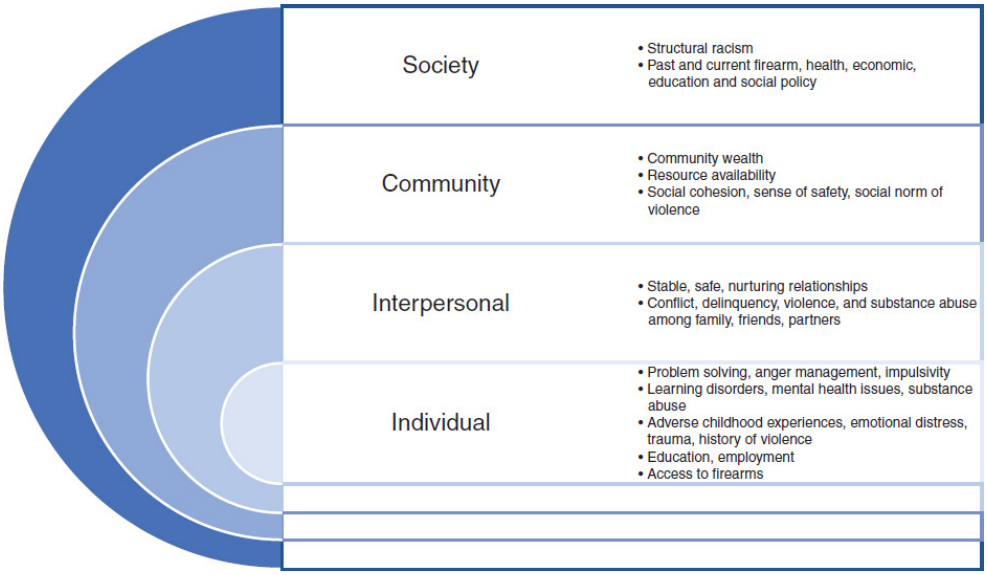

Figure 22.8 Social ecologic model for violence.

THE SOCIAL ECOLOGIC MODEL

4 The social ecologic model is used as a framework for the dynamic risk and protective factors of gun violence on various levels, including individual, interpersonal, community, and society (**Fig. 22.8**). This framework is vital in identifying opportunities to reduce risk, bolster protective factors, and identify stakeholders. The preponderance of factors is unifying across different types of violence (child abuse, IPV, suicide/self-harm, and assault/homicide).[71] Therefore, relevant programing and policy should be recognized as generalized violence prevention.

An individual's personal characteristics, health, experiences, and demographics affect the likelihood of violence. The ability to problem solve, manage anger and control impulsivity are essential skills in conflict resolution. A personal history of learning disorders, mental health issues, and substance abuse all increase risk. Prior adverse childhood experiences, chronic or severe emotional distress, attitudes toward violence, and witnessing or experiencing violence increase the likelihood of becoming a victim or perpetrating violence. Level of education and employment have also been shown to correlate with violence. Easy access to unlocked and unprotected firearms increases risk of suicide and homicide.[67,71–76]

The next level, interpersonal relationships, hinges on social support. The presence or absence of stable, positive social connections among family, friends, and partners can contribute as a risk or protective factor. Unstable, conflict-ridden relationships along with the presence of delinquent, violent (toward self or others), and substance abuse behaviors among family, friends, and partners can negatively impact the individual. Nurturing, safe, stable relationships, however, have the ability to positively influence outcomes even in the setting of other individual, community, or societal risk factors.[67,71,73,74]

Neighborhoods, schools, workplaces, and places of worship are in the community level of the social ecologic model. It is where an individual lives, learns, works, prays, and plays. Community wealth is measured directly by unemployment and poverty levels and indirectly by the residential instability, crowded housing, concentration of liquor stores, and availability of green space and fresh food. Pertinent resource availability includes readily accessible health services (mental health, primary care, trauma

centers, and substance abuse programs) and a trusting relationship with law enforcement. The sense of social cohesion and community safety at this level are important factors. Crime levels and the social norm of violence and substance abuse contribute to the sense of safety. Community-level poverty, lack of resources, and low sense of safety and social cohesion all increase the risk of violence. The violence that results acts as a positive feedback mechanism in that violence lowers property values, drives out resources, and propagates low sense of safety.[76–81]

Society-level factors can be at city, state, and national level. This includes past as well as current firearm, health, economic, education, and social policy that tickle down to lower social ecologic levels. It has been well documented that individual, interpersonal, and community risk factors for violence are not evenly distributed. In fact, this was discussed on the national level as early as President Johnson's National Commission on the Causes and Prevention of Violence.[57] They identified violence as a reflection of a myriad of social problems, including, but not limited to, racial segregation, low income, low levels of education, low home ownership, physical deterioration, and broken homes. The range of extreme concentration of risk factors to extreme concentration of protective factors exists to this day. The dichotomy begs the question: are there forces on a societal level that concentrate risk versus protective factors?

The discussion necessitates careful consideration of structural violence, or the unequal power and opportunity driving social determinants of health.[82,83] The long-standing history of race-based inequity, therefore, is at the root of health disparities. This goes far beyond interpersonal acts of racism, to the institutional level discriminatory policies and practices based on race. As this has occurred across sectors including housing, education, employment, health care, and criminal justice, these discriminatory systems reinforce one another to result in the phenomenon of structural racism.[84–86] The role institutional and structural racism play in the outcome of firearm injury can be illustrated with the example of housing.

When communities were still legally segregated by race, they were economically diverse. In the early 1930s, the Federal Housing Administration initiated a mortgage lending process called Redlining, by which the housing market prices were determined based on race, ethnicity, and religion. After neighborhoods were legally desegregated in the 1960s,

only wealthy minorities could afford to move into nicer communities. This combination resulted in the concentration of poverty among the disenfranchised minority still evident today.[87] Multiple studies have shown that racially segregated, low-income communities have higher rates of firearm injury.[88–93] Even further, restrictive firearm policies may be less effective at decreasing injury in these communities.[94]

Despite the 1960 Civil Rights Act, many laws have systematically targeted poverty-stricken minority populations. The War on Drugs provides just one example. With the crack cocaine epidemic, national rhetoric created a discriminatory stereotype of "crack babies," "crack whores," "gangbangers," and "welfare queens." From 1980 to 2010, crack cocaine sentencing laws were 100 times those for powder cocaine. Even with the Fair Sentencing Act of 2010, the sentencing is still 18 times greater. Laws such as these have contributed to incarceration rates of Blacks being 3 to 10 times higher than non-Hispanic Whites. Mass incarceration has destabilized minority families and communities and further reduced education, employment, and housing opportunities. Similar examples could be discussed within education, policing, and health sectors.[84,95]

This is not to suggest impoverished White communities and wealthy minority communities do not exist with varying degrees of risk and protective factors. Rather, it is to bring attention to the societal-level forces which have systematically concentrated risk factors among minorities over time. Without knowing the societal forces at play, it is all too easy to oversimplify prevention efforts around a "bootstrap" narrative by putting the entire emphasis on the individual.

THE SURGEON'S ROLE IN FIREARM-RELATED INJURY AND VIOLENCE PREVENTION

The scope of the firearm-related injury and violence prevention is vast. It encompasses injury and violence in multiple forms (unintentional, suicide, interpersonal, intimate partner, child abuse) with pertinent risk factors throughout the life span across all ecologic levels (individual, interpersonal,

community, and society). Thus, there are nearly endless opportunities for preventative programming and policy.[96]

5 Firearm-related injury and violence prevention takes place on a continuum: before the injury occurs (primary prevention) or after the injury occurs by minimizing the mortality, likelihood of reoccurrence (secondary prevention), and reducing long-term morbidity (tertiary prevention). The social ecologic risk and protective factors span the timeline of an injury (**Fig. 22.9**). Prevention initiatives, including programs and policies, should involve an array of stakeholders, including gun owners, vulnerable communities, law enforcement, educators, health professionals, public health professionals, and lawmakers.[97] Prior to discussing specific opportunities for surgeon involvement in prevention, it is important to review the standpoint of the surgical community on gun violence.[98–100]

There have been a variety of Association statements, including the American Association for the Surgery of Trauma, Eastern Association for the Surgery of Trauma, and the American College of Surgeons Committee on Trauma (ACS-COT).[101–103] The ACS-COT published a Consensus on firearm-related injury based on member survey (93% response rate) and meetings with surgeon leaders in town halls and professional organization meetings. While the community had varying personal opinions on gun ownership, there was agreement on the need to address the preventable morbidity and mortality of firearm injury. The majority supported healthcare worker rights, education, and training to counsel patients on safe firearm ownership (90%), federal funding for gun violence research, and the development of a research agenda (92%), universal background checks (86%), severe penalties for individuals who illegally supply guns to others (92%), and trauma center involvement in addressing the root causes of firearm injury.[104,105] The ACS-COT also created the Firearm Strategy Team (FAST), a group of firearm-owning surgeons as they offer a truly unique perspective on safe gun ownership and the prevention of injury.[70,106,107]

6 In February of 2019, the ACS hosted the Medical Summit on Firearm Injury Prevention, joining together 44 medical, public health, legal, and injury prevention Associations to develop a consensus, nonpartisan approach to unintentional, intentional, and suicide injury prevention. This meeting, the first of its kind, adopted a public health approach based on epidemiology, program development, evaluation, and dissemination. Programs discussed

included safe storage, patient counseling, patient screening, hospital/community-based violence prevention programs, and public policy. The final consensus statements can be found in **Table 22.1**.[98,103]

Thus, the surgical community, along with the general medical community, has reached a consensus that firearm injury and violence is a cause of preventable morbidity and mortality. It is within 7 the surgeon's scope practice for their patients, hospitals, and communities to address the root causes of violence and make gun ownership safer. The following are specific mechanisms to do so.

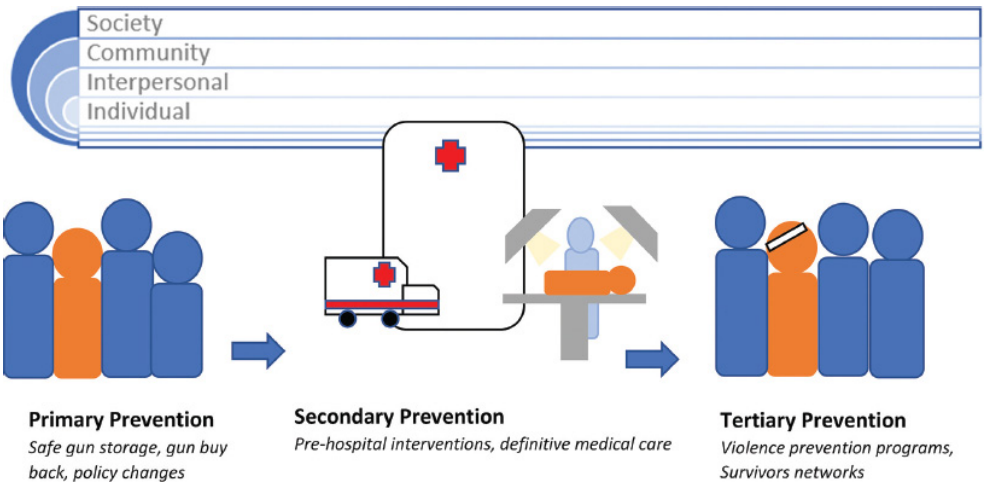

Figure 22.9 Primary, secondary, and tertiary violence prevention.

Table 22.1 Medical Summit on Firearm Injury Prevention Consensus Statements

Reproduced from: February 2019 Medical Summit on Firearm Injury Prevention Consensus Statements
Firearm injury is a public health crisis.
A comprehensive public health and medical approach is required to reduce death and disability from firearm injury.
Research is needed to better understand the root causes of violence, identify people at risk, and determine the most effective strategies for firearm injury prevention.
Federal and philanthropic research funding must be provided to match the burden of disease.
Engaging firearm owners and populations at risk is critical in developing programs and policies for firearm injury prevention.
Healthcare providers should be encouraged to counsel patients and firearm safety and safe storage. Educational and research efforts are needed to support culturally competent messaging.
Screening for the risk of depression, suicide, intimate partner violence, and interpersonal violence should be conducted across all healthcare settings and in certain high-risk populations (such as those with dementia). Comprehensive resources and interventions are needed to support patients and families identified as high risk for firearm injury and who have access to a firearm.
Hospitals and healthcare systems must genuinely engage the community in addressing the social determinants of health of disease, which contribute to structural violence in underserved communities.
Our professional organizations commit to working together and continuing to meet to ensure these statements lead to constructive actions that improve the health and well-being of our fellow Americans.

Primary Prevention

Primary prevention initiatives target the upstream causes of gun injury and violence in order to prevent incidents in the first place.

Access to a firearm is an independent risk factor for homicide and suicide.[108–110] Physicians and their representative professional associations, including internists, pediatricians, and surgeons, have agreed physicians should screen and counsel patients on firearm safety.[111–116] However, the available data suggests few attending physicians and even fewer residents are discussing the topic despite the majority of patients being receptive to the conversation.[117–119] Studies regarding firearm safety counseling in outpatient and hospital settings have demonstrated an increase in the safe storage of firearms, decreased firearm access among suicidal teens, and reduction in firearm injury recurrence. Supplying safety devices to patients increases sustained safe storage of firearms.[117,120–124]

In outpatient and inpatient settings, surgeons can and should be systematically screening and counseling patients on safe firearm storage much like the way we counsel on smoking cessation or weight loss. Various tools can be found to guide this conversation include courses by the American Medical Association, Massachusetts Medical Society, the University of Michigan and Scrubs Addressing the Firearm Epidemic. The ACS-COT has a Gun Safety Brochure available in English and Spanish.[125–129]

The surgeon should illicit access to firearm, safe storage, and intent to harm. Easy access to firearms is particularly risky in households with children and/or individuals with cognitive impairment, dementia, substance use disorder, mental illness, and history of violence. Nearly 5 million American children live in a home where a gun is not safely stored.[130] The patient should be asked to share their opinions regarding firearm storage. Other adults in the home may have similar or conflicting opinions. Patients should be educated that guns should be stored locked, unloaded, separate from ammunition away from any individuals at risk for unsafe use or harm to self or others. If the patient has access to a gun, the physician should assess suicidal or homicidal intention. Any expressed intent to harm should result in the patient being committed for emergent psychiatric evaluation.[131] In some states, there are Extreme Risk Protection Orders which allow healthcare

professionals, family, or law enforcement to file petitions for temporary removal of a firearm from the home.[132] Patients can and should also be made aware of any local gun buy-back programs for unwanted firearms.[133]

Surgeons can be advocates for local, state, and federal policy changes to prevent firearm injury without infringing upon the rights of firearm owners. Data-driven legislation may affect gun licensing, firearm and ammunition availability, and research funding. The number of state firearm laws varies widely (<10 to >100).[134] Studies have demonstrated cities and states with stricter firearm laws are correlated with fewer associated mortalities.[135–141] A state's homicide rates are not only associated with their own laws, but also the laws of surrounding states.[142] Restrictive laws include comprehensive background checks, which may identify a history of protective/restraining orders, domestic violence charges, fugitive status, psychiatric disorders, and misdemeanor crimes in addition to state or federal crime convictions. These features have been associated with overall decreased homicide, including intimate partner homicide, and suicide rates.[143–150] Importantly, studies have identified these laws only have an effect when properly enforced.[151,152] Restrictive legislation, however, is not uniformly beneficial. In particular, these laws were not correlated with lower homicide rate among Blacks.[94,153,154] Given the historical and contemporary structural violence and racism to this population, beneficial legislation may need to target this etiology.

In addition to tighter regulation on who can purchase a firearm, legislation also dictates the type of firearms and ammunition available to the public. High-capacity magazines, gun caliber, semiautomatic weapons, and bump stocks are all features that increase a firearm's lethality, or its capacity to render more severe injuries in a shorter time frame.[155–157] In 2004, the federal ban on assault weapons expired. Seven states have since passed new assault weapon bans. Such laws are vital given that the rate and severity of firearm injuries has been increasing.[158] While there is data to support the merit of stricter firearm legislation, there is a paucity of funding allocated for firearm injury research. This dates back to the Dickey Amendment in 1996, which dried up federal funding for gun violence prevention research. Therefore, legislation to increase and maintain the federal appropriation for firearm injury research is imperative.[159]

Surgeons are poised to leverage clinical experience to advocate for data-driven legislation regarding gun licensing, firearm and ammunition regulation, and research funding.[160–163] The ACS advocates on behalf of and alongside surgeons and their patients. In 2019, this included legislation which would increase in the appropriation for firearm injury prevention research. For the first time in more than 20 years, Congress appropriated federal dollars for gun violence research. Federal agencies received $25 million from Congress to study gun violence in a government spending deal reached by House and Senate negotiators. The deal included $12.5 million each for the CDC and National Institutes of Health to study gun violence and ways to prevent it.[160,164] The College is a major resource for advocacy resources ad activities. Partnering with nonprofit and grassroots organizations, including the Brady Campaign, Gifford's, Mom's Demand Action, is another practical mechanism to identify advocacy opportunities on the local, state, and federal levels.[160]

Social media campaigns have also proven to be an effective mechanism to educate the public and inform policy. In the fall of 2018, front-line trauma workers joined together to share collective experiences treating firearm injury patients using the #Thisisourlane. This campaign was in response to the National Rifle Association's tweet suggesting physicians should "stay in their lane," suggesting a lack of expertise in firearm policy. The public and many policy makers were galvanized as a result of the campaign.[160] While advocacy work may seem overwhelming to some, there are many practical ways for a surgeon to share their professional opinion with the public, local organizations, and policy makers. In 2018, 67 pieces of gun reform legislation were passed.[165] Hopefully, this trend will continue with the support of the surgical community.

Secondary and Tertiary Prevention

Secondary and tertiary prevention initiatives aim to decrease the mortality and morbidity after an injury occurs. Survival after a firearm injury depends on location and severity of the injury as well as expedient and effective prehospital stabilization and definitive hospital care.

Unfortunately, not all regional trauma systems provide the same care resulting in a wide range of geographic-based survival rates. In the 2016

National Academies of Science Engineering and Medicine report entitled "A National Trauma Care System" the argument is made up to 20% of the annual trauma deaths may have been preventable. This landmark paper calls for a national trauma system in which the military and civilian trauma experience is shared to improve quality of care and patient outcomes.[166] These two sectors have relied on one another for high-quality preclinical and clinical research on countless topics including nonoperative versus nonoperative management, prehospital and hospital resuscitation, and mass casualty care.[167–174] This proposed system would provide infrastructure to a longstanding relationship between the military and civilian traumatologists with the goal of having zero preventable deaths due to trauma.[166]

Uncontrolled hemorrhage was found to be a major cause of preventable deaths in the military. To address this problem, the Tactical Combat Casualty Care training was developed. It taught soldiers immediate life-saving maneuvers like applying a tourniquet and combat gauze and relieving an obstructed airway. This program proved to be efficacious.[175,176] These skills translate to civilian traumatic injury.[177] In the aftermath of the Sandy Hook Elementary School shooting in 2013, a wide variety of stakeholders joined to develop the Hartford Consensus. They identified bystanders to injury as the true "first care responders" who, with the proper skill set, can control hemorrhage while waiting for first responders to arrive (EMS, police, fire). In 2015, the White House National Security Council's Office of Medical Preparedness Policy announced the Stop the Bleed campaign which would aim to target the same skill set as the Hartford Consensus based on the military's successful program (https://www.dhs.gov/stopthebleed). In 2016, the initiatives joined to train nonmedical first responders (police and fire) and, ultimately, the public.[178–181] These trainings taught the same skills and made tourniquets available in public settings. Participants reported increased ability and willingness to apply this skills should the need arise.[182]

Survivors of firearm injury face a long mental and physical recovery.[183] There are hospital-based and national trauma survivors networks to assist patients in the aftermath of injury.[184] Victims of violent injury are at increased risk of future victimization or perpetration of violence. These negative effects are felt not only by the victim, but also the community where the violence occurred.[185–187] For these reasons, community and hospital-based prevention programs intervene after an injury as a teachable moment to

address modifiable risk factors. This is a similar principle used in cardiac rehabilitation programs used to change diet and exercise following a myocardial infarction.

While these violence prevention programs are diverse in activities and scope, there are several unifying principles. Employees are typically from the community, who will be deemed credible and relatable to the patients. They are charged with the task of building and maintaining a relationship as mentors and case managers. The program assists the patient overcome barriers to meet basic needs and achieve goals. This is not an easy task, as it requires navigating the systems that have all too often already failed the individual, including health care (mental, physical and substance abuse), employment, education, housing, and legal aid. The patient continues to work with the program after discharge with the ultimate goal of reducing risk and increasing protective factors for future injury.[189]

The Wraparound Program based out of University of California, San Francisco and Violence Intervention Program at University of Maryland are among the well-established and well-studied hospital-based programs.[188,189] Across 22 randomized control trials of 14 different programs, there was an increase in service utilization, change in attitude regarding violence, decrease in violent behavior, and decreased repeat injury. There was a cost–benefit among the intervention arms from reduced hospital readmissions and legal costs of conviction and incarceration.[189–197] As the evidence has grown, several states have increased funding availability for these programs, including California, New Jersey, and Virginia.[189]

The Health Alliance for Violence Interventions (HAVI), formerly called the National Network of Violence Prevention Programs, aims to provide infrastructure to the hospital-, community-, and health department-based programs across the country. HAVI has partnered with ACS-COT and the American Foundation for Firearm Injury Reduction. They provide technical assistance, conduct research, and issue best practice guidelines. While guidelines and evidence have been produced based on program experience, this infrastructure will allow for rigorous evaluation across institutions and program models.[198–200]

As this chapter outlines, the etiologies of intentional (assault and self-harm) and unintentional firearm injuries span multiple disciplines. Policy and programing prevention initiatives, therefore, extend far beyond the hospital.

Surgeons may find opportunities to support other professionals, including law enforcement, education, and public health, in their efforts to reduce firearm injuries locally and nationally.

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23

Neck Injuries

Brandon R. Bruns and Thomas M. Scalea

Key Points

1 An intimate understanding of the neck anatomy is necessary for optimal management of injuries in this region.

2 Obtaining a secure airway is vital for management of all major injuries, especially those in the neck.

3 Gentle digital pressure or balloon tamponade may control life-threatening hemorrhage from vascular injuries in the neck while definitive measures are arranged.

4 Though classic teaching mandated exploration of all zone II injuries with penetration of the platysma, modern trauma care allows some discretion.

5 A high index of suspicion and recognition of injury patterns is necessary to diagnose blunt cerebrovascular injury.

6 Blunt cerebrovascular injury is often present in patients who do not manifest traditional screening criteria and recognition is important as untreated injuries may lead to strokes.

7 A combination of endoscopy and contrast-enhanced radiography presents the best opportunity to diagnose esophageal injury when present.

INTRODUCTION

1 Many vital structures reside within the neck and exist in close proximity to one another. These structures include the aerodigestive tract, blood vessels, bones, and the spinal cord. The close proximity can lead to multiple injuries in a wide variety of structures within a relatively small area. Of penetrating injuries to the neck, the vast majority are caused by stab wounds.[1–3] Blunt injury to the neck is the result of various mechanisms including direct blows, automobile shoulder belts, and various hanging mechanisms with neck hyperextension. The anatomic complexity and diverse injury mechanisms make diagnosing and treating neck injuries challenging.

FUNCTIONAL ANATOMY

The exterior anatomic barriers of the neck include the lower border of the mandible anteriorly, to the nuchal line of the occipital bone posteriorly. Inferiorly, the clavicles serve as the anterior border with a line drawn toward the seventh cervical vertebral spinous process encompassing the posterior border.

Triangles are classically used to divide the neck into zones; however, they are only rarely used to classify and plan treatment in the trauma patients. The posterior triangles are bordered by the sternocleidomastoid muscles anteriorly, the trapezius muscles posteriorly, and the clavicles inferiorly. The sternocleidomastoid muscles, the midline, and the angles of the mandible border the anterior triangles bilaterally.

In 1969, Monson and colleagues[4] arbitrarily divided the neck into three anatomic zones: zone I consisted of the area below the sternal notch, zone II was the area between the clavicles and the mandibles, and zone III was described as the upper cervical region and consisted of the area above the mandibles. Roon and Christensen[5] introduced a more modern version of the neck zones in 1979 and defined zone II as the area between the cricoid and the angle of the mandible, zone I as the area below the cricoid cartilage, and zone III remained the area above the mandibular angle (**Fig. 23.1**).

The zones of the neck are important as the approach to injury within each zone is different and is limited by anatomic barriers. This is particularly true when one considers vascular exposure, as exploration of all major vascular structures in zone II is accomplished via a standard sternocleidomastoid neck incision. Via a single incision, proximal and distal vascular control can both be obtained within zone II, and injuries repaired.

Proximal control for zone I injuries may require control within the chest. Depending on the location of injury, a variety of incisions can be utilized. A full sternotomy provides access to the mediastinal great vessels and the proximal left subclavian artery, along with the origin of the left common carotid artery. A partial sternotomy allows control of the innominate artery through a smaller incision. A periclavicular incision provides access to the bilateral subclavian arteries. In short, full exposure is achieved through a variety of incisions. After proximal control, subsequent distal control is obtained in zone II.

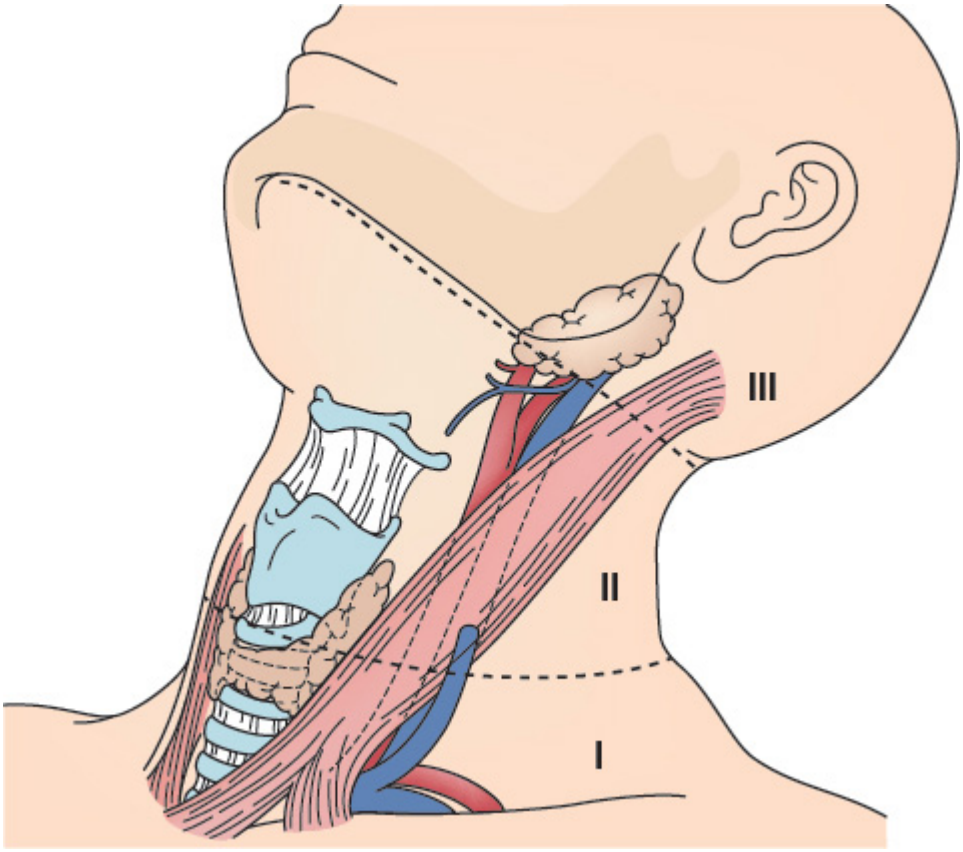

Figure 23.1 Zones of the neck.

Proximal control for zone III injuries can be achieved in zone II without much difficulty; however, distal control may be difficult as the mandible and skull base prevent wide exposure. Several methods, such as mandibular subluxation or osteotomy, have been described to control the carotid artery at the base of the skull.[6] A muscle splitting incision can also help give access to the carotid artery and the base of the skull.[7]

The inferior and lateral extensions of zone I are often contested and debated. While this is not well described, our practice is to classify lateral and inferior (superior mediastinal) injuries by zone I principles. Because proximal control involves a thoracic incision, we believe zone I extends to the junction of the subclavian and axillary arteries laterally and inferiorly to the mediastinal great vessels.

Injury to the posterior neck is inherently different than injury to the anterior neck. It makes sense that tracheal and esophageal injuries would be less common with posterior injury, as they are protected by the spine. Injuries to the spine should be more common in this anatomic region.

Often, more than one zone can be injured by a single trajectory; such as an injury through both zone II and zone I. Management of these "multizone" injuries is guided by the standard principles used for the more challenging zone, usually zone I or zone III.

The platysma muscle envelops the neck and originates from the pectoralis major and deltoid muscles. Though clinical practice has evolved, most classic algorithms of treating penetrating neck trauma stated that injuries penetrating the platysma muscle in zone II of the neck mandated direct operative intervention, whereas those penetrating the platysma in zones I and III mandated additional studies via either angiography or other imaging modalities.[5]

INITIAL MANAGEMENT

Basic trauma management of patients with injury to the neck should proceed as outlined in the American College of Surgeons 2 course, Advanced Trauma Life Support (ATLS).[8] Initial priority is given to securing the patient's airway. Early control of the airway with intubation is considered in every patient with a neck injury. Even in seemingly stable nonbleeding patients, a cough may dislodge a thrombus producing sudden hemorrhage. An airway that had previously been straightforward to control is now much more complicated and may require advanced techniques.

Obvious injury to the neck, with the presence of an expanding hematoma or other hard signs of vascular injury (pulsatile hemorrhage, thrill, bruit), should lead the provider to obtain definitive endotracheal access as the first step in the resuscitation. Similarly, air bubbling through the wound, hoarseness, or an obviously transected trachea, should guide the treatment team toward immediate and definitive airway control.

In the event that orotracheal intubation cannot be accomplished (rapidly expanding hematoma, destructive laryngeal trauma, patient habitus, excessive debris within the oropharynx), an emergent surgical airway should be expeditiously obtained. Cricothyroidotomy and emergency tracheostomy remain the safest and most reliable methods of emergent surgical control of the airway. Some investigators have shown promising results with percutaneous tracheostomy performed in the emergency setting, though this

should only be contemplated by experienced clinicians.[9] If tracheal transection is visualized in the wound, intubation of the distal tracheal segment with an endotracheal tube, or any available airway device, can be lifesaving (**Fig. 23.2**).

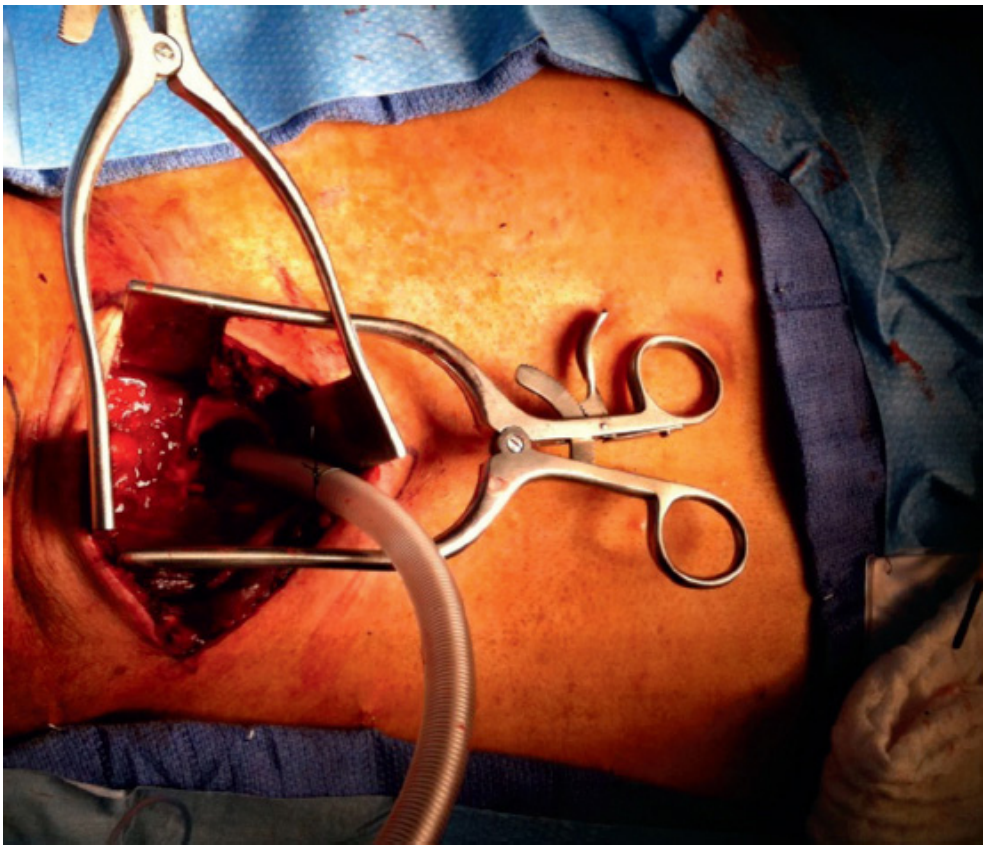

Figure 23.2 Intubation of a distal tracheal transection in the neck.

Though obtaining a safe and definitive airway is the priority in all injured patients with airway compromise, blunt trauma patients are at high risk for cervical spine injury. Maintaining the head and neck in neutral position, with the help of a competent assistant trained in such maneuvers, accomplishes cervical stabilization during intubation attempts. The same caution is not needed in patients with penetrating trauma, as patients presenting alive and neurologically intact are highly unlikely to have unstable cervical spine fractures.[10,11]

After securing an adequate airway, patient care should proceed in an orderly fashion by using ATLS principles with the next priorities being breathing and circulation. In evaluating the chest, the clinician must remain

aware that penetrating injury to zone I can violate the cupula of the lung and result in pneumothorax or hemothorax, which may require evacuation. Circulatory issues focus on intravenous access with resuscitation and assessment of the blood pressure, but it 3 also entails control of any obviously bleeding focus. Pulsatile bleeding emanating from a neck wound is best managed with gentle digital compression. Occasionally, a urinary catheter or a Fogarty catheter can be delicately placed into a bleeding neck wound with gradual inflation of the balloon in an attempt to tamponade hemorrhage. Insert the catheter until it no longer goes easily; inflate the balloon slowly until the bleeding stops.

A rapid assessment of the neurologic state of the patient can give insight into the nature of a neck injury as a dense hemiplegia may be the result of carotid arterial injury and subsequent ischemic stroke. It is imperative to recognize the patient with a lateralizing neurologic defect early, as revascularization may result in hemorrhagic conversion of a cerebral infarction.

After the primary survey and adjunctive radiographic procedures (chest radiograph, abdominal sonography), a thorough secondary survey should be performed, with focus on the structures of the neck. A hematoma across the base of the neck caused by an automobile seatbelt may portend a blunt cerebrovascular injury (BCVI). Extensive subcutaneous emphysema in the tissues of the neck usually represents air tracking up from a pneumothorax, but can represent an injury to the airway. Injury to the esophagus is possible, but subcutaneous air is rarely the only symptom of esophageal injury. Similarly, an audible bruit or palpable thrill may indicate major vascular injury that requires prompt attention.

SELECTIVE VERSUS MANDATORY EXPLORATION

Few would argue that penetrating injuries to the neck, with hard signs of injury (pulsatile hemorrhage, expanding hematoma, shock, air emanating from the wound, and massive hemoptysis), mandate immediate surgical exploration. In the absence of these hard signs of injury, most favor a

selective approach with clinical examination and diagnostic workup. The work up includes radiographs, but may also include non-radiographic modalities such as endoscopy.

Overall Approach

4 Traditional surgical teaching calls for neck exploration in patients with penetrating zone II neck injuries that violate the platysma muscle. Those supporting the concept of mandatory surgical exploration cite the low incidence of significant morbidity with surgical exploration, despite the high likelihood of negative exploration.[2,12] Proponents of operation also point to the lack of physical examination findings in patients that did proceed to have positive findings.[3] In contrast to mandatory exploration, many investigators advocate a more selective approach to operative therapy, suggesting surgery only in symptomatic patients. Authors supportive of the more limited approach cite a low morbidity and mortality associated with observation of zone II injuries and high likelihood of negative exploration.[1]

While diagnostic exploration may make sense for some zone II injuries, diagnostic preoperative evaluation certainly makes sense for injuries in zone I and zone III. Penetrating injury in zone I puts vascular structures, trachea, and esophagus at risk. Physical examination can be misleading and different incisions may be needed depending on which structures are injured and the level at which they are injured. Thus, in stable patients, additional imaging is indicated.

Additional diagnostic adjuncts generally involve endoscopy, contrast studies, or both to investigate the possibility of an esophageal injury. While asymptomatic tracheal injuries are quite rare, many have favored a diagnostic bronchoscopy in these injuries. In the past, vascular structures were investigated by means of catheter angiography, with noninvasive axial imaging as the most common modality in the current era.

Unfortunately, in unstable patients with a zone I trajectory, localization of the injury may not be possible preoperatively. In such a case, the clinician should make an estimate as to which structures are most likely to be injured. The initial incision should be tailored to quickly expose that area. If exposure is inadequate or a different structure has been injured, the incision

should be lengthened, or a second incision should be made. This process continues until the injury is controlled or the patient has died.

Aerodigestive injuries are not an issue in zone III; however, the difficulty in surgical management of vascular injuries in zone III makes preoperative imaging very attractive. In the past, angiography was used as the sole diagnostic test in stable patients. If patients are unstable, clinicians must weigh the difficulty of diagnostic exploration against the time it would take to use alternative hemostatic methods. In some cases, if catheter hemostasis is immediately available, temporary control with finger pressure or a balloon, as a bridge to rapid diagnostic angiography and catheter hemostasis, may actually be quicker than direct operative exploration. In most areas of the world, this approach is only appropriate in a few highly advanced centers. In most centers, while difficult, direct surgical exploration is the wisest course in the unstable patient.

Current Imaging Technology

In recent years, computed tomography (CT) has become the imaging modality of choice to evaluate neck injuries. CT is extremely attractive as it provides a three-dimensional evaluation of the neck and is rapidly available. In patients with injury patterns that put the upper mediastinal structures at risk as well, CT can simultaneously evaluate both areas for injury.

CT may be very effective at excluding injuries in certain cases. For example, a patient with a gunshot wound to the neck that has a clearly demonstrated CT trajectory that avoids all vital structures. In this case, close observation without additional studies is appropriate. Other patients, such as those with significant amounts of subcutaneous air or a trajectory that is close to vital structures, may need additional diagnostic testing (angiography, endoscopy).

Penetrating Neck Trauma

In 2002, Gonzalez et al. prospectively evaluated patients with penetrating injury to zone II of the neck that did not have an indication for emergent surgical exploration.[13] Patients then underwent dynamic CT imaging and had a barium esophagram, followed by mandatory surgical exploration of the

neck. Investigators noted a total of four esophageal injuries. Two of the four were seen on surgical exploration only and were not identified on either CT scan or esophagram; however, both injuries missed on imaging were less than 0.5 cm and were the result of stab wounds. The authors speculated that the injuries may have healed spontaneously. The most commonly missed injury by CT scan was jugular venous injury; which likely needed no therapy.[13]

In a large prospective study involving Los Angeles County, University of Southern California Medical Center and the R Adams Cowley Shock Trauma Center at the University of Maryland, all asymptomatic patients presenting with a penetrating neck injury and no signs of injury were safely observed and investigators reported zero missed injuries. In the same series, patients with soft signs of injury (venous oozing, nonexpanding or nonpulsatile hematomas, minor hemoptysis, dysphonia, dysphagia, and subcutaneous emphysema) underwent multidetector CT angiography (CTA). Investigators achieved 100% sensitivity and 97.5% specificity in detecting all clinically significant injuries.[14]

Blunt Neck Trauma

Plain film radiography is not adequate to identify injuries to structures in the neck; however, pneumothorax, hemothorax, air in the subcutaneous tissues, nasogastric tube displacement, or mediastinal widening are all indicative of potential injuries in the neck.

BCVI diagnosis deserves special mention. In the past, BCVI was typically diagnosed after the patient had a stroke. Diagnostic angiography then virtually always demonstrated an internal carotid artery injury. Therapy included anticoagulation, but was mainly supportive, as the damage was done.

As screening protocols were developed, the incidence of BCVI seemed to increase, even in patients with no identifiable risk factors for BCVI.[15] As CTA became more entrenched as a diagnostic tool, the rate of vascular injury again seemingly radically increased.[16,17] It seems obvious that the patients did not change, but our ability to diagnose injuries did. One must question whether some of these injuries, particularly those of low grade, have significant clinical importance.

Additional debate has focused on the ideal test for diagnosis of BCVI, with some suggesting angiography and some CTA. In a study of 146 patients at risk for BCVI, investigators imaged all patients with 16-slice CTA and four-vessel cerebral angiography. They noted a sensitivity of 97.7% and a specificity of 100% with the utilization of CTA for the diagnosis of BCVI.[18] Authors in Memphis examined 684 patients and found the sensitivity of CTA to be 51% with a specificity of 97%.[19] Despite the disparate findings, survey results illustrate that 90% of trauma surgeons utilize CTA as their preferred diagnostic modality for BCVI.[20]

MANAGEMENT OF SPECIFIC INJURIES

Blunt Cerebrovascular Injury (BCVI)

Blunt injuries to the carotid and vertebral arteries are the result of a direct blow to the vessel itself or an extreme flexion, extension, or lateral rotational injury. If located in the carotid artery, these injuries typically occur at the base of the skull. Vertebral artery injury usually is located in the portion of the vessel protected by the cervical spine. These areas are difficult to explore surgically.

Table 23.1 Signs and Symptoms of Blunt Cerebrovascular Injury
Hemorrhage of potential arterial origin
Expanding cervical hematoma
Cervical bruit in a patient <50 yrs old after trauma
Unexplained lateralizing neurologic deficits, transient ischemic attack, amaurosis fugax, or Horner syndrome after trauma
Cranial neurologic deficits incongruous with brain CT findings
Evidence of cerebral infarction on CT scan

From Biffl WL, Moore EE, Elliott JP, et al. Blunt cerebrovascular injuries. *Curr Probl Surg* 1999;36(7):505–599.

BCVI is reported to occur in 1% to 2% of blunt trauma patients and the incidence of stroke is approximately 25%, with a mortality rate of up to 13%, if left untreated.[16,21–24] Treatment for these injuries is centered on antiplatelet therapy and systemic anticoagulation to decrease the risk of stroke. Early recognition and initiation of treatment has been shown to decrease the rate of cerebral ischemia.[25,26]

The work of Biffl and colleagues in 1999[21,24] highlighted the importance of screening for BCVI when certain anatomic injuries or injury patterns were observed (**Table 23.1**). Subsequently, organizational guidelines have been disseminated by the Eastern Association for the Surgery of Trauma (EAST) based on review of the literature with the aim of guiding screening practices for BCVI (**Table 23.2**).[27] Investigators have shown that up to 30% of patients diagnosed with BCVI may have no radiographic or clinical risk factor that would guide the clinician to screen for these injuries.[15] Recent data has also identified an association between BCVI and nontraditional risk factors such as serious chest injury.[17] Thus, a high index of suspicion 5 must be maintained in order to effectively diagnose and treat BCVI.

Table 23.2 Screening Criteria for Blunt Cerebrovascular Injury

Injury Mechanism
Severe cervical hyperextension/rotation or hyperflexion
Displaced midface or complex mandibular fracture
Closed head injury inconsistent with diffuse axonal injury
Near hanging result in anoxic brain injury
Physical Signs
Seat belt abrasion or other soft tissue injury of the neck resulting in swelling or altered mental status
Fracture in proximity to internal carotid or vertebral artery
Basilar skull fracture involving the carotid canal
Cervical vertebral body fracture

From Bromberg WJ, Collier BC, Diebel LN, et al. Blunt cerebrovascular injury practice management guidelines: The Eastern Association for the Surgery of Trauma. *J Trauma* 2010;68(2):471–477.

Given the seeming inability of screening guidelines to accurately identify patients at risk for BCVI, some centers have gone to blanket screening.[15] All polytrauma patients with a blunt mechanism of injury undergo CT scan of the cervical spine with contrast timed to image the carotid and vertebral arteries in conjunction with a chest and abdominal CT scan, obviating the need for a second contrast study. While data on this blanket screening is limited, it does enable the identification of injuries early in the course of workup and identifies injuries in patients that would otherwise not be screened secondary to lack of criteria.[15] Patients with identified injuries generally receive a formal CT angiogram as their follow-up study.

6 If stroke can be avoided with prompt initiation of therapy, functional outcomes after BCVI are good,[28] however, many patients with BCVI have multisystem trauma and are thus deemed not suitable for antiplatelet therapy or systemic anticoagulation. In a 2009 study, almost one-third of patients with BCVI were identified as not candidates for therapy, with an overall stroke rate of 12% and stroke-related mortality of 50%.[16] Experience with BCVI and stroke has led our institution to a fairly aggressive stance on treating

BCVI judged to be severe, even in the face of concomitant injuries (including traumatic brain injury in certain circumstances).

It is tempting to assign treatment for BCVI to a relatively lower priority. Patients with BCVI often have concomitant injuries such as intra-abdominal solid visceral injury or traumatic brain injuries. The traditional approach has been to simply decide that these patients are not candidates for anticoagulation and defer therapy. While this may be acceptable with low-grade injuries, given the relatively high rate of stroke with higher-grade injuries, this may not be wise. Recent data suggest that in Grade IV carotid injuries (complete occlusion), recanalization and subsequent stroke is extremely common.[29] This would seem to suggest that the presence of higher-grade injuries mandates therapy. For instance, in a patient with splenic injury and carotid artery injury, one should consider whether splenectomy followed by anticoagulation is wiser than nonoperative management and withholding treatment for the BCVI.

OPERATIVE EXPLORATION

As many general surgeons do not routinely operate in the neck, early consideration of potential injuries is important. Immediate availability of vascular instruments, advanced airway devices, endoscopic towers, and scopes are important.

The patient is positioned supine, with a full surgical prep from the chin to the knees. Utilizing a widely prepped surgical field allows easy access to various body cavities. If unilaterality of injury is assumed or known, it may be beneficial to position the patient's head in the direction opposite to the injury, which opens the surgical field for better exploration. Given the very real possibility of a "multizone" injury, a sternal saw should be immediately available for possible entry into the mediastinum. Similarly, a chest retractor and deep vascular instruments should be immediately available.

Penetrating Vascular Injury

The presentation of penetrating vascular injury in the neck is dependent on the vessel injured and its location. Arterial injuries, specifically the carotid

arteries, may present with pulsatile arterial hemorrhage emanating from the wound, a palpable thrill, an audible bruit, or a rapidly expanding hematoma. Venous injuries tend to have a more insidious presentation and may be clinically undetectable. Penetrating vertebral artery injury is rarer given the relatively protected position of the artery within the osseous spinal canal.

Cerebral ischemia secondary to carotid artery injury can lead to stroke and long-term neurologic sequelae, or even death. In some series, patients who present in hemorrhagic shock have a mortality of 41%, but have 50% mortality when presenting with stroke.[30] Patients presenting with any neurologic deficit, short of coma, should undergo carotid arterial repair with revascularization if technically feasible, as results are improved with revascularization. In patients presenting with a Glasgow Coma Scale (GCS) <8 (coma), a poor outcome is likely regardless of the therapy selected.[31,32]

Often, diagnosis of carotid injury occurs intraoperatively, as there is no time for preoperative imaging. Carotid artery injuries are managed using standard principles of vascular repair. Exploration of the neck is through a generous sternocleidomastoid incision. Control of the proximal carotid artery is obtained at the base of zone II. If possible, it is wise to control the artery distally, before entering the hematoma. Unfortunately, distal control is often not possible. As the neck is a compact region, during dissection to control the distal carotid artery, the contained hematoma often ruptures. Digital control should then be utilized to prevent exsanguinating hemorrhage while the distal dissection is performed. Once the distal carotid artery (whether it is the internal carotid artery or distal common artery) is controlled, digital pressure is released and careful dissection performed.

Injuries to the common carotid artery can be primarily repaired, particularly if the injury is caused by a stab wound and has clean edges. More complex injuries, as those from gunshot wounds, usually require resection of the injured segment. Even after resection of a segment of the carotid artery, primary anastomosis may be possible. Full mobilization of the common carotid artery will often give additional length and allow for a tension-free anastomosis. For injuries located more distally, ligating the external carotid artery will give additional mobility to the common carotid artery. If primary anastomosis or repair is not feasible, a bypass graft using either saphenous vein or PTFE is equally acceptable. PTFE should be

avoided in the event of contamination or concomitant tracheal or esophageal injury.

Internal carotid artery injury represents a distinct subset of carotid artery injuries. Unlike common carotid artery injury, the initial neurologic presentation is not a good predictor of final neurologic presentation. Injuries to the internal carotid artery have 20% mortality and the majority of these deaths are secondary to cerebral ischemia.[26] Interventional techniques, including embolization, may be effective in some injuries thus obviating the need for exploration.[27]

Control of the internal carotid artery proceeds along the same principles as with common carotid artery injuries, though distal control may be even more problematic. During the dissection, one must take care not to injure the hypoglossal nerve, which passes across the distal internal carotid artery. The surgeon should ascertain adequacy of back bleeding from the distal internal carotid artery. Pulsatile back bleeding confirms patency of the circle of Willis. In patients with poor back bleeding, use of a shunt should be considered. We routinely use full-dose IV heparin unless there is a contraindication.

The internal carotid artery is repaired using the same principles as mentioned for the common carotid artery, though several scenarios require special mention. If there is injury to the proximal internal carotid artery and the distal vessel is thrombosed, dissection should be carried out as distal as possible. If the vessel is thrombosed as far as is surgically accessible, the surgeon should avoid the temptation to do catheter thrombectomy as this is virtually never complete and, once revascularized, the patient has significant risks of embolic stroke. In addition, one should avoid ligating the thrombosed internal carotid artery at the base. If one forcefully ligates the internal carotid artery, there is high likelihood that distal clot will be dislodged, causing a stroke of clinical significance.

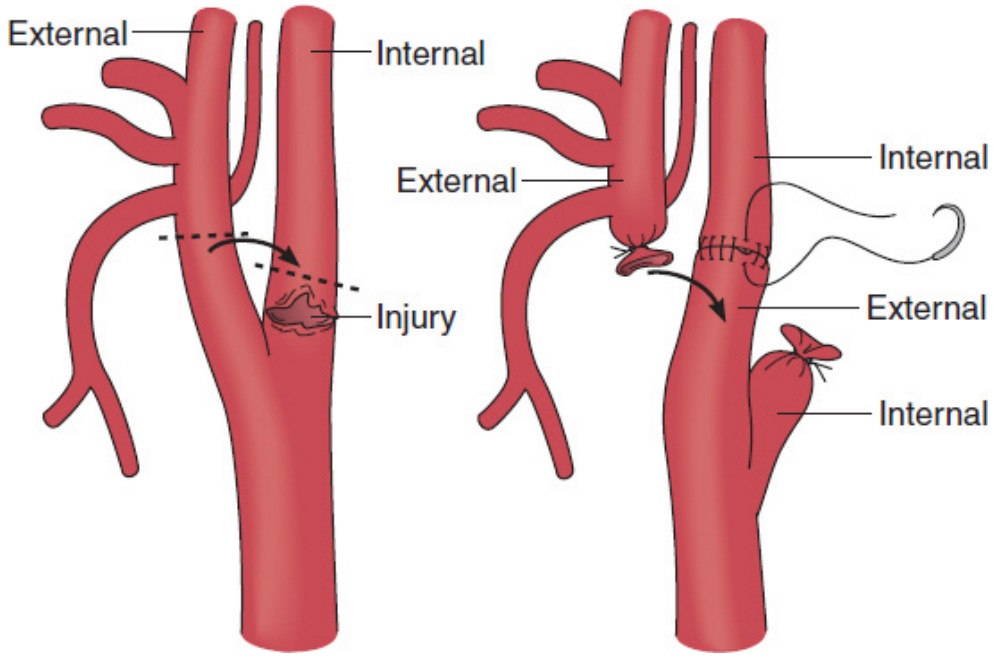

Figure 23.3 A proximal internal carotid artery injury managed with resection and transposition of the external carotid artery to obtain inflow to the native internal carotid artery.

Occasionally, one will encounter an injury in the very proximal internal carotid artery. Once the vessels are controlled, consideration should be given to use the external carotid artery as the conduit, if primary repair is not feasible. The damaged internal carotid artery can be dissected down to the level of the bifurcation (**Fig. 23.3**). The external carotid is ligated at the level of the first branch and the external carotid artery rotated over to use as the conduit. A single vascular suture line then connects the external to the internal carotid artery.

For the most part, the external carotid artery is expendable. If an external carotid artery injury is diagnosed at the time of surgical exploration, it can simply be ligated. Those that are diagnosed preoperatively, with images, are often amenable to catheter-based hemostatic techniques.[29] If there is a distal injury to a branch of an external carotid artery, such as the facial or lingual arteries, particularly if caused by penetrating facial trauma, catheter-based hemostasis is by far the most attractive option. Proximal ligation of the external carotid artery will decrease inflow, but the robust collateral circulation from the contralateral external carotid may be sufficient to cause

continued hemorrhage. Angiographic options are then essentially nil, as the ligated external carotid prevents an angiographic solution.

Secondary to the posterior anatomic location and protection provided by the cervical spine, penetrating vertebral artery injuries are less likely. Additionally, injuries to the vertebral arteries are less likely to cause neurologic sequelae than those to the carotids.[30] Operative exposure of the vertebral artery is quite difficult secondary to its protected location in the posterior neck. If necessary, it is best approached via an anterior approach with proximal ligation of vertebral artery.[31]

Combined carotid and vertebral artery penetrating injuries are very morbid, with mortality rates of approximately 50%.[32] Occasionally, a vertebral artery injury will be discovered at the time of diagnostic neck exploration. This is an extremely challenging situation, as direct pressure will only temporarily control the artery. Rather than attempting to expose the artery by unroofing the cervical spine over the vessel, we have generally maintained digital pressure or controlled the artery temporarily with a Fogarty balloon, after which the patient is transported to a site where angiographic embolization is possible.

Trachea and Larynx

Blunt laryngotracheal trauma is uncommon[33] and low-grade injuries can be clinically occult. Thus, these injuries require a high index of suspicion. The most typical mechanism of injury involves an anterior to posterior vector of force that drives the thyroid cartilage into the rigid cervical spine. Such forces can be the result of a motor vehicle collision with compression of the neck against the steering wheel or dash of the automobile. The most common symptoms include hoarseness, dyspnea, and dysphagia.[33,34] Careful attention must be paid to the airway as laryngotracheal separation can be catastrophic. Definitive diagnosis is made with a combination of CT scanning and endoscopy. Definitive airway management is best obtained with tracheostomy if endotracheal intubation is not prudent.[35]

The presentation of penetrating laryngotracheal injuries are less subtle, as impressive symptoms and physical findings present in high-grade injuries. Management focuses on rapid airway control, either via endotracheal intubation or via a surgical airway. In the rare instance of tracheal transection

in the neck with two visible lumens, the distal lumen should be intubated with any available airway device. Concomitant esophageal injury is a source of major morbidity; therefore, the esophagus should be evaluated with early endoscopy or operative exploration.[36]

Cervical tracheal injuries, particularly if they are isolated, are best approached via a collar incision performed approximately two fingerbreadths above the sternal notch. If other injuries are present and/or if full exploration is needed, the trachea can be exposed and repaired using a sternocleidomastoid incision. If a collar incision is used, subplatysmal flaps are created and the strap muscles are then divided in the midline. The thyroid isthmus can be retracted cephalad and the entire cervical trachea is then clearly visualized. If the location of the tracheal injury in the neck is clearly in zone II, surgical exploration confirms the diagnosis and allows for prompt therapy.

Occasionally tracheal injuries are located closer to the thoracic inlet. In these cases, preoperative bronchoscopy is vital in order to plan the best operative course. If the injury is located in the upper mediastinum, several options exist. The patient can be explored via a collar incision and the anterior trachea identified. The trachea can be mobilized using digital dissection into the upper mediastinum. The trachea can then be grasped with a tracheal hook and retracted up into the neck. It is possible to mobilize the trachea for approximately three rings, thus allowing the surgeon to repair these injuries with a relatively small incision. Injuries that are located in the more distal mediastinum are best approached with a right-sided posterolateral thoracotomy.

Occasionally, tracheal injuries will be located at a level above the endotracheal balloon. When performing diagnostic bronchoscopy, the endotracheal tube must be withdrawn (with the cuff deflated) over the bronchoscope, up to the level of the vocal cords. This allows complete visualization of the proximal trachea. Not pulling back the endotracheal tube risks missing proximal tracheal injuries.

Injuries to the posterior membranous trachea are relatively difficult to approach. In patients with blunt trauma, small injuries may be observed; however, if repair is thought to be prudent, the best way to approach this is through the anterior trachea. The anterior trachea is opened transversely at the level of the injury and the posterior injury is then visualized and repaired.

The anterior trachea is closed primarily. Intraoperative bronchoscopy can help locate the level of the injury.

The blood supply to the trachea enters posterolaterally on both sides; therefore, circumferential mobilization of the trachea risks causing ischemia, which may manifest either as tracheal necrosis, dehiscence of a repair, or postoperative tracheal stenosis. In addition, the recurrent laryngeal nerve runs in the tracheoesophageal groove and care must be taken to avoid damage to it during mobilization or tracheal repair. Postoperatively, patients undergoing tracheal repair should be extubated as soon as possible. It is often tempting to think that the tracheal repair is protected with longer-term tracheal intubation, but the chances of complication are less if the patient is extubated at the end of the operative procedure. One should avoid a tracheostomy in a patient with tracheal repair, because stenosis at the level of tracheostomy and the level of tracheal repair can make future reconstruction exceedingly difficult.

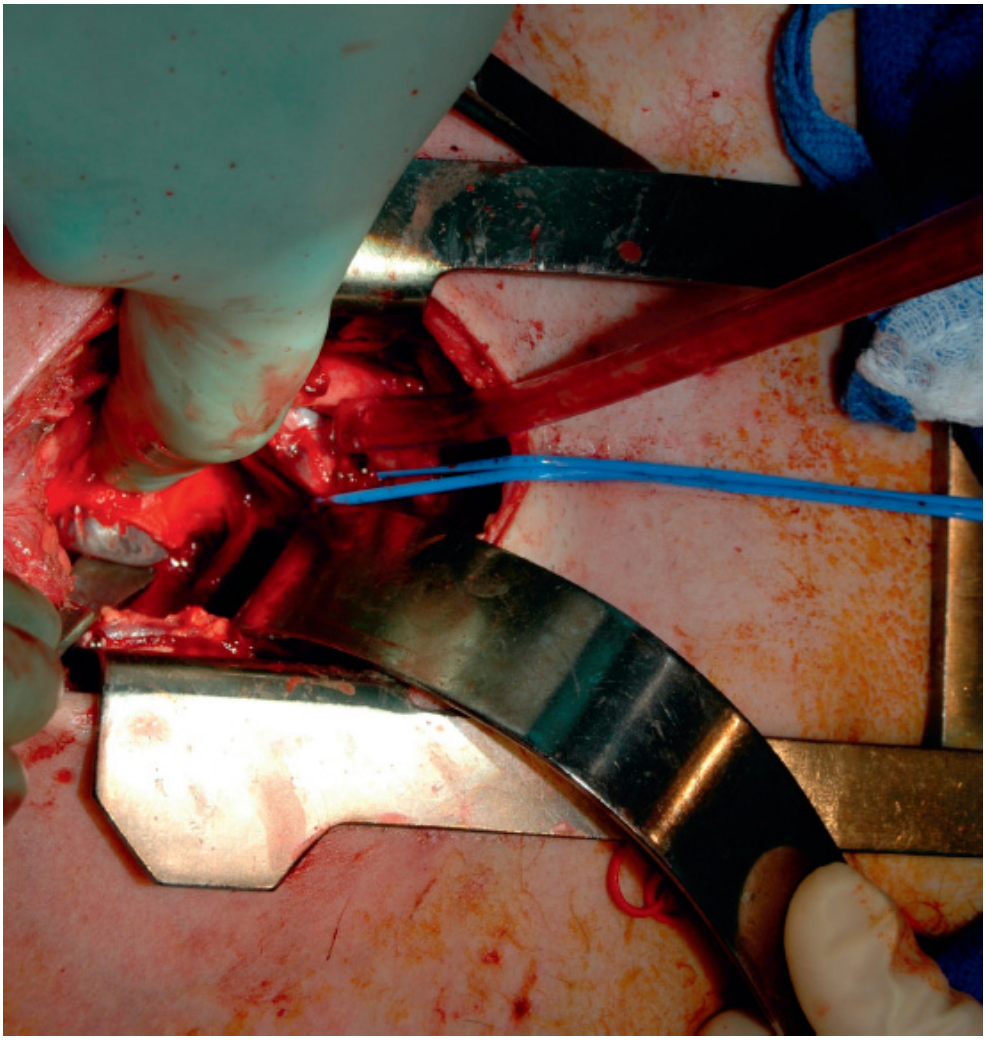

Figure 23.4 Partial sternal split for evaluation of tracheal injury. The endotracheal tube balloon is visualized within the lumen of the injured trachea.

In the event that the injury extends into the thoracic inlet, a partial sternal split (**Fig. 23.4**) or full sternotomy can be performed for better visualization. Tracheal injuries are preferentially repaired primarily with single layer absorbable suture, though resection of up to 2 to 4 cm with primary anastomosis is technically feasible. Suture lines should be buttressed with autologous, well-vascularized tissue, such as strap muscle (**Fig. 23.5**).

Esophagus

Early diagnosis of esophageal injury is imperative, as missed injury and/or a delay in diagnosis can lead to disastrous consequences. In a review of 109

penetrating esophageal injuries, the mortality rate was 2% with immediate operation. Mortality increased to 44% with delayed diagnosis and operation. In this same series, mortality increased to 100% for patients with a delayed diagnosis and no operative procedure.[37]

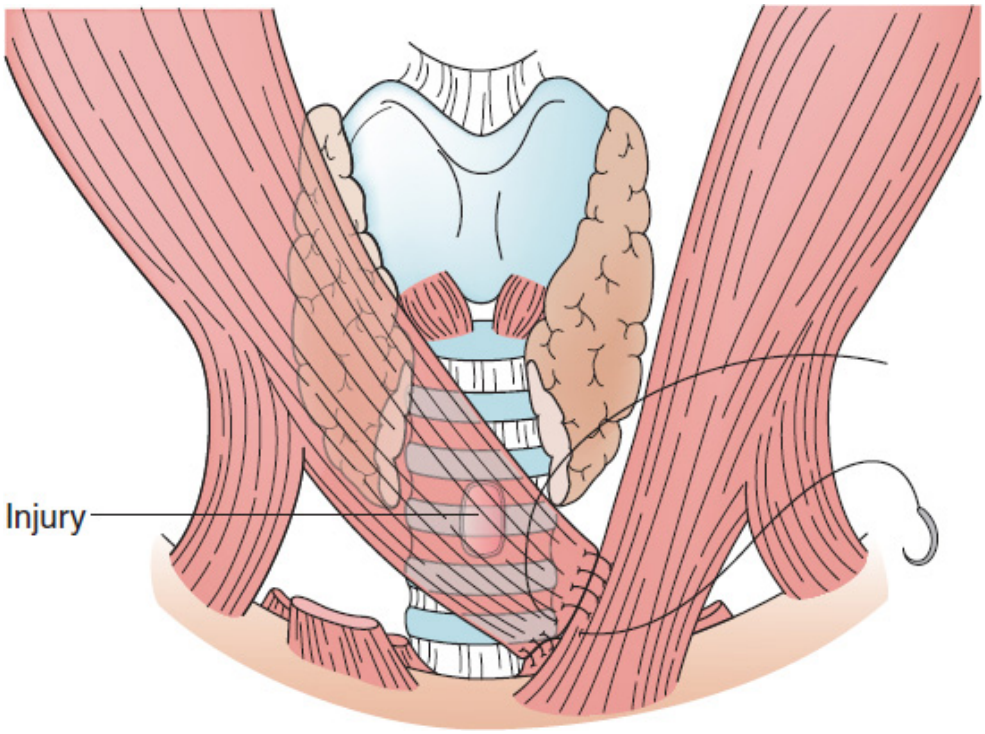

Figure 23.5 Divided strap muscle utilized to buttress tracheal injury/repair.

As the course of the esophagus is relatively superficial within the neck, diagnosis can occasionally be made on physical examination findings alone. Food particles or salivary secretions within the wound are highly suggestive of esophageal injury. Additional physical examination findings may include esophageal or oropharyngeal bleeding, subcutaneous emphysema, and neck hematoma. Plain film radiographic findings may include air within the subcutaneous tissues and pneumomediastinum.[38] In a review of 77 patients with noniatrogenic esophageal injury, 58% occurred in the cervical esophagus, with physical examination findings present in only 26% of the cohort.[39]

Given the pervasive nature of CT scanning in the trauma patient, investigators have evaluated the utility of this imaging modality for esophageal injury. A study from the Aga Khan University Hospital showed

53% sensitivity for CT scanning in diagnosing esophageal injuries.[40] The gold standard for diagnosis 7 of most esophageal injuries remains a combination of esophagoscopy and contrast-enhanced esophagography. When these two imaging modalities are used in combination, an accuracy of almost 100% is achieved.[41] The sensitivity of esophagography alone varies from 50% to 90%, while the sensitivity of endoscopy alone varies from 29% to 100%.[42]

As with the trachea, the location of the esophageal injury defines the approach for repair. Those injuries that are clearly in zone II can easily be approached via a sternocleidomastoid incision. Those in the chest are best approached via a posterolateral right thoracotomy. As with the trachea, localization of the injury, particularly those at the junction between the neck and chest, is the easiest way to ensure optimal exposure. Intraoperative endoscopy can be very helpful in positively identifying the location of an injury and helping to direct therapy.

Small, nondestructive injuries in the hypopharyngeal region can occasionally be managed nonoperatively with antibiotics, upright positioning, limited oral intake, and close clinical observation.[43] The vast majority of cervical esophageal injuries are best managed operatively. Cervical esophageal injuries are most easily approached via a left anterior sternocleidomastoid incision. If a collar incision has been initiated, it can be extended to the left, along the anterior border of the sternocleidomastoid muscle to facilitate better exposure. Preoperative placement of a nasogastric tube may assist with identification of the esophagus in the neck, as the hard nasogastric tube can be palpated within the lumen. After lateral retraction of the sternocleidomastoid muscle, the dissection progresses medially until the esophagus is encountered. Care must be taken to avoid injury to the recurrent laryngeal nerve in the tracheoesophageal groove.

Circumferential dissection of the esophagus and placement of large rubber drain around the organ can facilitate retraction and mobilization. As the blood supply of the esophagus runs vertically within the muscle, the esophagus can be circumferentially mobilized without risk of ischemia. Thus, injuries located in the superior mediastinum can be mobilized into the neck and repaired. After repair, liberal drainage of the injured area is highly recommended in an effort to avoid salivary fistula and deep neck infection.[38,43] Delays in diagnosis of more than 12 hours are associated with

poor outcomes and in these cases, proximal diversion and wide drainage may be the safest option.

Primary repair of the injury is the goal in most circumstances. During repair, the entirety of the mucosal injury must be visualized, as it may extend beyond the field of view under the longitudinal outer muscle of the esophagus. Debridement of all devitalized tissue is required. Repairs are typically performed in two layers with absorbable sutures, though single-layer repair is possible.[38,44] Similar to tracheal repair, a well-vascularized muscle is highly recommended to buttress the repair. Given the likelihood that the patient will be on a restricted oral diet, placement of a small-bore enteral tube, distal to the repair, should be considered intraoperatively. Imaging repairs at 7 to 10 days with a contrast-enhanced swallow study is recommended prior to removal of drains.

Table 23.3 Common Complications after Neck Injury

Pneumonia and ventilator-dependent respiratory failure
Surgical site infection
Anastomotic dehiscence and repair breakdowns
Suture granulomas
Trachoesophageal fistula

COMPLICATIONS

As in all forms of injury, neck injuries are associated with a variety of morbidities (**Table 23.3**). The most common complications after tracheal repair include postoperative suture granuloma, pneumonia, and surgical site infection.[45] Complications after tracheal repair were once thought to be numerous; modern studies have questioned this supposition. In a 2013 paper, investigators showed that complications after tracheal injury alone were associated with an exceedingly low rate of complications. In patients with

combined tracheal and esophageal injuries, the rate of complications is drastically increased.[46]

Tracheoesophageal fistula occurs when an abnormal passage forms between the trachea and esophagus, manifesting as respiratory distress and recurrent pulmonary infections. Management includes a variety of operative techniques aimed at restoring the continuity of both the trachea and esophagus and the interposition of well-vascularized tissue flaps between the repairs. Though endoluminal stenting is discussed, its utility is currently minimal.[47]

Esophageal leak from repair dehiscence and anastomotic breakdown creates an ongoing source of intrathoracic infection and inflammation, which makes primary management and repair exceedingly difficult. Though relatively early in the experience, the use of endoluminal stenting in this situation has shown promise and avoids the need for full operative exploration.[48] Leaks in the neck are more easily controlled by opening of the wound and wide drainage with avoidance of enteral nutrition past the site of injury. In rare instances, cervical esophagostomy may be required.

SUMMARY

Management of injuries to the neck requires a thorough understanding of three-dimensional anatomy and an appreciation for the severity of injuries possible in this region. A relatively small anatomic region, the neck contains many structures vital to meaningful survival. Attention to airway is of the utmost importance, because without a secure airway, the remainder of workup is meaningless. In the presence of vascular injury, all management options must be rapidly reviewed and the most easily obtained and efficacious maneuver should be chosen. As nonoperative management of many traumatic injuries continues to expand, it is the obligation of the surgeon to remember basic surgical principles and apply them in an expeditious and safe manner as the situation mandates.

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24

Thoracic Trauma

Jill Streams and Marc de Moya

Key Points

1. The mortality associated with penetrating thoracic trauma is higher than blunt trauma.
2. The most common blunt thoracic injury is rib fracture and the most effective pain relief is thoracic epidural analgesia.
3. Occult and small simple pneumothoraces do not necessitate drainage but if drainage is needed for larger pneumothoraces, it can be accomplished effectively with a small caliber catheter (e.g., 8- to 14-Fr pigtail catheter).
4. 28-Fr chest tubes are effective at draining hemothoraces but if there is a significant retained hemothorax after tube thoracostomy, early operative evacuation with video-assisted thoracoscopy should be employed.
5. Operative repair of blunt aortic injuries may be delayed and treated medically in the face of severe associated injuries.

INTRODUCTION

Thoracic trauma is a common occurrence with an incidence of approximately 25% of all traumas.[1] Thoracic injuries are also commonly associated with head and abdominal trauma with a blunt mechanism, the so-called polytrauma patient. The most common thoracic injury is rib fracture and mortality/morbidity increases as the number of ribs fractured increases. Mortality is most pronounced in the elderly where there is a 19% increase in mortality 1 with each additional rib fracture.[2] The majority of deaths from thoracic trauma are due to a penetrating mechanism, but overall 85% of penetrating injuries to the chest can be managed with a chest tube. Regardless of the mechanism or obvious injuries, one should always proceed with a systematic approach to the trauma patient, via Advanced Trauma Life Support (ATLS).[3]

INITIAL IMAGING

The initial imaging in the trauma bay for suspected chest trauma is the screening chest x-ray (CXR) and the extended FAST (eFAST) examination. The CXR is typically a supine anteroposterior (AP) single film to evaluate for life-threatening injuries that require immediate intervention. The screening CXR can also help identify additional injuries such as bony fractures, mediastinal hematoma, pneumothorax, hemothorax, lung contusions, elevated diaphragm, large diaphragmatic rupture, or confirm position of endotracheal tube/any central lines in internal jugular or subclavian positions.[4] If the spine is cleared, particularly in the case of penetrating trauma, then an upright AP film may be obtained, which increases sensitivity for hemothoraces and pneumothoraces. These films are often limited due to movement, clothing, backboards, or inadequate exposure but serve as reasonable screening images (**Fig. 24.1**).

The FAST (focused assessment with sonography for trauma) has become a standard adjunct in the trauma bay. The standard FAST examination views include the right upper quadrant, left upper quadrant, pelvic view, and the pericardium. For the purposes of this chapter, the pericardial view will best demonstrate hemopericardium. Hemopericardium is typically the result of penetrating trauma to the heart but may also be due to blunt rupture of the heart.[5] Rozycki et al.[6] used the FAST examination to evaluate for pericardial

fluid in 1,540 patients with truncal injuries, with 100% sensitivity and 99.3% specificity. The eFAST includes the evaluation of lung and pleural spaces to detect pneumothorax and hemothorax. Sonographic findings of pneumothorax include absence of lung sliding, presence of A-lines, loss of comet tails, and the presence of a lung point sign.[7] When lung sliding and comet tails are absent, the sensitivity and specificity for pneumothorax are 81% and 98%, respectively. The presence of a lung point sign is less sensitive for pneumothorax, but highly specific with reported rates of 98% to 100%.[8,9]

Computed tomographic scans (CT scans) are often employed in thoracic trauma after the secondary survey and provide additional information as they are highly sensitive for hemo/pneumothoraces, fractures, vascular injuries, and lung contusions/lacerations. CT scans are typically performed with intravenous contrast to better visualize vascular injuries and lung parenchyma.

COMMON INJURIES

Rib Fractures

The most common injury in thoracic trauma is the rib fracture, occurring in approximately 10% of all trauma patients. The spectrum of injury patterns ranges from a single nondisplaced rib fracture to large flail segments with severe displacement. Injury patterns are related to age and degree of flexibility of ribs. The younger population has innately more mobile/flexible ribs and therefore requires a higher force to create fractures. This higher force also translates to a higher degree of underlying lung injury. The older population with more brittle ribs requires less force to fracture the ribs and therefore may not have severe associated injuries. The diagnosis is usually made by initial physical examination (tenderness and chest wall paradoxical movement for flail segments) and CXR. However, CXR only visualizes 30% of rib fractures. CT scan is extremely sensitive for rib fractures and also allows quantification of any associated hemothorax, pneumothorax, or contusion.

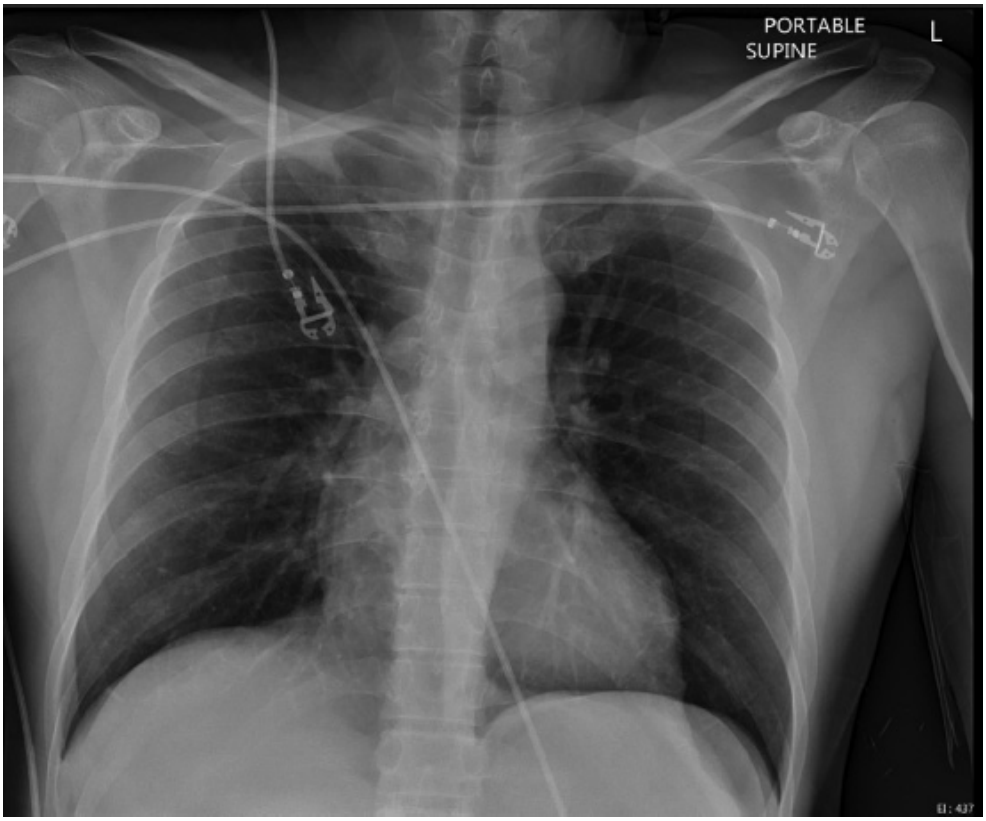


Figure 24.1 Supine AP CXR in the trauma bay.

Flail chest is defined as three or more consecutive ribs broken in two or more places. These segments may exhibit a "mechanical" flail which is the paradoxical movement of the flail segment in relation to the surrounding chest wall. As the patient inspires and expands the chest to produce a negative intrathoracic pressure, the flail segment is pulled inward (**Fig. 24.2A**). The opposite occurs during expiration and the flail segment bulges outward (**Fig. 24.2B**). The respiratory compromise that occurs in the face of a flail segment is multifactorial: (1) underlying lung contusion, (2) pain with respirations, and (3) mechanical disadvantage. Pain control and contusion are the most influential on clinical outcomes when compared to the mechanical disadvantage.

Treatment

2 The most important aspect of care for rib fractures is pain management. The majority of complications are directly related to lack of pain control. A recent EAST practice management guideline conditionally recommends

multimodal analgesia to include acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentin or pregabalin, ketamine, opioids, and regional/neuroaxial blockade, though the supporting literature is sparse for improved outcomes.[10] Additionally, the theoretical basis for multimodal pain control is extrapolated from ERAS protocols. However, there are studies suggesting that thoracic epidurals are superior to intravenous narcotics for treatment of pain related to rib fractures.[11,12] Polytrauma patients may have contraindications to thoracic epidural but other regional analgesia options exist including intercostal nerve blocks, serratus anterior blocks, paravertebral blocks, erector spinae blocks. An aggressive pain management program will allow the patient to be more mobile and promote good pulmonary toilet.

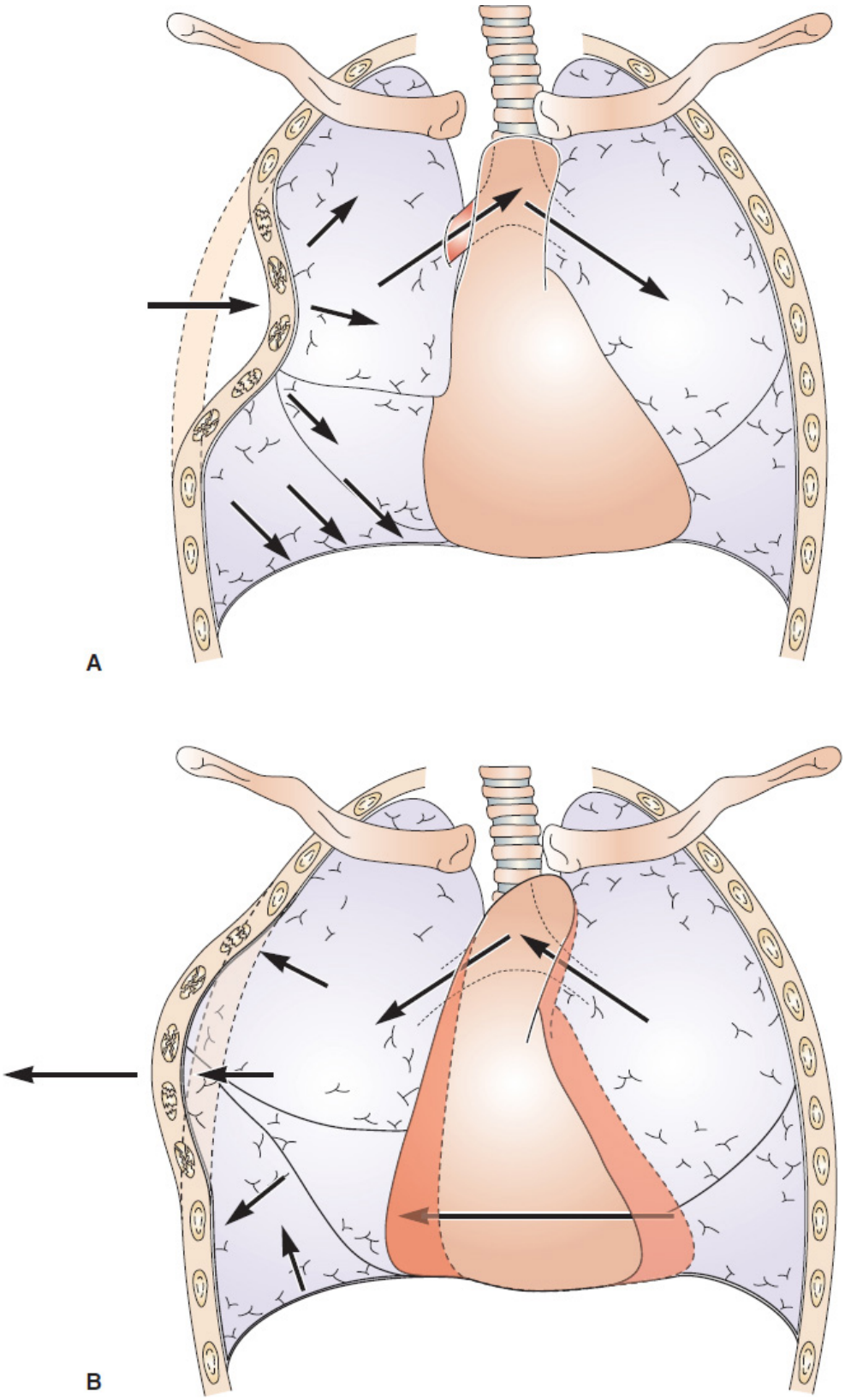


Figure 24.2 Pathophysiology of flail chest. **A:** Inspiratory phase: Chest wall collapses inward, causing air to move out of the bronchus of the involved lung into

the trachea and bronchus of the uninvolved lung, causing a shift of mediastinum to the uninvolved side. **B:** Expiratory phase: Chest wall balloons outward so that air is expelled from the lung on the uninvolved side and enters the lung on the involved side with an associated shift of mediastinum to the involved side.

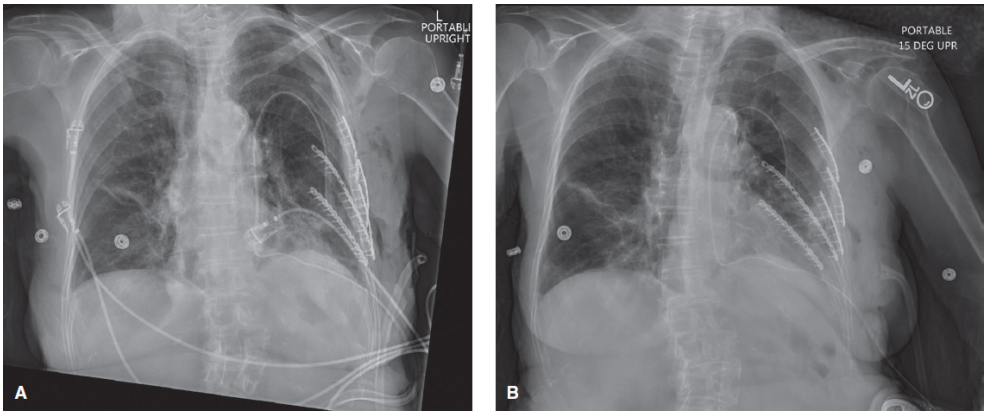


Figure 24.3 **A:** Rib fractures on CXR. **B:** Rib fixation with plates on CXR.

Operative fixation of the ribs (open reduction and internal fixation) has been increasingly utilized in recent years, following several prospective studies demonstrating a benefit to surgical repair of rib fractures (open reduction and internal fixation) versus mechanical ventilation alone in ICU length of stay, ventilator days, and respiratory complications for patients with flail chest.[13–15] However, a recent systematic review was not able to show a mortality benefit to rib fixation,[16] in contrast to previous meta-analysis that did show mortality benefit to operative fixation.[17] Contention exists over the benefit of rib fixation for those patients with multiple, nonflail rib fractures (**Fig. 24.3A**). In general, the author's approach is to consider rib fixation for any patient with three or more ribs fractured with severe displacement (more than the width of a rib) with some physiologic derangement (i.e., poor pulmonary function, inability to control pain, etc.), which is consistent with a recent prospective investigation comparing rib fixation for both flail and nonflail rib fractures to multimodal and multidisciplinary nonoperative management.[18] There are multiple types of rib fixators available (**Fig. 24.3B**) and no system or approach to the repair has proven to be superior. The majority of ribs repaired are number 4 to 9, approached via a thoracotomy incision (**Fig. 24.4**), though more minimally invasive techniques are evolving.

Pneumothorax

Pneumothoraces can be classified into three subtypes: occult, simple, and tension. Diagnosis of pneumothorax can be physical examination, CXR, or eFAST. The standard of care in the trauma bay is upright (if spine is cleared) or supine AP x-ray (if the spine is not cleared). Although radiographs are less sensitive than ultrasound for small pneumothoraces, they are used to screen for other associated injuries as described above. The pathophysiology of pneumothorax is the accumulation of air in the pleural space secondary to underlying pulmonary parenchymal injury or entrainment of atmospheric air from penetrating injury.

An occult pneumothorax is one that is seen on CT scan (which is the most sensitive test for pneumothorax) but not seen on CXR (**Fig. 24.5A,B**). Occult pneumothoraces are detected in 15% to 20% of blunt thoracic trauma. Subcutaneous emphysema on screening CXR should alert the clinician to possible pneumothorax (**Fig. 24.6**). A simple pneumothorax is one that is seen on either CT scan or CXR but is not associated with hemodynamic compromise. Those patients with a pneumothorax and hemodynamic compromise must be considered a tension pneumothorax until proven otherwise. A tension pneumothorax is a pneumothorax that has progressed to the point of pressurizing the pleural space, resulting in shifting of the mediastinum and compromising the venous return to the heart. Kinking of the great vessels leads to an acute decrease in cardiac output and shock. Signs and symptoms of a tension pneumothorax include; shortness of breath, dyspnea, tachypnea, hypotension, distended neck veins, and tracheal deviation (away from the site of injury). If any of these signs are present immediate decompression is necessary.

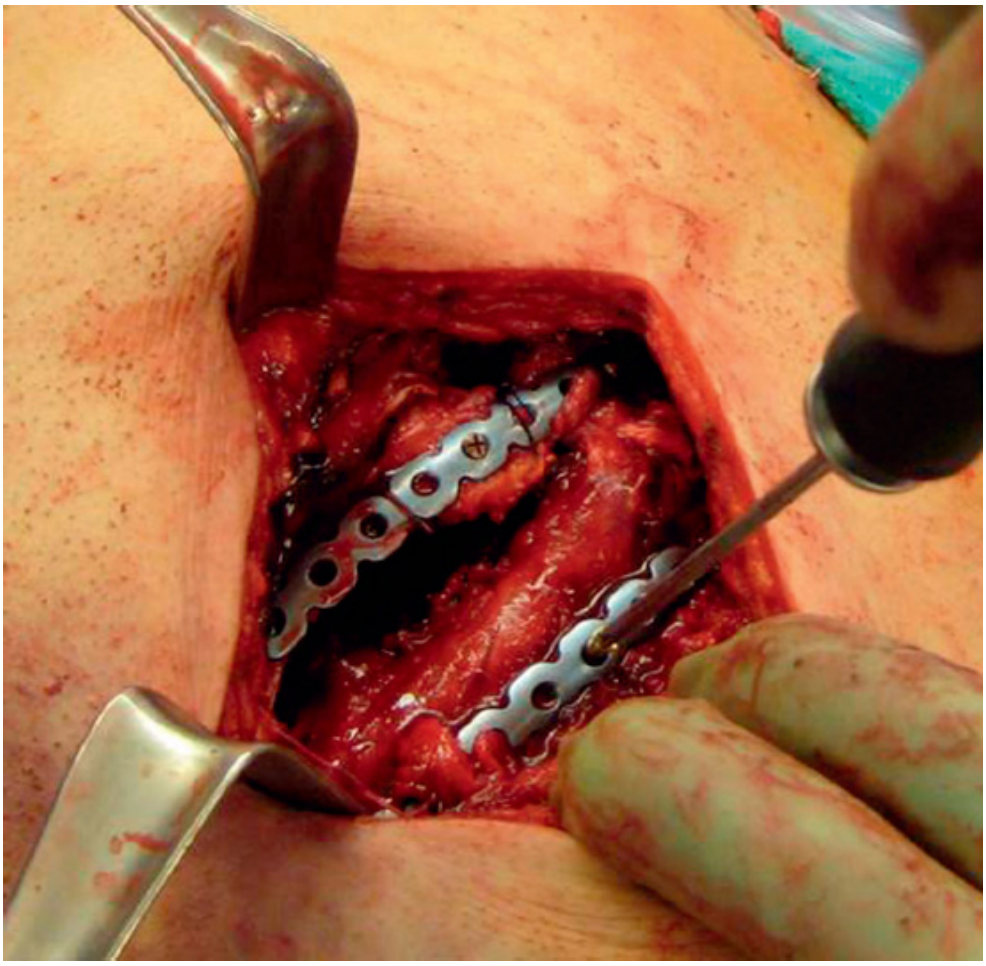


Figure 24.4 Rib fixation with plates (photo).

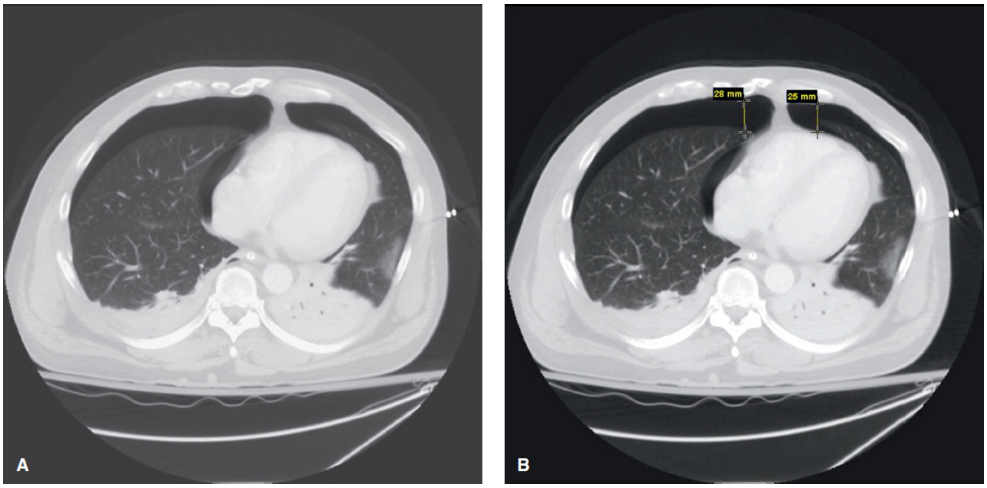


Figure 24.5 **A:** Occult pneumothorax seen on CT scan. **B:** Measurement of largest air pocket in a line drawn perpendicular to the chest wall.

Treatment of Pneumothorax

If the patient is hemodynamically unstable and a tension pneumothorax is suspected, needle decompression or finger thoracostomy may be considered. For needle decompression, a 14- or 16-gauge angiocatheter is inserted into the pleural space at either the anterior second intercostal space in the midclavicular line or the fifth intercostal space in the midaxillary line. There is cadaveric data that suggest that the fifth intercostal space in the midaxillary line has the least distance from the skin to the pleural cavity and therefore, may be superior to the anterior position.[19] This converts the tension pneumothorax to a simple pneumothorax which can subsequently be drained with a proper tube thoracostomy.

Finger thoracostomy achieves the same pleural depressurization as needle decompression. The procedure for finger thoracostomy is essentially the first steps of a traditional tube thoracostomy utilizing only a scalpel and a sterile gloved finger. An incision is made in the fourth or fifth intercostal space in the midaxillary line and carried down sharply above the rib to incise the intercostal muscles and parietal pleura. The pleural space can then be entered with a finger to provide pleural decompression. Advocates of finger thoracostomy argue that it has a higher success rate than needle decompression and can be performed quickly, however, detractors note pain from incision and infectious concerns if the subsequent chest tube is placed via the same incision.

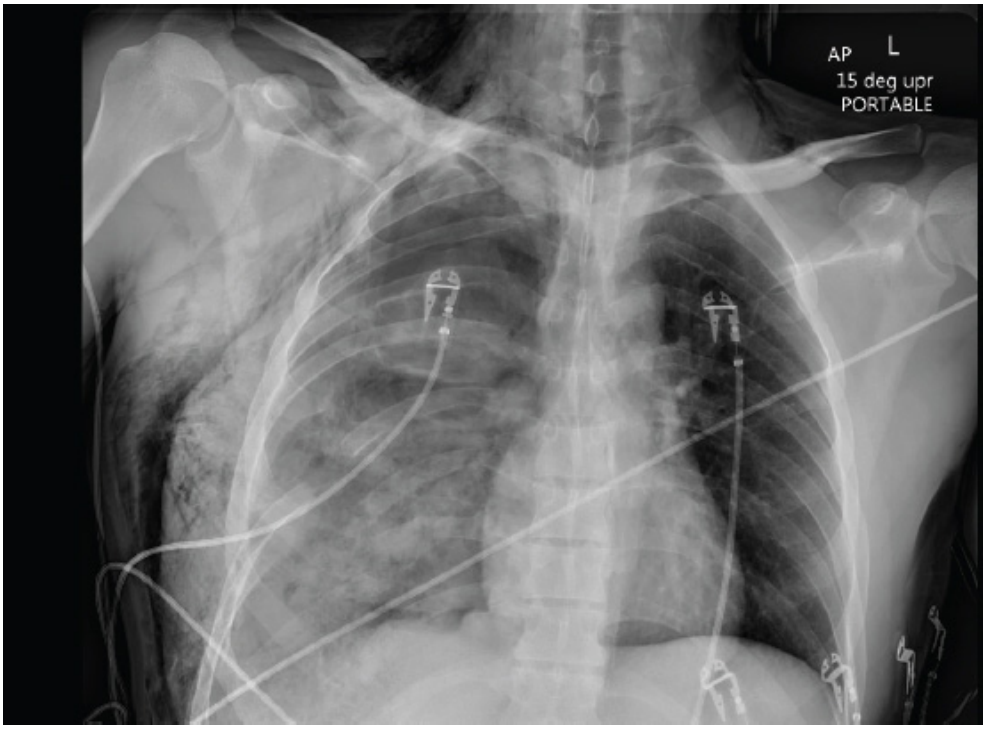


Figure 24.6 Subcutaneous emphysema.

If one has access to a chest tube quickly, there is no need to perform a needle decompression or finger thoracostomy. A tube thoracostomy placed in the zone of safety may be performed expeditiously. The zone of safety is outlined by the pectoralis major lateral border, the nipple line in men (two fingerbreadths above the inframammary fold, women), and the anterior border of the latissimus dorsi. The triangle formed by these borders is a guide for the practitioner for the safe placement of the chest tube (**Fig. 24.7**). If the tube is placed too far caudal, it can inadvertently enter the abdominal cavity. A 28-Fr chest tube may be placed as there is no difference between a 36 Fr and 28 Fr in ability to adequately drain the chest 3 of either pneumothorax or hemothorax but if there is no hemothorax component, one can consider a small caliber tube as described above.[20] In those patients with a pure pneumothorax, an 8.3- to 14-Fr pigtail catheter is acceptable and may be superior, given the significantly less pain/discomfort of the tube as described in a randomized clinical trial.[21,22] Pigtail catheters are placed using a Seldinger technique in the identical areas as the open chest tube technique.

Drainage of all traumatic pneumothoraces via chest tube or pigtail catheter is no longer mandatory even for patients on positive pressure ventilation. For those with small simple or occult pneumothoraces, one should be guided by progression of the pneumothorax or the development of signs/symptoms of cardiopulmonary compromise. In a series of 146 patients with pneumothoraces, 90% of pneumothoraces that were 3.5 cm or less in widest dimension were successfully observed. This holds true in the intubated patient on positive pressure ventilation as well.[23,24] Therefore, as a general rule, if the patient is stable, one should repeat the CXR and should only treat the pneumothorax if it has significantly increased in size or if the patient becomes symptomatic.

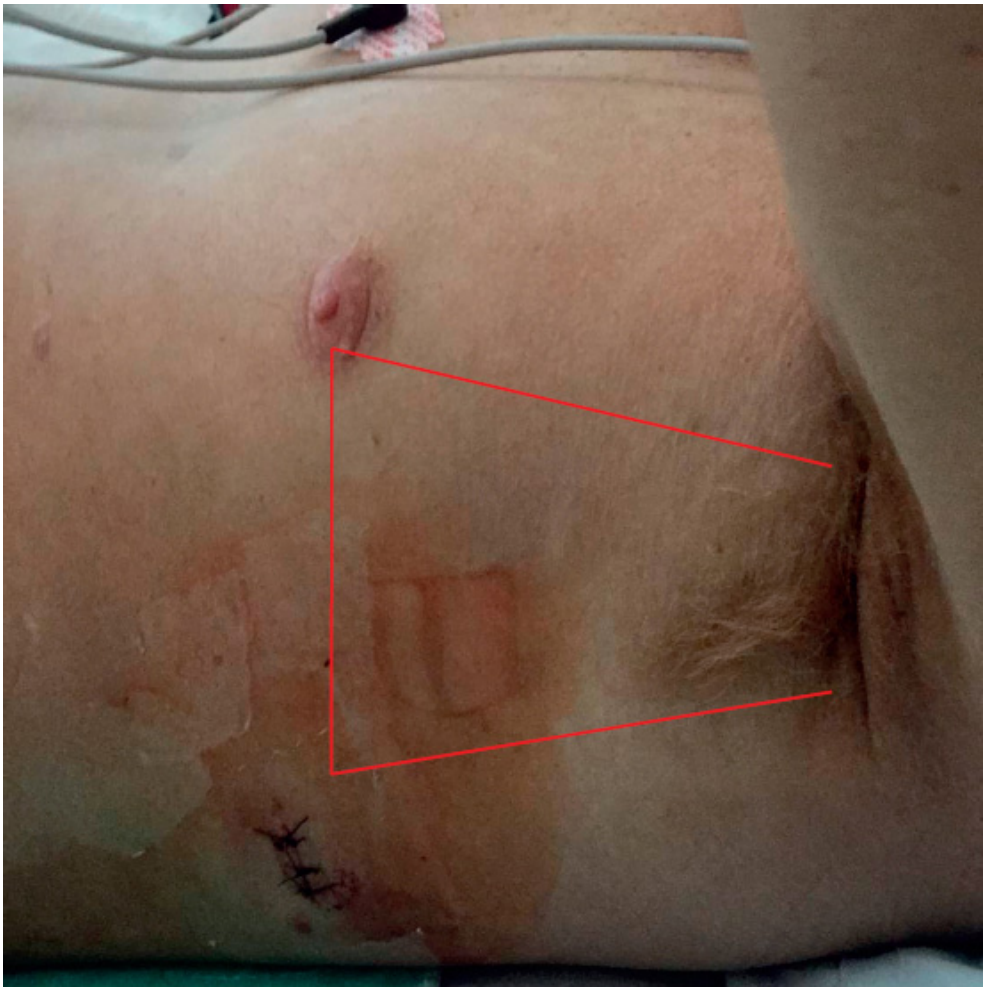


Figure 24.7 Zone of safety.

In the rare circumstance of an open pneumothorax where there is a loss of a portion of the chest wall, the normal negative pressure of the pleural space is lost. Due to the intrinsic nature of the lung parenchyma to collapse, there must be negative pressure in the pleural space to allow for lung expansion. The chest wall defect of an open pneumothorax is usually secondary to a high-velocity bullet or close range shotgun blast. As a temporary measure during transport or early resuscitation, a partially occluding dressing can be applied. This dressing is sealed in a way that allows air to escape from a corner of the dressing while preventing atmospheric air from entering the pleural space. Formal operative closure of the chest wall defect and placement of a chest tube is the definitive treatment. If the defect is large, a rotational flap may be necessary to close the defect or the chest wall may require reconstruction with mesh.

Pulmonary Contusion

The transmission of energy across the chest wall can result in pulmonary contusion from traumatic disruption of pulmonary capillaries and lymphatic vessels. Lung contusion is the extravasation of blood into the interstitial space of the lung parenchyma impairing gas exchange from alveoli to the pulmonary capillary bed. Bleeding may extend to the alveolar space as well in severe cases. One may observe a significant decrease in the PaO_2/FiO_2 ratio with severe pulmonary contusions. Patients with flail chest or multiple rib fractures are most likely to have concomitant contusion. Hypoxia in flail chest is most consistently a result of underlying lung contusion rather than a function of the disruption chest wall mechanics. Diagnosis of pulmonary contusion is typically made with CXR or CT scan. CT scan is more sensitive and specific than CXR with greater than 70% of contusions being seen on CT only.[25]

Treatment

The treatment for lung contusion is primarily supportive care to include minimizing intravenous crystalloid fluid administration, early mobilization, and aggressive pulmonary hygiene. For hypoxia due to contusion, treatment includes the application of positive end-expiratory pressure (PEEP) either

noninvasively (through face mask) or through an endotracheal tube. In a small study, it was found that 100% of patients who had five or more ribs fractures, two-thirds or more of lung affected by contusion, and a decrease in mental status (GCS ≤14) required intubation.[26] Intubations did not necessarily occur on the first day but often on the second day as the contusion "blooms" with surrounding interstitial edema. Therefore, it is important to identify patients at risk for respiratory failure and place them in a higher level of care.

Hemothorax

The causes of hemothorax are varied, the most common being hemorrhage from rib fractures, intercostal muscle bleeding, intercostal artery laceration, pulmonary parenchymal laceration, azygos vein or great vessel injury, or cardiac injury with communication to the pleural space through a pericardial defect.

Initial imaging to detect a hemothorax is the screening trauma bay CXR. This x-ray may make the diagnosis of a hemothorax challenging due to layering of blood posteriorly in a supine patient, thus the CXR may appear hazy when compared to the contralateral side rather than demonstration of a fluid level seen on an upright film. In the face of a large hemothorax, the CXR can appear as a whiteout of the affected hemithorax with or without mediastinal shift. The eFAST examination has a high sensitivity for detecting a hemothorax. Just as occult pneumothorax, small-volume occult hemothorax may only be demonstrated on CT imaging.

The urgency of the treatment of hemothorax is dictated by the physiologic state of the patient with rapid control of hemorrhage being the first priority. Hemothoraces associated with hemodynamic instability or those that drain >1,500 cc immediately or >200 cc/hr for >4 hours after placement of a chest tube should be taken directly to the operating room for exploratory thoracotomy. The recommended size of chest tubes has decreased over time and contemporary data suggest that there is no difference in the ability of the 28-Fr versus the 36-Fr chest tube to effectively drain a hemothorax. Some have advocated using a 14-Fr pigtail catheter for drainage of a hemothorax[27] though multicenter, prospective trials are ongoing. A recent investigation suggests that the position of the chest tube within the pleura does not make a difference in the ability of the tube to drain a hemothorax.[28] This is likely a

result of the pleura being a closed system and therefore, suction applied to one area will apply equal amounts of pressure to other areas of the pleural space. The fluid component of a hemothorax will be drained from any position, however, clotted blood will not 4 be effectively drained even with optimal tube position. The volume of hemothorax that requires drainage is somewhat controversial. In general, patients with a hemothorax greater than approximately 300 cc require drainage when estimated using the following volumetric formula on CT scan: Estimated volume (cc) = $d^2 \times l$, where d equals the greatest dimension in centimeters from the chest wall to the lung or mediastinum across the largest fluid pocket, and l is the craniocaudal height (number of axial slices on the CT scan × the thickness of those slices in centimeter).[29]

Retained Hemothorax

Retained hemothoraces may occur in 30% of the patients.[30] A retained hemothorax is defined as hemothorax that persists despite attempted drainage. Consequences of retained hemothorax include increased risk of empyema, entrapped lung parenchyma, and fibrothorax. Kugler and colleagues reported thoracic irrigation at the time of chest tube placed decreased the rate of retained hemothorax requiring secondary intervention.[31] For retained hemothoraces, there are two therapeutic options: (1) early video-assisted thoracostomy for evacuation or (2) tissue plasminogen activator (TPA) with or without DNase administered via chest tube. The key point is that early intervention allows the clot to be evacuated and prevent a fibrothorax from forming. A meta-analysis of 476 patients undergoing VATS for retained hemothorax demonstrated that earlier intervention (days 1 to 3) was superior.[32] There are no trials comparing VATS to TPA, however, it is the author's practice to utilize VATS for evacuation of retained hemothorax in all appropriate operative candidates, reserving TPA for poor operative candidates only.

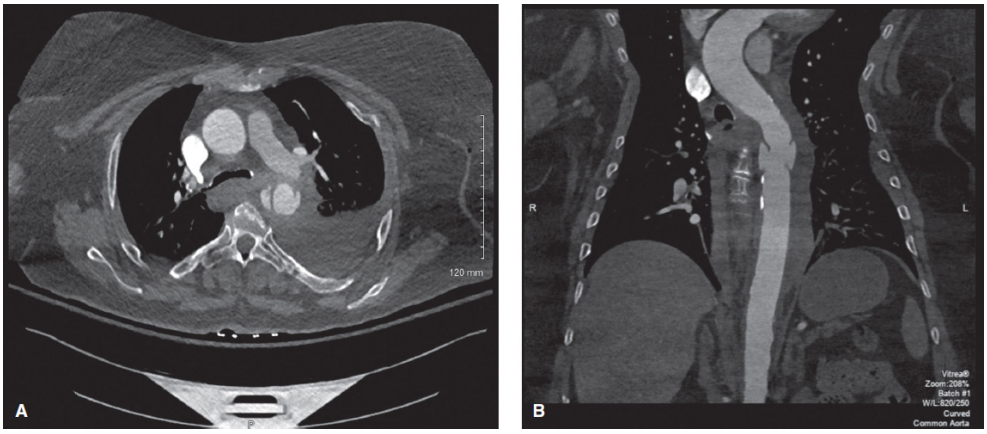


Figure 24.8 **A:** Axial view of type IV blunt aortic injury. **B:** Coronal view of type IV blunt aortic injury.

Aortic Injury

Penetrating injury to the aorta is typically fatal as most patients exsanguinate in the prehospital setting. Those bluntly injured patients with evidence of mediastinal hematoma on CXR (widened mediastinum >8 cm, loss of aortic knob, loss of aortopulmonary window, depression of left mainstem bronchus >110 degrees, deviation of nasogastric tube, apical cap, or tracheal deviation) or those with a high-risk mechanism (i.e., T-bone motor vehicle collision) should have a CT scan of the chest with intravenous contrast to evaluate for aortic injury. CT scan has become the standard of care for diagnosis and classification of aortic injuries. Blunt aortic injuries most commonly occur at points of aortic fixation. These locations in decreasing order of occurrence include: (1) ligamentum arteriosum (just distal to the left subclavian artery), (2) diaphragmatic hiatus, (3) root of the aorta, and (4) left mainstem bronchus. The current classification of aortic injuries divides the extent of injury into four grades: (I) intimal tear, (II) intramural hematoma, (III) pseudoaneurysm, and (IV) periaortic rupture (**Fig. 24.8A,B**).

Treatment

Treatment of blunt aortic injury is dictated by grade of injury. The Society for Vascular Surgery consensus guidelines for management of blunt aortic injury recommends medical management of grade I injuries.[33] Medical management consists of aggressive impulse control (heart rate and blood pressure

control). The recommended goal HR is <80 and goal systolic blood pressure is <100 to 120 mm Hg. This control is achieved with the administration of short-acting beta blocker (i.e., esmolol) with additional agents such as nicardipine or nitroprusside as needed. Beta blockers must precede nitroprusside because of the possible tachycardic side effects of nitroprusside. Antiplatelet therapy with aspirin is also utilized when possible given the patient's other injuries. Repeat CT angiogram to evaluate for progression of the injury is recommended, though the time interval to repeat imaging is variable.

The management of grade II aortic injuries is evolving. Traditionally, it was recommended that these injuries undergo repair either via thoracic endovascular aortic repair (TEVAR) or an open approach, however, there is a trend toward treating these lesions with medical management alone.[34] Fortuna and colleagues reported no aortic-related mortality of grade II injuries treated with medical management alone, however, there may be a selection bias given that some of the grade II injuries in the study population underwent TEVAR.[35]

The EAST and SVS practice management guideline for blunt aortic injuries agree that Grade III and IV injuries should undergo endovascular repair.[33,36] When compared to open clamp and sew repairs, incidence of paraplegia is lower in the endovascular treatment group,[37] which has resulted in its adoption as the contemporary standard of care (**Fig. 24.9**). Timing of repair is dictated by both grade of injury and the presence of other life-threatening injuries. Grade IV injuries are repaired emergently in most situations. For traumatic aortic pseudoaneurysms (grade III injuries), these do not need to be repaired immediately as long as impulse control can be achieved. This allows time for resuscitation and treatment of other traumatic injuries such as intracranial hemorrhage, intra-abdominal 5 bleeding, or severe pelvic fracture. Delayed repair has been shown to be safe and actually has a lower overall mortality rate.[38]

Figure 24.9 Aortic stent graft for blunt rupture.

Diaphragmatic Injuries

Injuries may be the result of either penetrating or blunt trauma. In a 2015 review, there were 3,873 diaphragmatic injuries among the sample size of 833,309 trauma patients giving an incidence of 0.46%.[39] The average size of a diaphragmatic injury for penetrating trauma is approximately 2 cm and the average size of the injury for blunt trauma is 8 cm. Small injuries are unlikely to be detected on initial CXR imaging; however, large injures that allow herniation of stomach, colon, or liver into the chest cavity may be demonstrated on CXR. Even with current 256-slice CT scanners, the sensitivity for diaphragmatic injuries on CT scan is approximately 60%.[40] For the small injuries seen in penetrating trauma, one must maintain a high index of suspicion for diaphragmatic injury based upon the trajectory of the

knife or bullet. Diagnostic laparoscopy or thoracoscopy can effectively rule out a diaphragm injury and can be undertaken in a semielective fashion, unless there is a large injury resulting in respiratory compromise necessitating emergent repair.

Treatment

Once the diagnosis is made (either pre- or intraoperatively), repair of the diaphragm should occur. In the case of the penetrating trauma patient who is undergoing a diagnostic laparoscopy, the repair can proceed laparoscopically. For those with an acute rupture following blunt trauma, the repair is usually undertaken via laparotomy to also evaluate the abdominal organs for injury. For chronic hernia defects, strong consideration is made for repairing from the chest via a thoracotomy or via video-assisted thoracoscopy.

The repair is with a nonabsorbable suture in either an interrupted or running fashion. The classic repair is with an interrupted horizontal mattress suture. The repair must be air tight and a chest tube is usually placed at the time of the repair. It is important to lavage the pleural space and ensure complete evacuation of any hemothorax. When primary suture repair is not possible due to tissue loss, a mesh (synthetic or biologic) may be used or the diaphragm can be sewn to a lower rib, in essence transposing it to a slightly lower position to achieve closure of the hemithorax.

Cardiac

Cardiac injury can occur with either penetrating or blunt mechanisms. The most common chamber affected with penetrating injury is the right ventricle since it has the largest anterior surface area. The right atrium is the most common chamber that ruptures from blunt mechanisms because of its thin wall. Laceration or chamber rupture leads to hemopericardium. The diagnosis of hemopericardium is usually made via the FAST examination which is 95% sensitive and specific for pericardial fluid.[5] The presence of hypotension and hemopericardium defines cardiac tamponade and should be treated emergently.

Treatment

For an awake trauma patient with pericardial fluid, emergent transport to the operating room for median sternotomy is preferred. There is very limited role for pericardiocentesis in the acute trauma scenario, given the difficulties in evacuating clot from the pericardium, though this may be employed by nonsurgeons to temporize a patient for transport to a trauma center. A pericardial window is typically a diagnostic test restricted to those patients who have confounding medical issues, that is HIV-positive with chronic pericardial effusions, or to rule out cardiac injury in patients with a concerning trajectory with an equivocal pericardial windows on FAST exam. However, there are reports of therapeutic pericardial window with drain placement for hemopericardium.[41] Typically, a positive pericardial FAST mandates surgical exploration via a sternotomy or thoracotomy. If the patient has lost vital signs in the trauma bay or is rapidly deteriorating with loss of consciousness, then a resuscitative thoracotomy is indicated.[42,43] This allows rapid opening of the pericardium to relieve tamponade and temporize underlying cardiac injuries.

With impending cardiac tamponade due to hemopericardium, it is important to note that the decrease in preload with induction of anesthesia and positive pressure ventilation may cause the patient to lose vital signs. Therefore, coordination between the anesthesiologist and the surgeon is paramount to quickly perform median sternotomy if needed. The patient should be prepped and draped from the chin to the thighs prior to the induction of anesthesia and should be volume loaded to counteract peri-induction drop in cardiac preload.

Once in the chest preferably via median sternotomy, the pericardium is opened and the cardiac injury identified. The injury can usually be controlled with digital pressure or other adjuncts such as skin stapler, Foley catheter (careful not to rip the thin right ventricle with the balloon), or two stay sutures on either side of the injury that are crossed to close the wound. Formal repair with 3-0 Prolene is then performed with or without pledgets in an interrupted fashion. It is helpful to ask for a suture with a larger needle (i.e., MH). It is important to note the relationship of the injury to the coronary vessels. If the injury is juxtaposed to a coronary vessel, one should perform a horizontal mattress and pass the needle deep to the coronary artery. If the

proximal two-thirds of a coronary vessel are injured, it must be bypassed or repaired. Injuries to the distal third of a coronary vessel can be ligated. Intra- or postoperative echocardiography should be performed to evaluate for valve or septal injury, both of which are indications for cardiopulmonary bypass and expert consultation with a cardiac surgeon.

Blunt Cardiac Injury

There is a spectrum of blunt cardiac injuries. Injuries may cause mild dysrhythmias or lead to wall rupture (**Fig. 24.10**) and death. Any patient who undergoes a rapid deceleration mechanism is at risk for blunt cardiac injury. These patients are screened with a 12-lead ECG and troponin I; if both are normal then blunt cardiac injury is ruled out and the patient does not require observation.[44] If EKG changes (new arrhythmia or conduction abnormality) or troponin elevation is present, then the patient requires cardiac monitoring. If ST segment changes occur, a cardiac catheterization is necessary to rule out coronary dissection. Hemodynamic instability due to blunt cardiac injury may require ICU admission for inotropic support and such patients also need echocardiography to evaluate for valvular insufficiency or other structural issues.

Tracheobronchial Injury

Tracheobronchial tree injury can occur from either blunt or penetrating mechanisms and usually presents with a pneumothorax, subcutaneous emphysema, pneumomediastinum, and air leak after chest tube placement. The patient may be difficult to ventilate due to large air leaks. In rare cases, there may be the need for selective lung ventilation with a bronchoscopically placed bronchial blocker or may even require extracorporeal membrane oxygenation (ECMO) to temporize and allow for surgical repair. The majority of penetrating injuries to the tracheobronchial tree occur in the cervical trachea, while blunt injuries are typically in proximity to the carina. Intrathoracic injuries can be easily visualized via bronchoscopy, however, distal injuries with associated pneumatocele formation can be seen on CT scan.

Treatment

Bronchoscopy provides direction for surgical exposure if the injury is visualized. The majority of intrathoracic injuries are to the right mainstem bronchus and therefore a right posterolateral thoracotomy is the best surgical approach as this also grants access to the carina. Left thoracotomy is reserved for injuries to the left bronchus. Median sternotomy is not the preferred approach to tracheobronchial tree injuries due to limited visualization posterior to the heart. Once surgically exposed, the bronchus or trachea can usually be primarily repaired using a 3-0 absorbable suture. The repair can be buttressed with intercostal muscle or pleural flaps. Care should be taken not to devascularize the tracheal repair with excessive circumferential dissection. Chest tubes are placed and extubation is guided by the underlying lung contusion and hypoxia. Ideally, these patients should be taken off positive pressure ventilation as soon as possible, even immediately postoperatively.

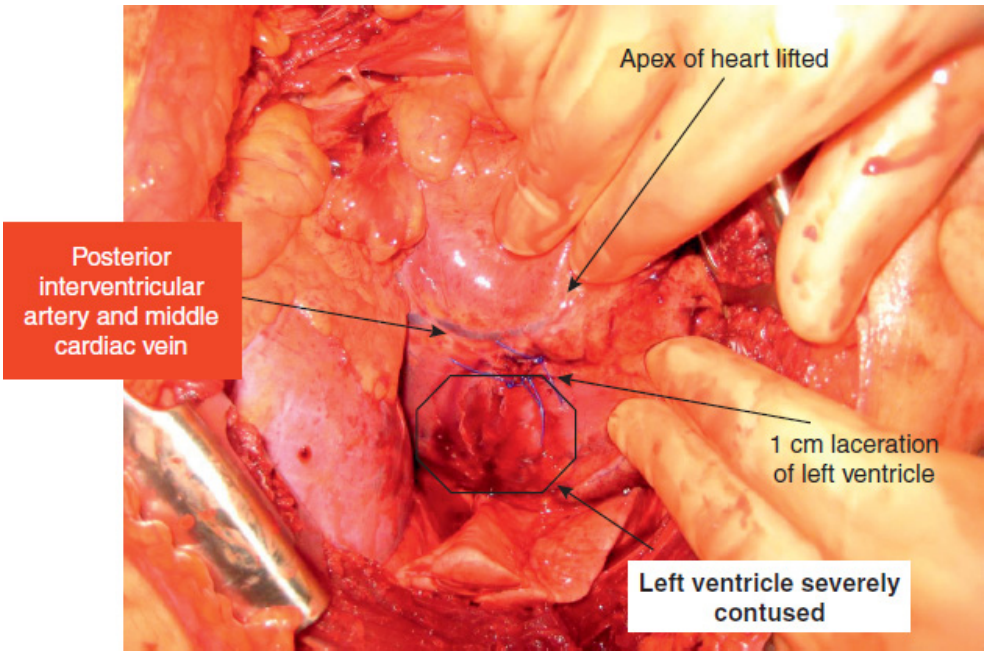


Figure 24.10 Blunt cardiac rupture/contusion.

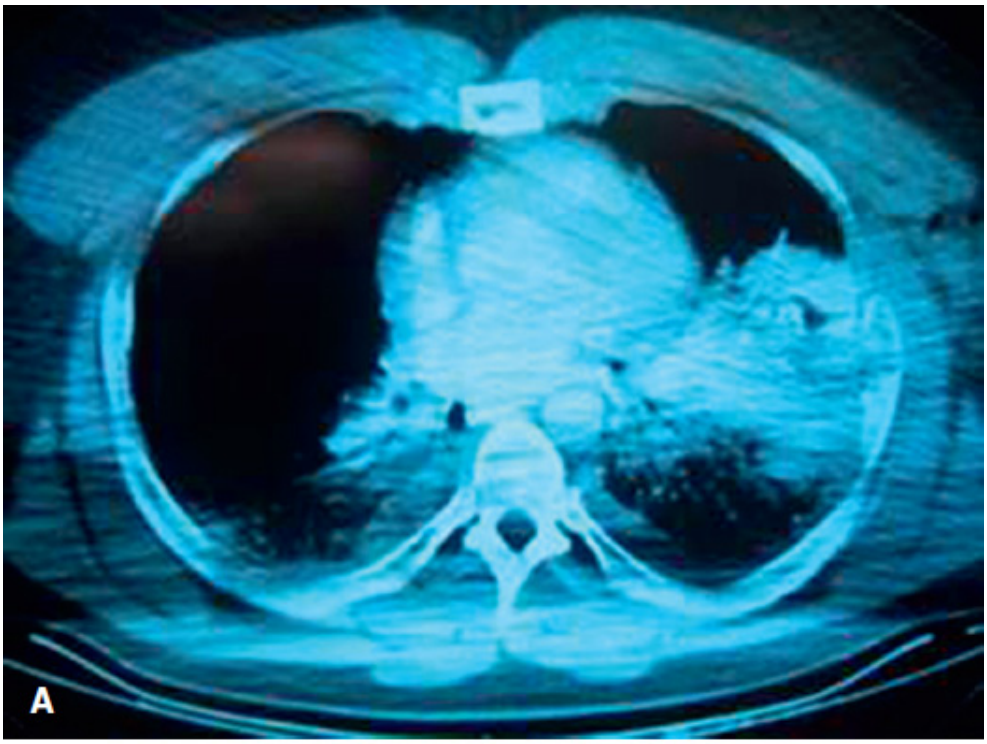
Thoracic Esophageal Injury

Esophageal injuries are almost exclusively secondary to penetrating trauma as blunt rupture of the esophagus is exceedingly rare.[45] If the trajectory of the

penetrating injury crosses the midline, the mediastinal structures must be evaluated. Hemodynamically unstable patients with penetrating torso trauma should be promptly explored in the operating theatre for hemorrhage control and evaluation of injury. If the patient is stable, one may perform diagnostic studies to evaluate the esophagus.

The initial imaging study is a CT scan of the chest with IV contrast to better delineate the track of the missile (**Fig. 24.11A**). Secondary signs of esophageal injury may be present including pneumomediastinum, pleural effusion, or mediastinal hematoma. If the missile track is in close proximity to the esophagus (<2 cm) then additional diagnostic investigations are necessary given the high mortality of esophageal injuries. An AAST multicenter retrospective review reported a 19% overall mortality rate for patients with esophageal injury with increasing mortality directly related to AAST grade of injury.[46] There is also a direct correlation between time to repair and morbidity/mortality, therefore any delay must be minimized. The most commonly utilized diagnostic modality is flexible endoscopy, which has been shown to have high sensitivity and specificity.[47] Otherwise, diagnostic imaging with a water-soluble followed by a barium-contrast study is warranted. The water-soluble contrast is used first in case there is a large leak (**Fig. 24.11B**). If no obvious leak is identified then the water-soluble contrast should be followed up with a barium study to increase the sensitivity for a small leak. If the barium esophageal imaging is negative, one can be assured there is no full-thickness injury to the esophagus.[48]

Distal thoracic esophageal injuries are repaired via a left thoracotomy and the proximal two-thirds are repaired via a right thoracotomy, which allows one to dissect the esophagus up to the thoracic outlet since the aortic arch is not obscuring the view. Once the esophageal injury is identified, it should be debrided and repaired in a full-thickness single layer. The repair should be buttressed with either a pedicled intercostal muscle flap or a pleural patch. Some have used a tongue of omentum for distal esophageal repairs. Of note, single lung ventilation is necessary to adequately visualize the injury and ensure a safe repair.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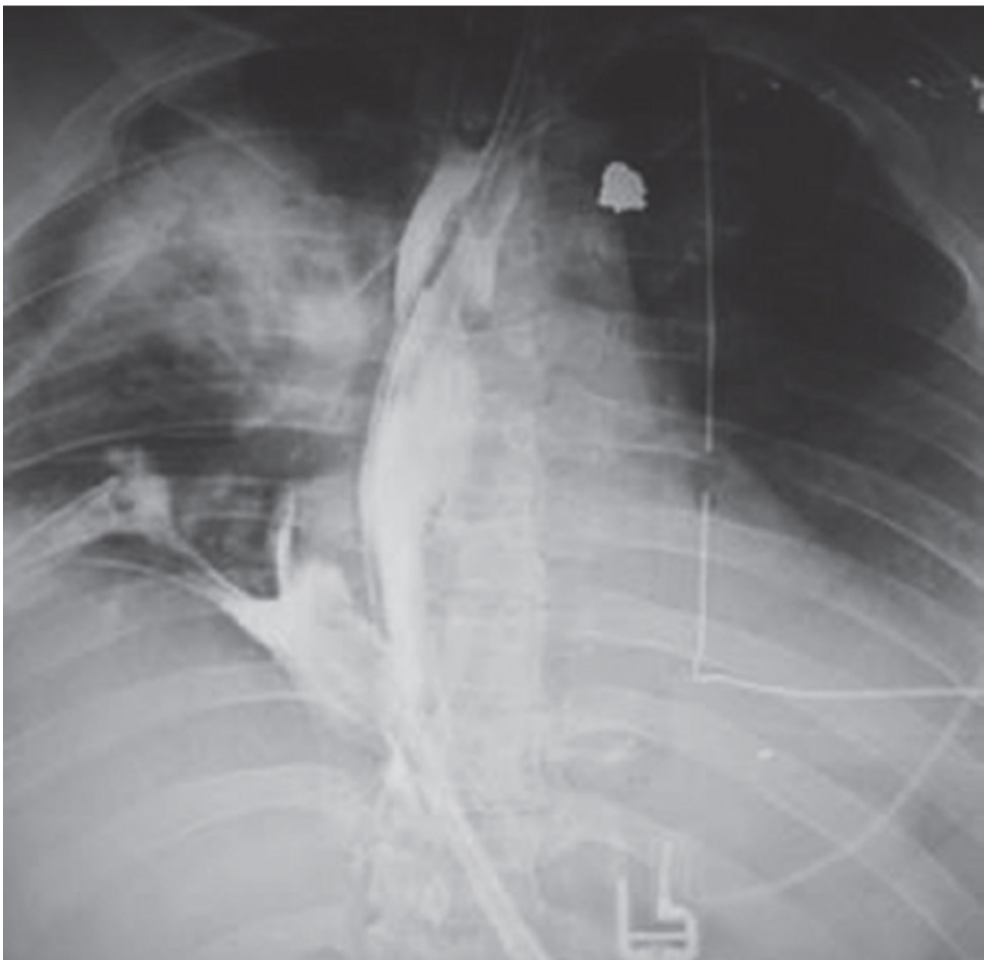

Figure 24.11 **A:** Tract of bullet coursing to posterior mediastinum. **B:** Contrast leaking from an injury to the esophagus.

RESUSCITATIVE THORACOTOMY

Resuscitative thoracotomy is an emergent procedure done to gain primary vascular control of an injured thoracic vessel, open the pericardium to relieve cardiac tamponade, repair cardiac injury, perform internal cardiac massage, gain control of the pulmonary hilum, and cross-clamp the aorta to gain proximal control of intra-abdominal hemorrhage. The resuscitative thoracotomy is a left anterolateral or clamshell thoracotomy (**Fig. 24.12**). The survival from resuscitative thoracotomy is as high as 24% for victims of penetrating thoracic trauma, however, survival decreases to about 4% if the patient arrives without a pulse, assuming a less than 15-minute cardiac arrest time.[49] In blunt trauma, survival after a resuscitative thoracotomy is 1.4% overall.[50] The odds of regaining a blood pressure in bluntly injured patients who lose vital signs in the trauma bay is about 4% but drops to 0.2% if vital signs were lost prior to arrival. For these reasons, the generally accepted indications for an ED thoracotomy in penetrating trauma are if the patient loses vital signs in the trauma bay or within 15 minutes of arrival. For blunt trauma, it is strongly recommended to limit the procedure to the patients who lose vital signs in the trauma bay.

Control of an intercostal artery can be difficult particularly if caudal and posterior. At times, it may be necessary to encircle the rib proximal and distal to the bleeding vessel to compress the vessel indirectly. This suture can be absorbable or even brought out through the full thickness of the chest wall and cut in 48 hours. At times, one may be dealing with a deep hole from a gunshot wound into the musculature of the posterior chest wall. Under these circumstances, aggressive and tight packing may suffice or a Foley catheter may be placed in the tract and inflated to tamponade the bleeding. The Foley may even exit the chest wall via a separate stab incision and be deflated 24

to 48 hours later and removed while the patient is observed for recurrent bleeding.

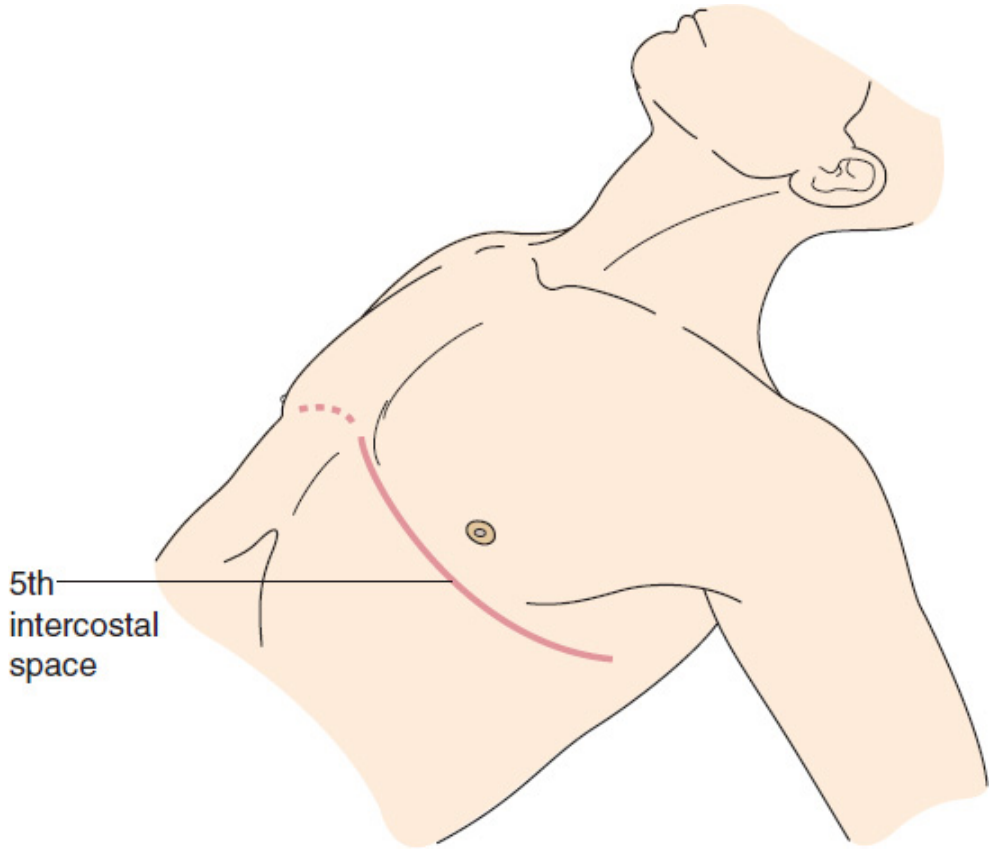

Figure 24.12 Left anterolateral thoracotomy incision.

The other common injury that may be found on exploration is laceration of the lung. It is important to understand that bleeding from the track of a penetrating trauma must not be closed superficially. Closing the entrance or exit holes may simply cause more bleeding into the bronchi or allow air to embolize from the bronchi to the pulmonary venous system. Patients will die from cardiac arrest from air emboli that enter the coronary vessels. Instead the pulmonary tract should be opened (tractotomy) with either clamps or GIA stapling devices. This opens the tract where the raw surface area can be oversewn or stapled while saving lung tissue. Peripheral lesions can simply have wedge resections performed.

CONCLUSION

Thoracic injuries are a common entity with rib fractures being the most common injury. A careful and systematic approach to the trauma patient is key to uncovering significant thoracic injuries. Life-threatening injuries, that is, massive truncal hemorrhage, tension pneumothorax, or cardiac tamponade must be identified quickly within the trauma bay and treated without delay.

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25

Abdominal Trauma

Kenji Inaba, Elizabeth R. Benjamin, and Demetrios Demetriades

Key Points

1. Clinical examination is the cornerstone of the diagnostic workup after blunt abdominal trauma and any patient with peritonitis or instability with a positive FAST requires immediate laparotomy. CT is a high-yield diagnostic modality for the intra-abdominal contents with high degree of sensitivity and specificity for clinically significant injuries.
2. For stable, evaluable patients without peritonitis or evisceration after penetrating abdominal trauma, selective nonoperative management is an acceptable treatment option. For those undergoing nonoperative management, close clinical observation and CT scan are utilized to detect those patients with an occult injury that will ultimately require laparotomy and repair.
3. Rapid access to an operating room with immediate access to the instrumentation, consumables and support services such as the blood bank and radiology are required for the successful treatment of patients with abdominal trauma.
4. Standard positioning is supine, however, for injuries in stable patients where the rectum or perineum is at risk, lithotomy may be utilized. The initial incision is usually a midline laparotomy. Extension into the subcostal regions and across the inguinal ligament or into the thoracic cavity may be required to facilitate exposure.
5. Damage control laparotomy, which consists of rapid bleeding and contamination control, followed by temporary closure and resuscitation with delayed definitive repair of injuries should be considered for any patient who is physiologically depleted, has a burden of injury which will result in compromise if definitive repair is attempted, or has an injury profile beyond the scope of the surgeon skillset or facility resources.
6. Abdominal compartment syndrome can occur after trauma laparotomy and all patients should be monitored closely with bladder pressures in the recovery area. Any elevation in the intra-abdominal pressures warrants consideration of decompressive laparotomy.

7 Angioembolization is an important adjunct for patients who are undergoing damage control surgery and may be of particular benefit for patients with ongoing bleeding from complex solid organ or pelvic trauma.

INTRODUCTION

For patients who have sustained a stab wound (SW), gunshot wound (GSW), or blunt multisystem injury, the abdomen remains a high-risk cavity with the potential to hide occult but life-threatening injuries. Unlike the extremity or neck for example, where bleeding occurs externally, for the abdomen, significant bleeding and enteric spillage can occur with minimal symptoms until late. In patients presenting after both blunt and penetrating traumas, injury to the abdominal contents is common. In the National Trauma Data Bank, the largest repository of trauma registry data that exists in the United States, from 2007 to 2016, of the approximately 7,743,420 patients entered, 12.0% had an abdominal injury, with 75.8% due to a blunt mechanism. Broken down by regional abbreviated injury scale (AIS), 36.4% of these had an AIS 1, 31.2% an AIS 2, 19.0% an AIS 3, 9.4% an AIS 4, and 2.9% an AIS 5 injury.

Abdominal injuries are therefore common and a systematic approach to the rapid diagnosis and treatment of these injuries is essential. This chapter will provide a pragmatic approach to the patient with abdominal trauma, focusing on the acute resuscitation, diagnosis, and treatment of clinically relevant injuries to the abdominal structures.

BLUNT INITIAL EVALUATION AND DIAGNOSTICS

Resuscitation

For the patient that sustains abdominal trauma, unlike the extremity, where a tourniquet can be placed, there are currently no validated prehospital

methods for direct or indirect hemorrhage control. Rapid transport to definitive care therefore remains the primary goal. With the increasing interest in resuscitative endovascular balloon occlusion of the aorta,[1] in the appropriate clinical setting with trained personnel, this procedure could theoretically be performed in the prehospital setting. The general principles of resuscitation that apply to all trauma patients as outlined elsewhere in this textbook should be followed. Specific to patients with abdominal trauma, whenever possible, venous access should be gained in the upper limbs or torso. Resuscitation through a femoral central venous catheter is suboptimal as the return of blood products into the systemic circulation is compromised if the patient has an injury to the iliac system or vena cava. In the resuscitation area, once the diagnosis of an intra-abdominal injury requiring operative repair has been made, travel to the OR should take precedence over continued resuscitative efforts which can be continued concurrent to definitive hemorrhage control.

Diagnostics

The diagnostic workup of a blunt multisystem injury patient is often more difficult than for a penetrating injury patient. In general, the most practical approach to the patient in the resuscitation area depends on hemodynamic status. Patients can be categorized into those that are arresting, unstable, or stable.

For any arresting patient, if the decision to intervene is made, airway control, venous access with blood product infusion, and resuscitative thoracotomy with evaluation for concurrent right chest tube insertion are the immediate priorities. The outcomes for resuscitative thoracotomy performed for traumatic arrest due to blunt trauma are poor,[2] especially if the source of hemorrhage is in the abdomen, however survival to discharge and organ donation are possible in rare cases. If a resuscitative thoracotomy is performed, and the primary source of hemorrhage is in the abdomen, an aortic cross-clamp is placed. If the procedure is successful and a perfusing rhythm is regained, the patient should be taken immediately to the OR for laparotomy and definitive injury management. A Western Trauma Association Algorithm outlining the management of this injury is available at: https://www.westerntrauma.org/wp-

content/uploads/2020/07/WTACriticalDecisionsResuscitativeThoracotomy.pdf

For the unstable patient, aggressive resuscitation with blood products should be initiated immediately, and the patient will either stabilize, in which case a complete workup can be performed as described below, or they will remain unstable. If they remain unstable despite resuscitative efforts, rapid hemorrhagic source identification to determine potential operative intervention is the priority. Bilateral diagnostic chest tubes should be considered if chest x-ray (CXR) or ultrasound are not immediately available. Concurrent with the ongoing resuscitation, a focused assessment with sonography in trauma (FAST) should be performed. If free abdominal fluid is visualized, the patient should immediately be taken to the OR and a laparotomy should be performed. If the FAST is negative, a confirmatory diagnostic peritoneal aspirate (DPA) looking for gross blood may be performed. If this is positive, the patient undergoes laparotomy. In the setting of ongoing hypotension and a negative FAST, a pelvic x-ray may be performed to identify retroperitoneal source. If the above studies are negative, alternative sources for the hemorrhage are sought.

In the stable patient, a complete diagnostic workup can be completed. This begins with an external examination for any soft tissue evidence of injury. A seatbelt sign for example has been associated with an eightfold increase in the incidence of intra-abdominal injuries, impacting both the solid organs and hollow viscus.[3,4] While not sufficient to warrant mandatory laparotomy, a very low threshold for imaging with CT should be maintained and the patient should undergo a mandatory period of observation. With this mechanism, the seatbelt can cause a "bucket-handle" type injury (**Fig. 25.1**) where the mesentery is sheared away from the more elastic bowel wall causing ischemia. Clinical evidence of the ischemic GI tract injury can take hours to manifest and close observation is warranted.

1 If on initial examination, the patient already has peritonitis, in the setting of trauma, immediate laparotomy should be performed. This is a high-yield indication for operation. Although data were accrued in penetrating trauma, the urgency of peritonitis was made clear in a study examining 139 patients who were hemodynamically stable with peritonitis as the sole indication for operation. Of these, 97% had an intra-abdominal injury, with 11% having between 750 and 1,500 mL and 7% having >1,500 mL of blood

on opening with 25% sustaining intraoperative hypotension and 39% requiring blood transfusions despite being hemodynamically normal at presentation.[5]

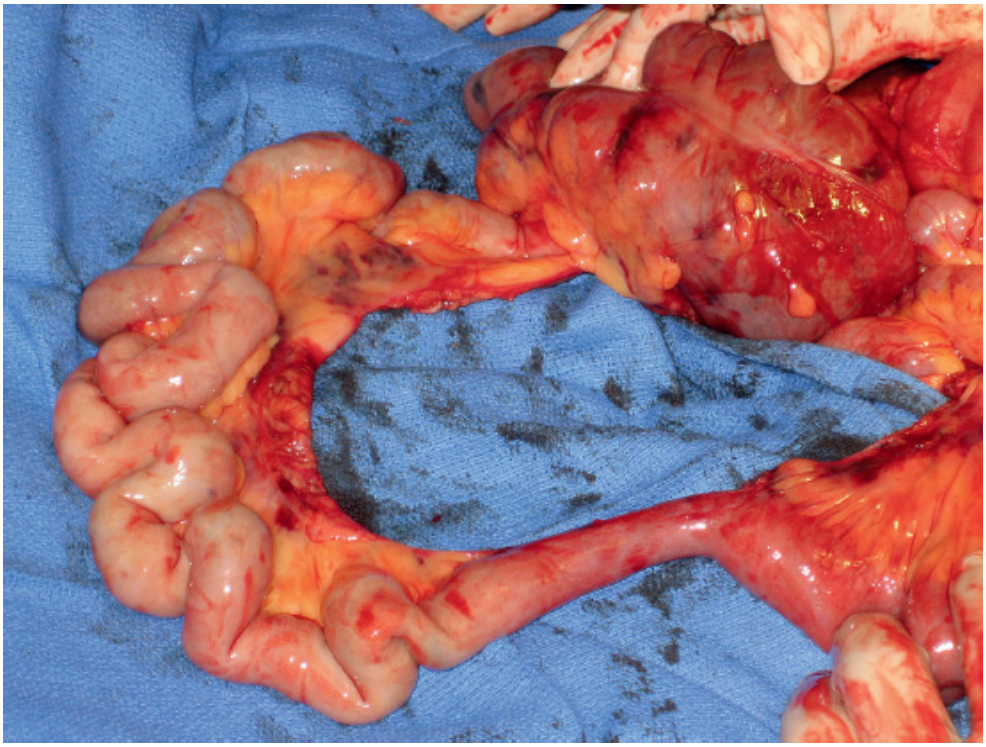

Figure 25.1 Bucket handle–type injury of small bowel.

For patients without peritonitis, the initial imaging modality is FAST. Because cardiac rupture is so rare in blunt trauma patients presenting alive,[6] the abdominal windows are of primary importance. The presence of free fluid is assumed to be blood. The presence of free fluid should trigger additional imaging with CT. For blunt trauma, there is no role for plain radiographs of the abdomen. For the stable patient, a pelvic x-ray is unnecessary especially if the patient is to undergo CT. CT scans should be performed with IV contrast. PO contrast is not required for the initial CT. A baseline creatinine level for all patients and a pregnancy test in females of child-bearing age should be obtained. In general, a CT should be considered in the stable patient when there is external evidence of significant force transfer to the abdomen such as a seatbelt sign, or with free fluid on FAST or when there is significant abdominal tenderness on examination. Mechanism as a sole criterion for deciding which patients require CT scan is unreliable,

but a high-energy mechanism is often considered when making this decision. Based on the CT results, patients can be categorized into three groups, those with no injury, those with an injury, and those with an equivocal finding. If the CT demonstrates no abnormalities, the likelihood of a clinically significant injury is extremely low.[7] For patients with a CT that demonstrates injury, the nature of the injury will determine management. Any hollow viscus injury including the GI tract or bladder, will require operative repair. For solid organ injuries, the indications for operative management will depend on the extent of injury, the physiologic status of the patient including comorbidities, and their tolerance for blood loss and associated injuries. In general, the majority of solid organ injuries can be successfully managed nonoperatively.[8] In centers where there is access to interventional radiology, endovascular solutions, such as stenting or embolization and percutaneous management of complications such as a biloma can also be used as an adjunct to nonoperative management. This will be further elucidated in the following organ-specific sections. This then leaves the patient with equivocal findings of a hollow viscus injury on CT. Equivocal findings would include subtle findings such as mesenteric fat stranding, free fluid without solid organ injury, and bowel wall thickening. These patients should be observed clinically, ideally by a single provider and collateral evidence of injury such as the WBC count, heart rate, temperature, and abdominal examination are used to detect worsening, indicative of a hollow viscus injury requiring operative intervention. The exact period of time required for observation is unknown, however, it is expected that a patient who is improving at 24 hours has a low likelihood of a clinically significant missed injury.

PENETRATING INJURY—INITIAL EVALUATION AND DIAGNOSTICS

General Approach to Penetrating Abdominal Injury

Following the experience of World Wars I and II, with the high rates of destructive injuries, penetrating abdominal trauma was historically treated with universal surgical exploration. Starting in the 1960s with SWs, followed by GSWs, this paradigm began to shift.[9–11] Patient selection for operative versus nonoperative management based on the clinical picture and radiologic evidence began to evolve. With improved access, and the growing body of evidence regarding the potential morbidity of nontherapeutic operations, contemporary evidence now supports a nonoperative approach to the management of penetrating abdominal trauma in select circumstances.[12]

The balance between prompt surgical management of traumatic injury and avoiding unnecessary operation remains a central diagnostic and management challenge in penetrating 2 abdominal injury. Patients who present *in extremis,* with hemodynamic instability, peritonitis, or are unevaluable mandate immediate operation. For the remaining patients, the practice of universal exploration would result in a high rate of nontherapeutic laparotomy which is associated with a morbidity of at least 20%.[13,14] This not only impacts patient-centered outcomes, but also trauma resource utilization as nontherapeutic laparotomy is associated with increased hospital length of stay and healthcare cost.[13,15–18]

Although a subset of patients with penetrating abdominal trauma will ultimately require exploration, a significant number can be managed nonoperatively. In a retrospective analysis of abdominal SWs, mandatory exploration was associated with a negative laparotomy rate of 37%.[13] A Western Trauma Association Multicenter Study including 359 patients with anterior abdominal SWs found that 64% of patients did not require laparotomy.[19] The need for laparotomy is even lower after SWs to the back with only 15% of patients noted to have clinically significant injury.[20] GSWs to the abdomen are more likely to require operative exploration, but the presence of gunshot injury alone does not necessitate mandatory laparotomy. In an analysis of 1,856 patients with abdominal GSWs, had a policy of mandatory laparotomy been employed, 47% of patients would have undergone an unnecessary laparotomy.[18] Similar to SWs, posterior and transpelvic injuries are less likely than anterior injuries to require exploration.[18,21,22]

Indications and Contraindications to Selective Nonoperative Management

Peritonitis and hemodynamic instability in the setting of penetrating abdominal trauma remain absolute indications for laparotomy. Although soft tissue injury can cause local tenderness, diffuse peritonitis after penetrating abdominal trauma is associated with a 97% chance of intra-abdominal injury at laparotomy.[5] Given the central role of physical examination in patient triage, unevaluable patients including those with concomitant head or spinal cord injury or those undergoing urgent nonabdominal operations are not candidates for selective nonoperative management. Although not an absolute contraindication to selective nonoperative management, patients with omental or visceral evisceration after penetrating abdominal trauma should be strongly considered for operative intervention. Significant intra-abdominal injury is present in 46% to 85% of patients with omental evisceration, and even higher rates with visceral evisceration.[17,19,23,24] A Western Trauma Association Algorithm outlining the management of this injury is available at: https://www.westerntrauma.org/wp-content/uploads/2020/07/WTACriticalDecisionsAbdominalGunshotWounds.pdf https://www.westerntrauma.org/wp-content/uploads/2020/07/WTACriticalDecisionsAbdominalStabWounds.pdf

Peritoneal penetration alone after penetrating trauma is not an absolute indication for operative exploration. For this reason, invasive evaluation including diagnostic laparoscopy for the sole purpose of determining peritoneal violation is not indicated.

Diagnostics

Radiologic imaging is a key component of the diagnostic workup of patients who have sustained penetrating abdominal trauma, especially those undergoing a trial of nonoperative management. In hemodynamically stable evaluable patients without peritonitis, a detailed evaluation of the external wounds and retained fragments using plain radiographs is imperative to plot missile trajectories. External wounds do not always correspond to internal injury and, especially in the setting of multiple missiles, trajectory may be

misleading from external wounds alone. For example, paired lateral abdominal wall bullet wounds may represent a superficial tangential trajectory or two separate transabdominal injuries with retained missiles. Management will change significantly based on the internal trajectory.

FAST examination is a central component of the early assessment after blunt trauma. The utility of this imaging modality in penetrating trauma, however, is less uniformly accepted. The primary use of the FAST examination in penetrating abdominal trauma is to evaluate for pericardial fluid. A positive cardiac FAST after penetrating trauma mandates immediate median sternotomy. For the intra-abdominal fluid windows, while the FAST examination is highly specific for fluid, the sensitivity is poor ranging from 46% to 67%.[25–27] In the hemodynamically *unstable* patient with multiple cavitary sources of hypotension, a positive FAST can still be helpful as a rapid tool for operative incision planning. For *stable* patients however, it rarely impacts clinical decision-making as the patient either meets criteria for selective nonoperative management and will be undergoing CT, or will be going to the OR, irrespective of the FAST findings.

CT has become universally accepted as an integral component in the evaluation of the penetrating trauma patient undergoing selective non-operative management. For patients undergoing exploration, CT is unnecessary and should not be routinely obtained. For patients with a GSW who are stable, evaluable, and without peritonitis and are undergoing a trial of nonoperative management however, CT is a requisite next step.

GSWs follow a linear path and have an associated air bubble tract that allows for trajectory identification on CT scan. Understanding the missile trajectory provides critical information regarding potentially injured structures and those to which injury is unlikely. CT scan imaging after abdominal GSWs has been shown to be highly reliable for injury identification, with a sensitivity and specificity of 90.5% to 96% and 95% to 96%, respectively.[28,29] The injury tract on CT scan is often more subtle after SWs due to the lower velocity and smaller volume of air bubbles along the tract, and as a result, CT scan has been shown to be a less useful adjunct in patient triage.[30,31]

Based on the CT scan findings, patients may be divided into four groups. (1) Patients with no peritoneal violation on CT scan. In this population, it is exceedingly rare that operative intervention will be required. (2) Patients

with peritoneal violation but no obvious intra-abdominal injury on CT scan. This is the ideal patient population for selective nonoperative management with serial abdominal examinations and observation. (3) Patients with peritoneal violation and evidence of vascular or hollow viscus injury on CT scan. Although there are no strict criteria for diagnosing hollow viscus injury on CT scan, findings concerning for injury include bowel wall edema, missile trajectory traversing bowel, extraluminal fluid, air, or contrast. In this group, laparotomy is mandatory. (4) Patients with peritoneal violation and solid organ injury. In the absence of hollow viscus injury, solid organ injury alone does not mandate laparotomy.[32,33] For patients meeting all other criteria for nonoperative management, this remains a treatment option with a high rate of success.

In patients selected for nonoperative management, clinical observation becomes the next important step. This is the most time-consuming aspect of nonoperative management and one of the primary reasons it is not feasible in all practice settings. This observation should be performed by a consistent team, ideally by the same provider, who can carefully examine for changes in abdominal pain, collateral markers of occult injury such as tachycardia or fever, and laboratory abnormalities such as an increasing white blood cell count. During this observation period, it is expected that a certain percentage of patients initially selected for nonoperative management will progress to operative intervention based on imaging or changes in clinical examination. Selective nonoperative management hinges on the ability to perform frequent, consistent physical examinations. Patients should receive no narcotics, or antibiotics and undergo serial hemodynamic and laboratory testing including white blood cell count, lactate, and hemoglobin levels. Strict adherence to a protocol is necessary to ensure early identification of patients who fail nonoperative management and require operative intervention.

In patients selected for nonoperative management after penetrating abdominal wounds, the duration of observation should meet a minimum standard. After abdominal GSWs, a review of 270 patients found that all injuries requiring laparotomy were apparent within 24 hours of observation.[34,35] Similar results have been described for abdominal SWs with injuries requiring laparotomy detected within 12 hours of observation.[36]

Penetrating left thoracoabdominal injuries, bounded by the nipple, scapular tip, and costal margin, present a unique challenge due to the risk of

occult diaphragmatic injury. Diaphragmatic injuries are notoriously difficult to diagnose on CT scan and are often asymptomatic in the early, postinjury setting. Over time, as the injury expands, the patient will be at risk for visceral herniation and strangulation. This complication is less likely after right-sided injuries due to buttressing of the injury by the liver but is a serious consideration after left-sided injury. The incidence of diaphragmatic injury after thoracoabdominal injury is as high as 17% to 40%.[37–39] For this reason, patients treated nonoperatively for left thoracoabdominal penetrating injuries should undergo a period of clinical observation commensurate with the mechanism. If peritonitis develops, the diaphragm can be directly examined at laparotomy. If the patient passes the period of observation, the patient can be offered diagnostic laparoscopy to specifically evaluate the diaphragm on the left side. As the patient has already been clinically evaluated and other intra-abdominal injury excluded, laparoscopy can be focused on diaphragmatic evaluation and a full exploration is not necessary. Insufflation for this procedure should be done carefully with close monitoring of the vital signs. With any evidence of the development of tension physiology due to a diaphragmatic injury, immediate release of pressure and insertion of a chest tube should be performed before proceeding.

THE TRAUMA LAPAROTOMY

3 For any hospital that cares for trauma patients, the ability to emergently perform an operative intervention is critical. Preparation before the critically ill patient arrives is key. An operating room that is easily accessible from the resuscitation area as well as the ICU should be earmarked for use in these situations. A plan for securing the room for high-profile patients should be in place and there should be a designated waiting area for family members. A contingency plan for multiple casualty situations should be available, with operating rooms located in close proximity to facilitate surgical, anesthesia, and nursing cross-coverage. Transportation of critically ill patients is high-risk, and preplanned routes that minimize distance, elevator use, and public exposure should be well known to all providers. Instruments and disposables should be centrally located and redundant so that multiple casualty situations

can be dealt with effectively. Having a dedicated trauma pack that allows for a laparotomy and thoracotomy, with add on sets for a sternotomy, amputation, and peripheral vascular injuries will facilitate circulator efficiency. With the high rate of retained foreign bodies after emergent trauma cases, the use of radiofrequency detection device embedded fabric is recommended. In higher-volume centers, access to a satellite blood bank with uncross-matched packed red blood cells and plasma is ideal, otherwise a system for communication with the main blood bank and product delivery to the OR should be in place. If a hybrid room is available, the operative and nursing teams should be familiar with the indications for starting an emergent case in this room. For all rooms, access to fluoroscopy and plain films is critical. Because of service line cross-coverage, ongoing in-servicing of the nursing and support staff is important to ensure that practices such as massive transfusion protocols, are universally understood.

4 For all emergent laparotomies, the patient should be placed in the supine position with arms abducted at 90 degrees. Even with a concomitant thoracic injury, this is the preferred starting position. Rarely, for patients with a penetrating injury with a transpelvic trajectory, where endoscopic evaluation may be required, the lithotomy position may be used. Likewise, in the blunt trauma patient where there is external perineal injury, this may be considered. At a minimum, the torso, neck, and upper half of the lower extremities should be prepared into the field for maximum flexibility. With any concurrent limb injuries, the entire extremity should be prepared. If there is any concern of a urethral or bladder injury, the Foley catheter should be prepared into the field to allow manipulation by the surgeon. Forced air warming on the lower half of the extremities, and other warming adjuncts should be utilized. All preoperative patient preparation including venous and arterial access, catheterization, and confirmation of patient identification should be a team effort with full participation by the surgical team.

The trauma laparotomy incision extends from the xiphoid process to the symphysis pubis. Traditionally made with a scalpel, unless emergent, electrocautery can be utilized to minimize bleeding. This extensile midline incision can be extended across the right or left inguinal ligament for distal iliac vascular injuries. Superiorly, a subcostal extension can be added to improve access to the liver on the right, especially with retrohepatic venous injuries, or to the left for gastroesophageal (GE) junction injuries. The

incision can be extended into a sternotomy for concurrent thoracic cavity injuries or to facilitate suprahepatic vena cava control for high-grade liver injuries not amenable to packing. If the patient has a pre-existing right thoracotomy, this can be joined to the laparotomy with incision of the diaphragm to afford the same view of the liver, retrohepatic venous structures, and intrapericardial vena cava.

On entry to the abdomen, the falciform should be taken down so as to minimize traction damage to the liver. Traditionally, blind four quadrant packing was advocated. In reality, this maneuver is not very helpful. In order to prevent iatrogenic damage, it is preferable to remove large amounts of central clotted blood, followed by selected packing of any areas with active bleeding. A rapid examination of the retroperitoneum should also be performed. Focusing on an obvious bowel injury that is encountered first while a retroperitoneal vascular injury remains unattended to is a pitfall. The goal of the initial packing and survey of contents is to identify and temporize any major sources of bleeding. A plan for surgical control can then be made. This includes notifying the circulator of any necessary additional equipment and close communication with anesthesia to optimize the resuscitation needs of the patient. Early consideration of damage control, addressed later in the chapter should be considered. The need for adjunctive services such as angiography prior to proceeding to the SICU should be considered and initiated early to allow lead-time for preparation. Once active hemorrhage has been temporized, a careful and complete survey of all of the abdominal contents should be performed. In the exsanguinating patient who is undergoing a damage control procedure, this may not be possible, but in the stable patient, this is critical. The potential for a missed injury can be mitigated by a systematic approach to the abdominal contents. We recommend that the entire abdomen be reviewed in the same manner for every case, regardless of the mechanism. Specific areas warrant extra care during the examination. For blunt injuries without preoperative imaging, duodenal injuries may present with only a subtle hematoma in the retroperitoneum. For hematomas in this area, a right visceral medial rotation should be performed. For penetrating injuries, especially those due to shotguns, colonic, rectal, and small bowel injuries, especially on the mesenteric surface, may only be visible as a small bloodstain or hematoma in the overlying fat. These need to be inspected carefully. The posterior surface

of the stomach is also a common area for missed injuries and should be inspected carefully.

While exceedingly uncommon for blunt injuries, for both SWs and GSWs, ureteric injuries can be difficult to diagnose and for any trajectories in this region, care should be taken to inspect the at-risk segment of the ureter without devascularizing the structure. Likewise, whereas blunt bladder injuries are often large and located near the dome, penetrating injuries, even those that are intraperitoneal, can be small and asymptomatic. Most small extraperitoneal injuries can be managed nonoperatively with urinary catheter drainage however, large injuries, especially those with an intact connection to the skin can be problematic. If there is an intraperitoneal component of bladder injury, this can be extended and the interior of the bladder visualized. If not, we recommend injection of methylene blue containing sterile water into the bladder retrograde to look for any visible extravasation. If this is identified, the bladder should be taken down and these injuries repaired.

For retroperitoneal hematomas, the abdomen is traditionally broken down into three zones. Zone I is the central portion from the aortic hiatus to the sacral promontory encompassing the aorta, IVC, and major branches. Zone II covers the lateral retroperitoneum which contains the kidneys. Zone III is the pelvis, which encompasses the sacral venous plexus and iliac vessels. For penetrating injuries, all zones undergo exploration. For blunt injuries, traditionally, all zone I hematomas would be explored with zones II and III only warranting exploration if the hematoma was large, expanding or pulsatile. The retrohepatic area is distinct from the remaining areas and we often refer to this as zone IV, containing the retrohepatic IVC and major hepatic veins. This area is difficult to expose and as such, if bleeding is controlled with packing, should not be explored for either blunt or penetrating injuries.

DAMAGE CONTROL LAPAROTOMY

Damage control[40] has become a common practice in the management of patients with complex abdominal trauma and has been credited with saving more lives than many of the other surgical techniques developed over the last

two decades. Abdominal damage control techniques should always be combined with damage control resuscitation, which includes permissive hypotension, early empiric balanced blood component therapy minimizing crystalloid usage, and the 5 prevention and treatment of hypothermia. Abdominal damage control includes three key components: (a) temporary rapid control of bleeding and contamination with early termination of the operation, (b) postoperative resuscitation with correction of coagulopathy, hypothermia, and acidosis, and (c) subsequent definitive repair of injuries.

The standard indications for damage control include: (a) patients with severe physiologic compromise with coagulopathy, hypothermia, or acidosis, (b) bleeding from difficult to control injuries or an injury burden which will result in physiologic compromise if treated definitively at the index operation, and (c) austere environments with limited resources or surgeon skillset, such as in a rural or combat setting. There is evidence that early damage control, even prior to physiologic decompensation, may be associated with better survival and as such, patients with a large injury burden at risk of becoming physiologically depleted should also be considered as candidates for damage control surgery. The exact timing of damage control should be determined by the complexity of the injuries, the physiologic condition of the patient, the available resources, and the experience of the surgical team.

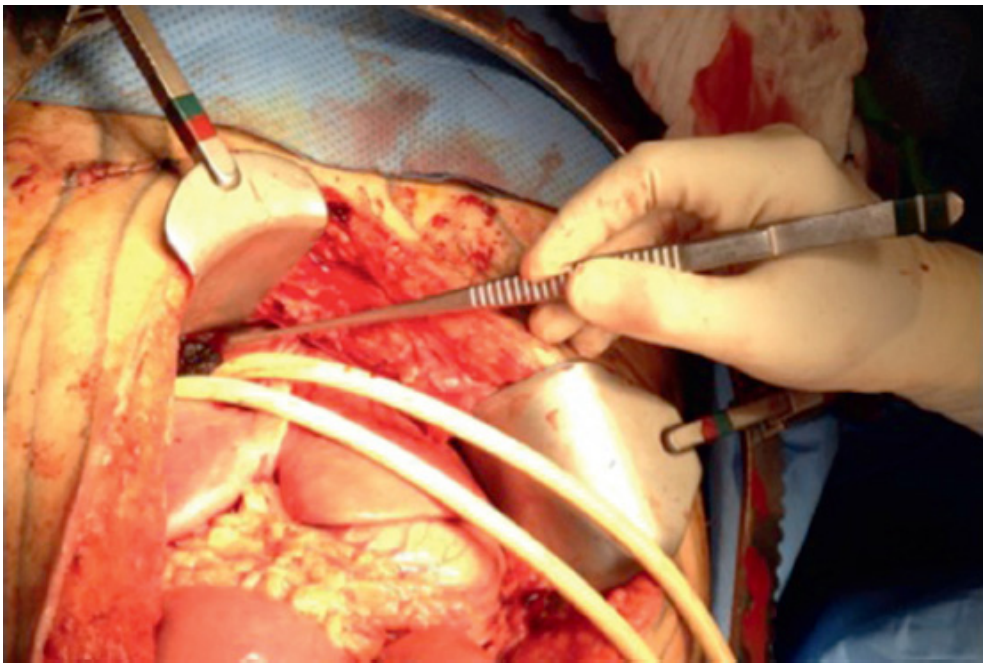

Figure 25.2 Gunshot injury through the center of liver requiring balloon tamponade using Foley catheters for damage control.

Effective temporary hemorrhage control can be achieved by mechanical compression or gauze packing in most cases. However, packing is usually not effective for major vascular injuries and surgical control with ligation or shunting[41] may be necessary. For deep tracts, for example in the liver, balloon tamponade[42] can be very effective (**Fig. 25.2**). Angioembolization may be a useful adjunct for abdominal damage control and should be considered early, immediately following the operation.

Control of intestinal spillage is also an integral part of damage control. Stapling of the bowel, without reestablishing continuity can be considered in severe instability for injuries requiring resection. Definitive reconstruction is performed at a later stage, once the patient is stabilized. As this temporary obstruction may promote bacterial and toxin translocation especially in patients requiring vasopressors, whenever possible, reconstruction of the bowel should be considered at the index operation.

6 Following damage control, the abdominal fascia or skin should never be closed because of the high risk of intra-abdominal hypertension and abdominal compartment syndrome.[43] The ideal method of temporary abdominal closure should prevent evisceration, preserve the fascia and abdominal wall domain, facilitate reoperation, allow effective removal of

toxin-loaded intraperitoneal fluid, reduce the risk of enteroatmospheric fistulas, and help achieve early definitive fascia closure (**Fig. 25.3**). Several systems that utilize negative pressure therapy are described for temporary abdominal closure. A Western Trauma Association Algorithm outlining the management of this injury is available at: https://www.westerntrauma.org/wp-content/uploads/2020/07/WTACriticalDecisionsManagementOfOpenAbdomenFollowingDamageControl.pdf

Once the patient has had their initial abbreviated procedure and temporary abdominal wall closure, they can then be taken to the ICU for continued resuscitation. After physiologic status has normalized, the patient can then return to the OR for definitive exploration and repair of all injuries. Even prior to normalization of the patient's physiology, if significant bleeding is noted, the patient should return to the operating room for reexploration. Although rare, even with a temporary abdominal wall closure in place, intra-abdominal hypertension may still occur. It is important that bladder pressures are monitored routinely during the first few hours after laparotomy.

Figure 25.3 Temporary abdominal closure after damage control laparotomy.

DIAPHRAGM

Anatomy

The diaphragm consists of a central aponeurotic portion which fuses with the pericardium and a peripheral muscular portion which is attached to the lower sternum, the lower six ribs, and the lumbar spine. During exhalation, the diaphragm rises to the level of the nipples at the fourth to fifth intercostal space. Penetrating injuries of the lower chest or insertion of a thoracostomy tube below the nipple, therefore has the potential to cause injury to the diaphragm.

Epidemiology

Blunt trauma may cause diaphragmatic injury through three different mechanisms which include a sudden increase in intra-abdominal pressure causing a bursting of the diaphragm, fractured ribs perforating the diaphragm, and deceleration injuries causing detachment of the diaphragm from the ribs. For blunt trauma, a diaphragmatic injury is found in approximately 7% of all laparotomies and in about 7.5% of autopsy studies. The left hemidiaphragm is involved in approximately 70% of cases and the right in 30% presumably due to the protective presence of the liver. Blunt tears (**Fig. 25.4**) are usually 7- to 10-cm long as compared with 2 to 3 cm for penetrating trauma (**Fig. 25.5**). A right diaphragmatic rupture indicates a more severe traumatic insult and in almost all cases there are associated intra-abdominal injuries, compared to 77% for left diaphragmatic ruptures.

Diagnostics

Isolated and uncomplicated diaphragmatic injuries are difficult to diagnose as they may be completely asymptomatic or present with minor, nonspecific signs. Classic findings such as shortness of breath, bowel sounds in the chest, GI obstruction, or ischemia, are rare, and require acute herniation of abdominal contents.

The natural history of unrecognized diaphragmatic injuries is unknown and although some small injuries may heal, this is not uniform. For right

hemidiaphragm injuries, the presence of the liver generally protects against diaphragmatic herniation. However, for the left side, unrepaired diaphragm injuries commonly result in a diaphragmatic hernia, which may present within hours, days, weeks, months, or even years after the injury.

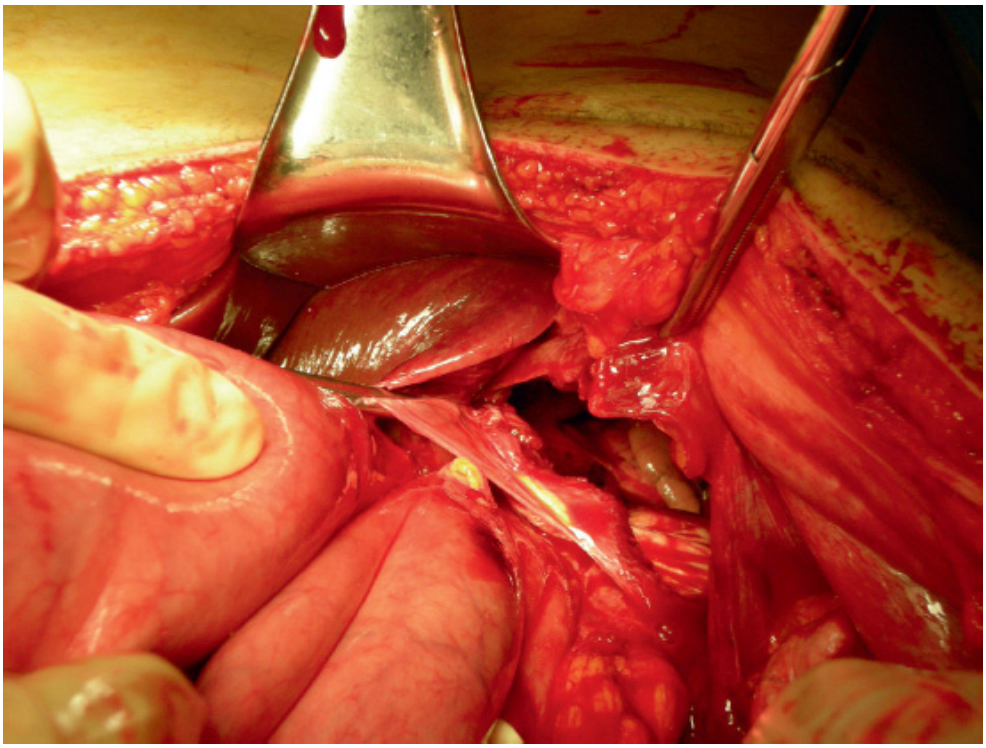

Figure 25.4 Large blunt diaphragm injury.

For blunt injuries, imaging can be useful. Plain radiologic findings suspicious of diaphragmatic injury include an elevated diaphragm, an irregular diaphragmatic contour, and nonvisualization of the diaphragm. Classically, an NG tube may be seen in the thoracic cavity. Once GI tract herniation has occurred, CXR (**Fig. 25.6**) and CT (**Fig. 25.7**) have higher sensitivity. Although injuries are not always detected on CT, this modality is the highest yield study to evaluate for diaphragmatic injury as it allows concurrent evaluation of any associated intra-abdominal injuries.

Treatment

All diaphragm injuries should ultimately have the abdominal contents reduced and the defects repaired. Acutely, diaphragmatic injuries should be

approached through a laparotomy to facilitate exploration of the remaining intra-abdominal contents if needed. In chronic, elective cases, access and repair of the hernia can be performed through a thoracotomy. The repair should be performed using nonabsorbable sutures and if there is contamination of the pleural cavity, extending the incision and washing the cavity out prior to closure are warranted. Tube thoracostomy should be considered in most cases. In rare cases where there is loss of diaphragmatic tissue, synthetic prosthetic reconstruction can be utilized. If the diaphragm has been avulsed from the chest wall, careful reconstruction of the diaphragmatic architecture utilizing nonabsorbable sutures is required. In some cases where there is significant tissue loss, apposition of the remaining diaphragm to the chest wall several rib spaces up may be required to create a tension-free repair.

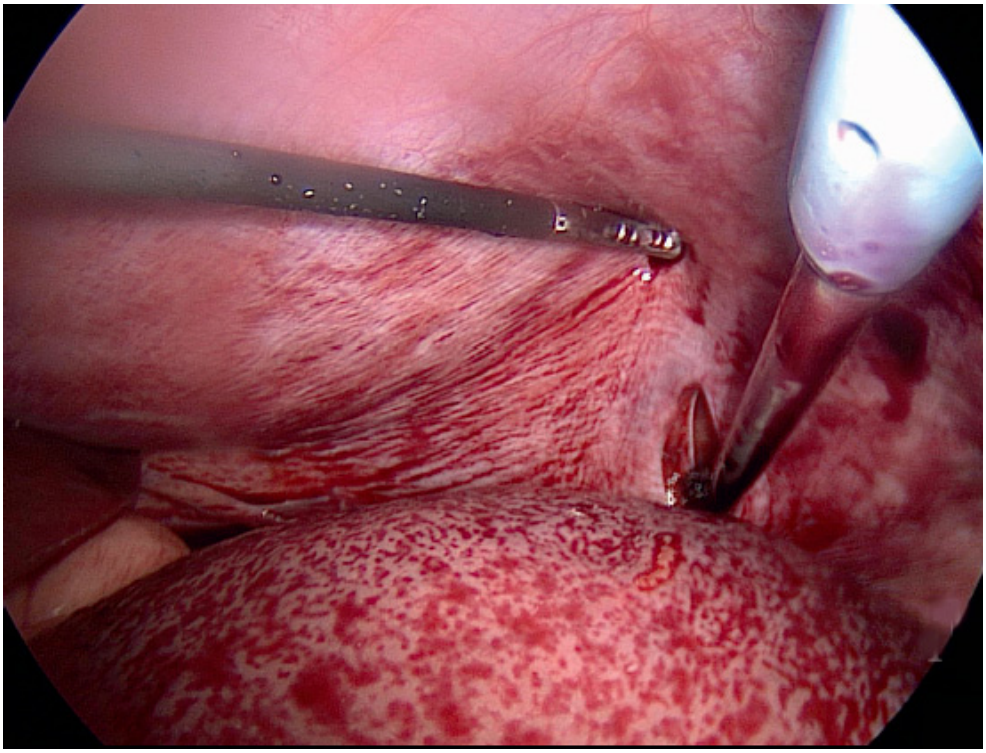

Figure 25.5 Small diaphragm injury after a stab wound to the left thoracoabdominal region.

Figure 25.6 Chest x-ray demonstrating blunt left diaphragmatic injury with herniating gastrointestinal tract.

LIVER AND BILIARY TRACT

Anatomy

The anatomical division of the liver into the classic Couinaud segments has no practical application in trauma. Parenchymal resection should be minimized and does not follow anatomical boundaries. An understanding of the blood supply however is important. The retrohepatic IVC is approximately 8 to 10 cm long and in most patients is partially covered by the liver parenchyma. In approximately 7% of individuals the IVC is completely embedded in the liver. For outflow, there are three major hepatic veins (right, middle, and left), with numerous accessory veins. Only the proximal 1 to 2 cm of the major hepatic veins are extrahepatic. In approximately 70% of individuals, the middle hepatic vein joins the left hepatic vein, near the IVC. The portal vein provides approximately 70% of hepatic blood flow, and 50% of the hepatic oxygenation. It divides into right

and left branches at the level of the liver parenchyma. The common hepatic artery originates from the celiac artery. In most individuals it branches into the left and right hepatic arteries at the hilum of the liver. In some individuals the right hepatic artery originates from the superior mesenteric artery. The left hepatic artery may originate from the left gastric artery. The porta hepatis contains the hepatic artery to the left, and the common bile duct to the right. The portal vein lies posteriorly and between the common bile duct and the hepatic artery. The left hepatic bile duct, the left hepatic artery, and the left portal vein enter the undersurface of the liver, near the falciform ligament.

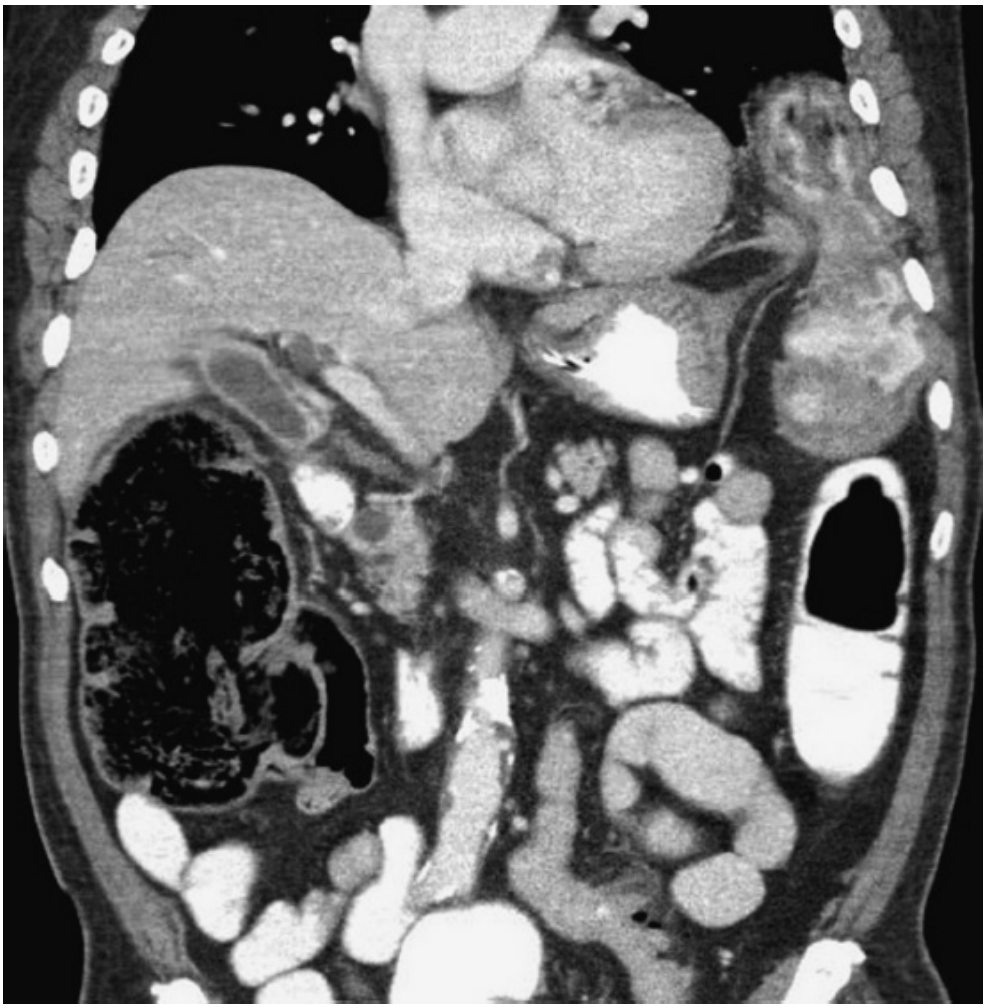

Figure 25.7 CT demonstrating left blunt diaphragmatic injury with herniating gastrointestinal tract contents.

Epidemiology

The liver is one of the most commonly injured intra-abdominal organs following blunt trauma. In penetrating trauma the liver is the most commonly injured solid organ. High-velocity missiles can cause massive tissue destruction and are associated with high mortality. The AAST-OIS grading system (**Table 25.1**) ranges from a mild grade I injury to a grade VI total hepatic avulsion which is lethal.[44] In the modern era of selective nonoperative management of solid organ injuries, the organ injury grading system was updated in 2018 to include radiologic criteria of vascular injury as a component of risk stratification for failure of nonoperative management.[45]

Table 25.1 OIS-AAST Grading Scale for the Liver

Grade[a]	Type	Injury Description
I	Hematoma Laceration	Subcapsular, <10% surface area Capsular tear, <1 cm parenchymal depth
II	Hematoma Laceration	Subcapsular, 10–50% surface area; intraparenchymal, <10 cm in diameter 1–3 cm parenchymal depth, <10 cm in length
III	Hematoma Laceration	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma, >10 cm or expanding >3 cm parenchymal depth
IV	Laceration	Parenchymal disruption involving 25–75% of hepatic lobe or 1–3 Couinaud segments within a single lobe
V	Laceration Vascular	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud segments within a single lobe Juxtahepatic venous injuries; that is, retrohepatic vena

		cava/central major hepatic veins
VI	Vascular	Hepatic avulsion

[a]Advance one grade for multiple injuries, up to grade III.

Moore EE, Cogbill TG, Jurkovich GJ, et al. Organ injury scaling: spleen and liver (1994 revision). *J Trauma* 1995;38:323–324.

Figure 25.8 Gunshot injury to the liver successfully managed nonoperatively.

Diagnostics

A FAST will detect free intraperitoneal bleeding, but it does not provide any information about the source of this bleeding. An abdominal CT scan with intravenous contrast is the highest-yield imaging modality. CT provides accurate information about the architecture of the injury, the amount of intraperitoneal blood, the presence of active bleeding, pseudoaneurysms or arteriovenous fistulas, and the presence of associated injuries. CT is a valuable tool in the selection of patients for operation, angiographic embolization, or observation (**Fig. 25.8**).

Treatment

Selective nonoperative management of blunt liver trauma is the standard of care. The criteria for selection of patients for nonoperative management include clinical examination, CT scan findings, and the presence or absence of associated injuries. Hemodynamic stability and the absence of peritonitis are absolute requirements for nonoperative management. The success rate of nonoperative management for blunt hepatic trauma, including those with high-grade injuries, is high.[46,47] In a recent National Trauma Data Bank study of 6,402 patients with grade IV or V blunt liver injuries, 68% were managed nonoperatively.[48] For these high-grade injuries, especially with evidence of contrast extravasation (**Fig. 25.9**), angiointervention has been shown to be an independent predictor of survival and should be used liberally as a postoperative adjunct. Most failures of nonoperative management occur within the first 24 hours of admission. There is some evidence that patients with high injury severity score (ISS), severe grade IV or V liver injuries, multiple transfusions, major associated injuries, and associated chronic conditions such as cirrhosis, are at an increased risk for failure of nonoperative management. Angiographic embolization may be a significant adjunctive therapeutic modality which increases the success rate of nonoperative management of high-grade injuries.[47,49] Although selective nonoperative management of blunt liver trauma has become the standard of care, selective nonoperative management of penetrating liver trauma has only recently gained wide acceptance (**Fig. 25.9**).[32,33,50] For both blunt and penetrating injuries being managed nonoperatively, continuous close monitoring in an ICU environment and frequent serial clinical examinations are critical for success. A Western Trauma Association Algorithm outlining the management of this injury is available at: https://www.westerntrauma.org/wp-content/uploads/2020/07/WTACriticalDecisionsOperativeManagementOfAdultBluntHepaticTrauma.pdf

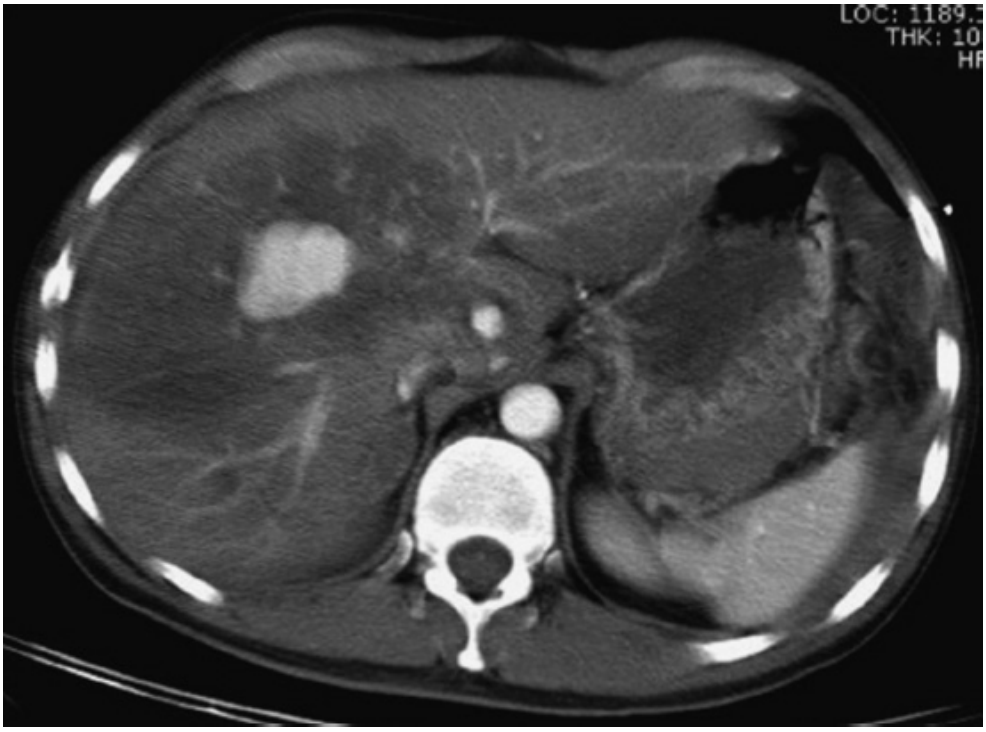

Figure 25.9 High-grade blunt liver injury with active contrast extravasation.

For operative management, the initial incision should be a midline laparotomy. For improved access to posterolateral liver injuries, a right subcostal incision may be added. In rare occasions, addition of a sternotomy may be required in order to obtain access to the intrapericardial inferior vena cava for total vascular isolation of the liver (**Fig. 25.10**), or exposure of the heart for placement of an atriocaval shunt (**Fig. 25.11**). Alternatively, as discussed earlier in the chapter, if the patient has a right thoracotomy, the thoracotomy and laparotomy can be joined with incision of the diaphragm for unimpeded access to the posterior liver and suprahepatic segment of the IVC.

In this case a cuff of diaphragm should be left so that if the patient survives, reconstruction is facilitated. In approximately 80% to 85% of patients undergoing operation, the liver injury can be managed by relatively simple surgical techniques, such as application of local hemostatic agents, electrocoagulation, or superficial suturing. Bleeding from deep liver lacerations can be controlled by clipping or suture ligation of any major vessels, followed by deep, figure-of-eight sutures, on a large blunt liver needle. Omental packing of large liver defects is useful in eliminating any dead space. Significant bleeding from deep bullet or knife tracts in the liver

may require a tractotomy for peripheral wounds or balloon catheter tamponade and perihepatic packing for central wounds.

Severe blunt trauma or high-velocity GSWs associated with extensive parenchymal damage are not amendable to deep suturing. Bleeding control in these cases may be achieved with perihepatic packing, with or without liver resection. Perihepatic packing and damage control is critical in the management of complex liver injuries. In order to be effective it needs to be performed early, before the patient becomes unstable. The presence of intact hepatic ligaments enhances the effectiveness of the perihepatic packing. Laying a piece of absorbable mesh on the raw surface of the liver prior to packing facilitates pack removal at the take back as the mesh with its integrated clot can be left undisturbed once the packs 7 are removed. Angioembolization following perihepatic packing should be considered early postoperatively and ideally, intraoperatively, if a hybrid operating room (**Fig. 25.12**) is available. The perihepatic packing should be removed as soon as feasible after correction of coagulopathy and other physiologic abnormalities. Delaying removal for more than 48 hours may be associated with an increased risk of infection. In general packing is highly effective and major hepatic resections are rarely indicated in the acute setting. Once the patient has stabilized, and the liver has demarcated and the patient is able to tolerate resection, any nonviable parenchyma can be resected. If required acutely, the liver resection can be performed with finger dissection of the parenchyma, with suture ligation of vessels and biliary branches, or with the use of an electrothermal bipolar vessel sealing system. Selective hepatic artery ligation or clipping may be a useful adjunct to packing in rare cases and should be considered if packing by itself is insufficient and temporary occlusion results in reduction of the bleeding.

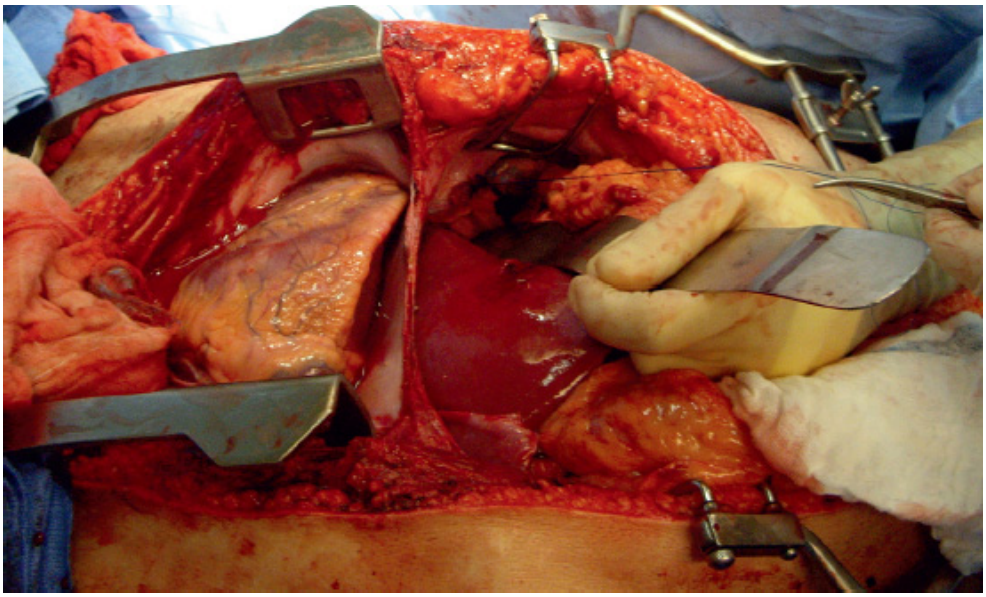

Figure 25.10 Laparotomy and sternotomy demonstrating excellent access to the liver and the intrapericardial segment of the suprahepatic IVC.

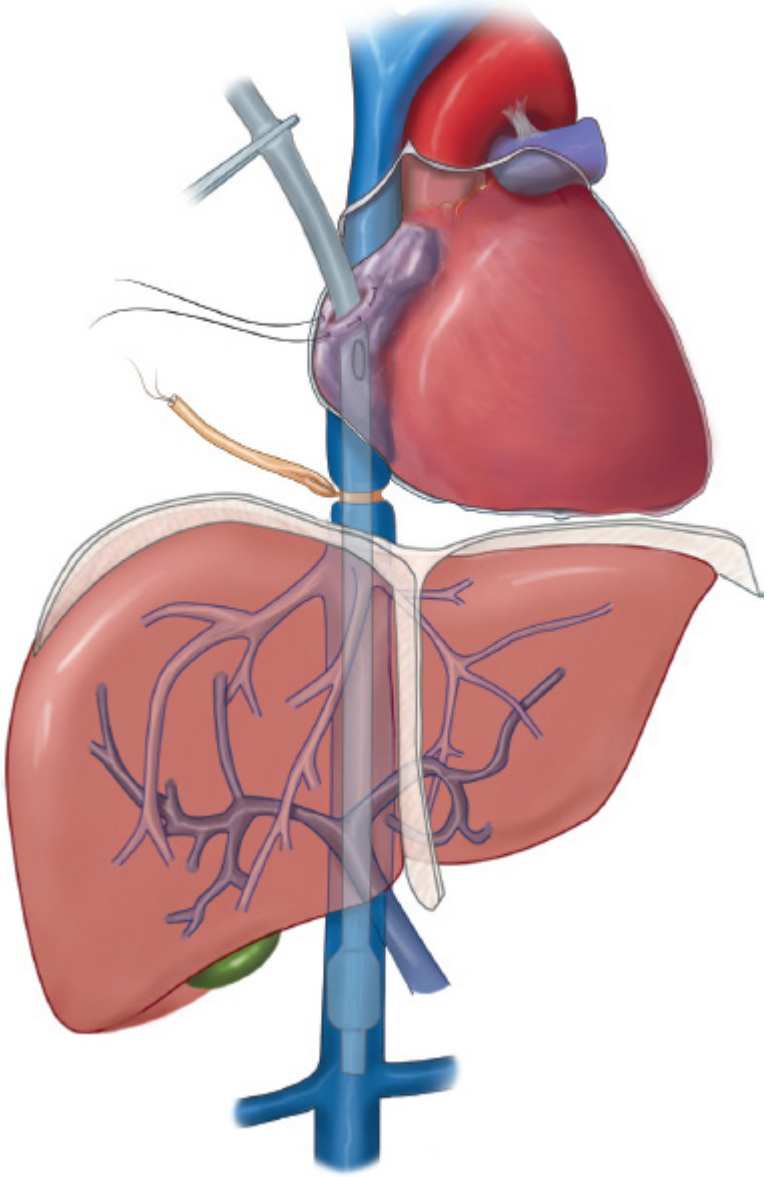

Figure 25.11 Schematic demonstrating an atriocaval shunt. (From Demetriades D, Inaba K, Velmahos G, eds. *Atlas of Surgical Techniques in Trauma*. New York: Cambridge University Press; 2015, with permission.)

Figure 25.12 Hybrid operating room.

Contained retrohepatic hematomas from blunt or penetrating injury, should not be explored because of the risk of uncontrollable hemorrhage. If the hematoma is not contained and perihepatic packing fails to achieve hemorrhage control or bleeding worsens with anterior retraction of the liver, injury to the hepatic veins or retrohepatic vena cava should be suspected. In this situation, exploration and repair or ligation of the bleeding vessel is mandatory. Total vascular isolation of the liver may be required to identify and repair the injury. The procedure consists of cross-clamping of the infradiaphragmatic aorta, the suprahepatic and infrahepatic inferior vena cava, and the porta hepatis. Control of the suprahepatic IVC is extremely challenging in the intra-abdominal segment as this is usually where the primary source of bleeding necessitating the procedure has occurred. Consequently, it is recommended that the intrapericardial segment is accessed for control.

Addition of a subcostal incision improves exposure of the liver and the retrohepatic veins. Division of the falciform and coronary ligaments allows inferior-medial rotation of the liver and direct visualization of the inferior vena cava and the right hepatic vein. As described earlier, an alternative to

the subcostal incision is a median sternotomy or if the patient already has a right anterolateral thoracotomy, division of the diaphragm, straight down to the inferior vena cava.

The use of an intracaval shunt may be considered in selected complex retrohepatic venous injuries which cannot be controlled with simpler approaches. The procedure involves extension of the laparotomy incision into a median sternotomy and opening of the pericardium. A tape tourniquet is then applied around the intrapericardial IVC. A purse–string suture (2-0 silk) is placed in the right atrial appendage and a size 8 endotracheal tube with a side hole cut at approximately 8 to 10 cm from the clamped proximal end, is then inserted through the purse–string and guided into the IVC. The balloon of the tube is then inflated just above the renal veins and the tape tourniquet around the intrapericardial IVC is tightened.[51] Alternatively, a 36-Fr chest tube, with fenestrations cut into the proximal segment of the tube to allow blood flow from the IVC into the right atrium may be used. The intracaval shunt may reduce bleeding but in reality, rarely achieves complete hemostasis. The reported results with atriocaval shunts are generally poor, and should only be considered if all other techniques have failed.

For completion, other techniques which have been used in the management of retrohepatic venous injuries include intravascular balloons inserted through the femoral vein, extracorporeal venovenous bypass, hypothermic circulatory arrest, and liver transplantation.[52]

The incidence of postoperative liver-related complications after high-grade liver injuries has been reported to be as high as 50%.[53] The clinical presentation of these complications may vary from a few days to many months. Complications include early or late hemorrhage, pseudoaneurysm, arteriovenous fistula, biloma, biliary fistula, liver necrosis, liver abscess, hemobilia, and intrahepatic biliary strictures. Approximately 35% of patients with significant liver-related postoperative complications are asymptomatic and have the complication diagnosed on CT.[53] The majority of these complications can safely be managed nonoperatively, with percutaneous endovascular or endoluminal interventional radiology-based or ERCP-guided solutions.

Extrahepatic Biliary Tract Injury

Trauma to the extrahepatic biliary tree is rare and is usually due to a penetrating mechanism. Bile duct injuries are usually diagnosed during laparotomy, although some cases may present late, occurring even days after injury. The diagnosis may be confirmed with a hepatobiliary iminodiacetic acid (HIDA) scan, MRCP, or ERCP. The management of injuries to the biliary tree is determined by the location and extent of the biliary injury, the time of diagnosis, and the presence of associated intra-abdominal injuries. Injuries to the gallbladder are treated by cholecystectomy. Complete duct transections are best managed with a Roux-en-Y biliary-enteric anastomosis because primary repair is associated with a high stricture rate.

Incomplete injuries to the extrahepatic ductal system discovered intraoperatively, can be managed with primary repair, if the transection involves less than 50% of the duct circumference. Placement of a T-tube through a separate choledochotomy facilitates the repair. Transections involving more than 50% of the circumference of the duct, especially with questionable tissue viability, should be treated like a complete transection. All repairs of the biliary tract should be drained externally with closed suction drains.

In the damage control setting, the duct may be ligated or an external catheter may be placed into the proximal duct and exteriorized through the skin. Definitive repair can be performed after physiologic stabilization of the patient or once expert assistance becomes available.

SPLEEN

Anatomy

The spleen is held in place by four ligaments which include the splenogastric ligament medially, the splenocolic ligament inferiorly, and the splenophrenic and splenorenal ligaments posterolaterally. The splenogastric ligament is the only vascular ligament and contains five to seven short gastric vessels, which originate from the distal splenic artery. The tail of the pancreas is in close proximity to the splenic hilum and is at risk of injury during splenectomy or hilar clamping. The splenic artery courses superior to the pancreas and near the splenic hilum it divides into upper and lower pole arteries. The splenic

vein is located posterior and inferior to the splenic artery, receives the inferior mesenteric vein and joins the superior mesenteric vein to form the portal vein.

Epidemiology

The spleen is a commonly injured intra-abdominal organ following blunt and penetrating trauma. The severity of splenic injury is graded by the OIS-AAST spleen injury scale (**Table 25.2**). Generally, grades I and II are considered minor injuries, grade III a moderate injury, and grades IV and V are severe injuries.

Diagnostics

The clinical presentation of a spleen injury depends on the volume of blood loss and the presence of associated injuries. Many low-grade splenic injuries may be asymptomatic or have only minor local tenderness and the diagnosis is made on CT. Classically, those with large splenic hematomas may experience pain in the left upper quadrant, radiating to the left shoulder (Kehr sign), especially when placed in the Trendelenburg position. Although plain CXRs are not diagnostic, the presence of fractures of the left lower ribs or an elevated left hemidiaphragm can be associated with an increased possibility of splenic injury. The FAST may show free fluid around the spleen. Abdominal CT scan with intravenous contrast is the most widely used and highest-yield investigation (**Figs. 25.13** and **25.14**). It provides accurate information about the grade of injury, the amount of intraperitoneal bleeding, evidence of active bleeding, and associated injuries.

Treatment

Approximately 80% of blunt splenic injuries in adults and 90% to 95% in children can be safely managed nonoperatively.[54] Recent studies suggest that approximately 10% of all penetrating splenic injuries may also be managed nonoperatively.[55] The selection of patients for nonoperative management should be based on clinical examination and CT scan findings. The patient should be hemodynamically stable and have no signs of peritonitis. Although

associated head trauma is not an absolute contraindication for nonoperative management, it should lower the threshold for operative intervention, because head trauma–related coagulopathy increases the risk of splenic bleeding and the splenic bleeding may cause hypotension which would be detrimental to the injured brain. A Western Trauma Association Algorithm outlining the management of this injury is available at: https://www.westerntrauma.org/wp-content/uploads/2020/07/WTACriticalDecisionsAdultBluntSplenicTrauma-2016Update.pdf

Table 25.2 OIS-AAST Grading Scale for the Spleen

Grade[a]	Type	Injury Description
I	Hematoma Laceration	Subcapsular, <10% surface area Capsular tear, <1 cm parenchymal depth
II	Hematoma Laceration	Subcapsular, 10–50% surface area, <5 cm in diameter 1–3 cm parenchymal depth not involving a trabecular vessel
III	Hematoma Laceration	Subcapsular, >50% surface area or expanding; ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma, ≥5 cm or expanding >3 cm parenchymal depth or involving trabecular vessels
IV	Laceration	Laceration involving segmental or hilar vessels producing major devascularization (>25% of the spleen)
V	Laceration Vascular	Shattered spleen Hilar vascular injury with devascularized spleen

[a]Advance one grade for multiple injuries, up to grade III.

Moore EE, Cogbill TG, Jurkovich GJ, et al. Organ injury scaling: spleen and liver (1994 revision). *J Trauma* 1995;38:323–324.

Low-grade splenic injuries are much more likely to be successfully managed nonoperatively, but many high-grade injuries may still be managed nonoperatively. Patients with higher-grade splenic injuries selected for nonoperative management should be observed in the ICU. Development of hemodynamic instability, peritonitis or the need for blood transfusion should trigger operative exploration. Most failures occur within the first few days, although in some cases, especially those with subcapsular hematomas or pseudoaneurysms, delayed bleeding may occur days to weeks after the injury. Patients with severe splenic injuries selected for nonoperative management should receive prophylactic vaccinations against *Streptococcus pneumonia, Neisseria meningitidis,* and *Haemophilus influenza,* in case conservative management fails and the patient requires splenectomy.

Figure 25.13 CT image of a high-grade spleen injury.

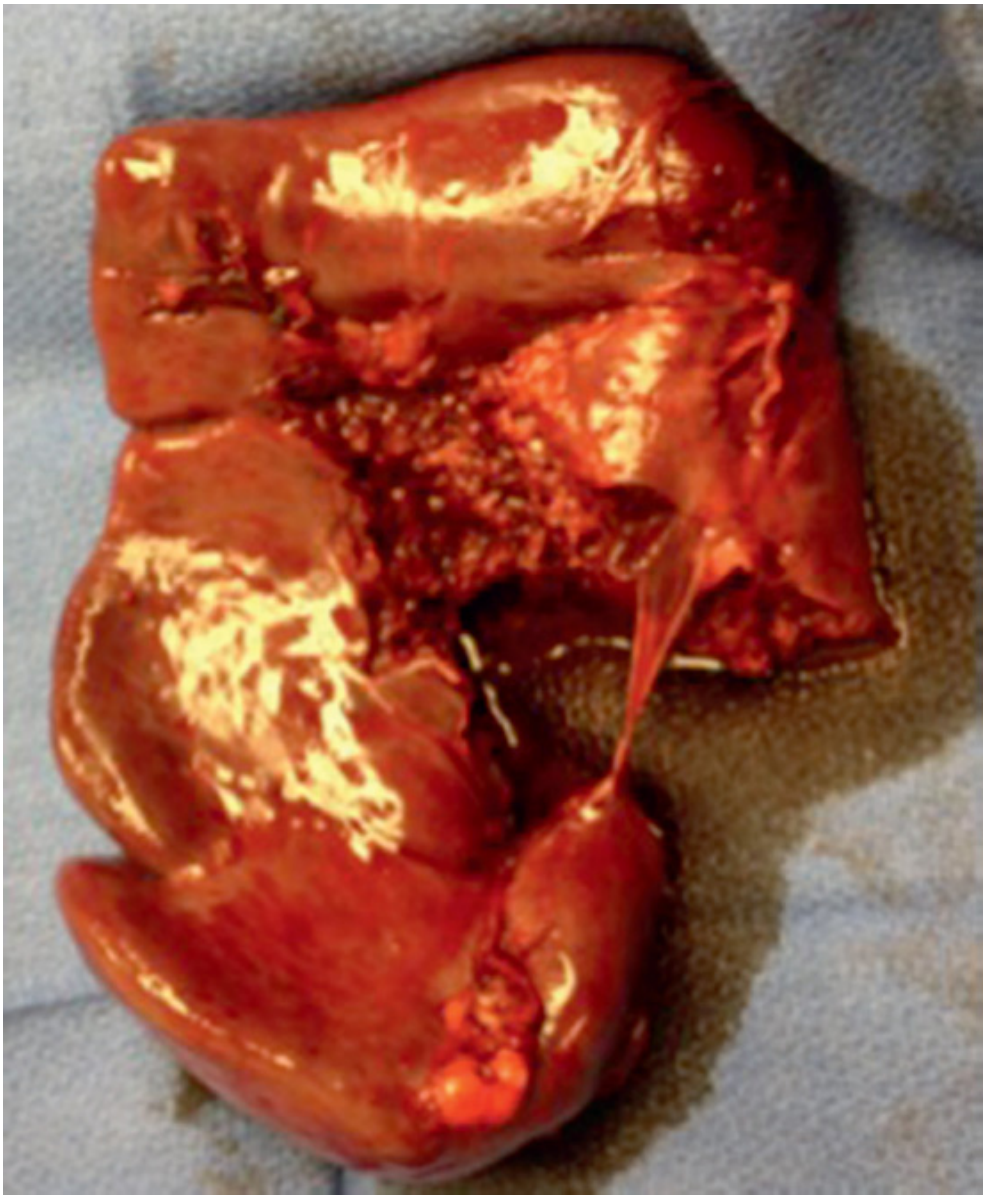

Figure 25.14 Spleen after removal as seen on CT in **Figure 25.13**.

A follow-up CT scan should be performed for all grade III to V splenic injuries within 2 to 3 days of admission to rule out the development of a pseudoaneurysm or progression of the hematoma. Subsequent follow-up CT scan evaluation should be considered in selected cases with high-grade injuries, especially those with subcapsular hematomas.

The duration of avoidance of vigorous physical activities and contact sports should be individualized, taking into account the severity of the spleen injury, the findings on follow-up CT scan, and patient's lifestyle. Most

surgeons recommend a minimum period of approximately 4 to 6 weeks before resumption of full unrestricted activity.

Angioembolization has been used as an adjunct to nonoperative management for patients with CT scan evidence of active contrast extravasation or pseudoaneurysm. Proximal splenic artery embolization consists of coil occlusion of the splenic artery distal to the dorsal pancreatic artery and promotes hemostasis by reducing blood flow to the spleen. Distal selective embolization consists of coil or gelfoam deployment as close to the bleeding site as possible. The available evidence is inconclusive and suggests that the two approaches may be equally effective in preventing significant rebleeding. Both techniques are associated with the same incidence of infarctions and infections requiring splenectomy. Distal embolization is associated with a higher rate of asymptomatic segmental infarctions.[56] A Western Trauma Association multicenter trial which included 140 splenic artery embolizations reported an overall complication rate of 32%, including splenic infarctions in 21% and splenic abscess in 4.3%.[57]

For operative management, after entering the peritoneal cavity any free blood is evacuated and the left upper quadrant is packed for temporary bleeding control. This allows a rapid evaluation of the rest of the abdomen to rule out any other major injuries which may require immediate attention. The next step is the assessment of the type and severity of the splenic injury, in order to determine if the spleen is salvageable. After removal of the temporary packing, the organ is rotated inferomedially. Several laparotomy pads are then placed under the left diaphragm and behind the spleen, aiding in the exposure of the spleen. Excessive traction on the stomach or the splenic flexure of the colon or excessive medial rotation of the spleen may cause avulsion of the delicate splenic capsule, resulting in bleeding and decreasing the possibility of splenic preservation.

Profuse bleeding from the spleen can temporarily be controlled with digital compression of the hilum or direct digital compression of the splenic parenchyma. A vascular clamp can also be placed across the hilum, taking care not to injure the tail of the pancreas.

The critical move for a quick and safe splenectomy is adequate mobilization and inferomedial rotation of the spleen. This is achieved by sharp division of the splenophrenic and splenorenal ligaments posterolaterally and medial rotation of the spleen. The next step is division

and ligation of the vascular gastrosplenic ligament, as far away from the stomach as possible, in order to avoid injury or ischemic necrosis of the gastric wall. Likewise, the splenic artery and vein should be ligated as close to the hilum as possible, in order to avoid injury to the tail of the pancreas. The final step is division of the splenocolic ligament. Although this stepped approach to mobilization of the spleen is applicable to most patients, the order of taking down the splenic ligaments should be determined by the anatomy and may vary from patient to patient. In fact, for acutely injured spleens, many of these ligaments may already be avulsed.

Preservation of the spleen should be considered in low-grade injuries if the patient is hemodynamically stable with a low overall injury burden. In cases with avulsion of the splenic capsule or minor lacerations, hemostasis can be achieved with electrocautery and local hemostatic agents. Splenic lacerations may be repaired with absorbable figure-of-eight or horizontal mattress sutures, on a blunt liver needle. The presence of an intact splenic capsule makes the placement of the sutures technically easier. If the parenchyma is fragile and does not hold sutures, pledgets may be used. An absorbable splenic mesh can also be used (**Fig. 25.15**) as an adjunct to splenorrhaphy, especially in cases with multiple stellate parenchymal injuries.

Early local postsplenectomy complications include recurrent bleeding, pancreatic complications (pancreatitis, pseudocyst, and pancreatic fistula), gastric complications (gastroparesis, necrosis of the greater curvature), subdiaphragmatic abscess, splenic vein thrombosis, splenic arteriovenous fistula, left lower lobe atelectasis, or pleural effusion. Complications after splenorrhaphy include intrasplenic hematoma or abscess, splenic infarcts, and pseudoaneurysms or arteriovenous fistulas. A follow-up CT scan with intravenous contrast should be performed in all high-grade splenic injuries managed with splenorrhaphy. Early postsplenectomy hematologic changes include leukocytosis and thrombocytosis. The leukocytosis is usually moderate, rarely exceeding 16,000 to 18,000/mm^3 and may last several weeks. More severe leukocytosis may indicate an infectious complication, especially in the presence of fever or tachycardia.[58] Thrombocytosis is usually moderate, may last for a few weeks and in most cases is clinically irrelevant.

Postsplenectomy infections may occur early or late. There is evidence that splenectomy is associated with an increased risk of early postsplenectomy infections. A recent prospective observational, multicenter study of 269 patients with blunt splenic injury surviving at least 72 hours, reported that splenectomy had a significantly higher incidence of infectious complications than splenic preservation.[59] A regression analysis identified splenectomy as an independent risk factor for infectious complications.

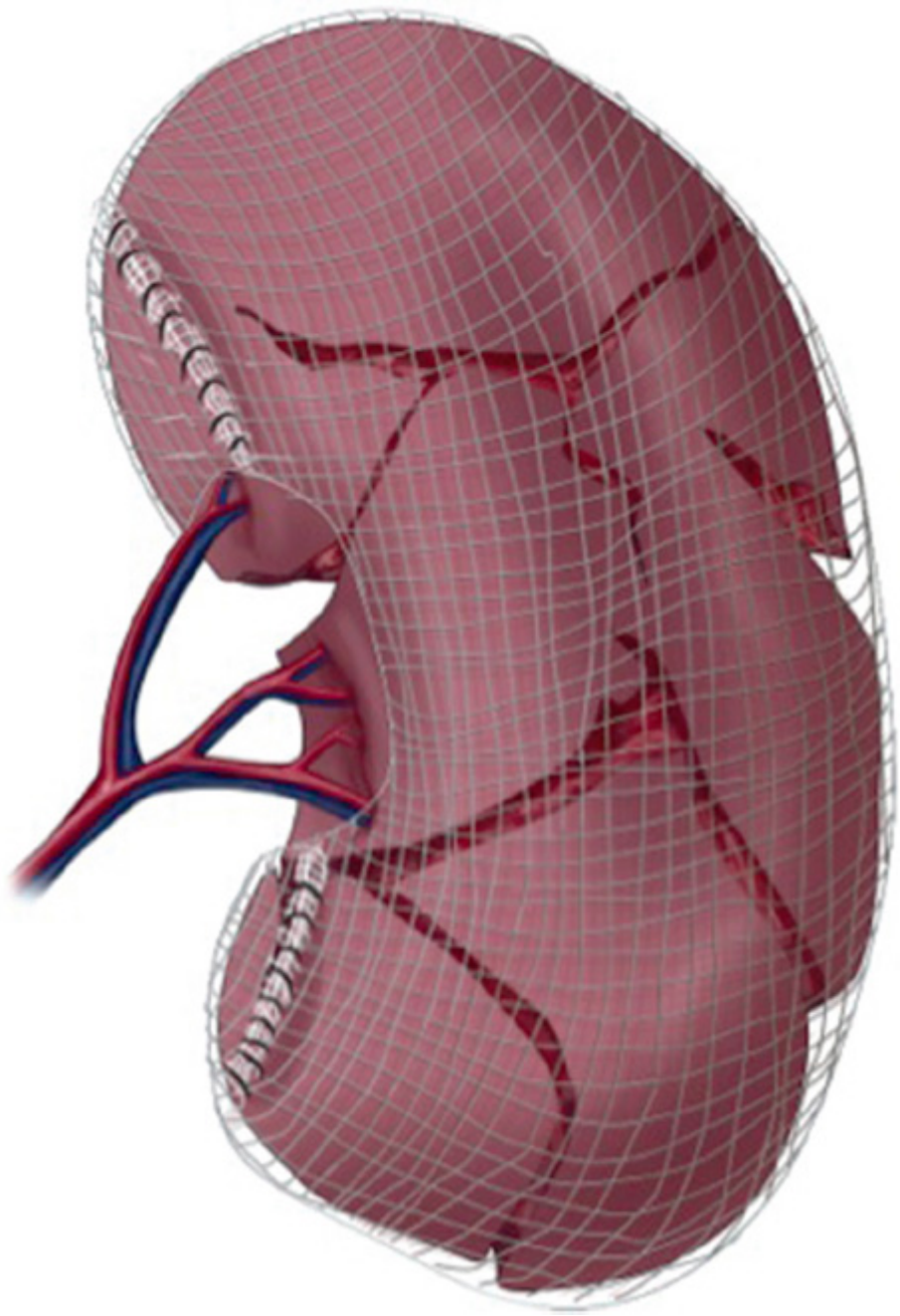

Figure 25.15 Splenic preservation with use of an absorbably mesh bag. (With permission from Demetriades D, Inaba K, Velmahos G, eds. *Atlas of Surgical Techniques in Trauma*. New York: Cambridge University Press; 2015.)

Overwhelming postsplenectomy infection (OPSI) is a rare but life-threatening complication, especially in children. The reported mortality varies from 10% to 80%. Encapsulated organisms, such as *H. influenza, S. pneumonia,* and *N. meningococcus*, are the most common pathogens.

Although the majority of infections occur within the first 3 to 4 years, OPSI may occur at any time after splenectomy. The Surgical Infection Society recommends that all splenectomized patients 2 to 64 years old receive the 23-valent pneumococcal vaccine.[60] In addition, high-risk patients should receive *H. influenza* and meningococcal vaccines. The timing of administration of the vaccines after trauma may be optimal at 14 days after splenectomy.[61] There is no evidence to support routine long-term prophylactic antibiotic administration in splenectomized patients. Patients should be educated on postsplenectomy sepsis, wear a medical alert bracelet, inform caregivers of their asplenic state, and be advised to seek medical care with the onset of any signs of infection.

PANCREAS

Anatomy

The pancreas is a retroperitoneal organ with its head directly situated over the inferior vena cava and its neck over the superior mesenteric vessels and the proximal portal vein. The body extends over the suprarenal aorta and the left renal vessels, closely related to the splenic artery and vein. The uncinate process wraps around the superior mesenteric vessels. As described for the spleen, the splenic vein courses inferior to the splenic artery and joins the superior mesenteric vein at a right angle to form the portal vein behind the neck of the pancreas. The inferior mesenteric vein drains into the splenic vein behind the body of the pancreas (**Figs. 25.16** and **25.17**).

The major pancreatic duct of Wirsung travels down the entire length of the pancreas and drains into the ampulla of Vater, approximately 8 cm downstream from the pylorus. The lesser duct of Santorini branches off the superior aspect of the major duct, at the level of the neck of the pancreas. This drains into the duodenum, approximately 2 to 3 cm proximal to the ampulla of Vater. The pancreatic head and the proximal duodenum receive their blood supply from the anterior and posterior pancreaticoduodenal arcades. Because these arcades lie on the surface of the pancreas, close to the duodenal loop, separating these can result in ischemic damage to the duodenum.

Epidemiology

Pancreatic trauma is seen in approximately 0.2% of blunt trauma and about 1% of penetrating trauma patients. Overall, about 60% of patients with blunt trauma and about 90% with penetrating trauma will have associated intra-abdominal injuries. The most commonly associated injury in blunt trauma is the spleen. Associated intra-abdominal vascular injuries are common in penetrating trauma and are found in more than 75% of penetrating injuries to the head of the pancreas. A concomitant major vascular injury increases the likelihood of a poor outcome. The most widely used grading system (**Table 25.3**) is the OIS-AAST.[44] The classification is based on CT and operative findings.

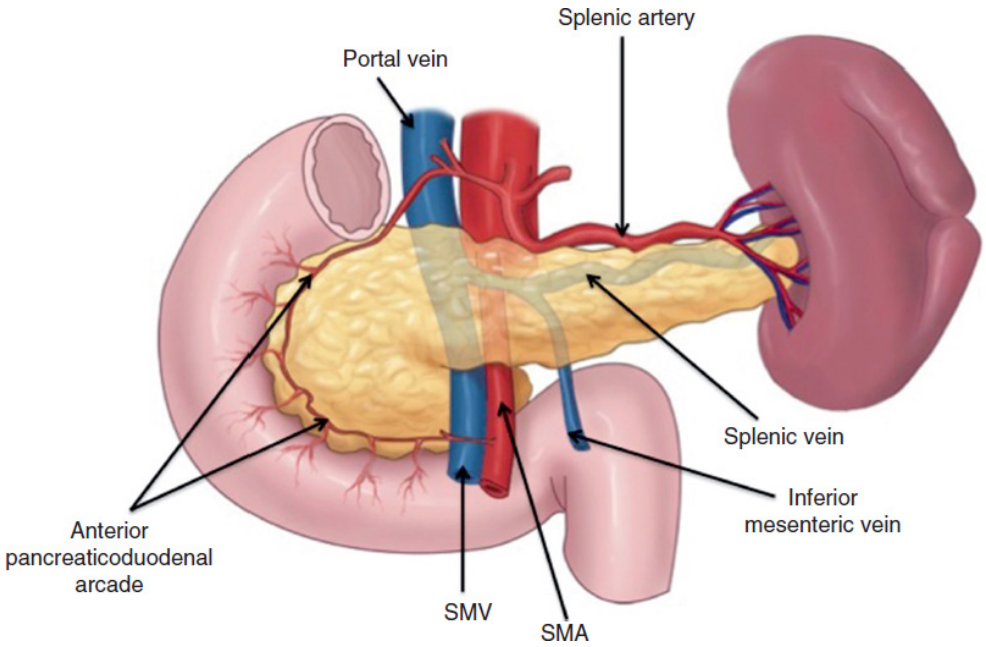

Figure 25.16 Pancreatic anatomy demonstrating relationship to vascular structures and spleen. (With permission from Demetriades D, Inaba K, Velmahos G, eds. *Atlas of Surgical Techniques in Trauma*. New York: Cambridge University Press; 2015.)

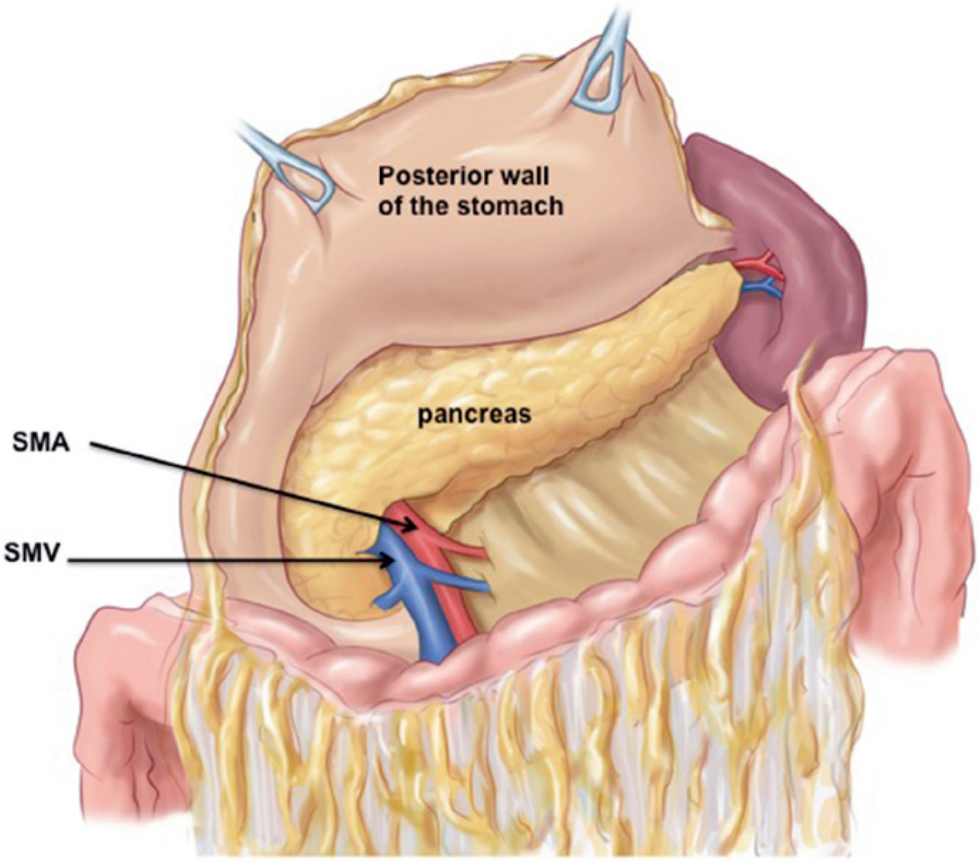

Figure 25.17 Pancreatic anatomy demonstrating relationship to stomach. (With permission from Demetriades D, Inaba K, Velmahos G, eds. *Atlas of Surgical Techniques in Trauma*. New York: Cambridge University Press; 2015.)

Diagnostics

The diagnosis of penetrating pancreatic injury is usually made intraoperatively. The diagnosis in blunt trauma, especially for isolated injuries, may be difficult because the initial symptoms may be occult. Clinical signs may take hours or even days to manifest. Serial serum amylase and lipase levels may be useful as a screening test for pancreatic trauma but isolated values have poor sensitivity and specificity. Contrast-enhanced CT scan (**Fig. 25.18**) is the investigation of choice in suspected pancreatic trauma.[62,63] Its accuracy increases with time from injury and in cases with an equivocal initial test, a repeat CT scan 6 to 8 hours after the initial investigation should be considered. MRCP or ERCP can be considered in

selected cases with pancreatic trauma to establish the integrity of the pancreatic duct.[64,65]

Table 25.3 OIS-AAST Grading Scale for the Pancreas

Grade[a]	Type	Injury Description
I	Hematoma	Minor contusion without duct injury
	Laceration	Superficial laceration without duct injury
II	Hematoma	Major contusion without duct injury or tissue loss
	Laceration	Major laceration without duct injury or tissue loss
III	Laceration	Distal transection or parenchymal injury with duct injury
IV	Laceration	Proximal transection or parenchymal injury involving ampulla
V	Laceration	Massive disruption of pancreatic head

[a]Advance one grade for multiple injuries to the same organ.

Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling, II: pancreas, duodenum, small bowel, colon, and rectum. *J Trauma* 1990;30:1427–1429.

Treatment

The management of pancreatic trauma is determined by the mechanism of injury and the presence or absence of pancreatic duct injury. Many penetrating injuries require operative management. However, most patients with isolated blunt trauma to the pancreas with an intact pancreatic duct can safely be managed nonoperatively.[66,67] Complications associated with

nonoperative management include pancreatic pseudocyst and pancreatitis. A Western Trauma Association Algorithm outlining the management of this injury is available at: https://www.westerntrauma.org/wp-content/uploads/2020/07/WTACriticalDecisionsManagementOfPancreaticInjuries.pdf

For patients undergoing operative management, the pancreas is exposed through the lesser sac. This allows access to the anterior, superior, and inferior surfaces of the body and tail of the pancreas. The posterior aspect of the pancreas can be mobilized by incising the peritoneum over the inferior border of the pancreas and retracting upward. If more extensive mobilization is required for the distal pancreas, this can be achieved by en-block mobilization and medial rotation of the spleen and tail of the pancreas. For the head and uncinate processes, exposure is achieved with an extended Kocher maneuver.

Figure 25.18 CT image of pancreatic transection after blunt trauma. Oval demonstrates the pancreatic transection.

As a general rule, all peripancreatic hematomas should be explored to examine for any underlying ductal injuries.[68] However, hematomas localized to the head of the pancreas may be left undisturbed, because the duct in this

area is deep in the parenchyma and exploration is difficult and potentially dangerous. These injuries should be drained externally with closed drains and postoperatively the integrity of the duct can be evaluated using MRCP or ERCP and treated with stenting.[65]

Low-grade injuries without obvious ductal disruption should be treated with the debridement of nonviable tissue, hemostasis, and wide external drainage. For severe parenchymal injuries with known or suspected ductal disruption, the optimal procedure will depend on the condition of the patient and the site of the pancreatic injury (head and neck vs. tail). Severe pancreatic injuries involving the body to the left of the superior mesenteric vessels are best treated by distal pancreatectomy, with or without splenic preservation (**Fig. 25.19**).[69] For destructive injuries to the head of the pancreas, especially with concurrent duodenal injury, if the operative procedure is to undergo damage control, or if this is beyond the skill set of the operating surgeon, the safest option is hemostasis and external drainage. Damage control packing and temporary abdominal closure with delayed resection and reconstruction can be performed. If, however, a pancreaticoduodenectomy is to be performed, even for hemodynamically stable patients with an experienced surgeon, a two-stage procedure is highly recommended. The initial operation includes temporary control of bleeding by means of packing and in the appropriate cases, arterial shunting or if there is a concomitant venous injury, ligation. The duodenal and pancreatic head resection is performed and the common bile duct is ligated or drained externally. The definitive reconstruction should be performed only after normalization of the patient's physiology. The reconstruction, which includes pancreaticojejunostomy, choledochojejunostomy, and gastroenterostomy, is similar to that in elective cases and should be performed with expert assistance in an optimized patient.

Pancreas-related local complications occur in about 25% of patients and include pancreatic fistulas, pseudocysts, pancreatitis, and perihepatic infection. Most of these complications can successfully be managed nonoperatively or with percutaneous drainage and endoscopic stenting of the duct.[70] Endocrine and exocrine pancreatic insufficiencies may occur after major pancreatic resections, but the incidence of this complication is low.[71]

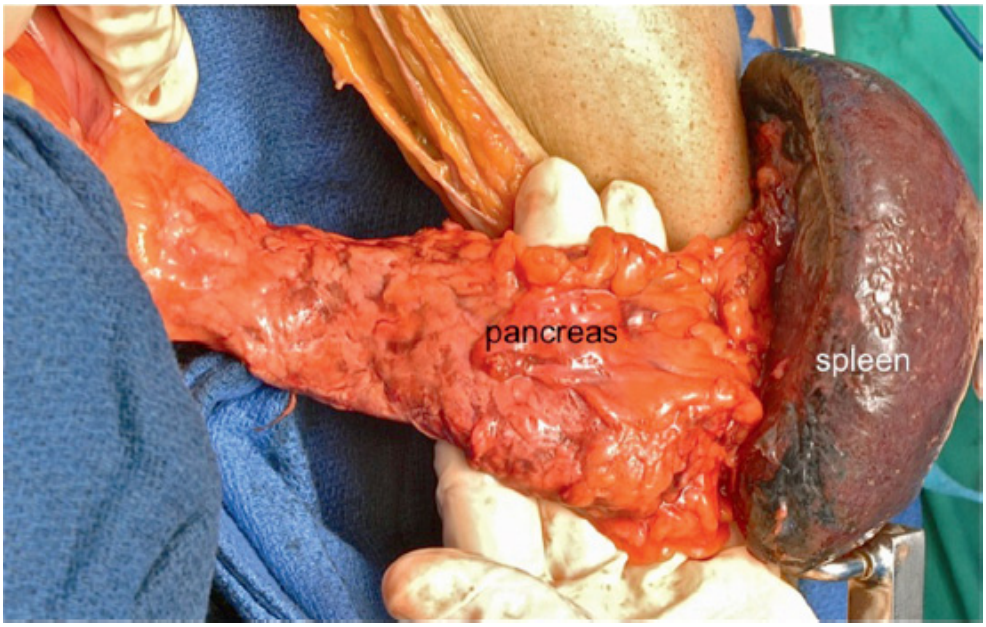

Figure 25.19 Distal pancreatectomy specimen with splenectomy specimen after blunt trauma.

STOMACH

Anatomy

The stomach is a hollow viscus organ located in the left upper quadrant of the abdomen with the fundus, GE junction, and often a significant portion of the body lying above the costal margin. The stomach has a robust blood supply including the left and right gastric arteries, the right and left gastroepiploic arteries, and the short gastric arteries. This level of vascularity can result in significant bleeding after injury but also provides redundancy, making devascularization and necrosis of the stomach relatively rare after trauma.

Diagnostics

Gastric injury usually results from either significant blunt force trauma or after penetrating trauma to the left upper abdomen or lower chest. Presence of blood upon placement of an NG tube is concerning for gastric injury. The majority of patients with full-thickness gastric injury after trauma will

present with spillage of gastric contents and peritonitis resulting in direct transfer to the operating room. Blunt injury to the stomach can cause local contusion with gastric wall hematoma or hollow viscus rupture, similar to bladder rupture, with a large full-thickness defect.

After blunt or penetrating trauma, in the absence of peritonitis or hemodynamic instability, additional diagnostic workup with CT imaging is appropriate. CT scan findings concerning gastric injury include extraluminal contrast, air, blood, or fluid, or localized thickening, or enhancement and discontinuity of the gastric wall.[72–74]

Treatment

Gastric repair is generally well tolerated due to the redundancy of tissue and blood supply of the stomach. After penetrating injury, if a single gastric injury is identified, the operating surgeon must assume there is an additional injury corresponding to the entry or exit site. A single gastric injury is exceedingly rare and even a linear laceration should not be mistaken for a tangential wound unless meticulous inspection has ruled out an additional enterotomy. The anterior border of the stomach is fully inspected from the esophagus to the pylorus. The left lobe of the liver may need to be retracted or mobilized for better visualization of the proximal third of the stomach. The posterior aspect of the stomach is evaluated by accessing the lesser sac below the gastroepiploic vessels. The posterior gastric wall must be fully evaluated and visualized all the way up to the GE junction to avoid missed injury. Blood or fluid upon entry into the lesser sac should alert the surgeon to a likely gastric and/or pancreatic injury. Care must be taken when inspecting the GE junction and greater curvature not to apply excess tension on the gastric fundus as this may result in iatrogenic splenic capsular tear or laceration.

Low-grade injuries including hematomas and contusions should be evaluated and evacuated as appropriate. After hematoma evacuation and hemostasis is achieved, the area may be reinforced with Lembert sutures. Full-thickness injuries can be repaired in one or two layers. A two-layered repair includes an inner layer of running absorbable suture and an outer layer of Lembert sutures. Injuries of the greater curvature or larger injuries of the body can be controlled with a stapling device and wedge resection. In

gunshot injuries, it is important to debride the devitalized tissue surrounding the injury prior to repair. Given the tissue redundancy of the stomach, stapling devices may be used liberally for wedge resection. Care must be taken, however, to avoid narrowing the GE junction or pylorus. Injuries involving the pylorus may be incorporated into a pyloroplasty for repair.

Significant destructive injuries or those involving the GE junction or pylorus may require a proximal or distal gastrectomy with reconstruction. In rare cases, a total gastrectomy with esophagojejunostomy is required. Proximal gastric injuries or those at the GE junction may present a technical challenge for surgeons not accustomed to these operations. Attempts to repair these complex injuries without appropriate experience can lead to significant morbidity and mortality for the patient. In such cases, a two-staged procedure should be considered. At the initial operation, the distal esophagus or proximal stomach may be stapled and internally drained with a nasogastric tube thus controlling the injury in a damage control manner. An additional staple line distal to the injury will prevent reflux contamination. The area may be drained and the patient stabilized with a delayed reconstruction performed under optimal conditions with all of the requisite expertise present.

DUODENUM

Anatomy

The duodenum is the first portion of the small intestine and forms a C-loop around the head of the pancreas. The duodenum is divided into four parts, an anatomic distinction that can help guide management of traumatic injury. The first portion is intraperitoneal and associated with the portal structures and the gastroduodenal artery. The second and third portions are retroperitoneal and curve around the head of the pancreas. The common bile and pancreatic ducts drain into the ampulla in the second portion of the duodenum. The fourth portion of the duodenum ascends to the ligament of Treitz to join the jejunum.

Epidemiology

Duodenal trauma is rare, occurring in less than 5% of all trauma patients, and is associated with a high morbidity and mortality.[75–77] Patients with duodenal trauma frequently have additional intra-abdominal injury, most commonly of the liver, pancreas, and small bowel.

Treatment

Most low-grade duodenal hematomas secondary to blunt trauma without perforation can be managed conservatively with NG tube decompression and supplemental nutrition. The majority of duodenal trauma, however, is secondary to penetrating injury (**Fig. 25.20**) and is identified during operative exploration. Duodenal hematomas encountered intraoperatively require exploration to evaluate for underlying perforation. A Western Trauma Association Algorithm outlining the management of this injury is available at: https://www.westerntrauma.org/wp-content/uploads/2020/07/WTACriticalDecisionsDiagnosisManagementOfDuodenalInjuries.pdf

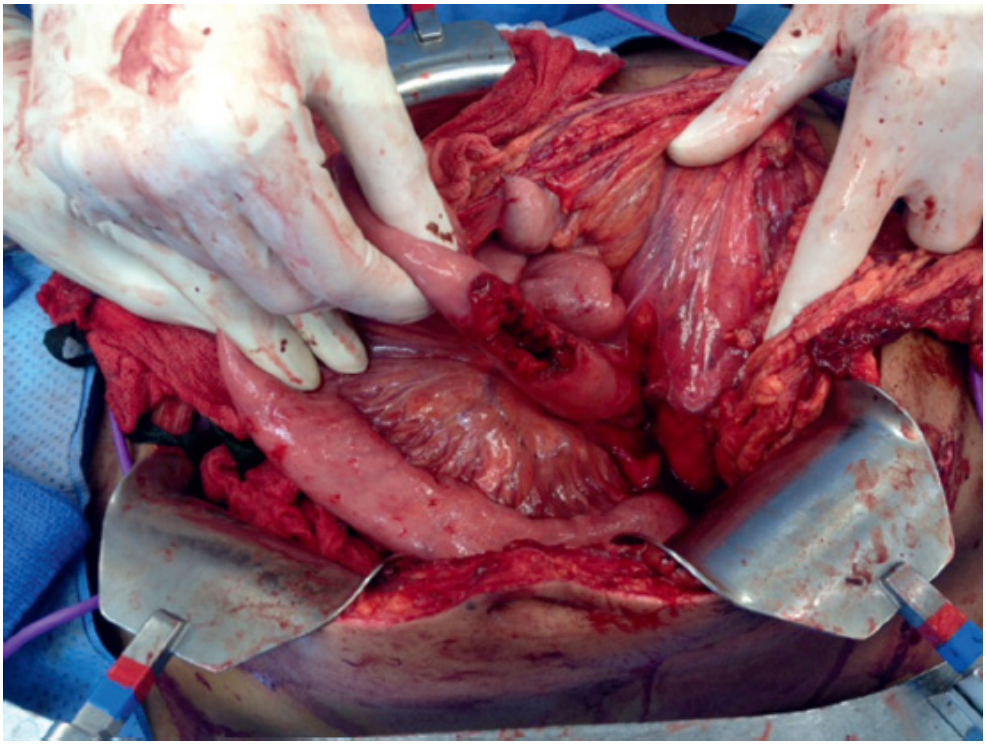

Figure 25.20 Gunshot injury to duodenum just proximal to the ligament of Treitz.

Mobilization of the duodenum is most commonly achieved with a Kocher maneuver. This allows for medialization of the second and third portions of the duodenum, evaluation of the posterior wall, and exposure of the underlying vascular structures to examine for injury. Separation of the second portion of the duodenum from the head of the pancreas is not advised as disruption of the blood supply puts the duodenum at high risk of ischemia.

Most duodenal injuries can be repaired primarily in one or two layers with a transverse closure to avoid luminal narrowing. Segmental resection is rarely needed but, in the event of injury >50% of the duodenal circumference, resection with primary, end-to-end anastomosis may be performed when appropriate. Segmental resection is not recommended for the second portion of the duodenum due to the presence of the ampulla and inability to mobilize the medial wall. In complex injuries, pyloric exclusion with gastrojejunostomy may be utilized to protect the repair, however, routine exclusion should not be used for all duodenal injuries. In an analysis of 193 consecutive patients with duodenal injuries, pyloric exclusion offered no morbidity or mortality benefit over primary repair.[78] If performed, external stapling of the pylorus with a TA stapler and internal cerclage with a suture

are both acceptable techniques for pyloric exclusion. Most frequently, a gastrojejunostomy to restore continuity is performed. Additional surgical adjuncts include a serosal patch and duodenojejunostomy. In the unstable patient, damage control techniques may be safely applied to duodenal injury with delayed repair or diversion.[79] The traumatic Whipple is rarely indicated and carries a high mortality.[80,81] This should be considered only in patients with complex destructive injuries to the duodenum and pancreas, as discussed above.

One of the major complications after duodenal injury repair is fistula formation, occurring in 4% to 33% of patients.[76,79,82] These are managed, when possible, with percutaneous drainage. In rare cases, reoperation and repair or diversion is required.

COLON

Epidemiology

Colon injuries occur in approximately 30% of abdominal GSWs and 20% of SWs undergoing laparotomy. In blunt trauma, approximately 10% of patients undergoing laparotomy will have a colon injury. Many of the blunt trauma injuries are superficial with only 3% of patients undergoing laparotomy having a full-thickness perforation. The presence of an external seatbelt mark sign is associated with an increased risk of colon injury.

Diagnostics

The definitive diagnosis of colon injury is almost always made intraoperatively. Preoperative diagnosis of colon injury following blunt trauma is difficult, especially in unevaluable patients. If a CT is obtained, mesenteric stranding, bowel wall thickening, and unexplained fluid can be seen, increasing the level of suspicion for a bowel perforation. Free extraluminal air is rare. Intraoperatively, all colonic hematomas should be explored to rule out any underlying colon injury without devascularizing the wall. Particular care should be taken for penetrating injuries, especially due to shotgun wounds, where the injury can be hidden within the fat.

The severity of colon injury can be graded by the OIS-AAST colon injury scale (**Table 25.4**), which is based on the operative findings.[44] A practical classification used by many surgeons breaks injuries down into two severity groups, nondestructive injuries involving <50% of the bowel wall without devascularization versus destructive injuries which involve >50% of the bowel wall or demonstrate devascularization.

Table 25.4 OIS-AAST Grading Scale for the Colon

Grade[a]	Type	Injury Description
I	Hematoma	Contusion or hematoma without devascularization
	Laceration	Partial thickness, no perforation
II	Laceration	Laceration <50% of circumference
III	Laceration	Laceration ≥50% of circumference without transection
IV	Laceration	Transection of the colon
V	Laceration	Transection of the colon with segmental tissue loss
	Vascular	Devascularized segment

[a]Advance one grade for multiple injuries to the same organ.

Moore EE, Cogbill TH, Malangoni MA, et al. Organ injury scaling, II: pancreas, duodenum, small bowel, colon, and rectum. *J Trauma* 1990;30:1427–1429.

Treatment

The management of colon injuries has undergone major changes over the last two decades.[83–85] For nondestructive injuries there is sufficient class I and class II evidence supporting primary repair irrespective of risk factors, such

as the site of colon injury, associated injuries, or physiologic status.[86–88] A Western Trauma Association Algorithm outlining the management of this injury is available at: https://www.westerntrauma.org/wp-content/uploads/2020/07/WTACriticalDecisionsManagementOfColorectalInjuries.pdf

For destructive colon injuries, defined as those with loss of >50% of the bowel wall circumference or with devascularization, segmental colonic resection is required. The management of these cases is controversial. These injuries were traditionally managed with diversion because of the perceived high risk for anastomotic leak and intra-abdominal sepsis. Although the safety of primary anastomosis was demonstrated in several small studies,[86–88] for specific circumstances such as a penetrating abdominal trauma index ≥25 or hypotension or large-volume blood transfusions or patient comorbidities, the potential benefit of diversion remains unclear.[88,89]

The Eastern Association for the Surgery of Trauma (EAST) guidelines based largely on class III evidence recommended that diversion be considered in patients with shock, significant associated injuries, peritonitis, or underlying disease.[90] Since these were published, a more recent American Association for the Surgery of Trauma prospective multicenter study examined 297 patients with penetrating colon injuries requiring resection.[91] This was a prospective observational study examining the outcomes associated with diversion versus primary anastomosis without diversion. The overall colon-related mortality was 1.3% and all deaths occurred in the diversion group. The incidence of anastomotic leaks was 6.6%. Multivariate analysis identified severe fecal contamination, >4 units of blood transfusions within the first 24 hours, and antibiotic choice as independent risk factors for abdominal complications. The method of colon management, anastomosis, or diversion did not impact outcomes. For both blunt and penetrating destructive injuries, if the patient meets criteria for a damage control procedure, contamination control with stapling of the colon should be performed. Whenever possible, an anastomosis should be performed at the index operation. The choice of a stapled versus hand-sewn anastomosis has been shown not to make a difference.[92] In a prospective study of 207 patients undergoing resection and anastomosis, the leak rate was 7.8% for hand-sewn and 6.3% for stapled anastomoses. For edematous bowel, often seen at the

take back after an initial damage control resection, a hand-sewn anastomosis may be preferred.

Abdominal complications after colon injuries are common, with an abdominal sepsis rate of approximately 20%. Retained bullets that have passed through the colon are not associated with an increased risk of infection and therefore their routine removal is not required.[93]

Colonic leaks causing abdominal sepsis after repair or resection and anastomosis have been examined in detail. For primary repairs, in a review of 35 prospective or retrospective studies including 2,964 primary repairs, a leak rate of 2.2% was seen.[94] For patients undergoing resection and anastomosis, which are more likely to leak, the rate was 5.5%.[94] Anastomotic leaks occur more commonly with a colon–colon anastomosis when compared to an ileocolic anastomosis.[91]

The majority of leaks can be managed nonoperatively with percutaneous drainage. They are usually small and seal off on their own. CT imaging should be obtained to examine for the presence of any intra-abdominal collections and to guide drainage. Reexploration of the abdomen for drainage and either fecal diversion or resection and reanastomosis is only required if the patient fails percutaneous drainage or develops evidence of generalized peritonitis.

For patients who require a colostomy, there is a significant complication burden associated with the colostomy itself as well as the subsequent closure. In a large series of 528 stomas performed in the trauma setting, approximately 22% of patients sustained an early complication and 3% a late complication.[95] In another study of 110 colostomy closures, a local complication rate of 14.5% was noted.[96]

RECTUM

Anatomy

As the colon continues downstream, the rectum begins where the tenia coli coalesce as the terminal part of the large intestine. The rectum is approximately 12- to 15-cm long and is both intra- and extraperitoneal. Anteriorly, the upper two-thirds and laterally the upper one-third are

intraperitoneal, with the lower third being completely extraperitoneal. The blood supply is derived from the superior rectal artery branching from the inferior mesenteric artery, the middle rectal artery from the internal iliac artery, and the inferior rectal artery which is from the internal pudendal artery.

Epidemiology

Most rectal injuries result from a penetrating mechanism, usually secondary to GSWs although anally inserted foreign body trauma and endoscopic trauma are also seen. Because of its protected location, blunt injury is only seen in approximately 5% to 10% of injuries, and is often associated with a pelvic fracture.

Diagnostics

The clinical presentation of rectal injuries that are intraperitoneal does not differ from that of colon injuries. For extraperitoneal injuries, the clinical symptomatology can be masked by containment of the perforation in the retroperitoneal tissues. As a direct consequence, operative exploration, direct visualization on anoscopy and sigmoidoscopy, or CT rather than clinical examination is used to make the diagnosis.

For blunt trauma patients, because the majority of injuries are in the intraperitoneal segment, the same diagnostic principles for colonic injuries apply. For penetrating injuries, both intraperitoneal and extraperitoneal injuries can occur. The diagnostic approach depends on the patient's clinical presentation. Patients with peritonitis, instability, or who are unexaminable should proceed directly to the operating room. For unstable patients, positioning should be supine with an emphasis on the laparotomy and hemorrhage control. Intraoperative sigmoidoscopy and anoscopy can be performed to examine the extraperitoneal segment of the rectum. For those that have peritonitis or instability, the patient may be placed in lithotomy to facilitate sigmoidoscopy and anoscopy. For those who are stable and who meet the criteria for a trial of nonoperative management, the highest-yield initial examination is CT (**Fig. 25.21**). On the CT, the bullet trajectory is tracked. If the trajectory appears to traverse the rectum, the patient can be

brought to the operating room for laparotomy, sigmoidoscopy, and anoscopy. If the tract is clear of the rectum on CT, no further investigations or treatment is required. For the equivocal CT scan where there is a questionable rectal injury, several options exist. The patient can be brought to the operating room for a laparotomy, sigmoidoscopy, and anoscopy. Another option is to perform diagnostic laparoscopy to look for intraperitoneal breach as well as a sigmoidoscopy and anoscopy. Any entry into the peritoneal cavity can then trigger a laparotomy and closer evaluation.

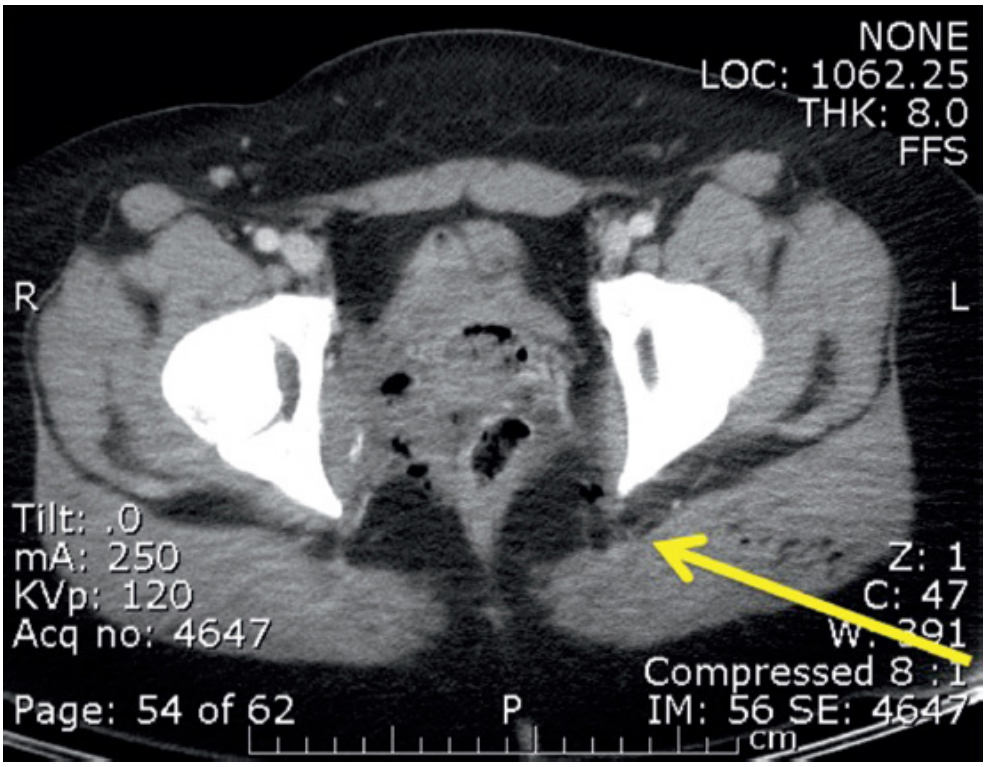

Figure 25.21 CT demonstrating a gunshot wound tract traversing the rectum, *arrow* demonstrates bullet tract.

For intraperitoneal injuries, the management principles are the same as those that apply to colon injuries. The vast majority undergo primary repair without the need for diversion. For extraperitoneal injuries, the management has evolved over the last decade. The classic approach to rectal injuries which included diversion, presacral drainage, and distal rectal washout is no longer performed.[97–106]

For distal extraperitoneal injuries that are accessible through a transanal approach, local repair can be performed without colostomy.[99,105,106] For

higher extraperitoneal injuries inaccessible in this manner, the most common treatment is fecal diversion without taking down the rectum and repairing the injury.[103,104] This can even be done laparoscopically with a low rate of morbidity. The absolute need for colostomy, however, has never been demonstrated.

Figure 25.22 Large perineal and groin avulsion injury after pedestrian struck by train.

If there is an associated bladder injury, a tissue barrier using omentum should be placed between the suture lines as a method of decreasing rectovesical fistula formation, a complication seen in upward of a quarter of patients with combined injuries.[107] In the rare case where there is a combined destructive anorectal injury (**Fig. 25.22**), acutely, hemostasis and diversion are recommended. Once the patient has been stabilized, assessment of the anal sphincter function should be performed, and semielective reconstruction should be performed by a colorectal specialist.

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26

Genitourinary Trauma

Bradley A. Rittenhouse and Martin Schreiber

Key Points

1. Hematuria is the most sensitive indicator of genitourinary trauma, but the absence of hematuria is insufficient to rule out a genitourinary injury.
2. Renal injuries in hemodynamically stable patients can most often be treated nonoperatively and this often reduces the need for nephrectomy.
3. Genitourinary injuries can result in multiple complications including abscess, sepsis, urine leak, stricture of urethra or ureter, hypertension, and renal insufficiency.
4. CT scan is the primary modality for evaluating genitourinary injuries. It must include a delayed phase to evaluate the renal collecting system and ureter and a cystogram to evaluate the bladder if indicated.
5. Intraperitoneal bladder injuries require repair, while many extraperitoneal bladder injuries can be managed nonoperatively with Foley catheter drainage.
6. Urethral injuries are most commonly associated with pelvic fractures and are evaluated with a retrograde urethrogram.

Trauma produces a high healthcare burden both in the United States and throughout the world. As of 2017, unintentional injuries are the leading cause of death for people 1 to 44 years of age, and road traffic deaths alone are the eighth leading cause of death worldwide.[1,2] The genitourinary system is infrequently injured in isolation, but it is involved in 10% of all abdominal trauma.[3–5] These injuries are rarely life threatening alone, but they contribute to significant morbidity. Multiple organizations have guidelines for the evaluation and management of injuries to the genitourinary system including the American Urological Association, European Association of Urology, and the Société Internationale d'Urologie. These recommendations as well as recent updates are reviewed to provide an efficient organized method to evaluate genitourinary injuries in the trauma patient.

KIDNEY

Evaluation

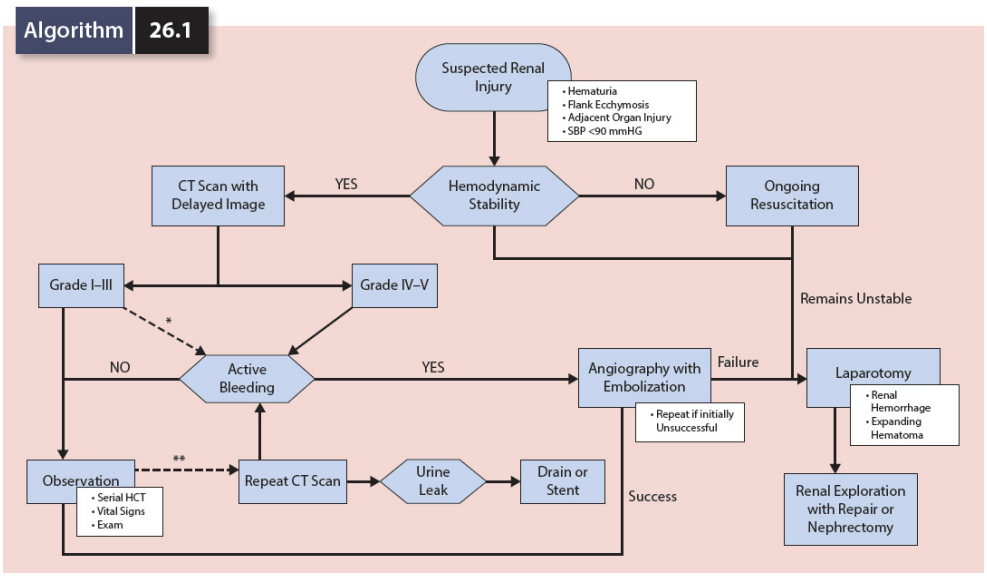
1 Renal injuries are the most common genitourinary injuries. These injuries most often result from blunt mechanisms including road traffic accidents and falls.[6,7] The kidney lies within the rib cage in the retroperitoneum surrounded by perinephric fat and encapsulated in Gerota's fascia. It is associated with adjacent anatomic structures including the liver; adrenal; duodenum and colon on the right; and the spleen, adrenal, and colon on the left. Within the kidney, the collecting system begins with the renal pelvis which then becomes the ureter as it leaves the kidney at the ureteropelvic junction (UPJ). The ureter remains in the retroperitoneum traversing along the psoas muscle crossing the common iliac vessels to enter the pelvis. Injuries result from crush or impact to the renal parenchyma or collecting system from external impact as well as impact against the nearby ribs. Also, deceleration injuries from the kidney's fixation at the renal pelvis and vasculature can result in avulsion injuries. History and physical findings that suggest renal injury includes a direct blow to the flank, lower rib fractures, injury to liver or spleen, flank hematoma or ecchymosis, hematuria, or a penetrating wound to the flank. As with any trauma patient, ensuring hemodynamic stability is paramount before proceeding to additional diagnostic testing. In hemodynamically stable patients with concern for renal injury, **Algorithm 26.1** provides an algorithm for evaluation.[5,8,9]

Hematuria is the most sensitive indication of renal injury, but the amount of hematuria is not indicative of the severity of injury and false-negative rates are as high as 30%.[8,10,11] The primary method for evaluation of renal injuries is the CT scan. The ideal protocol to evaluate for renal injuries is a three phase contrast CT scan with an arterial phase to evaluate for active extravasation, a venous or nephrographic phase to evaluate the renal parenchyma, and a 5-minute delayed phase to evaluate the collecting system. However, a significant number of trauma patients will have a contrast-enhanced CT scan as part of their initial evaluation for intra-abdominal trauma. The addition of a delayed phase (5 to 10 minutes) scan is effective for evaluating renal injury including the collecting system.[5,8] CT imaging provides a basis for grading the severity of injury. The American Association

for the Surgery of Trauma (AAST) organ injury scale (OIS) is the most commonly used grading system, and the recent update in 2018 combines, imaging, operative, and autopsy findings (**Table 26.1**).[12] A single-shot intravenous pyelogram may be used if CT is unavailable or to verify the presence of the contralateral kidney if laparotomy is performed without a CT. MRI offers no benefit over CT, has increased logistical challenges, and is not recommended.[5,8]

Treatment

2 AAST grading provides a basis for treatment decisions. Grade I and II injuries generally do not require additional treatment. Blunt grade III and IV injuries can often be managed nonoperatively, and some grade V injuries are managed through angiography and drainage instead of operative exploration (**Fig. 26.1**). Penetrating injuries are more often treated operatively and are more likely to result in nephrectomy. However, nonoperative management is safe to use in a selected group of stable patients.[13,14] As the availability and sophistication of angiography and less invasive drainage of hematoma and urinoma have increased, high-grade injuries are more frequently treated with less invasive interventions (**Fig. 26.2**). The primary indications for angiography are active bleeding, pseudoaneurysm, and vascular fistula.[15] Patients who are hemodynamically stable and have high-grade injuries defined as grades III–V can be managed nonoperatively in up to 80% of cases without increased hospital stay or complications.[9,16] However, if open exploration is required, nephrectomy is the most common outcome with nephrectomy rates of 0.4% to 4.5% in grade III, 15% to 24% in grade IV, and 57% to 62% for grade V injuries.[17–20]



Algorithm 26.1 Evaluation of renal trauma. *Grade III with active extravasation is frequently self-limited. **Grade IV–V should have routine repeat CT scan at 48 hours. Grade I–III routine repeat CT is not recommended, but should be performed selectively.

Table 26.1 AAST Grading of Injuries to Urologic Structures

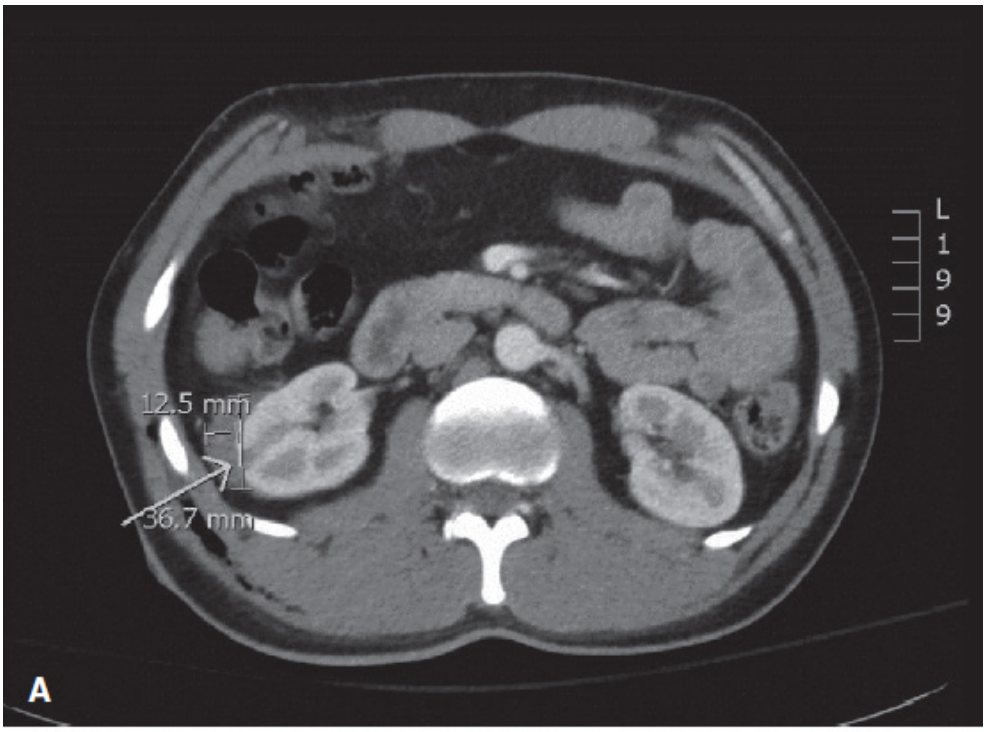
Injured Structure	AAST Grade	Description of Injury
Kidney	I	▪ Subcapsular hematoma/contusion without laceration
	II	▪ Laceration <1 cm in depth without collecting system involvement ▪ Perinephric hematoma within Gerota's fascia
	III	▪ Laceration >1 cm in depth without collecting system involvement ▪ Active bleeding or vascular injury within Gerota's fascia
	IV	▪ Urine extravasation from laceration ▪ Laceration of renal pelvis or ureteropelvic disruption ▪ Injury to segmental artery or vein/segmental infarct ▪ Active bleeding outside Gerota's fascia
	V	▪ Shattered kidney

		▪ Avulsion or devascularization at renal hilum
Ureter	I	▪ Contusion or hematoma without devascularization
	II	▪ Laceration with <50% transection
	III	▪ Laceration with >50% transection
	IV	▪ Complete transection with <2 cm of devascularization
	V	▪ Avulsion/Laceration with >2 cm of devascularization
Bladder	I	▪ Contusion, intramural hematoma ▪ Partial thickness laceration
	II	▪ Extraperitoneal bladder wall laceration <2 cm
	III	▪ Extraperitoneal laceration >2 cm ▪ Intraperitoneal laceration <2 cm
	IV	▪ Intraperitoneal laceration <2 cm

	V	▪ Laceration of involving bladder neck or ureteral orifice
Urethra	I	▪ Contusion with blood at urethral meatus, RUG normal
	II	▪ Stretch with elongation of urethra without extravasation
	III	▪ Partial disruption with contrast extravasation at injury site and within bladder
	IV	▪ Complete disruption with contrast extravasation at injury site and none progressing to bladder <2 cm of urethral separation
	V	▪ Complete disruption >2 cm ▪ Extension of disruption into the prostate or vagina

If injuries are bilateral, increase one grade up to III (in table refers to kidney and ureter).

If there are multiple injuries in one organ, use the highest grade (in table refer to kidney, ureter, bladder and urethra).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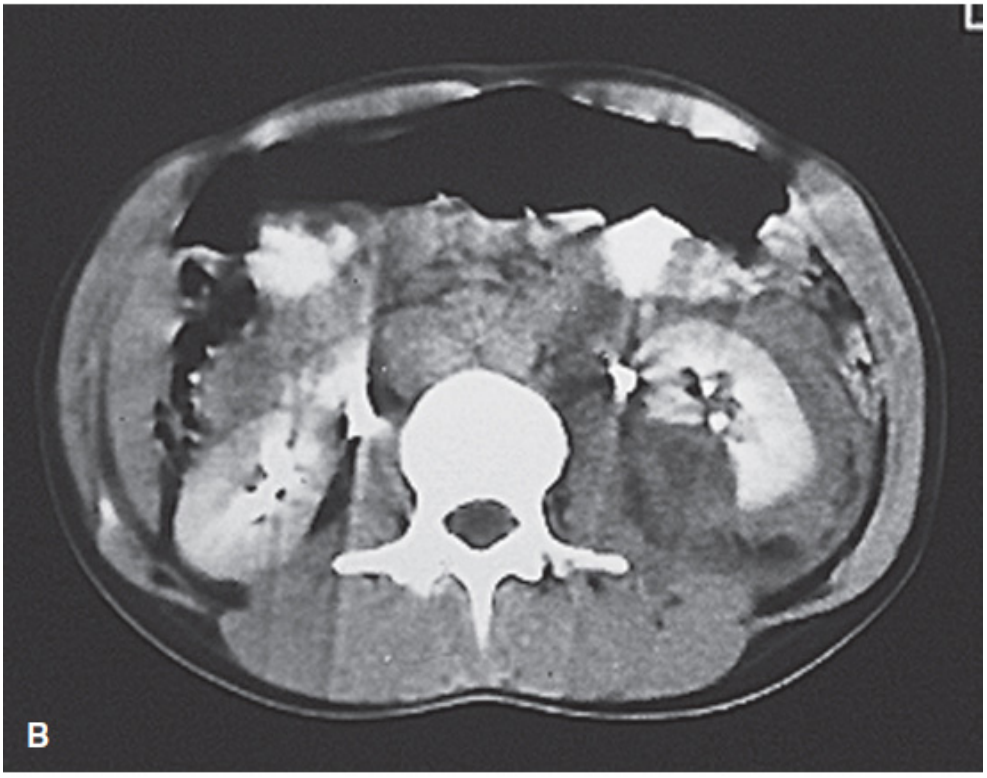
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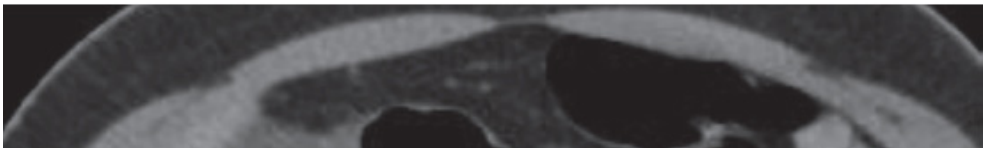


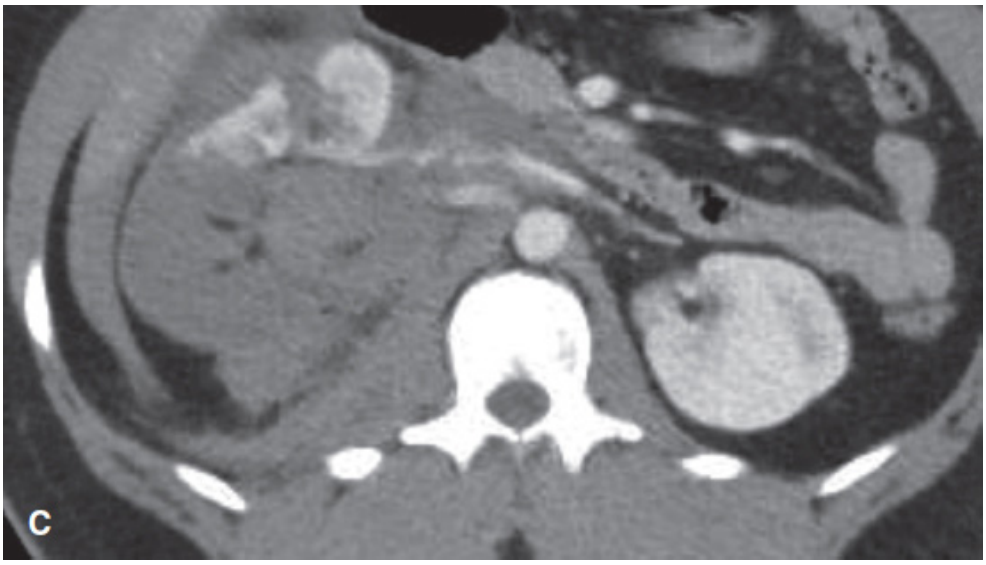


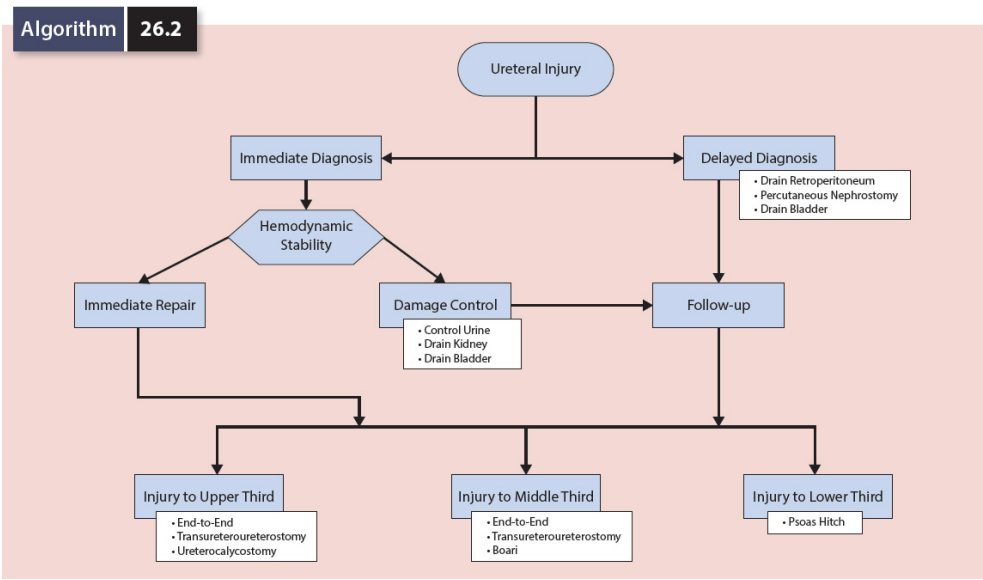
Figure 26.1 CT scan of renal injuries. **A:** Grade I. **B:** Grade III. **C**: Grade V.

Should operative exploration be required, the kidney and upper urinary tract is accessed through an upper midline incision. Prior to exploring the kidney, proximal control of the renal vasculature can be obtained by creating a window in the posterior peritoneum medial to the inferior mesenteric vein (IMV). This allows isolation of the renal vasculature.[21] However, if rapid access is required, mobilization of the right or left colon will allow access to the kidney and the hilum and allow compression of the kidney and control of the vasculature to stop exsanguinating hemorrhage.[22] The kidney may be explored following identification and opening of Gerota's fascia. Nonviable renal tissue is debrided sharply, preserving the capsule for closure. The collecting system is repaired at this time. Finally, the capsule is closed using absorbable suture. A drain is placed in the retroperitoneum away from the repair and is removed once drainage has decreased. If the volume remains high, the drain fluid is sent for a creatinine level to determine the presence of urine. Vascular injuries of the kidney often require nephrectomy. Left renal vein injuries may be ligated due to collateral drainage through gonadal and lumbar veins; however, this is not the case on the right side and the right renal vein must be repaired or a nephrectomy performed.

Complications

3 Early complications within 1 month include perinephric abscess, urinary extravasation, and urinary fistula. Delayed complications can include hydronephrosis, pseudoaneurysm formation, calculus formation, and hypertension. Hypertension may result acutely from external compression due to perirenal hematoma (Page kidney). Hypertension may also develop in a delayed manner through compressive scar formation, renal artery thrombosis, or renal artery stenosis (Goldblatt kidney). Hypertension from renal trauma is a rare complication but is initially treated medically with ACE inhibitors; however, it may require interventions to drain perinephric hematomas or even nephrectomy if hypertension cannot be controlled.[4,23]

Figure 26.2 Angiogram of grade V renal injury.



Algorithm 26.2 Evaluation of ureteral injury.

URETER

Evaluation

4 Ureteral trauma is rare due to the small size and relative mobility of the ureter. Injury to the ureter accounts for only 1% to 2.5% of urinary tract trauma. Penetrating injuries frequently occur due to gunshot wounds and blast injuries with most blunt injuries associated with pelvic fractures.[24–26] The diagnosis of penetrating ureteral injuries is most often made at laparotomy and should be suspected when nearby structures are damaged including the psoas muscle, kidney, colon, etc. The diagnosis of blunt injuries is more difficult and may be delayed. This injury requires a high index of suspicion with multiple intra-abdominal injuries to nearby, or mechanisms with hyperextension that may avulse the ureter at the UPJ. Hematuria is a poor indication of injury.[5,27,28] Contrast-enhanced CT scan with delayed imaging is the evaluation of choice. In addition to extravasated contrast on the delayed images, unilateral ureteral dilation, urinoma, or ascites may be indications of injury. Exploration is recommended if laparotomy is required for other injuries. Retrograde urography may be performed if the diagnosis is unclear.[5,7,8] Delayed presentation with fever, flank pain, tenderness

atelectasis, urinoma, hematoma, or oliguria is evaluated in a similar manner with contrast-enhanced CT scan (**Algorithm 26.2**).

Treatment

The management of ureteral trauma is operative repair in most instances. Grading is based upon the AAST system (**Table 26.1**). The ureters begin at the renal hilum. They course through the retroperitoneum along the psoas muscle. Entering the pelvis, they course behind the gonadal vessels and over the lilacs to enter the inferior aspect of the bladder. The blood supply is segmental along their course. Patients with ureteral injuries primarily require laparotomy for other associated injuries. During this exploration, the ureter should be examined for injury and viability. In the hemodynamically stable patient, ureteral injuries should be repaired at the index operation.[5,8] The type of repair depends on the location of injury and amount of tissue destruction. **Figure 26.3** demonstrates anatomic considerations for type of repair and **Figure 26.4** describes the techniques utilized.

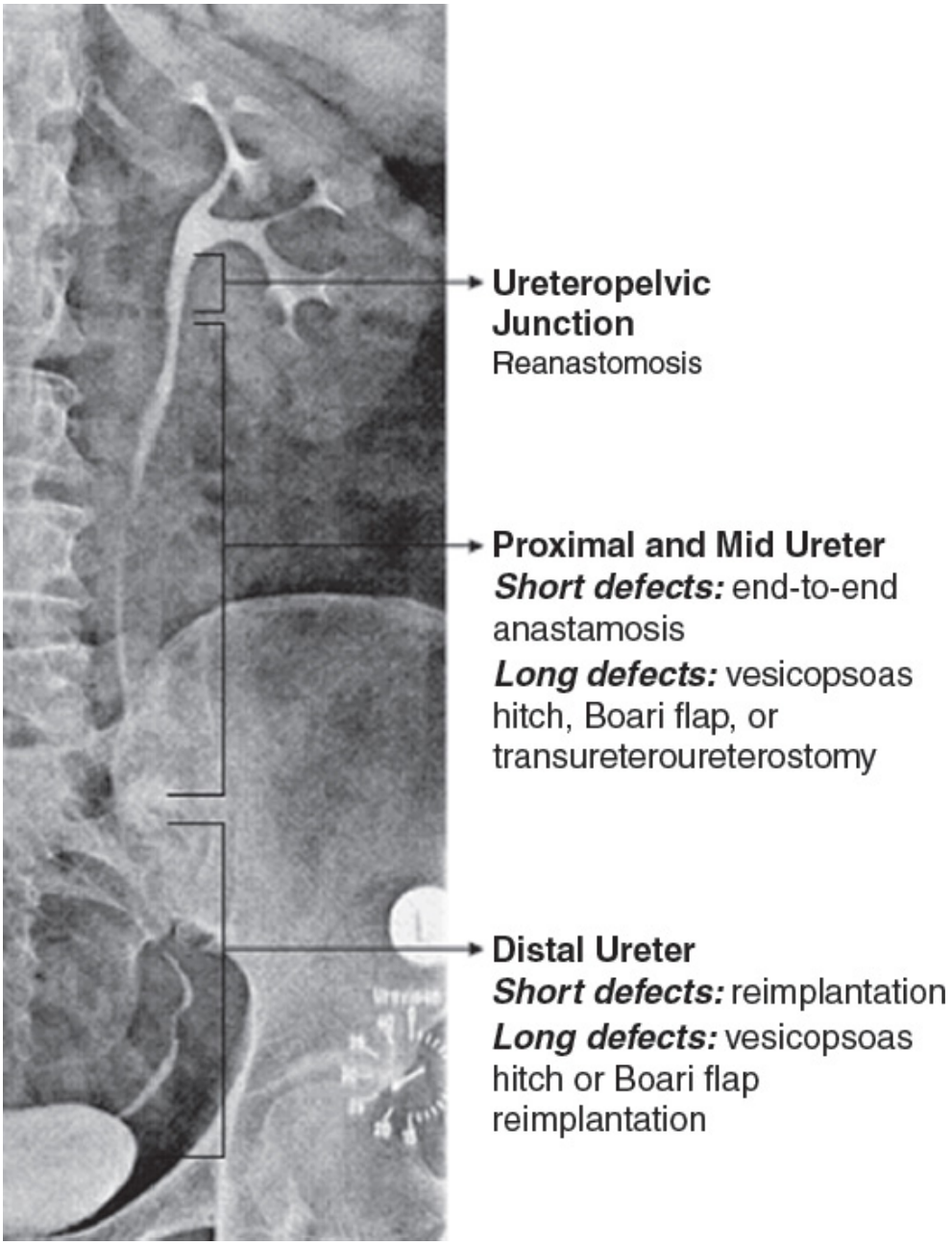


Figure 26.3 Locations of ureteral injury.

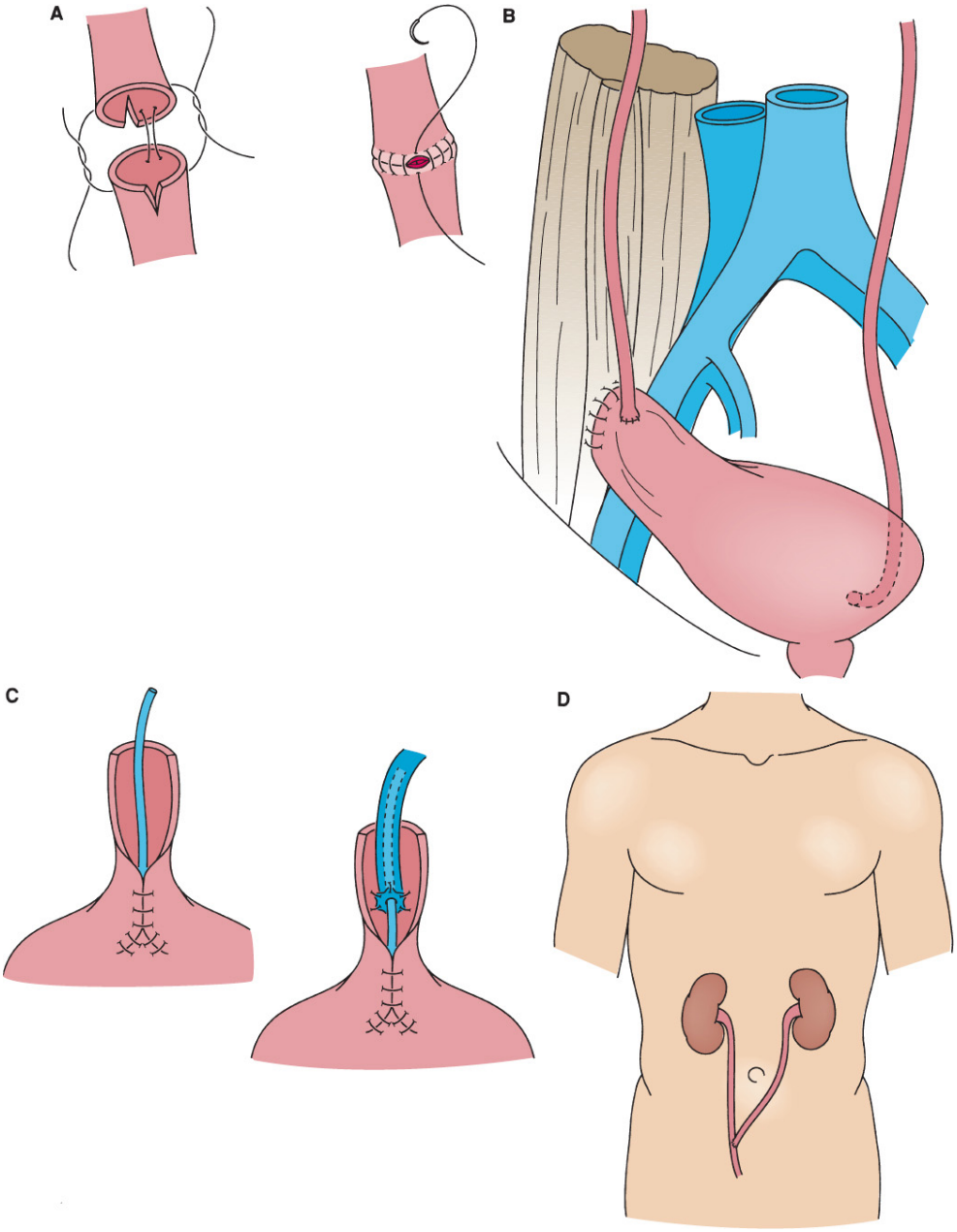


Figure 26.4 Techniques of ureteral repair. **A:** End-to-end ureteroureterostomy. **B:** Vesicopsoas hitch reconstruction with reimplantation performed by suturing of the bladder to psoas tendon after mobilization. **C:** Boari flap performed using a tubularized bladder flap based on the ipsilateral superior vesical artery. **D:** Transureteroureterostomy (TUU). For all repairs, the principles include tension free, watertight, stented, spatulated, mucosa-to-mucosa anastomosis using absorbable suture with drain placement.

In a hemodynamically unstable patient, repair of the ureter is not recommended, given the time required and the risk of ischemia. However,

control of urine is needed. This may be accomplished by draining the retroperitoneum and bladder, ligation with percutaneous nephrostomy or diversion utilizing a drainage tube placed into the injured ureter.

Patients who present in a delayed manner should not undergo operative intervention as this often results in nephrectomy.[29] These patients are initially treated with urinary diversion utilizing stenting, percutaneous nephrostomy, percutaneous drainage of the urinoma, and Foley catheter placement. After 3 to 6 months and resolution of the inflammatory response, reconstruction can be undertaken. Sequelae of these delayed diagnoses can include fistulae, stricture, infection, and obstruction. Patients who have sustained a high-grade ureteral injury should have repeat imaging with ultrasound, radio nucleotide scan, or CT urography to evaluate for stricture or urinoma.

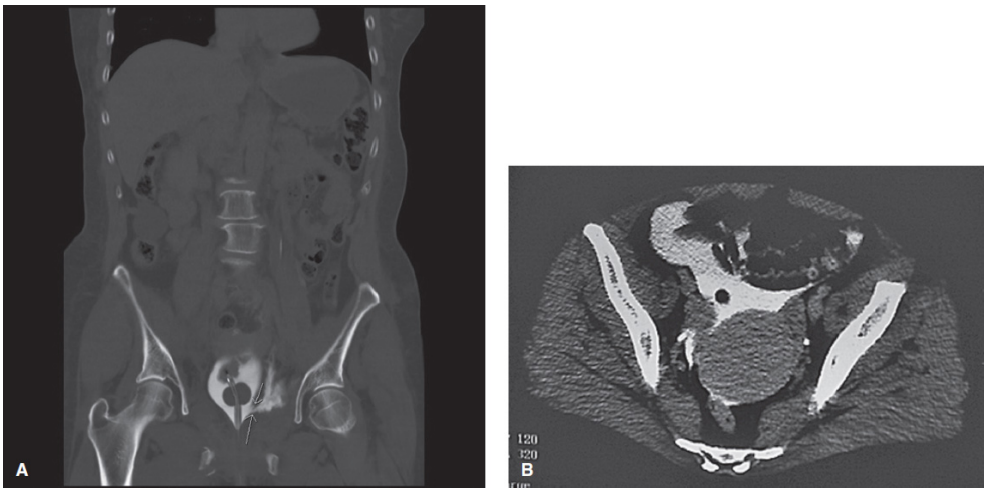


Figure 26.5 CT cystogram with bladder injury. **A**: Extraperitoneal bladder rupture. **B**: Intraperitoneal bladder rupture.

BLADDER

Evaluation

Most bladder injuries result from blunt trauma including motor vehicle crashes and falls. Pelvic fracture is associated with 60% to 90% of these injuries, and other abdominal organ injuries occur in 55% to 68%. However, less than 10% of pelvic fractures have associated urogenital injuries.[8,30,31] Bladder injuries are characterized as either extraperitoneal or

intraperitoneal. Extraperitoneal injuries are associated with pelvic fractures. The mechanism can be from deceleration causing shearing at the attachments of the bladder as well as direct injury from bony fragments. The highest risk for bladder injuries occurs with pelvic ring fractures and >1 cm of displacement.[5,32,33]

Gross hematuria occurs in greater than 90% of bladder ruptures. The presence of gross hematuria with pelvic fracture has a greater than 30% incidence of bladder injury and mandates evaluation.[5,34] In patients without pelvic fractures, evaluation for bladder injury should be strongly considered with gross hematuria and a mechanism that is high risk for bladder injury such as high impact lower abdominal injury, inability to void, imaging consistent with urinary ascites, or uremia.[4,5,8]

Imaging of the bladder is performed with retrograde cystography (**Fig. 26.5**). Either CT cystography or plain film cystography is acceptable.[5,8,35,36] However, CT cystography may be better at identifying bony fragments in the bladder as well as bladder neck injuries.[8] This involves instilling 300 to 350 mL of contrast into the bladder through a Foley catheter and then obtaining images. Simply clamping the Foley catheter during the standard trauma CT scan is inadequate to rule out bladder rupture.[36] Intraperitoneal injuries are identified by visualizing free flow of contrast material into the abdomen where it outlines bowel loops and intra-abdominal organs. Extraperitoneal bladder injuries produce more localized extravasation of contrast that is often described as flame shaped.

Treatment

5 Extraperitoneal bladder rupture is treated with Foley catheter drainage of the bladder for at least 2 to 3 weeks to allow the injury to heal. This observation period is typically followed by repeat cystogram to ensure healing. Complicated extraperitoneal bladder rupture which includes the presence of boney shards within the bladder, concomitant rectal or vaginal injuries should be repaired surgically. Also, repair may be required for injuries to the bladder neck or when internal fixation of pelvic fractures is performed.[4,5,34]

Intraperitoneal bladder injuries must be explored and repaired. The size of these injuries and risk of peritonitis preclude nonoperative treatment.[4,5,8,30]

Bladder exploration includes assessment of the bladder wall as well as the ureteral orifices and bladder neck. These structures are assessed through an anterior cystotomy or the injury itself. Injuries are closed in two layers using a running absorbable suture. Foley catheter drainage following repair is sufficient in most cases. Closed suction drains are placed away from the repair and may be removed in 48 hours unless there is a high volume of fluid that has a creatinine level greater than serum. The urethral catheter can be removed in 7 to 10 days with repeat cystogram.[4,5,8,30]

URETHRA

Evaluation

6 Urethral injuries are most commonly the result of blunt trauma and much more common in males than females. The male urethra can be divided into anterior and posterior portions. Injuries to the anterior portion can result from straddle mechanism or perineal kicks causing compression against the pubic symphysis. Posterior injuries are associated with pelvic fractures. Blood at the urethral meatus in men warrants evaluation with a retrograde urethrogram. Other signs that are suggestive of urethral injury include inability to void with a distended bladder, pain or hematuria, or difficulty/inability to pass a urethral catheter. Also, a rectal examination should be performed to rule out concomitant rectal injury and a "high-riding prostate" may be identified, although this is unreliable.[4,5,8,31] If there is concern for an injury, a retrograde urethrogram should be performed prior to the placement of a urethral catheter. Retrograde urethrography (RUG) is performed by instilling 20 to 30 mL of contrast into the urethra while occluding the meatus. An x-ray is then taken at a 30-degree oblique angle. Any contrast extravasation from the urethra is indicative of an injury (**Fig. 26.6**).[5,32,34] Flexible cystourethroscopy is helpful to differentiate between partial and complete injury, and is preferred with penile fracture as a RUG can be falsely negative in this setting.[8,34,37,38]

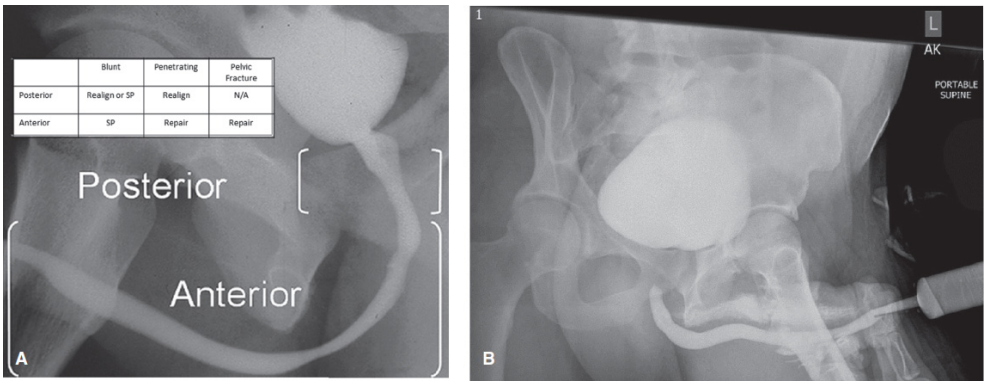


Figure 26.6 Retrograde urethrogram. **A**: Normal. **B**: Partial injury. (Demonstrated by contrast in corpus cavernosum and incompletely opacified posterior urethra.)

Treatment

In hemodynamically stable patients, primary realignment may be attempted. This consists of urethroscopy and fluoroscopy to pass a wire across the injury and then placement of a urinary catheter over the wire. If this is unsuccessful, suprapubic urinary drainage may be performed. Care must be taken as pelvic trauma may distort the normal location of the bladder and ultrasound should be utilized to assist with placement if available. Early realignment may decrease the risk of stricture from nearly 80% to 45% without increased risk of incontinence (5%) or erectile dysfunction (20%).[8,39,40] If realignment is not possible, urethral injuries are repaired in a delayed fashion when swelling and hematomas have decreased. Uncomplicated penetrating injuries should be repaired promptly. However, with associated injuries or high-energy destructive injuries, suprapubic drainage with delayed reconstruction is appropriate.[4,5,8]

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27

Vascular Trauma

Kendal M. Endicott, Shahab Toursavadkohi, and Todd E. Rasmussen

Key Points

1. Vascular injury is the leading cause of mortality and morbidity in both civilian and military trauma.
2. Mechanisms of vascular injury are broadly categorized as either blunt or penetrating.
3. Patient examination is the most important step in evaluation of a suspected vascular injury.
4. Hard signs of vascular injury suggest near or complete disruption of the vessel in question and include pulsatile bleeding, expanding hematoma, palpable thrill, audible bruit, or evidence of acute ischemia distal to the injury site.
5. Contrast-enhanced computed tomography angiography (CTA) is the most widely used diagnostic imaging modality to identify and localize arterial and venous injuries in patients with suspected vascular injury in the emergency setting.
6. In the trauma patient, hemorrhage leads to both the overall metabolic consequences of shock and end-organ ischemia specific to the injured vessel.
7. Damage control resuscitation involves permissive hypotension with concurrent massive transfusion of packed red blood cells, plasma, and platelets in a 1:1:1 ratio.
8. Basic tenants of the operative management of vascular trauma include hemorrhage control, restoration of blood flow, and prevention of further reperfusion injury.
9. Neck trauma is classically divided into three anatomic zones. Zone I is from the thoracic inlet to the cricoid cartilage, zone II is between the cricoid cartilage and the angle of the mandible, and zone III is above the angle of the mandible to the base of the skull.
10. Control of bleeding from vascular disruption within the torso is not readily amenable to control with direct pressure and is therefore referred to as noncompressible torso hemorrhage (NCTH).

11 While open surgical therapy remains the gold standard for treatment for traumatic injuries, endovascular management presents an alternative option particularly with injury to the arch vessels and thoracic aorta.

BACKGROUND

1 Vascular disruption and hemorrhage is the leading cause of mortality and morbidity in both civilian and military trauma.[1–3] Arterial and venous injuries often occur concomitantly due to their anatomic proximity and are frequently associated with injury to other vital structures. Optimal management of traumatic vascular injury requires an understanding of the epidemiology and anatomic distribution of vascular injury patterns, consideration of mechanism, and attention to key tenants of diagnosis and management. The objective of this chapter is to familiarize the reader with current knowledge pertaining to the topic of vascular trauma including the circumstances in which vascular injury occurs and different approaches to diagnosis. Additionally, this chapter will provide guidance to the management of different patterns of vascular injury including extremity, cervical, and torso traumatic injury.

EPIDEMIOLOGY AND MECHANISMS OF VASCULAR TRAUMA

The epidemiology of vascular trauma can be broadly categorized into contextual circumstances (military and civilian), mechanism of injury (blunt and penetrating), and anatomical location of injury (extremity, cervical, and torso).

Wartime Vascular Injury

Contemporary data confirm that exsanguination is the major cause of death in wounded service personnel. The prevalence of wartime vascular trauma has

increased markedly over the past century (**Fig. 27.1**).[1–3] Estimates from allied surgeons in World War I (WWI) suggest overall vascular trauma rates of 0.4% to 1.3%.[4] DeBakey characterized the vascular injury burden in World War II (WWII) and the Korean and Vietnam wars at 0.96% and 2% to 3%, respectively.[4–6]

Coalition militaries engaged in recent combat operations in Afghanistan and Iraq have reported rates of vascular trauma higher than the previously mentioned military campaigns.[2,7–9] In a study reporting the U.S. military experience, White and colleagues analyzed vascular cases entered into the U.S. Joint Theater Trauma Registry (JTTR) from 2002 to 2009 (**Fig. 27.2**).[2] Defining the denominator as battle-related injuries sufficiently severe to prevent return to duty in the combat theater, the specific incidence of vascular injury (defined as the *total incidence injury*) was found to be 12% (1,570 of 13,076 cases). The incidence of injuries requiring an operation (defined as the *operative incidence*) was found to be 9% (1,212 of 13,076 cases). Injuries were most common in the extremities (79%) followed by those in the torso (12%) and cervical regions (8%).

Overall, the authors concluded that the rate of vascular injury in these modern wars was five times that previously reported from Vietnam and Korea (**Figs. 27.1** and **27.2**). An update of that data from the final years of war in Afghanistan from 2009 to 2015 estimated 17.6% of injuries to involve the vasculature, with most involving the extremities (45%). That study also cited an increase in endovascular methods of vascular injury management.[10]

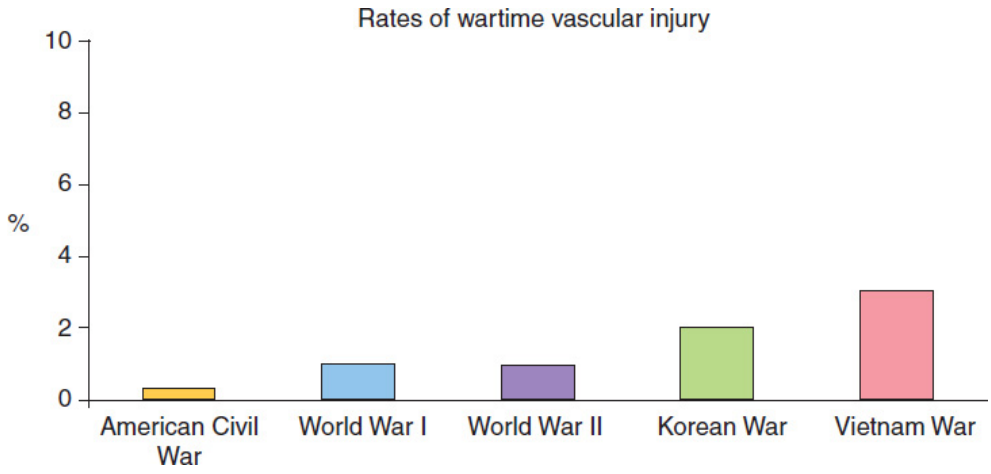

Figure 27.1 The rate of vascular injury reported from the wars of the previous two centuries. (From White JM, Stannard A, Burkhardt GE, et al. The epidemiology of vascular injury in the wars in Iraq and Afghanistan. *Ann Surg* 2011;253(6):1184–1189.)

Civilian Population Vascular Trauma

The impact of vascular trauma in the civilian setting is less well characterized than wartime vascular injury. According to data from the National Center for Injury Prevention and Control, in 2011 in the United States, injuries accounted for 51.3% of all deaths among persons 1 to 44 years of age, which is more deaths than those caused by noncommunicable and infectious diseases combined.[11] Fatalities stemmed mainly from motor vehicle accidents (32%), gunshot wounds (22%), and falls (9%). Vascular injuries represented 1% to 2% of total trauma patients but accounted for more than 20% of all trauma-related deaths and had the highest utilization of resources among the trauma population.[3]

In 2010, Demetriades and colleagues characterized vascular injury in 22,089 patients drawn from a population of more than 1.8 million in the National Trauma Data Bank (NTDB).[12] Acknowledging the reporting bias that accompanies analysis of such retrospective data, it was determined that the incidence of vascular injury (2002 to 2006) was 1.6%. Four-fifths of the injured were male, and the average age was 34 years. Half of the patients (51%) sustained a penetrating mechanism. Just under a quarter of patients presented in hemorrhagic shock and over half had an Injury Severity Score of more than 15. Abdominal and chest injuries accounted for more than 25% and 24% of the injury burden, respectively, with arm and leg injuries

contributing 26% and 18%, respectively. Mortality among those with vascular trauma was 23%, and vessels associated with the highest rates of amputation were the axillary (upper limb amputation rate of 6%) and popliteal arteries (lower limb amputation rate of 15%).[12]

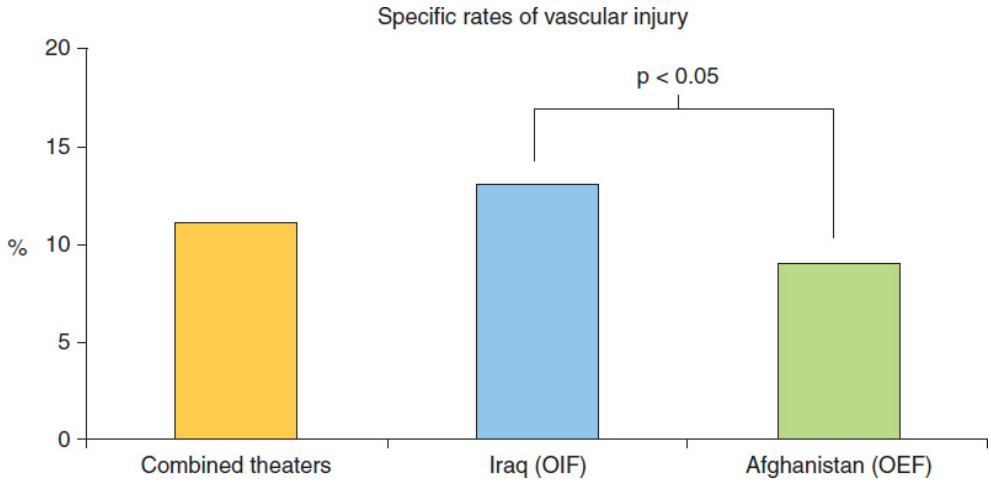

Figure 27.2 The rate of vascular injury reported during the wars in Afghanistan and Iraq. This specific rate refers to the 1,570 U.S. service personnel identified within the Department of Defence Joint Theater Trauma Registry (JTTR) as having sustained vascular injury during the wars (between 2002 and 2009). Note that the overall rate of 12% is severalfold higher than the rate of vascular injury reported in previous wars. (From White JM, Stannard A, Burkhardt GE, et al. The epidemiology of vascular injury in the wars in Iraq and Afghanistan. *Ann Surg* 2011;253(6):1184–1189.)

In other reports of vascular trauma from civilian centers in New York and El Paso, the rates of injury, in the context of all presenting to each trauma center, were 2.3% and 3.4%, respectively.[13,14] These reports confirm the "at-risk demographic" to be young and male, and demonstrate that mortality in those with vascular trauma is twice that of patients without this injury pattern. Not surprisingly, penetrating mechanisms are overrepresented in patients with vascular injury. A single-center study of vascular trauma from Houston in 1988 demonstrated that the wounding pattern in civilian circumstances does not follow that seen in wartime, even where ballistic penetrating injury is common.[3] Torso and neck injuries accounted for two-thirds of all injuries, while lower extremity injuries (including the groin) comprised only 20%.

Mechanism of Vascular Trauma

2 Vascular injuries are broadly categorized by mechanism as either blunt or penetrating. Either mechanism can disrupt the normal integrity of the blood vessel wall (intima, media, and adventitia) with varying degrees of integrity. Blunt vascular trauma is produced by local tissue compression or acceleration–deceleration resulting in disruptive shear forces. Motor vehicle crashes are the main cause of blunt vascular trauma in the civilian setting, and these patients usually have injuries to other areas of the body including extremity fractures or dislocation, brain injury, and injury to structures in the abdomen or thorax including aortic disruption. Blunt mechanism is also recognized as a source of vascular disruption with specific extremity fractures or dislocation patterns (e.g., posterior knee dislocation, tibial plateau fracture, and supracondylar fracture of humerus).

Penetrating mechanisms typically result in direct injury of the vessel causing either laceration or contusion of the wall as well as separation or destruction of soft tissues surrounding the vessel. Penetrating vascular injury may result from simple, low-velocity sharp objects (i.e., knife or glass), irregular fragments from explosives, and uniform munitions fired from a weapon. For ballistic injuries, damage to the vessel and surrounding soft tissues often results from a concussive shockwave that is conducted through the tissues as the object moves through the body dissipating energy. Unlike blunt injuries, which more commonly affect torso vascular structures, penetrating injuries more commonly affect the extremity vasculature.

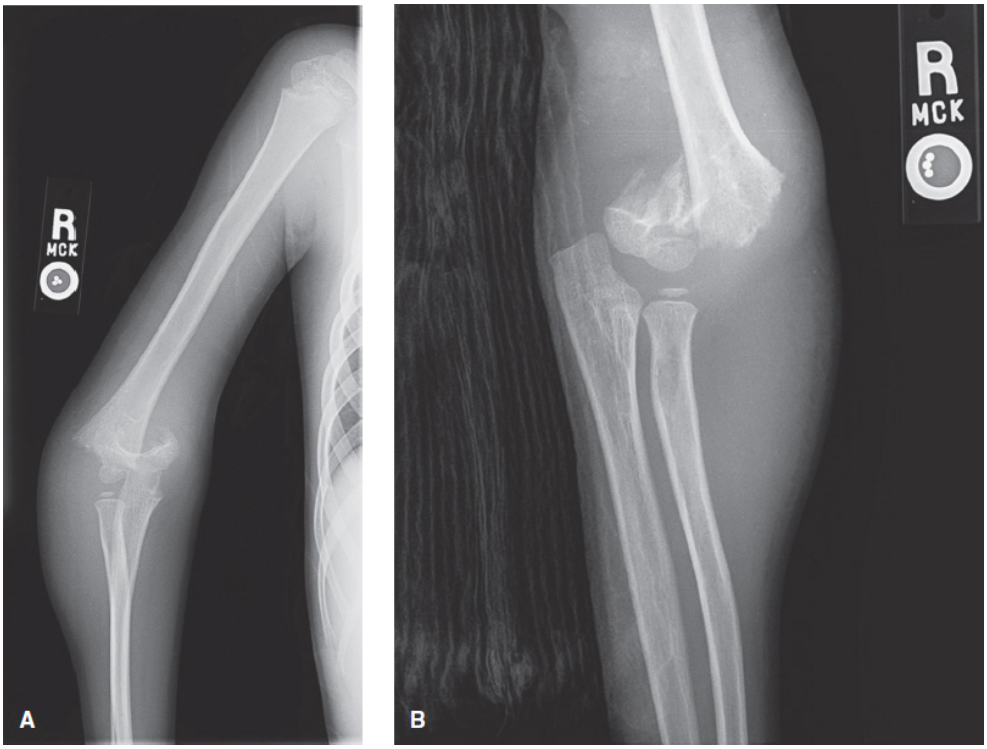

Figure 27.3 **A, B:** Radiographic images of a Gartland type III fracture of the right supracondylar humerus which is commonly associated with brachial artery injury.

DIAGNOSIS OF VASCULAR INJURY

Physical Examination

3 Patient examination is the most important step in evaluation of a suspected vascular injury. The physical examination should include complete exposure of the patient, identification of all wounds, and palpation of all extremities to assess for fracture or dislocation. The extremity vascular examination should also include assessment of distal perfusion by examination of the general appearance of the extremity and identification of pulses. Similarly, the neck and cervical region should be examined for signs of penetrating wounds, the presence of carotid pulses, and bruising or hematoma.[15,16]

Vascular trauma physical examination findings can be divided into hard versus soft signs of injury.4 Hard signs of vascular injury suggest near or complete disruption of the vessel in question and include pulsatile bleeding, expanding hematoma, palpable thrill, audible bruit, or evidence of acute

ischemia distal to the injury site. Depending on the degree of extremity ischemia, a patient may exhibit one or more of the classic six "P's" including pulselessness, pain, pallor, paresthesia, paralysis, and poikilothermia. Soft signs of vascular injury suggest partial disruption of the vessel in proximity and include trauma in proximity to a named vessel (i.e., certain fracture or dislocation patterns) (**Figs. 27.3** and **27.4**), diminished pulse distal to the site of injury, nonexpanding hematoma or severe bruising, and a peripheral neurologic deficit. Although torso vascular injury is more difficult to diagnose with physical examination alone, it should be suspected in patients with asymmetric arm pulses or pressures and those presenting in shock with evidence of fluid in the peritoneum or thoracic cavity.

Adjuncts to the Physical Examination

A plain chest radiograph is frequently performed during the initial evaluation of the trauma bay and is a useful adjunct in the diagnosis of blunt aortic injury. Classic signs of this injury pattern include a widened mediastinum (greater than 8 to 10 cm), an apical cap, loss of the characteristic aortic nob, downward displacement of the left mainstem bronchus, and hemothorax. Although multiple rib fractures are not a sign of aortic injury itself, it is a marker of severe blunt injury with significant shear and should raise one's index of suspicion for injury to the thoracic aorta. In addition, a persistent discrepancy of blood pressure cuff measurements from both arms greater than 20 mm Hg suggests a proximal vascular injury to the subclavian or axillary arteries.

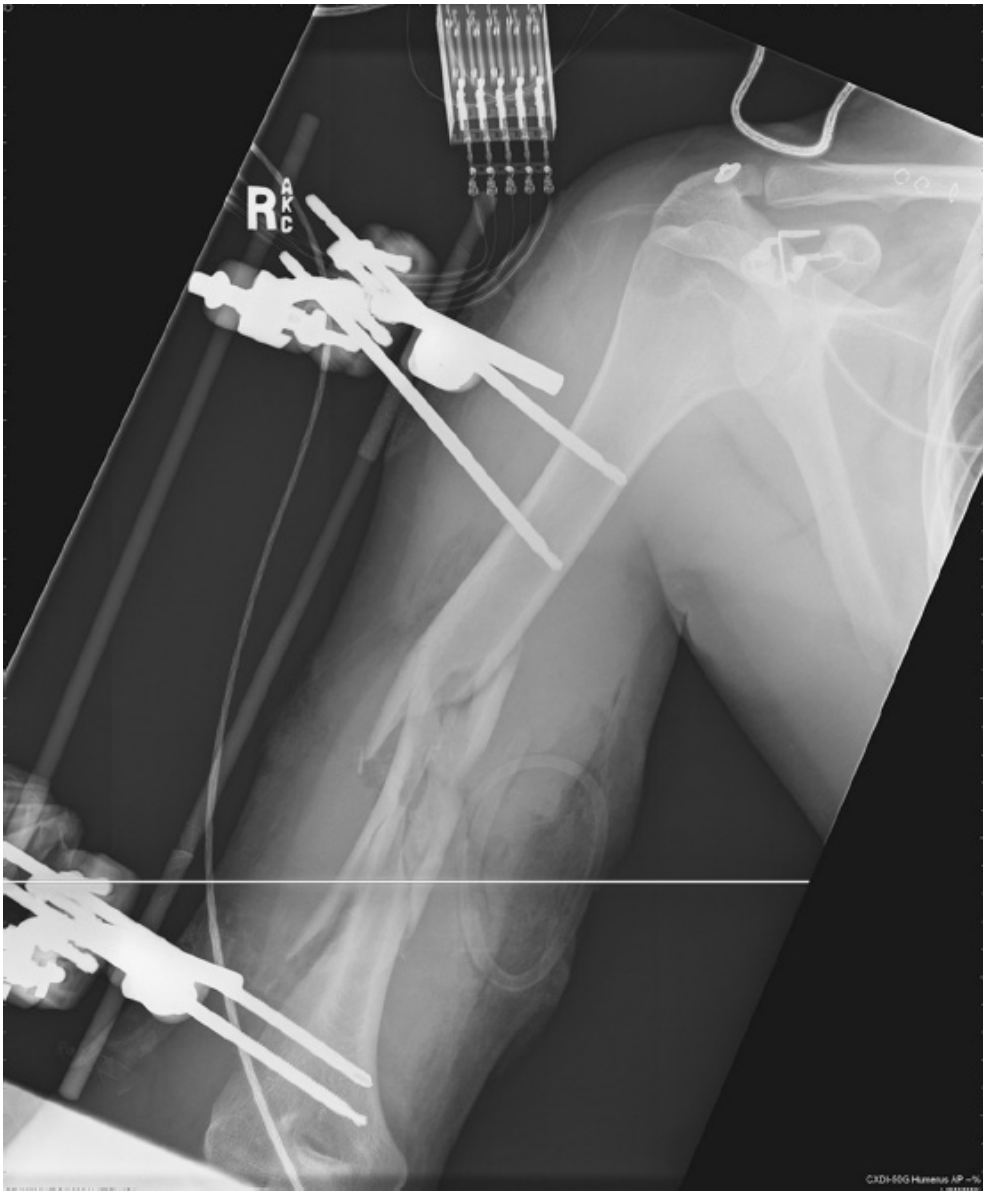

Figure 27.4 Radiograph of right upper extremity demonstrating an open humerus fracture. The brachial artery was found to be severed by the fracture.

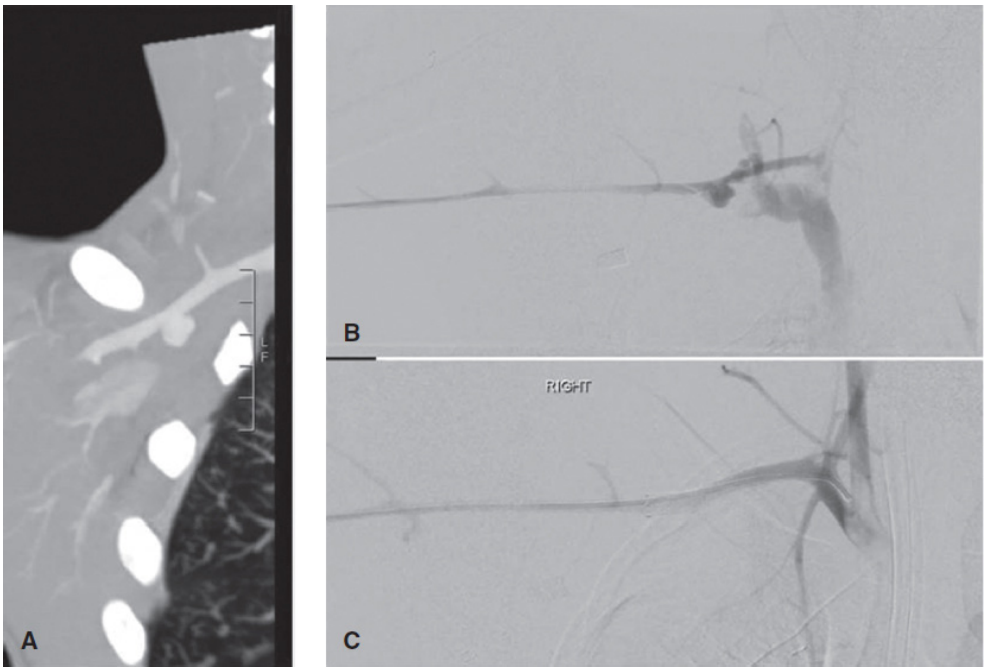

Figure 27.5 **A:** CT angiogram demonstrating a traumatic right proximal axillary artery injury as a result of ballistic injury. **B:** Angiogram demonstrating a small pseudoaneurysm and large arteriovenous (AV) connection with immediate filling of the right axillary vein. **C:** A 7 × 50 mm covered stent was placed across the injury with resolution of both the pseudoaneurysm and AV fistula.

Continuous-wave Doppler is another adjunct to the physical examination of patients in whom there is a concern for vascular injury. Doppler signals in the distal extremity should be recorded as present or absent and, if present, graded as strong and bi- or triphasic or weak and monophasic.[17,18] In the lower extremity, signals should be assessed in the dorsalis pedis and posterior tibial arteries, while in the upper extremity, signals should be examined over the radial, ulnar, and brachial arteries. While describing the quality of Doppler signals can be somewhat subjective, identifying the presence of extremity perfusion by noting the presence of an arterial signal is an important step that is typically less subjective than palpation for a pulse with one's finger.

The addition of a manual blood pressure cuff to continuous-wave Doppler allows one to calculate an ankle branchial index (ABI) or injured extremity index (IEI). The normal ABI or IEI is 0.9 or greater, although caution should be used in interpreting the ratio in patients who are hypotensive, in severe pain, or hypothermic.[16–18] Peripheral vasoconstriction is a normal response

to significant trauma and shock and may result in a transiently decreased ABI or IEI in the absence of an injured axial vessel. In this context, assessment of the Doppler occlusion pressures and measurement of ratios should be viewed as dynamic and repeated after resuscitation, administration of pain control, and rewarming.

Ultrasound is another noninvasive modality that can be used in the evaluation of patients with vascular trauma. Brightness or B-mode ultrasound is ubiquitous in most emergency departments and critical care settings and allows one to make basic assessments that provide insight into the presence and severity of some patterns of vascular injury.[15,16] The focused assessment with sonography for trauma (FAST) examination of the abdomen is based on B-mode ultrasound and is commonly used to determine the presence or absence of fluid in the peritoneum following severe injury. Although not specific for vascular injury, fluid seen on a positive FAST examination in a hypotensive trauma patient should be assumed to be blood. In these cases, the source of bleeding may be a solid organ injury (liver, kidney, or spleen) or a larger named vessel.

Computed Tomography and Magnetic Resonance Imaging for Vascular Trauma

5 Contrast -enhanced computed tomography angiography (CTA) is the most widely used diagnostic imaging modality to identify and localize arterial and venous injuries in patients with suspected vascular injury in the emergency setting.[19] CTA has a high degree of sensitivity in identifying dissection, occlusion, and active extravasation of blood into a contained space (i.e., pseudoaneurysm) or into an open space or cavity (**Fig. 27.5**). CTA is particularly useful in the assessment of anatomic regions where physical examination of the vasculature is limited. Growing experience with CTA in the assessment of the peripheral vasculature and several clinical reports now demonstrate this modality's sensitivity and specificity in the diagnosis of extremity vascular injury.[20] Extremity CTA is particularly appealing for the polytrauma patient who has soft signs of vascular injury as it can be performed with imaging of other body regions (i.e., head, neck, abdomen, and pelvis).[20]

Contrast Angiography

CTA has largely replaced the need for diagnostic contrast angiography in the trauma setting. Exception to this statement is the unstable patient who does not undergo imaging prior to operative exploration. In this circumstance, on-table angiogram can be performed in the operating room while other injuries are addressed with ongoing resuscitation.[21] Angiogram can demonstrate active extravasation of contrast if bleeding from an injured vessel is brisk and ongoing. Extravasation may not however be visualized if the bleeding is slow or under tamponade. Bleeding may also be missed if a contrast bolus is too small, mistimed, or injected into a different vessel not in direct continuity with the injury. Angiographic interruption of vessel continuity usually indicates disruption or thrombosis. With sufficient contrast and time delay, distal reconstitution of flow beyond the injured segment from collateral vessels can typically be demonstrated. Imaging of distal arterial beds can be compromised by hypoperfusion and vasoconstriction, typical manifestations of shock. Vasospasm with tapering of arteries (sometimes to occlusion) and slow flow can be prominent in young patients who have a greater degree of vasomotor reactivity.[19–21] Endovascular therapies such as embolization and placement of covered stents or stent grafts can be placed immediately following injury diagnosis when appropriate.

MANAGEMENT OF THE PATIENT WITH VASCULAR TRAUMA

Trauma Patient Pathophysiology

6 In the trauma patient, hemorrhage leads to both the overall metabolic consequences of shock and end-organ ischemia of the specific injured vessel. Ischemia of both types results in anoxic cell death. Resuscitation is directed toward minimizing ischemia and the "lethal triad" of acidosis, hypothermia, and coagulopathy. Hypoperfusion or ischemia leads to acidosis which causes platelet morphology changes and dysfunction and declining coagulation factor activity leading to decreased thrombin generation and the degradation of fibrinogen. Hypothermia likewise causes platelet dysfunction, less

coagulation factor activity, and the induction of fibrinolysis. Both of these pathways lead to coagulopathy and endothelial damage. Unbalanced massive blood transfusions can also lead to tissue injury, hypoperfused vascular beds, hemodilution, and depletion or dilution of clotting factors and platelets, all of which can contribute to a coagulopathic state.

Reperfusion injury following revascularization can precipitate additional metabolic insults in the trauma patient. Reperfusion of ischemic tissues releases reactive oxygen species and activates multiple proinflammatory processes including lipid peroxidation. This activation causes injury to the microvasculature which increases cell permeability and edema. An increase in interstitial pressure in turn leads to more stasis in microvasculature and therefore worsened ischemia. Ensuing cell lysis, also called rhabdomyolysis, leads to hyperkalemia, metabolic acidosis, and eventually myoglobin-induced renal failure.

Resuscitation of the Trauma Patient

Resuscitation of the trauma patient should begin immediately following initial assessment of injuries. Venous access with large-bore catheters in peripheral veins of uninjured extremities is preferred over central access in the emergent setting. Venous cutdowns are sometimes necessary. Radial or femoral arterial lines are also often placed for hemodynamic monitoring.[22 7] Damage control resuscitation, a term coined in 2005, involves permissive hypotension with a goal of a palpable radial pulse in patients without head injury.[23] Massive transfusion of packed red blood cells, plasma, and platelets should be conducted in a 1:1:1 ratio.[24–26]

General Intraoperative Considerations and Pearls

The principles of "damage control" guide the surgical management of vascular trauma [8] . Basic tenants include hemorrhage control, restoration of blood flow, and prevention of further reperfusion injury.

1. Prep widely, considering all possible sites of injury given the mechanism of disability. In particular, consider the need for autogenous venous conduit,

namely saphenous vein. With chest or abdominal injuries, prep down to bilateral knees. With leg injuries, prep circumferentially and include the chest and abdomen. With neck or upper extremity wounds, include the shoulders and chest.

2. Patients should receive preoperative antibiotics based on local guidelines.
3. Longitudinal incisions parallel to neurovascular bundles should be used for the wide exposure and best control. This may necessitate and "S"-shaped incision over joint spaces.
4. Proximal and distal control for any vascular injury is critical. This may be obtained with a digit, vessel loop, vascular clamps, or a Foley or Fogarty balloon. Consider remote proximal control when hematomas or open blast wounds impede visualization. Shunts should also be considered to decrease ischemic time when orthopedic stabilization or other lifesaving procedures must occur first. Nonbleeding wounds should not be disturbed including removal of debris or foreign objects until surgical control is obtained.
5. Temporary application of a lower extremity tourniquet may be helpful with complex wounds prior to obtaining surgical proximal control. An inappropriately applied tourniquet inflated to venous pressure can however increase exsanguinating hemorrhage. As systemic blood pressure increases with resuscitation, tourniquet pressure may need to be increased to remain effective.
6. Injury may require orthopedic fracture reduction and limb stabilization prior to formal vascular, nerve, or soft tissue repair. Relining of the bony structures will often improve vessel spasm, and vascular examination should be repeated following any orthopedic intervention.
7. Use of systemic heparin is individualized and contingent upon multiple factors including preoperative blood loss, hemodynamic stability, the presence of brain injury, and the overall physiologic status of the patient with regard to acidosis, hypothermia, and coagulopathy. Local administration of heparin and papaverine can be used in the wound and flushed directly into the vessel during repair. In general, systemic heparin can be obviated in young patients with healthy vessels and adequate revascularization.
8. Choice of surgical incision is dictated by the injury pattern and anatomic exposure needed for proximal control and subsequent revascularization

(**Table 27.1**). Aggressive debridement of devitalized tissue may be necessary for adequate visualization and postoperative healing.

9. Inflow and outflow must be assessed before beginning an anastomosis. Thrombectomy of both the inflow and outflow vessels with a Fogarty embolectomy catheter may be required.
10. Decision to perform immediate vascular reconstruction versus shunt placement with delayed reconstruction should consider the overall physiologic status of the patient. Arterial reconstruction should be prioritized over venous reconstruction in most cases.
11. Decision for direct repair with and without patching, primary anastomosis, or interposition grafting should consider factors outlined in **Table 27.2**.
12. Appropriate conduit is obtained, if applicable. Reversed greater saphenous vein of the uninvolved leg is the ideal conduit although synthetic grafts can be used if needed.
13. Repair is performed with nonabsorbable, monofilament running suture.
14. Adjuvant hemostatic agents can be parenteral (tranexamic acid for hyperfibrinolysis) or topical (**Table 27.3**).
15. Following completion of repair, perfusion should be assessed in the operating room with Doppler and arteriogram when indicated.
16. Soft tissue coverage over vascular repairs is necessary to prevent contamination, vessel desiccation, and anastomotic disruption. If large tissue defects are present, vacuum-assisted dressings are useful for tissue approximation and temporary closure.
17. Reperfusion injury and compartment syndrome must be considered and fasciotomies performed as clinically indicated.

Table 27.1 Exposures in Vascular Trauma Surgery

Vessel Injured	Exposure/Maneuver
Right subclavian artery Ascending aorta Innominate artery	Median sternotomy
Left subclavian artery Descending thoracic aorta	Left thoracotomy
Paravisceral, infrarenal aorta Left renal artery Left iliac artery	Left colon mobilization
Inferior vena cava Right renal artery Right iliac artery	Right colon mobilization, extended Kocher maneuver (duodenal mobilization)

Table 27.2 Options for Treatment of Vascular Injuries

Type of Repair	Description of Injury
Primary repair	<25% vessel compromise
Patch angioplasty	<50% vessel compromise
End-to-end anastomosis	<2 cm defect, ends mobilized, spatulated (smaller vessels)
Interposition graft	>2 cm defect, reversed vein graft or synthetic conduit
Extra-anatomic bypass	Extensive defect, multiple level injury, contamination

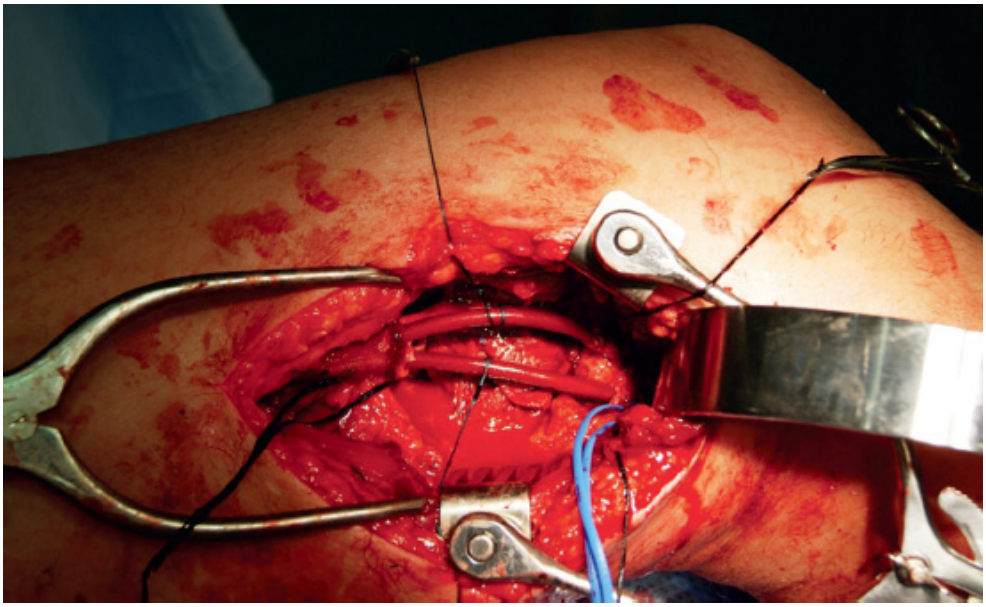

Figure 27.6 Operative photograph showing temporary vascular shunt placement as a damage control maneuver in the proximal popliteal artery and vein of the left lower extremity. The shunts were secured with silk suture ties, and both were patent with Doppler flow several hours following the injury.

MANAGEMENT OF SPECIFIC INJURY PATTERNS—EXTREMITY

Extremity trauma requiring operative intervention is often readily identifiable from physical examination alone. Exceptions to this statement include more proximal vessel injury entering the chest or pelvis including the subclavian and femoral arteries. For all extremity trauma, the goals of management include hemorrhage control, revascularization of an ischemic extremity, and limb stabilization to minimize future disability.[27] Injuries with hard signs of vascular injury should be taken immediately to the operating room for open or endovascular exploration without further imaging workup. Decision to perform immediate reconstruction versus temporary shunt placement should be dictated by the overall physiologic status of the patient (**Figs. 27.6** and **27.7**). "Soft signs" of vascular injury suggest less devastating injury allowing time for further workup, imaging, and potential nonoperative management.[28]

An additional critical issue in all extremity trauma management is evaluation for compartment syndrome. Elevated fascial compartment

pressures can be due to reperfusion, hematoma, swelling from crush injury, or major fractures. Compartment syndrome should be suspected if reperfusion occurs greater than 4 to 6 hours following injury, crush injuries, combined arterial and venous injuries, vessel ligation, and tense muscle compartments on examination. The classic physical examination finding in the awake patient concerning for compartment syndrome is calf pain with passive motion and paresthesia in the 2nd dorsal web space. Compartment pressures can be measured as an adjunctive aid in diagnosis with pressures greater than 30 mm Hg considered abnormal, however, normal pressures in a patient in whom compartment syndrome is clinically suspected should not discourage compartment release. Low threshold for fasciotomy should be adopted as risk of limb loss is high if a compartment syndrome goes undiagnosed.

Table 27.3 Topical Hemostatic Agents

	Indications	Agent Potency/ Mechanism	Uses	Examples
Level I (mechanical hemostat)	Min or mild bleeding, localized	Contact activation ± platelet aggregation	Capillary, arteriolar ooze	Gelfoam, procine gelatin, bovine collagen, surgical, nu-knit, Arista
Level II (Thrombin)	Min or mild bleeding diffuse	Converts fibrinogen to fibrin-activated platelet aggregation Contact activation + fibrinogen converted to fibrin	Capillary, ooze Capillary, arteriolar ooze, spurting	Bovine thrombin, recombinant thrombin Collagen or gelatin + thrombin; Floseal, Surgiflo
Level III (fibrin sealant, combination hemostat)	Mild bleeding diffuse; moderate bleeding	Fibrin sealant, replicates final stage of clotting cascade Synthetic sealant, covalently and mechanically bond Other	Capillary, arteriolar ooze High pressure sealing	Thrombin + fibrinogen ± fibrinolysis inhibitor; Tisseel, Evicel PEG polymer; CoSeal BioGlue

Adapted from Shander A, Kaplan LJ, Harris MT, et al. Topical hemostatic therapy in surgery: Bridging the knowledge and practice gap. *J Am Coll Surg* 2014;219(3): 570–579.e4.

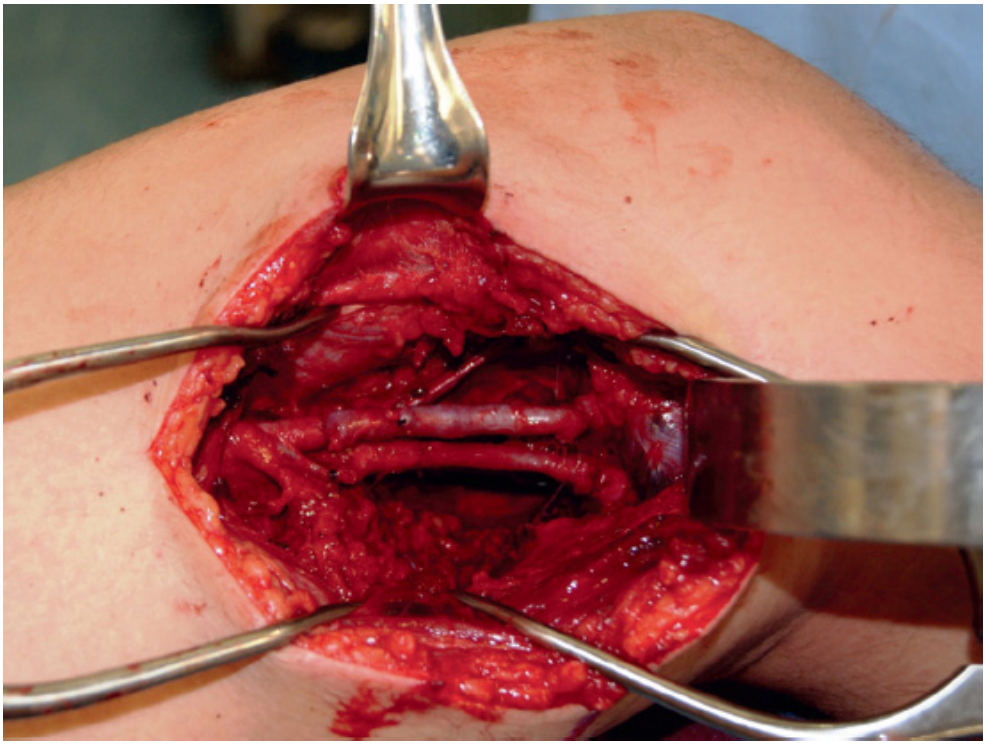

Figure 27.7 Operative photograph showing an interposition vein graft repair of the left proximal popliteal artery and vein. The interposition greater saphenous vein grafts were harvested from the right (contralateral) leg and performed following removal of the temporary vascular shunts.

Postoperatively, patient should be started on low-dose aspirin once hemodynamics permit. Deep vein thrombosis (DVT) prophylaxis is also an essential component of treatment in the polytrauma patient to prevent thromboembolic complications. Elevation of the injured extremity will reduce swelling. Twenty-four hours of antibiotics is adequate following isolated vascular repairs.

Upper Extremity

The axillary artery is defined proximally by the lateral margin of the first rib and distally by the lateral edge of the teres major muscle. The artery is protected proximally within the shoulder from penetrating injury but susceptible to forceful blunt trauma due to its fixation. Proximal exposure may require infra- and supraclavicular incisions to gain control with potential sternotomy if more proximal intrathoracic control of the subclavian artery is needed. The mid- and distal axillary artery can be approached

through a traditional infraclavicular incision. Complications with more distal exposure are due to increasing branches and associated nerve supply in the shoulder and arm. Employing endovascular techniques for temporary balloon occlusion or placement of stent grafts may be advantageous in these locations.[29]

The axillary artery becomes the brachial artery after passing the lower margin of the teres major. The brachial artery runs in the anterior compartment of the arm with the median nerve. The basilic and brachial veins accompany and often crossover the artery in the upper arm. The brachial artery is most often injured during penetrating trauma, but injury should be considered with any humeral fracture, especially posterior or lateral fractures. The brachial artery's main proximal branch, the profunda brachii, can provide significant perfusion to the distal upper extremity if it remains intact.

The radial artery is a terminal branch of the brachial just distal to the elbow and travels in the anterior compartment to become the deep palmar arch. The ulnar artery is the larger terminal branch of the brachial artery and runs to the wrist to form the superficial palmar arch and joins the deep arch. If temporary control of bleeding is needed, a blood pressure cuff can be used as a tourniquet. Evaluation should include a neurovascular examination with addition of the Allen test to determine patency of the palmar arch. Single-vessel injury with no ischemic changes can be ligated if the palmar arch is intact. If both forearm arteries are injured, repair of the usually dominant ulnar is preferred with either mobilization and primary end-to-end repair or interposition vein graft.

Lower Extremity

Femoral artery trauma constitutes 20% of all traumatic arterial injuries. Supracondylar femur and tibial plateau fractures are associated with distal superficial femoral artery and popliteal artery injuries. In the case of exsanguinating hemorrhage, an assistant's digit may be prepped into the field until more formal proximal control can be obtained. Options include tourniquet, temporary balloon catheter, or exposure of the distal external iliac artery in the preperitoneal space with compression against the iliac fossa for femoral triangle injuries. Incision should be longitudinal just below the

inguinal ligament. Primary repair or interposition grafting is the mainstay of therapy as acute ligation of the femoral artery leads to 50% amputation rate.[30] Although vein conduit is always preferred, prosthetic graft can be used when necessary in larger vessels with good muscle coverage.[31] Prosthetic grafts have also been described as a bridge to definitive therapy in the setting of severely injured patients in wartime injuries.[32]

Popliteal trauma is classically due to posterior knee dislocation. Historically, amputation rates were 20% for both penetrating and blunt popliteal injuries.[33] Failure to repair a popliteal occlusion results in amputation rates as high as 60%. Incision should be medial, employing the use of a bump under a slightly flexed leg (**Figs. 27.6** and **27.7**). Repair can be performed primarily following debridement to healthy tissue or with an interposition graft. Primary repair should be attempted only with defects less than 1 cm which can be repaired without tension. Completion angiography is recommended in most situations.

A single terminal vessel including the anterior and posterior tibial artery and peroneal artery can be ligated in the lower extremity in a patient with no signs of ischemia and no preexisting peripheral vascular disease. When all three arteries are damaged, repair of the anterior or posterior tibial artery via lateral and medial calf incisions, respectively, should be performed.

MANAGEMENT OF SPECIFIC INJURY PATTERNS—CERVICAL

9 The location of penetrating trauma in the neck is classically divided into three zones to identify which structures are at risk for injury. Zone I is from the thoracic inlet to the cricoid cartilage, zone II is between the cricoid cartilage and the angle of the mandible, and zone III is above the angle of the mandible to the base of the skull. The carotid and vertebral arteries are at risk in all three zones.[34] In addition to the carotid artery, injury to the jugular veins and branches, nerves (vagus, hypoglossal), trachea, and esophagus must also be considered with wounding in the neck. Hard signs of vascular injury include expanding hematoma, bruit, and hemiparesis.

Zone II of the neck is the most commonly injured region in penetrating neck injuries with vascular injuries in up to 20% of cases. Prior to widespread CTA use, zone II neck injuries mandated operative exploration if the injury violated the platysma. This mantra led to a high negative exploration rate which has now been negated by CT imaging. Currently, CTA of the neck through the aortic arch is utilized in stable patients to rule out injury. Multiple studies have demonstrated a 90% sensitivity and near 100% specificity rate for vascular injuries requiring treatment.[35–37] Of note, significant ballistic fragments in the neck may obscure arterial segments. In these cases, conventional angiography should be considered.

Zone I injuries with hard signs of vascular injury should raise suspicion for injury to the great vessels and may require median sternotomy or a high anterolateral thoracotomy for proximal control. Endovascular attempts at proximal control with balloon occlusion can be attempted, however, should not delay definitive operative control.

Injuries in zone II of the neck with hard signs of injury mandate neck exploration via a cervical incision along the anterior border of the sternocleidomastoid muscle. Occasionally a collar incision may be utilized if both sides of the neck require exploration. Exposure with proximal and distal control of the carotid artery should be performed expeditiously. The internal carotid artery should always be repaired as there is a high reported mortality with ligation (up to 45%).[38] Stab wounds can often be repaired primarily or with a patch as dictated by the degree of vessel disruption, while ballistic injuries typically require segmental resection with an interposition graft. Greater saphenous vein should be used as conduit whenever possible. Heparinization with or without shunting is employed during these repairs unless major contraindications exist in the multi-injured trauma patient. The external carotid artery can be ligated without significant consequence. The internal jugular vein can be ligated in an emergent setting but if possible, should be repaired, especially if injury is bilateral.

Zone III injuries are more difficult to expose using an open approach and can require subluxation of the mandible or mandibulotomy. Endovascular or hybrid strategies can be lifesaving in high injuries inaccessible to open repair.[39]

Vertebral artery injuries are less common and more difficult to expose operatively compared to carotid artery injuries. Vertebral artery injuries are

most often associated with cervical spine transverse process fractures, subluxations, or penetrating injuries to the back of the neck. Open exposure is similar to that for the common carotid artery, however, more lateral. After the sternocleidomastoid and anterior scalene muscles are mobilized, the vertebral artery can be isolated and ligated. In this procedure, care must be taken to avoid injury to the phrenic nerve and thoracic duct. Proximal and distal control of a more distal vertebral artery injury may require endovascular techniques as with a zone III carotid injury. In a recent review of the contemporary management of combat-related vertebral artery injuries, injuries included occlusion, pseudoaneurysms, dissection, and arteriovenous fistula. Injury was most commonly in the V2 segment, and treatment included coils and covered stents.[40]

Blunt cerebrovascular injury (BCVI) includes both carotid and vertebral injuries. While BCVI represents less than 1% of admissions for blunt trauma, these injuries can lead to mortality rates from 23% to 28% with 48% to 58% of survivors having permanent severe neurologic deficits.[41] Given the high morbidity of unrecognized BCVI in the asymptomatic patient, many screening protocols recommend screening CTA in trauma patients presenting with petrous bone fractures, diffuse axonal injury, Glasgow Coma Scale score less than 8, complex C1 to C2 cervical fractures, and Le Fort II or III facial fractures.[42] Treatment is dictated by the severity of the injury as defined by Biffl's grading score (Table 27.4, **Fig. 27.8**).[43] While no prospective data exist to define optimal treatment regiments, low-grade injuries should be treated with antithrombotic agents such as aspirin or heparin. Grade III injuries rarely resolve with observation and medical therapy alone, therefore surgical therapy should be considered. Patients presenting with severe deficits generally do not improve with revascularization.[42]

Table 27.4 Grading of Blunt Cerebrovascular Injury

Injury Grade	CT Characteristics
Grade 1	Intimal irregularity with <25% narrowing
Grade 2	Dissection or intramural hematoma with >25% narrowing
Grade 3	Pseudoaneurysm
Grade 4	Occlusion
Grade 5	Transection with extravasation

MANAGEMENT OF SPECIFIC INJURY PATTERNS—TORSO

10 Control of bleeding from vascular disruption within the torso is not readily amenable to control with direct pressure and is therefore referred to as noncompressible torso hemorrhage (NCTH). Civilian studies demonstrate that NCTH accounts for 60% to 70% of mortality following otherwise survivable injuries clearly emphasize the lethality of this injury pattern. Hemorrhage is also a significant problem in the wartime setting, accounting for up to 60% of deaths in potentially survivable injury scenario. The distinction between compressible extremity hemorrhage and NCTH is notable. There has been a demonstrable reduction in mortality from extremity injury with a better understanding of its epidemiology and the need to rapidly control hemorrhage with tourniquets and topical hemostatic agents. To date, there has been no such reduction in mortality in the setting of NCTH.[44]

The initial management of torso hemorrhage is dictated by a patient's hemodynamic stability and the site of injury. A proportion of patients with NCTH and penetrating trauma present with circulatory collapse with profound hypotensive or cardiac arrest. Management of patients presenting in such a fashion has been extensively studied, and the current civilian standard

of care is a resuscitative thoracotomy (RT) which permits the following maneuvers:

- Release of cardiac tamponade
- Management of thoracic bleeding

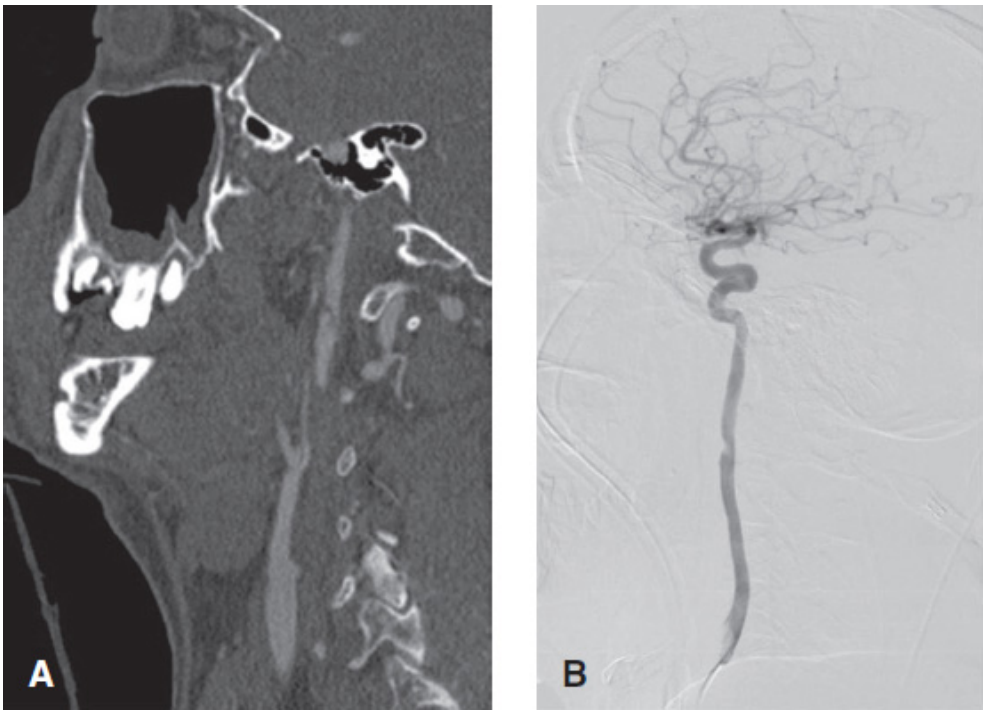

Figure 27.8 **A:** CT angiogram demonstrating a grade 3 blunt cerebrovascular injury to the left internal carotid artery with small pseudoaneurysm. **B:** Corresponding cerebral angiogram of the internal carotid artery.

Figure 27.9 Fluoroscopic image of a compliant balloon inflated in the descending thoracic aorta (resuscitative endovascular balloon occlusion of the aorta or REBOA). This endovascular maneuver was accomplished through a percutaneous sheath in the right femoral artery and can be accomplished in certain scenarios in lieu of resuscitative thoracotomy with aortic clamping. (From Scott DJ, Eliason JL, Villamaria C, et al. A novel fluoroscopy-free, resuscitative endovascular aortic balloon occlusion system in a model of hemorrhagic shock. *J Trauma Acute Care Surg* 2013;75(1):122–128.)

- Control of massive air leaks
- Internal cardiac massage
- Thoracic aortic occlusion

RT provides rapid access to the thoracic cavity via an anterolateral thoracotomy through the 4th interspace with the patient in the supine position. This approach allows extension of this incision across the sternum called a

"clam-shell incision" permitting access to both the mediastinum and contralateral thoracic cavity if needed.

Aortic control permits time for transfusion and enhances cerebral and myocardial perfusion until definitive operative repair can occur. Published neurologically intact survival rates following RT range from 3.9% to 11.7%[45] with penetrating thoracic injury. Patients presenting pulseless with blunt injury demonstrated neurologically intact survival rates from 0.7% to 2.4%. Given the dismal outcomes with RT in the setting of blunt trauma, many centers do not perform RT in the absence of penetrating injury.

The use of resuscitative endovascular balloon occlusion of the aorta (REBOA) has been introduced and studied as an adjunct for temporary hemorrhage control with NCTH (**Fig. 27.9**).[46–48] This technique for hemorrhage control has been used in trauma as early as the Korean War.[49] While increased data have led to more widespread use of REBOA in tertiary care trauma centers across the world,[50–52] the role of REBOA in the control of exsanguinating torso hemorrhage both in the prehospital and emergency room setting remains controversial.[48]

Thoracic Cavity

Patients with vascular trauma to the aortic arch and its major branch vessels often present in shock requiring immediate surgical intervention in the form of tube thoracostomy, RT, or median sternotomy. Aortic arch injuries are associated with multiple other vascular injuries including vena cava, innominate vein, and pulmonary artery injuries. Median sternotomy provides the widest and most versatile exposure for the arch vessels with the exception of the proximal left subclavian artery. This vessel injury is best approached via a left anterior lateral thoracotomy in the 3rd rib space given its origin in the posterior mediastinal. Sternotomy followed by division of the innominate vein allows the pericardium to be opened for release of cardiac tamponade as well as evaluation and repair of a cardiac injury. Exposure of aortic branches more distally can be facilitated by extending the sternotomy incision proximally as a supraclavicular incision with division of the sternocleidomastoid muscle. The descending aorta and pulmonary hilum can be approached most rapidly via a left anterolateral thoracotomy or if patient stability permits, a left posterolateral thoracotomy.

Abdomen and Retroperitoneum

Abdominal vascular trauma is conventionally divided into the intraperitoneal and retroperitoneal area. The retroperitoneum can further be divided into four zones. Zone I is centrally located and contains the aorta and major branches as well as the inferior vena cava (IVC). This zone is further divided into the supramesocolic and inframesocolic areas. Zone II (left and right) contains the kidneys and renal vessels. Zone III includes the pelvic retroperitoneal and contains the iliac vessels. Zone IV includes the perihepatic area containing the retrohepatic IVC and hepatic vines.

The abdomen should be opened through a midline incision from the xiphoid process to the pubic symphysis to permit access to all four quadrants. Initial packing remains the best method of initial hemostasis, allowing time for resuscitation. Packs are then removed in a stepwise fashion allowing for more directed hemostasis. In penetrating trauma, all retroperitoneum hematomas should be explored with the exception of zone IV retrohepatic hematoma. In blunt trauma, only zone I hematomas should be opened unless expanding. Hematomas at the root of the mesentery in the presence of ischemic bowel should be explored to rule out injury to the superior mesenteric artery.

In zone I injuries, proximal control should be obtained of the supraceliac aorta by cross-clamping at the diaphragm. In cases where a retroperitoneal hematoma extends to the aortic hiatus, proximal control may be best approached with surgical control of the thoracic aorta or placement of a REBOA. Supramesocolic bleeding involving the origin of major aortic branch vessels should be exposed via a left medial visceral rotation (the Mattox maneuver) by mobilizing the left colon, spleen, tail of the pancreas, stomach fundus, and left kidney medially. If supramesocolic IVC bleeding is suspected, bleeding can be identified with a right visceral rotation (the Cattell–Braasch maneuver) by mobilization of the right colon, hepatic flexure, and Kocher mobilization of the duodenum and pancreatic head. Inframesocolic bleeding can be exposed with cephalad retraction of the transverse colon and displacement of the small bowel to the right of the abdomen.

Zone II injuries require partial medial visceral rotation on the affected side. Nephrectomy may be required. If there is concern for injury or violation

of the collecting system, drains should be left in the perinephric retroperitoneal space. Zone III injuries should only be explored if large vessel injury is suspected. Dissection of the paracolic peritoneum and medial rotation of the right or left colon may be necessary, as well as mobilization of the terminal aorta. Operative management of zone IV is fraught with difficulty and high mortality. In the absence of exsanguinating hemorrhage, these contained venous injuries should be managed with packing alone.

In general, reconstruction of any major vessel should utilize autogenous vein (typically greater saphenous vein) especially in the presence of intestinal spillage (**Fig. 27.10**). In the setting of damage control laparotomy for patients with severe physiologic derangements, temporary shunting with later definitive repair may be appropriate. Small venous injuries should be ligated, however, large venous injuries should be repaired whenever possible. Because large veins often do not tolerate clamps in the setting of trauma and hematoma, direct pressure should be applied with sponge-sticks or smaller Kittner dissector sponges to allow for visualization.

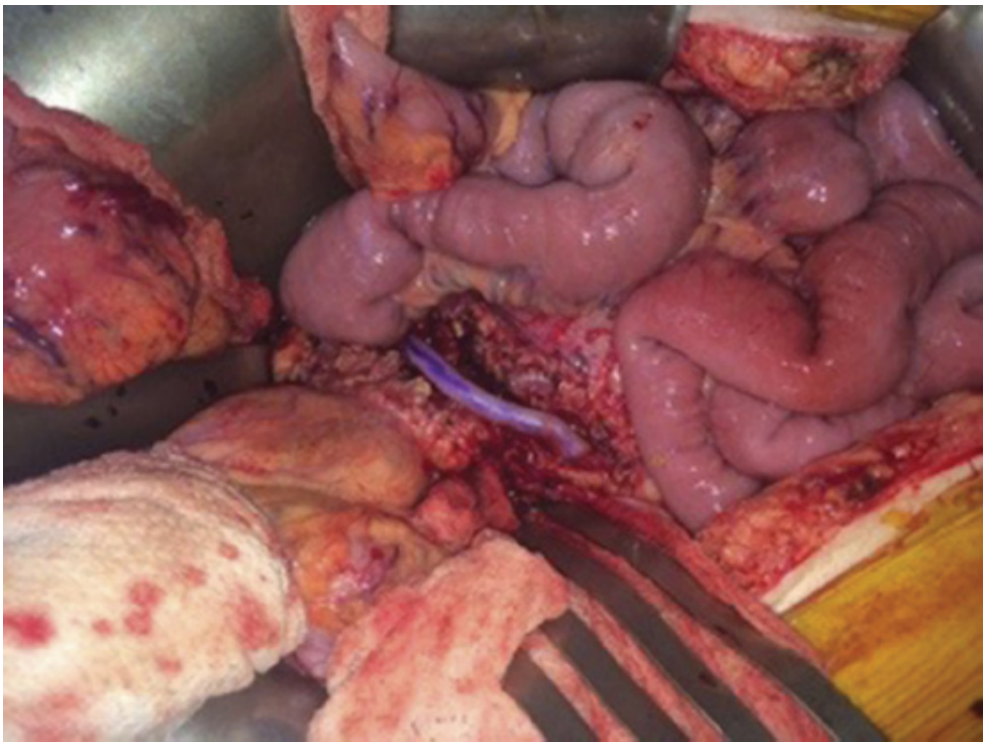

Figure 27.10 End-to-end interposition graft repair of midsuperior mesenteric artery injury with great saphenous vein.

ENDOVASCULAR MANAGEMENT OF TRAUMATIC VASCULAR INJURIES

11 While open surgical therapy remains the gold standard for treatment for traumatic injuries, endovascular management presents an alternative option particularly with injury to the arch vessels and thoracic aorta. The injury pattern in which endovascular therapy has revolutionized treatment algorithms is blunt thoracic aortic injury (BTAI). In those 20% of patients who arrive to the hospital alive following BTAI, endovascular treatment has essentially replaced open aortic repair as the gold standard of treatment due to improved outcomes (**Fig. 27.11**).[53,54] The BTAI grading system can be used to determine which patients are candidates for medical therapy alone versus repair (**Table 27.5**).[55] Studies have also demonstrated that in the absence of free rupture, delayed repair if preferred.[53]

Table 27.5 Grading of Blunt Thoracic Aortic Injury

Injury Grade	CT Characteristics
Grade 1	Intimal tear
Grade 2	Intramural hematoma
Grade 3	Pseudoaneurysm
Grade 4	Free rupture

CONCLUSION

Vascular trauma remains a leading cause of mortality and morbidity following civilian and military injuries despite improvement in damage control protocols and an improved understanding of resuscitation principles. While the operative management of vascular trauma has changed with the growth of endovascular approaches to hemorrhage control, the principles of proximal and distal control remain paramount. Regardless of experience and training level, the foundational principles provided in this chapter will guide

one's attempts to improve management of one of the most challenging and devastating injury patterns in trauma.

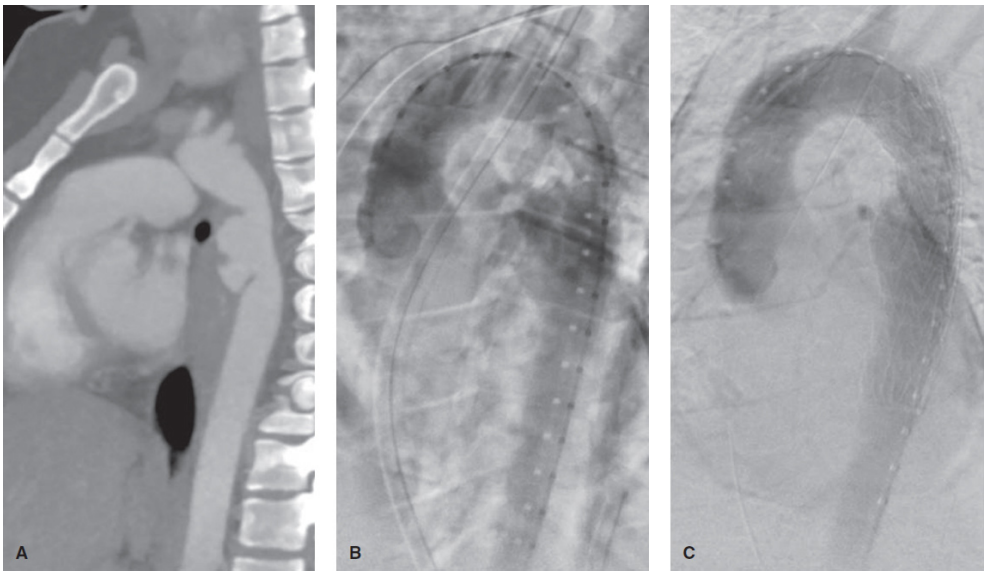

Figure 27.11 **A:** CT Angiogram depicting a grade 4 thoracic aortic injury. **B, C:** Angiograms demonstrating active extravasation with subsequent stent graft repair.

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28

The Principles of Orthopedic Surgery for Trauma

Raymond Malcolm Smith

Key Points

1. Establishing bony stability significantly reduces local bleeding.
2. Major pelvic fractures occur in recognizable patterns that predict other injuries.
3. Obtaining bony stability can significantly reduce pelvic bleeding and is an essential part of their initial care.
4. Early stabilization of major fractures in polytrauma patients facilitates general patient care and saves lives.
5. Early radical management of open fractures with adequate debridement by wound excision, bony stabilization, and early healthy soft tissue cover significantly reduces the risk of infection and decreases morbidity.
6. Establishing reliable bony stability is the key for local soft tissue healing.
7. The principles of accurate reduction, stable fixation, preservation of a healthy soft tissue envelope, and early rehabilitation with joint and patient mobility are the keys to general fracture management.

INTRODUCTION—AIMS AND PRIORITIES IN ORTHOPEDIC TRAUMA CARE

The subspecialty of orthopedic traumatology concentrates on skeletal reconstruction after injury and the overall management of these patients. This involves the management of routine fractures but also the more complex problems presented by very severe localized high-energy injury and combination multisystem polytrauma. In critical multisystem injury, it is very important to correctly manage the orthopedic injuries which can easily be underestimated. Their management has a critical role in ensuring survival of the patient and ensuring practical overall clinical management. In severe local injury, life is also at risk but useful limb salvage needs orthopedic management often combined with plastic surgery to manage severe soft tissue

injury. Patients with less severe fractures still have major problems, the orthopedic care should limit the medium- and long-term disability caused by fractures and severe peripheral soft tissue injuries. This overview is illustrated in **Table 28.1**.

ORTHOPEDIC TRAUMA SURGERY TO SAVE LIFE

In patients with severe multisystem trauma, musculoskeletal injuries are commonly a major part of the trauma burden and a threat to life. This threat comes from hemorrhage (from individual or multiple injury sites), the general effect of multiple major skeletal injuries and specific injuries such as vascular injury and compartment syndrome or later complications such as infection, immobility, and thromboembolic disease.[1]

Hemorrhage

The most immediate and absolute need for surgery in trauma is the control of bleeding; this critically involves the orthopedic traumatologist in two scenarios, massive bleeding from multiple high-energy fractures or severe localized bleeding associated with a specific major injury, most typically from the pelvis. Bleeding from multiple fractures is common and often underestimated. In general, early transfusion protocols and early 1 fracture management controls the situation. Bleeding from fractures will be invariably slow and usually stops spontaneously when the fracture is reduced, stabilized, and the compartment tension restored. However, it is very easy to underestimate the collective blood loss from multiple injuries and get too far behind in resuscitation, a situation that can then become uncontrollable. Aggressive transfusion protocols with appropriate attention to replace volume and clotting factors with early use of blood with plasma and platelets are essential in parallel with the provision of skeletal stabilization for early hemorrhage control.[2] This may involve wound debridement and hemostasis in the complex open injury or early long-bone stabilization in multiple closed fractures. Occasionally, temporary external fixation may be required to

provide rapid control of skeletal instability when the more extensive surgery required for definitive stabilization would be inappropriate.

The Bleeding Pelvis

Put simply, patients with major pelvic ring injuries can bleed to death. Often presenting after a high-energy injury, the signs of major hemorrhage from the pelvis may be obvious with massive local swelling and clear instability. At presentation, a primary plain pelvic x-ray remains the best way to quickly understand the fracture. It will allow immediate assessment of the fracture pattern, energy involved, degree of displacement and leads to an estimate of the risk of local bleeding and presence of local or distal associated injuries.[3–7] Today many patients have a binder applied in the field for transport. This is a very effective way to initially control pelvic volume and tamponade bleeding but may reduce the deformity and also lead to the initial x-ray, underestimating the degree of injury.

Understanding the pelvic fracture is essential, Young and Burgess[3,4] (**Fig. 28.1**) presented a classification system based on the implied direction of the initial force and defined injuries essentially as anterior–posterior compression (APC), lateral compression (LC), and vertical shear (VS) injuries. This allows an assessment of the direction of the force applied, the resultant instability, and can predict mortality, transfusion requirements, and 2 associated injuries. In general, injures that make the pelvic ring bigger bleed locally while ones that make it smaller can bleed but are more commonly markers of the injury mechanism and remote injuries, specifically, the associated ipsilateral chest and abdominal injury. The Tile[8,9] (**Fig. 28.1**) system considers the injury with regard to the resultant instability and has now been adopted by the AO Foundation (AO) and Orthopedic Trauma Association (OTA). An "A"-type fracture has a stable pelvic ring and essentially includes more minor avulsion fractures and mechanically stable pelvic ring injuries (includes APC I & LC I). "B"-type injuries are rotationally unstable but vertically stable with an intact posterior soft tissue hinge providing some stability (corresponding to APC II or LC II/III injuries), while "C"-type injuries are both rotationally and vertically unstable, implying that the posterior hinge is torn (corresponding to APC III and VS injuries). The latter carry the highest risk of bleeding and death.

Table 28.1 Why We Operate on Fractures: Priorities in Trauma Care

Orthopedic surgery to save a life
Orthopedic surgery to save a limb
Orthopedic surgery to limit disability

From a surgical management perspective, A-type injuries are unlikely to be a source of major bleeding while B type and, specifically, C types are increasingly life threatening. After initial assessment, primary radiology, and consideration of the response to initial resuscitation, pelvic fractures can then be considered by the mechanical stability resulting from the injury and the resultant hemodynamic response (**Table 28.2**).

Table 28.2 Principles of Management of Major Pelvic Ring Injuries

	Mechanically Stable Pelvis	**Mechanically Unstable Pelvis**
Hemodynamically stable	Nonoperative	Early, planned operative stabilization of pelvic ring
Hemodynamically unstable	Likely extrapelvic cause Angiography/embolization	Emergent provision of mechanical stability ± Packing/angio

The role of the orthopedic surgeon is to assess the injury with regard to the local and associated problems and to provide pelvic mechanical stability when required. A hemodynamically stable patient with a stable pelvic ring injury does not require major active orthopedic management, although it should be noted that rarely even the most apparently simple injury can cause local bleeding and transfusion may be required.[10] The hemodynamically stable patient with a mechanically unstable pelvic ring injury needs early but

not emergent surgery to restore mechanical stability to the pelvis for pain relief, normal daily care, and mobilization. Hemodynamically unstable patients need emergent care to restore their physiologic stability. If the pelvis is mechanically stable, orthopedic intervention has little to offer, either there is an extrapelvic cause for the bleeding or hemostasis should be obtained by provision of appropriate clotting factors and platelets, packing or angiographically.

The patient in hemorrhagic shock with a major unstable pelvic ring is a very different problem.[10,11] Early coordinated multidisciplinary care in the right hospital is essential, with appropriate resuscitation within an established massive transfusion protocol. It is well established that the site of hemorrhage in most bleeding major pelvic fractures is from the fractured bone surfaces and extensive soft tissue injury, and rarely 3 from major named arteries. Fortunately, the majority of pelvic bleeding will slow or stop when skeletal stability is achieved. However, rapid stabilization of the pelvic ring is a major expert intervention at best and is rarely easily achievable in the acute bleeding situation. Initial reduction, stability, and some local tamponade is provided by a pelvic binder. In critical cases, it should not be removed without an available alternative method to provide stability. Internally rotating the hips, slightly flexing the knees, and binding the legs at the thigh should also be used if possible and provides additional effective control. The provision of early pelvic fixation or a primary angiographic approach to bleeding control depends on local expertise and protocol. Recently, a move to emergent operative provision of skeletal stability and packing of bleeding from the pelvis has entered common practice.[2,12] The major bleeding pelvic injury is considered similar to a bleeding liver and where general hemorrhage control is achieved with packing for local pressure. For the severe pelvic injury, a systematic protocol of bleeding control and transfusion that emphasizes the importance of not getting out of control or reacting too late, "The Denver Protocol"[2,12] begins with a patient with shock, a pelvic ring injury, and a failure to respond to 2 L of crystalloid resuscitation and 2 units of blood transfusion (**Algorithm 28.1**). The essential principle is an early trigger to aggressive surgical management for hemorrhage control with preperitoneal packing and rapid blood and factor replacement before the patient becomes grossly coagulopathic. From the orthopedic point of view, restoring skeletal stability

is a critical part of this process and close cooperation with the general traumatologist is essential.

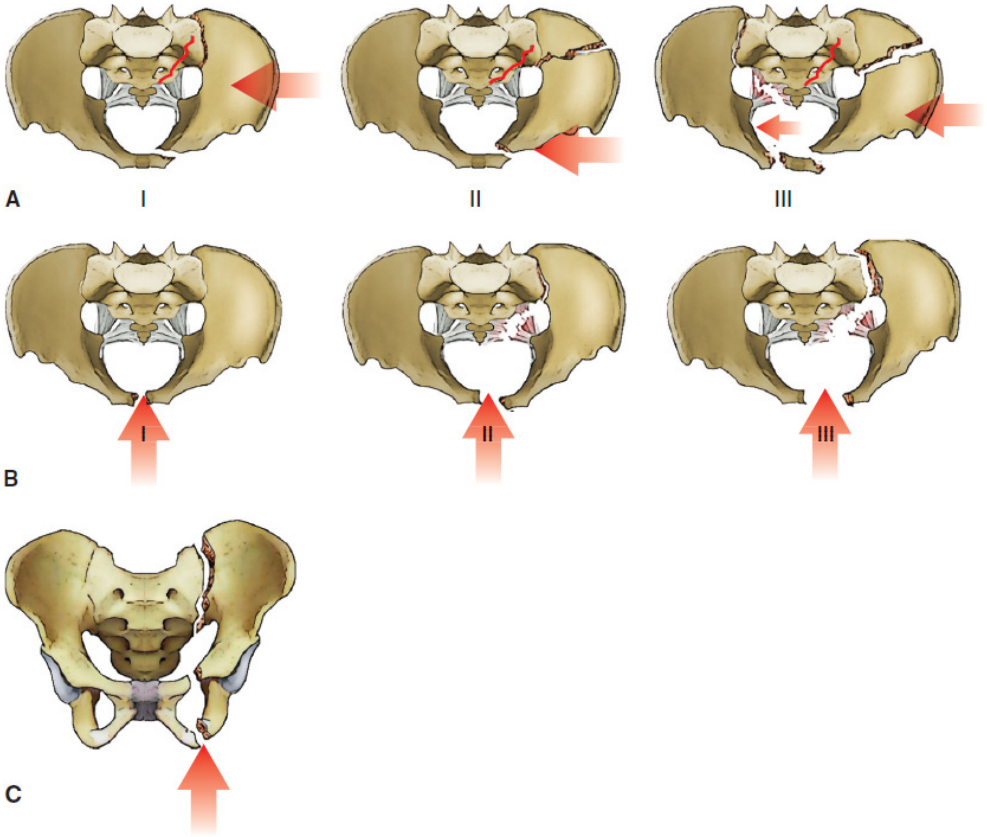
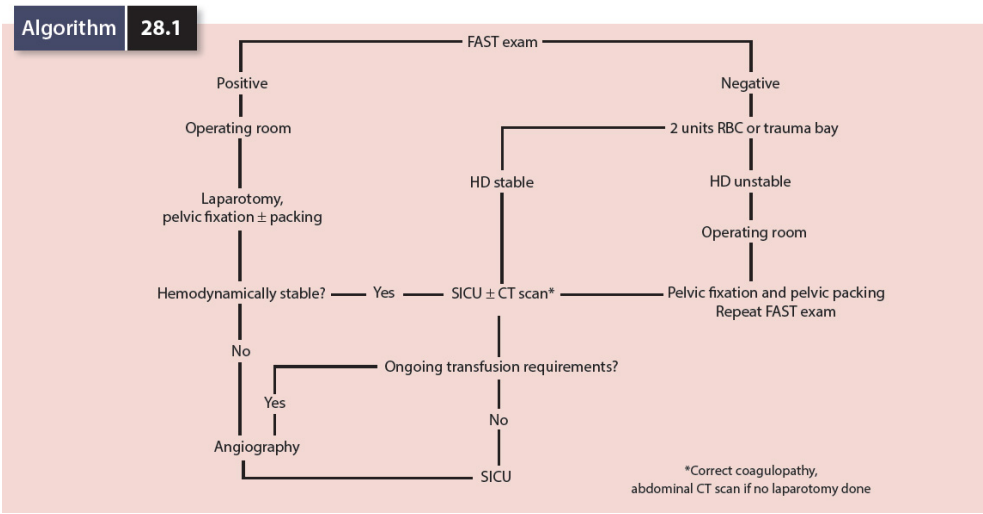


Figure 28.1 **A–C:** Young and Burgess, and Tile (AO/OTA) classifications of pelvic fractures. (From Wiss DA. *Master Techniques in Orthopaedic Surgery: Fractures*. 3rd ed. Philadelphia, PA: Wolters Kluwer Health; 2012.)



Algorithm 28.1 The Denver Protocol for management of major pelvic fractures. (Reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery. Mauffrey C, Cuellar DO 3rd, Pieracci F, et al. Strategies for the management of haemorrhage following pelvic fractures and associated trauma-induced coagulopathy. *Bone Joint J* 2014;96(9):1143–1154.)

Pelvic Packing

The procedure of packing a pelvis for hemorrhage is well within the capabilities of most surgeons but some form of pelvic bony stability has to be achieved first to give a solid base to pack into. In the emergency situation, this commonly means the application of an anterior external fixation frame although if possible, internal fixation has many advantages. Occasionally, emergency provision of posterior stability with emergent percutaneous sacroiliac fixation or application of a "C clamp" can be dramatically effective in restoring stability and markedly slowing bleeding. Preperitoneal packing is done through a small anterior incision just above the pubis. After separating the rectus muscles (which may be avulsed from the pubis), the cavity created by the trauma is entered, the hematoma evacuated and rapid mechanical stability obtained (often temporarily, applying a bone-reduction clamp across the pubis). The bleeding cavity, already produced by the trauma, is then packed with as many packs as required. These should be placed as far back into the true pelvis as possible. The hematoma cavity created by the injury will be obvious and it is not required or desirable to extend the dissection outside this area but it is essential to get the packs right to the back of the cavity. Assuming hemostasis is achieved, the packs are left

in, often for 48 hours and under an open but sealed abdomen before they are changed or simply removed depending on the physiologic response.

COMPLICATED PELVIC INJURIES—OPEN FRACTURES OR ASSOCIATED VISCERAL INJURY

The initial assessment of any patient with a pelvic fracture must also include an inspection of the perineum with rectal and vaginal examination to check for complex open injuries or associated urologic injuries. Open pelvic fractures and those associated with local visceral damage carry significant mortality and need specific treatment based on the wound or specific injury sustained.[13,14] The degree of contamination and size of the zone of injury in the pelvis massively worsens the situation and may prove fatal such that aggressive decontamination and protection of this extensive zone of injury from further contamination by diversion of the fecal stream may be essential.

Complex urologic injuries are commonly seen with specific patterns of pelvic fracture. A significant APC injury is commonly associated with an extraperitoneal bladder rupture of the anterior bladder wall directly in line with the plane of injury. LC injuries may be associated with urethral tears as the inferior ramus cuts the male membranous urethra as it is forced across the midline by the injury. In all cases, the presence of hematuria or blood at the meatus is the pathognomonic sign of injury and necessitates appropriate investigation and joint management with the urologic service. Again from the orthopedic point of view, no soft tissue reconstruction can work without an underlying stable bony skeleton to support the repair and prevent reinjury. In many situations, the best access the urologist will have is at the time of the primary bony stabilization and early urologic repair or diversion avoids many problems, although a staged urologic procedure may be required.

THE ORTHOPEDIC MANAGEMENT OF MAJOR POLYTRAUMA

Major trauma is a surgical problem, and the essence of management is to take control and stay in control of the trauma and 4 limit further harm. From the orthopedic point of view, this means that it is essential to gain control of the skeletal instability. This concept has developed through studies focused on the femur fracture, which has become the index injury in this regard. Essentially, despite the development of long-bone nailing by Kuntscher[15] in the 1940s, though till the late 1980s most Western surgeons generally believed that seriously injured patients were "too sick to operate on" and used traction devices as the primary mode of treatment for major fractures. Concern that this was not the best mode of treatment led to the term "Horizontal Crucifixion" and several early publications[15–17] suggested that early surgical stabilization of the fractures, specifically with femoral nailing was valuable. Johnson[18] confirmed this effect and showed that it appeared to be greater the more severely the patient was injured. In 1989, Bone[19] published his landmark paper, a prospective randomized trial of early against late femoral nailing after severe injury. Essentially, he showed that there was a major advantage in early nailing and the pendulum now swung from nonoperative care to enthusiastic universal early skeletal stabilization after polytrauma. The patient was considered "too sick not to operate on" and a management philosophy now termed "Early Total Care" developed. This practice was soon questioned, specifically in Germany where the orthopedic trauma surgeon is closely involved with intensive care and inevitably observed the combined effect of other injures. Pape et al.[20] again considering the femur, looked specifically at the effect of early and late femoral nailing in severe polytrauma and showed a deleterious effect of an associated chest injury in association with femur fractures treated by early reamed nailing. While statistically the effect seemed more related to the chest injury than the nailing, this alerted the profession to the combination effect of these injuries and stimulated an outpouring of research looking at the general and immunologic effects of orthopedic procedures and specifically of reaming the femur.[21–36] Eventually, an understanding of the general effects of polytrauma and bony injury has become more widely accepted and a concept of the appropriate surgery (damage control orthopedics [DCO]) for the most severely injured patients developed.

Damage Control Surgery in Orthopedics

Damage control in orthopedics means taking control of the musculoskeletal elements of the injury without creating an increased trauma load due to increased surgical bleeding or a lengthy surgery associated with definitive care of complex fractures (**Fig. 28.2**). The priorities are hemorrhage control, wound management, tissue revascularization (including compartment decompression), and general restoration of major skeletal stability usually by the rapid application of external fixators. The basic physiologic parameters are then normalized in a critical care environment unit and definitive stabilization is delayed until the peritraumatic immunologic storm has settled.[25,26,28,29] The most critical element is the speed and accuracy of the initial surgery as the critical injured patient cannot tolerate a long orthopedic procedure. However, the principle of establishing early skeletal stability remains; this is the major lesson from Johnson and Bone[18,19] and is not disputed. The issue is not if, but how this is obtained. Today's question is how do we identify which patients are too sick for what? Long orthopedic procedures and protracted bleeding must be avoided and nailing the femur in a sick, under resuscitated patient seems to be particularly poorly tolerated. A variety of parameters have been investigated to understand this,[25] despite early enthusiasm, interleukin-6[24] has proved mainly to be a research tool and today a spectrum of parameters considering the patient's general condition are commonly used.[30] This essentially means close communication and protocol agreement with the anesthetic/general trauma team to decide what extent of surgery should be done. Basic parameters to be considered include the hemoglobin/hematocrit, ventilation parameters, platelet count and coagulation studies, patient temperature, and a measure of acidosis, usually the lactate level. The latter is now the primary decision-making parameter used by many orthopedic surgeons. Currently, Vallier et al.[30] have suggested a lactate level of 4 mmol/L is a safe cutoff above which it is not safe to continue surgical reconstruction and only DCO can proceed (**Table 28.3**). If DCO has been performed to obtain temporary skeletal stability, it is accepted that the definitive reconstruction should be delayed until the patient is well enough, usually at least 5 days.

Figure 28.2 Early damage control of extensive limb injuries with external fixation.

Table 28.3 Essential Priorities in Orthopedic Damage Control

Principle	Example
Surgical hemorrhage control	Direct control, pelvic packing, long-bone stabilization
Cavity decompression	Compartment syndrome
Debridement/decontamination	Major open wounds/fractures
Revascularization	Repair vascular injury to revascularize the limb if patient is well enough, if not amputate
Fracture stabilization	Usually rapid external fixation of major long-bone injury/pelvis
Critical care	Ongoing resuscitation, rewarming, and factor replacement prior to delayed secondary surgery
Delay reconstructive surgery	Conversion of external fixation to nails, definitive joint reconstruction

Special Polytrauma Situations—Head Injury

There are specific scenarios that change priorities, the most obvious being the associated head injury. When the brain is at risk, the primary aim of care is to maintain cerebral oxygenation and cerebral perfusion pressure (CPP). Orthopedic procedures, especially those that would lead to bleeding, swings in blood pressure and thus episodes of reduced CPP should be avoided. However, this does not eliminate the benefit of the stable skeleton in general critical care such that DCO and appropriate bony stabilization at the right time are still strongly indicated.[37,38]

Special Polytrauma Situations—Chest Injury and Femur Fractures

The effect of the chest injury is discussed above. It was emphasized by Pape and Tscherne and innumerable papers that followed.[20] While multiple studies have shown the advantages of early skeletal stabilization, there is no doubt that the lungs are vulnerable to further insults after injury, and that the acute lung injury can be worsened by fat embolization especially during instrumentation of the femoral canal. While improvements in reamer design reduce canal pressurization and smaller nails have been advocated, delaying definitive nailing for 5 days after initial external fixation in the most critical patient is probably the standard of care. The patient with bilateral femur fractures is at a significantly increased risk and some surgeons avoid bilateral femoral nailing at the same time even in healthy patients.[39–42]

SPECIFIC ORTHOPEDIC SCENARIOS

Major Wounds

The ongoing effect of major wounds can be critical. In the first instance, debridement of necrotic tissue from the trauma is essential and is commonly inadequately done at the initial surgery. Wounds will never stabilize until adequately excised and when associated with fractures, will not heal until bony stability has been established. The management of open fractures is described below; in polytrauma cases the principles remain the same but the ability to obtain early definitive care may be compromised by the patient's general situation.

ORTHOPEDIC TRAUMA SURGERY TO SAVE LIMBS

Open Fracture Principles

Open fractures can range from simple to destructive injuries but in all, the important feature is that the fracture hematoma communicates with the outside environment and the fracture is contaminated. As such, the specific management revolves around limiting the chance of this contamination converting to established infection. General measures include the provision of tetanus cover, early broad spectrum antibiotics, early splintage, and wound dressing and are followed by early surgical management. The latter is designed to reduce the degree of contamination, to remove necrotic or threatened tissue likely to become infected, and to protect the limb by making it unlikely to develop further infection due to an unstable open wound (**Tables 28.4** and **28.5**).

Table 28.4 Op en Fracture Surgical Principles

Debridement to healthy margins and profuse lavage/decontamination
Bony stabilization
Early, healthy soft tissue cover

The debridement of an open fracture is one of the most difficult surgical procedures; it should not be relegated to inexperienced staff and, if possible, not attempted out of normal hours unless the limb is very seriously threatened. The whole zone of injury must be assessed and all dead and dying tissue removed, only nerve and vessel must be preserved and poor muscle specifically removed. It may more appropriately be termed wound excision. Any free bone or fragments attached by flimsy soft tissue should also be removed and the resulting defect dealt with accordingly, although only rarely is a significant defect produced. Wound extensions need to be placed with specific consideration for the later closure and must not make the soft tissue reconstruction more complex. An adequate appropriate debridement must be performed the first time. Repeated debridements “to make sure” are a result of an inadequate initial operation and massively increase delay and the infection rate. This should be avoided at all costs.

Establishing early bone stability is essential, this reduces the chance of late infection and facilitates the subsequent soft tissue reconstruction. In truth, the ability to perform an adequate debridement and the best bony reconstruction depends directly on the orthopedic surgeons’ confidence in the

subsequent soft tissue closure and thus the working relationship with the plastic surgery team. While soft tissue reconstruction is often delayed for practical reasons, there is excellent evidence that the earlier a healthy closure is obtained the better. This is true to the extent that the best data in the most complex (IIIb) injuries are with immediate flap cover after an adequate initial debridement and definitive bony reconstruction as one primary procedure (**Fig. 28.3**). Few units can achieve this at primary presentation, such that definitive debridement, fracture stabilization, and appropriate soft tissue assessment at the primary procedure followed by definitive soft tissue cover at the second visit to the OR (at about 48 hours) after the patient has been appropriately counseled is probably the best achievable standard. Cooperative care with the plastic surgical service from the start is essential.[44–50]

Table 28.5 Open Fracture Classification (after Gustillo & Anderson[43])

Grade I	Small low-energy wound <1 cm, no high-energy features
Grade II	Small low-energy laceration over fracture 1–10 cm, no high-energy features
Grade IIIa	High-energy open fracture (degloving, periosteal stripping, bone comminution) with adequate soft tissue cover
Grade IIIb	High-energy open fracture with inadequate soft tissue cover
Grade IIIc	Any open fracture with a vascular injury requiring repair for viability

Figure 28.3 **A–E:** Management sequence of a major open fracture. This is a III-C injury in a 12-year-old treated by immediate "fix and flap" incorporating the anastomosis for the latissimus dorsi free flap into the vascular repair. The subsequent course shows good soft tissue and bony healing.

VASCULAR INJURIES

An acutely ischemic limb with a fracture or dislocation is a major surgical emergency. At presentation, all fractures must have the distal circulation assessed and documented; if the blood supply is affected, the fracture or dislocation must be rapidly reduced. Fortunately, this commonly results in restoration of circulation and normal fracture care can continue. If not an emergent, combined vascular–orthopedic procedure is required. Sometimes a temporary shunt will be used to obtain distal flow while a bony reconstruction is performed. Bony stability at the correct length must be obtained before definitive vascular reconstruction, both to allow the vascular repair to be at the correct level and tension, and to protect it from disruption. Any subsequent reconstruction must be done with provision for awareness and care of the vascular repair and should include fasciotomy to prevent reperfusion compartment syndrome.

COMPARTMENT SYNDROME

A compartment syndrome is a major surgical emergency as the muscle is acutely ischemic due to an increased compartment pressure reducing tissue perfusion to below a critical level. Accordingly, the classical presentation is pain out of proportion to the injury due to the muscle ischemia. The compartment may be obviously hard with loss of muscle function and distal neurologic symptoms due to pressure on the nerves passing through the compartment. Loss of arterial flow through the compartment is exceedingly rare and not useful diagnostically, the presence of a distal pulse does not contribute to the diagnosis of compartment syndrome. While the diagnosis is often clinical and straightforward, a formal measurement of the perfusion pressure of the compartment (similar to CPP in head injuries) has been popularized by McQueen.[51] Assessing the anterior compartment of the lower leg after tibial fractures with constant compartment pressure monitoring, they showed that if the compartment pressure remained at least 30 mm Hg below the diastolic blood pressure (known as the D*p* >30), the consequences of compartment syndrome (muscle necrosis and contractures) did not occur. Accordingly, today the definitive test for compartment syndrome is a direct measurement of the compartment pressure and comparison to the diastolic pressure. This is particularly seen in situations when the patient is not able to respond appropriately to pain. These include, during anesthesia, particularly under regional anesthesia; patients sedated on intensive care; patients where any strong analgesia is being used; or if the patient is poorly responsive after a medication overdose.[52] The diagnosis must not be missed, as immediate fasciotomy is needed to restore muscle perfusion.

Rarely, compartment syndromes present late when muscle necrosis is established. There will be a high creatinine kinase level, myoglobinuria, and even frank renal failure if several compartments are involved. If compartment syndrome is established at presentation, perhaps if diagnosed after 12 to 24 hours, fasciotomy is not indicated as it will only expose the necrotic compartment to infection. Unless deemed that muscle debridement is the only way to reduce the myoglobin level and reduce the renal damage, the tight limb should be simply observed and the subsequent distal contracture more safely dealt with later by specific muscle or tendon releases.[53]

INDICATIONS FOR AMPUTATION/FAILURE OF RECONSTRUCTION

The indications for amputation can be remembered as the three "D's" referring to a limb that is "Dead," "Dangerous," or a "Damn" nuisance. In the early trauma situation, this may be clearly obvious and early amputation may be lifesaving while the latter refers to later reconstructive scenarios. While limb salvage is always the aim, the injury may be too severe and should not be attempted if it puts life at risk. This requires experienced decision making at the acute stage and, when possible, agreement between staff surgeons. In an isolated injury situation, the decision essentially depends on the degree and site of necrotic tissue and the functional potential of the limb after reconstruction. This can be a most difficult decision and should be made by a surgeon experienced in reconstructive options and their functional outcome. In many situations, an amputee will function as well as, if not better than a poor reconstruction especially if several muscle compartments have been lost. This is clearly a decision for experienced staff and should involve the patient as much as possible. The application of a temporary external fixator to the critically injured limb with a view to appropriate discussion prior to initiating further treatment has much to recommend it.

ORTHOPEDIC TRAUMA SURGERY TO LIMIT DISABILITY—MANAGEMENT OF FRACTURES

6 The management of fractures has been a core medical discipline for millennia and has developed from primitive bone setting, through the guild of army barber surgeons to the modern day orthopedic traumatologist. In general orthopedic practice today, almost half of the work is the care of injury and in most modern trauma centers 80% to 90% of the surgical care of the injured falls to the orthopedic service.

Fortunately, fractures have an intrinsic tendency to heal and bone is one of only two tissues to heal by reforming its own tissue and not with a scar. There are four essential phases in fracture management: assessment, position,

healing, and rehabilitation. The first mandates a full limb assessment with documentation of the relevant clinical signs. This must include assessment and documentation of the neurovascular state of the distal limb. X-rays need to be taken of the whole bone involved and centered on the fracture. For example, an x-ray of the humerus which includes the shoulder is inadequate to assess a specific shoulder injury and separate views of the relevant part must be obtained. These views must include an AP and appropriate lateral specifically of the appropriate part. In many situations, the injury anatomy is still not adequately defined by these views and specific additional x-ray views or a computed tomography (CT) scan will be required to fully understand the injury and for surgical planning. Fracture management then centers on obtaining and holding the position of the fracture through healing. Essentially, middiaphyseal fractures need to be held in a position to maintain overall length, alignment, and rotation but do not need an anatomical reduction of individual fragments. In modern practice, this is usually achieved by intramedullary nailing which also provides the relative stability needed at the fracture site and facilitates healing with callus (**Fig. 28.4**). As a contrast, articular fractures usually need a direct open approach to ensure accurate reduction of the joint surface and stabilization with absolute stability. The recovery of joint function is directly related to the quality of the reduction and provision of stable fixation to allow early motion. In this situation, the bone at the joint would be expected to heal by primary bone union without callus (**Fig. 28.5**).

Essentially, the method chosen to hold the position of the fracture will be more or less stable depending on how firmly it holds the bone. A traditional cast on the tibia will provide only relative stability but should lead to a high rate of healing with callus. There can be a very good functional recovery if an adequate position is maintained and cast complications are avoided, but it essentially provides a less reliable hold than an implant directly applied to the bone. Accordingly, the patient undergoing nonoperative management in cast has to be followed closely, often with weekly x-rays for up to a month or until the position is deemed stable. The cast then stays until bone healing is considered adequate to maintain the position faced with functional loads and the cast can be removed. A stable, painless fracture on clinical examination suggests adequate healing to stay out of cast which should be confirmed by good bone healing on x-ray.

Table 28.6 Bone Healing Timeframes

Guideline Fracture Healing Times (in Cast)	Upper Limb (wks)	Lower Limb (wks)
Children	3	6+
Adults	6	12

Nonoperative fracture management is a highly skilled art that has been practiced for years but in the developed world is used today only for stable relatively undisplaced fractures. This includes undisplaced articular fractures, low-energy nonarticular fractures, and many fractures in children who have a large capacity for remodeling during and after bone healing and obtain bony healing in about half the time adults with excellent function results (**Table 28.6**).

The phase of bone healing from fracture to a stable skeleton progresses from an inflammatory reaction through fibrous tissue and cartilage formation before immature bone and finally mature remodeling. A number of biologic stimulatory molecules and specific mechanical features then drive the normal healing response. Overall, there is a progressive stiffening of the fracture environment until bone can form when the local strain is at or below 2%.[54,55] This may be produced by the gradual tissue stiffening provided by the natural healing process or by an orthopedic implant that creates a local strain environment in conjunction with the specific fracture anatomy and intrinsic fracture stability. Normal healing with splintage or with devices that produce relative stability (some fracture motion under physiologic loads) lead to the progressive stiffening effect described briefly above and healing by callus when the strain reduces to a level where bone can form. If an implant confers absolute stability, usually through direct compression of the fracture surfaces, the strain is less than 2% from the start and the bone heals by a modified remodeling process termed "primary bone healing," callus does not form. In planning a bony reconstruction, the surgeon specifically decides what degree of stability is required to treat a specific fracture 7 and the appropriate implant to do this. This follows basic AO[56,57] principles which are the key to

fracture surgery. Essentially, diaphyseal fractures need treatment with relative stability and indirect reduction techniques to maximize the local healing process. In contrast, articular fractures usually require a direct reduction for perfect anatomy and subsequent fixation with absolute stability (no deformation occurs under physiologic load) to facilitate joint recovery.

The rehabilitation process should be considered as soon as the soft tissues are stable enough to allow dependency and joint motion. This confers the major advantages of mobility to the limb and whole patient. With articular fractures, the cartilage is only nourished by diffusion from joint fluid which is effectively pumped into the hyaline cartilage as a secondary effect of motion. Accordingly, fracture fixation must be stable enough to allow early range of motion (ROM) exercises as tolerated but weight bearing is usually limited to protect the reconstruction from early displacement.

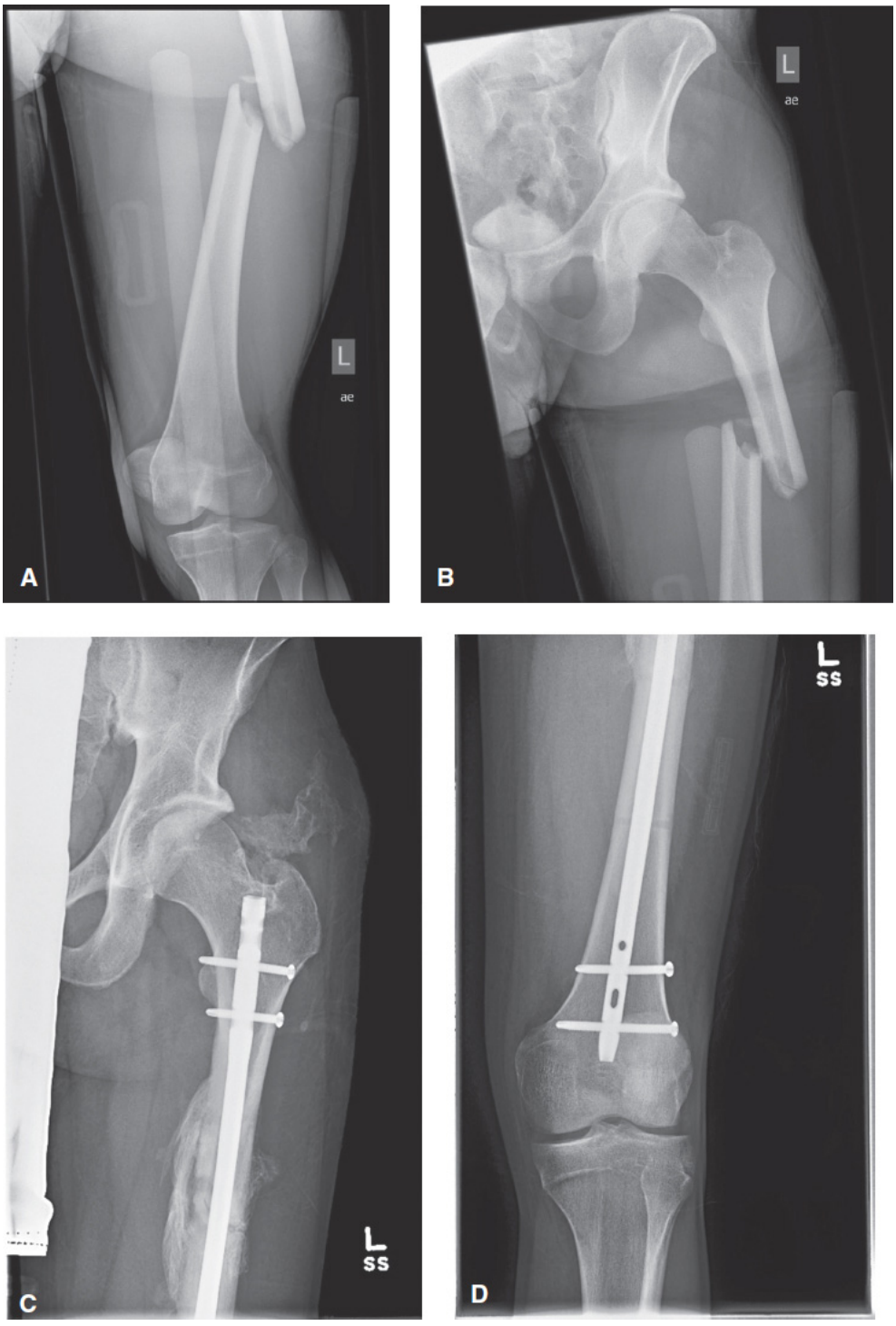


Figure 28.4 Assessment and surgical management of a diaphyseal fracture of the femur. **A, B:** Anteroposterior x-rays of a diaphyseal femur fracture. **C, D:** Reamed fully locked intramedullary nailing of a diaphyseal femur fracture showing progressive healing.

Complex Articular Fractures

Major joint injuries are significant threat to joint function.[58–60] The aim of care involves articular reconstruction with perfect joint anatomy and stable fixation with absolute stability. Surgical reconstruction often requires detailed preoperative assessment with a CT scan and application of specific implants often designed for the specific joint and side involved. The basic principles used for surgical reconstruction of these injuries were developed over 50 years ago by the AO and have only seen minor modifications since. However, modern implants and particularly the development of locking plates have improved the capability of our implants to hold fractures securely and specifically allow fractures to be held in position with less extensile exposures. Occasionally, the primary injury (even if closed) is associated with significant degloving of the local soft tissues, manifest by major fracture blisters and precludes an early open surgical approach.[61] Surgical management then takes the form of temporary bridging external fixation, applied outside the zone of injury which confers some stability and allows the soft tissues to settle prior to conversion to an internal fixation often after 1 to 2 weeks. However, in most fractures, excellent results can be obtained by much earlier surgery which is much easier than a delayed reconstruction.[61]

SPECIAL FRACTURE GROUPS—PROXIMAL FEMUR

Like many injuries, fractures of the proximal femur have a bimodal distribution with rarer high-energy injuries in the young and extremely common bone fragility fractures in the elderly. As a public health issue, osteoporosis and its related fractures are at epidemic proportions.[63] The general medical care of the elderly dominates the clinical picture where the mortality is of the order of 15% to 20% in the 3 months after fracture, and the injured frail elderly produce a major load on hospital and rehabilitation services. In addition, specific attention to long-term bone health is essential. The orthopedic issues of proximal femoral fracture take two forms and produce specifically different problems and solutions. The fractures

essentially occur inside (intracapsular) or outside the hip capsule (extracapsular). Intracapsular fractures carry a risk of avascular necrosis (AVN) of the femoral head depending on the displacement of the fracture, while intratrochanteric fractures are mechanically unstable due to the anatomy and offset of the proximal femur creating marked mechanical instability with a tendency to collapse into varus.

Figure 28.5 Assessment and surgical management of a complex articular fracture of the distal tibia (pilon). Despite virtually anatomic reduction, it progresses to degenerative arthritis in the medium term. **A, B:** AP and lateral x-rays of an intra-articular fracture of the distal articular surface of the tibia. **C, D:** CAT scans show the marked damage and displacement at the joint surface, underappreciated by initial x-rays. **E:** Open reduction and internal fixation to restore the joint surface for function and joint longevity. **F:** After healing and removal of the majority of the hardwear, there is significant degenerative arthritis of the joint that may need joint arthrodesis.

Intracapsular fractures (femoral neck) are classically classified by Garden.[64] Garden grade 1 and 2 injuries are essentially undisplaced and carry a low risk of AVN, they are usually treated by fixation unless the patient's bone quality is considered too poor for fixation. In that situation and in displaced fractures (Garden grade 3 and 4), a replacement of the femoral head with hemiarthroplasty or total hip replacement in a biologically younger patient is required.[65,66]

Extracapsular fractures (trochanteric) are mechanically unstable. They will collapse into varus without fixation and have a tendency to settle and shorten with healing due to the intrinsic bone weakness and pull of local muscles. Accordingly, fixation devices need the ability to mechanically control the angle of the femoral neck and accommodate some shortening without protrusion of the device into the hip. The instability is associated with the degree and position of any comminution which also indicates which device is appropriate to use. Essentially, a sliding hip screw device can be used for any trochanteric fracture unless the lateral wall is incompetent (reverse obliquity injuries or their equivalent) or where there is subtrochanteric extension. In these cases, an intramedullary nail with a retrograde locking device is specifically indicated, although many surgeons use these nails for most fractures. When using a sliding hip screw for a trochanteric fracture, it is essential to get the tip of the screw close to the articular surface.[67,68]

COMPLICATIONS

Infection Nonunion and Malunion

Specific healing problems may require later specialist care.[69] Infection is unfortunately common after complex fracture care, especially if the initial injury was open. Failure of healing (nonunion) is not usually diagnosed before 6 months and commonly suggested by persistence of pain on loading and failure of progression of bone healing on x-ray. Malunion is assessed with regard to the specific deformity and may require corrective surgery for limb alignment, joint function, or longevity. Commonly, infection and failure of bone healing occur together. In principle, infection after fracture creates a

similar situation to osteomyelitis with acute and chronic clinical pictures. In general, the management of infection involves the same principles as the management of open fractures with debridement and lavage, skeletal stability and healthy soft tissue cover; with the addition of long-term antibiotics guided by perioperative cultures and under the supervision of an infectious disease specialist. Again, adequate debridement of the poor often dead infected bone, the provision of bony stability and healthy soft tissue cover is the key to management.

Surgical management of the acute infection before fracture healing involves urgent washout of the wound, biopsy, cultures, appropriate antibiotics, and healthy wound management, often necessitating delayed primary closure after a secondary washout. While unstable fixation should be removed and stability restored, stable fixation should be maintained even if superficially contaminated until adequate fracture union. An implant can then be safely removed and usually any residual infection eradicated. Chronic infection with a united fracture needs similar treatment but if the fracture is stable, the key here is removal of a contaminated implant and debridement of dead bone to remove the source of infection. Local washout and healthy soft tissue closure then proceeds as above. However, in the chronic situation, affected tissues are stiff and nonpliable such that bone and soft tissue debridement may produce a dead space, soft tissue defect, or skeletal instability with a bony defect, each of which may require specific management.[70,71] Unfortunately, often limb salvage carries significant morbidity and may not be the best option for the patient.

Malunions cause considerable disability and can be very rewarding to correct (**Fig. 28.6**). Each needs to be fully assessed for the specifics of the deformity and consideration to a variety of methods of correction given. There are champions of a variety of acute correction methods with an osteotomy and fixation or gradual correction usually with a ring-fixation device.

Orthopedic Injury/Disaster Triage

Given the predominance of orthopedic injuries in the injured patient and the frequency of multiple patient events, surgeons are often faced with prioritizing the care of a number of injuries in one complex patient or of a

number of patients at the same time. In common day practice, a major motor vehicle crash with several victims can stress a system and require appropriate prioritization. In major international disasters, these situations can be extreme. In these situations, simple reliable rules are needed to guide staff through the process especially when there are multiple problems to consider and the situation is critical. ATLS dealt with this superbly with the A, B, C, alphabetic system for the primary survey. While this remains an excellent system for initial patient evaluation and can guide some immediate surgical decisions, it does not help the surgeon who will have to make critical priority decisions beyond this. From the orthopedic traumatology point of view, the variety of injuries often cover the whole spectrum of clinical need and produce complex decision-making situations. The easiest way for the supervising surgeon to plan the care of an individual is to stand back and work along simple priority guidelines, asking "what is needed here to save the life," "what is needed to save a limb," and "what is disability limiting." Considering each injury in turn then allows a logical plan to be made to prioritize the care required. In multiple patient scenarios, the process is the same but modified by the number of patients involved and the medical resources available. With adequate resources, each patient's problems are dealt with individually as needed and no consideration to major disaster triage is required. If resources are available although stressed, patients with life-threatening problems are dealt with first prioritized by their individual acuity while others with important but initially stable issues can be managed later. In the massive disaster situation, priorities change, resources are overwhelmed, and first priority is given to the group of patients who will gain the most while not tying up or exhausting scarce resources. This is extremely difficult to do as the critical patient who would often be dealt with first if more resources were available is not prioritized as their care would swamp the resources available and not allow simpler care to many others.[53] Going into situations (such as the immediate medical relief after the 2010 Haiti earthquake) without preplanning or the experience to deal with difficult decisions like this is not advisable.

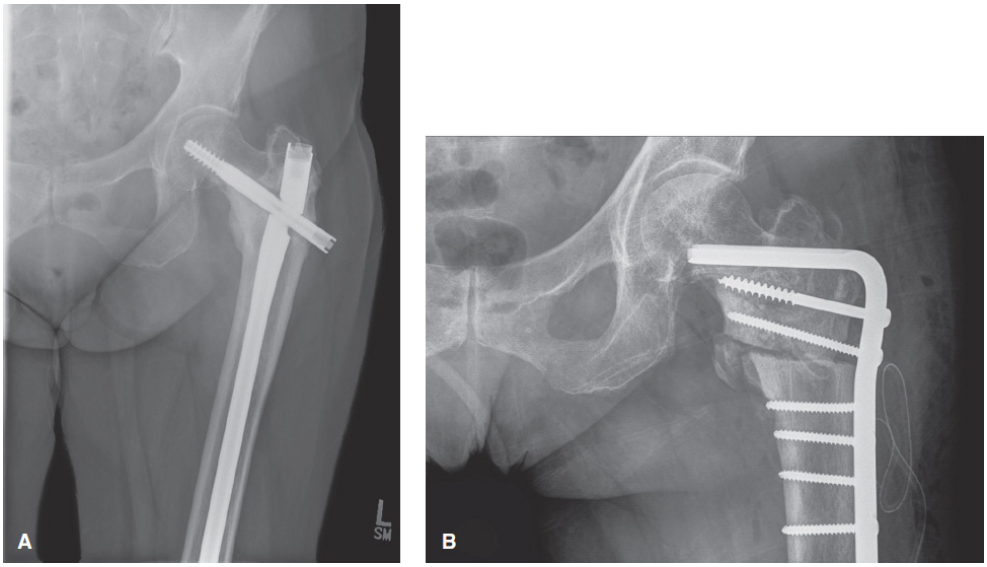


Figure 28.6 Assessment and surgical management of a proximal femoral malunion after implant failure. **A:** Proximal femoral malunion (collapsed into varus) with a broken implant in place. **B:** Correction of the malunion with a valgus osteotomy held with a blade plate.

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29

Pediatric Trauma

Peter T. Masiakos, Cornelia L. Griggs, and Danielle B. Cameron

Key Points

1. **Epidemiology:** Pediatric trauma remains a significant public health problem. Traumatic injuries are the top cause of mortality for children and adolescents in the United States and account for more than 50% of deaths in children younger than 18 years. Management strategies should include emergency medical care as well as injury prevention and systems of trauma care to meet the needs for pediatric patients.
2. **ABCs:** The primary survey should focus on the identification of acute life-threatening injuries. Attention to the airway, breathing, and circulation (ABCs) supersedes all other interventions in the initial resuscitation phase. Centers that care for children should have pediatric resuscitation equipment, such as appropriately sized endotracheal tubes, laryngoscopes, catheters, passive warming lamps, and the Broselow Pediatric Emergency Tape which aides in estimating the weight of the child and facilitates safe, weight-based resuscitation.
3. **Nonaccidental trauma:** Nonaccidental trauma may be difficult to recognize, and a high index of suspicion is needed when evaluating children with injuries. The American Academy of Pediatrics guidelines published in 2015 provide a resource to help identify these children, because unrecognized cases of abuse can represent with serious or even fatal injuries.
4. **Injury prevention:** As policy makers struggle to allocate limited resources to improve population health, injury prevention programs will play a particularly important role. Regulatory efforts specifically aimed at primary and secondary injury prevention, can reduce health care cost, thereby freeing resources for other concerns.

INTRODUCTION AND EPIDEMIOLOGY

Pediatric trauma has a significant impact on the lives of children and families in the United States and around the world. Traumatic injuries remain the no. 1 killer of children and adolescents in the United States. Injury, both accidental and nonaccidental, accounts for more than 50% of deaths in children younger than 18 years.[1] The pediatric mortality rate from trauma in the United States is double that of other developed countries, and for every pediatric death there were more than 2,000 emergency department visits.[2] In the United States alone, more than 50,000 children are permanently disabled after trauma, most commonly as the result of traumatic brain injury (TBI).[2] According to data that are now longer than 20 years, these disabilities account for $14 billion in lifetime medical spending and $66 1 billion in future wages lost.[3] Therefore, pediatric trauma is a significant public health problem, and management strategies that should target not only emergency medical care but also injury prevention and systems of trauma care to meet the needs for pediatric patients.[3]

Although there is a rise in the incidence of penetrating trauma, which now accounts for up to 10% to 20% of trauma activations, the vast majority of pediatric injuries result from blunt trauma with associated closed head injuries that require nonoperative management.

TRAUMA SYSTEMS

The concept of a trauma system was shaped by the publication of a U.S. government report in 1966 "Accidental Death and Disability: the Neglected Disease of Modern Society"[4] and has led to improvements in infrastructure, processes of emergency response, communication, and outcome measurements and quality indicators of responding hospital centers. The Committee on Trauma first categorized Trauma Center designations in 1976.[2] The first Pediatric trauma centers were organized in the 1970–1980s; however, even today in the United States, there are too few designated pediatric trauma centers to care for all pediatric trauma patients. The vast majority of pediatric patients are cared for at adult trauma centers,[5,6] the exchange of ideas between adult and pediatric trauma centers and the development of integrated regional trauma systems remain critically important for our care of injured children.[2,7]

Inclusive trauma systems are comprised of facilities within a region according to a tiered-triage system. Each participating facility receives a level designation, and this is used to appropriately triage and refer patients as necessary. Along with these regionalization efforts, advances in pediatric transport have also improved how we care for injured children. Inclusive systems have been shown to improve outcomes because more timely and appropriate transfers can occur. It has become increasingly important to develop and study various "performance indicators" of the quality of care that is delivered to injured pediatric patients. For example, rate of successful splenic salvage is a commonly cited quality indicator in pediatric trauma, and there are reports that children cared for at an adult trauma center have a fivefold higher risk of splenectomy than those at pediatric trauma center.[6,8,9] Beyond benchmarking mortality rates, other measurable quality indicators include availability of a pediatric intensive care unit with in-house intensivists, radiation exposure from imaging, early neurosurgical intervention for severe head injury, early fixation of femur fractures, operative rates for solid organ injuries, and participation in registry databases to monitor performance over time, such as the Trauma Quality Improvement Program set up by the American College of Surgeons-Committee on Trauma.[10,11] It is unclear whether superior care is offered to injured children in a dedicated pediatric hospital, compared to an adult hospital; however, it has been demonstrated that pediatric trauma certification and expertise in care of trauma patients are both important factors in optimal care.[12–17]

INITIAL ASSESSMENT, RESUSCITATION, AND STABILIZATION

The evaluation and treatment of traumatic injuries of infants and children requires specific knowledge of pediatric physiology and the physiologic response to injury. Generally, the trauma resuscitation of children follows similar rules that have been described for adults by advanced trauma life support standards. However, there are several special considerations in the

initial assessment and subsequent care for children and specific paradigms regarding ancillary studies that are different from those in adults.

As in adults, the primary survey should focus on the identification of acute life-threatening injuries. Attention to the airway, breathing, and circulation (ABCs) is critical in the initial resuscitation phase (**Table 29.1**). All centers that care for children should have sequestered resuscitation equipment designed for children, that is, endotracheal tubes (ETTs), laryngoscopes, catheters, and passive warming lamps. Room temperature should be kept warm to limit insensible heat losses in small children. The Broselow Pediatric Emergency Tape aids in estimating the weight of the child by measuring his or her length. A color-coded bar on the tape measures the length of the child and indicates the appropriate equipment sizes and medication doses to perform emergency resuscitation on the child. Designated resuscitation equipment is contained in corresponding, color-coded equipment pouches or drawers (**Fig. 29.1**).

Vital Signs

Pediatric vital signs vary by age (**Table 29.2**). Children are able to maintain normal blood pressures until late hemorrhagic shock (>30% blood loss), and, therefore, subtle changes in heart rate and respiratory rate must be noted. As a general rule, the lower limit of acceptable systolic blood pressure = (Age × 2) + 70 mm Hg. For newborns, acceptable systolic blood pressure is 60 mm Hg or greater. Initial fluid resuscitation is indicated when there are signs of hypovolemic shock.

2 **Table 29.1** Pediatric Resuscitation ABC's

Airway "A"

- Cardiac arrest most often of respiratory etiology
- Use jaw thrust technique and in-line cervical stabilization
- Key anatomic differences: larger tongue, more narrow and anterior glottis, and shorter trachea
- Miller blade may be easier than the curved Mac blade because the epiglottis is floppy
- Size of ETT can be estimated by the size of pinkie finger or Broselow Pediatric Emergency Resuscitation Tape
- Consider using an uncuffed ETT in a child less than 8 yrs or 60 lb
- With acute airway obstruction, needle cricothyroidotomy with a 14 g catheter is preferential to open cricothyroidotomy

Breathing "B"

- Assess for potential life-threatening thoracic injuries: pneumothorax (open chest wound or tension pneumothorax), hemothorax, flail chest/pulmonary contusions, and rib fractures
- Mediastinum of a child is very compliant and can lead to rapid decline from a tension pneumothorax
- Children are diaphragmatic breathers; ensure stomach is decompressed with nasogastric tube or orogastric tube in infants, who are obligate nose breathers

Circulation "C"

- Hemorrhage is the most common etiology of circulatory compromise in trauma
- Also consider obstructive etiologies (cardiac tamponade and tension pneumothorax) and distributive etiologies (neurogenic shock)
- Assessment of volume status and shock is difficult because children have impressive physiologic reserve
- Tachycardia, tachypnea, altered level of consciousness, and poor peripheral perfusion (mottled cool extremities, weak thready pulses, narrowed pulse pressure, delayed capillary refill) are early but subtle signs of blood loss
- Peripheral intravenous lines are ideal, but when they cannot be obtained, intraosseous lines are quick, reliable, and allow high-volume infusion of any fluid

- Definitive intravenous (IV) access can be obtained with a central line
- Initial fluid resuscitation is indicated when there are signs of hypovolemic shock. Initial bolus consists of 20 mL/kg of warmed normal saline or lactated Ringer solution
- After two initial boluses, all subsequent volume resuscitation should be performed with blood products (10 mL/kg = "1 unit") (**Table 29.3**)
- Massive transfusion protocols may be initiated if indicated
- Once resuscitated, maintenance fluid requirements (**Table 29.3**) can be estimated using the "4-2-1" rule and isotonic fluids should be administered for all children greater than 28 d

Disability "D"

- Perform a brief neurologic assessment
- Head injury accounts for the highest degree of morbidity and mortality in children
- Secondary insults include ischemia, hypoxia, hypotension, hyperthermia, hypercapnia, acidosis, and increased intracranial pressure (ICP)
- The Glasgow Coma Scale (GCS) is modified in young children who are preverbal to measure neurologic function and prognosis. The motor response scale tends to provide the most reliable assessment of function in a preverbal or intubated child (**Table 29.4**)

Exposure ("E")

- Allows for a complete head-to-toe physical examination
- Children have a larger body surface area ratio and, therefore, lose heat and water quickly and can become hypothermic
- Use warm fluids, bare huggers, warming lights, and warm ambient room temperature to prevent heat loss

Figure 29.1 Broselow pediatric emergency resuscitation tape.

Fluid Resuscitation

Initial bolus consists of 20 mL/kg of warmed normal saline or lactated Ringer solution. This may be repeated if there is no response or only a transient response. All subsequent volume resuscitation should be performed with blood products (10 mL/kg = "1 unit") (**Table 29.3**). If there is no time for cross-matched, type-specific blood, "O-negative" blood is indicated. Massive transfusion protocols may be initiated at this time if indicated and should include hemostatic resuscitation with packed red blood cells, fresh frozen plasma, and platelets, targeting high plasma-to-red blood cell and platelet-to-red blood cell ratios.[18] In the most recent advanced trauma life support protocols, this has become known as "damage control resuscitation,"[19] espousing permissive hypotension, minimizing crystalloid resuscitation, and promoting early blood product administration for the treatment of the lethal triad (acidosis, coagulopathy, and hypothermia) of severe uncontrolled hemorrhage. There is, however, no evidence-based support for permissive hypotension strategies in pediatric trauma patients. As

in adults, ongoing hemodynamic instability from blood loss in a child must be controlled expeditiously. Sources of bleeding can be thought of in terms of body compartments: including the chest, peritoneal cavity, retroperitoneum/pelvis, femur fracture/thigh compartment, and external injury (especially the scalp). In an infant, prior to suture closure of the skull, intracranial hemorrhage may produce hemodynamic instability. Once resuscitated, maintenance fluid requirements (**Table 29.3**) can be estimated using the "4-2-1" rule and isotonic fluids should be administered for all children >28 days (**Fig. 29.2**).[20]

Table 29.2 Pediatric Vital Signs

	Pulse (Beats/Min)	Systolic Blood Pressure (mm Hg)	Respiration (Breaths/Min)
Newborn (<1 mo)	95–145	60–90	30–60
Infant (1 mo to 1 yr)	125–170	75–100	30–60
Toddler (1–2 yrs)	100–160	80–110	24–40
Preschool (3–4 yrs)	70–110	80–110	22–34
School age (4–12 yrs)	70–110	85–120	18–30
Adolescent (>12 yrs)	55–100	95–120	12–16

Table 29.3 Fluid Management in Children	
Resuscitation Fluids (NS or LR)	
If hypotension or signs of shock:	Bolus 20 mL/kg. Repeat if transient or no response and then switch to blood transfusions (10 mL/kg)
Daily Maintenance Fluid Requirements (D5 1/2NS or D10 1/2NS)	
Weight <10 kg	100 mL/kg/d
Weight 11–20 kg	1,000 mL + 50 mL/kg/d (for every kg over 10)
Weight >20 kg	1,500 mL + 20 mL/kg/d (for every kg over 20)

SECONDARY SURVEY AND ADJUNCT DIAGNOSTIC MODALITIES

Only after the primary assessment is complete, and ABCs are secured, do we move on to the full secondary survey. In reality, with a team approach to management of the pediatric trauma patient, much of the supportive care happens concurrently with the primary and secondary surveys, including placement of intravenous lines, drawing laboratories, applying monitors and oxygen, and obtaining ancillary diagnostic tests. Adjunct diagnostic modalities and imaging may be used to provide additional information in the evaluation of a pediatric trauma patient. Although diagnostic peritoneal aspiration has been traditionally used to evaluate intra-abdominal injuries in the unstable patient, it has no role in the pediatric population where solid organ injuries are unlikely to require surgery. Focused assessment with sonography in trauma (FAST) examination has significant advantages over more invasive diagnostic maneuvers: the FAST examination can be performed quickly and exposes the patient to no potential harm from delay or ionizing radiation. However, children with intra-abdominal injuries are more frequently managed nonoperatively, and thus the need for rapid decision

making regarding operative management is less common. Children also have a relatively higher incidence of solid organ injury without free fluid, and consequently, a negative FAST examination may not obviate the need for an abdominal computed tomography (CT) when there is a clinical suspicion of significant injury. The FAST examination should not be relied on as a stand-alone screening tool in the pediatric population.[21,22] The utility of the FAST exam in pediatric trauma continues to evolve. To date, the largest prospective trial of FAST in stable pediatric trauma patients showed no evidence of benefit, leading the authors to conclude that their findings do not support the routine use of FAST among hemodynamically normal children treated in an ED following blunt trauma.[23] Despite this, FAST represents an emerging area of study in pediatric trauma and continues to be an integral part of pediatric trauma algorithms. Findings from chest radiography, anteroposterior pelvis radiography, and the FAST examination, along with the primary and secondary surveys, guide decisions regarding further radiographic examination, including CT or plain radiography.

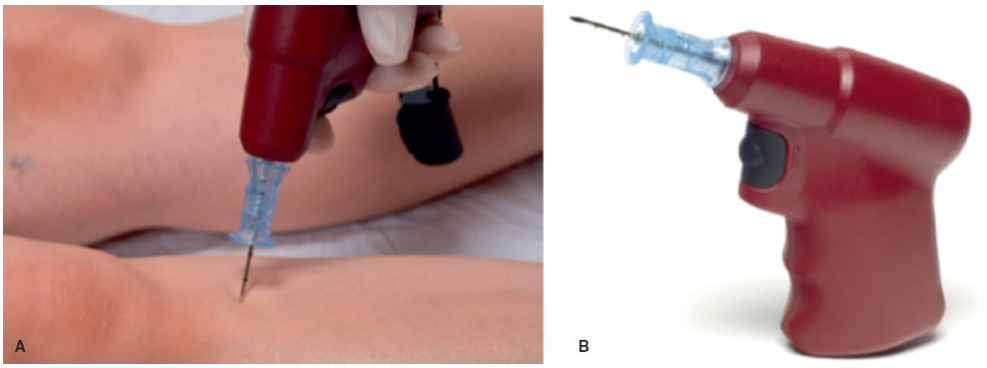


Figure 29.2 **A:** Intraosseous line placement. **B:** EZ-IO drive.

In addition to a full physical examination, a brief history is essential and is often provided by emergency medical services (EMS) personnel or the parents. An "AMPLE" history helps the provider focus on essential information such as Allergies, Medications, Past medical history, Last meal, and Events surrounding the traumatic incident. Blunt trauma is the most common mechanism after which children present for evaluation. Children are more prone to multisystem trauma due to their small body size and more compliant body (less protective bones, muscle, and torso fat). Blunt trauma can result in injury patterns that resemble penetrating injuries, without

significant external signs of trauma. Careful attention to a bruise on the abdominal wall resulting from a bicycle handlebar should lead to a more thorough investigation of the abdomen. A lap belt mark across the abdomen may raise concerns of lumbar spine fracture (Chance fracture), with an associated risk of small bowel injury. A history of significant hemorrhage at the scene may instigate a more thorough investigation of the vessels in the proximity of injury in an otherwise hemodynamically stable patient who has no hard signs of vascular injury. Therefore, a thorough history, mechanism of injury, and focused examination of the entire child is mandated so that signs of forceful impact can be elucidated.

MANAGEMENT OF SPECIFIC INJURIES

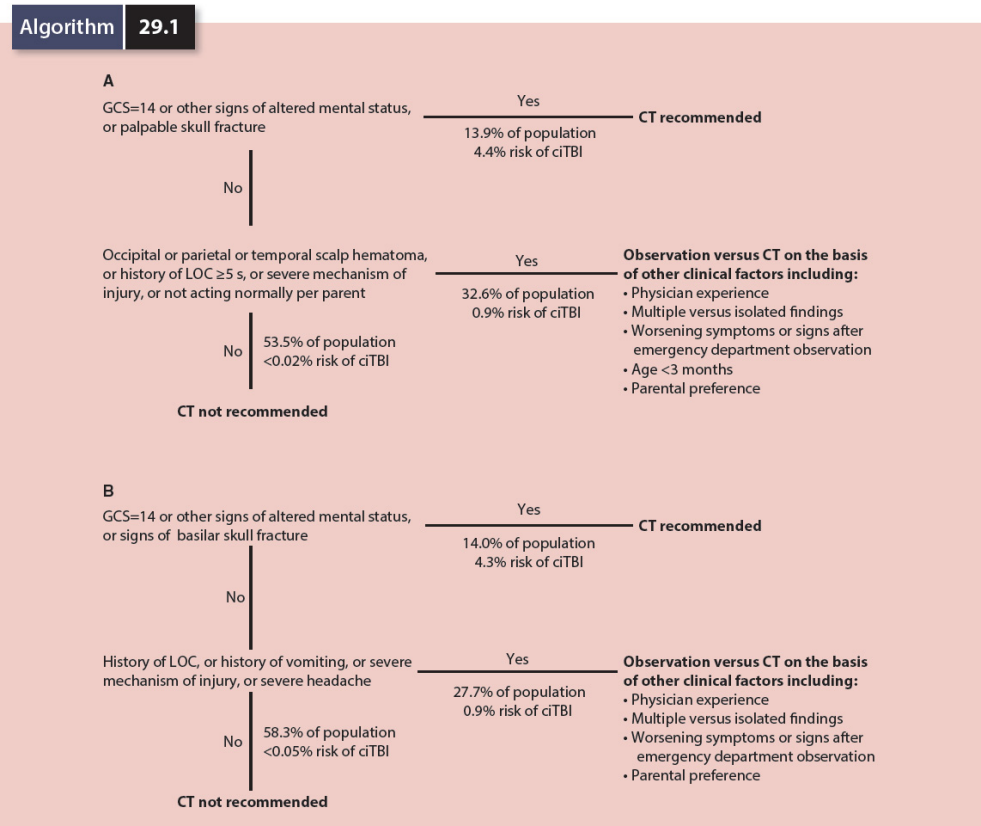
Traumatic Brain Injury

Traumatic brain injury is the leading cause of death and disability in children,[24–26] and is an important determinant of outcome. Nonaccidental trauma is the most common cause of head injury in children younger than 2 years, and blunt head trauma from motor vehicle accidents, falls, or bicycle/pedestrian accidents are responsible for most injuries in children older than 2 years. Injury prevention strategies are necessary for improving outcomes of the primary TBI. However, reduction of secondary injury patterns is critical in children, who have impressive physiologic reserve and potential for rehabilitation after brain injury. The focus must be on preserving cerebral oxygenation and perfusion, and mitigation of toxic exposures to minimize secondary brain injury. This includes treating or preventing hypotension, hypo/hyperoxia, hyper/hypocarbia with generation of ischemia reperfusion free-radicals, hyperthermia, seizures, and intracranial hypertension.

Mild Traumatic Brain Injury

Children with minor head trauma can present the greatest challenge to emergency department personnel. Eastern Association for the Surgery of Trauma (EAST) guidelines define mild traumatic brain injury (MTBI) to be

interchangeable with the term "Concussion," involving a blunt force mechanism with alteration in brain function (i.e., GCS score of 13 to 15) but by definition must have a normal head CT if performed.[27] Significant brain injuries need to be identified early and treatment instituted rapidly. CT scans provide the most accurate and expeditious means of diagnosis but expose many pediatric patients to unnecessary radiation. Evidence-based clinical decision tools have helped identify the population of children who benefit most from radiologic evaluation. The TBI study group for PECARN (Pediatric Emergency Care Applied Research Network) has developed tools for assessment of children after blunt head injury.[27–32] The "PECARN Rules"[29] (**Algorithm 29.1**) identify children at very low risk (<0.05%) of having clinically important TBI requiring intervention. These patients can avoid CT and be discharged safely with appropriate instructions. Children with abnormal GCS score (GCS score of ≤14) or evidence of skull fracture are at the highest risk for clinically important injury and should be evaluated emergently by CT scan. If there is a history of loss of consciousness, severe injury mechanism, abnormal behavior to the parent or nonfrontal scalp location (<2 years), or vomiting and severe headache (≥2 years), then further observation or CT should be offered as reasonable management options. Subsequent analyses also identified children with only isolated loss of consciousness (and no other PECARN predictors) to be at very low risk for clinically important TBI.[29] Children with MTBI (GCS score of 14 to 15) who underwent CT can be safely discharged home without further neurologic monitoring, if their head CT scan is normal.[27,30] Even those with an isolated skull fracture can be discharged home from the emergency department with strict discharge instructions and return precautions.[31–34] At this point, routine structural or functional imaging modalities such as magnetic resonance imaging, functional magnetic resonance imaging, or positron emission tomography for diagnosis or prognosis of MTBI are not supported.[27]



Algorithm 29.1 PECARN rules to identify children at very low risk of clinically important TBI. CT algorithm for children younger than 2 years (**A**) and for those aged 2 years and older (**B**) with GCS scores of 14–15 after head trauma. ciTBI, clinically important traumatic brain injury; GCS, Glasgow Coma Scale; LOC, loss of consciousness. (From Kuppermann N, Holmes JF, Dayan PS, et al. Identification of children at very low risk of clinically-important brain injuries after head trauma: A prospective cohort study. *Lancet* 2009;374[9696]:1160–1170.)

Prognosis and outcome in MTBI, especially as it relates to "return to learn or return to play" after concussion, is still hotly debated. Most studies agree that patients with MTBI return to baseline within 3 months (majority within 10 to 14 days), but certainly symptom resolution can take longer. Lingering symptoms of headache, dizziness, fatigue, sleep disturbance, impairment in memory and concentration, irritability, anxiety, or depression are referred to as the "postconcussive syndrome," which is not a well-understood entity.[27] Standardized tools exist, such as the Immediate Postconcussion Assessment and Cognitive Testing Battery (ImPACT), to aid clinicians in functional assessment of patients with MTBI.[35] The well-known NCAA Concussion Study from 2003 found that high-level athletes were more likely to sustain repeat concussions, which were associated with a longer recovery time,[36]

and it has been increasingly recognized that repeat concussions can have permanent and sometimes devastating effects. In 2010, the American Academy of Pediatrics officially endorsed the International Conference on Concussion in Sport recommendations for a graduated "Return to Play" protocol.[37,38] The CDC HEADS UP guidelines also incorporate these recommendations[39] and provide resources for schools, coaches, and primary care providers on returning to school and sports after a concussion. Data are lacking in the efficacy of these guidelines and their role in preventing recurrent concussions.[40]

Moderate to Severe TBI

More serious head injury needs to be evaluated and treated expeditiously. The GCS (and modified GCS for infants) is a universal tool that can be used for rapid assessment of neurologic function and is based on verbal response, motor function, and eye opening. Moderate TBI is considered GCS score of 9 to 12 or 13 and severe TBI includes GCS score of ≤8, the definition of a coma. The goal of initial assessment and resuscitation in a severely brain injured patient is to minimize or prevent secondary brain injury. Attention to ABCs is critical, with maintenance of normotension and normoxia. Management of severe TBI in the pediatric intensive care unit is largely focused on management of elevated ICP and maintenance of cerebral perfusion pressure.[41] In 2003 and again in 2012, guidelines for the acute medical management of severe TBI in infants, children, and adolescents were published, which represented the first recommendations made specifically for pediatric patients (**Tables 29.4** to **29.6**).[42–45] These guidelines, composed mostly of class II or III evidence, included recommendations on management of intracranial hypertension, hypoxia/airway management, indications for ICP monitoring, thresholds for treatment and management of cerebral perfusion pressure, and hypotension. It also addressed therapies such as cerebrospinal fluid drainage, hyperosmolar therapies, hyperventilation, barbiturates, decompressive surgery, temperature control, corticosteroids, and supportive care such as sedatives/neuromuscular antagonists and nutrition, although the guidelines are mostly based on expert panel opinion rather than large clinical trials. Prehospital management focused on the benefit of pediatric trauma centers rather than adult trauma centers for

children with severe TBI. Supplemental oxygen should be administered. There was no superiority of endotracheal intubation versus bag-mask ventilation in the prehospital setting, but if endotracheal intubation is to be undertaken, specialized training and the use of end-tidal CO_2 monitoring is encouraged. Hyperventilation with hypocarbia (pCO_2 <30 to 35) is to be avoided. There was class II support for ICP monitoring for children with GCS score of 8 or less; using an ICP threshold of 20 mm Hg and a cerebral perfusion pressure of 40 to 65 mm Hg; efficacy of hypertonic saline solutions in lowering ICP; and the role for decompressive surgery in the treatment of elevated ICP. From these guidelines, an algorithm for the management of acute intracranial hypertension was developed on the basis of the expert opinions of the committee (**Algorithm 29.2**), which has served as a template for clinical protocols for patient care and research. The 2012 guidelines changed a few of the recommendations (**Table 29.6**). Only hyperosmolar therapy was supported by two small studies (class II data); the remaining therapeutics could not be supported by the literature, including use of corticosteroids, immune-modulating diets, and induction of moderate hypothermia ("Cool Kids" trial).[44–47] Other topics with class III evidence were added including advanced neuromonitoring (using a brain–tissue oxygen partial pressure of 10 mm Hg), neuroimaging (avoiding routine repeat head CT unless neurologic deterioration), cerebrospinal fluid drainage, and the use of antiseizure prophylaxis (phenytoin prophylaxis) to reduce posttraumatic seizures. For a variety of other topics, including glycemic control, cerebrospinal fluid drainage, and analgesics/sedatives/neuromuscular blockade, definitive recommendations could not be made on the basis of the available literature. Overall, there is still a paucity of high-quality evidence to make specific treatment plans for children with severe TBI, but this allows for a wide variety of clinical approaches that are considered within the guidelines of pediatric care.

Table 29.4 Modified Glasgow Coma Scale in Children

	Infant	Child
Eye Opening		
4	Spontaneous	Spontaneous
3	To verbal stimuli	To verbal stimuli
2	To pain only	To pain only
1	None	None
Verbal Response		
5	Coos and babbles	Oriented, appropriate
4	Irritable cries	Confused
3	Cries to pain	Inappropriate words
2	Moans to pain	Incomprehensible sounds
1	None	None
Motor Response[a]		
6	Moves spontaneously and purposefully	Obeys commands
5	Withdraws to touch	Localizes painful stimuli
4	Withdraws in response to pain	Withdraws in response to pain
3	Abnormal flexion posture to pain	Flexion in response to pain
2	Abnormal extension posture to pain	Extension in response the pain
1	None	None

[a]If patient is intubated, unconscious, or preverbal, the most important part of this scale is motor response and should be closely evaluated.

Spine Trauma

Cervical spine injuries (CSIs) in blunt trauma pediatric patients occur in less than 2% of seriously injured children. Despite this low incidence, it is clear that many clinicians obtain radiographs in order to exclude CSI. The added benefit of routine imaging in the pediatric trauma evaluation is debatable. In recent years, concerns have been raised about the liberal use of plain films, CT scans, and magnetic resonance images in children with reference to imaging-related short- and long-term morbidity, resource consumption, and cost. The increased risk of fatal and nonfatal cancers associated with CT-related radiation has gained attention both by physicians and also by consumers. Both the U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health and the National Cancer Institute have published guidelines designed to limit unnecessary imaging in children. Although proponents of liberal imaging argue that a single missed CSI may cost more than multiple diagnostic tests, the use of non–evidence-based tests may inspire suboptimal practice with an undefined risk–benefit ratio.

Table 29.5 Summary of Standards, Guidelines, and Options Generated from the 2003 Pediatric TBI Guidelines

Topic	Level of Evidence	Recommendation
Trauma systems, pediatric trauma centers, and the neurosurgeon	Guideline	"In a metropolitan area, pediatric patients with severe TBI should be transported directly to a pediatric trauma center, if available"
	Option	"… should be treated in a pediatric trauma center or in an adult trauma center with added qualifications to treat children in preference to a level I or II adult trauma center without added qualifications …"
Prehospital airway management	Guideline	"Hypoxia must be avoided … and attempts made to correct it immediately. Supplemental oxygen should be administered … no evidence to support an advantage of endotracheal intubation over bag-valve-mask ventilation …"
	Option	"If prehospital

		endotracheal intubation is instituted …, then specialized training and use of end-tidal CO_2 detectors is necessary”
Resuscitation of blood pressure and oxygenation	Guideline	“Hypotension should be identified and corrected … defined as systolic blood pressure below fifth percentile for age or by clinical signs of shock …”
	Option	“Airway control should be obtained in children with a GCS ≤8 to avoid hypoxemia, hypercarbia and aspiration … hypoxia should be identified and corrected … blood pressure should be monitored frequently and accurately …”
Indications for intracranial pressure monitoring	Option	“ICP monitoring is appropriate … (GCS ≤8). The presence of an open

		fontanelle and/or sutures does not preclude the development of intracranial hypertension or negate the utility of ICP monitoring”
Threshold for treatment of intracranial hypertension	Option	“Treatment for intracranial hypertension … should begin at an ICP ≥20 mm Hg”
Intracranial pressure–monitoring technology	Option	“… a ventricular catheter or an external strain gauge transducer or catheter tip pressure transducer device is an accurate and reliable method of monitoring ICP”
Cerebral perfusion pressure	Guideline	“A CPP >40 mm Hg … should be maintained”
	Option	“A CPP between 40 and 65 mm Hg probably represents an age-related continuum for optimal treatment threshold … Hypotension should be avoided”

Sedation and neuromuscular blockade	Option	"… the choice and dosing of sedatives, analgesics and neuromuscular blocking agents … should be left to the treating physician …"
Hyperosmolar therapies	Option	"Hypertonic saline is effective at control of increased ICP … Mannitol is effective for control of increased ICP …"
Hyperventilation	Option	"… Prophylactic hyperventilation … should be avoided. Mild hyperventilation ($PaCO_2$ 30–35 mm Hg) may be considered for longer periods of intracranial hypertension … Aggressive hyperventilation ($PaCO_2$ <30 mm Hg) may be considered as a second tier option in the setting of refractory

		intracranial hypertension …”
Barbiturates	Option	“High-dose barbiturate therapy may be considered in hemodynamically stable patients with refractory intracranial hypertension … appropriate hemodynamic monitoring and cardiovascular support are essential …”
Temperature control	Option	“… Hyperthermia should be avoided …”
Surgical treatment of intracranial hypertension	Option	“Decompressive craniectomy should be considered ….”
Corticosteroids	Guideline	“The use of steroids significantly reduces endogenous cortisol production … may have an associated increased risk of complications of infection”
	Option	“The use of steroids is not recommended for improving

		outcome or reducing ICP …”
Nutritional support	Option	“Replace 130%–160% of resting metabolism expenditure … nutritional support should begin by 72 h with full replacement by 7 d”

CPP, cerebral perfusion pressure (mean arterial blood pressure minus intracranial pressure); GCS, Glasgow Coma Scale; ICP, intracranial pressure; $PaCO_2$, partial pressure of carbon dioxide; TBI, traumatic brain injury.

From Bell MJ, Kochanek PM. Pediatric traumatic brain Injury in 2012: The year with new guidelines and common data elements. *Crit Care Clin* 2013;29(2):223–238, with permission.

Table 29.6 Summary of Evidence Generated from the 2012 Pediatric TBI Guidelines

Topic	Level of Evidence	Recommendation
Indications for ICP monitoring	Level III	"Use of ICP monitoring may be considered …"
Threshold for the treatment of intracranial hypertension	Level III	"Treatment of ICP may be considered at a threshold of 20 mm Hg"
Cerebral perfusion pressure thresholds	Level III	"A minimum CPP of 40 mm Hg may be considered … A CPP threshold of 40–50 mm Hg may be considered …"
Advanced neuromonitoring	Level III	"If brain oxygenation monitoring is used, maintenance of a partial pressure of brain-tissue oxygen ($Pbto_2$) ≥10 mm Hg may be considered"
Neuroimaging	Level III	"In the absence of neurologic deterioration … routine repeat CT scan … may not be indicated …"
Hyperosmolar therapy	Level II	"Hypertonic saline should be considered … for intracranial hypertension …

		effective doses … range between 6.5 and 10 mL/kg”
	Level III	“Hypertonic saline should be considered … effective doses as a continuous infusion of 3% saline range between 0.1 and 1.0 mL/kg/h administered on a sliding scale …”
Temperature control	Level II	“Moderate hypothermia … for only 24 h duration should be avoided … moderate hypothermia starting within 8 h after injury and lasting for 48 h duration should be considered to reduce ICP … rewarming at a rate of 0.5°C/h should be avoided”
	Level III	“Moderate hypothermia … for 48 h duration may be considered”
Cerebrospinal fluid drainage	Level III	“CSF drainage through an externalized

		ventricular drain … may be considered … The addition of a lumbar drain may be considered …”
Barbiturates	Level III	“High-dose barbiturate therapy may be considered in hemodynamically stable patients with refractory intracranial hypertension … continuous arterial blood pressure monitoring and cardiovascular support to maintain adequate CPP are required”
Decompressive craniectomy for the treatment of intracranial hypertension	Level III	“Decompressive craniectomy with duraplasty … may be considered for pediatric patients … showing early signs of neurologic deterioration or herniation or are developing intracranial hypertension refractory to medical management …”

Hyperventilation	Level III	"Avoidance of prophylactic severe hyperventilation to a $PaCO_2$ <30 mm Hg may be considered within the first 48 h … If hyperventilation is used … advanced neuromonitoring for evaluation of cerebral ischemia may be considered"
Corticosteroids	Level II	"The use of corticosteroids is not recommended to improve outcome or lower ICP …"
Glucose and nutrition	Level II	"The evidence does not support the use of an immune-modulating diet … to improve outcome"
	Level III	"… glycemic control … should be left to the treating physician"
Antiseizure prophylaxis	Level III	"Prophylactic treatment with phenytoin may be considered to reduce the incidence

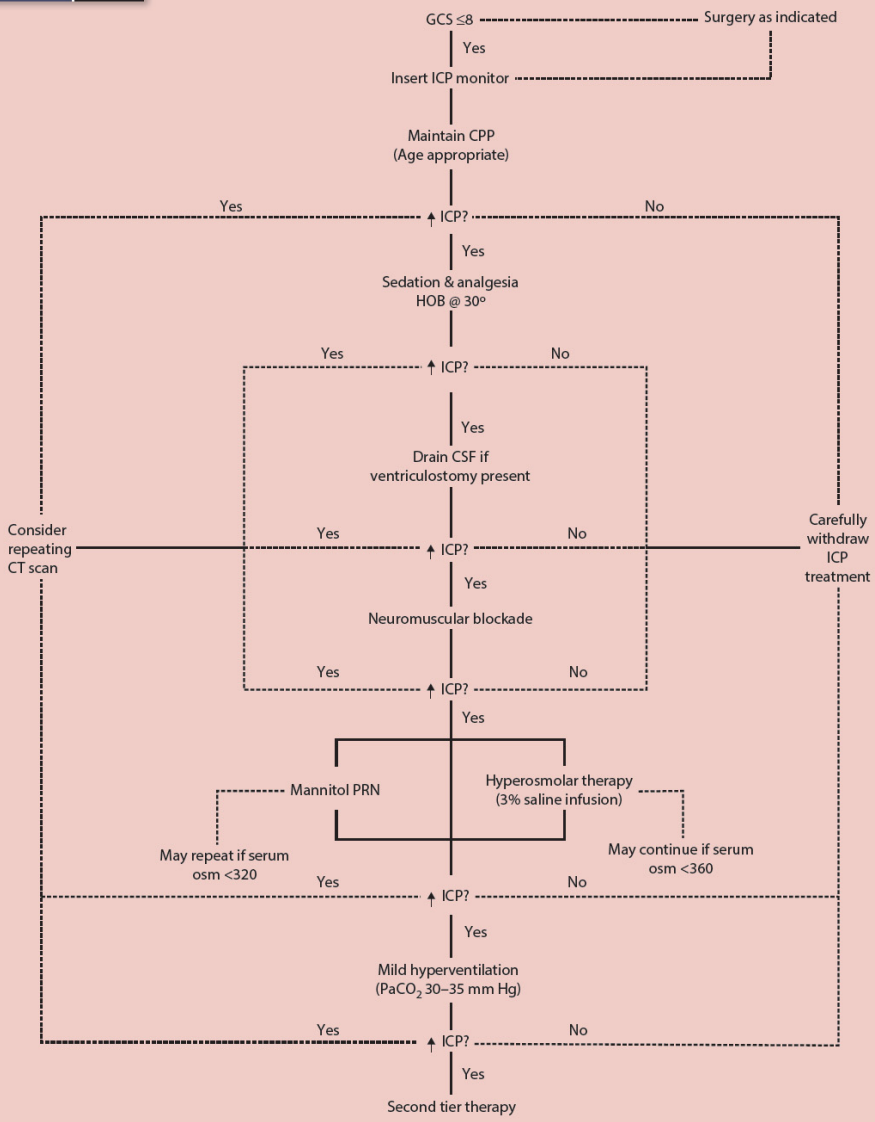
	of early posttraumatic seizures …”

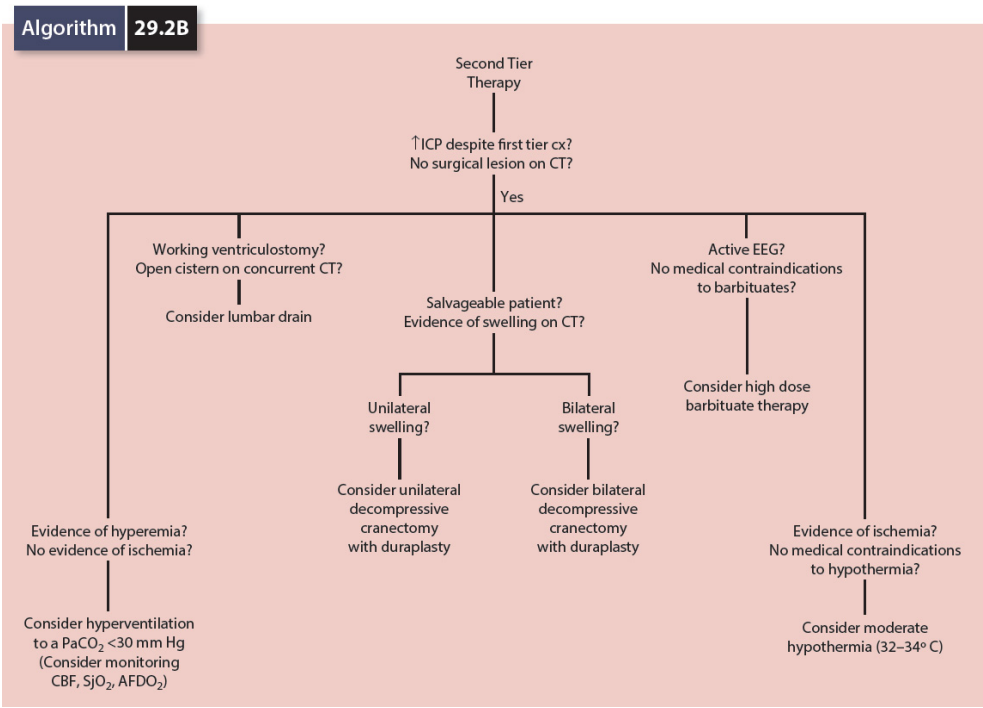
CPP, cerebral perfusion pressure (mean arterial blood pressure minus intracranial pressure); CSF, cerebrospinal fluid; CT, computed tomographic; ICP, intracranial pressure; $PaCO_2$, partial pressure of carbon dioxide.

From Bell MJ, Kochanek PM. Pediatric traumatic brain injury in 2012: the year with new guidelines and common data elements. *Crit Care Clin* 2013;29(2):223–238, with permission.

Two seminal studies (NEXUS and Canadian Cervical Spine Rules [CCR])[48–49] have examined whether clinical criteria (neurologic deficit, cervical spine tenderness, intoxication, decreased mental status, and distracting injuries) can rule out CSI in adults without the need of imaging. These criteria have been applied to pediatric patients in a manuscript by Viccellio and colleagues,[50] who evaluated 3,065 blunt trauma patients younger than 18 years and found that nearly 20% of patients fell into the “low-risk” category where imaging could have been avoided. In another retrospective review of 206 pediatric patients (from birth to 16 years of age), Jaffe and colleagues[51] suggested that the absence of eight clinical criteria (neck pain; neck tenderness; abnormality of reflexes, strength, or sensation; direct trauma to the neck; limitation of neck mobility; abnormal mental status) enabled a clinician to detect CSI in children with a sensitivity of 98% and a specificity of 54%. The PECARN group has also reported on its series of 540 CSIs in children, presenting a model with eight predictors to identify children who should be evaluated for CSIs after blunt trauma.[52] These include altered mental status, focal neurologic deficits, complaint of neck pain, torticollis, substantial torso injury, predisposing condition, diving, and high-risk motor vehicle crash, with a sensitivity of 98%.

Algorithm 29.2A





Algorithm 29.2A Algorithm generated by the Brain Trauma Foundation Committee for the first edition of the *Guidelines for the Medical Management of Severe Traumatic Brain Injury in Infants, Children, and Adolescents* for first-tier therapies (**A**) and second-tier therapies (**B**). $AFDO_2$, arteriovenous difference in oxygen; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; GCS, Glasgow Coma Scale; HOB, head of bed; ICP, intracranial pressure; $PaCO_2$, partial pressure of carbon dioxide; PRN, as needed; SjO_2, jugular bulb venous oxygen saturation. (From Bell MJ, Kochanek PM. Pediatric traumatic brain injury in 2012: The year with new guidelines and common data elements. *Crit Care Clin* 2013;29[2]:223–238, with permission.)

The American College of Radiology published updated guidelines based on current evidence and a panel of expert pediatric specialists.[53] These guidelines summarize the best current imaging practice in children with accidental spine trauma. For children ages 3 to 16 years with acute cervical spine trauma that meets low-risk criteria based on PECARN or NEXUS, imaging is not recommended. For children in the same age group with at least one risk factor with a reliable clinical exam, radiographs of the cervical spine are usually appropriate. There was no consensus among the expert panel and there are insufficient data regarding the benefit of CT or MRI of the cervical spine in these patients. For children younger than 16 years with suspected thoracolumbar spine trauma, plan radiographs are usually

appropriate as the initial imaging. There was no consensus among the panel regarding the use of CT or MRI for these patients and similarly there was a lack of high level evidence to support CT or MRI as the initial imaging modality for this cohort.[53]

Location of Injury

Conventional wisdom has taught that the position of a CSI in children was related to age with the predominance of upper C-spine injuries seen in infants and toddlers and lower C-spine injuries seen in adolescents. This was thought to be a result of the mechanism of injury (flexion/extension and axial load, respectively). However, in a recent evaluation of the pediatric national trauma database, Polk et al.[54] identified a greater percentage of injuries to the lower C-spine than previously reported. A large database study evaluated the tendency for injuries to occur at certain levels of the cervical spine over a 5-year period and found that younger children (≤10 years of age) sustained upper (C1–C4) CSI more frequently than lower (C4–C7) CSI (87% vs. 57%).[51] Data from a 24-year retrospective study of patients admitted with CSI to a level 1 trauma center similarly concluded that for younger patients (≤8 years of age), significantly more injuries occurred in the upper cervical spine.[48] However, the National Trauma Data Bank (NTDB) data for this study revealed that the number of fractures to the upper C-spine and lower C-spine was nearly equal (53% and 47%), and that more than half of cervical spinal cord injuries were located in the lower C-spine (53%).[54]

Mechanism of Injury

Motor vehicle crash (MVC) remains the most common mechanism of CSI for the youngest age group.[48–51,55] A study of children younger than 14 years observed that while MVC was the most common mechanism for this large age group, when ages were further stratified, MVC ranked the highest for infants.[56] This same study also found that falls were the most common mechanism for the 2 to 9 years age group. While the focus on children younger than 3 years in this study was unique, conclusions about mechanism of injury remained consistent with previous literature. The frequency of MVC as mechanism for blunt trauma CSI is significantly greater than all other

mechanisms, with falls ranking second (66% and 15%, respectively). Given that this patient population is just learning to walk, falls are a concern. However, the high energy of an MVC has greater potential for major neurologic impairment and mortality.

The observations generated from analysis of the NTDB data suggest that the lower C-spine needs to be adequately evaluated on the basis of the near equal distribution of injuries. In addition, the association of CSI with high-energy mechanisms (i.e., MVAs) warrants a higher index of suspicion of this subset of young pediatric patients. In addition, those patients requiring at scene intubation and/or admission to the intensive care unit (ICU) should also be evaluated thoughtfully. Despite the low incidence of CSI, until the cervical spine is cleared, it should be immobilized, ideally with an age/size appropriate hard collar. Such collars should be stocked in all trauma centers that care for pediatric patients.

The authors of the reviewed paper[56] implemented a similar clinical guidelines strategy emphasizing the use of physical examination and NEXUS criteria in order to clear the cervical spine in children presenting after trauma. The primary outcome measure was to determine the use of CT scans in children younger than 15 years and to compare the extent of use of CT scans for cervical spine clearance 12 months before and after implementation of these guidelines. A total of 233 children were evaluated during the 2-year period (128 before guidelines were in place and 105 afterward). For children clearable by NEXUS criteria, the implementation guidelines had an immediate effect, decreasing CT use by 23%. Furthermore, there were no missed injuries. These results offer additional evidence that much of the imaging obtained for C-spine clearance in a child is unnecessary. The clinical evaluation of pediatric trauma patients with suspected C-spine injury is quite effective in predicting which subset of patients will benefit from cross-sectional imaging. Simple clinical criteria, like GCS, used in concert with the physical examination, can safely predict CSI in children, safely reducing the utilization of imaging for the vast majority of patients (even the very young).

Spinal Cord Injury without Radiographic Abnormality

Spinal cord injury without radiographic abnormality was first defined in a series of children with signs of acute traumatic spinal cord injury in the absence of bony findings on cervical spine radiographs, flexion–extension films, or CT scans.[57] The authors noted that these patients had neurologic deficits or a history of transient paresthesia, numbness, or paralysis, and a delay of symptoms occurred in approximately half of the patients.

In recent years, as efforts to limit ionizing radiation exposure in children have increased, magnetic resonance imaging has become a mainstay in the workup of children with presumed CSI or neurologic deficits on physical examination. As a result, more children have been found to have demonstrable injury to the spinal cord, soft tissue components of the spinal column vertebral body growth plates.[58,59] As a result of this advent of new neuroimaging paradigms, the diagnosis of spinal cord injury without radiographic abnormality has become questionable. Although the trend has been to limit radiography in children (with good reason), it is important to remember that young patients with blunt trauma who have a history of any transient neurologic symptom may have a significant injury to the spinal cord and/or spinal column, and these children warrant thorough radiographic evaluation.

Cerebrovascular Injury

Blunt trauma force to the neck and cervical spine fractures can result in vascular injuries to the carotid or vertebral arteries. Stroke and permanent neurologic deficit are the most feared outcomes from this rare injury, and in children, because of ill-defined screening criteria, neurologic deficit is the most common presenting symptom for diagnosis. 2010 EAST guidelines are aimed at adult patients and provide little evidence toward screening criteria or management in either adults or children.[60] Risk factors for cerebrovascular injury include trauma mechanism with severe hyperextension or hyperflexion with rotation, maxillary or mandibular injuries, TBI with diffuse axonal injury, near hanging, “seat belt sign” or other soft tissue contusion to the neck, and fractures involving the carotid canal or cervical vertebral body, particularly the vertebral foramen. A recent meta-analysis of pediatric blunt cerebrovascular injury recommended

screening high-risk pediatric patients with CT angiography of the neck and treatment with anticoagulation in patients with confirmed injuries.[61]

Thoracic Trauma

Blunt trauma, most commonly from motor vehicle crashes, is the most common mechanism for thoracic trauma in pediatric patients. Children have a more flexible, cartilaginous rib cage, and, therefore, serious intrathoracic injuries can occur in the absence of obvious external trauma or rib fractures. Children also have a more mobile mediastinum, predisposing them to tension pneumothorax with subsequent cardiopulmonary collapse from impaired venous return. The primary survey is designed to identify these acute life-threatening thoracic injuries such as airway injury, tension pneumothorax, open pneumothorax, hemothorax, flail chest with pulmonary contusion, or cardiac tamponade, which require immediate intervention (**Table 29.7**).[62] Once bilateral breath sounds and adequate ventilation and oxygenation are confirmed, CXR is an urgent part of any pediatric trauma evaluation and can identify most other acute thoracic injuries. FAST examination can evaluate for pericardial fluid and in experienced hands can identify pneumothorax or pleural effusion. Many injuries can be observed or managed with tube thoracostomy.

Pulmonary contusions are one of the most common thoracic injuries after blunt trauma. The diagnosis is made on CXR in which infiltrates are identified that do not follow anatomic boundaries. Parenchymal edema peaks at 24 to 36 hours postinjury, as the contusion "blossoms" on CXR, and requires admission for monitoring, oxygen therapy, or intubation and respiratory support if needed. Any evidence of hemothorax or pneumothorax seen on CXR should be managed initially with tube thoracostomy. Stable patients with an occult pneumothorax (seen only on CT scan but not on CXR) may be safely observed without thoracostomy drainage, even if requiring positive pressure ventilation. Traditional indications for thoracotomy in adults include an initial chest tube output of 1,500 mL and a persistent output of 150 to 200 mL/hr for 4 hours. In children, this equates to a chest tube output of approximately 20% of the patient's estimated blood volume, or ongoing output of 2 to 3 mL/kg/hr. However, patient physiology should be the primary indication for surgical treatment rather than the absolute blood

output. The thoracoscopic approach has become increasingly acceptable in stable patients for the management of retained hemothorax, persistent air leak, or select diaphragmatic injuries after penetrating thoracoabdominal trauma. The EAST practice management guidelines for thoracic trauma provide a good overview of the evidence for management of thoracic trauma in adults, but no specific guidelines exist for pediatric patients.[63]

Table 29.7 Acute Life-Threatening Thoracic Injuries

Injury	Diagnosis	Management
Airway obstruction	Apnea or stridor, maxillofacial trauma.	Definitive tracheal intubation (oro- or nasotracheal) or cricothyroidotomy
Flail chest	Paradoxical chest wall motion.	Positive pressure ventilation
Tension pneumothorax (PTX)	Respiratory distress, tracheal deviation, hypotension, distended neck veins, absent unilateral breath sounds, **hyperresonance to percussion**	Needle decompression (2nd interspace, midclavicular line), followed by placement of chest tube (4th interspace, anterior axillary line)
Open pneumothorax	Open wound into chest → "**sucking chest wound**"	Sterile gauze (secure on three sides) and placement of chest tube
Hemothorax	Absent breath sounds, **dullness to percussion**, hypotension	Chest tube placement. Massive hemothorax necessitates thoracotomy
Cardiac tamponade	Distended neck veins, muffled heart sounds, hypotension (**Beck triad**), pulsus paradoxus	Pericardiocentesis (or emergency thoracotomy if pulseless)

Emergency bedside thoracotomy is indicated for patients who present pulseless to the emergency department with signs of life and penetrating thoracic trauma. The evidence is more controversial for patients who do not have signs of life or who sustained penetrating extrathoracic injuries or blunt trauma and should be based on clinical judgment. There is no role for emergency thoracotomy for patients without signs of life after blunt trauma.[64] Advanced trauma life support guidelines recommend application of these guidelines to children on the basis of existing literature,[65,66] but these data are sparse.

Other serious thoracic injuries are very rare in children but include blunt aortic injury and blunt cardiac injury. Aortic injury can be effectively diagnosed with CT scan with IV contrast (CT angiogram). Widened mediastinum on CXR from a physiologic thymic shadow is quite commonly seen in young children. However, with the appropriate mechanism, including blunt thoracic trauma with a significant deceleration mechanism, and abnormal contour of mediastinum, CT chest angiography with contrast may be required to rule out this injury.[67,68] Treatment, as in adults, relies on strict antihypertensive therapy and operative repair, including the endovascular approach in those children who are big enough to accommodate a stent (although this has not been standardized in pediatric patients). Blunt cardiac injury (most commonly myocardial contusion) can also be challenging to diagnose but occurs most commonly after motor vehicle collision or pedestrian trauma. Abnormalities on EKG are the main findings in myocardial contusion. Traditional risk factors such as sternal fracture or upper rib fractures do not appear to correlate with blunt cardiac injury. The new EAST guidelines, although designed for adult patients, recommend an EKG and troponin I if blunt cardiac injury is suspected.[69] If both studies are normal, this effectively rules it out. If either is abnormal, the child should be admitted to a monitored bed. Echocardiogram is recommended only for patients with hypotension or arrhythmias.[66]

Traumatic asphyxia occurs in children because of their flexible thoracic wall in the setting of direct blunt compression, most often after a motor vehicle collision or crush injury. At the time of injury, if the glottis is closed and the thoracoabdominal muscles are tensed, the increased intrathoracic pressure is transmitted through the central venous system (inferior and superior vena cava) to the brain and solid organs. Typical signs of traumatic

asphyxia include subconjunctival hemorrhage and petechiae of the chest, shoulders, and head, with subsequent bronze discoloration of the skin. Supportive care in a monitored setting is the standard of care for these children, watching for signs of airway edema.

Abdominal Trauma

Blunt mechanism of injury is the most common cause of abdominal trauma in children. Assessment of abdominal trauma in pediatric patients can be challenging. Vomiting, abdominal tenderness, and seat belt signs are signs and symptoms that increase the likelihood of abdominal injuries. FAST examination is a standard assessment in adult trauma patients, but its role in pediatric patients is still controversial. In an unstable patient, FAST examination can help identify the presence of hemoperitoneum and triage a patient to the operating room or interventional radiology suite. CT scan with IV contrast is the best assessment for abdominal trauma in a stable pediatric patient. Despite concerns for radiation exposure, this is an important study if indicated. PECARN has similarly developed rules and algorithms to identify a low-risk patient who can safely avoid abdominal CT.[70–72] If an examinable child (GCS score of >13) had no evidence of abdominal or chest wall trauma (including seat belt sign), no abdominal pain, tenderness or vomiting, and normal bilateral breath sounds, the rule had a 99.9% negative predictive value for intra-abdominal injuries requiring intervention[70,72] and was more sensitive than clinical suspicion.[71] After a normal abdominal CT scan, most patients can safely be discharged if otherwise stable (sensitivity 97.8%). However, most missed injuries were hollow viscous injuries, which are difficult to identify on CT and should be suspected in patients with seat belt sign, free fluid on CT, or leukocytosis.[73]

Penetrating abdominal trauma is much less common in children than in adults but should be managed similarly. There is increasing evidence toward a nonoperative, conservative approach to abdominal stab wounds that penetrate the fascia, relying on serial examinations and imaging to guide operative approach. Laparotomy is still largely recommended for gunshot wounds to the abdomen on the basis of the most recent 2010 EAST guidelines, although this area remains controversial.[74]

Damage control laparotomy is an established operative approach for hemodynamically unstable trauma patient in hemorrhagic shock and is utilized in approximately 5% of all laparotomies for trauma in both adults and children. The goal of this approach is to avoid the onset of the lethal triad: hypothermia, coagulopathy, and acidosis. The procedure is abbreviated and focused on maintaining the priorities of hemorrhage control, followed by control of contamination and temporary abdominal closure, with plans to return for definitive repairs after resuscitation and warming in the ICU, usually 24 to 48 hours later. The decision for damage control should be made early in the operative course in order to minimize exposure time in the operating room and avoid irreversible shock and its sequelae. Although well described and widely adopted within the adult trauma population, data are less available in the pediatric population but theoretically of even greater importance as children have small circulating blood volumes and are more prone to hypothermia.[75] As discussed in a previous section, damage control resuscitation is managed in parallel, with a focus on initiating the massive transfusion protocol, minimizing crystalloid fluids, and resuscitating with blood products using a high ratio of plasma and platelets for each unit of red blood cells transfused.[75]

Solid Organ Injuries

Most solid organ injuries (spleen, liver, and kidney) are managed nonoperatively after blunt trauma.[76] Most of these injuries are identified or evaluated by CT and can be graded according to American Association for the Surgery of Trauma (AAST) grading system for prognostic value.[77] In a large series of pediatric patient with solid organ injury, 11% received a blood transfusion, 1.4% underwent angiographic embolization, and 4% required laparotomy.[78] Laparotomy rates ranged from 5.4% at adult trauma centers to 2.8% at freestanding children's hospitals, raising concerns for optimal and consistent management of pediatric patients who are cared for in adult centers.[78–80] Across all institutions, there is wide variability of care of pediatric patients with solid organ injuries. In those managed successfully with nonoperative management, there is no standard of care for level of monitored care (whether children are admitted to ICU vs. floor vs. home), frequency of blood draws, duration of bed rest or bowel rest, and timing of

discharge home and resumption of activities.[78] In the 1990s, the American Pediatric Surgical Association (APSA) proposed an algorithm for posttrauma management of solid organ injuries, which has commonly been adopted by institutions but has never been rigorously verified.[81] These recommendations include ICU admission only for grade IV solid organ injury, observation on the pediatric floor for a duration of injury grade +1 days, liberation of diet and ambulation once the hematocrit has stabilized (and hematuria resolved in renal injuries), and exertional activity restriction for a duration of injury grade +2 weeks. No routine reimaging of injuries is recommended.[81] Indications for laparotomy include hemodynamic instability, ongoing blood loss (hematocrit drop) with blood transfusion requirement of greater than 20 mL/kg, or evidence of hollow viscous injury. More recently, the American College of Surgeons' pediatric trauma consortium (ATOMAC) developed a practice management guideline for solid organ injury, which is now used at many additional pediatric trauma centers throughout the United States.[82] The guidelines support management on the basis of hemodynamic status rather than injury grade. Transfusion triggers have been debated and although there are no class I data to support a number at which blood should be given, it is generally agreed that transfusion should be considered at a threshold of 7.0 g/dL. It supports abbreviated bed rest and earlier discharge than the older APSA guidelines (**Algorithm 29.3**). The approach to angiographic embolization for splenic salvage is still controversial in pediatric patients and has a wide variability among institutions.[82–85] In 2019, the APSA Outcomes and Evidence Based Practice committee published updated guidelines for the management of solid organ injuries in children, suggesting that the length of stay (LOS) for children with isolated solid organ injury should be based on clinical findings and may not be determined by grade of injury, consistent with more recent practice patterns supported by the ATOMAC guidelines (**Algorithm 29.3**). In addition, the updated APSA guidelines queried the role of interventional radiology in the management of isolated solid organ injuries.[86] They concluded that arterial embolization is a useful tool for non-operative management of solid organ injuries with radiographic findings concerning for ongoing bleeding (e.g., blush) and hemodynamic compromise. Finally, these guidelines suggest that routine follow-up imaging for asymptomatic and uncomplicated solid organ injures

is not indicated. These recommendations are based on a systematic review of 202 articles that met inclusion criteria for the study.[86]

The role of FAST examination for diagnosis of solid organ injury in children is still unclear. Whereas its use has long been the standard of care in adults, recent PECARN data of pediatric trauma centers suggest that only 13% of pediatric trauma patients with a suspicion for intra-abdominal injuries undergo FAST examination.[87,88] Sensitivity in pediatric patients ranges from 50% to 92%, with a rigorous meta-analysis suggesting the sensitivity to be around 66%.[21,22,89–91] Specificity is also very low, and in a hemodynamically stable patient, a positive FAST examination should be followed up with an urgent CT. Bedside FAST may have utility in hemodynamically unstable patients to rapidly identify or rule out intraperitoneal hemorrhage when patients cannot undergo CT, but decision making should include other features such as patient physiology, mechanism, clinical suspicion, and responsiveness to initial resuscitation measures.[22,92] As its use in children increases, it is likely that FAST will become more reliable, with greater sensitivity and specificity. Additionally, while strong evidence in favor of the use of FAST as a screening tool is lacking, the sensitivity may increase with improvement in technology and as the pediatric trauma community collectively becomes more experienced with this skill.[93]

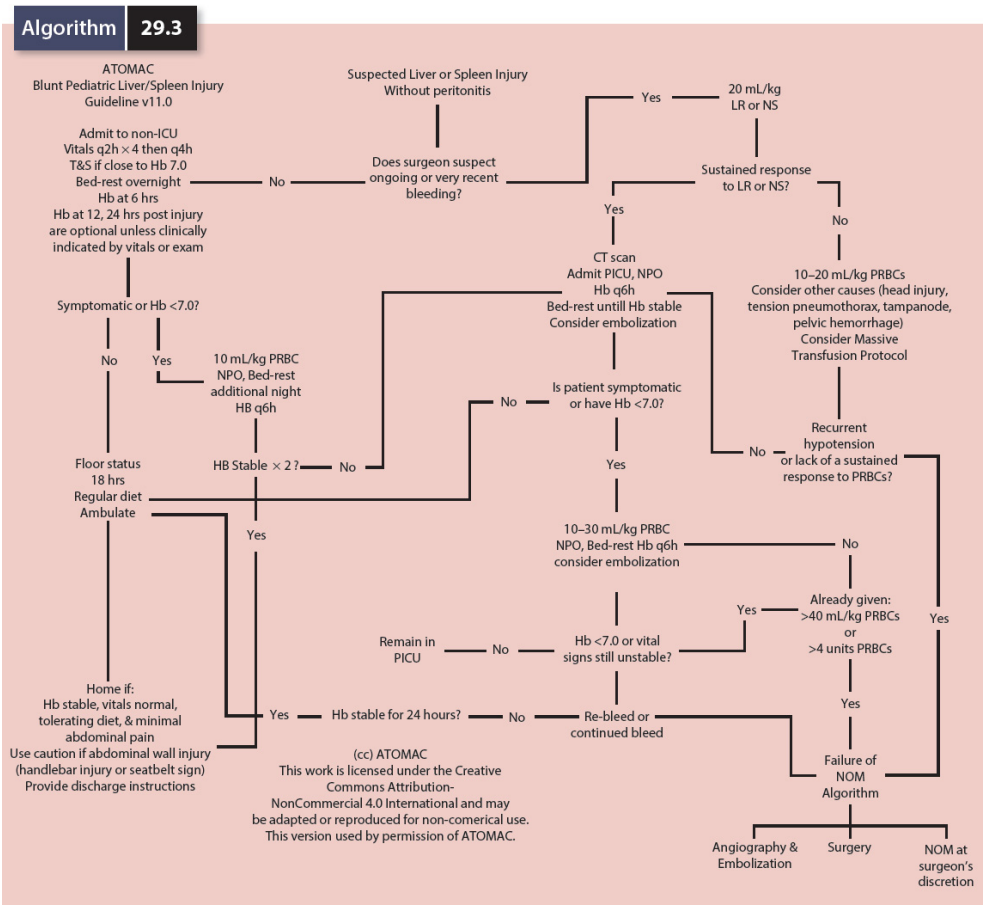
Hollow Viscous Injury

Hollow viscous injuries occur after blunt abdominal trauma, such as bicycle handlebar injuries or lap belt injuries (often associated with Chance vertebral fracture). Diagnosis can be challenging with current radiographic techniques. Findings on CT might include free fluid in the absence of solid organ injuries, free intraperitoneal air, or extravasation of oral contrast. In the setting of abdominal wall ecchymosis (seat belt sign), leukocytosis, or abdominal tenderness, patients should be closely monitored with serial abdominal examinations and blood count. Evidence for evolving peritonitis, fever, leukocytosis, or systemic inflammatory response syndrome physiology should prompt surgical exploration, either laparoscopic or by laparotomy. Intramural duodenal hematomas are managed conservatively without surgical intervention but may take several weeks to resolve, requiring nasogastric tube (NG) drainage and Total Parenteral Nutrition (TPN) in the interim.

Delayed stricture after partial thickness luminal injury or mesenteric injury can present days to weeks after an injury, with symptoms of partial or complete small bowel obstruction.

Pancreatic and Biliary Injury

Pancreatic injury classification by AAST injury grade divides patients into those without ductal injury (grades 1 to 2) and those with duct disruption (grades 3 to 5). Currently there is no universal standard for management of pancreatic trauma in pediatric patients, but evidence is emerging.[94–102] Amylase and lipase are useful to screen for pancreatic injury but may be normal immediately after trauma; by 3 hours after trauma, they are universally elevated (100% sensitivity), although with low specificity.[96] Abdominal CT scan can determine the integrity of the duct, and endoscopic retrograde cholangiopancreatography (ERCP) may be a useful adjunct in some patients. Higher-grade pancreatic injuries with duct disruption typically require operative intervention. Although early literature promoted nonoperative management for pediatric pancreatic injuries,[96–100] recent reports and multi-institutional studies have suggested improved outcomes, reduced need for drainage procedures, and decreased LOS for operative intervention, most commonly distal pancreatectomy.[94,101,102]



Algorithm 29.3 New ATOMAC guidelines for management of pediatric solid organ injury. Hb, hemoglobin; ICU, intensive care unit; LR, lactated Ringer's; NOM, nonoperative management; NPO, non per os; NS, normal saline; PICU, pediatric intensive care unit; PRBC, packed red blood cell; q6h, every 6 hours. (From Notrica DM, Eubanks JW III, Tuggle DW, et al. Nonoperative management of blunt liver and spleen injury in children: Evaluation of the ATOMAC guideline using GRADE. *J Trauma Acute Care Surg* 2015;79[4]:683–693, with permission.)

Biliary injury is rare in children, representing <0.1% of all trauma patients, and includes intrahepatic and extrahepatic ductal injuries, biloma, and gallbladder injury. Literature is sparse but many injuries can be managed nonoperatively with ERCP with biliary stent placement and percutaneous peritoneal drainage. These patients are at risk for delayed stricture and require close follow-up. Hepaticojejunostomy remains the definitive repair for extrahepatic biliary tract transections.[103]

Anorectal Injuries

Anorectal injuries are uncommon in children and usually occur after penetrating mechanism. Isolated anal trauma can be repaired primarily, including sphincter repair. Extraperitoneal rectal injuries should be repaired primarily if possible and often require fecal diversion and/or presacral drainage. Intraperitoneal rectal injuries can be managed similarly to colon injuries, with or without fecal diversion. Associated genitourinary injuries should be sought with examination under anesthesia.[104,105]

Pelvic Fracture and Extremity Trauma

Fractures represent one of the most common injuries in pediatric trauma patients. Children have more malleable bones, more absorptive cartilage, and a higher potential for bone remodeling and healing than adults. Anatomic differences in radiology of pediatric bones can make recognition of injuries challenging. Injury to the growth plates can result in premature fusion and asymmetric limb growth. Greenstick fractures occur when the bone bends before it breaks. Options for stabilization include casting, splinting, traction, internal fixation, or external fixation. A thorough neurovascular examination is essential. Although vascular injury requiring repair is rare, children are more prone to vascular spasm, resulting in asymmetric pulse examination and transient ischemic symptoms.[106]

Pelvic fractures are a source of morbidity and mortality in pediatric patients and occur most commonly after high-mechanism blunt trauma such as MVC or pedestrians struck. Pelvic fractures are usually present in the setting of multiple injuries including TBI, abdominal injuries, and genitourinary trauma. The Young–Burgess Classification system for pelvic fractures is most commonly used in adults and categorizes injuries into lateral compression, anterior–posterior compression, and vertical shear injuries to the pelvic ring. Pediatric classifications exist but are not standard. The pediatric pelvis is more elastic, allowing for significant displacement before fracture. Pelvic hematoma and ongoing hemorrhage requiring angiographic intervention or preperitoneal packing occurs less commonly in children than in adults but should be a major consideration in the hemodynamically unstable child. The 2011 EAST guidelines for the treatment of hemorrhage in pelvic fracture are limited to adult data, but many principles can be extrapolated to the pediatric population.[107] These guidelines recommend the

use of early external stabilization, particularly with a size-appropriate pelvic orthotic device, to stabilize fractures, reduce pelvic volume, and theoretically limit blood loss. The hemodynamically unstable pediatric patient with a pelvic fracture represents a diagnostic challenge—does one proceed to the operating room for abdominal exploration or to the angiography suite for embolization? FAST examination does not have the sensitivity to rule out abdominal hemorrhage. If stable enough, a CT scan of the abdomen and pelvis is preferable to help identify the injuries and determine treatment course. Despite classification systems, fracture patterns on anteroposterior pelvic plain film do not predict bleeding or need for angiographic embolization. Angiographic embolization should be considered in hemodynamically unstable patients after other sources of hemorrhage have been ruled out. In the adult literature, arterial contrast extravasation on CT scan warrants empiric embolization, even in a stable patient, but these data are unclear in the pediatric population. Similarly, preperitoneal packing is a newer technique for the control of pelvic hemorrhage, and its use can be considered alongside pelvic embolization.[107] Treatment of pelvic fractures in children is usually nonoperative with non–weight bearing, Spica casts, or traction. In some cases, external fixation or open reduction, internal fixation (ORIF) is necessary. Fractures involving the acetabulum are complex, especially when the triradiate cartilage complex is involved, as premature fusion can result in long-term problems with leg-length discrepancy and acetabular failure.

Venous Thromboembolism

The incidence of venous thromboembolism in pediatric trauma patients is very low, ranging from 0.02% to 0.3%.[108] Practice guidelines from the Trauma EAST and Pediatric Trauma Societies proposed the following guidelines for the use of chemical prophylaxis in the pediatric trauma population. In children hospitalized after trauma who are at low risk of bleeding, pharmacologic prophylaxis should be considered in children older than 15 years and in younger postpubertal children with and injury severity score greater than 25. Routine pharmacologic prophylaxis in prepubertal children, even with ISS greater than 25 is not currently recommended. Mechanical prophylaxis should be considered either alone or as an adjunct to

pharmacologic prophylaxis in children older than 15 years and in younger postpubertal children with ISS greater than 25.[109] It is worth noting that these guidelines were developed from a thorough summary of the limited literature regarding VTE prophylaxis in children hospitalized after trauma. The authors did note that current available evidence is of very low quality and observational in nature. As such, prophylaxis and detection of venous thromboemobolism in the pediatric trauma population continues to be an area of debate.

Nonaccidental Trauma (Child Abuse)

Nonaccidental trauma is a leading cause of trauma in children, with 650,000 confirmed cases of physical abuse annually in the United States, accounting for 1,500 deaths per year, mostly in 3 children younger than 4 years.[110] Nonaccidental trauma and abuse may be difficult to recognize and a high index of suspicion is needed when evaluating children with injuries. The American Academy of Pediatrics guidelines published in 2015 provide a resource to help identify these children, because unrecognized cases of abuse can represent with serious or even fatal injuries. Features of the history that should increase suspicion include unexplained significant injury, denial of trauma, changes in the story or differences in the story by different witnesses, explanation that is inconsistent with the pattern, age or severity of injury or with the child's developmental capabilities, and delay in seeking medical care. Findings on examination that may suggest abuse include any injury in a preambulatory infant, multiple organ system injuries or multiple injuries at different stages of healing, patterned injuries, injuries to unusual locations (mnemonic "TEN-4" = injury to torso, ears, or neck in a child younger than 4 years), or other evidence of neglect (failure to thrive, dental caries, poor hygiene). Burns with sharply demarcated edges, bite marks, cigarette burns, and other markers of being hit with an object are high-risk injuries. Certain fracture patterns should raise concern for nonaccidental trauma including fractures in nonambulatory patients, multiple fractures, rib fractures, infants and toddlers with midshaft femur or humerus fractures, and other unusual fractures such as scapular and metaphyseal fractures. Skeletal survey is recommended in children younger than 2 years who have suspicion for abuse (see Indications for Obtaining a Skeletal Survey available online from the

study by Christian[110]; see Skeletal Survey Guidelines available from the study by Wood et al.[111]). If there is a reasonable suspicion that a child has been abused, a report to child protective services for further investigation is mandated by law. See Christian, CW[110] for outlines recommending workup in a child suspected of nonaccidental trauma, including blood work, imaging, and consultation of specialists such as ophthalmology, in order to identify injury and obtain forensic evidence.

4 INJURY PREVENTION

In 1968, the National Traffic and Motor Vehicle Safety Act established the National Highway Traffic Safety Administration, which has influenced the improvement of road infrastructure, automobile, and driver and passenger safety, resulting in precipitous drops in roadway fatalities.

There are many examples where comprehensive state and federal laws have resulted in statistical drops in injuries and deaths.[112–114] In the following section, we provide several examples where federal mandates and state laws have been implicated in the reduction of pediatric injuries. In many cases, surgeon advocates where integral in the legislative process.

Smoke Detectors and Carbon Monoxide Detectors

Smoke detectors have been legislated into building codes in all 50 states. As a result, the early warnings of a fire are thought to have prevented thousands of deaths. More than 10,000 Americans are poisoned by carbon monoxide and more than 500 people in the United States die annually from carbon monoxide poisoning. As of August 2015, 30 states have enacted statutes regarding carbon monoxide detectors, and another 11 have promulgated regulations on CO detectors. Several states now require CO detectors in hotels and schools.

Drunken Driving Laws

Alcohol is known to play a role in many MVCs. Drivers younger than 21 years are more likely than older drivers to be involved in fatal crashes, and alcohol use adds to the risk of fatal crashes. This group has been the target of several interventions to reduce alcohol-impaired driving, including "zero tolerance" blood alcohol concentration standards for drivers under the legal drinking age with mandatory license revocation after a first offense.[115]

Junior Driver Laws/Safe Driving Laws

The increased risk of car crashes associated with texting and cell phone use has been well documented—among adults and teens alike. But for teens, who are immersed in a world of smart phones and texting, these types of laws send a powerful message that driving demands their undivided attention. Although not exclusive to children or adolescents, "safe driving laws" ban text messaging for all drivers, prohibit junior drivers from using cell phones, and institute new license renewal procedures for mature drivers, among other provisions. Graduated driver licensing programs that require new drivers to progress through stages allowing them increased driving privileges as they gain experience have, in some form, been enacted in all 50 states. Many states have also incorporated parental education and curfews to these laws and have seen up to a 40% decrease in the number of injuries and fatalities as novice drivers have become engaged in this process.[116,117]

Child Passenger Restraints

Seat belt use around the country has steadily increased. There is mounting evidence that seat belt use and airbag implementation have been the greatest cause for decreased road fatalities per miles driven, which is at an all-time low according to National Highway Traffic Safety Administration statistics. Furthermore, there is evidence that educating pediatricians improves the use of car seats for children. Although the rate of use of car seats for newborns and infants is approximately 75%, their use in toddlers is estimated at only 29%, and more than half of car seats for children are not used correctly. In the child older than 4 years or 40 lb, there is ample evidence that booster seats should be used rather than adult-type restraints. Many states now have legislation aimed at this population.

All-Terrain Vehicle Laws

In the United States, all-terrain vehicle crashes account for a rising number of injuries and deaths in all age. Approximately 30% of the injured/dead are children. In 1988, in response to this trend, the Consumer Product Safety Commission and the all-terrain vehicle industry agreed upon a set of standards designed to limit injury. This included regulations that restricted operators younger than 16 years halted the sale of three-wheeled vehicles and included a mandatory educational safety training module and improved safety warnings. However, in 1998, 10 years after they were established, these consent decrees expired and since that time, the rate of injuries has risen steeply. Several states have recently enacted restrictions on ridership and in Massachusetts, where these restrictions have included an age cutoff, the number of injuries have fallen dramatically (unpublished data).

Finally, as policy makers struggle to allocate limited resources in order to improve population health, injury prevention programs will play a particularly important role. The rationale is straightforward: regulatory efforts specifically aimed at injury primary and secondary prevention, if well designed, can be very successful at health care cost reduction, thereby freeing resources for other concerns.

GUN VIOLENCE PREVENTION

Between 2009 and 2018, mass shootings took center stage in the nation's consciousness. A total of 194 mass shootings resulted in the death or serious injury of nearly 2,000 Americans, and one in four of them were children or adolescents.[118] However, these numbers represent a small fraction of the yearly death toll (nearly 40,000) from modern American gun violence—now an undeniable health epidemic for children and adults living in the United States. Without understanding their implications of the psyche of our children, active shooter drills have become a routine part of school preparedness and emergency planning in over 95% of our nations' schools.[119] While we are constantly reminded about mass shootings, deaths from suicide and homicide contribute far more American lives to this toll and their determinants are poorly understood. Furthermore, nonfatal injuries,

estimated to be greater than 150,000 per year, also strain our healthcare systems and impose a cost that has been shown to exceed the budget of the U.S. department of Education.[120] Recognizing the important perspective that surgeons and healthcare providers bring to the public debate over gun control policy, organized medicine has developed working groups and published statements with the goal of influencing the nation's policy makers. In November 2018, the American College of Surgeons Committee on Trauma (ACS COT) released its initial set of recommendations to develop an effective and durable strategy for reducing firearm injury, death, and disability in the United States.[121] In 2020, the federal budget included $25 million dedicated to the Centers for Disease Control and the National Institutes of Health for gun violence research, the first time federal funding has been dedicated to this cause since the Dickey Amendment was passed in 1996. The authors look forward to more organizations coming forward in this effort.

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Geriatric Trauma

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Key Points

1. The physiology of aging affects nearly every organ system including cardiovascular, pulmonary, renal, and gastrointestinal. Altered physiology may also be associated with comorbid conditions in the elderly patient including hypertension, cardiac disease, chronic obstructive pulmonary disease (COPD), chronic renal insufficiency, and altered drug metabolism.
2. The American Geriatrics Society has published the Beers Criteria for potentially inappropriate medication use in older adults that can be used to refine inpatient medication management for elderly trauma patients.
3. Falls are far and away the most common mechanism of injury in elderly trauma patients, causing almost 75% of injuries in elderly patients; nearly 1 in 3 adults over 65 years old will experience ground level falls each year.
4. An underreported but important mechanism of injury in elderly trauma patients is elderly abuse.
5. Imaging with head CT in elderly trauma patients should be used liberally.
6. Severely injured older patients may not display standard signs of hemodynamic instability.
7. Due to the broad range of age-related factors that can contribute to injury and adversely affect recovery in geriatric patients, injured individuals should receive a comprehensive geriatric assessment during their hospital stay.
8. Frailty is a syndrome of decreased physiologic reserve distinct from the normal aging process and other comorbidities. Frailty is associated with higher mortality and complications, and worse functional outcomes after trauma, and is more predictive than age or injury severity of hospital complications, in-hospital mortality, or discharge to an institution.
9. Four-fifths of in-hospital deaths among geriatric trauma patients involve decisions to withdraw or withhold of life-sustaining

therapies.

INTRODUCTION

The elderly population in the United States is steadily growing and according to the U.S. Census Bureau, the number of Americans >65 years old is expected to reach 80 million by the year 2040.[1]

Trauma and acute care surgeons will be increasingly responsible for caring for this complex population of patients. Even prior to injury, the elderly patient brings unique challenges including altered physiology, numerous comorbid conditions, and preinjury medications. The epidemiology and triage complexities of elderly trauma patients make it challenging to ensure these patients are transported to the appropriate receiving facility. Elderly patients are most often injured by a blunt mechanism and are particularly at risk for falls from standing. In addition, they sustain unique injuries that may escape diagnosis during the initial evaluation. Trauma centers may need to alter activation criteria for elderly trauma patients in order to avoid the pitfall of undertriage that is associated with poor outcomes in this population. Though the initial trauma evaluation for elderly patients is similar to younger adults, the trauma surgeon must understand the nuances associated with caring for the injured elderly patient. The elderly trauma patient more frequently has issues that relate end-of-life care in the postinjury period.

PHYSIOLOGY, COMORBIDITY, AND PREINJURY MEDICATIONS

Elderly individuals present with a vast array of body systems affected by the deranged physiology associated with aging. 1 The physiology of aging affects nearly every organ system including cardiovascular, pulmonary, renal, and gastrointestinal. Altered physiology may also be associated with comorbid conditions in the elderly patient including hypertension, cardiac

disease, chronic obstructive pulmonary disease (COPD), chronic renal insufficiency, and altered drug metabolism.

Cardiovascular

The cardiovascular system is most commonly affected by the physiology of aging and has a significant impact on care of the injured elderly patient. Alterations to physiology of the vascular system in the aging adult are primarily the result of changes in the large arteries including elongation, dilatation, and arterial wall thickening as a result of changes in the intima and media.[2] Changes in both small and large arteries lead to decreased compliance, stiffness, and hypertension or other cardiovascular diseases in elderly adults. Decreased endothelial cell turnover resulting in endothelial dysfunction, contributes to and promotes these changes even in atherosclerosis-free, normotensive aging individuals.[3] The aging process will affect cardiac physiology including reduced systolic and diastolic functions of the right ventricle as well as left ventricular hypertrophy with associated impaired contractility and relaxation. Resting cardiac output and ejection fraction are preserved.[4] While there are significant changes in cardiac and vascular physiology in elderly patients at baseline, the lack of cardiovascular response to stress may be the most important component of altered cardiovascular physiology in elderly patients, especially in the setting of hemorrhagic shock. The blunted response to alpha-adrenergic stimulation limits vasoconstriction[2,5] while lack of response to beta-adrenergic stimulation limits the ability to mount a tachycardic response.[4,6] Elderly individuals are also at increased risk to develop atrial fibrillation, ischemic heart disease, and congestive heart failure.

Table 30.1 Changes in Cardiovascular and Pulmonary Physiology and Commonly Encountered Comorbidities in the Elderly

System Involved	Physiologic Changes	Common Comorbidity
Cardiovascular	Elongation, dilatation, and wall thickening of large arteries Decreased arterial compliance and stiffness Reduced systolic and diastolic function of right ventricle Left ventricular hypertrophy Lack of cardiovascular response	Hypertension Ischemic heart disease Atrial fibrillation Congestive heart failure
Pulmonary	Kyphosis Decreased intervertebral height Decreased muscular strength Loss of elasticity and recoil Emphysematous changes Dysfunction of mucociliary system Alterations in lung volumes, gas exchange, and respiratory drive Diminished physiologic response to hypoxia and hypercapnia	Chronic obstructive pulmonary disease (COPD) Asthma Obstructive sleep apnea

Pulmonary

The aging process also brings significant baseline anatomic and physiologic changes to the pulmonary system.[7] The chest wall of the elderly individual changes over time with decreasing strength of intercostal muscles and diaphragm. A decrease in height of intervertebral spaces and the development of kyphosis is associated with decline in FEV1/FVC ratio.[8] Chest wall stiffness resulting from calcification of costal cartilage and joints leads to decreased chest wall compliance.[8] After trauma, these anatomic changes place elderly patients at risk for earlier or more rapid respiratory failure as well as difficulty in liberation from the ventilator.[7,9,10] In addition to alterations in the chest wall, there are several changes in the pulmonary parenchyma of elderly individuals. These changes lead to increased compliance due to loss of elasticity and elastic recoil, emphysematous changes, and dysfunction of the mucociliary system. While anatomic changes are important, the altered pulmonary physiology of aging may lead to significant clinical implications when caring for the injured elderly patient. The elderly individual will have changes to pulmonary physiology including alterations in lung volumes, gas exchange, and respiratory drive.[7] Lung volumes in elderly patients will have increased residual volume and functional residual capacity but decreased vital capacity and FEV1.[11,12] Alterations of pulmonary gas exchange in elderly patients include increased ventilation–perfusion mismatch as well as decreased diffusion across the alveolar–arterial membrane, both associated with a decrease in baseline PaO_2.[13,14] Due to deranged respiratory drive seen with aging, elderly patients will have a diminished physiologic response to both hypoxemia and hypercapnia.[15] Some of the most common pulmonary comorbidities in the elderly trauma patients include COPD, asthma, and obstructive sleep apnea. **Table 30.1** displays changes in cardiovascular and pulmonary physiology as well as common comorbidities encountered in the elderly trauma patient.

Renal and Gastrointestinal

Aging causes deterioration in renal function over time due to alterations in renal vasculature, microanatomy, as well as changes in renal physiology.[16] Over time, glomerular tissue is replaced with fibrous tissue causing 30% to

50% loss of cortical glomeruli by 70 years of age.[17] The aging kidneys also have a diminished capacity to preserve their own function as a result of renovascular dysautonomy.[17] These changes put elderly patients at increased risk for development of acute kidney injury after trauma. Avoiding nephrotoxic agents, intravenous contrast, hyperglycemia, and hypovolemia can help prevent acute kidney injury in elderly trauma patients. Gastrointestinal derangements in the elderly patient may include dysphagia, gastroesophageal reflux, gastroparesis, and diarrhea or constipation.[18] In addition, many elderly trauma patients will present in a state of malnutrition established long before the time of injury. It is important to screen elderly trauma patients for nutritional status and begin enteral nutrition early in the postinjury course.

Elderly trauma patients present with a wide array of altered physiology and comorbid conditions. These pre-existing medical conditions are usually treated in the outpatient setting by primary care providers, and the mainstay of treatment is often a long list of medications. These preinjury medications can have a profound effect on the management and outcomes of elderly trauma patients. In addition, elderly individuals have an altered ability to metabolize the medications they encounter prior to injury as well as during their hospitalization.

Medications

Elderly trauma patients may be taking a variety of medications that may affect initial presentation, evaluation and treatment, and eventually outcomes. As hypertension is the most common comorbidity, elderly trauma patients will often be taking preinjury antihypertensive medications. Diuretics will cause patients to present in a hypovolemic state prior to injury or hemorrhage. Preinjury beta blockers will blunt the tachycardic response and may confound the initial presentation.[19] The most significant preinjury medications in elderly trauma patients are anticoagulants and antiplatelet agents. Elderly patients may be on anticoagulants or antiplatelet agents for a variety of conditions including atrial fibrillation, ischemic cardiac disease, valvular heart disease, cerebrovascular accidents, or thromboembolic disease. The most common outpatient anticoagulant is coumadin (vitamin K antagonist). For many years it was the only anticoagulant on the market and

its use is associated with many food and drug interactions and the need for frequent monitoring. Over the last decade the pharmaceutical industry has developed and brought several novel oral anticoagulants to the market. These include the direct thrombin inhibitor dabigatran as well as the Xa inhibitors, rivaroxaban, apixaban, edoxaban, and betrixaban. The most common antiplatelet agents include aspirin (cyclooxygenase inhibitor) and clopidogrel (ADP inhibitor). Newer antiplatelet agents include newer ADP inhibitors, prasugrel and ticagrelor.

Reversal of anticoagulants and antiplatelet agents in elderly trauma patients can be a challenging and complex clinical scenario. The clinician must balance reversal to eliminate hemorrhage and thromboembolic complications associated with reversing anticoagulation or antiplatelet agents. Coumadin may be reversed with either fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC).[20,21] In recent years there has been more evidence regarding the reversal of direct thrombin inhibitors and Xa inhibitors.[22–25] Dabigatran may be reversed with idarucizumab (Praxbind), a 2015 FDA-approved antidote that binds to dabigatran with 350 times affinity than dabigatran to thrombin.[24] Treatment resulted in complete reversal of the anticoagulant effects of dabigatran with over 98% of patients reaching a median reversal of 100%.[24] Thrombotic complications occurred in 4.8% of patients at 30 days.[24] Intragastric-activated charcoal may be administered if drug has been taken within 2 hours of presentation or hemodialysis may be considered. PCC may be considered for reversal of dabigatran but FFP is unlikely to have any therapeutic effect. Andexanet alfa is a 2018 FDA-approved reversal agent for the Xa inhibitors, rivaroxaban and apixaban.[22] The ability of andexanet alfa to reverse other Xa inhibitors is pending ongoing study. Activated charcoal may be used or PCC may also be considered. Lastly, a new universal antidote called ciraparantag is under investigation by the FDA. It was designed as a broad-spectrum reversal agent for novel oral anticoagulants, unfractionated heparin, and low–molecular-weight heparin activity.[23] Antiplatelet agents may be reversed with either DDAVP or platelet transfusion, but the indications for either therapy have not been elucidated.[26] **Table 30.2** displays common preinjury anticoagulants and antiplatelet agents in the elderly trauma patient.

Once hospitalized, particular attention must be paid to medications ordered for the elderly trauma patient. Elderly patients have changes in

pharmacokinetics and pharmacodynamics including alterations in absorption, bioavailability, distribution, metabolism, and elimination.[27] 2 The American Geriatrics Society has published the 2019 updated Beers Criteria for potentially inappropriate medication use in older adults that can be used to refine inpatient medication management for elderly trauma patients.[28] Of particular importance to the management of the elderly trauma patients is the plan for pain control. Pain medications may have significant side effects in elderly patients including delirium, nausea, vomiting, constipation, renal dysfunction, and gastrointestinal bleeding. A multimodal approach with the lowest effective dose for pain control should be used for elderly trauma patients.[27]

MECHANISM AND INJURIES

Mechanisms of injury for elderly trauma patients are most often a result of blunt trauma with falls, motor vehicle crashes, and pedestrian struck by auto being the most frequent. 3 Falls are far and away the most common mechanism in elderly trauma patients, causing almost 75% of injuries.[19] Nearly 1 in 3 adults over 65 years old will experience ground level falls each year.[17] After hospitalization, older patients are at further risk for inpatient falls.[29] There are a variety of reasons that elderly individuals are at risk for falls including weakness, deconditioning from chronic illness, vision loss, gate and balance disturbances, slowed reaction time, and cognitive impairments.[19] The American Geriatrics Society has developed clinical practice guidelines (**Table 30.3**) for the prevention of falls in older adults.[30]

Table 30.2 Common Preinjury Anticoagulants in the Elderly

Mechanism of Action	Drugs	Reversal Strategies
Vitamin K antagonist	Warfarin	FFP or PCC
Direct thrombin inhibitor	Dabigatran	Reversed with idarucizumab (Praxbind) Intragastric charcoal Hemodialysis Consider PCC
Xa inhibitors	Rivaroxaban Apixaban Edoxaban Betrixaban	Andexanet alfa approved for reversal of rivaroxaban and apixaban only Intragastric charcoal Consider PCC
Antiplatelet agents	Aspirin Clopidogrel Prasugrel Ticagrelor	DDAVP Platelet transfusion

Elderly Abuse

4 An underreported but extremely important mechanism of injury in elderly trauma patients is abuse. Elderly abuse is committed by an individual who has a relationship with and is responsible for the well-being of an elderly individual. Abuse can be further classified as physical abuse, verbal or psychological abuse, sexual abuse, financial abuse, and neglect.[31] Perpetrators of elderly abuse may include family members or caregivers either in the home or at an assisted-living facility. Abuse of the elderly is associated with depression, cognitive impairment, loss of functional capacity, and increased morbidity and mortality.[32] Several risk factors and

warning signs for elderly abuse have been identified and are listed in **Table 30.4**.[33] If elderly trauma patients appear to be at risk for or display warning signs of possible abuse, they may be assessed using a variety of available screening tools[33] including the American Medical Association (AMA) screening tool, the Conflict Tactics Scale (CTS), the Brief Abuse Screen for the Elderly (BASE), the Elder Assessment Instrument (EAI), or the Comprehensive Geriatric Assessment (CGA). Some recommended strategies for intervention in suspected cases of elder abuse are outlined in **Table 30.5**.[31]

Traumatic Brain Injury

Traumatic brain injury (TBI) is a significant cause of morbidity and mortality in elderly trauma patients.[34] In 2013, TBI-related ED visits among the elderly population totaled over 480,000.[35] The most common mechanism causing TBI in elderly patients is falls followed by motor vehicle collisions.[34] Falls account for 55% of all TBIs in patients 65 to 74 years old and 85% of TBIs in patients >85 years old.[34] 5 Imaging with head CT in elderly trauma patients should be used liberally for several reasons: (1) Elderly patients have progressive brain atrophy leading to stretching of bridging veins and increased risk of subdural hemorrhage after trauma,[36] (2) clinical tools such as the New Orleans Criteria and Canadian CT Head Rule exclude elderly patients,[37,38] and (3) neurologic examination may be unreliable in elderly trauma patients.[39,40] The catastrophic combination of TBI and preinjury anticoagulation should prompt to rapid reversal of anticoagulation.[41,42]

Table 30.3 AGS/BGS Clinical Practice Guideline: Prevention of Falls in Older Persons

Summary of Recommendations

Screening and Assessment

1. All older individuals should be asked whether they have fallen (in the past year).
2. An older person who reports a fall should be asked about the frequency and circumstances of the fall(s).
3. Older individuals should be asked if they experience difficulties with walking or balance.
4. Older persons who present for medical attention because of a fall, report recurrent falls in the past year, or report difficulties in walking or balance (with or without activity curtailment) should have a multifactorial fall risk assessment.
5. Older persons presenting with a single fall should be evaluated for gait and balance.
6. Older persons who have fallen should have an assessment of gait and balance using one of the available evaluations.
7. Older persons who cannot perform or perform poorly on a standardized gait and balance test should be given a multifactorial fall risk assessment.
8. Older persons who have difficulty or demonstrate unsteadiness during the evaluation of gait and balance require a multifactorial fall risk assessment.
9. Older persons reporting only a single fall and reporting or demonstrating no difficulty or unsteadiness during the evaluation of gait and balance do not require a fall risk assessment.
10. The multifactorial fall risk assessment should be performed by a clinician (or clinicians) with appropriate skills and training.
11. The multifactorial fall risk assessment should include the following:

Focused History

a. History of falls: detailed description of the circumstances of the fall(s), frequency, symptoms at time of fall, injuries, and other consequences
b. Medication review: all prescribed and over-the-counter medications with dosages

c. History of relevant risk factors: acute or chronic medical problems (e.g., osteoporosis, urinary incontinence, cardiovascular disease)

Physical Examinations

a. Detailed assessment of gait, balance, and mobility levels and lower extremity joint function
b. Neurologic function: cognitive evaluation, lower extremity peripheral nerves, proprioception, reflexes, and tests of cortical, extrapyramidal, and cerebellar function
c. Muscle strength (lower extremities)
d. Cardiovascular status: heart rate and rhythm, postural pulse, blood pressure, and, if appropriate, heart rate and blood pressure responses to carotid sinus stimulation
e. Assessment of visual acuity
f. Examination of the feet and footwear

Functional Assessment

a. Assessment of activities of daily living (ADLs) skills including use of adaptive equipment and mobility aids, as appropriate
b. Assessment of the individual's perceived functional ability and fear related to falling (assessment of current activity levels with attention to the extent to which concerns about falling are protective [i.e., appropriate given abilities] or contributing to deconditioning and/or compromised quality of life [i.e., individual is curtailing involvement in activities he or she is safely able to perform due to fear of falling])

Environmental Assessment

a. Environmental assessment including home safety

Fractures

Elderly patients have decreased cortical bone mass increasing their risk for fractures at lower levels of kinetic energy. As a consequence, older patients have increased risk of rib, spinal, pelvic, and extremity fractures after falls and other low-impact mechanisms than younger patients.

Rib fractures are a significant cause of morbidity and mortality among older patients.[43] Retrospective studies show that in-hospital mortality for patients >65 years is double that of younger patients.[44] The risk of mortality and pneumonia increases with increasing number of ribs fractured, and patients with more than three fractures have worse outcomes.[44,45] Up to a third of older patients with rib fractures develop pneumonia and rib fractures are associated with longer mechanical ventilation days and ICU length of stay.[44]

Osteoporosis, prior fracture, and functional impairment are all risk factors for pelvic fracture.[46] Over 80% of pelvic fractures are caused by falls, and morbidity and mortality after pelvic fractures is significant. In-hospital mortality approaches 8% and is up to five times higher than for younger patients.[47] Many patients after pelvic fracture require a cane or a walker, up to one-third are institutionalized, and 27% will die within a year of injury.[46]

Spinal trauma is increasingly common in elderly patients.[48] The risk of cervical fracture after falls increases with age due to higher rates of cervical stenosis and degenerative disk disease.[19] An estimated 5% to 10% will sustain spinal injury and permanent neurologic deficit after cervical fracture, and 1-year mortality is estimated to be 20% to 30%.[49]

Fourteen percent of elderly patients who sustain hip fracture after falls die within 6 months and almost one-fourth dies within a year.[50,51] Most do not regain prior functional abilities, and patients after hip fracture are five times more likely to live in an institution a year after injury. Hip fracture in older patients often leads to depression,[52] social isolation, and worse overall health. Up to half of patients with hip fracture experience pain for many months after injury.[53] Shorter time to surgery is associated with decreased mortality and fewer complications.[54]

Table 30.4 Risk Factors and Warning Signs for Elderly Abuse

History	**Physical/Mental Status Examination**
Advanced age (>80 yrs)	Indicators of sexual abuse: pain, bruises, lacerations, bleeding in anal–genital areas; bruised breasts or abdomen; signs of venereal diseases
Disability in self-care	Lacerations (including large skin tears, abrasions, burns, and bruises) without adequate explanation, especially on the trunk or other unusual locations
Dementia	Suspicious fractures in sites other than those seen in osteoporotic fractures, that is, wrist, hip, or vertebral body
Depression	Malnutrition
History of hip fracture	Focal findings on neurologic examination
History of stroke	Signs of dehydration
Social isolation	Pressure ulcers
Poor socioeconomic status	Dementia, psychiatric disorders, lack of mental capacity
External family stressors	
Unfavorable caretaker characteristics (mental illness, substance abuse, history of violent or antisocial behavior, depression, or financial dependency on the victim)	
Institutional staffing shortages	
Inappropriate or excessive medications; failure to get needed medications; lack of appropriate monitoring of medications and their effects	
Substance abuse	

Table 30.5 Strategies for Intervention by Physicians in Suspected Cases of Elder Abuse

Suspected Type of Abuse	Intervention Strategies
Neglect	Optimize assistance, including home care Address burden and stress on the caregiver Educate caregiver that care being provided may be aberrant Identify alternative potential caregivers Arrange for social work assistance to ensure benefits and services are optimized Consider nursing home placement Consider adult day care and other respite programs
Verbal abuse	Refer victim for psychiatric or social work assistance Recognize and treat depression and other mental health issues Address burden and stress on the caregiver Educate caregiver that care being provided may be aberrant Identify alternative potential caregivers Address substance abuse
Financial exploitation	Stop the loss of resources as soon as possible Consider power of attorney, daily money management, or guardianship Alert banks and financial institutions to victim's vulnerability

	Consider referral to local law enforcement, district attorney, or both
Physical/sexual abuse	Evaluate, treat, and document physical and sexual violence Refer case to local law enforcement and district attorney Consider filing an order of protection with assistance of law enforcement Consider referral to a shelter for victims of elder abuse Emphasize the need for a safety plan

TRIAGE CRITERIA FOR OLDER PATIENTS

Trauma center care reduces in-hospital mortality for older trauma patients,[55,56] and the benefit of treatment at trauma centers for older patients increases with age.[57] However, triage of older patients can be quite challenging. 6 Even severely injured older patients may not display standard signs of hemodynamic instability. Furthermore, because older patients cannot tolerate large blood loss and shock, some have advocated that systolic blood pressure ≤120 mm Hg should trigger trauma activation to prompt earlier intervention.[58] The Centers for Disease Control suggests that injured patients >55 years should be transferred to a trauma center, regardless of injury severity.[59] The Eastern Association for Trauma (EAST) guidelines recommend that trauma centers should lower threshold for trauma team activation for elderly patients. Further, the guidelines suggest that older patients should be transferred to a level I center if they have a base deficit of −6 or greater, or one body system AIS is >3.[60] In a retrospective study using the National Trauma Data Bank, Pandit et al.[61] showed that shock index (HR/SBP) >1 was associated with higher rates of blood transfusions, exploratory laparotomy, in-hospital complications, and in-hospital mortality.

Based on these findings, the authors recommend that patients with a shock index >1 should be transferred to level I trauma centers.

Despite evidence supporting higher triage, multiple studies show that older patients are routinely undertriaged.[62] Data from the Washington State database showed that the likelihood of being transferred to a trauma center decreased above age 45.[63] Compared to younger patients in the cohort, patients 81 years and older were only 11% as likely to be transported to a level I trauma center from the scene, and only 24% as likely to be transferred from a lower level center to a level I center. The relationship between trauma center admission and longer-term outcome is controversial. One study of severely injured older patients (ISS >15) in three counties in California showed that older patients were less likely to receive care at trauma centers, yet mortality at 60 days after injury was no different.[64]

EVALUATION AND MANAGEMENT

Trauma Evaluation

Although the majority of trauma patients suffer from low energy mechanism of injuries such as ground level falls, initial evaluation of geriatric trauma patients should follow Advanced Trauma Life Support (ATLS) principles. As described previously, older patients are much more likely to have medical comorbidities and extensive lists of medications. It is estimated that approximately 80% of geriatric trauma patient live with at least one comorbid condition.[17] These patients most commonly have hypertension (30%), diabetes (16%), and other cardiovascular comorbidities.[65] These comorbidities along with the changes in physiology described previously should be taken into consideration on assessment of hemodynamic stability. Furthermore, a diligent medication history should be taken to identify beta blockers, ACE inhibitors, anticoagulant and antiplatelet medications. Standard laboratory evaluation should include complete blood counts, comprehensive metabolic panel, coagulation studies such as prothrombin time with international normalized ratio and partial thromboplastin time, lactate, and cardiac enzymes. Imaging should include a chest and pelvis x-ray and focused assessment for sonography and trauma for all high-energy blunt

mechanisms and low-energy mechanisms with signs or physical examination findings concerning for underlying injuries. One should consider the injuries that geriatric patients are more prone to as detailed previously, and CT imaging should be used liberally when concern for a TBI, spinal or rib fractures exists.[66]

Comprehensive Geriatric Assessment

7 Due to the broad range of age-related factors that can contribute to injury and adversely affect recovery in geriatric patients, patients should receive a CGA during their hospital stay. This is a multidimensional and multidisciplinary evaluation including functional ability, physical health, cognition and mental health, and medication review. A recent meta-analysis of 22 randomized trials showed that hospitalized elders who receive a CGA are less likely to die in hospital, have higher rates of discharge home, and improved long-term functional outcomes.[67] Functional status is evaluated with a review of activities of daily living (ADLs) (eating, dressing, bathing, transfers, toileting, continence) and instrumental ADLs (housework, bills, meal preparation, medication management, using the telephone).[68] Physical and occupational therapists can assess gait, balance, home safety, and ability to carry out ADL.

Medications commonly used in older patients can exacerbate injury. Postural hypotension is a common condition in older adults, leading to falls, and can be caused by medication side effects (diuretics, antiarrhythmics, benzodiazepines, antidepressants, and psychotropic agents).[69,70] Antidepressants and psychotropic agents can cause gait impairment. Most patients should receive a nutritional assessment because malnutrition in elderly patients is highly prevalent; 38% of community-dwelling elders are either malnourished or at risk of malnourishment.[71] Social workers can assess social supports, caregiver needs, financial assets and identify resources for the patient and family after hospital discharge. Poverty rates are highest for those 85 and older, and rates are increasing.[72] Social isolation is also a major contributor to poor health in this age group.[73] Those without social support have more frequent hospitalizations and higher healthcare costs near the end of life.[74] They are also more likely to be discharged to institutions. In cases where it is impractical to thoroughly evaluate each

condition during hospitalization, patients should be referred for outpatient follow-up at discharge.

Assessing Frailty

8 Frailty is a syndrome of decreased physiologic reserve, includes physical, cognitive, social and psychological components that can worsen over time, and is distinct form the normal aging process and other comorbidities.[75] Frailty is associated with higher mortality and complications, worse functional outcomes after trauma, and is more predictive than age or injury severity as a predictor of hospital complications, in-hospital mortality, or discharge to an institution.[76] The prevalence of frailty increases with age: 7% of patients at the age of 65 are frail compared to 30% of patients aged 80 and older.[77] Components of the frailty syndrome include shrinkage, weakness, exhaustion, low physical activity, and slowness. Presence of three or more of these indicates frailty.[78]

Frailty can be assessed using a number of different instruments.[79] The Trauma Specific Frailty Index and the Rockwood Frailty Score were recently shown to be better predictors of poor outcomes compared to two other commonly used instruments.[80] A recent meta-analysis sought to identify the optimum frailty assessment tool.[81] The authors noted that despite variations in outcome measures, timing and personnel involved in frailty assessment, and data sources used for assessment, each of the 28 studies reviewed all showed a correlation between frailty and adverse outcomes, and concluded that early assessment of frailty will lead to identification of geriatric patients that may benefit from modified trauma care. Furthermore, frailty has also been shown to correlate with 6-month readmission, recurrent falls, and 6-month mortality.[82] Other investigators have considered sarcopenia, a loss of muscle leading to decreased strength and impaired mobility, as a surrogate measure of frailty in trauma patients. Sarcopenia is associated with more days on the ventilator, and higher postacute care needs, and can be measured using the cross-sectional area of the psoas or masseter muscles.[83,84] The Vulnerable Elders-13 Survey, an assessment of functional status, has been validated as a screening tool to predict discharge to nursing facility, and surgical complication or death in trauma patients 65 years or older. In a

prospective study of 63 geriatric trauma patients, each VES-13 point increased the odds of complication by 1.53.[85]

Patient Management

Data published over the last decade have shown that geriatric trauma patients benefit from care at trauma centers and management by multidisciplinary teams. Various studies have shown that trauma centers with higher volumes and proportions of geriatric trauma patients have lower mortality, fewer complications, and lower rates of failure to rescue.[86,87] This suggests that the greater experience of these centers leads to improved outcomes. Furthermore, there is a great deal of interest in the value of geriatricians to the care of trauma patients. Data also show that routine geriatric consultation leads to lower mortality rates, lower rates of delirium, fewer discharges to facilities among patients admitted from home, and better long-term functional recovery.[88–90]

Some centers have reported success in developing clinical pathways for geriatric trauma patients. Studies evaluating protocolized treatment involving using serial arterial blood gas and base deficit assessment for guided treatment, admission to the ICU, and geriatric consultation show improvement in mortality using these protocols.[91–93] Previously, Mangram et al.[94] described their experience with a dedicated geriatric service and hospital unit, known as the G-60 service, which is a multidisciplinary serviced aimed at providing comprehensive care. Patients were evaluated by a surgeon and a hospitalist at the time of trauma activation and admitted to the surgical service. Other services including physical medicine and rehabilitation, palliative care, physical and occupational therapy, respiratory therapy, the G-60 nurse supervisor, social work, nutrition, pharmacy were also notified at the time of activation and evaluated patients within 24 hours of admission. Surgeon-led multidisciplinary rounds occurred twice weekly. As compared to historical controls, patients on the G-60 service had significantly shorter ED length of stay, time to OR, hospital length of stay, and ICU length of stay. Although mortality was unchanged, there were also significantly lower rates of medical complications. Furthermore, when applied to patients based on frailty rather than age, the use of this multidisciplinary approach was shown to decrease delirium and

readmission.[95] The evidence supporting multidisciplinary care of geriatric trauma patients is strong, and organizations such as the American Association for the Surgery of Trauma and American College of Surgeons Committee on Trauma advocate their implementation at centers caring for these patients.

OUTCOMES

Mortality Outcomes

The relationship between age and adverse outcomes among older trauma patients is well recognized.[96] As compared to younger patients, in-hospital mortalities for older patients are 4.4% versus 1.6% for low severity injuries and 5.9% versus 1.4% for moderate severity injuries. Furthermore, in patients over the aged 85 and older, mortality has been reported as high as 60%.[97] Moreover, mortality among older trauma patients increases with the number of comorbidities; patients with minor injuries and comorbidities are at increased risk of death compared to age-matched counterparts without comorbidities.[98] It is important for clinicians to recognize that significant numbers of geriatric trauma patients die shortly after hospital discharge, and 30 days postdischarge mortality rates have been shown to be double in-hospital mortality.[99] Other than the impact of age and comorbidities on mortality, in-hospital complications such as respiratory failure and delirium are associated with increased mortality. Medications including analgesics and their effect on delirium are well understood. It is imperative to use nonnarcotic options for pain control as first-line treatment in the geriatric patient. Regional anesthesia has long been advocated to minimize narcotic use, and was recently shown to decrease the risk of delirium in geriatric patients with rib fractures.[100]

Functional Outcomes

Most older trauma patients will return to their prior level of function, and thus an initial aggressive approach to treatment in a trauma center is warranted.[60] However, a significant portion of patients experience long-term functional decline after injury. A follow-up study of blunt trauma patients

showed that 87% were functionally independent 1 to 3 years after injury, and another with mean follow-up 2.8 years after injury showed that 63% remained independent but with reduced function.[101] Studies with 12 months or less follow-up show higher rates of decreased functional abilities. In a prospective study of 37 patients >65 years, Kelley-Quon et al.[102] showed that most patients had lost one ADL at 12 months. More recent data from this group show that a geriatric consultation during the index hospitalization is associated with less long-term functional decline.[90] Quality of life in older patients is significantly impaired. Among patients 1 year after hip fracture 90% have reduced mobility, 69% have pain, and 33% who were independent live in a nursing home. As compared to patients without TBI, a cohort of patients >50 years old had poorer cognitive and psychosocial function a year post injury.

PALLIATIVE AND END-OF-LIFE CARE IN THE GERIATRIC TRAUMA PATIENT

Palliative care is an approach to medical care aimed at relieving suffering and improving quality of life for patients with serious illness and for their families. Palliative care is appropriate in the management in a broad range of injured patients who die or suffer with acute and chronic pain, functional disability, or life-limiting conditions such as severe frailty and underlying organ failure.[103] Clinical domains of palliative care encompass symptom management. Spiritual, religious, psychosocial, and bereavement support can be delivered alongside aggressive life-prolonging care and should not be limited to only those patients near the end of life.[104] Thus palliative care can be provided to patients who are "cured" of their illnesses or recover from injury. Palliative care should not be confused with hospice care which is an administrative benefit provided to patients with terminal illness and typically provided to patients expected to survive less than 6 months.

End-of-Life Care

9 Four-fifths of in-hospital deaths among geriatric trauma patients involve decisions to withdraw or withhold of life-sustaining therapies.[105] Advanced directives, including living wills and proxy forms are intended to guide medical decisions in the event a patient loses capacity to make decisions. Unfortunately, many patients, even those with terminal illness, do not have advanced directives or the advanced directives are too specific or too broad to be useful.[106] Therefore, it is critically important that clinicians make every effort to engage patients and their families in conversations about resuscitation status, the overall goals of care, and expectations for recovery early in the hospital course. Patients may forego heroic measures and prolonged life-sustaining treatments if all possible outcomes are not acceptable to them.[107] Furthermore, lack of decision-making capacity, whether it be from pre-existing comorbidities, sequelae of injuries, or delirium, often complicates this discussion with the patient. It is advisable for clinicians to identify healthcare proxies as early in the hospital course as possible should this be the case. Palliative care services, which focus on improving quality of life in seriously ill patients, are an integral part of critically ill geriatric trauma patients.

Physicians play an important role in providing a comfortable death experience for patients and families. In death, patients want to minimize discomfort, to avoid a prolonged dying process, to achieve a sense of control, and time to strengthen relationships with loved ones.[108] Survivors and surrogates suffer high rates of depression, posttraumatic stress disorder, and complicated grief after a loved one dies in the ICU.[109] Better outcomes for survivors are achieved when they feel that they have been well informed and had appropriate responsibility in decision making.[110] It is important for physicians to provide emotional support for surrogates who are often conflicted and distressed.

In cases where the primary goal is comfort, liberal use of opioids can reduce pain and dyspnea. Some clinicians may be reluctant to use opioids for fear of causing respiratory depression and death. Opioid use is ethically justifiable in these scenarios as long as the intent is symptom relief and not euthanasia. Patients should receive doses adequate to achieve comfort; target respiratory rate is 15 to 20 breaths/min. When patients die, physicians should be available to answer questions and address bereavement needs. The way death is communicated is important. In a study of survivors of patients who

died in the ICU, failure to find the physician comforting was most strongly associated with developing a psychiatric diagnosis in the year after death.[109] In another study of 70 survivors of cancer patients, feeling unprepared was a predictor of major depressive disorder up to 9 months.[111]

Hospice

Hospice is an interdisciplinary approach to care that provides comprehensive, medical, nursing, counseling, and bereavement to terminally ill patients and their families. Referral for hospice care is appropriate when patients have a limited prognosis and the primary goal is comfort and symptom management. In the care of geriatric trauma patients, hospice may be relevant to patients with severe TBI or patients who sustain injury in the setting of other advanced serious underlying illnesses with life expectancy 6 months or less. Hospice care is associated with better quality of life, better bereavement outcomes, lower healthcare costs, and either equivalent or improved survival in patients with a terminal diagnosis.[112–115] The impact of transition to hospice on trauma center mortality reporting is unclear. Kozar et al. found wide variation among 167 trauma centers enrolled in the Trauma Quality Improvement Project as to whether they reported patients discharged to hospice as in-hospital deaths or survivors. The authors advised that hospice discharge should be considered death across centers to prevent distortion of actual performances.[116]

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31

Trauma in Pregnancy

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Key Points

1. The management of the pregnant women presents challenges that can impact outcomes for both the mother and child.
2. Treatment priorities remain the same as for the nongravid patient but plans should be tailored for the anatomic and physiologic changes in the gravid trauma patient.
3. Anatomic and physiologic changes in the gravid trauma patient vary by trimester impacting management considerations.
4. Relative hypervolemia of pregnancy may mask physiologic changes associated with massive hemorrhage.
5. Compression of the inferior vena cava (IVC) and hypotension can result from supine positioning. Positioning with a wedge is recommended.
6. A Kleihauer–Betke test should be performed in all pregnant trauma patients >12 weeks of gestation and prophylactic anti-D immune globulin given within 72 hours for high-risk patients.
7. The increased risk for deep venous thrombosis (DVT) should be mitigated with subcutaneous unfractionated heparin prophylaxis.
8. Limit radiation exposure from imaging studies if possible. Ultrasound (including focused abdominal sonography for trauma [FAST]) is a useful imaging modality.
9. Angiography and angioembolization may be useful in life-threatening hemorrhage, recognizing the risks of increased radiation exposure.
10. Intimate partner violence (IPV) and substance abuse are common and should be screened for.

INTRODUCTION

The leading cause of nonobstetric death in women of child bearing age is trauma. Pregnant patients present a unique scenario in that treatment is

required for two (or more) patients 1 simultaneously. The management of pregnant women who suffer trauma is complicated by altered physiology, anatomic distortions, and additional diagnostic considerations. These complexities are highlighted by increased mortality as compared to nonpregnant women.[1,2] More than 1 in 20 pregnancies are complicated by trauma of varying degree which leads to increased rates of preterm labor, placental abruption, and fetal demise.[3,4] Evaluation of pregnant women after trauma can be a daunting task but should follow the same priorities as for nonpregnant patients. Recognition of the predictable changes of anatomy and physiology as gestation progresses, pregnancy-related conditions, and specific challenges in critical care and operative management will guide a knowledgeable provider. Early consultation with an obstetrical provider should be strongly considered.

Pregnancy is a well-known risk factor for intimate partner violence (IPV) but is an often-ignored issue by healthcare providers. The primary focus of resuscitation should be to stabilize the mother. While fetal survival and outcome must be considered, preterm and emergency deliveries are associated with poorer outcomes for infants.

EPIDEMIOLOGY

Women seek medical attention following trauma in 5% to 7% pregnancies but few require hospitalization.[5–8] More than 40% of maternal deaths in the United States are due to trauma. Fetal death is reported in nearly half of pregnancies when the mother has life-threatening injuries, but even minor trauma can be associated with fetal loss. In fact, the majority of fetal loss occurs after minor injuries due to their much higher incidence.[9] Most traumas occur later in pregnancy, with the majority occurring during the third trimester. Motor vehicle collisions are the most common mechanism of injury, followed by falls and interpersonal violence.[10] Motor vehicle collisions are a leading cause of fetal death due to their frequency (207 cases per 100,000 pregnancies).[11,12] Interpersonal violence between intimate partners occurs in up to 30% of pregnant women, with a fetal mortality of 5%. While it is more common earlier in pregnancies, violence is prevalent

throughout gestation and increases immediately after delivery.[13–15] Almost 10% of trauma in pregnant patients is intentional.[16]

MECHANISMS OF INJURY

Phases of fetal maturation and uterine size during pregnancy correlate with injury patterns based on stage of development. Early in pregnancy, before 12 weeks of gestation, the uterus remains thick walled and within the pelvis. As the uterus enlarges, it becomes increasingly thin walled and emerges from the protection conferred by the bony pelvis. By week 20, the uterus reaches the umbilicus and by week 34, the costal margin. Additionally, the relative volume of amniotic fluid decreases further limiting the defenses for the fetus to blunt trauma.

Falls during pregnancy are underreported. When surveyed, 27% of pregnant women reported a fall during their pregnancy.[17] Normal changes in pregnancy (i.e. increased weight, increased joint laxity, and hypermobility) predispose women to falls. Fortunately, most falls result in only minor trauma to the mother, but they still represent a risk to the fetus.

Motor vehicle collisions, the most common mechanism of significant trauma for pregnant women can be mitigated using seat belts. Maternal use is associated with superior outcomes and decreased fetal mortality.[18] With increasing gestational age, the fetus is at higher risk for direct blunt force either from the seat belt or the steering wheel. Trauma to the fetus can results in skull fracture and/or intracranial hemorrhage. Placental abruption, separation of the placenta from the uterus, is the most common direct cause of fetal demise after trauma. Uterine rupture, while rare, is exceptionally lethal with rare fetal survival and maternal mortality of 10%. Maternal pelvic fractures, a high-energy marker, should raise concern for retroperitoneal hemorrhage of the mother and direct injury to the fetal head especially late in pregnancy.

Penetrating trauma in pregnant woman has a high fetal mortality rate, ranging from 40% to 80%, depending on mechanism, gestational age, and location.[16,19,20] Gunshot wounds (GSWs) result in represent 73% of penetration abdominal wounds in pregnancy.[16] Fetal injury is identified in 70% these cases. All abdominal GSWs should be explored but stabs wounds

may be managed nonoperatively in the stable patient if there is no fascial violation.[21]

EVALUATION OF THE PREGNANT TRAUMA PATIENT

2 The American College of Surgeons' Advanced Trauma Life Support guidelines apply for both pregnant and nonpregnant trauma patient.[22] Evaluation begins with a primary survey, according the ABCDE approach pausing to correct immediately life-threatening problems when identified. A complete head-to-toe assessment, the secondary survey, follows. Prioritizing resuscitation of the mother leads to overall the best outcomes for the fetus. A detailed obstetric history including gestational age, prenatal care, complications, and names of obstetrical providers can be invaluable information.

The goals of fetal assessment are to evaluate for fetal injury or death, uteroplacental integrity, and signs of maternal fetal hemorrhage (MFH). Key to the assessment is knowing gestational age and sonography. For viable pregnancies (≥23 weeks) at least 4 hours of electronic fetal heart rate (FHR) and uterine activity monitoring is recommended to start as soon as it is feasible. Heart tones can be heard as early as 10 weeks and should be confirmed but previable fetal monitoring is not indicated.[23] As fetal distress often precedes maternal signs, FHR monitoring can help guide resuscitation. Fetal tachycardia (FHR >160) and bradycardia (FHR <120) are signs of fetal distress and should prompt additional resuscitation for the mother (see **Table 31.1**).

Airway

Pregnant women increase their oxygen consumption 30% to 60% and have a decreased functional expiratory reserve volume and functional residual capacity. The space occupied by a gravid uterus retards diaphragmatic excursion into the abdomen diminishing respiratory reserve potentially leading to precipitous hypoxia of mother and fetus.

Normal weight gain during pregnancy increases BMI and Mallampati scores making airway management more challenging with higher morbidity and more failed intubations.[24] Hormone-related fluid retention leads to generalized edema, including in the tongue, oropharynx, and trachea, further complicating laryngoscopy and intubation. These difficulties lead to much higher rate of failed intubation during pregnancy.[25] The physiologic changes of pregnancy should be accounted for while avoiding hypoxia and hypotension.[22] Pregnant women should be considered high risk for aspiration due to decreased esophageal sphincter tone and upward compression of the stomach from the uterus.

3 **Table 31.1** Physiologic Changes in Pregnancy

Cardiovascular	Increased heart rate (10–15 bpm) Increased plasma volume Decreased systemic vascular resistance Decreased blood pressure (first and second trimesters)
Pulmonary	Elevated diaphragm Increased tidal volume Increased minute ventilation Increased oxygen consumption Decreased functional residual capacity Decreased PCO_2 (30 mm Hg)
Gastrointestinal	Decreased lower esophageal sphincter competency Decreased gastric motility Increased transaminase levels Impaired gallbladder contractions
Genitourinary	Increased glomerular filtration rate Increased renal plasma flow Decreased blood urea nitrogen levels Decreased creatinine levels Hydronephrosis/hydroureter
Hematologic	Relative anemia but increased overall RBC volume Increased WBC counts (9.8–15k) Increased clotting factors VII, VIII, IX, X, XII (hypercoagulability) Increased fibrinogen Decreased fibrinolytic activity (hypercoagulability)

Pulmonary System

4 High concentration of supplemental oxygen should be provided to pregnant women during the primary survey. Chronic hyperventilation and a 30% to 40% increase in minute ventilation during pregnancy is compensatory for a decrease total lung capacity and functional residual capacity due to anatomical changes. Chronic respiratory alkalosis, a side effect of hyperventilation, sets up a gradient for diffusion of fetal CO_2 to the maternal circulation. Overaggressive correction of maternal alkalosis can impact the fetus negatively.[26] Hypocapnia ($PaCO_2$ of <30 mm Hg) is normal in pregnancy and a "normal" CO_2 (~40 mm Hg) may be a sign of impending hypercarbic respiratory failure.

Mechanical ventilation is poorly studied in pregnant patients and there is no consensus on optimal mode for support even in acute respiratory distress syndrome (ARDS). However, as general principle, hypercapnea should be avoided and oxygenation should be optimized.

In cases of pneumothorax or hemothorax, if chest tubes are required, they should be placed one to two interspaces higher than usual late in pregnancy to avoid inadvertent injury to the hemidiaphragm.

Cardiovascular System

Relative hypervolemia of pregnancy can blunt typical signs of shock after hemorrhage. As much as 35% of maternal blood volume can be lost prior to signs and symptoms of shock. The pulse rate is 10 to 15 beats/min faster until delivery and circulating blood volume increases steadily during pregnancy to 150% or more at term.[27] Early and robust volume resuscitation is recommended to maintain maternal circulation. Maternal hypovolemia will lead to fetal compromise. During resuscitation, the patient should be placed in a slight left decubitus position with a wedge to tilt her >15 to 30 degrees or manually 5 displacing the uterus to her left to alleviate the inferior vena cava (IVC) compression and subsequent decreased venous return associated with supine positioning. Spinal precautions should be maintained. If CPR is needed this position decreases effectiveness of chest compressions. Standard

advanced cardiac life support (ACLS) voltage should be used for defibrillation of shockable rhythms for pregnant patients.

Resuscitation should be treated with crystalloid and blood component therapy in accordance with the principles of balanced resuscitation emphasizing early use of blood and blood products for suspected life-threatening hemorrhage.[28,29] Resolution of fetal distress signs may lag up to 30 minutes after maternal stabilization.[30] When deemed appropriate for transfusion, O-negative blood products should be used until type specific or cross-matched blood is available. Pressor support should be reserved for fluid-refractory shock because uteroplacental prefusion is highly sensitive to their use and could decrease fetal perfusion.[23] If needed, ephedrine and phenylephrine have the least effect on fetal circulation and are recommended by some for initial pressor support in pregnant patients. Norepinephrine and epinephrine can be considered, especially in those without a viable pregnancy.[31]

Hematologic System

There is a disproportionate increase in plasma volume relative to the approximately 15% increase in red blood cell (RBC) mass initially yielding a functional physiologic anemia as early 10 weeks. RBC production augments as pregnancy progresses and hematocrits are near normal by term. A hematocrit of 32 is considered normal until the third trimester.[5] White blood cell counts (WBCs) also are also elevated ranging from 9.8 to 15 k/mm.[4]

Maternal and fetal circulations are normally separate but as little as 0.001 mL of fetal blood crossing into the maternal system can trigger sensitization in a Rh-negative mother. Up to a third of pregnant trauma patients have some degree of MFH.[23] Therefore, anti-D immune globulin (RhoGAM™) should be given within 72 hours to all Rh-negative mothers with 6 confirmed or suspected MFH. Kleihauer–Betke (KB) testing is advocated for all Rh-negative mothers with >12 weeks of gestation; its utility in Rh-positive women is less clear.[23,32,33]

Pregnancy is a hypercoagulable state and increases the risk of venous thromboembolic events (VTEs) fivefold.[34] The phenomenon is attributed to an increase in coagulation factor production, decreased fibrinolysis, and

venous stasis from aortic and IVC compression. The hypercoagulability of trauma compounds 7 this risk. The heightened risk warrants prophylactic treatment with heparin, either fractionated or unfractionated, as well as pneumatic compression devices, in conjunction with early ambulation.[34] Warfarin, a known teratogen, should be avoided.[35] Direct-acting oral anticoagulants (DOACs) are not recommended in pregnancy.[36]

FETAL EVALUATION AND MONITORING

After maternal evaluation and resuscitation, examination of the fetus should be performed, including an obstetrical history and examination, including estimation of uterine size and fundal height. A vaginal examination should be performed looking for bleeding, a nonspecific sign of many unfavorable obstetrical conditions including premature cervical dilation, early labor, abruption placentae, and placenta previa. A vaginal examination should be performed to evaluate for rupture of membranes, cervical dilatation, effacement, fetal presentation, and station after previa has been excluded. Cervical dilatation, bleeding, strong contractions, or bulging of the perineum can signal impending delivery. Early involvement of obstetrics and neonatology is advised (see **Table 31.2**).

Table 31.2 Obstetrical Examination Points

Fundal height
Evaluation for vaginal bleeding
Rupture of membranes
Bulging perineum
Contractions
Fetal heart rate and rhythm
Amniotic fluid pooling
Gestational tissue
Perineal lacerations
Cervical dilation and effacement
Bleeding
Fetal presentation
Fetal engagement

DIAGNOSTIC IMAGING

The ideal imaging test in all patients should be convenient, quick, safe, and accurate. The choice of tests balances pressure for expedient diagnosis while minimizing risk to mother and fetus. During pregnancy, radiation exposure should be avoided or minimized whenever possible. Low levels of exposure, less than 5 rad of radiation at any gestational age, is deemed safe and has not been associated with fetal anomalies or fetal demise. The risk is highest in weeks 5 to 10 during organogenesis.[23] Radiation exposure to the fetus can be reduced with proper shielding during plain films (**Table 31.3**). Indicated radiologic examinations should proceed without delay for concerns over fetal radiation exposure. Patients and families should be reassured by the healthcare team that the radiation exposure from a single diagnostic test is not sufficient to cause harmful effects to the fetus.[37] Patients' reluctance often stems from anxieties inconsistent with the actual risks.[8]

8 Focused abdominal sonography for trauma (FAST) is a useful imaging modality to guide initial resuscitation and is safe for both mother and fetus. It has a reported sensitivity of 61% to 83% and a specificity of 94% to 100%

in detecting intraperitoneal free fluid consistent with hemoperitoneum.[38–40] Pregnant women with direct blunt force to the uterus can have massive hemorrhage from engorged uterine vessels. FAST has excellent negative predictive value in detecting pericardial, pleural, and peritoneal free fluid in the hemodynamically unstable mother.[2] Fetal ultrasound is recommended to evaluate for gestational age, cardiac activity, and movement. Ultrasound is particularly useful in the evaluation of intrauterine contents, but can miss 50% to 80% of placental abruptions.[41] Diagnostic peritoneal lavage (DPL) may be useful in evaluating unstable patients but has been largely replaced by FAST. If DPL is performed, it should be performed in the supraumbilical position above the fundus to avoid inadvertent injury to the uterus and fetus.

Table 31.3 Estimated Fetal Radiation Doses from Common Imaging Studies

Diagnostic Test	Fetal Dose (rad)
Chest x-ray	<0.01
Abdominal x-ray	0.1–0.3
Pelvis x-ray	0.04–0.24
Extremity x-ray	<0.01
CT head	<0.05
CT chest	0.1–0.45
CT abdomen	0.24–2.6
CT pelvis	0.73–4.6

Adapted from Williams PM, Fletcher S. Health effects of prenatal radiation exposure. *Am Fam Physician* 2010;82(5):488–493.[45]

Computed tomography (CT) scans are a staple in trauma evaluations because they are very sensitive for identifying injuries. Providers should utilize dose reduction strategies when possible.[42] Head and neck CT scans can be performed with minimal radiation exposure to the fetus. Radiation levels from chest, abdomen, and pelvis CT scans vary but newer scanning

techniques and algorithms can reduce radiation dosing by 25% without significantly degrading diagnostic accuracy.[43]

Magnetic resonance imaging (MRI) poses minimal risk to the fetus but it has very limited role in initial evaluation of trauma patients, largely restricted to the evaluation spine, spinal cord, and neurologic injuries in a delayed fashion. The utility of this modality is limited due to availability, scheduling, length of the examination, and inconvenience relative to imaging techniques. MRI should only be performed in hemodynamically normal patients without ongoing resuscitative efforts.

Angiography and endovascular treatments are increasingly a part of trauma care to control life-threatening hemorrhage. Radiation dosage increases with duration fluoroscopic examination and generally range from 2 to 10 rad/min. Embolization of nonuterine pelvic vessels is feasible and potentially lifesaving in pelvic fractures. However, embolizing the gravid uterus is not recommended (see **Table 31.3**).[44]

The American College of Obstetricians and Gynecologists position on diagnostic imaging for pregnant women states, "With few exceptions, radiation exposure through radiography, CT scan, or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal 9 harm. If these techniques are necessary in addition to ultrasonography or MRI or are more readily available for the diagnosis in question, they should not be withheld from a pregnant patient."[46]

Pelvic Fractures

Of all fractures in pregnancy, pelvic fractures have the worst outcomes. They are associated intrauterine fetal demise (IUFD) up to 40% of the time.[47,48] Hemorrhage from engorged pelvic veins and the hyperdynamic circulation of pregnancy can combine to produce maternal shock leading to fetal death.[8] Angiography and embolization can be helpful to control maternal hemorrhage.

The direct and high-energy blunt force associated with pelvic fractures is also transmitted to the uterus, placenta, and fetus. This can result in abruption or direct injury to the fetus, especially traumatic brain injuries. If the pregnancy continues, a pelvic ring fractures does not contraindicate vaginal delivery, but there is a higher cesarean section rate from multiple factors.[49]

Abruptio Placentae

Abruption, the separation of the placenta from the uterus, is the most frequent etiology of late maternal hemorrhage and the primary cause of intrauterine fetal death following trauma.[50] Severe trauma is associated with a six-fold increase in incidence, but abruption can occur with even minor trauma.[51] Both direct impact and rapid deceleration confer shear forces on the interface of an unyielding placenta against a comparatively pliable uterus resulting in separation, maternal bleeding, and compromised perfusion to the fetus. Fetal mortality may be as high as 70%. More severe cases, more than 50% disruption by surface area, are considered highly lethal and may lead to preterm labor. Smaller insults, less than 30% disruption, may not even show signs of fetal distress.

Table 31.4 Evaluation of Abruption

Maternal Risk Factors	Signs	Symptoms
Previous abruption	Vaginal bleeding	Abdominal pain
Diabetes mellitus/HTN	Intense uterine contractions	Back pain
Advanced maternal age		
Multiparity		
Tobacco use		
Cocaine or methamphetamine use		
Prior cesarean delivery		

Abruption can lead to life-threatening bleeds which may be occult if the blood is retained in the uterus. Even at lower volumes of blood loss, mothers

may develop disseminated intravascular coagulation (DIC) and hemodynamic collapse.[3] Delayed presentation of abruptio placentae has been reported but fortunately the majority presents within the first 6 hours after trauma and nearly all in the first 24. Monitoring of pregnant women with blunt injury to the abdomen is widely accepted as standard.[52] The signs and symptoms, abdominal or back pain with vaginal bleeding, are unfortunately nonspecific. All vaginal bleeding after trauma must be evaluated with at least a sonogram.[3] Ultimately, diagnosis of abruption is clinical and treatment decisions are based on laboratory data and fetal evaluation. Severe placental abruption is potentially fatal for the fetus; expedient Caesarean delivery may result in higher survival (see **Table 31.4**).[23]

Uterine Rupture

Traumatic uterine rupture, which accounts for 17.5% of MVC-related perinatal deaths, is uncommon, but is seen more often in women with uterine scarring from cesarean sections or other causes.[53] Maternal mortality risk is up to 10% and fetal survival is negligible.[9,54] Like pelvic fractures, and placental abruption, uterine ruptures result from direct high-energy blunt force and often have a larger constellation of injuries. Patients may present with abdominal pain as the only symptom of uterine rupture. Excellent outcomes in subsequent pregnancies can be achieved in those with prior uterine rupture who undergo uterine repair.[55]

Amniotic Fluid Embolism

Amniotic fluid embolism is exceptionally rare but may accompany uterine rupture and is thought to be caused by the maternal proinflammatory reaction to exposure of fetal tissue in her circulation. It manifests suddenly as respiratory distress and hemodynamic collapse. It has 20% to 60% mortality in all pregnancies.[56] Diagnosis is rooted in clinical suspicion. Chest imaging may show evidence of pulmonary vascular congestion or bilateral scattered infiltrates like ARDS. DIC may also develop in 30% of these women. There are no proven interventions available only supportive management of affected systems.[57]

Table 31.5 Eclampsia	
Risk Factors	**Signs**
Advanced maternal age (>35 yrs)	Hypertension (most reliable)
Obesity	Edema
Diabetes mellitus	Proteinuria
Prior or family history of preeclampsia	Hyperactive reflexes

Eclampsia

Preeclampsia is new-onset gestational hypertension with evidence of significant end-organ dysfunction. In the context of trauma, preeclampsia is important because it is relatively common (5% of pregnancies), and it can progress to eclampsia, with the new onset of seizures. Development of seizures is infrequent, occurring in about 0.05% to 0.2% of pregnancies. When diagnosed or suspected treatment with intravenous magnesium sulfate is recommended and emergency Caesarian delivery should be considered (see **Table 31.5**).

Disseminated Intravascular Coagulation

DIC is a dysregulation of the clotting cascade triggered by many pathologic conditions in pregnancy some of which can arise from trauma. Normal pregnant women are prone to clot due to the marked elevation of their coagulation factors. The departure from the normal state predisposes their hematologic system to DIC when activated by trauma. Major trauma, especially those with hypoperfusion, abruption, uterine rupture, eclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count), and amniotic fluid embolism, can lead to DIC. Treatment consists of blood component therapy and supportive care.

EMERGENCY CAESARIAN SECTION

Caesarian section should be deferred in favor of vaginal delivery when it is feasible. Labor can continue in appropriate patients even the onset of labor precedes completion of the trauma evaluation and treatment of identified injuries. This is true even if treatment includes laparotomy or other operative intervention (**Table 31.6**).[58]

Perimortem caesarian section can be considered for fetuses greater than 20 to 22 weeks of gestation depending on local availability of neonatology. This decision can be difficult but must be made expediently as the best fetal outcomes are correlated with time from arrest to delivery. There is also evidence that 60% of mothers have improved circulation after perimortem caesarian sections. Current recommendations advocate for perimortem caesarian section for the viable fetus within 4 minutes of maternal cardiac arrest without return of spontaneous circulation or malignant arrhythmia.[59–61] Early involvement of the obstetrics team facilitates the decision to perform an emergent caesarian section and ensures the timeliest delivery of the child should one be necessary.

Table 31.6 Indications for Emergency Caesarian

Maternal shock
Massive exsanguination
Unstable thoracolumbar spinal injuries
High risk of fetal demise
Facilitation of maternal treatment

SOCIAL CONSIDERATIONS

IPV is much too frequent. It is reported in 10% to 30% of pregnancies. Women from any age group, religion, ethnic background, income level, educational attainment, and sexual 10 orientation can be victims of IPV. Universal screening of pregnant patients for IPV is strongly recommended. Women with multiple episodes of trauma, suspicious patterns of injury, or injuries inconsistent with the reported history are concerning indicators.

Screening during trauma evaluation may not be possible. There are effective brief screening tools that can be used at a slightly delayed time. It is important that screening be performed without the partner, or the information obtained may be inaccurate. Picking up the signs and providing options for safety with referrals to social work and local resources, best ensures the safety of both mother and fetus.[62,63]

Pregnant women are not immune to substance abuse issues. In some urban facilities 50% to 80% of women were screened positive for illicit drugs.[64] Traumas affecting pregnant women were alcohol or drug related 12.9% and 19.6% respectively according to National Trauma Data Bank figures.

TEAM APPROACH TO TRAUMA IN THE PREGNANT PATIENT

Collaborative care delivery with input from prehospital providers, the Emergency Medicine, Nursing, Obstetrics, Critical Care, Neonatology, and Surgery optimizes management of the pregnant trauma patient. Early notification obstetrics (even prior to arrival of the patient) may provide the critical time that can be invaluable for both mother and fetus in extremis.

SUMMARY

Predictably, injured pregnant women are more likely to have a cesarean delivery. The risks of preterm birth and perinatal death seem to be exclusive to deliveries immediately after the trauma, a fortunately rare event attributable to the severity of trauma.[65] Fetal survival is best achieved by appropriate resuscitation and care of the mother. Recognition of the unique issues and potential complications of associated with trauma in pregnancy ensure the best possible outcome for both mother and fetus. Optimal treatment requires special attention to the evolving anatomical and physiologic changes of gestation. Evaluation and management should be tailored to the stage of pregnancy and requires a multidisciplinary, team approach.

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32

Postinjury Management

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Key Points

1. Coagulopathy is common in trauma and is multifactorial, with dilution and consumption being contributing factors. Empiric replacement of coagulation factors is an important aspect of early resuscitation.
2. Damage control resuscitation involves limited use of crystalloid fluids and early more liberal use of massive transfusion to restore volume and maintain organ perfusion.
3. Multiple metrics should be used to determine adequate endpoints of resuscitation since vital signs alone can be falsely reassuring.
4. Abdominal compartment syndrome, characterized by increased intra-abdominal pressures and a tense, distended abdomen, causes oliguria, multi-organ failure, decreased venous return and impaired cardiac output, and emergent decompressive laparotomy is required in severe cases.
5. Traumatic brain injury (TBI) is a major cause of mortality and morbidity in trauma patients. Care of these patients must be focused on preventing secondary brain injury by avoiding hypotension, fevers, elevated intracranial pressures and seizures.
6. Early nutritional support is important in trauma patients and enteral nutrition is preferred over parenteral nutrition when possible.
7. Trauma patients can be a source of organ donation. Therefore, resuscitation should be continued even after brain death or irreversible neurological devastation is determined and until the necessary conversations can be held by the appropriate people with the families.
8. Chest trauma and rib fractures are a major cause of mortality and morbidity in trauma patients, especially in the geriatric population. Early, aggressive pain control and pulmonary toilets are essential in preventing pneumonia and respiratory failure. Surgical rib fixation is sometimes indicated to restore chest wall mechanics and effective breathing.

9 Blunt cardiac injury can often be managed with supportive measures. A high index of suspicion must be maintained for more serious cardiac injury as this can be fatal without surgical intervention.

INTRODUCTION

Trauma is now the leading cause of death for ages 46 and below in the United States.[1] Hemorrhagic shock is the most common cause of mortality during the first 6 hours following trauma and 16% to 80% of those deaths may be preventable.[2] Postinjury management predominantly focuses on two goals, early control of bleeding and resuscitation.

ACUTE TRAUMATIC COAGULOPATHY

1 Coagulopathy will worsen posttraumatic hemorrhage and is associated with increased mortality and worse outcomes. Interestingly, up to 25% of trauma patients are already coagulopathic upon arrival to the hospital.[3,4] Current data suggest that coagulopathy develops in the early posttraumatic period even before resuscitation begins and is now referred to as acute traumatic coagulopathy.[4–6] Diffuse endothelial damage, activation of the protein C pathway, and massive catecholamine release are some of the proposed mechanisms for acute traumatic coagulopathy.[7] Acute traumatic coagulopathy is exacerbated by hypothermia, acidosis, and dilution of clotting factors. Hypothermia in trauma patients results from a multitude of factors that include radiant heat losses to the environment, failure of shivering response during anesthesia, intraoperative heat loss from exposed peritoneal surfaces, and tissue hypoxia during hemorrhagic shock with decreased metabolism. Another major cause of hypothermia is the use of relatively cool room temperature resuscitation fluids or cold refrigerated blood products that were not warmed before infusion.[8–10] These cumulative factors produce qualitative and quantitative defects in platelet function and decrease coagulation factor activity.[11–13]

In addition to reducing coagulation factor activity, dilutional coagulopathy from large-volume crystalloid resuscitation and acidosis from prolonged tissue hypoxia perpetuates the bloody vicious cycle.[14,15] The combined presence of three factors, hypothermia, acidosis, and coagulopathy, is known as the "lethal triad." Modern trauma resuscitation is defined as damage control resuscitation (DCR) and aimed at reducing the iatrogenic development of this "lethal triad."

DETECTION OF TRAUMATIC COAGULOPATHY

The early identification of acute traumatic coagulopathy remains a challenge. Conventional coagulation assays like PT, aPTT, and INR are insensitive and unreliable in trauma patients, as they do not provide an accurate assessment of the in vivo state of coagulation. Moreover, these assays are performed at physiologic pH and temperature; because of this they are unable to account for the effects of hypothermia and acidosis on coagulation.[7] Acute traumatic coagulopathy involves changes in both coagulation and fibrinolytic pathways, and detection requires a more dynamic view of all components of the coagulation cascade, which is provided by viscoelastic tests, that is, thromboelastography and rotational thromboelastometry. These assays rely on changes in clot strength to detect coagulation defects and provide an in vivo picture of the coagulation and fibrinolytic processes. These tests also assess the interaction between coagulation factors and platelets and can detect functional changes in platelet function even with normal platelet counts. They can be performed with much more rapidity and have been shown to detect coagulation abnormalities with higher sensitivity as compared to conventional coagulation assays.[16–18]

Table 32.1 Components of Damage Control Resuscitation
Permissive hypotension
Early definitive hemorrhage control
Reduced crystalloid use
Use of hypertonic saline
Early correction of coagulopathy with drugs (Factor Vila, PCC, TXA)
Increased use of blood products in 1:1:1 ratios

PCC, prothrombin complex concentrate; TXA, tranexamic acid.

Viscoelastic tests have also shown to be more accurate in predicting blood product requirements and massive transfusion and can therefore guide blood transfusion in trauma patients.[19,20] Despite these advantages, viscoelastic tests come with inherent disadvantages such as cost and the need for greater expertise in performance and interpretation.

DAMAGE CONTROL RESUSCITATION

2 The primary objective of resuscitation following hemorrhage is to restore effective circulating volume to allow adequate tissue perfusion and oxygenation. Historically, the standard of practice had been to aggressively resuscitate patients with high volumes of crystalloids to restore volume and blood pressure. In recent years, there has been a paradigm shift away from the large-volume resuscitation, and specifically away from large volumes of crystalloid. Current strategies combine the principles of permissive hypotension, liberal use of blood products instead of isotonic fluids, the use of hypertonic saline to pull water back into the vascular system, and early correction of coagulopathy with blood products as well as drugs (**Table 32.1**).

Permissive hypotension aims at restoring systolic blood pressure to 90 mm Hg so that adequate tissue perfusion can be maintained while not exacerbating blood loss, before definitive hemorrhage control is achieved.

Large-volume resuscitation with crystalloids before definitive hemostasis can raise blood pressure which can "pop off" the clot and worsen hemorrhage.[21] A target mean arterial pressure (MAP) of around 60 mm Hg is thought to maintain adequate tissue perfusion without the potential for increased blood loss.[22–25] A brief period of hypotension with a MAP around 60 mm Hg can be safely maintained for short periods of time without risk of irreversible damage or an increase in mortality.[26] Permissive hypotension has been shown to reduce the risk of death and development of coagulopathy.[3,27] However, in patients with hemorrhagic shock and concurrent traumatic brain injury (TBI), the safety of permissive hypotension has not been demonstrated and thus it is not yet recommended.[28] It is important to note that permissive hypotension is intended for young, otherwise healthy patients with penetrating trauma in hemorrhagic shock. It should not be applied to patients with blunt trauma or in elderly patients, especially since the latter are more likely to have comorbidities such as cardiac and carotid disease where hypotension may lead to catastrophic results. Furthermore, hypotension in traumatic brain injury may worsen outcomes and should thus be avoided in that patient population. Up to 5% of civilian trauma patients require massive transfusion, defined as the need for more than 10 units of red blood cells in 24 hours. These patients are at greatest risk for developing dilutional coagulopathy from large volumes of resuscitation even if packed red cell transfusion is used early in the resuscitation phase.

DCR utilizes massive transfusion protocols and early use of red cells, fresh frozen plasma, and platelets in a 1:1:1 ratio in an attempt to reconstitute whole blood. The use of blood products early in the course of resuscitation is not only an attempt to combat the coagulopathy in trauma patients requiring massive transfusion but to also minimize the use of crystalloids and colloids.[29–31] The use of predefined massive transfusion protocols has shown improved survivals and decrease in adverse outcomes.[32,33] This approach requires the ability to predict the need for massive transfusion in trauma patients at the time of arrival which is often difficult even for experienced surgeons. Multiple scoring systems have been developed to help define the cohort requiring massive transfusion.[34,35]

The appropriate ratios of packed red cells, fresh frozen plasma, and platelets in exsanguinating trauma patients have been debated. The concept of

a 1:1:1 ratio stems from military data that show improved survival with the use of fresh whole blood. Since civilian trauma centers do not have fresh whole blood available, component therapy is an attempt to reconstitute whole blood by giving red cells, fresh frozen plasma, and platelets in a nearly physiologic ratio. Most studies have shown improved mortality with the use of high plasma and pRBC ratios with even greater survival in those with early (6 to 12 hours) use of high ratios.[5,8,36–41] The use of a 1:1 ratio for pRBC and platelets has also shown improved survival.[38] Despite the survival advantage with the use of a 1:1:1 ratio for transfusion, the potentially lethal complications of blood transfusion need to be kept in mind. The PROPPR trial was a multicenter prospective randomized study in hemorrhagic trauma patients that demonstrated an early survival benefit when the patients were resuscitated with a 1:1:1 ratio compared to a 2:1:1 ratio but the 28-day mortality was not statistically significantly different. FFP is an essential component of MTP but it is logistically challenging to use because it needs to be stored at −18°C and needs about 30 minutes lead time before use. These requirements can make it difficult to use in a hemorrhaging patient. In patients who require immediate MTP, pre-thawed FFP, which can be stored for 5 days, can be used immediately.[42]

Hypertonic saline has many potential advantages in that it can resuscitate with low volume by pulling water into the vascular space and thus avoids excess water during resuscitation. This concept has advantages especially in the military field environment. Hypertonic saline is also thought to be an immune modulator that potentially decreases inflammation associated with resuscitation injury.[43] However, a multicenter prospective trial in trauma patients with hemorrhagic shock was halted before completion as the outcome was similar between the groups. Overall there was no survival disadvantage in the hypertonic saline arm of the study except in a small subset of patients who did not require blood transfusion. This subset of patients had higher mortality if given hypertonic saline in the field. There was also a subset that required ICU treatment that showed higher survival and decreased multiple organ failure when hypertonic saline was given.[44] Since 7.5% hypertonic saline is not commercially available, an alternative is to use 5% hypertonic saline. Those who use 5% hypertonic saline administer it as a one-time bolus in the initial phase of resuscitation. This approach may

be beneficial in patients with TBI. The safety of using 5% hypertonic saline has been shown in two studies.[45,46]

A caveat of using hypertonic saline is that it causes hyperchloremic acidosis, but clinical significance has not yet been demonstrated. Because of the capability of increasing intravascular volume, the ideal time and place for hypertonic saline use may be in the field, especially in the military setting.[47] Hyperfibrinolysis associated with traumatic coagulopathy may decrease levels of fibrinogen. High plasma:pRBC ratios adequately replenish the fibrinogen pool required for adequate hemostasis and thus the use of cryoprecipitate rich in fibrinogen as an adjunct to DCR is rational.[8] The use of cryoprecipitate has additional advantages as it provides particles that act as a low-volume colloid resuscitation and draw water into the vascular system, and is an adjunct in resuscitation. Tranexamic acid is an antifibrinolytic agent found to be safe and effective in reducing the risk of bleeding if used within 3 hours of injury.[48] The military Tactical Combat Casualty Care Committee has recommended its use in the military setting.

Several other novel strategies have also been used as an adjunct in DCR including the use of activated recombinant factor VII (rFVIIa). rFVIIa activates factor Xa at the site of tissue injury by complexing with tissue factor on the surface of platelets. Use of rFVIIa in the initial studies appeared to reduce blood loss and mortality in trauma patients; but subsequent larger randomized trials failed to confirm these benefits.[49–52] Prothrombin complex concentrate (PCC) is another cost-effective option that reverses coagulopathy in traumatic injury[53]; however, it is not appropriate for every trauma patient and is mostly used as a second line therapy as part of a massive transfusion protocol. While each component of resuscitation is important, it is the combination of these methods that is essential. Specifically, avoiding hypothermia and acidosis, early temporizing measures and expeditious definitive control of hemorrhage with surgical or angiographic methods, use of the correct ratios of blood products and adjunctive pharmacologic agents, such as tranexamic acid and use of viscoelastic assays all compose the hemorrhage control bundle, which has been associated with decreased mortality from hemorrhage and overall improved outcome.[54]

The discussion of DCR should also include damage control laparotomy (DCL). The principle of the DCL is to explore the patient, control hemorrhage, contain contamination, and temporize the damage but to refrain

from definitive repairs that may subject the patient to a prolonged operation before they are properly resuscitated, which would exacerbate the lethal triad and increase chance of death. In these cases, the abdomen remains open and the patient is brought to the ICU for continued resuscitation. One hallmark study suggested that DCL is of benefit in trauma patients with numerous major visceral injuries that also have vascular injury; this study also showed that DCL in patients without major injuries was associated with worse outcome.[55] While the use of DCL is necessary in certain circumstances, there can be significant morbidity associated with them. Specific complications include abdominal abscesses, gastrointestinal fistulas, as well as complex ventral hernias and loss of domain. Furthermore, the prolonged ICU course and multiple trips to the operating room that occur in the patient with an open abdomen contribute to the associated morbidity.

A more recent study evaluated the variability in practice of DCL. There is no strict practice management guideline for its use, but the standard general criteria are major abdominal vascular injury, coagulopathy, acidosis, and hypothermia. Outside of these criteria, its use is left to the discretion of the surgeon. This study examined the variability of DCL in level 1 trauma centers by evaluating patients from the PROPPR Trial who underwent immediate laparotomy and categorized them to having either DCL or definitive surgical management (DSM). The study found that there is significant variability among centers in the use of DCL but that there was no difference in mortality. DCL was associated with higher rates of sepsis and VAP. This study suggests that reducing the use of DCL might lessen the morbidity burden while not affecting the mortality.[56] Definitive laparotomy may have survival benefit with decrease in morbidities known to accompany DCL such as open abdomens and enterocutaneous fistulas. Because of the decreased number of surgeries and morbidities, the cost benefits were significant.[57,58]

ENDPOINTS OF RESUSCITATION

3 The ultimate goal of resuscitation is to ensure adequate oxygen delivery to tissues. Prolonged tissue hypoxia is associated with multiorgan dysfunction syndrome, risk of infection, and increased mortality. Advanced trauma life

support (ATLS) guidelines define the correction of vital signs like blood pressure and heart rate as markers of adequate resuscitation. However, up to 82% of severely injured patients with normalized vital signs have ongoing occult ischemia that is associated with adverse outcomes.[59] While normalization of vital signs may describe the current perfusion status, they do not assess oxygen debt, defined as ongoing oxygen deficits that have accumulated during the period of shock. Oxygen debt is known to be associated with increased mortality.[60,61] Arterial lactate and base deficit may serve as indicators for severity of shock and may help to stratify patients. Trends in serum lactate levels indicate adequacy of resuscitation.

Invasive monitoring with central venous pressure (CVP) and pulmonary artery catheter (PAC) has been extensively used to guide resuscitation. CVP and pulmonary capillary wedge pressure monitoring provide information regarding the intravascular volume, but concurrent factors like mechanical ventilation and changes in ventricular compliance from myocardial dysfunction limit their efficacy in accurately guiding resuscitation.[62] Moreover, PAC use in critically ill trauma patients has not been shown to improve outcomes.[63] $ScVO_2$ and SVO_2 measure central venous oxygen saturation from the upper body and mixed venous oxygen saturation from both the upper and lower body, respectively. Inadequate oxygen supply from ongoing shock or increased oxygen demand leads to an increased tissue extraction of oxygen, which is reflected as a decrease in the values of $ScVO_2$ and SVO_2. SVO_2 of less than 65% even in the presence of normal vital signs indicates blood loss and need for transfusion to optimize oxygen supply and demand.[64] Therefore, $ScVO_2$ and SVO_2 provide a real-time picture of tissue perfusion and are able to detect very subtle changes in oxygen delivery. The ideal marker for resuscitation may be to determine blood volume, but there is currently no simple way to determine ideal circulating blood volume.

ABDOMINAL COMPARTMENT SYNDROME

4 Abdominal compartment syndrome is an undesired consequence of elevated intra-abdominal pressure and a cause of morbidity and mortality.[65] The incidence of abdominal compartment syndrome is decreasing with recent

evolution in resuscitation strategy, suggesting a possible iatrogenic etiology.[66] Intra-abdominal hypertension is defined as a pressure of greater than or equal to 12 mm Hg. Intra-abdominal hypertension is graded based on increasing intra-abdominal pressure (**Table 32.2**). Abdominal compartment syndrome is defined as a sustained intra-abdominal pressure greater than 20 mm Hg (with or without an abdominal perfusion pressure of less than 60 mm Hg) with new organ dysfunction or failure.[67] Experimental data indicate that hepatic arterial, portal venous, and hepatic microcirculatory blood flow are markedly reduced when intra-abdominal pressure is increased.[64,68]

Table 32.2 Grades of Intra-Abdominal Hypertension

Grade	Intra-Abdominal Pressure (mm Hg)
I	12–15
II	16–20
III	21–25
IV	>25

Typically, abdominal compartment syndrome is observed after severe abdominal trauma with intra-abdominal hemorrhage, severe liver and kidney injuries, and in both operatively and nonoperatively managed settings (primary abdominal compartment syndrome).[69–71] Excessive large-volume resuscitation, even in the absence of any direct abdominal trauma, can also lead to abdominal compartment syndrome (secondary abdominal compartment syndrome).[72–74] Recurrent or tertiary abdominal compartment syndrome refers to a condition following a previously treated primary or secondary abdominal compartment syndrome.[62] Risk factors for development of abdominal compartment syndrome include diminished abdominal wall compliance, increased intraluminal and intra-abdominal content, crystalloid resuscitation/leak, and other risk factors such as age, shock, high BMI, coagulopathy, and mechanical ventilation.[75–85]

Abdominal compartment syndrome can even occasionally occur in patients with an open abdomen. The diagnosis often begins with findings of a tense

and distended abdomen in the presence of high end-inspiratory airway pressures and other signs of organ dysfunction (i.e., oliguria, rising serum creatinine). Additional clinical signs consistent with abdominal compartment syndrome are a reduced cardiac output, elevated systemic vascular resistance, and elevated pulmonary capillary wedge pressure with simultaneous low or normal calculated estimates of end-diastolic volume. The standard for monitoring intra-abdominal pressure is bladder pressure measurement via intravesical technique. Bladder pressure is measured in end expiration with the patient supine, by distending the bladder with 25 mL of sterile saline.[86,87] Surgical decompression of the abdomen is an option for established abdominal compartment syndrome with associated organ dysfunction and persistent shock with no absolute thresholds for urine output and airway pressure.[88] Protocols on fluid resuscitation are recommended to avoid a sustained increase in intra-abdominal pressure.[89]

In addition to decompressive laparotomy for abdominal compartment syndrome, numerous medical and minimally invasive therapies have been proposed such as sedation and analgesia for anxiety relief and brief trials of neuromuscular blockade as temporizing measures. Body positioning and colonic/nasogastric decompression are also suggested noninvasive treatment options.[90–92] Patients with abdominal compartment syndrome may have ascites and drainage of fluid with various catheters can be tried before performing decompressive laparotomy as a less invasive alternative. A common factor among all cases of abdominal compartment syndrome seems to be the use of aggressive crystalloid resuscitation causing resuscitation injury. Use of excessive crystalloid resuscitation is discouraged in DCR and studies show decreased rates of abdominal compartment syndrome in association with decreased rates of crystalloid resuscitation.[63] Attempts to achieve "supranormal" endpoints (cardiac index of >4 L/min/m^2 or oxygen delivery index of >600 mL/min/m^2), while theoretically desirable, have not been shown to be effective as this often requires excessive resuscitation volumes that contribute to abdominal compartment syndrome.[93]

As resuscitation has changed with DCR, the incidence of abdominal compartment syndrome has been decreasing. In the trauma setting, abdominal compartment syndrome has been disappearing rapidly but in the general surgery setting, it is more common. Sepsis as a source of inflammation can create abdominal compartment syndrome even when resuscitation injury is

minimized. Source control of the bacterial contamination is the best treatment for abdominal compartment syndrome. End organ failure with microcirculatory disruption and endothelial leak is another source of the syndrome.

TRAUMATIC BRAIN INJURY

TBI remains one of the leading causes of injury-related deaths. Initial management of TBI includes hyperosmolar resuscitation, intracerebral pressure (ICP) monitoring, and prevention of hypoxia and hypotension.

Secondary Brain Injury

5 Injury prevention and better safety are the mainstays for primary brain injury. After the initial insult, the main goal is to prevent or minimize secondary brain injury. Secondary brain injury can be influenced by a cascade of inflammatory responses, occurring as a consequence of the primary injury. Secondary brain injury is also exacerbated by potentially preventable factors such as hypotension, hyperthermia, seizure activity, hyperglycemia, and hypoxemia. Hypotension at any point (even brief time periods) is associated with a doubling of mortality in patients with severe TBI.[94,95] Although hyperventilation temporarily reduces intracranial pressure and may help to prevent herniation, evidence suggests that excessive hyperventilation may be harmful for patients with TBI. Therefore, brief hyperventilation is only recommended in order to reduce ICP temporarily until surgical decompression can be performed.

Imaging in TBI

Computed tomography (CT) scanning remains an essential tool in the initial evaluation and postinjury management of TBI. Patients with mild and moderate TBI who are examinable and not on any anticoagulant medications can be monitored by clinical examination without the need for routine serial CT scans of the head.[96–98] With technologic improvements made to the CT scanners around the world, the incidence of TBI has been increasing. Small

insignificant intracranial radiologic findings are the main reason for the increase in the diagnosis of TBI. With increased awareness of mild TBI and with the increased attention to mild TBI with posttraumatic stress disorder, CT scans of the head are being ordered more often and routinely. In trauma, the single most common reason for obtaining a CT scan of the head has been loss of consciousness. Thus increased screening for TBI and improved technology identifying small clinically insignificant intracranial injuries has resulted in the increase of incidence of TBI.

TBI is a clinical diagnosis and not just a radiographic diagnosis. There are patients with TBI with normal CT scans of the head who have cognitive deficits as well as posttraumatic stress disorder and there are many with radiographic TBI that do not have clinical deficits. Therefore, significant deterioration in neurologic examination should be considered in the decision for whether repeat head CT scan or consultation of a neurosurgeon is needed. CT scans and neurosurgical consultations are valuable resources with costs to the health care system as well as to the patient. The use of routine repeat head CT and neurosurgical consultations should be restricted to patients on prehospital antiplatelet and anticoagulants, and those with depressed skull fractures. A Brain Injury Guideline has been developed which helps guide when the resources should be used (**Table 32.3**).[99–101] Progression of lesions on repeat head CT scan promptly identify patients who require more invasive neurosurgical interventions and medical therapies. Routine repeat head CT is still recommended for those patients with GCS less than 8 and for those who do not have a reliable clinical examination such as patients that are under general anesthesia or patients that are in the ICU under sedation.

Coagulopathy in TBI

A decreased platelet count (less than 100,000/μL) and/or impaired platelet function after TBI is associated with progression of intracranial hemorrhage, need for neurosurgical intervention, and mortality.[102–104] Admission INR greater than 1.5 also predicts progression of intracranial hemorrhage. The treatment of coagulopathy after TBI is multipronged due to the complexity of the problem. Therapeutic strategies should focus on the treatment of the primary cause and controlling the progression of intracranial bleeding. Fresh

frozen plasma, platelets, recombinant factor VII, and PCC can be used in various combinations to improve outcomes.[53,105]

Table 32.3 Brain Injury Guideline

Variables	BIG 1[a]	BIG 2
Neurologic Examination	Normal	Normal/abnormal
Intoxication	Yes/no	Yes/no
CAMP	No	Yes/no
Skull Fracture	No/simple, nondisplaced	Other
SDH	<4 mm	>4 mm
EDH	<4 mm	>4 mm
IPH/Contusion	One location and <4 mm	Other
SAH	Trace/pinpoint	Other
Therapeutic Plan		
Neurosurgical Consult	No	Yes
RHCT	No	Yes
ICU Admission	No	Yes

[a]Patients should meet all criteria for BIG 1.

Intoxication, alcohol/drugs; CAMP, Coumadin, aspirin, Motrin, Plavix; SDH, subdural hematoma; EDH, epidural hematoma; IPH, intraparenchymal hemorrhage; SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage; RHCT, repeat head CT; NSC, neurosurgical consult.

Antiplatelet and Anticoagulation Therapy in TBI

Antiplatelet medications, anticoagulants, and nonsteroidal anti-inflammatory drugs are among the most frequently encountered medications in TBI patients, especially the elderly. Existing evidence shows an increased risk of progression of intracranial bleeding in patients on high-dose aspirin and clopidogrel, whereas low-dose aspirin and ibuprofen do not cause progression on CT or neurologic examination.[106–108] A platelet count of less than 135,000/μL in patients on antiplatelet therapy is predictive of both radiographic and clinical worsening.[109] Reversal of the effect of anticoagulants and antiplatelets is suggested to improve the outcomes. Use of newer oral anticoagulants like direct thrombin inhibitors and factor Xa inhibitors is increasing. Despite their safety advantage over Coumadin, concerns for progression of intracranial bleed, and adverse outcomes exist in TBI patients. There are limited reversal agents for the newer oral anticoagulants. Andexanet Alfa is used to reverse Apixaban and Rivaroxaban, but is very expensive and not widely available yet. Oral charcoal administration, hemodialysis, PCC, and rFVIIa have shown some efficacy in the reversal of these agents.[110–115]

Seizure Prophylaxis after TBI

Posttraumatic seizures increase the cerebral metabolic rate, ICP, and may cause secondary brain injury. Seizures after TBI are associated with worse outcome. It is not known if poor outcomes are due to underlying injury which is associated with posttraumatic seizures or if posttraumatic seizures exacerbate injury. Studies have shown that prophylactic therapy with phenytoin during the first 7 days after injury is effective in reducing the number of early posttraumatic seizures.[116] Long-term use of prophylactic anticonvulsants has not been shown to be of benefit. Anticonvulsant prophylaxis is not indicated for late onset posttraumatic seizures (after 7 days). Because phenytoin is cumbersome to use, as it requires frequent drug-level monitoring and can lead to neurodepressive side effects, the use of levetiracetam has become common. However, recent studies have shown that the seizure rate after TBI is very low and the use of levetiracetam has not equated to reduced seizures.[117]

Penetrating Brain Injury

Gunshot wounds to the brain are the most lethal of all firearm injuries. Aggressive postinjury resuscitation is associated with significant improvement in both survival and organ donor eligibility.[118,119] Early aggressive management includes blood products, hyperosmolar therapy, vasopressors, and/or PCC. Early aggressive T4 (levothyroxine) therapy and correction of coagulopathy increases the organ donation rate in nonsurvivable patients.[117,120]

NUTRITIONAL AND METABOLIC SUPPORT

Nutritional support after injury imparts significant acute and long-term effects on outcomes. Understanding of the nutritional and metabolic derangements following injury has increased exponentially over the past few decades. This has resulted in a more focused and goal-oriented approach toward nutritional support. Once patients are stabilized and recovered from shock, attention should be directed to metabolic and nutritional support. The route of administration and timing of initiation of nutritional support have been issues of controversy. 6 Current evidence supports the use of enteral nutrition in all trauma patients as soon as possible.[121–126] There are certain situations where enteral nutrition is not a feasible option; in such patients total parenteral nutrition is an alternative. Even in cases where enteral nutrition cannot be administered due to frequent or impending operative intervention or intolerance of enteral feeding, total parenteral nutrition should be used as a bridging measure. The literature on nutritional support in critically injured trauma patients consistently reports higher septic morbidity in patients on total parenteral nutrition.[123–125,127] Current guidelines on the nutritional support provide a level 1 recommendation on the advantages of enteral nutrition over nutritional support via the parenteral route.[128] Recent recommendations aim for early enteral nutrition. The definition of early varies in the literature, ranging from a few hours after injury up to 72 hours.[125,126] Although the benefits are yet to be established, safety of early (within 24 hours of injury) enteral feeding is well documented.[127] In patients with severe burns it is recommended to initiate enteral feeding within 18

hours of injury.[129] Early feeding in this group of patients reduces the risk of gastroparesis. In the case of severe TBI enteral feeding is safe and should be administered early.[130–132]

Nasogastric and nasojejunal routes are the preferred modes of initial nutritional access. If long-term nutritional support is required, the planning of feeding access should be based on individual patient circumstances. In patients undergoing laparotomy, insertion of a surgical feeding tube either in the stomach or small intestine is a feasible option. For patients in need of long-term nutritional support and not requiring surgical intervention the preferred route is via endoscopically guided percutaneous feeding tube. The percutaneous endoscopic route is increasingly popular, but the literature is not well established on its safety and complications.[133,134] While choosing one route over the other, special consideration should be given to individual patient factors as there is no single feeding access that stands out among the others for safety and efficacy.[135–138]

The goal of nutritional support during postinjury phase is twofold, first to provide enough calories to meet basal energy expenditure and second to complement the special micronutrient requirements of ongoing inflammation. Basal energy expenditure during postinjury phase ranges from 30 to 35 kcal/kg/d. Basal energy expenditure is higher in TBI patients and lower in spinal cord injury patients. The estimation of basal energy expenditure in critically ill patients remains challenging and current calculators frequently overestimate caloric requirements. A high-caloric dietary supplementation is associated with hyperglycemia, hypercapnia, and higher in-hospital complications.[139] While underfeeding is also a concern in critically ill patients, a more balanced approach is permissive underfeeding. Permissive underfeeding focuses more on maintaining nitrogen balance than meeting caloric requirements alone. Diets containing higher protein content and lower caloric value than target serve such a purpose. Permissive underfeeding results in better glycemic control, rapid recovery, and overall better in-hospital patient outcomes.[140–142]

In the setting of trauma and critical illness, the ongoing catabolic response demands special micronutrients and dietary considerations along with standard protein and caloric replacement. Nonessential amino acids such as arginine and glutamine become conditionally essential. Addition of these amino acids along with omega-3 fatty acids to standard dietary formulas has

been shown to improve outcomes and immune function. Enhanced diets containing higher protein content, and including a combination of arginine, glutamine, omega-3 fatty acids, minerals (zinc, copper, etc.), nucleic acids, and vitamins have shown to improve overall immune function.[143–146] The assessment of nutritional requirement in critically ill patients is primarily done by the indirect calorimetry method. The standard measure of nutritional requirement uses a metabolic cart, but this is expensive and cumbersome.[147] An alternative approach uses predictive equations but these are imprecise and often over- or underestimate the nutritional requirement.[148] In recent years, several handheld indirect calorimeters have been marketed. They provide ease of use as they are portable and relatively accurate.[149] To assess the adequacy of nutritional supplementation, anthropometric measurements and biochemical data can be utilized. While there is no single measure which accurately predicts adequacy of nutritional support, prealbumin levels provide a reliable estimate compared to albumin, transferrin, and retinol-binding protein.[150]

ORGAN DONATION

Trauma donors are the major contributor in the organ donation pool.[151] There remains great potential to enhance the conversion rate in this group of trauma donors. Over the past decade significant changes occurred in resuscitation protocols in general and specifically in potential organ donors. These changes in resuscitation have resulted in better organ donation in this group of potential donors. Wide spread acceptance of DCR has led to better end organ preservation, which not only improves outcomes in surviving patients but can improve overall organ donation rates in patients who become brain dead. 7 The guidelines defining organ donor management recommend continuation of this aggressive resuscitative support even after declaration of brain death.[119,152] A feasible goal for resuscitating any potential donors is to follow a rule of 100s, that is, maintaining a systolic blood pressure of >100 mm Hg, heart rate of 100 mL/hr, and PaO_2 >100 mm Hg. Along with hemodynamic resuscitation, focus should also be given to pulmonary edema, coagulopathy, and hypothermia. Coagulopathy and hypothermia are not only

associated with adverse outcomes in trauma patients but also render them ineligible for organ donation.[153]

The focus of resuscitative efforts after declaration of brain death shifts from cerebral preservation to organ preservation. The shift in resuscitation focus is a continuum of ongoing resuscitation.[154] Donors should be managed in a critical care setting and attention should be directed toward moderation of post brain death physiologic changes. Along with ongoing resuscitation, initiation of a T4 protocol should ensue. T4 protocol or hormone replacement therapy takes into account the disruption of hypothalamic–pituitary axis.[155] The essential components of the T4 protocol include methylprednisolone, triiodothyronine (T3)/levothyroxine (T4), arginine, vasopressin, and insulin. The goal of this resuscitative cocktail is to prevent potential cardiac arrhythmias, diabetes insipidus, hypotension, and metabolic acidosis. Early initiation of hormonal therapy has shown improved organ donation rates and should be considered in all brain-dead potential organ donors.[156–158]

Organ donation is a legitimate outcome in trauma patients. As aggressive resuscitation protocols for trauma patients closely align with donor management goals, the spectrum of care in potential organ donors can easily be extended to address organ preservation. Trauma patients presenting with previously fatal neurologic injuries provide an excellent cohort where aggressive resuscitation can not only improve survival rates but also the organ donation rates.[119,159] The care of a potential organ donor is a multidisciplinary task. Involvement of organ procurement networks and social services can improve the communication between the treatment team, procurement agency, and the donor's relatives. Bridging this gap is of utmost importance as family decline still remains a major cause of loss of potential donors.

Rib Fractures

Traumatic rib fractures are most often caused by blunt force trauma 8 to the chest. The mainstay of management is to control the pain and prevent the pulmonary sequelae, such as pneumonia and respiratory failure, which increases mortality. Rib fractures are associated with significant morbidity and mortality and therefore early recognition and aggressive proactive pain

control are essential to good outcomes. Rib fractures occur in approximately 10% of trauma patients and are often markers for significant concomitant internal injuries, such as pulmonary contusion, pneumo- or hemothorax, diaphragm injury, or blunt cardiac injury (BCI).[160,161] There are numerous associated pulmonary complications, most notably pneumonia, retained hemothorax, aspiration and ARDS.[162,163] The number of rib fractures correlates to the mortality and associated complications, which has been demonstrated in several studies.[163] One study that looked at patients in the National Trauma Data Bank (NTDB) over 7 years found that one rib fracture was associated with a 5.8% mortality and the chance of death increased with each rib fractured, culminating in a mortality rate of 34.4% in patients with eight or more rib fractures. Furthermore, increased number of rib fractures was associated with more complications, specifically ARDS, pneumonia, pneumothorax, empyema, and ICU and hospital length of stay.[163] Flail chest is defined both radiographically and clinically. On imaging, it is multiple consecutive rib fractures (>4) unilaterally with fractures in two or more locations in a single rib. Clinically, it is when a segment of the chest wall moves paradoxically within the respiratory cycle. This type of injury has a greater impact on respiratory function and is associated with increased complications.[164]

A particularly vulnerable patient population is the elderly who experience the most significant morbidity and mortality secondary to rib fractures. Patients over the age of 65 with rib fractures have twice the rate of mortality than younger patients with similar injury patterns. Furthermore, for each rib fractured, there is an increase in mortality of 19.4%. The overall mortality in elderly patients with rib fractures has been shown to 20.1% while the mortality rate in this population without rib fractures has been reported at 7.6%.[165] Given the higher risk of death and complications in this patient population, trauma centers often admit elderly patients with rib fractures to the ICU. One study compared two groups of elderly patients once there was a change in protocol regarding admission criteria for patients with rib fractures. Patients over the age of 65 with blunt thoracic trauma and three or more rib fractures were automatically admitted to the ICU regardless of other injuries or respiratory status. The two groups had comparable ISS. They compared outcomes of the patients from before and after the change in admission ICU admission criteria and found that patients in the latter group

had shorter lengths of stay, lower mortality rates, lower rates of unplanned ICU admission, and few complications. The improved outcomes were attributed to the more concentrated nursing care that could provide aggressive pulmonary hygiene, the comprehensive care provided by the multidisciplinary teams and the continuous monitoring that allows for earlier recognition of clinical deterioration.[166]

The cornerstone of management of blunt thoracic trauma with rib fractures is aggressive pain control and pulmonary hygiene so that patients can breathe effectively and mobilize, which helps reduce the risk of pulmonary complications and death. Multimodal pain therapy has become the standard of care and involves a combination of medications including opiates, NSAIDs, acetaminophen, and sometimes ketamine. A common strategy is to use standing doses of acetaminophen and NSAIDs with on-demand opiates via an oral or intravenous route. Each drug class has advantages and disadvantages. NSAIDs are readily available, do not dampen respiratory drive, and have no addictive potential but carry the risk of peptic ulceration and some clinicians are hesitant to use them when there is a concern for bleeding. Opiates are also readily available but depress respiratory function and are addictive. Lidocaine and ketamine infusions are also reasonable options but should be managed with the help of pain specialists. Early consultation of an acute pain service has been shown to be beneficial to patients and outcomes.[167] Regional anesthesia is another mode of therapy that has demonstrated benefits in rib fracture management and includes intercostal blocks, paravertebral catheters, and epidural catheters. Paravertebral catheters are most beneficial in unilateral rib fractures as opposed to bilateral fractures. Studies have reported decreased delirium with the use of regional anesthesia in the management of multiple rib fractures, which is especially important in the elderly population.[168]

Surgical fixation involves open reduction and internal fixation of the fractures. There is no clear consensus on which patients benefit the most from rib fixation or the optimal timing of the procedure and there is much debate among trauma surgeons. However, some common accepted indications include flail chest, symptoms with displaced segments, refractory pain or persistent respiratory failure, and fixation in conjunction with a thoracotomy for another reason.[169] Several randomized studies have been conducted and have demonstrated decreased rates of pneumonia and fewer

days on the ventilator.[168,170,171] On meta-analysis there was no significant difference in mortality but there was a lower rate of pneumonia.[172] The randomized studies have been small and of lower quality so larger multicenter studies are still needed.[170] A single-institution prospective study compared nonoperative and surgical fixation for specific indications (flail chest, >3 displaced fractures, >30% volume loss, and failure of medical therapy) and found that the operative group had a reduced likelihood of respiratory failure and tracheostomy.[173] A different study performed in two trauma centers in Canada demonstrated contradictory results and showed significantly improved outcomes in the nonoperative group in terms of rates of pneumonia, ventilator days, and length of stay in the ICU and in the hospital overall.[174] Given the variable data on the role of surgery in rib fractures and the lack of consensus, each patient should be evaluated individually with regard to the risks and benefits of the procedure. Regarding the technical aspects of the procedures, preoperative imaging with CT scan and 3D reconstruction of the chest wall is important in operative planning. The procedure is usually performed through a thoracotomy incision and there are various plating systems available. The goal of the procedure is to stabilize the ribcage while restoring mechanical function to the chest wall. Careful attention should be paid not to overly restrict the chest wall with excessive fixation so that the breathing mechanics are impaired.[170]

Blunt Cardiac Injury

9 BCI refers to the trauma to the myocardium secondary to blunt trauma. There is a wide range of clinical manifestations, from asymptomatic and clinically silent to life-threatening. Due to this spectrum in severity there is a range in management from monitoring to open heart surgery, however, the majority of cases are managed with telemetry and supportive care.

Severe cardiac injuries often result in instant death. Up to 25% of deaths from trauma were found to have cardiac or aortic injuries.[175] The most common cause is motor vehicle collisions, motorcycle collisions, falls, and crush injuries.[176] Most patients with BCI who survive to the hospital have relatively minor cardiac injury. Therefore, there should be a high index of suspicion whenever there is significant blunt force trauma to the chest. Specifically if there is a sternal fracture, hemopneumothorax, esophageal

injury, or multiple rib fractures and pulmonary contusion since many patients present insidiously and delay in diagnosis increases morbidity and mortality.[177] In a retrospective study that examined NTDB blunt trauma patients over 8 years found that a 0.3% incidence of BCI with hemopneumothorax being the strongest independent risk factor for BCI, followed by sternal fracture and esophageal injury.[177]

There are various types of BCI, including myocardial injury, which involves a laceration of the walls of the heart or papillary muscles, myocardial contusion, for which there is no clear consensus for diagnostic criteria but is generally thought to be bruising of the heart, pericardial laceration, septal injuries, and valvular injuries. The most common chamber injured is the right ventricle due to its anterior location.[177] Myocardial injury carries a high mortality rate, especially when the pericardium is intact because of tamponade.[178]

There is a spectrum of clinical presentations, including chest pain and bruising, arrhythmias, hypotension, and flash pulmonary edema from valvular injury and dysfunction. In addition to ATLS, when evaluating for BCI, the initial workup should include an EKG and a troponin. The negative predictive value of a normal EKG and negative troponin is approximately 100%, so if both are normal then no further evaluation or monitoring for BCI is necessary.[178,179] If these tests are abnormal then the patient should be admitted to a telemetry unit and if there are arrhythmias or any hemodynamic instability, then an echocardiogram should be obtained to evaluate for any wall motion abnormalities, effusion, and valvular issues. Elevated troponin has been associated with higher mortality rates in BCI in retrospective analysis.[180] Hypotension may occur and bleeding should be ruled out as is the case in all trauma patients. Once bleeding has been addressed and ruled out, hypotension secondary to cardiac dysfunction in patients with BCI should be managed with vasopressor support in a monitored setting. Most BCI can be managed nonoperatively, however, if there is valvular, pericardial, or myocardial disruption, rupture or laceration, then surgery is required, often emergently.

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33

Environmental Injuries

J. Patrick Walker and Gregory J. Jurkovich

Key Points

1 Of the 3,700 species of snakes worldwide, only 200 are significantly venomous, with approximately 6 deaths per year in the United States caused by snakebite. In contrast, there are over 150,000 species of Hymenoptera in the world that cause approximately 40 deaths per year, mostly as a result of severe anaphylactic reactions.

2 Snakebite produces immediate pain, edema, and erythema at the site. Spread of the swelling greater than 30 cm/hr indicates severe envenomation. Initial incision and suction and the use of a proximal tourniquet are contraindicated. Use of purified ovine antivenin is effective for serious Crotalidae envenomation and has replaced equine antivenin with its associated risk of serum sickness. Because of the presumed safety of the newer antivenom, overuse is more likely.

3 Snakebite morbidity depends on the type of snake and the degree of envenomation. Venoms consist of numerous polypeptides that can disrupt endothelial cells and blood flow, produce neuromuscular blockade, or generate a coagulopathy via procoagulants. Some snakes (particularly Elapids [represented by the coral snakes in North America]) also have direct neurotoxins and cardiotoxins.

4 Spider bites produce toxicity by local tissue necrosis (brown recluse and hobo spiders) and painful muscle contractions (black widow spider). Death may be caused by stinging Hymenoptera, including bees (particularly aggressive Africanized bees), fire ants, and scorpions. The death is usually secondary to anaphylaxis, but occasionally massive envenomation occurs—especially with Africanized honeybees. The estimated lethal dose is approximately 20 stings/kg in most mammals.

5 The initial response to hypothermia is an intensive sympathetic type reaction with tremulousness, profound vasoconstriction, marked increase in oxygen consumption, and accelerated heart rate and minute ventilation. As core temperature falls to between 33° and 30°C this response is lost and deeper core hypothermia rapidly develops.

6 Hypothermia risk is high in the severely injured patient as a result of exposure, loss of normal protective metabolism (i.e., shivering), rapid massive infusion of cold fluids/blood, and open thoracic and abdominal cavities.

7 Hypothermia increases risk of mortality at every level of traumatic injury. There is no improvement in outcome when hypothermia is applied to the severe TBI; trauma patients rapidly rewarmed require less resuscitation volume and have improved survival.

8 Treating hypothermia begins by preventing further heat loss and allowing endogenous rewarming. Active rewarming has many adjuncts, including warm blankets, heating pads and lights, and immersion in warm water or internally by core rewarming. Internal core rewarming is more effective and includes heated intravenous fluids; heated body cavity lavage; heated moist inhaled air; extracorporeal circulatory rewarming (ECMO or CPB) or closed circuit intravascular countercurrent heat-exchange devices.

9 Frostbite involves ice crystal formation and unpredictable loss of tissue. Early definitive rewarming (avoiding refreezing) by submersion in 40° to 42°C water is preferable with subsequent meticulous care, awaiting demarcation, and avoidance of early debridement to optimize outcomes and tissue salvage.

10 Early thrombolytic therapy might be beneficial in select frostbite patients.

INTRODUCTION

Although most of us will not suffer a gunshot wound or a small-bowel obstruction, we will all receive insect bites and those of us who frequent the outdoors will be exposed to many other facets of the environment. This chapter is about those encounters—the heat, the cold, venomous bites and stings. It is essential that all physicians know the basics of care for injuries produced in this manner.

ENVENOMATION

Snakebite

The legends and lore of snakes are spread across history; with serpents mentioned in 42 Bible verses, implicated in the death of Cleopatra, and the medical field—the snake is essential to the rod of Aesculapius and the Caduceus. Few emergencies have been surrounded with as many types of treatment and little scientific fact as snakebite (some very innovative—electrical shock and TASER®, tourniquets with ice emersion, crosscut of the bite with suction of the wound, etc). We will attempt to address the management of envenomation with as much evidence as possible.

An estimated 5.4 million people are bitten each year with up to 2.7 million envenomations. This results in around 81 000 to 138 000 people deaths each year.[1] In the United States, the CDC estimates there are 7,000 to 8,000 bites per year with 5 to 6 deaths.[2] Most of the deaths are secondary to rattlesnake envenomation, with only two fatalities from Copperhead snakebite in the past 5 years.

1 More than 3,300 species of snakes exist in the world of which approximately 200 are deadly.[3] They range in size from 10 cm to greater than 9 m. Nonvenomous snakes predominate on all continents except for Australia. There are five families of poisonous snakes worldwide: Colubridae, Elapidae, Hydrophidae, Viperidae, and Atractaspididae. The boomslang and the bird snake represent the Colubridae—found mostly in Africa. The Elapids are found throughout the world and include snakes, such as mambas, kraits, adders, and cobras. The only Elapids in North America are the coral snakes. The Hydrophidae are the sea snakes. The Viperids have long hinged fangs. They include the pit vipers that, like the Boidae family (boas and pythons), have infrared sensors in a nasal pit that is located between the nose and the eye (**Fig. 33.1**). These are excellent sensory organs that can differentiate a temperature differential of 0.003°C. All venomous snakes in North America with the exception of the coral snakes are in this family. Poisonous snakes in North America are therefore of the phylum Chordata, class Reptilia, order Squamata, suborder Serpentes, and of the Crotalidae (subfamily Crotalinae) or Elapidae family. Venomous snakes are distributed throughout the United States with at least one species in every

state except for Hawaii, Alaska, and Maine. Water moccasins are found primarily in the southeastern United States. Copperheads are found from Massachusetts westerly to Illinois and to the south from Florida to Texas. Rattlesnakes are found coast to coast. The genus *Crotalus*—the true rattlesnakes—is found only in the New World.

Figure 33.1 Heat sensor—nasal pit. (Photo courtesy of Ronny Stewart, MD.)

Snakes are easily identifiable reptiles, marked anatomically by the large number (greater than 120) of precloacal vertebral bodies. They also have a reduced (almost absent) left lung, a single ventricle (no ventricular septum), and no muscles in the ciliary body of the eye. Despite the absence of a ventricular septum, oxygenated and deoxygenated blood channels separately though the heart.[4] All snakes are strictly carnivores. The size of the snake dictates the size of the prey.

The pit vipers (the genera *Crotalus, Sistrurus*, and *Agkistrodon*) are morphologically distinguished by elliptical pupils, a triangular head (**Fig. 33.2**), and retractable fangs. The fangs are tubular, injecting venom similar to a hypodermic needle. This is in contradistinction to the Elapids in

which the fangs are fixed and grooved—wicking the venom into the victim. Venomous snakes have a single row of caudal plates distal to the anal plate, whereas nonvenomous snakes have a double row of caudal plates. There are 32 species of rattlesnakes in the New World, ranging from southern Alberta to central Argentina.[5,6] Rattlesnakes are only found in the Americas. All true rattlesnakes have a rattle (except for an endangered species in Mexico—the Santa Catalina rattlesnake, which has only a vestigial rattle). The rattle is a series of interlocking segments. A new segment is added with each shedding of the skin, which may occur two to three times per year. There are two genera of rattlesnakes; *Crotalus*—the true rattlesnakes and *Sistrurus*—the pigmy rattlers. There are 14 species of *Crotalus* (**Table 33.1**) in North America. The largest species of rattlesnake in North America is the eastern diamondback (*Crotalus adamanteus*), which is slightly larger than its cousin the western diamondback (*Crotalus atrox*). There are eight members of the *Agkistrodon* genus—moccasins and copperheads (**Table 33.2**).

Figure 33.2 Triangular shape of pit viper head. (Photo courtesy of Ronny Stewart, MD.)

Table 33.1 *Crotalus* Species
U.S. Rattlesnakes–Genus *Crotalus*
Timber rattlesnake (Canebrake)—*Crotalus horridus*
Eastern diamondback—*Crotalus adamanteus*
Western diamondback—*Crotalus atrox*
Prairie rattlesnake—*Crotalus viridis*
Mojave rattlesnake—*Crotalus scutulatus*
Rock rattlesnake—*Crotalus lepidus*
Black-tailed rattlesnake—*Crotalus molossus*
Red diamond rattlesnake—*Crotalus ruber*
Speckled rattlesnake—*Crotalus mitchellii*
Sidewinder rattlesnake—*Crotalus cerastes*
Tiger rattlesnake—*Crotalus tigris*
Twin-spotted rattlesnake—*Crotalus pricei*
Ridge-nosed rattlesnake—*Crotalus willardi*
Western rattlesnake—*Crotalus oreganus*

Table 33.2 *Agkistrodon* Species
U.S. Copperheads and Moccasins
Northern copperhead—*Agkistrodon contortrix mokasen*
Osage copperhead—*Agkistrodon contortrix phaeogaster*
Southern copperhead—*Agkistrodon contortrix contortrix*
Broad-banded copperhead—*Agkistrodon contortrix laticinctus*
Trans-Pecos copperhead—*Agkistrodon contortrix pictigaster*
Eastern cottonmouth—*Agkistrodon piscivorus piscivorus*
Florida cottonmouth—*Agkistrodon piscivorus conanti*
Western cottonmouth—*Agkistrodon piscivorus leucostoma*

By far the most critical step in management of snakebite is identification of the offending species. Most snakebites are nonvenomous and require no treatment. Most bites, such as those of copperheads (**Fig. 33.3**) and pigmy rattlers (**Table 33.3**), are almost always self-limiting and require little more than observation. Others such as the diamondback (**Fig. 33.4**) and Mojave rattlers can require intense medical management, occasional surgical management, and even rarely cause death. Identification of the species by the patient is notoriously invalid; however, a detailed description of the offending snake should be taken. The only snake where color is useful in identification is the coral snake—red and yellow kill a fellow, red and black venom lack (**Fig. 33.5**). (Note that this is true only in North America, as there are venomous coral snakes in Central and South America that have red bands touching black bands.) Other clues, such as geography and topography (proximity to water), can also at least help with identification of the genus. All snakebites should, at least initially, be considered an event with potential morbidity and possible mortality.

As snakes are cold-blooded animals, snakebites generally occur in the warm months, with an increase in incidence in the spring and fall. Most snakebites occur in young men, with up to 60% of bites occurring in victims that were deliberately provoking the snakes.

Figure 33.3 Copperhead. (Photo courtesy of Ronny Stewart, MD.)

Table 33.3 *Sistrurus* Species

U.S. Rattlesnakes–Genus *Sistrurus* (Ground Rattlers/Swamp Rattlers)
Massasauga—*Sistrurus catenatus*
Eastern—Subsp. *catenatus*
Western—Subsp. *tergeminus*
Desert—Subsp. *edwardsii*
Western pigmy rattlesnake—*Sistrurus miliarius streckeri*
Carolina pigmy rattlesnake—*Sistrurus miliarius miliarius*
Dusky pigmy rattlesnake—*Sistrurus miliarius barbouri*

Venom is produced in Duvernoy glands on the dorsal sides of the head (corresponding to parotid glands) enhancing the triangular appearance.

During envenomation the venom is forced through the fangs by the palatine muscles. If a fang is broken off, it will be replaced by the next in a row of "proto-fangs." Any clothing may limit the amount and depth of envenomation. The purpose of the venom is to immobilize or kill the prey and begin digestion. Pit viper venoms are complex—with up to 50 different proteins and enzymes identified.[7–9] Over 90% of the dry weight of venom is proteinaceous in nature. Although it is common to classify the venoms as neurotoxic or digestive in nature, all snakes have varying compositions of venoms. The Crotalids will have a higher percentage of digestive/enzymatic type proteins than the Elapids, which will contain a higher percentage of neurotoxins. Common enzymes are phospholipases, metalloproteases, collagenase, and hyaluronidase (**Table 33.4**). These peptides and polypeptides act by damaging vascular endothelium and other cellular membranes. Compliment is activated, fibrin is degraded, and platelets are activated. The increased permeability of the membranes leads to peripheral and pulmonary edema, hemorrhage, and hypotension. L-amino acid oxidase splits fibrinogen contributing to the induction of DIC. The Elapids in particular contain a higher percentage of proteins that block acetylcholine receptor sites. This can lead to dysphagia, slurred speech, seizures, coma, and death. Despite the very high toxicity of coral snake venom, only one fatality has been recorded in the United States in the past 50 years.

Figure 33.4 Western diamondback.

Figure 33.5 Coral snake.

When evaluating the snakebite victim, it is important to document both local and systemic signs and symptoms. Vital signs should be recorded and repeated at intervals guided by the clinical response. 2 Pain, edema, and erythema at the site are common. Secondary symptoms include muscle twitching, perioral paresthesia, and a metallic taste in the mouth. Marking lines at the site of documented discoloration (**Fig. 33.6**) can help the clinician follow the progression of the envenomation. Swelling in the affected digit or limb should be measured (circumference) and followed closely. The amount of local tissue destruction is an accurate marker of the degree of envenomation. It is probable that if there is no pain or erythema by the time that the patient arrives in the ED, no envenomation has occurred. Intravenous access should be obtained. Laboratory evaluation should include a CBC with platelet count, PT, PTT, CPK, fibrinogen level, creatinine, BUN, and urinalysis. Up to 30% of Crotalid envenomation will show an abnormality in the coagulation profile, although clinical bleeding is exceedingly rare.[10] In Lavonas' (2004) review of 400 copperhead bites from the Carolinas no hypotension, no respiratory failure, and no deaths occurred.[11] Eight patients did have laboratory abnormalities, but none

developed bleeding complications. However, in severe envenomation by one of the larger rattlesnakes, diffuse capillary leakage can lead to pulmonary edema, hypotension, and shock.[12] A consumptive coagulopathy may rapidly develop. Such patients may bleed spontaneously from any site. Acute renal failure may result from nephrotoxins as well as myoglobinuria. An electrocardiogram, or at least continuous cardiac monitoring, should be considered. If there appears to be no evidence of envenomation, the patient may be observed in the emergency department for several hours and discharged home. With evidence of envenomation our recommendation is for admission to the hospital (preferably a monitored bed) for observation and possible intervention for at least 24 hours.

Table 33.4 Composition of Venom

Main Enzymes of Snake Venom
Dehydrogenase lactate
L-Amino acid oxidase
Catalase
Alanine amino transferase
Phospholipase A2
Lysophospholipase
Acetylcholinesterase
5′-Nucleotidase
Phosphodiesterase
Deoxyribonuclease
Ribonuclease 1
Adenosine triphosphatase
Hyaluronidase
NAD-Nucleotidase
Factor-X activator
α-Fibrinogenase
Prothrombin activator
Collagenase
Elastase

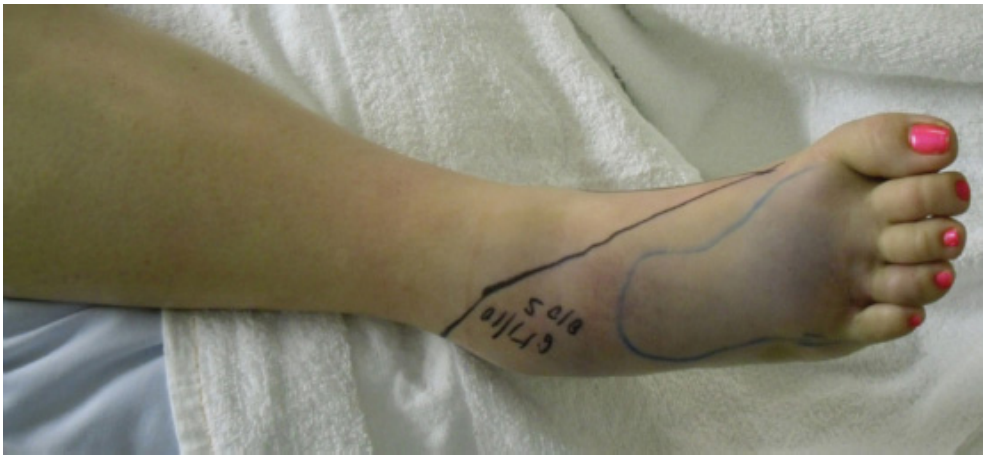

Figure 33.6 Demarcation of hemolysis after bite.

As noted, above treatment is largely dictated by the species of snake and the initial clinical presentation. Although a number of series have noted the appropriate treatment of Agkistrodon (copperhead and moccasin) bite is observation only,[13,14] extrapolation of this data to rattlesnakes could be misleading. In the rattlesnake bite victim with a moderate or severe envenomation, early use of antivenom is appropriate, and should be strongly considered (see below). Although there are a number of snakebite severity indices (grading systems) published, a modification of the simple system proposed by Dart in 1996 is probably the most useful.[15] A grade 1 envenomation is limited to the immediate bite site; a grade 2 envenomation extends onto less than a full extremity and may have non–life-threatening symptoms such as nausea, vomiting, mild tachycardia, and mild hypotension. A grade 3 envenomation involves more than an extremity and includes systemic signs such as severe hypotension/tachycardia or blood dyscrasias or clinically significant clotting abnormalities. Although enzyme-linked immunosorbent assays (ELISAs) have been developed that can directly measure serum venom antigens as well as identify the offending snake, clinical applicability of these types of tests are limited.[16,17]

Initial first aid on the scene should involve immobilization and splinting. There are no data to confirm this will limit the spread of venom but will be more comfortable. The application of ice or heat seems to have little effect on results. A number of historical treatments should specifically be avoided. Incision and suction, advocated for years, is no longer recommended.[18] A surgical incision in the field by a nonsurgeon can possibly involve vessels,

tendons, and nerves and increase morbidity, and only a small amount of venom can be extracted with suction. Limited cooling of the extremity may have some benefit, although a version of this—ligation cryotherapy—is associated with a high rate of amputation.[19] Although placement of a constrictor band may be of benefit in Australia (where Elapids predominate) to prevent rapid dissemination of a systemic neurotoxin, it is probably of little benefit in North America where the offending species is almost certainly a Crotalid. The use of a compression bandage has been shown to slow the systemic absorption of venom.[20,21] This may make it the treatment of choice in the field for a nonnecrotizing envenomation, such as produced by an Elapid. It may however increase local necrosis when used to treat the bite of a pit viper.

The wound should be cleansed, and the location of the puncture sites documented. The distance between the two fang marks is related to the size of the snake. The tetanus immunization status of the patient should be reviewed and updated. Steroids have no benefit in humans although these are often used by veterinarians.[22] Steroids do have a role in treating the infrequent acute allergic as well as delayed-onset serum sickness that may occur after the use of sheep-derived antivenom, as noted below.

The prophylactic use of antibiotics has been evaluated by several studies and does not seem to reduce infection rates.[23–25] Infection after snakebite is surprisingly uncommon and while patients are often given an antibiotic, there is no good clinical evidence for their use. Although many patients will have erythema, edema, and tissue necrosis and will appear infected, these are usually sterile; culture-proven infection occurring after snakebite should be treated appropriately. Culture of organisms in the mouth of the rattlesnake includes *Pseudomonas, Enterobacteriaceae, Staphylococcus,* and *Clostridia.*[26]

If the species is a coral snake or a nonindigenous Elapid, the administration of cholinergic agonists should occur at the first sign of symptoms. Calcium infusion may reduce the onset of seizures.

Certainly, the most controversial decision point in management of snakebite is the administration of antivenom. Although hundreds of antivenoms are available worldwide for various species, for all practical purposes in North America we are only dealing with envenomation by Crotalids. Snakebite by coral snakes is uncommon, and while the venom is

exceedingly toxic, the treatment is only supportive as antivenom is no longer available. Prior to 2000, the primary antivenom available in the United States for the bite of a Crotalid was a hyperimmune serum produced by envenomation of horses. Its use was associated with a high incidence of side effects: anaphylaxis, hypersensitivity, and delayed serum sickness.[27] In 2000, CroFab® (Crotalidae Polyvalent Immune Fab [Ovine]) was introduced obviating the use of now unavailable horse serum products.[11,28] This is now complimented by another purified product—Anavip®. CroFab is composed of small Fab fragment antibodies, while Anavip is made from larger V-shaped F(ab')2 fragments. Anavip has a much longer half-life. This may result in a lower incidence of late coagulopathy. Note that the Crotalidae Immune F(ab')2 antivenom is of Equine origin and may be problematic in those patients with horse allergies.[29] A detailed review of antivenom therapy for pit vipers is provided by Weinsten.[30]

CroFab is truly an elegant drug. It is produced by immunizing sheep with the venom from the western diamondback rattlesnake (*C. atrox*), the eastern diamondback rattlesnake (*C. adamanteus*), the Mojave rattlesnake (*Crotalus scutulatus*) or the cottonmouth water moccasin (*Agkistrodon*). The monovalent immunoglobulin from the sheep is prepared by fractionation of the immunoglobulin from the serum, digesting it with papain, and then utilizing ion exchange and affinity chromatography to separate the Fab fragments specific to each species.[31] The Fc portion of IgG is generally thought to be responsible for high rates of hypersensitivity and serum sickness seen with the horse serum product developed by Wyeth in 1954, and hence this ovine (sheep) version is generally considered safer. The four different monospecific antivenins are then mixed (**Table 33.5**). In a murine model there is good antigenic crossover in treating other North American Crotalid envenomations.[32]

Table 33.5 Components of Antivenom—CroFab® Antibodies
LD50 Neutralizing Units
Crotalus atrox (Western diamondback) 1,350
Crotalus adamanteus (Eastern diamondback) 800
Crotalus scutulatus (Mojave rattler) 5,210
Agkistrodon piscivorus (Cottonmouth water moccasin) 460

LD50, median lethal dose.

Utilizing CroFab to treat Crotalid envenomation is somewhat controversial, primarily because of the cost/benefit ratio. The cost of this drug is a significant factor with wholesale prices up to $3,200 per vial (2019). Certainly, any patient with life-threatening symptoms should immediately be given 4 to 6 vials of the antivenom.[33] Treatment is not based on the body mass of the patient—as the antivenom neutralizes the poison that is injected—this will vary with each envenomation. The lyophilized powder is reconstituted with 18 mL of normal saline, followed by dilution in 250 mL. Each dose is given over 1 hour. It is thought that venom is rapidly tissue bound, therefore the earlier the antivenom can be given, the more likely a favorable response. The packaging information states that treatment should begin within 6 hours of the bite. There is however at least one report of effective use of antivenom after significant delay.[34] Thus is the conundrum—there are certainly snakebites that initially appear innocuous that later become life-threatening. This has led physicians in the emergency room to overtreat large numbers of patients who do not require therapy, and why it is so important that every attempt be made to identity the offending species. Of note is the increasing use of antivenom by emergency room physicians. In a recent study, up to 84% of pit viper envenomations were treated with antivenom.[35] The reason for the high usage may be medicolegal, as it is certainly not to reduce mortality (in some cases it may reduce morbidity). If one can ascertain that the snake is one of the less virulent types (*Agkistrodon* or *Sistrurus* species), the patient can almost certainly be treated without the use of antivenom.[13] However, in the patient with a deteriorating clinical condition, antivenom treatment should always be given. Repeated dosing

should be given until clinical stability is achieved; although this is highly unlikely after 30 to 40 vials. The patient should be monitored for recurrence of symptoms and retreated if necessary.[36] CroFab has an estimated half-life of 12 to 23 hours.

Immediate adverse drug reactions will occur in 6% to 8% of patients.[37–39] This may be related to the rate of infusion. Although anaphylaxis would occur in up to 50% of patients treated with the older equine antivenin, it is an uncommon occurrence with CroFab—maybe up to 14% of patients.[40] It should be treated aggressively when occurring: The antivenin infusion should be stopped and a combination of antihistamines (diphenhydramine), epinephrine, and steroids administered, depending on the severity of the response. The airway should be assessed and secured if necessary. Appropriate volume resuscitation should be instituted. Steroid dosing ranges from a single 125-mg intravenous bolus of methylprednisolone to short-course prednisone pulse dosing (60 mg daily for 5 days).

Serum sickness will occur in 13% to 16% of patients treated with ovine antivenom (CroFab), certainly less common than with the older Wyeth equine antivenom.[27] Serum sickness is a type III hypersensitivity reaction in which soluble antigen–antibody complexes are deposited diffusely in the presence of antigen excess. Symptoms such as urticaria, itching, nephritis, and arthralgia can occur for weeks after the infusion. The treatment for serum sickness is a pulse of corticosteroids tapered over 7 to 14 days.

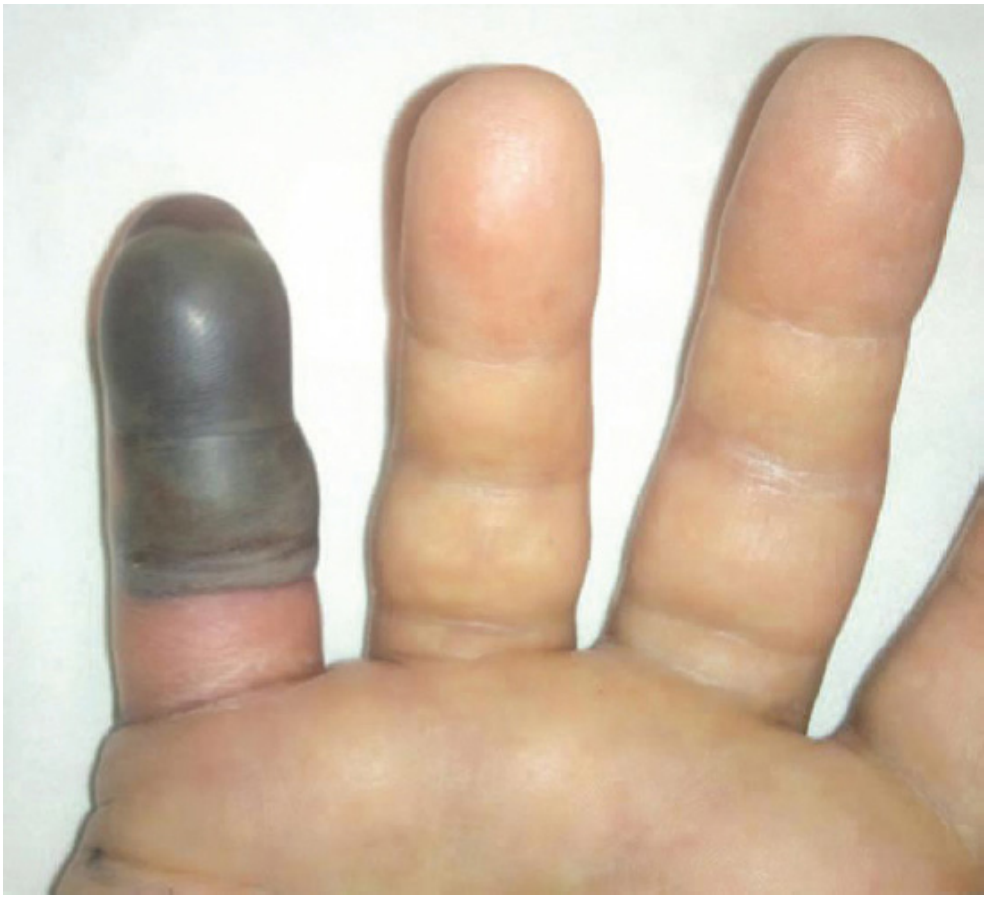

Figure 33.7 Hemorrhagic bulla.

There is no question that the purified ovine antivenin (CroFab), and now Anavip, is much safer than the older horse product.[30,41] This has led to some indiscriminate usage in emergency departments across the country. It should be recognized that the vast majority of snakebite victims will recover uneventfully with only supportive treatment. Each patient must be individually clinically evaluated and limit antivenom use to those in whom the potential benefits outweigh the risk of side. Note that while Anavip is only approved for rattlesnake envenomation, it has been used for Copperhead bites as well.

CroFab has been used extensively in children as young as 14 months,[42–44] and there are beginning to be reports of overuse of CroFab in both children and adults.[45] A special consideration should be use of antivenom in the pregnant patients. Certainly, coagulopathy could be lethal to the mother and fetus. There have been limited reports of use of CroFab in pregnancy.[46] Reports of fetal loss of up to 20% are noted in the worldwide literature with

snakebites of a variety of species. This seems to be improved with the use of antivenom.[47,48] Certainly, the risk/benefit ratio must be carefully weighed, but the general recommendation is to treat pregnant women with CroFab when indicated.

Figure 33.8 First debridement.

Figure 33.9 Second debridement.

In the rare patient that develops clinical bleeding, such as hemoptysis, intracranial hemorrhage, or gastrointestinal bleeding, correction of the coagulopathy should be undertaken with appropriate blood products. Antivenom should be given in these patients as initial therapy. Do not routinely treat thrombocytopenia or severe coagulopathy in the absence of bleeding. Coagulopathy can recur up to 2 weeks later.[36]

The use of surgery in the management of snakebite has a limited role. Although historically snakebite has been treated with various surgical procedures,[49] it should be in an unusual patient that more than simple debridement is needed. Crosscut and aspiration of the puncture sites was utilized for years, but this is no longer recommended. Several studies have shown the limitations of this practice. In dogs, up to one-half of the venom can be removed if incision and suction are begun within 3 minutes. In rabbits up to 37% of antivenom can be removed. However, in human studies only about 11% of the venom may be removed.[50,51] It is rapidly bound to tissues and is difficult to be removed by suction. Both partial and radical surgical excision of the involved bite area has likewise been attempted with no

proven benefit.[52–54] An uncommon finding is a local cytolytic response (**Fig. 33.7**) that produces a hemolytic bulla and requires debridement (**Figs. 33.8** and **33.9**). Actual tissue loss occurs in 7.8% of rattlesnake bites and 3.8% of Copperhead bites.[35] This can be expected to heal by secondary intention with a satisfactory cosmetic response (**Fig. 33.10**).

Figure 33.10 Healed wound.

Another use of CroFab is in the patient with impending compartment syndrome. The great majority of snakebites deposit venom in the subcutaneous tissues, not subfascial. It can sometimes be difficult to differentiate a swollen painful extremity from a true compartment syndrome. When in doubt, compartment pressures should be measured.[52,55] With rising pressures (greater than 30 to 40 mm), antivenom therapy should be initiated (or repeated). With failure of response to adequate dosing of antivenom, appropriate surgical fasciotomy can save extremities. Prophylactic

fasciotomy has no role in treatment. Stewart et al. at the University of Texas Health Science Center in San Antonio have an extensive experience with rattlesnake bites.[56] They have randomized animals to receive an intracompartmental injection of venom from the western diamondback rattlesnake. The animals received fasciotomy with debridement alone, antivenom alone, or antivenom with fasciotomy and debridement. Antivenom therapy prevented muscle loss and improved survival. Surgery alone did not. It was noted that muscle that had been debrided would have survived if treated with antivenom alone. Fasciotomy may increase the severity of local tissue loss.[57,58] When fasciotomy is required because of rising compartment pressures that do not respond to antivenom, consideration for postoperative negative-pressure wound therapy should be given.

Creative attempts at treating envenomation have even included the use of electrical current to neutralize the venom. The use of current from the generator of an outboard motor and an automotive battery has even been attempted.[59] As innovative and entertaining as these efforts may be, there is no improved outcome.[60] The TASER or conductive electrical weapon (stun gun) is a small handheld device that produces a very high voltage with a low current. It is used primarily by law enforcement agencies to temporarily immobilize attackers. A group of physicians practicing in Ecuador reported a series of 34 patients in letters to the editor of *Lancet* in which a modified stun gun was used to treat snakebites.[61,62] They claimed an immediate improvement with no mortality. The snakebites were most likely *Bothrops atrox*—the fer-de-lance—a pit viper. Unfortunately, this reported treatment was not a controlled study. Several animal studies have since proven electrical shock therapy to be ineffective in snakebite.[63–65]

Special Consideration of Elapid Envenomation

As noted, there are only three species of Elapids in the United States—the eastern coral snake, the Texas coral snake, and the Arizona coral snake. The eastern coral snake (*Micrurus fulvius*) is found in the southeastern United States up to Kentucky and North Carolina. The Texas coral snake (*Micrurus tener*) is found in west of the Mississippi across Arkansas, through Louisiana into eastern Texas. The eastern and Texas coral snakes inhabit forests and shrubbery. The Arizona coral snake (*Micruroides euryxanthus*) is found in

the desert climates of the southwestern United States into Mexico. Coral snakes are more active at night and hide under ground cover. Their behavior is elusive, and they will generally try to flee when disturbed. This family of snakes has a common feature—bilateral upper maxillary fangs that are fixed into position and angled down and back. The fangs are grooved for instillation of the venom, which is predominately a neurotoxin. The snakes are oviparous (lay eggs) and have round pupils. Their head is flat, with a smooth tapered tail and of course no rattles. They have characteristic coloration which is mimicked by several other nonvenomous species (such as the king snake and the scarlet king snake) in a biologic phenomenon referred to as batesian mimicry.[66] Although the North American coral snakes are relatively small (less than 5 ft), some Elapids from other continents are very large; the Black mamba is 14 to 15 ft and the king cobra can be up to 18 ft and weigh 25 lb. Although nonnative elapids bites have a substantial risk for death, only one known death from a coral snake has occurred in the United States since 1967 (Bonita Springs Florida, 2006).[2]

The bite of an Elapid is likely to produce much less tissue injury than the bite of a Crotalid.[67] There may be minimal pain. Envenomation may result in immediate neurotoxicity (within 15 to 30 minutes in the case of the mamba or Australian brown snake) or be delayed (2 to 5 hours with coral snakes). There is no longer any antivenom available for North American coral snakes, but local zoos may be able to provide antivenom for more exotic Elapidae. First aid should involve a compression bandage over the wound. The poison generally spreads by lymphatics; therefore, field compression to occlude lymph flow at the site of envenomation can slow toxicity. Symptoms will be related to the neurotoxicity—confusion, muscle spasm, nausea, vomiting, and dizziness. Blurred vision and difficulty with speech will occur. Finally, respiratory paralysis of the diaphragm occurs with resultant death. Cardiovascular and pulmonary support is essential to salvage patients that progress to this state. It should be noted that venom of an Elapid is incredibly toxic. The Taipan and Belcher sea snakes have an LD50 in mice of as little as 0.025 mg/kg of venom.[31] Any suspected Elapid bite should be managed with the possibility of rapid demise of the patient. If the bite is of a nonnative Elapid, antivenom (if it can be found) should be administered promptly at the first sign of clinical demise. Death rates for untreated nonnative Elapids vary from 20% to 30% for cobras to nearly 100% for the mambas.[68] Antivenom

for exotic snakebites may be obtained from the local zoo or through their national organization—the Association of Zoos and Aquariums (https://www.aza.org) or through the American Association of Poison Control Centers at 1-800-222-1222.

Venomous Lizards

There are two venomous lizards in North America: the Gila monster (*Heloderma suspectum*) and the Mexican beaded lizard (*Heloderma horridum*). Both species have heavy bodies with large heads. The Gila monster is found in the southwestern United States, ranging primarily in Arizona, extending into southeastern California, southwestern Utah and New Mexico, and into northern Mexico. There are two subspecies: the banded Gila monster (**Fig. 33.11**) that is found in the northern portion of the habitat and the reticulated that exists in the southern portion of the range. It is the largest lizard in the United States with a length of up to 56 cm. The Gila monster has generated substantial lore in the southwestern United States, because of its characteristic appearance and apparent fetid breath. It lives below ground and spends most of its life in or near its burrow. It is primarily seen in the spring, in the morning hours during breeding season. It has powerful jaws and the bite is characterized by the tendency to hang on with the animal difficult to dislodge. The Poison Control Center reported 105 human–bite-related calls from 2000 to 2011; 40% were seen in a hospital, 16% admitted, about 1/3 to an ICU. There were no deaths.[69]

The Gila lizard has eight labial glands on either side of the lower jaw. The venom is secreted into the floor of the mouth where it is wicked into the victim via grooved lower canine teeth. Envenomation is limited and deaths are virtually unknown.[70] The morbidity is usually secondary to local effects from the toxins present: serotonin, phospholipase A, amine oxidases, hyaluronidase, and proteases.[71,72] These produce pain at the site that usually resolves in less than 24 hours. Hypotension, coagulopathy, and myocardial infarction have been reported. Nausea and vomiting can occur. Malaise may persist for several days. The patient should be admitted for observation and a low threshold for surgical exploration/debridement is given because the teeth often shed into the bite and can serve as a nidus for infection.[73,74]

Figure 33.11 Gila monster.

Figure 33.12 Brown recluse.

The Mexican beaded lizard is found from Sonora to Guatemala and is represented by four subspecies. They are larger than the North American Gila monster; with a maximum size of up to 91 cm. They have similar venom as the Gila monster and bites should be managed in a supportive fashion.

Insect Bites and Stings

4 Although the bite of a venomous snake will certainly draw more attention in the emergency department, in fact insects kill many more Americans (greater than 100 deaths per year) than snakes (about 5 deaths per year).[75] Although most of these deaths are from anaphylactic reactions, some are from overwhelming envenomation, particularly from those of the Africanized honey bee (the "killer" bee). Most of the treatment recommendations below are from expert opinion; few randomized trials have been performed.

Spiders

There are six genera of spiders in the United States that can produce painful bites, tissue necrosis, and rarely death. These fall into three groups—the brown recluse (**Fig. 33.12**), the black widow (**Fig. 33.13**), and the hobo spiders.[76]

Figure 33.13 Black widow spider.

Brown Recluse

There are 13 species of *Loxosceles,* of which 5 have been known to produce tissue necrosis. Probably the species producing the most pathology is the brown recluse (*Loxosceles reclusa*). Envenomation by the hobo spiders (*Tegenaria agrestis*) produces a similar wound. The brown recluse is generally found in the southern states. Hobo spiders are found in the Pacific

Northwest.[77,78] Bites from these two species generally are initially painless and the victim may not recall being bitten. Pain and erythema develop over the next 6 hours. The venom can produce a painful, necrotic, slow-healing wound over the next 48 to 72 hours. Two to 7 days after the bite, an eschar develops with surrounding soft tissue induration. The eschar can conceal an underlying tissue necrosis that can persist for months.[13,79] Treatment is highly variable: eschars can require extensive debridement leading to skin grafting and even amputation, or they can be left alone and allowed to heal spontaneously, often with a residual shallow crater from loss of fat and soft tissue.

The venom is both hemolytic and cytotoxic. The enzyme that is thought to produce the "desmonecrotic arachnidosis" is sphingomyelinase D. The venom also contains hyaluronidase, lipase, arachidonic acid, and prostaglandins.[80,81] Systemic symptoms occur in less than 10% of victims, more commonly in children. Rarely hemolysis, hemodynamic instability, and death have occurred.[82] Initial treatment should include analgesia, wound care, and tetanus prophylaxis. Antibiotics should be reserved for infection/cellulitis. Early debridement should be withheld. Consideration for oral dapsone therapy should be given. Dapsone is thought to work as an inhibitor of polymorphonuclear leukocyte chemotaxis. It has significant side effects and can produce hemolysis in G6PD-deficient patients. Its use is somewhat controversial. It has been shown to reduce the size of the skin lesion and lessen the amount of surgical debridement, but these are not prospective studies. A controlled study of dapsone, electroshock therapy, and no treatment in guinea pigs showed some improvement with dapsone, but none with the electrical therapy. Hyperbaric oxygen has been studied in rabbits and pigs and has failed to demonstrate significant improvement. A trial of hyperbaric oxygen, dapsone, and cyproheptadine in rabbits failed to show any improvement.[83–87] Systemic steroids have not been shown to help. Initial surgical excision of the lesion has no clear benefit. Carlton has reported a favorable response with high-dose diphenhydramine, calling it a "uniquely conservative."[88] Delayed excision of the area of necrosis with skin grafting can be necessary. Recurrent necrosis in the same site can return even years later.

Black Widow Spiders

There are 31 species of the genus *Latrodectus,* the Black Widow spider, of which 4 are found in North America. These are marked by a prominent red hourglass figure on the ventral aspect of the thorax. Although both the male and the female possess venom, only the bite of the female can penetrate human skin. The female is four times the size of the male. The female of the species is known for eating the male after mating, which may or may not occur. The bite may produce only minimal local symptoms, with only a small area of redness, or a "target" appearance, or more dramatic erythema, induration, and purpura (**Fig. 33.14A,B**). The venom contains α-latrotoxin, which is neurotoxic. This produces chest and abdominal pain, and the patient's presentation may be confused as an acute surgical abdomen. Marked cramping and abdominal rigidity may be present. Fasciculations of facial muscles with ptosis and spasm may occur producing a particular facie. Hyperreflexia, paresthesia, cutaneous hyperesthesia, and nausea may also occur. Symptoms may occur within an hour and resolve over several days.[89,90] The muscle spasm should initially be treated with benzodiazepines. Antivenin is available and should be considered in the very young or ill patient. The dose is 1 ampule given in 50 mL of saline, and the response can be quite dramatic and immediate.[91] The antivenom is equine and hypersensitivity testing should be done prior to giving the antivenom.[92] A 1-mL test dose of horse serum is included with the antivenom for topical conjunctival testing. Calcium gluconate was often given in the past but is no longer recommended. Mortality is exceedingly rare.

Figure 33.14 **A, B:** Black widow spider bite.

HYMENOPTERA

More than 100,000 species of Hymenoptera exist. This includes bees, wasp, hornets, and fire ants. The venom injected by these insects is at least as toxic as that of the rattlesnake, but the volume is much less. The venom is primarily a hemolysin and neurotoxin. Anaphylaxis is a common clinical problem produced by the envenomation. Approximately 0.4% of the human population is at risk of anaphylaxis from Hymenoptera stings.[93] The anaphylaxis is modulated by preformed IgE that activates mast cells leading to massive histamine release. This leads to laryngeal edema, pulmonary edema, and cardiovascular collapse. This must be treated aggressively with intravenous diphenhydramine (Benadryl®), epinephrine, and fluid resuscitation, as well as with management of the airway and supplemental oxygen. Most stings are mild, however, resulting in only dermal reactions—pain, erythema, and edema. The stinger should be removed, and ice applied to the site. Application of meat tenderizer might be of some benefit. Patients with a history of insect sting anaphylaxis should be given a prescription for an epinephrine pen and be considered for venom immunotherapy. This is almost 100% successful in desensitization but can take up to 3 years.

Killer Bees

Africanized honeybees (killer bees) are hybrids of the African honeybee and the European honeybee, the one commonly found in the United States. The Africanized honeybee was originally brought from Tanzania to Brazil in 1957, with the hope of better honey production. The bees have spread up through Central America, Mexico, and into southwestern United States. They are continuing to advance at about 100 miles/yr, with some evidence of slowing in more recent years.[94–96] Africanized honeybees are indistinguishable from the European honeybee, so DNA (usually mitochondrial DNA) analysis is necessary to differentiate the subspecies.[97] They are termed "killer bees" because of increased aggressive traits. They show greater defensiveness of the hive, they have a bigger "alarm" area, and they deploy in greater numbers and will pursue perceived threats over much greater distances. Although their venom is of the same potency as the European bees, the number of stings received will usually be much greater. With more than 50 stings, nausea, vomiting, shock, hemolysis, rhabdomyolysis, coagulopathy, coma, and death may occur. Usually most patients will just complain of pain but delayed toxic reactions—6 to 48 hours—may also occur. It is recommended that any patient presenting with more than 50 stings be hospitalized and observed.[98] Laboratory evaluation with coagulation studies, platelet count, and liver function studies should be obtained.

Fire Ants

Fire ants are wingless members of the Hymenoptera order. They were brought to the United States from South America around 1918.[99] The red imported fire ants appear to have been introduced on a ship through Mobile, Alabama. Shipments of infested nursery stock and other agricultural products, natural mating flights, and floating on flood waters have contributed to their spread. Two species of imported fire ant now infect large areas of the Gulf Coast states.[100] Fire ants aggressively attack any perceived danger to themselves or their mound.[101] Each ant can produce multiple stings. The venom is a dialkylpiperidine that induces the release of histamine from increased mast cell reactivity. The fire ant sting produces a sterile pustule,

which does not usually require antibiotic therapy. Infectious complications can occur at the site that may be more common in diabetic or immunocompromised individuals. Fire ant venom shares at least four antigenic proteins with bees and wasps. More than 80 fatalities have been reported from fire ant anaphylaxis, notably in Australia and southern United States. The treatment is the same as with bee/wasp sting anaphylaxis.[102]

Scorpions

More than 1,500 species of scorpions can be found worldwide. Only about 20 or 25 are considered dangerous. They are in the class Arachnida, close relatives of ticks, mites, and spiders. Scorpions prefer dry habitats but may be found throughout the southern United States. Scorpions are nocturnal, hiding during the day and becoming active at night. The scorpion's body has a 5-segmented tail that can be arched over the back and becomes slenderer toward the end. On the end of the tail is the bulb-like poison gland/stinger. Between the last pair of legs are comb like structures called the pectines—sensory organs used to sense surface textures and detect prey. The venom toxicity varies greatly depending on the species, season, and age of the scorpion. Stings from dangerous species may cause paralysis, severe convulsions, cardiac irregularities, breathing difficulties, and death. In the United States most scorpion bites are not life-threatening and only result in local effects. In parts of Brazil, Mexico, North Africa, and Israel, however, the sting may be lethal. In Brazil the mortality rate is as high as 12% for adults and 60% in children.[51] In India, of 34 children admitted to a hospital for a scorpion sting, 14 had hypertension, 9 had acute pulmonary edema, 5 had a myocardial infarction, and 4 died.[103] Antivenins are typically available in areas where dangerous species are found, either from a local zoo or state or university agricultural extension departments. One species in the North America is particularly venomous—the Arizona bark scorpion (*Centruroides sculpturatus*) (**Fig. 33.15**). The sting produces a dramatic neuromotor syndrome and respiratory insufficiency. It has produced several deaths in the United States and hundreds in Mexico. Anascorp (an immune F(ab)2 equine antivenom) is now available for patients with systemic symptoms.[104] It (like CroFab) is very expensive (about $12,000 per vial in the United States—or $100 per vial in Mexico).

Figure 33.15 Arizona bark scorpion.

Figure 33.16 Asp caterpillar.

Centipedes and Millipedes

There are approximately 3,000 species of centipedes in the world. They are arthropods with a single set of legs on each body segment. The front pair of legs is modified to deliver venom. One of the largest members of this class is the giant desert centipede (*Scolopendra gigantea*). It can grow to 26 cm in length. Significant morbidity, including EKG changes and rhabdomyolysis, can occur from centipede bites, but death is exceedingly rare. The most common symptoms include erythema, swelling, and pain.[105] Treatment is largely symptomatic, with reports of both ice and heat improving symptoms.[106] There are approximately 7,000 species of millipedes. They have two pairs of legs on each body segment. Millipedes do not have a mechanism to inject a venom, but instead secrete an irritating liquid from pores covering their body.[107] This can produce a superficial burn that is self-limiting. Only symptomatic therapy is indicated.

Asp Caterpillars

The asp is a venomous caterpillar found in the southern United States. It is the larval stage of the Southern Flannel Moth (*Megalopyge opercularis*) (**Fig. 33.16**). It has the appearance of soft furry ball, encouraging the unwary to touch it. The long hairs of the asp conceal shorter spikes that discharge venom. Typically, an intense throbbing and pain occurs almost immediately. Erythematous spots occur at the site of envenomation. Symptoms include headache, nausea, vomiting, and the development of lymphadenopathy. Chest pain occurs occasionally. Rarely shock and respiratory distress have been reported. Death is exceedingly rare and is almost certainly because of a hypersensitivity reaction.[108–110] A similar caterpillar found in South America —*Lonomia*—has a death rate of 1.7%. The initial treatment should be to apply adhesive tape and pull it off to remove the spines. Ice packs and antihistamines may provide symptomatic relief. Intravenous calcium and steroids have been suggested as a treatment regimen.[111]

Hypothermia

Humans, like all mammals, will always attempt to maintain a constant body temperature despite changes in environmental temperature.[112] Normal human body temperature is 37° sublingually, 38° in the rectum, 32° at the skin, and 38.5°C deep in the liver, with normal daily (circadian) variation of about 0.5° to 1°C; we tolerate poorly even minor deviations from these norms.[113,114] Although humans have a remarkable capacity to dissipate heat by evaporating body water, our tropical evolutionary heritage has provided us with far less ability to cope with cold conditions. As a result, hypothermia can occur in a variety of clinical settings and from a number of causes (**Table 33.6**).

Table 33.6 Clinical Definitions of Hypothermia and Examples of Settings in Which They Occur

Type	Settings
Accidental	Recreational environmental exposure, cold-water immersion
Therapeutic	Treatment of Reye syndrome, cardiopulmonary bypass, organ preservation
Drug induced	Alcohol, anesthetics, barbiturates, phenothiazines, morphine, other drugs
Central nervous system dysfunction	Transection of spinal cord, hypopituitarism, cerebrovascular accidents
Hypothalamic dysfunction	Wernicke encephalopathy, anorexia nervosa, head trauma, pinealoma, other tumors
Metabolic	Hypoglycemia, hypothyroidism, hypoadrenalism, malnutrition
Dermal dysfunction	Burns, erythrodermas
Traumatic	Occurs after any major injury

Redrawn from Jurkovich GJ, Greiser W, et al. Hypothermia in trauma victims: An ominous predictor of survival. *J Trauma*. 1987;27(9):1019–1024.

Hypothermia is considered to be present in humans if the core temperature drops below 35°C (95°F). Hypothermia is usually classified by temperature zones: mild (32° to 35°C); moderate (28° to 32°C); or severe (<28°C). *Primary* accidental (vs. intentional) hypothermia is defined as a decrease in core temperature that occurs as a result of overwhelming environmental cold stress, such as recreational misadventures that lead to cold-water immersion or prolonged environmental exposure. *Secondary* accidental hypothermia is

considered to be triggered by, or at least associated with, underlying disease. Secondary accidental hypothermia occurs in patients with impaired thermoregulation, decreased heat production, or increased heat loss. These patients become cold despite only mild cold stress. The most significant risk factors are advanced age, mental impairment, and substance abuse (alcohol, primarily), although hypothyroidism, hypoadrenalism, trauma, and hypoglycemia are other risk factors.[114–116] Chronic hypothermia develops in patients with impaired heat generation (i.e., the elderly and infirm) who live in unheated apartments, are under continual cold stress, and after a time are found to have a chronically low temperature as if they have autoregulated to a new, lower-set core temperature.

It is estimated that each year about 1,500 patients in the United States have hypothermia listed on their death certificate, although the exact incidence and associated morbidity and mortality remain poorly characterized.[114] The 2015–2017 death rate from accidental hypothermia per 100,000 in the United States is depicted in **Figure 33.17**.[117] This figure emphasizes the problem of secondary hypothermia (exposure) in rural environments. A multicenter review of 428 cases of accidental hypothermia reported an overall mortality rate of 17%,[113] although other reports document mortality rates as high as 80%, primarily a result of infection and underlying illness. Treatment of accidental hypothermia remains highly variable. A study from Amsterdam reported that over an 8-year period (2000–2008), a total of 84 patients with accidental hypothermia were treated with 14 different rewarming techniques, with an overall mortality of 28.6%.[115] Most recently, Matsuyama reported on the national Japanese registry of hypothermia experience of 537 patients with secondary (accidental) hypothermia with an in-hospital death rate of 24.2%.[118] From 1979 to 2002, the CDC reported that a total of 16,555 deaths in the United States, an average of 689 per year (range 417 to 1,021), were attributed to exposure to excessive natural cold (**Fig. 33.18**).[119] From 1999 to 2002, a total of 4,607 death certificates in the United States had hypothermia-related diagnoses listed as the underlying cause of death for an annual incidence of 4 per 1,000,000 population. Most reported hypothermia-related deaths (67%) occurred in males (**Fig. 33.19**), but the overall death rate is the same for both males and females. Notable is that deaths occur in all states, even those that generally are considered to have warm climates. Hypothermia-related deaths are reported by states with characteristically

milder climates that experience rapid temperature changes and by western states that have high elevations and experience considerable changes from daytime to nighttime temperatures. States with the greatest overall death rates caused by hypothermia are Alaska, New Mexico, Wyoming, and Montana (**Fig. 33.20**).

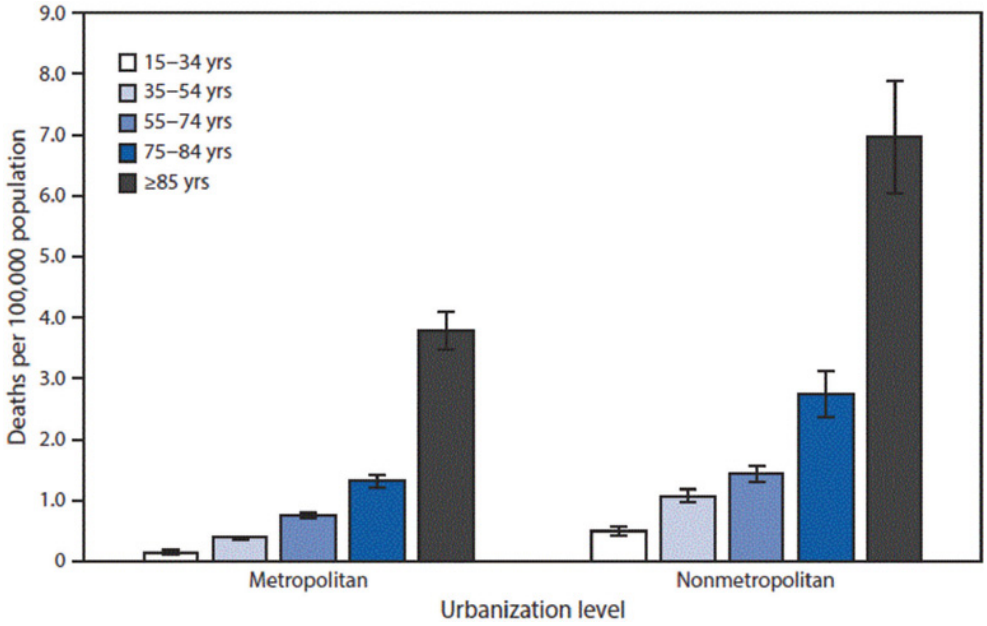

Figure 33.17 Rate of deaths due to hypothermia. Crude rate of deaths per 100,000 population; 95% confidence intervals indicated by error bars. Deaths attributed to excessive cold or hypothermia were identified using the International Classification of Diseases, Tenth Revision underlying cause of death code X31 (Exposure to excessive natural cold) or multiple cause-of-death code T68 (Hypothermia). Urbanization level is based on the Office of Management and Budget's February 2013 delineation of metropolitan statistical areas (MSA), in which each MSA must have at least one urbanized area of ≥50,000 inhabitants. Areas with <50,000 inhabitants are grouped into the nonmetropolitan category. (Adapted from CDC reference QuickStats: death rates attributed to excessive cold or hypothermia among persons aged ≥15 years, by urbanization level and age group —National Vital Statistics System, 2015–2017. *MMWR Morb Mortal Wkly Rep* 2019;68[7]:187.)

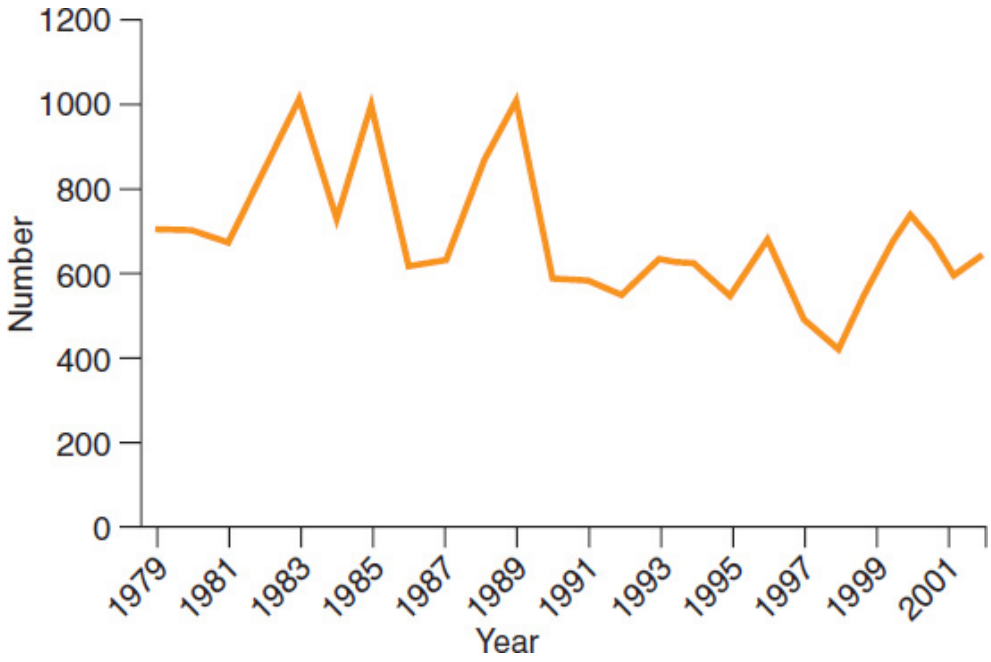

Figure 33.18 Number of hypothermia-related deaths by year in the United States, 1979–2002. (After Hypothermia-related deaths—United States, 2003–2004. *MMWR Morb Mortal Wkly Rep* 2005;54:173–175.)

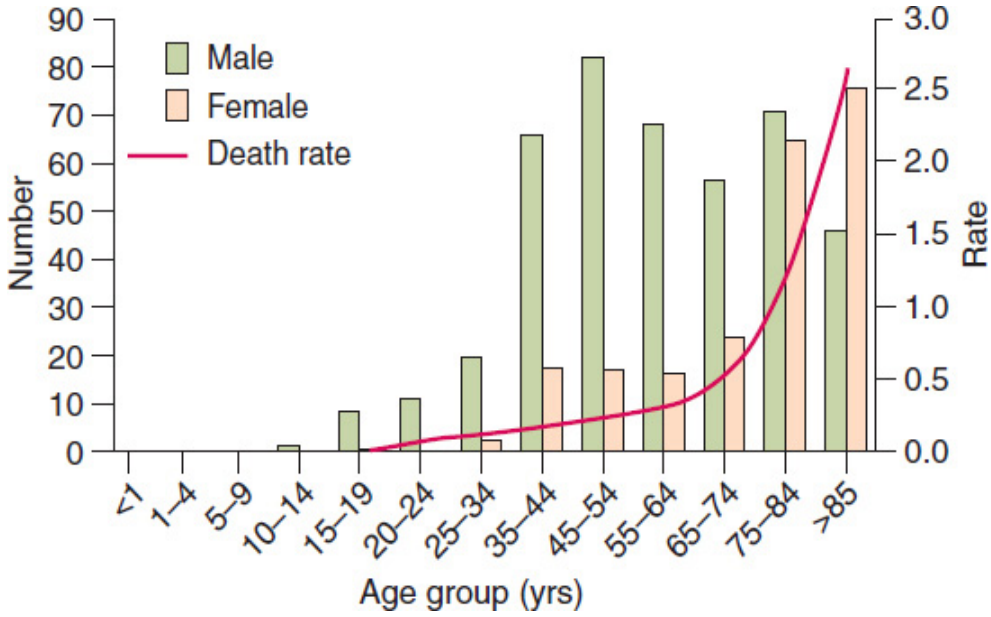

Figure 33.19 Number and rate (per 100,000 population) of hypothermia-related deaths, by age group and gender, in the United States, 1979–2002. (After Hypothermia-related deaths—United States, 2003–2004. *MMWR Morb Mortal Wkly Rep* 2005;54:173–175.)

The physiologic response to hypothermia is one of transitional changes, with few exact temperature-dependent responses (**Fig. 33.21**). Broadly speaking, the transition from a "safe zone" of hypothermia (in which physiologic adaptations to heat loss are working) to a "danger zone" of hypothermia (in which shivering is abolished, metabolism decreases, and heat loss is passively accepted) occurs between 33° and 30°C.[112] 5 The initial effects of hypothermia mimic intense sympathetic stimulation, with tremulousness, profound vasoconstriction, tremendous increases in oxygen consumption, and acceleration of heart rate and minute ventilation. When core body temperature cannot be measured, a four-stage hypothermia classification based on vital signs and level of consciousness has been developed by Swiss clinicians.[114,116] It should be emphasized that the purpose of the Swiss clinical grading is to direct treatment in the absence of the ability to actually measure core body temperature, so it should have its primary purpose in the austere or field care environment.

The cardiovascular response to hypothermia begins with tachycardia, but followed by progressive bradycardia, which starts at approximately 34°C and results in a 50% heart rate decrease at 28°C. Cardiac output initially increases with the tachycardia, and then progressively decreases, with a concomitant fall in blood pressure. The conduction system is particularly sensitive to hypothermia: the PR interval, then the QRS complex, and finally the QT interval become progressively prolonged.[120] As temperature falls below 30°C, atrial fibrillation, bradycardia, and ventricular dysrhythmia become common, with asystole occurring at temperatures below 25°C. Perhaps the most challenging management of an accidental hypothermia patient is the one with temperatures between 28° and 32°C (Swiss stage 2), as these patients are prone to develop poorly perfusing arrhythmias, yet they often can be rewarmed with active external and environmental rewarming if such arrhythmias do not occur. Hence gentle manipulation of such patients is required. Because palpating pulses or measuring blood pressure in cold, stiff, hypothermic patients is difficult, the presence of an organized cardiac electrical rhythm should be taken as a sign of life that contraindicates cardiopulmonary resuscitation chest compressions, despite the absence of a palpable pulse. Such a rhythm may provide diminished but sufficient circulation in patients with severely reduced metabolism, and it is likely that vigorous chest compressions will convert this perfusing rhythm to

fibrillation. Rewarming should occur with close monitoring of rhythm, pulse, and blood pressure. If cardiac arrest occurs (Swiss stage 3 or 4), extracorporeal cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO) for perfusion and rewarming is indicated.[114,121,122] Among patients with what is likely Swiss stage 4, those treated with ECMO or CPB have a reported survival rate without neurologic impairment of 47% to 63%, compared to 37% for similar patients treated without active core rewarming and oxygenation techniques. One report noted excellent long-term functional outcomes in 15 of 32 young patients successfully rewarmed with CPB.[121] All patients were intubated and ventilated and had received ongoing cardiac massage during transportation, and all 15 survivors had documented circulatory arrest (ventricular fibrillation or asystole) and fixed, dilated pupils. The mean interval from discovery of the patient to rewarming with CPB was 141 ± 50 minutes; the mean temperature was 21.8° ± 2.5°C. A report from Finland documents a 61% (14 of 23) survival to hospital discharge for adults undergoing CPB after a mean of 70 minutes of cardiopulmonary resuscitation following hypothermic arrest primarily from cold-water immersion or exposure.[123] A recent review of 18 studies in the literature and 286 hypothermic patients in cardiac arrest who underwent extracorporeal support documented a 37% survival rate, with 84% good neurologic outcome.[124] Finally, the lowest recorded temperature from which a person has been successfully resuscitated following accidental or secondary hypothermia is 13.7°C.[125]

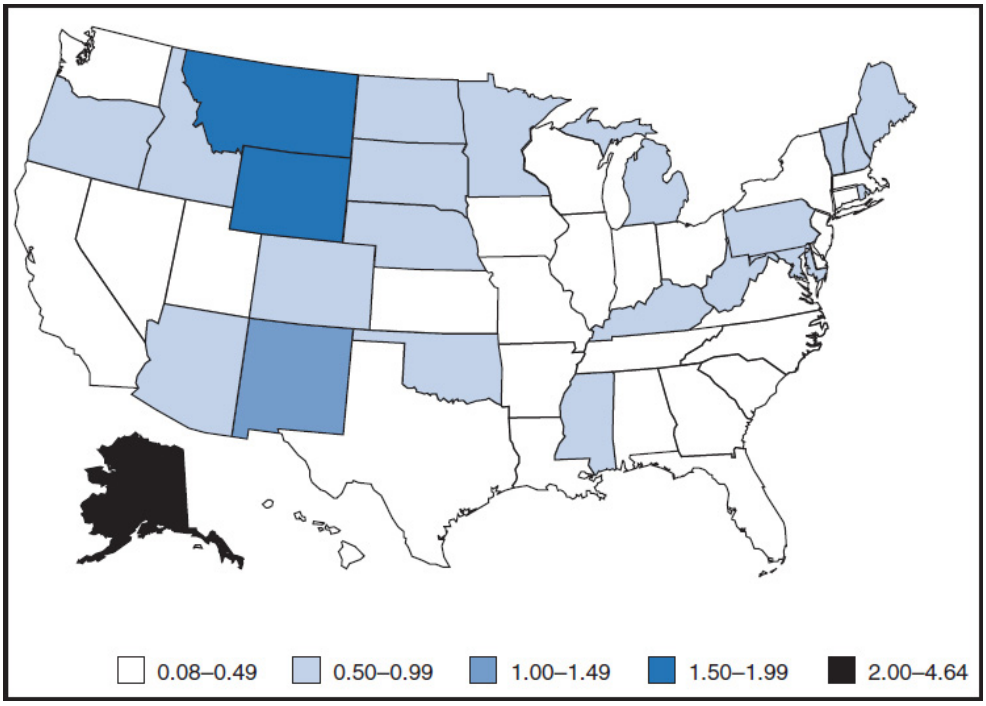

Figure 33.20 Average annual rate per 100,000 of hypothermia-related deaths by state, 1999–2002.

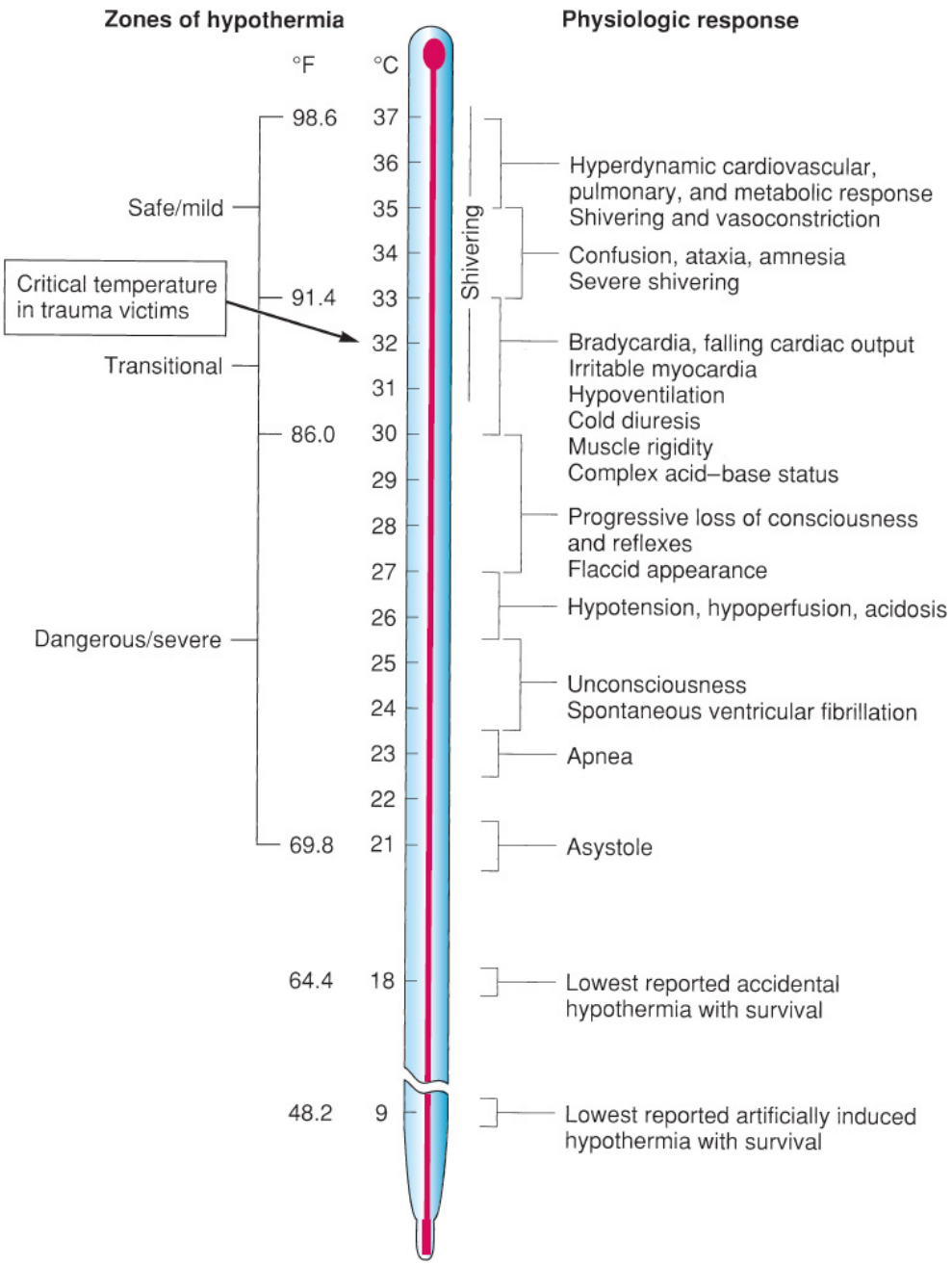

Figure 33.21 Zones of hypothermia and corresponding physiologic responses. Wide biologic variability accounts for physiologic changes rarely occurring at the exact temperatures noted. (Redrawn from Jurkovich GJ, Greiser W, et al. Hypothermia in trauma victims: An ominous predictor of survival. *J Trauma*. 1987;27(9):1019–1024.)

Respiratory drive is increased during the early stages of hypothermia, but below 33°C progressive respiratory depression occurs, resulting in a decrease in minute ventilation. This decrease is not usually a significant

problem until temperatures below 29°C are reached. Occasionally, hypothermia results in the production of a large amount of mucus (cold bronchorrhea).[126] This development predisposes to atelectasis and aspiration as ciliary action and the cough reflex are also depressed. Noncardiogenic pulmonary edema is also occasionally reported, especially in elderly patients and especially after prolonged periods of hypothermia.[127]

The effect of core hypothermia on arterial blood gas interpretation warrants a comment. Arterial blood gas samples are typically warmed to 37°C before measurement. A nomogram of Severinghaus mathematical corrections is then used to estimate the blood gas values at the patient's actual body temperature. With each 1°C temperature reduction, the PCO_2 decreases by 4.4% and the PO_2 decreases by 7.2%. The decrease in partial pressure is related to the increased solubility of gases in cold fluids and is not a result of a change in carbon dioxide content, oxygen content, or serum bicarbonate level. Clinicians often assume that the normal PCO_2 and PO_2 at 37°C are the values that should be attained at all temperatures. However, if normothermic endpoints for PCO_2 were attained in a hypothermic patient, they would have increased total-body CO_2 stores, which would manifest by a rising PCO_2 and a falling pH during rewarming. Likewise, attempts at increasing a PO_2 that reflects normal oxygen content at a lower temperature are also inappropriate. A far simpler strategy is to assess the blood gases at 37°C without temperature correction. Values that are normal and acceptable when reported at 37°C (without temperature correction) correspond to normal values and contents when "corrected" for hypothermic temperatures.

Temperature correction of blood gases for pH management is also unnecessary.[128] The pH of water rises with cooling, causing the pH of blood to rise by 0.015 pH units/°C, without a change in bicarbonate content.[129] Treating a patient with a temperature of 30°C with a pH of 7.40 instead of 7.47 fails to maintain the normal pH offset above the neutral point of water (relative alkalinity) and results in an acidotic cellular and chemical environment that has a multiplicity of effects on enzyme systems. Because blood with a pH of 7.40 assessed at 37°C is reported as having a pH of 7.47 when temperature corrected to 32°C, the simplest strategy when confronted

with a patient with a temperature of 32°C is to assess the blood gas at 37°C only and to use the 37°C uncorrected pH value for management.[129–131]

The neurologic response to hypothermia is heralded by progressive loss of lucidity and deep tendon reflexes and, eventually, by flaccid muscular tone. Patients are often amnestic below 32°C, and between 31° and 27°C they usually lose consciousness. Pupillary dilatation and loss of cerebral autoregulation occur at temperatures below 26°C, and electroencephalography becomes silent at 19° to 20°C.[132] These findings, combined with an unobtainable pulse and apparent rigor mortis, may cause the patient to appear dead. It is important to remember that patients have been revived from core temperatures as low as 13.7°C[125,133] and hence the saying "No one is dead until warm and dead."[134] An exception to this admonition probably includes the patient who has sustained an anoxic event while still normothermic and has a serum potassium level greater than 10 mmol/L, although the Bernese criteria for trauma and hypothermia have picked a level of 12 mmol/L as being nonsalvageable.[114,116,123,135]

The role of hypothermia in brain death determination remains controversial. Brain death is a medically and legally accepted mechanism of death in the United States and worldwide. Yet significant variability in individual institutional policies regarding the determination of brain death occurs. In 2010 the American Academy of Neurology (AAN) issued guidelines on the determination of brain death, reaffirmed in 2014 and 2017.[136] A recent study examined how well 52 organ procurement organizations and 508 unique hospitals have adopted these guidelines, determining that among other variables in policy, only 181 of 228 policies (80%) required the absence of hypothermia (temperature >36°C) in brain death determination.[137]

In classic surgical physiology research, Moyer and Debakey showed that with hypothermia, reduction in blood pressure and cardiac output decreases glomerular filtration rate, but urinary output is maintained because of impairment in renal tubular Na^+ reabsorption (the so-called "cold diuresis").[138,139] Vasoconstriction also results in an initial increase in central blood volume that prompts a diuresis. Ileus, bowel wall edema, depressed hepatic drug detoxification, punctate gastric erosions (Wischnevsky ulcers), hyperamylasemia, and, rarely, hemorrhagic pancreatitis are hallmarks of the intestinal response to hypothermia. Hypothermia inhibits insulin release and

insulin uptake at receptor sites, making hyperglycemia a relatively common finding, especially at temperatures below 30°C.[55] Exogenous insulin administration is unwarranted because it may result in rebound hypoglycemia during rewarming. Serum electrolyte changes are unpredictable, but serum potassium is often slightly increased in hypothermic patients because of renal tubular dysfunction, acidosis, and the breakdown of liver glycogen.[140] Hypothermia also appears to affect endothelial cell adhesion molecule function, which may partially explain increased infectious complications in hypothermic patients.[141] One study demonstrated a drop of 1.9°C core hypothermia triples the incidence of surgical wound infection following colon resection and increases the duration of hospitalization by 20%, leading to the now standard perioperative checklist monitoring of body temperature during surgery.[142]

Body temperature also has a significant effect on oxygen uptake. Oxygen consumption (VO_2) initially increases dramatically with any fall in body temperature. When involuntary muscle contractions in the form of shivering occur, oxygen consumption increases by threefold to fivefold.[143,144] This process is inefficient because shivering produces heat near the surface of the body, causing most of the heat to be lost to the environment, with less than 45% being retained by the patient. As core temperatures fall to between 33° and 30°C, shivering is abolished, and the patient will rapidly sink to ambient temperature.

The thermoregulatory drive is such a powerful one that it takes precedence over many other homeostatic functions. The resultant increase in oxygen utilization may result in anaerobic metabolism, acidosis, and significant cardiopulmonary stress. One study noted a 35% increase in oxygen consumption and a 65% increase in CO_2 production in postoperative patients after resolution of anesthesia, when the thermostatic drive reappeared.[145] In another study, a core temperature decrease of as little as 0.3°C in postoperative patients was associated with a 7% increase in VO_2, and temperature reductions between 0.3° and 1.2°C were associated with a 92% increase in VO_2, with proportional increases in minute ventilation.[144] Shivering can be iatrogenically abolished with low doses of meperidine (Demerol®) and possibly ondansetron (Zofran®, Zuplenz®). Further details of the specific organ system responses to hypothermia are beyond the scope of

this chapter, but the interested reader is referred to several excellent in-depth monographs.[146–149]

Hypothermia in Trauma Patients

Mild hypothermia is very common after traumatic injury. The thermoneutral environment for humans is a humid and warm 28°C (82.5°F) (think tropical islands). When ambient temperature falls below the thermoneutral temperature (i.e., the temperature at which no thermogenesis or heat dissipation is necessary), an increase in heat production is[149] required to maintain a normal body temperature. Combustion is the only source of endogenous heat production, and this process requires an increase in oxygen utilization. After shock or injury, however, oxygen supplies are often limited and further heat loss occurs owing to cold emergency department and operating room environments, cold fluid resuscitation, and open thoracic and abdominal cavities. Anesthetic and neuromuscular blocking agents that prevent the heat-producing shivering 6 response further aggravate this. Thus, the occurrence of hypothermia in surgical or critically injured patients is most often a form of secondary accidental hypothermia.

One study found that 57% of trauma patients admitted to a level 1 trauma center were hypothermic at some time and that temperature loss was most significant in the emergency department.[150] Another study reported that the average initial temperature for 94 intubated major trauma victims was 35°C, with no seasonal variation.[151] Of patients in this study, 66% were hypothermic on admission; 43% were mildly hypothermic (34° to 36°C), and 23% had temperatures below 34°C. Likewise, Jurkovich and Luterman reported that 42% of 71 adult trauma victims with an injury severity score (ISS) of 25 or higher had core temperatures below 34°C and in 13% the core temperature fell below 32°C.[27] Importantly, there were no survivors when core body temperature was below 32°C. Inaba reported that of 118 patients requiring emergent surgery following traumatic injury, hypothermia (<35°C) was present in nearly 30% of patients upon presentation to the operating room, and that a continued decrease in core temperature was associated with increased mortality. This mortality rose to 50% if temperature fell below 32°C.[152] Both mortality rate 7 and the incidence of hypothermia increase with higher ISS, massive fluid resuscitation, and the presence of shock, but

controlling for these variables still demonstrates that the mortality rate of the hypothermic trauma patient is greater than that of the warm trauma patient. Although the mortality rate for moderate (28° to 32°C) degrees of primary accidental hypothermia is approximately 20%,[113,114] moderate levels of hypothermia in trauma and critically ill patients are associated with a much higher mortality rate. Rutherford et al. reported that 9.4% of surgical intensive care unit patients had a core body temperature less than 35°C; the mortality rate of the hypothermic trauma patients was 53%.[153] In fact, compared with other patient populations, the mortality rate associated with hypothermia in the trauma victim is so high that the definition of mild, moderate, and severe hypothermia in the trauma patient warrants special classification (**Table 33.7**).[149] These data have resulted in the standard incorporation of aggressive techniques to prevent the occurrence of hypothermia in trauma patient beginning with field transport with warm blankets and heated IV fluids to routine use of body and fluid rewarmers in emergency departments and operating rooms. Hypothermia is simply not acceptable in any trauma patient, and if it occurs, should prompt a quality of care review.

Table 33.7 Zones of Severity for Hypothermia

Zone	Temperature
Mild hypothermia	36°–34°C (<96.8°–93.2°F)
Moderate hypothermia	34°–32°C (<93.2°–89.6°F)
Severe hypothermia	<32°C (<89.6°F)

Hypothermia appears to occur primarily in victims of relatively severe trauma. Little and Stoner, while reporting on a heterogeneous group of 82 trauma patients, observed that hypothermia occurred only in those patients with an ISS greater than 12.[154] Hypothermia did not occur in less severely injured patients, and shivering, which should be expected, was noted in only one of the hypothermic patients. Mild degrees of injury have, in fact, been associated with small elevations in core body temperature, particularly when the shivering response mechanism has not been abated.[149,155] The recognition

that hypothermia can be prevented has resulted in substantial changes in the management of the acute injured patient. As a result, the "lethal triad" of coagulopathy, acidosis, and hypothermia is much less frequently observed.[156]

The detrimental effect of hypothermia in the human trauma victim is contrasted by a large body of experimental evidence in animals suggesting that hypothermia has a protective role in shock. This extensive body of literature is reviewed elsewhere,[149] but in general, animals subjected to combined hypothermia and shock (hemorrhage, burn, and blunt trauma) usually survive longer than similarly injured but actively warmed animals. Blalock and Mason (1941) were among the first in modern times to recognize the ability of hypothermia to prolong survival times after shock,[157] but they emphasized that the overall survival rate was unchanged, an observation reaffirmed in 2003.[158] However, increases in both survival times and survival rates have been shown in a number of animal models of induced hypothermia after hemorrhagic shock.[159,160] The protective effects of hypothermia in preventing ischemia–reperfusion injury have been described in a number of models, including muscle, intestine, and rabbit ear.[161–163] These observations have prompted some to suggest that there is a role for iatrogenic-induced hypothermia in severe trauma patients, with the goal being a reduction of oxygen consumption in the setting of limited oxygen delivery (hypovolemic shock) to allow surgeons time to repair injured structures and then rewarm and resuscitate the patients.[164–166]

Hypothermia has also been utilized in attempts to protect the traumatically injured brain. The use of therapeutic hypothermia in a patient with traumatic brain injury was first reported in 1943[167] and sporadically over the ensuing two decades. In 2001, Clifton et al. reported a randomized, multicenter, controlled trial of core body hypothermia in trauma patients with severe closed head injury.[168] Select trauma patients (GCS 3 to 7) were intentionally cooled within 6 hours of injury to 32° to 33°C for 48 hours after injury and then rewarmed. The outcome was poor (defined as severe disability, a vegetative state, or death) in 57% of the patients in both groups. Mortality was 28% in the hypothermia group and 27% in the normothermia group (p = 0.79). The patients in the hypothermia group had more hospital days with complications than the patients in the normothermia group. This study has led most authorities to conclude that treatment with total-body hypothermia is not effective in improving outcomes in patients with severe brain injury. Other

authors have also reported higher rates of pneumonia and diabetes insipidus in patients with severe head injury and induced hypothermia.[169] Evidence further supporting the harmful effect of hypothermia in the trauma patient is provided by a prospective, randomized trial of rapid rewarming versus conventional rewarming of 57 multiple-trauma patients.[169] In this study, trauma patients who were rapidly rewarmed with continuous arteriovenous rewarming (CAVR) from less than 34.5°C to greater than 36°C required less resuscitation fluid volume and had a lower early mortality rate than those rewarmed more slowly. Failure to rewarm in either group was uniformly fatal. The survival rate at 3 days after injury was 82% in the rapid rewarm group versus 62% in conventionally managed patients. Approximately 50% of the patients in both groups had a severe head injury, defined as a head-abbreviated ISS of 3 or greater. In this well-controlled study, maintenance of hypothermia not only failed to confer an advantage but also was detrimental to early survival.

The use of hypothermia in the treatment of acute cardiac arrest is beyond the scope of this chapter. However, the principle of this common technique is the same as the principle of organ preservation for transplantation—cooling of the body decreased oxygen consumption and may allow for a longer period of relative anoxia with good recovery.[170–172] The advantage in these patients, or rather the difference between the acute arrhythmia patient and the patient with trauma is likely the total-body tissue injury and its effect in coagulation and the inflammatory response. But the attraction for the concept of "suspended animation" with induced hypothermia in trauma remains seductive.[166,173]

The role of hypothermia in the injured patient remains complex. It is apparent that the physiologic consequence of severe trauma is a drop in core body temperature, either as a protective response to shock or the result of diminished heat production caused by failing metabolism. The frequent presence of lactic acid accumulation in cold, seriously injured patients supports the latter hypothesis. The above-cited clinical studies indicate that even mild hypothermia in the trauma patient is predictive of a poor outcome, given our current capabilities of surgical repair of injured organs. Hypothermia does diminish metabolic demands and oxygen consumption, but the price appears to be malfunction of enzymes and physiologic systems necessary to recover from injury.

The systems most affected by hypothermia in victims of injury are those involved in clotting. Focused attention on the coagulation mechanisms in trauma patients over the past decade has exposed the lack of a comprehensive understanding of the complex relationship between injury, inflammation, and coagulopathy.[174] Temperature is yet another variable in this complexity. Reports of coagulation abnormalities in patients with apparently normal clotting factor levels surfaced shortly after the introduction of hypothermic cardioplegia for cardiac surgery.[175,176] Although hemodilution with volume expanders deficient in clotting factors and platelets is a cause of nonsurgical bleeding, cold platelets are known to undergo morphologic changes that affect adherence, including loss of shape, cytoplasmic swelling, and dissolution of cytoplasmic microtubules necessary for normal motility.[177] Platelet activation is also associated with activation of cell membrane phospholipases that hydrolyze phospholipids to arachidonic acid, a precursor to prostaglandin endoperoxides and thromboxane A2, a potent vasoconstrictor necessary for normal platelet aggregation.[178] Valeri et al. induced systemic hypothermia to 32°C in baboons, but kept one forearm warm using heating lamps and a warming blanket.[179] Simultaneous bleeding time measurements in the warm and cold arm were 2.4 and 5.8 minutes, respectively. This effect, which was reversible with rewarming, appeared to be mediated by cold-induced slowing of the enzymatic reaction rate of thromboxane synthetase, which resulted in decreased production of thromboxane A2. Bleeding observed at mildly reduced temperatures (33° to 37°C) results primarily from a platelet adhesion defect and not reduced enzyme activity or platelet activation; however, at temperatures below 33°C, both reduced platelet function and enzyme activity likely contribute to the coagulopathy,[180] perhaps helping to explain why 32°C is such a critical temperature in the coagulopathic injured patient.

As with blood gases, clinical tests of coagulation are temperature standardized to 37°C. Fibrometers contain a thermal block that heats the plasma and reagents to 37°C before initiating the assay. Thus, tests of coagulation reflect clotting factor deficiencies but are corrected for any potential effect of hypothermia on clotting factor function. A detailed study of the kinetic effects of hypothermia on clotting factor function has been undertaken by Reed et al.[181] He performed clotting tests (PT, PTT, and

thrombin time) on reference human plasma–containing normal clotting factor levels at temperatures ranging from 25° to 37°C. The results showed a significant slowing of all coagulation tests at temperatures below 35°C that was proportional to the degree of hypothermia. The prolongation of clot formation occurred at clinically relevant levels of hypothermia and was equivalent to that seen in normothermic patients with significant clotting factor depletion. For example, assays conducted at 35°, 33°, and 31°C prolonged the PTT to the same extent as would occur in a euthermic patient with reductions in factor IX levels to 66%, 32%, and 7% of normal, respectively.

Clotting factor supplementation is not the answer to a hypothermia-induced coagulopathy; rewarming is. However, in many seriously injured patients, clotting factor depletion exists in conjunction with hypothermia. A potentiating effect of hypothermia on coagulation dysfunction occurs in plasma of patients with deficient clotting factor levels, although there does not appear to be synergy between the two conditions.[182] Hypothermic, coagulopathic trauma patients still benefit from coagulation profile testing. If prolongation of PT and PTT is evident in plasma warmed to 37°C, clotting factor replacement is indicated. If PT and PTT are near normal, rewarming alone reverses the clinically apparent coagulopathy.

8 Treatment

Rewarming techniques are usually classified as passive external rewarming, active external rewarming, or active core rewarming.[183] Passive external rewarming simply implies allowing spontaneous rewarming to occur with the patient removed from a hypothermic environment and is usually used only for the mildly hypothermic patient. Active external rewarming techniques include surrounding the patient with warm blankets or heating pads, infrared heating lights, and immersion in warm water. Active core rewarming includes heated intravenous fluids, as well as heated peritoneal or thoracic lavage; heated gastric, bladder, or colonic lavage; heated and water-saturated inhaled air; and extracorporeal circulatory rewarming. Blood rewarming is currently limited to a maximum temperature of 42°C by the American Association of Blood Banks, but rewarming to 49°C with inline

microwave blood rewarmers has been reported as safe, as has intravenous fluid rewarming to 65°C.[184,185]

The advantages and disadvantages of each technique are regularly debated, particularly regarding the role of external versus core rewarming. It is clear, however, that the rate of heat transfer to the hypothermic patient is greatest using active core rewarming, particularly extracorporeal circulation rewarming. This may be a critical factor in surgical patients for whom rapid restoration of clotting and cardiac function is necessary.

The technique of rewarming the hypothermic victim by extracorporeal circulation has been described by numerous authors, initially based on small personal experiences and using CPB techniques of open-heart surgery.[121–123] This technique has appealed in cases of primary accidental hypothermia, in which maintenance of circulation, correction of hypoxia, and replenishment of intravascular volume may play a role as large as correcting the temperature change itself. The need for systemic anticoagulation has, however, generally limited the usefulness of full CPB rewarming in the trauma patient. More recently the use of ECMO for core hypothermia rewarming has been the subject of numerous publications as more centers become more experienced with this tool.[133,186,187]

A technique of extracorporeal active core rewarming that makes use of the patient's own blood pressure to drive an extracorporeal circuit through an efficient, but small countercurrent heat-exchange device was developed by Gentilello et al., and termed CAVR.[188] Systemic anticoagulation is not necessary as the tubing is heparin bonded and trauma patients are relatively anticoagulated. The ease of use made this device applicable in rewarming severely hypothermic patients not in shock and, in a prospective, randomized trial of rewarming trauma patients, demonstrated its efficacy by improved survival.[169] Unfortunately, the device used in that referenced study by Gentilello et al. is no longer in commercial production.

Direct intracirculation rewarming can be accomplished with commercially available devices that employ either a vena caval countercurrent heat-exchange device (InnerCool RTx®, Philips Healthcare, Best, the Netherlands or Thermogard XP® Temperature Management System, Zoll Medical Corp., Chelmsford, MA) or balloon catheters with large surface areas (Alsius/Zoll Medical Irvine, CA). The ownership and design of these devices changes rapidly, as the clinical need is limited. Although initially developed to cool

patients for neurosurgical procedures, they are now used primarily for inducing and maintaining hypothermia following sudden cardiac arrest; rewarming can be accomplished by simply changing the temperature of the closed loop circulating fluid. Requirements are the commercial bedside console and the specialized endovascular temperature control catheter, inserted via the femoral vein to the vena cava, usually with a larger size introducer (10 to 12 Fr). Data on rewarming cold patients suggest that rewarming can occur up to 3°C/hr compared to 6° to 9°C/hr with ECMO or CPB.[114,189]

The use of body cavity lavage with warm solutions is a simple, less invasive method of accomplishing active core rewarming; however, rewarming rates with body cavity lavage vary greatly based on initial core temperature, dialysate temperature, infusion rate, and dwell time. Several studies support the notion that active core rewarming by peritoneal lavage is preferable to active external rewarming.[146] Moss examined three techniques of rewarming hypothermic and cardiac-arrested dogs, concluding that both peritoneal lavage (55°C dialysate) and partial extracorporeal circulation were faster than active external rewarming with a heating blanket.[190] A frequently stated disadvantage of external rewarming is that the peripheral tissues are rewarmed in advance of the still cool "core," resulting in peripheral vasodilatation leading to shock. In the presence of inadequate volume resuscitation, this rewarming method may result in vascular collapse ("rewarming shock") and a subsequent fall in central temperature ("afterdrop") as the cold peripheral blood returns to the core.[191] Whether or not this process is the mechanism of the core afterdrop is debatable because continued cooling of a patient's core temperature during the initial states of rewarming has been noted to occur in animal models even during complete circulatory arrest. Volume contraction caused by vasoconstriction, cold diuresis, and cellular swelling coupled with inadequate fluid resuscitation may be a more appropriate explanation for circulatory collapse during rewarming.

The thermodynamic principles of heat transfer to the hypothermic patient are reviewed in greater detail elsewhere,[183,192] but a sense of rewarming rates and quantity of heat transferred by various techniques is instructional. Ventilating a patient with a core temperature of 32°C with water-saturated air at 41°C results in a maximum heat transfer rate of 9 kcal/hr. For comparison,

basal metabolic heat generation produces approximately 70 kcal/hr, and shivering produces up to 250 kcal/hr. Given the specific heat of the body (0.083 kcal/kg/°C), 58 kcal is required to raise the temperature of a 70-kg patient by 1°C. Thus, more than 6 hours would be required to warm a 32°C patient using 41°C humidified inspired air.

Heat transfer rates using body cavity lavage can be similarly calculated based on the specific heat of water (1 kcal/kg/°C). If 1 L of 44°C water infused into a body cavity dwells long enough to exit at 40°C, 4 kcal of heat will have been transferred to the patient. Thus, over 14 L of fluid is needed to increase core temperature by 1°C. However, warming becomes less efficient as the patient rewarms because a longer dwell time is required to reduce the temperature of the infusate to 40°C.

Warming by CPB or ECMO or CAVR is the most efficient method of core heating. With flow rates of 15 to 30 L/hr, it is possible to deliver 120 to 240 kcal/hr if the reinfused blood is heated to 40°C, a rate of heat transfer over 10 times that of the other methods. In any case, the urgency with which rewarming must be accomplished depends on how adversely the hypothermia is affecting the patient. With the exception of extracorporeal circulatory methods, most rewarming techniques serve primarily to prevent loss of endogenously generated heat and are ineffective in circumstances in which rapid rewarming is indicated. Early and direct attention to preventing heat loss is therefore essential in surgical patients. With more widespread adoption of ECMO capabilities for treating severe lung disease, centers are starting to report on the use of this modality as a rewarming technique. The combination of injury and hypothermia represents a particular challenge. Swiss physicians with experience in treating injured and hypothermia avalanche victims have developed the Bernese Hypothermia Algorithm, a detailed approach to rewarming techniques and injury care priorities in this population.[193,194]

Cold Injury and Frostbite

Frostbite is a cold injury limited to digits, extremities, or exposed surfaces that is the result of direct tissue freezing. Chilblain (aka pernio) and trench foot are the result of more chronic exposure to an environment just above freezing. Both types of cold injury have been a major cause of morbidity

during war experiences. They resulted in more than seven million lost soldier fighting days by Allied forces in World War II and were reportedly the most common major injury sustained by British soldiers in the Falklands expedition.[140] Upton Sinclair's novel *The Jungle* used the cold exposure of Chicago's meatpacking industry in the early 20th century to depict the pain of frostbite and chilblains and deplored the working conditions and exploitation of immigrants.[195,196]

The terms *chilblain* and *pernio* describe a form of local cold injury characterized by pruritic, red-purple papules, macules, plaques, or nodules on the skin. Chilblains can result in a specific form of a dermopathy secondary to cold-induced skin vasculitis. The lesions are often associated with edema or blistering and are caused by a chronic vasculitis of the dermis[197]; this entity does not appear to be related to hereditary protein C or S deficiency.[198] This pathologic process is provoked by repeated exposure to cold, but not freezing, temperatures. This injury typically occurs on the face, the anterior surface of the tibia, or the dorsum of the hands and feet, areas poorly protected or chronically exposed to the environment. With continued exposure, ulcerative or hemorrhagic lesions may appear and progress to scarring, fibrosis, and atrophy. Treatment consists of sheltering the patient, elevating the affected part on sheepskin, and allowing gradual rewarming at room temperature. Rubbing and massage are contraindicated because they can cause further damage and secondary infection. Chronic treatment strategies are similar to frostbite injuries, with similar limited success (see final paragraph).

Trench foot or cold immersion foot (or hand) describes a nonfreezing injury of the hands or feet, typically in sailors, fishermen, or soldiers, that is caused by chronic exposure to wet conditions and temperatures just above freezing.[199] It appears to involve an alternating arterial vasospasm and vasodilatation, with the affected tissue first cold and anesthetic and then hyperemic after 24 to 48 hours of exposure. With the hyperemia comes an intense, painful burning and dysesthesia; tissue damage is characterized by edema, blistering, redness, ecchymosis, and ulceration. Complications of local infection or cellulitis, lymphangitis, and gangrene may occur. A posthyperemic phase occurs 2 to 6 weeks later and is characterized by tissue cyanosis with increased sensitivity to cold. Treatment is best started during or before the reactive hyperemia state and consists of immediate removal of

the extremity from the cold, wet environment with exposure of the feet (or hands) to warm, dry air. Elevation to minimize edema, protection of pressure spots, and local and systemic measures to combat infection are indicated. Massage, soaking of the feet, or rapid rewarming is not indicated. Demyelination of nerves, muscle atrophy, fallen arches, and osteoporosis may all present long-term complications, and a tendency toward marked vasospasm during subsequent exposure to cold develops in some patients.[200]

Frostnip is the mildest form of cold injury. It is characterized by initial pain and pallor, with subsequent numbness of the affected body part. Skiers and other winter outdoor enthusiasts are most likely to experience this cold injury to the nose, ears, or tips of digits. The injury is reversible and warming of the cold tissue results in return of sensation and function with no tissue loss.

Frostbite is a more severe and common form of cold injury that can result in debilitating long-term irreversible morbidity.[201] [9] Frostbite damage is caused by direct ice crystal formation at the cellular level with cellular dehydration and microvascular occlusion. Indirect cellular injury, also referred to as progressive dermal ischemia, is a progressive microvascular insult. Following thawing, microvascular thrombosis, endothelial damage, intravascular sludging and reperfusion injury all occur, resulting in continued cell injury and death. Current treatment modalities have focused on minimizing the indirect cellular or reperfusion injury as discussed below.

Frostbite is traditionally classified into four grades of injury severity (**Table 33.8**). The affected body part nearly always initially appears hard, cold, white, and anesthetic, regardless of the depth of injury. Because the appearance of the lesion changes frequently during the course of treatment and because the initial treatment regimen is applicable for all degrees of insult, some authorities suggest discarding this classification as a prognostic impossibility and simply classifying frostbite as either superficial or deep.[202]

Table 33.8 Classification of Frostbite

Degree	Description of Frostbite
First	Tissue freezing with hyperemia and edema but without blistering
Second	Tissue freezing with hyperemia, edema, and characteristic large, clear blisters
Third	Tissue freezing with death of subcutaneous tissues and skin, resulting in hemorrhagic vesicles that are in general smaller than second-degree blisters
Fourth	Tissue necrosis, gangrene, and eventual full-thickness tissue loss

Weather conditions, altitude, degree of protective clothing, duration of exposure, and degree of tissue wetness are all contributing external factors to the development of frostbite injury. Because sensory nerve activity is abolished at 7° to 9°C, the disappearance of pain is an early warning sign of cold injury. Acclimation to cold may be protective, whereas a previous history of frostbite probably predisposes to another cold tissue injury. Smoking and a history of arterial disease also are contributing factors. In urban environments, more than 50% of frostbite injuries are alcohol related and in one report, 16% of these patients also had a significant underlying psychiatric illness.[203]

As noted, frostbite injury has two components—the initial freeze injury and a reperfusion injury that occurs during rewarming. The initial response to tissue cooling is vasoconstriction and arteriovenous shunting, intermittently relieved (every 5 to 7 minutes) by vasodilatation, the so-called hunting response.[204] With prolonged exposure, this response fails, and the temperature of the freezing tissue approximates ambient temperature until −2°C. At this point, extracellular ice crystals form, and as these crystals enlarge, the osmotic pressure of the interstitium increases resulting in

movement of intracellular water out of cells and into the interstitium. Cells begin to shrink and become hyperosmolar, disrupting cellular enzyme function. If freezing is rapid (>10°C/min), intracellular ice crystal formation will occur, resulting in immediate cell death.[205] In addition, endothelial cell disruption and red cell sludging associated with freezing result in cessation of circulation.

During rewarming, red cell, platelet, and leukocyte aggregation occurs and results in patchy thrombosis of the microcirculation. These accumulated blood elements are thought to release, among other products, the toxic oxygen-free radicals and the arachidonic acid metabolites $PGF_2\alpha$ and thromboxane A2, which further aggravate vasoconstriction and platelet and leukocyte aggregation.[206,207] However, the exact mechanism of tissue destruction and death after freeze injury remains poorly defined. Animal studies suggest that vascular injury in the form of endothelial cell damage and subsequent interstitial edema, but not vessel thrombosis, predominate as initial events in rewarming injury.[208] A substantial component of severe cold injury may be neutrophil mediated, as suggested by the observation that a monoclonal antibody to neutrophil–endothelial and neutrophil–neutrophil adherence can markedly ameliorate the pathologic process of a severe cold injury.[209] In this rabbit model, animals treated with anti-CD11/CD18 adhesion molecule after cold injury (30 minutes at −15°C) but before rewarming (39°C water bath) had significantly less tissue loss and edema. The implication of these observations is that much of the injury of severe frostbite occurs during rewarming or reperfusion, although the efficacy of intra-arterial thrombolytic therapy suggests that endovascular clotting does occur and can be reversed.[210–213]

Treatment

Prehospital or field care of the victim of cold injury should focus on removing the patient from the hostile environment and protecting the injured body part from further damage. Rubbing or exercising the affected tissue does not augment blood flow and risks further cold injury or mechanical trauma. Because repeated bouts of freezing and thawing worsen the injury, it is preferable for the patient with frostbite of the hands or feet immediately to

seek definitive shelter and care rather than rewarm the tissue in the field and risk refreezing. Although the initial symptoms may be mild and overlooked by the patient, severe pain, burning, edema, and even necrosis and gangrene may appear with rewarming. With severe injury the range of motion progressively decreases, and edema becomes prominent. The injury may progress to numbness and, eventually, to loss of all sensation in the affected tissue.

The emergency room treatment of a frostbite victim should first focus on the basic ABCs (airway, breathing, and circulation) of trauma resuscitation and then systemic hypothermia should be identified and corrected. Most patients are dehydrated, and resuscitation with warm fluids is an important part of early management. Fractures are often accompanied by frostbite in mountaineers, and although manipulation may be required to treat vascular compromise, open reduction is hazardous, and application of traction should be delayed until after postthawing edema has been assessed.

Rapid rewarming is the goal. Gradual, spontaneous rewarming is inadequate, particularly for deeper injuries, and rubbing the injured part in ice or snow often delays warming and 9 results in marked tissue loss.[214] Rapid rewarming should be achieved by immersing the tissue in a large water bath of 40° to 42°C (104° to 108°F). The water should feel warm, but not hot, to the normal hand. The bath should be large enough to prevent rapid loss of heat, and the water temperature should be maintained. Dry heat is not advocated because it is difficult to regulate, and the result of using excessive heat is often disastrous. The rewarming process should take approximately 30 to 45 minutes for digits, with the affected area appearing flushed when rewarming is complete and good circulation has been reestablished. Narcotics are required because the rewarming process can be quite painful.

The skin should be gently but meticulously cleansed and air-dried and the affected area elevated to minimize edema. A tetanus toxoid booster should be administered as indicated by immunization history. Sterile cotton is placed between toes or fingers to prevent skin maceration and extreme care taken to prevent infection and avoid even the slightest abrasion. The affected tissue should be protected by a tent or cradle, and pressure spots must be prevented. In one review, infection developed in 13% of urban frostbite victims, but one-half of these infections were present at the time of admission.[203] Most clinicians reserve antibiotics for identified infections.[215]

After rewarming, the treatment goals are to prevent further injury while awaiting the demarcation of irreversible tissue destruction. All patients should be hospitalized, and affected tissue gently cleansed once or twice a day in warm (38°C) whirlpool baths, with some clinicians adding an antiseptic such as chlorhexidine or an iodophor to the bath. Based on the findings of arachidonic acid metabolites in the blisters of frostbite victims, some authors advocate the use of topical aloe vera (thromboxane inhibitor) and systemic ibuprofen or aspirin. Heggers et al.'s report in a nonrandomized trial in which 56 patients treated with these agents, plus prophylactic penicillin, had less tissue loss, a lower amputation rate, and a shorter hospital stay than 98 patients treated with warm saline, silver sulfadiazine, or sulfamylon dressings.[216] Another report on frostbite treatment in rabbits demonstrated improved tissue viability when systemic pentoxifylline and topical aloe vera cream were used.[217] Uninfected blebs should be left intact because they provide a sterile biologic dressing for 7 to 10 days and protect underlying epithelialization. After resolution of edema, digits should be exercised during the whirlpool bath and physical therapy begun. Tobacco, nicotine, and other vasoconstrictive agents must be withheld. Weight bearing is prohibited until complete resolution of edema.

Numerous adjuvants have been tried to restore blood supply to frostbitten areas. The intense vasoconstrictive effect of cold injury has focused attention on increased sympathetic tone. Sympathetic blockade and even surgical sympathectomy continues to be advocated by some based on the theory that it releases the vasospasm that precipitates thrombosis in the affected tissue.[218,219] This method of treatment has produced inconsistent results and is difficult to evaluate clinically, with no prospective, randomized trials available. Although sympathectomy appears to mollify the pain and hyperhidrosis and vasospasm of cold injuries, it may increase vascular shunting and adversely affect healing. In one series, a more proximal demarcation of injury in sympathectomized limbs was noted than in nonsympathectomized ones, despite apparently equal bilateral injury.[214]

Experience with intra-arterial vasodilatory drugs, such as reserpine, tolazoline, and papaverine, has also been unrewarding. Bouwman et al. demonstrated in a controlled clinical study that immediate (mean 3 hours) ipsilateral intra-arterial reserpine infusion coupled with early (mean 3 days) ipsilateral operative sympathectomy failed to alter the natural history of

acute frostbite injury compared with the contralateral limb.[219] Iloprost (Ventavis®, Ilomedine®), a vasodilator used to treat Raynaud phenomenon and a synthetic analog of prostacyclin PGI2 has also been used in an effort to vasodilate microvascular arcades.[211] Low–molecular-weight dextran has been shown to alleviate postthawing circulatory obstruction as late as 2 hours after thawing and markedly reduced tissue loss in rabbit feet,[220] but similar results in humans have not been demonstrated. Heparin, thrombolytic agents, and hyperbaric oxygen have also failed to demonstrate any substantial treatment benefit, but hyperbaric enthusiasts continue to tout its role.[221] None of these adjuncts is considered routine care.

10 The most recent adjunct to the management of frostbite is the intra-arterial infusion of tissue plasminogen activator (tPA). In a nonrandomized study of a small number (n = 7) of patients who received intra-arterial tPA, the burn team at the University of Utah demonstrated that tPA infusion improved tissue perfusion and reduced amputations (10% vs. 41%) when administered within 24 hours of injury (6 of the 7), as compared with 25 patients managed in a more traditional fashion.[210] Since this 2007 report, isolated case reports have also suggested that this therapy is effective.[213,222] What is termed the "Helsinki frostbite protocol" involves the use of intra-arterial fibrinolytics (tPA) and/or intravenous vasodilator iloprost.[223] Candidates for this therapy should have minimal risk of bleeding from other injuries, have the tPA administered (intra-arterial or intravenously) within 24 hours of frostbite, with no episodes of rewarming or refreezing between injury and treatment, and have clear evidence of full-thickness tissue involvement, as well as abnormal perfusion on either angiogram or pyrophosphate scanning (**Fig. 33.22**, Table 33.9). In one study, 20 patients with frostbite were diagnosed between 2013 and 2016.[223] Nine patients underwent fibrinolytic treatment with tPA and/or iloprost. The overall digital salvage rate was 74.8%. However, as of January 2020 the American Burn Association guidelines stated that the data are insufficient to support routine treatment of all patients with frostbite with thrombolytics,[224] but do allow that patients with cyanosis persisting proximal to the distal phalanx (grade 3 or 4 frostbite injury) and demonstrated loss of perfusion at or proximal to the middle phalanx immediately after rewarming can be treated with thrombolytic therapy in accordance with local hospital protocols. The guidelines also support the concept that time to treatment is an important

quality metric in the treatment of frostbite. The work from Hennepin County Burn Center supports the notion that "time is tissue" similar to that of the treatment of ischemic stroke or myocardial infarction.[225]

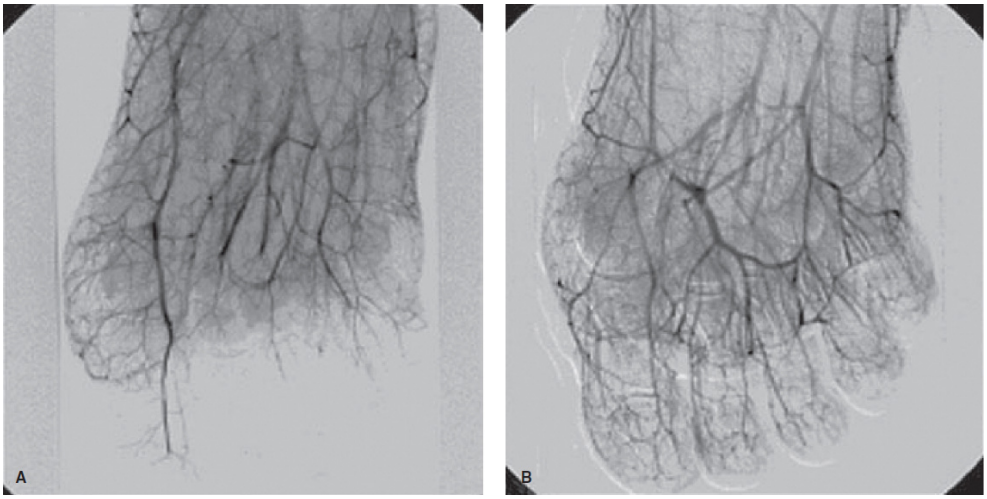

Figure 33.22 Digital angiography of a 19-year-old woman who sustained bilateral lower extremity frostbite following vehicle breakdown. **A:** The image demonstrates poor distal perfusion to the left toes. **B:** Following administration of tissue plasminogen activator via bilateral femoral catheters, angiography demonstrates return of perfusion. All 10 of her toes were saved. (Reproduced with permission from Bruen KJ, Ballard JR, Morris SE, et al. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg* 2007;142:546–553.)

Table 33.9 Amputation Outcomes of Patients Treated with Tissue Plasminogen Activator (tPA) Compared with All Other Patients by Frostbite

Agent	No. of Patients	No. of Involved Extremities	Extremities Requiring Amputation, No. (%)			No. of Digits Amputated/Total Digits Involved (%)
			None	Proximal	Digits only	
No agent[a]	26	57	25 (45)	14 (25)	18 (29)	97/234 (41)
tPA administration, <24 hrs	6	13	10 (77)	0	3 (23)	6/59 (10)[b]
Total	32	70	35 (50)	14 (20)	21 (30)	103/293 (35)

[a]Includes one patient who received tPA starting 48 hrs after exposure.
[b]$p < 0.50$ using Mann–Whitney U test.
Reproduced with permission from Bruen KJ, Ballard JR, Morris SE, et al. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg* 2007;142:546–553.

The difficulty in determining the depth of tissue destruction in cold injury has led to a conservative approach to the care of frostbite injuries.[215,226] For

digit frostbite, the Hennepin score may provide a useful way to track progress and compare experimental therapies.[227] As a general rule, amputation and surgical debridement are delayed for 2 to 3 months unless infection with sepsis intervenes, hence the adage: "frostbite in January, amputate in June." The natural history of a full-thickness frostbite injury is the gradual demarcation of the injured area with dry gangrene or mummification clearly delineating nonviable tissue. Often the permanent tissue loss is much less than originally suspected. In an Alaskan series, only 10.5% of patients required amputation, usually involving only phalanges or portions of phalanges.[199] The need for emergency surgery is unusual, but vigilance should be maintained during the rewarming phase for the development of a compartment syndrome requiring fasciotomy. Open amputations are indicated in patients with persistent infection and sepsis that is refractory to debridement and antibiotics. Mills convincingly demonstrated that of all the factors in the treatment of frostbite that may influence outcome, premature surgical intervention by any means, in any amount, was by far the greatest contributor to poor results.[228]

The use of technetium-99m methylene diphosphonate bone scanning has shown some promise in the early detection of eventual bone and soft tissue viability[229] as has the use of magnetic resonance imaging.[230,231] Technetium-99m "triple-phase" scanning (at 1 minute, 2 hours, and 7 hours) performed beginning 48 hours after admission has been used to assess early tissue perfusion and viability, in an attempt to define the extent of fatally damaged tissues and to allow for early debridement and wound closure.[232,233] The utility of this diagnostic modality continues to evolve, however, with one recent study suggesting that the moderate to severe frostbite lesion identified by technetium-99m scans can be "hibernating" (viable) tissue, which can show improvement up to 6 months following injury.[216,234] A nice review of all imaging studies and their role in the evaluation of frostbite injuries as of 2016 is provided by Millet et al.[235]

Frostbitten tissues seldom recover completely. Some degree of cold insensitivity invariably remains. Hyperhidrosis (in up to 72% of patients), neuropathy, decreased nail and hair growth, and a persistent Raynaud phenomenon in the affected part are frequent sequelae to cold injury.[212,234,236] The affected tissue remains at risk for reinjury and should be carefully protected during any cold exposure. Treatment with antiadrenergic agents

(prazosin hydrochloride, 1 to 2 mg/d) or calcium channel blockers (nifedipine, 30 to 60 mg/d) and careful protection from further exposure is often helpful.[197,234] However, few therapies afford significant relief to the chronic symptoms after tissue freeze injury, although β- and α-adrenergic blocking agents, calcium channel blockers, topical and systemic steroids, and a host of home remedies have been tried with occasional individual success.

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Section B: TRANSPLANTATION

34

Clinical Transplant Immunology

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Key Points

1. Understanding clinical transplant immunology is predicated on understanding mechanisms of innate and adaptive immunity, as well as T- and B-cell signal pathways.
2. T cells are responsible for regulatory and effector mechanisms in the immune response. T-cell effector activity is coordinated by regulatory cells driven by three signals of antigen presentation.
3. Acute rejection has a clinical phenotype and may involve cellular infiltration of the allograft as well as antibody-mediated mechanisms. Chronic rejection, or chronic transplant dysfunction, is driven by immune and nonimmune mechanisms and results in progressive graft fibrosis that is heretofore irreversible.
4. Clinical immunosuppression involves induction and maintenance therapies.
5. Induction therapies are used to prevent early acute rejection of allografts, and are generally aimed at reducing T-cell signaling. Commonly used drugs are lymphocyte depletion agents, IL-2 receptor antibodies, agents to block costimulatory signals.
6. Maintenance immunosuppression consists of calcineurin inhibitors, mTOR inhibitors, antimetabolite agents, and steroids. All agents have a clinically significant side-effect profile.
7. Major side effects of chronic immunosuppression include calcineurin inhibitor–related nephrotoxicity, major and minor infections, and cancer.

INTRODUCTION

Modern clinical transplantation has continued to evolve rapidly over the past 65 years. Massive advances in surgical technique and biologic science have saved the lives of thousands of patients. The bedrock of success in clinical transplantation is the result of growth in transplant immunology. The discovery era of the immune response to alloantigens and identification of

molecular targets for modern immunosuppressive agents have solidified clinical transplantation as the treatment of choice for patients with organ failure.

1 Understanding transplant immunology requires an in-depth understanding of the molecular mechanisms that lead to acute and chronic rejection. Transplant rejection is the clinical phenotype of organ injury brought on by the recipient immune system's recognition of allogeneity. The aim of this chapter is to review the scientific principles behind the use of modern immunosuppressive agents, the interplay between cell types involved in the alloimmune response, and an in-depth discussion of modern therapeutics. Additionally, the complications of immunosuppressive therapy and evolving therapies will be discussed.

SCIENTIFIC BASIS FOR MODERN CLINICAL IMMUNOSUPPRESSION

The Immune Response to a Solid Organ Transplant

The interaction of a host's immune system with foreign antigen is central to understanding the pathways that modulate organ-directed effector responses. *Operational tolerance* is defined as the immunologic acceptance of an organ allograft while maintaining global immune system integrity; downregulation of host effector mechanisms must be maintained while minimizing the suppression of recipient defense mechanisms. T- and B-cell activation and regulatory pathways are primary targets for conventional immunosuppressive regimens. Immunosuppressive regimens have been developed to impact isolated pathways in T-cell activation by recipient antigen-presenting cells (APCs). As the field of transplantation has matured, these pharmacotherapies have become more specific and less toxic to the host immune system.

The development of mature T cells begins with nascent thymocytes. Thymocytes contain T-cell receptors (TCRs) arranged and rearranged in a random individual-specific manner. These TCR-containing thymocytes are challenged by "self" antigen and undergo programmed cell death if they

express “high affinity” and activate. In contrast, these immature cells are programmed not to proliferate if they express “too low” an affinity. Thymocytes with an intermediate affinity are fostered to survive and differentiate into specific CD4- and CD8-expressing cells which interact with self-restricted major histocompatibility complexes (MHCs) on APCs, such as dendritic cells, in the peripheral blood.

The foundation of the adaptive immune response lies in the presentation of antigen to T cells which takes place via macrophages, B cells, and dendritic cells. Dendritic cells present antigen via their MHC class I or II molecules to $CD8^+$ T cells and $CD4^+$ T cells, respectively. The most common scenario occurs when a T cell interacts with an APC-MHC complex–presenting “self” antigen. In normal (nonautoimmune) circumstances, this is usually a very weak bond and the T cell removes itself from the interaction and begins to recirculate. In the context of infection or transplantation, the APC-MHC complex presents a foreign peptide which the T cells recognize as “nonself” and begin the cascade of activation as well as clonal expansion.

2 T cells are activated by a process that requires three sequential signals. The “three-signal” process of T-cell activation begins with **signal 1** as the TCR interacts with the MHC–foreign peptide complex presented by an APC. T cells become maximally activated only after a threshold number of TCRs have been occupied. Multiple costimulatory–supporting molecules on the periphery of both the APC and T cells travel to the immunologic synapse and begin to interact with each other, comprising **signal 2**. The engagement of TCR by MHC–peptide complexes in combination with the interaction of costimulatory, accessory, and adhesion molecules results in a cascade of signaling pathways. This includes activation of NF-κB and translocation of the nuclear factor of activation and transcription (NFAT) to the nucleus of the T cell which translates and transcribes proteins such as interleukin-2 (IL-2). IL-2, formerly known as T-cell growth factor, then contributes to the clonal expansion of other T-cell populations allowing for cellular expansion to fight against the inciting foreign antigen. IL-2 also engages with CD25 on the T cell itself thereby activating a doublet complex known as the mammalian target of rapamycin, or mTOR. Signaling through mTOR constitutes **signal 3** of activation which affects cell cycling and cytokine production, cellular proliferation, and T-cell differentiation into an effector cell against the

grafted organ. This pathway initiates the slower, more sophisticated, adaptive immune response (**Fig. 34.1**).

Immediately following implantation and reperfusion of an organ allograft, markers of inflammation are upregulated which act as homing signals to effector T cells. These inflammatory mediators also allow for a more efficient uptake of antigen by dendritic cells. Organ-derived dendritic cells are released to the host's secondary lymphoid tissue. Termed "passenger leukocytes," these dendritic cells are primed to present antigen to naive host T cells. These activated $CD4^+$ T cells specialize into subsets of helper T cells each identified by a distinct signature of cytokines. Interferon-γ (IFN)–secreting TH1 cells are central to various cell-mediated rejection responses including acute and chronic or delayed-type hypersensitivity responses. TH2 cells support B-cell production of antibody and secrete cytokines with a suppressive capacity such as IL-4 and IL-10.

Memory T-cell subsets react in a more rapid manner to the graft and incite an accelerated rejection response. Seminal studies investigating memory responses to allografts proved that antigen-experienced memory T-cell subsets can cause graft destruction in the absence of secondary lymphoid tissue. Clinically, these "memory" T cells are generated throughout the life span of a potential recipient due to various infections that the patient may have experienced. Memory T-cell subsets that have been generated by these infections may then react against an organ at the time of transplant if the antigenic response from the organ mimics that of the previous infectious episodes. It is now established that these memory T cells are spared by conventional induction immunosuppression allowing their graft alloreactivity to induce acute rejection responses. Thus, circulating memory responses remain a roadblock to immunologic tolerance.

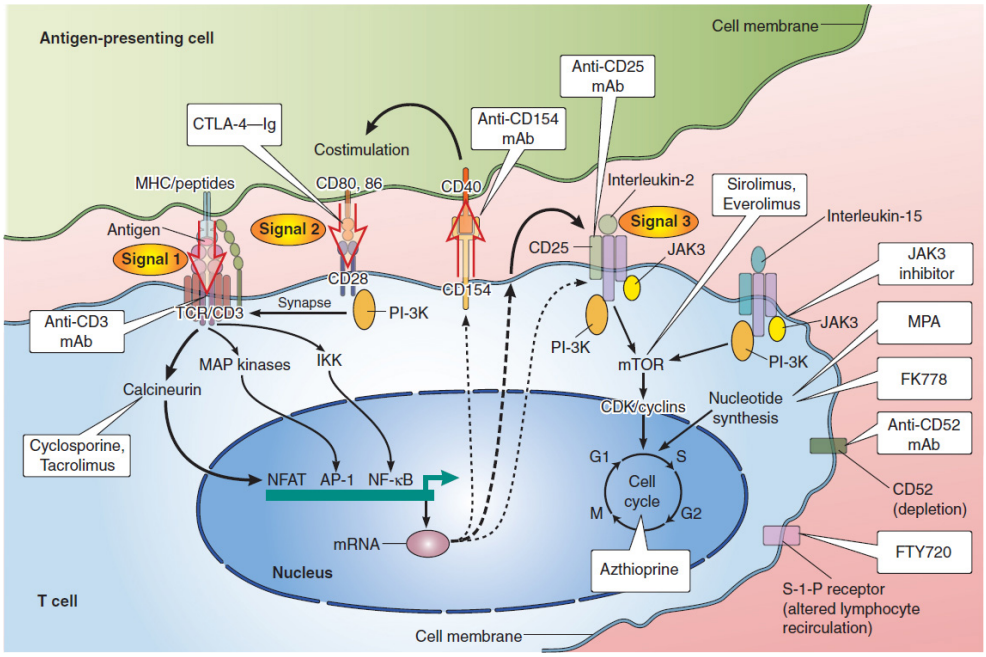

Figure 34.1 The signal hypothesis of T-cell activation and molecular targets of modern clinical immunosuppression. T-cell activation requires three signals to initiate an effector response: antigen presentation of nonself MHC, costimulatory signal, and regulation of cytokine signaling at the cell surface. These three signals are thus targets for therapeutic drugs used in modern clinical immunosuppression in both induction and maintenance phases, as well as in the treatment of rejection. The figure demonstrates the site of action of these agents.

REJECTION IN SOLID ORGAN TRANSPLANTATION

Immunologic rejection can occur minutes to years after an organ transplant. The early phases of rejection, termed hyperacute rejection, can occur on the operating room table to 24 hours after surgery and are mediated by the humoral immune system. Acute rejection is a cell-mediated phenomenon which often manifests days to months after transplant. Chronic rejection occurs in the months to years after transplant and continues to be one of the leading causes of graft loss in the long term. Acute and chronic antibody-mediated rejection (AMR) is a separate phenomenon that may occur days to years after transplant and remains an important barrier to successful engraftment of organs.

Hyperacute Rejection

Hyperacute rejection is rare in modern clinical transplantation. Hyperacute rejection is generally attributed to ABO blood group incompatibility or the presence of preformed anti-HLA antibodies. In the allograft, the capillary endothelium expresses blood group antigens which may join with circulating antibodies to A and B glycoproteins. For example, a blood group B transplant candidate would have circulating anti-A IgG antibodies in blood. If a blood group A kidney allograft were transplanted into that recipient without any other treatment, these antibodies would react with the donor endothelium and activate complement and humoral immunity effector mechanisms, which would lead to endothelial injury, thrombosis, as well as intraparenchymal hemorrhage. This response usually happens within minutes after reperfusion of the allograft and requires removal of the allograft in order to prevent a systemic inflammatory response which may lead to multiorgan failure. Prevention of this type of rejection is central to the practice of clinical transplantation, and mandates confirmation of donor and recipient compatibility via ABO blood group verification and cross-matching prior to implantation of the allograft (**Fig. 34.2**).

Acute Rejection

3 Induction protocols in combination with immunosuppressive therapy successfully prevent the acute rejection episodes. In the case of renal transplantation, induction therapies in combination with maintenance therapies have fostered a significant improvement of 1-year outcomes. Less than 10% of organs experience clinically significant acute cellular rejection (ACR) episodes leading to graft loss at 1 year. ACR is an adaptive response characterized by T-cell interactions with donor antigens either presented directly by the donor APC or indirectly by the recipient professional-presenting cells. Once clonal expansion occurs, “effector” T cells then infiltrate the graft and mediate various methods of organ injury.

The gold standard in pathologic categorization of renal transplant rejection is the Banff classification model. The Banff classification originated at a consensus conference in 1991 aimed at ranking the levels of rejection seen on kidney transplant biopsies based on degree of structural damage, such as

tubulitis, arteritis, and cellular infiltrate. In renal transplantation, the diagnosis of ACR occurs with tissue confirmation after ruling other causes for declining graft function. Treatment of ACR is usually dictated by the Banff classification. For example, borderline rejection characterized by Banff class IA or IB is often treated with pulse corticosteroids and increases in maintenance immunosuppression whereas, more severe ACR is more often treated with multiple doses of thymoglobulin. Today, ACR is often the result of inadequate immunosuppression due to noncompliance/adherence or early immunosuppression withdrawal/underdosing. Repeated episodes of acute rejection are associated with chronic dysfunction and early graft failure.

Chronic Rejection

The clinical sequelae of chronic rejection (chronic transplant dysfunction or CTD) are varied and organ specific. The unifying factor of CTD among all organs transplanted is the histopathologic effect of arterial intimal thickening in the vessels supplying the organ, termed transplant arteriosclerosis or transplant vasculopathy. Both immune and nonimmune stimuli may upregulate pathways leading to progressive graft fibrosis. Immune-dependent mechanisms, including HLA mismatching, inadequate immunosuppression, and episodes of acute rejection, promote the development of CTD and eventual graft failure. Additionally, immune-independent mechanisms, such as prolonged ischemia time and usage of brain-dead donor organs, as well as recipient factors such as native hypertension may also play a role in the onset of CTD.

Clinically, the manifestations of CTD depend on the type of organ allograft. Recipients of renal allografts with CTD often manifest with proteinuria, decreases in glomerular filtration rate (GFR), increases in plasma creatinine, and arterial hypertension. Patients who have undergone liver transplantation may present with abnormal liver function tests or an increase in serum bilirubin secondary to the so-called *vanishing bile duct syndrome*. Bronchiolitis obliterans, detected by computed tomography and altered pulmonary function tests indicate the onset of CTD in lung transplant recipients. Patients receiving cardiac allografts may present with a range of symptoms from arrhythmias to fatal myocardial infarction.

Type of Rejection	Time of Onset	Mechanism	Morphology
Hyperacute	Minutes to few hours	Preformed antibodies bind to graft endothelium	Vessel thrombosis; Ischemic necrosis
Acute Cellular	Days to weeks, months to years	T cells injure graft by direct cytotoxicity and type IV hypersensitivity	Interstitial infiltrates of lymphocytes; Focal necrosis of graft tissue
Acute Humoral (Rejection Vasculitis)	Days to weeks, months to years	Antidonor antibodies against graft antigens	Vasculitis; Intimal thickening; Thrombosis
Chronic	Months to years (Irreversible)	T-cell cytokines stimulate vascular smooth muscle proliferation	Arteriosclerosis; Ischemic atrophy; Interstitial fibrosis

Figure 34.2 Time course, mechanism, and morphology of transplant rejection. Allograft rejection responses have many different phenotypes, which also lead to different therapies. This figure provides a summary of the types of clinically significant rejection episodes, the root cause behind them, and histopathologic features identified on biopsy.

Antibody-Mediated Rejection

AMR can occur in both the acute and chronic phases of transplantation. Increasingly, AMR has been shown to occur in multiple organs including liver and heart. AMR starts with production of donor-specific antibody (DSA) directed to the endothelial lining of organ allografts. DSA–endothelial cell interactions lead to complement activation as well as innate responses resulting in allograft injury. In the chronic setting, persistent DSA leads to microthrombotic events and late graft failure. Diagnostically, along with serum titers of circulating DSA, tissue biopsy reveals deposition of complement split products including C4d and inflammation of capillaries and renal tubules.[1] AMR has also been diagnosed using newer endothelial, cell-specific biomarkers of capillaritis. Liver allografts have shown susceptibility to AMR and DSA in recent studies.

The treatment of acute AMR is based on removal of inciting antibodies. Although there are no high-quality evidence-based treatments for acute AMR, strategies include plasmapheresis, immunoadsorption, use of B-cell toxic

antibodies such as rituximab, newer proteasome inhibitors such as bortezomib, and even splenectomy. In patients with drug-resistant AMR, monoclonal antibodies to complement C5 (eculizumab) have been used off-label with some encouraging results although the extreme expense of the drug has hindered its investigation in randomized control trials.

IMMUNOLOGIC PHARMACOTHERAPY IN SOLID ORGAN TRANSPLANTATION

Induction

Human immunity depends on innate and adaptive responses to foreign antigen. The innate response is rapid and nonspecific when foreign antigen is encountered while the adaptive response develops over time and is focused on recall of foreign antigen. [4] While the innate immune system sets the scene for the adaptive response, it is the specificity of antigens which allows for the activation and proliferation of effector cells to rid the system of the pathogenic insult.[2] Current therapies in clinical immunosuppression target global T-cell activation and proliferation. Induction immunosuppression is used perioperatively as a prophylactic treatment to attenuate acute rejection.

CELL SURFACE RECEPTOR BLOCKADE

In order to interrupt the signal 3 T-cell activation pathway, various pharmacotherapies have targeted signal 2, or costimulation. This effectively targets the clonal proliferation of effector T cells. [5] Costimulation pathways have been targeted by monoclonal antibodies as well as recombinant fusion proteins.

B7/CD28 CTLA4 Blockade

The expression of CD80 (B7.1) and CD86 (B7.2) on the surface of APCs provides T cells with either activation signals, if engaged to CD28, or inhibitory signals, if ligating cytotoxic T-lymphocyte antigen 4 (CTLA4).

CD80 and CD86 interact preferentially with CTLA4 (CD152) when compared to CD28.[3] CTLA4 is also upregulated following the activation process and its ligation results in inhibition of activation thereby controlling clonal expansion. Additionally, CTLA4 is constitutively expressed on regulatory T cells. Blockade of each CD80 and CD86 molecule monotherapy has not led to significant allograft survival in nonhuman primate models. In contrast, blockade of both molecules together did lead to prolonged graft survival but was not able to induce tolerance as rejection occurred once therapy was stopped. An immunoglobulin fusion protein of CTLA4 (abatacept) has been shown to inhibit graft rejection in xenogeneic and allogeneic systems. These promising early results have prompted the development of CTLA4-Ig variants.

LEA29Y (belatacept) is a second-generation molecule, derived as a result of mutating two amino acids of CTLA4-Ig. Belatacept possesses a twofold greater ligation capacity for both CD80 and CD86. The increase in avidity allows for a more complete blockade of the B7 molecules and a 10-fold greater suppression in in vitro assays. Belatacept has shown improved renal function, reduction in chronic allograft nephropathy, decreased calcineurin-related toxicity, and no thromboembolic complications in phase II trials. Phase III trials have evaluated the efficacy and renal protection of belatacept in standard (BENEFIT) and expanded criteria donors (BENEFIT-Ext). There was an increased incidence of posttransplant lymphoproliferative disease in Epstein–Barr virus (EBV)–seronegative patients and acute rejection at 1 year in the belatacept treatment groups compared to calcineurin inhibitors (CNIs). Additional results revealed an improved GFR and lipid profile over a 5-year period.

IL-2 Receptor Blockade

Basiliximab is a chimeric mouse/human IgG1 monoclonal antibody to the α-chain of CD25 (IL-2 receptor) which has proven to reduce acute rejection rates in adult and pediatric renal and pancreas transplant recipients. In clinical trials with 6-month follow-up, basiliximab had a significant impact on acute rejection rates with no increase in infectious complications. Basiliximab can be used as induction therapy for kidney transplant recipients or in liver transplant recipients to spare the nephrotoxic effects of tacrolimus.

Recent studies have cast doubt on the renal protective effects of basiliximab induction and CNI reduction, however long-term follow-up remains to be provided.

LEUKOCYTE DEPLETION

In order to achieve tolerance to an organ transplant, it may be necessary to maximize the potential of engraftment by depleting the alloreactive effector T cells (and B cells in some therapeutic regimens) which mediate a rejection response. Depleting the recipient of leukocytes creates a window of opportunity for an allograft to "settle in" without attack by effector immunocytes.[4] The recipient's transient immunodeficiency is dictated by the strength and duration of depletion. Many investigators have identified the value of monoclonal or polyclonal antibodies designed to bind to peripheral alloreactive lymphocytes. The short-term depletion of leukocytes using antithymocyte globulin, anti-CD3, anti-CD2, anti-CD4, and anti-CD8 has proven successful in terms of long-term graft survival in animal models; these results are further enhanced with thymectomy prior to transplantation in order to prevent posttransplantation peripheral effector cell repopulation.

Polyclonal leukocyte–depleting antibodies, such as thymoglobulin (rabbit antithymocyte globulin [rATG]), are useful as induction agents, and are mainstays of induction therapy in renal transplant recipients. Upon binding various T-cell epitopes, rATG lyses leukocytes using complement-dependent pathways and opsonization leading to mononuclear cell phagocytosis of T cells. rATG also binds to surface receptors on dendritic cells, which impair antigen presentation. Polyclonal antithymocyte globulin is wrought with serious side effects including a predisposition to posttransplant lymphoproliferative disorder and the cytokine release syndrome.

MAINTENANCE IMMUNOSUPPRESSION

Calcineurin Inhibitors

6 One of the greatest medical discoveries of the 20th century was the identification of the CNIs with their effects on T-cell signaling. This class of agents has potent biologic activity and minimal myelosuppressive effects, which were a significant limitation in early clinical transplantation. CNIs, as a class, disrupt regulatory T-cell signaling and lead to a downregulation of IL-2 production, which eventually decreases the activity of cytotoxic T cells. Antigen presentation at the TCR leads to an increase in cytoplasmic calcium levels through a protein kinase and G-protein reaction within regulatory T cells. This calcium binds to calmodulin, a regulatory subunit of the phosphatase calcineurin, prevalent in immunocompetent lymphocytes and nerve cells. Calcineurin is responsible for cleaving the phosphate bound to NFAT (nuclear factor of activated T cells) which in its activated form traverses the T-cell nuclear membrane and promotes transcription of IL-2. Inhibition of calcineurin occurs through the activation of immunophilins, such as cyclophilin and FK-binding protein, which are endogenous cytosolic peptides. The cyclosporine–cyclophilin complex and its counterpart, the FK506-FKBP12 complex, prevent dephosphorylation of NFAT, which in turn leads to reduced IL-2 production and diminished T-cell signal transduction to effector lymphocytes.[5]

Cyclosporine A was the first of these drugs identified, initially found in a soil sample from the fungus *Tolypocladium inflatum.* The clinical efficacy of cyclosporine A was demonstrated in human kidney transplantation, opening the gates to a new era for clinical organ transplantation. Cyclosporine remained the mainstay of clinical immunosuppression for several years and was used across organ types by thousands of patients. In 1984, FK506 (tacrolimus) was identified as another CNI with a similar mechanism of action. FK506 is a macrolide immunosuppressant that was approved by the U.S. Food and Drug Administration for use in liver transplantation. Tacrolimus has become the mainstay of maintenance immunosuppression in solid organ transplant programs due to a gentler side-effect profile and potency of immunosuppression and is used in virtually all solid organ types.

CNIs have a variety of side effects which present challenges in the clinical management of transplant recipients. Common interactions that may boost levels of CNIs occur in patients requiring antifungal therapy, particularly in the azole class, as well as other drugs metabolized by hepatic/intestinal cytochrome P450 3A4 enzyme. The most significant long-term effects include

chronic nephrotoxicity that may precipitate end-stage renal disease, as well as new-onset diabetes mellitus after transplantation. Registry analyses suggest that 7% to 21% of nonrenal transplant recipients are at risk for renal failure, and patients treated with CNIs are at significantly increased risk of requiring dialysis treatment in the months and years after transplant.[6] As implied by the name, calcineurin is also present in nerve tissue as well as lymphocytes. Drug activity in nerve tissue leads to several clinical effects including tremors, seizures, and posterior reversible encephalopathy syndrome. Additional side effects include hyperkalemia, hypercholesterolemia, and gastrointestinal dysfunction including diarrhea. Cyclosporine has also been associated with gingival hyperplasia that is seen less frequently with tacrolimus. Consultation with a transplant pharmacist is integral to the successful management of the posttransplant patient to prevent toxicity and achieve therapeutic immunosuppression goals.

Steroids

Steroids have represented the mainstay of immunosuppressive therapy since the beginning of clinical transplantation. Glucocorticoids are steroids that arise from the zona fasciculata in the adrenal gland. These molecules have a plethora of effects in humans, and their receptors are omnipresent across human cell types. In lymphocytes, glucocorticoids act on cytosolic receptors that in turn lead to a variety of intracellular signals that are responsible for gene transcription, and decrease the expression of several cytokines, including IL-2. Glucocorticoids also reduce the number and function of both T cells and B cells.

Steroid therapy is used in a variety of clinical treatments including maintenance immunosuppression and in high doses as a rescue therapy in patients presenting with acute rejection. There are several side effects to chronic corticosteroid use, which have prompted transplant clinicians and researchers to develop protocols that reduce the need for chronic steroid use. Common side effects include glucose intolerance, weight gain, skin and tissue frailty, osteopenia and osteoporosis, muscle breakdown, neuropsychiatric dysfunction, glaucoma and cataracts, secondary hypercortisolemia, and other effects. Many transplant programs are shifting

toward steroid avoidance in maintenance immunosuppression in low-risk patients.[7]

mTOR Inhibitors

Like CNIs, mTOR inhibitors lead to decreased IL-2 proliferation. The first discovered mTOR inhibitor was sirolimus. Sirolimus (rapamycin) is a bacterial macrolide derived from *Streptomyces hygroscopicus,* found initially in a soil sample from Easter Island (Rapa Nui). Sirolimus binds to FK-binding protein 12, as does tacrolimus. The site of action of the sirolimus–FKBP12 complex is known as the mammalian target of rapamycin, or mTOR. Despite having structural similarity to tacrolimus, sirolimus has limited activity on calcineurin when bound to FKBP12. The complex disrupts signal transduction of the IL-2 receptor and decreases nuclear transcription of molecules active in lymphocyte homing. Sirolimus also has significant antiproliferative properties and inhibits cell cycle activity in lymphocytes and fibroblasts.

Sirolimus has been adopted in a variety of clinical protocols. Sirolimus is currently used primarily in place of CNIs, most commonly in patients who are weeks to months out from the transplant operation. Sirolimus has less nephrotoxicity than CNIs, but has been associated with a higher risk of acute rejection in some studies. In liver transplantation, conversion from tacrolimus to sirolimus in patients with reduced kidney function was associated with more acute rejection episodes but did not have a tangible benefit in terms of kidney function in a randomized control trial. Some have advocated for lower-dose CNIs as maintenance therapy in patients with impaired renal function compared to sirolimus monotherapy, and studies have demonstrated the potential of low-dose CNIs in conjunction with sirolimus for maintenance immunosuppression. Importantly, there is an FDA black box warning against using sirolimus in conjunction with higher-dose CNIs due to higher risk of mortality and graft loss in liver transplantation, as well as an increased risk of hepatic artery thrombosis within the first month after transplant.

Everolimus is another mTOR inhibitor approved for use in kidney and liver transplantation. Everolimus is a hydroxylated derivative of sirolimus, and its preserved structure allows for a similar mechanism of action via

FKBP12 binding and mTORC1 inhibition. In a multicenter prospective clinical trial, patients with reduced-dose tacrolimus and everolimus had improved GFR at 2 years posttransplant compared to patients on standard tacrolimus-based regimens, without any higher risk of biopsy-proved acute rejection or major side effects. This improvement in GFR has also been identified retrospectively in patients converted to everolimus in maintenance immunosuppression.

Sirolimus has been associated with impaired wound healing after transplant, including anastomotic dehiscence in lung transplantation, surgical site infections, and fascial union problems. Surgeons confronted with transplant patients who are on mTOR inhibitors should consult with transplant professionals prior to operative intervention if possible, in order to guide alterations in immunosuppressive therapy to minimize complications. Several other complications have been noted in patients on mTOR inhibitors. Pulmonary toxicity manifested as pneumonitis has been identified, and caution should be taken in administering the drug to patients with pre-existing lung disease. Metabolic complications including hyperlipidemia and new-onset diabetes mellitus after transplant have also been identified as significant side effects. In low- to moderate-risk renal transplant recipients, conversion from tacrolimus to mTOR inhibitors was associated with a higher risk of acute rejection, higher rates of proteinuria, hypercholesterolemia, and anemia.

Antimetabolite Drugs

Antimetabolite drugs in solid organ transplantation comprise a class of agents aimed at suppressing lymphocyte proliferation by 7 reducing the rate of de novo purine synthesis, which prevents effective nucleotide synthesis and DNA transcription. Typically, these drugs are used in combination with CNIs and steroids. One of the first antimetabolite drugs applied in clinical transplantation was azathioprine. While it is effective in reducing T- and B-cell propagation, azathioprine is also a potent suppressive agent of bone marrow, increases the risk of anemia, and is also associated with pancreatitis. A newer antimetabolite, mycophenolic acid (MPA), has emerged as a mainstay in solid organ transplantation. MPA was identified in

a *Penicillium* fungal species and is hepatically metabolized. MPA has less myelosuppressive activity than azathioprine, but side effects are common.

Myelosuppression and leukopenia are common side effects of this class of agents. Mycophenolate is also associated with a significant risk of gastrointestinal dysfunction including diarrhea, nausea, and vomiting. Azathioprine has been recognized as a group 1 carcinogen by the National Toxicology Program in the United States, related to length of use and dosage. Mycophenolate should be avoided in pregnancy or in transplant recipients trying to conceive due to the risk of miscarriage and congenital malformations.

Infections after Transplant

Posttransplant infections are directly related to the level of immunosuppression in the host. In the early period after transplant, when levels of immunosuppression are high and proximal to the use of T-cell–depleting induction agents, the risk of opportunistic infection is highest, and management is focused on antimicrobial prophylaxis. Further from transplant, less immunosuppression is typically required, and prophylaxis is not necessary. However, the prevalence and incidence of infectious diseases in solid organ transplant recipients mandate close monitoring of clinical signs and symptoms, and appropriate diagnostic testing when a clinical suspicion arises of a bacterial, viral, parasitic, or fungal infection. Infections after transplant may consist of donor-derived infections transmitted with the organ, recipient-derived infections due to colonization or other pretransplant exposure, nosocomial infections acquired in the healthcare setting, and community-acquired infections. **Figure 34.3** demonstrates the peak incidence of common opportunistic infections as a function of time after transplant. When faced with a transplant patient with a high clinical suspicion of an infection, transplant providers and infectious disease specialists use this information, clinical history, affected organs and systems, and a battery of cause-oriented diagnostic tests to establish the diagnosis and treatment strategy (see **Fig. 34.3**).

Donor-Derived Infections

Deceased organ donors may be exposed to community-acquired infections prior to death, infectious risk related to lifestyle exposures (i.e., intravenous drug abuse), as well as nosocomial infections acquired during hospital care. Several infectious transmissions have occurred as a result of donor transmission, including human immunodeficiency virus (HIV), West Nile virus, rabies, Chagas disease, and lymphocytic choriomeningitis virus. Careful attention must be paid to the circumstances surrounding the donor's death as well as reported signs and symptoms such as fever and altered mental status. Prior to organ recovery, organ donors are routinely serologically screened for several infectious pathogens, including HIV, hepatitis, cytomegalovirus (CMV), EBV, and syphilis. Routine blood, urine, and sputum cultures may be used in premortem care. Serologic testing consists of antibody testing, which is not 100% sensitive, but the recent inclusion of nucleic acid testing in many centers may help mitigate risk in organ acceptance and aid patient counseling. In the case of CMV, hepatitis, and EBV serologic testing, serologic matching between donors and recipients drives the perception of posttransplant infectious risk and guides antimicrobial prophylaxis decisions and selection of immunosuppression.

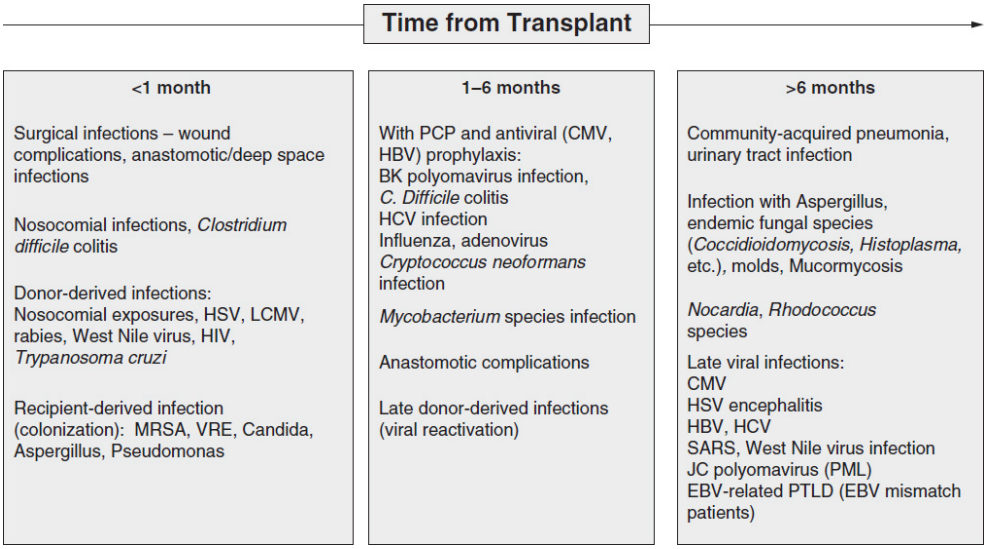

Figure 34.3 Timeline of common infections after transplantation. Immunosuppression predisposes transplant recipients to infection by deterring host defenses. In this context, bacterial, viral, and fungal infections may arise which have distinct peaks of onset. Treatment of these infections usually involves withdrawal or reduction of immunosuppression in most cases, particularly when infections are life-threatening or are causing significant morbidity. (Adapted from Fishman JA. Infection in solid-organ transplant recipients. *N Eng J Med* 2007;357[25]:2601–2614.)

Pathogen	Site of Disease	Disease Manifestations	Prophylaxis	Treatment
Cytomegalovirus (CMV)	CNS, Respiratory, GI tract, Bone marrow	Fever, neutropenia, pneumonitis, diarrhea, mucosal ulceration, chorioretinitis, meningoencephalitis, graft dysfunction	Low-risk patients: Acyclovir High-risk patients: Valganciclovir	Valganciclovir Ganciclovir CMV-immunoglobulin Minimization of immunosuppression
Epstein–Barr Virus (EBV)	Bone marrow, spleen, CNS	B-cell–derived post transplant lymphoproliferative disease (PTLD)	Antiviral prophylaxis such as acyclovir or valganciclovir	Minimization of immunosuppression Chemotherapy Radiation Therapy (CNS) Anti-CD20 antibody therapies
BK Virus	Kidney	Renal Dysfunction	None	Minimization of immunosuppression Experimental antiviral therapies (cidofovir)
Pneumocystis	Respiratory	Pneumonia/pneumonitis	Trimethoprim/sulfamethoxazole Pentamidine Dapsone	

Figure 34.4 Common infections after transplantation, prophylaxis, and treatment strategies. After transplant, while predisposed to multiple infections related to immunosuppression, certain infections are particularly common and virulent. Clinical decisions regarding prophylaxis against these pathogens and how this affects immunosuppression are key decision points in managing the posttransplant patient.

Recipient-Derived Infections

The incidence of posttransplant infections that arises from pretransplant exposure to the recipient is increasingly recognized. Transplanting patients with active infections should be undertaken with extreme caution due to the risk of dissemination of disease with early immunosuppression. Nosocomial pathogens may colonize the recipient prior to transplant, when healthcare utilization may be high due to organ failure, or may infect patients at any point after transplant. Pathogens may acquire antibiotic resistance which may make treatment difficult, such as in cases with vancomycin-resistant *Enterococcus,* methicillin-resistant *Staphylococcus,* azole-resistant *Candida,* as well as in *Clostridium difficile* colitis, several gram-negative enteric pathogens, and fungi. Recipient exposure via travel or residence in geographically endemic areas can also be a risk for infection (fungal infections such as histoplasmosis, aspergillosis, coccidioidomycosis, atypical bacterial infections such as *Mycobacterium tuberculosis,* parasitic infections caused by *Strongyloides* or *Trypanosoma cruzi*), as well as reactivation of dormant viruses (hepatitis, CMV, or varicella-zoster virus). Exposures to relatively benign pathogens may result in major infections after transplant. Respiratory viruses may further weaken natural tissue defenses in the bronchopulmonary tree and lead to superinfection with other pathogens. Fungal infections derived from the soil such as *Nocardia* or *Aspergillus* may arise in this fashion and require changes in immunosuppression to prevent exacerbation of infection.

While the spectrum of potential infectious pathogens is broad, infectious epidemiology in the immunocompromised population guides targeted prophylaxis strategies. Common posttransplant infections are listed in **Figure 34.4**. Immunosuppression management in the infected transplant recipient is often challenging and dependent on the relative immunogenicity of the organ transplanted, the virulence of the pathogen, and the presence or potential of disseminated disease. Minimization of immunosuppression is a mainstay during infectious episodes but must be balanced with the risk of intervening acute rejection.

Cancer

Chronic immunosuppressive therapy weakens host defenses against neoplastic processes. There is well-established evidence that solid organ

transplant recipients of every type have an increased risk of malignancy, both related to immunosuppression and oncogenic viral infections. The most common cancers incurred by solid organ transplant recipients are skin cancers, followed by posttransplant lymphoproliferative disease. In this context, posttransplant patients are strongly recommended to have yearly skin examinations by a dermatologist. Screening for malignancy in chronically immunosuppressed patients follows general screening guidelines. Treatment of cancers is driven by site and extent of disease, but in all cases includes reduction in the amount of immunosuppression.

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35

Organ Retrieval and Preservation

Mary T. Killackey

Key Points

1. Despite advances in survival and expanded indications for transplant, the gap between organ availability and organ supply has widened.
2. Efforts to expand organ donation are critical to save lives. Organ donation must be done within a regulated system that is deeply rooted in ethical standards of care.
3. A balance must be maintained between using every viable donor organ and ensuring each patient a chance of successful posttransplant outcome.
4. Organ retrieval requires coordination of a multi-disciplinary team including surgeons, anesthesiologists, nurses, and organ perfusion technicians. Careful retrieval and perfusion techniques are necessary for a successful outcome.
5. Organ retrieval and storage results in significant alterations in the homeostasis of the organ. The degree of organ preservation injury contributes to organ dysfunction. Current trials aim to rehabilitate injured or otherwise discarded organs.

1 Organ transplantation has become the standard of care for end-organ failure and often it is the only lifesaving therapy available. Despite our significant advances in survival and expanded indications for transplant, the gap between organ availability and organ supply has widened significantly and patients are unable to receive the treatment they need. As of January 2020, in the United States, more than 110,000 patients are waiting for an organ transplant.[1] The total number of transplants has been increasing, reaching almost 40,000 in 2019, due in large part to the increase in opioid-related deaths.[2] Yet the disparity continues as a new patient is added to the waitlist every 10 minutes and on average, 22 patients die each day waiting for transplant (**Fig. 35.1**).[3]

ORGAN DONATION

(**Fig. 35.2**)

Living Donation

Considering high waitlist mortality and long wait times, early transplant for patients with end-organ failure has significant benefits. For example, patients who receive a kidney transplant prior to initiating dialysis (a preemptive transplant) have a lower rate of allograft failure and mortality and a higher quality of life compared to patients who receive a transplant after beginning dialysis (**Table 35.1**).[4]

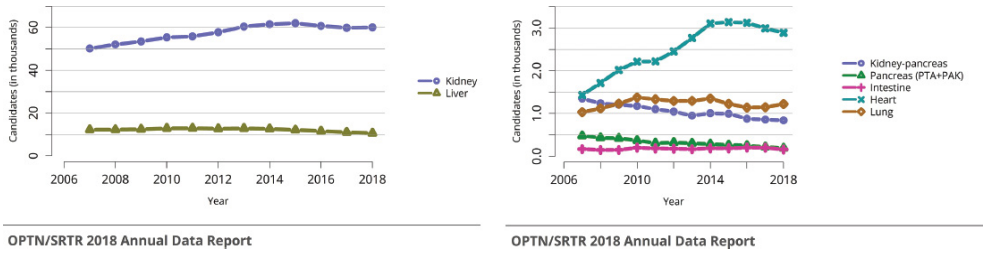

Figure 35.1 Active candidates on the UNOS waitlist as of 12/31/2019 by organ.[1] (Data from UNOS Transplant Trends. http://www.unos.org. Accessed January 2020.)

Living donation facilitates this early intervention and is available to those waiting for liver and kidney transplants. In the United States, 23% of liver and kidney transplants utilize living donor organs.[1] In certain parts of the world, living donation predominates due to multiple ethnic, social, cultural and religious factors resulting in absent or very low rates of deceased donation.[5] Since 2004, living donation had been in a steady decline until recently as a result of intentional efforts to increase living donation. For the third year in a row, the annual volume of living donors has increased and reached a new peak in 2019 (**Table 35.2**).[3]

In paired kidney exchange programs, donor–recipient pairs that were previously determined to be incompatible can swap donors with another pair if appropriately matched by blood type, HLA type, and antibody sensitization (**Fig. 35.3**). Criteria for living donation are strict. Living donors must be excellent surgical candidates with minimal medical comorbidities and a stable psychosocial assessment. Regulation is in place to ensure the donors have not been coerced.

Deceased Donation

In 2019 in the United States, the majority (77%) of organs used for transplantation came from deceased donors.[1] In general, deceased donors are brain dead, previously in good health, and free of life-threatening communicable disease or malignancy. Steadily increasing over the past 5 years, deceased after-cardiac death donors account for 19% of the deceased donors.[3]

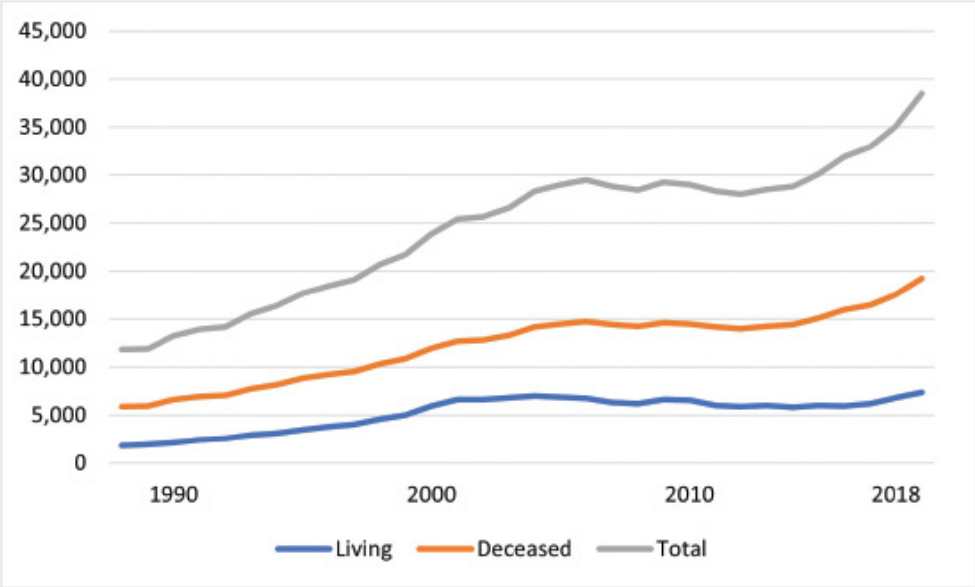

Figure 35.2 Number of annual donors by type as reported on 12/31/2019.[1] (Data from UNOS Transplant Trends. http://www.unos.org. Accessed January 2020.)

2 Considering the desperate need for lifesaving organs, regulations are necessary to ensure fair and equitable distribution across populations. Current issues facing the transplant community focus on the disparity of waiting times, which can vary significantly across the country. In 2018, a lawsuit was filed arguing the current system of distribution violated federal law. HRSA responded by ordering the OPTN/UNOS to remove artificial geographic boundaries from the organ allocation policy which was completed in 2019.[6]

Implementation of these policies in a fair and efficient way is carried out by an organ procurement organization (OPO) which is a not-for-profit entity that is not directly involved in the care of the recipient. The primary role of the OPO is to ensure the safe retrieval of every possible organ available. The OPO, as well as the transplant surgical team, are separated from the declaration of death process. Patients who are not brain dead may donate following cessation of cardiac function; this is known as donation after cardiac death (DCD).

Declaration of Death

In the United States, a patient is considered dead when they have irreversible cessation of brain function (brain dead) or irreversible cessation of

circulatory and respiratory functions. The definition of brain death is established locally by hospitals using rules that conform to the *Harvard Criteria* and comply with the Uniform Determination of Death Act.[7] In 2010, the American Academy of Neurology updated its established guidelines for determination of death (**Table 35.3**).[8] Donors declared brain dead are supported by mechanical ventilation and the necessary medications to maintain a blood pressure, allowing the organs to be perfused by the donor's heart throughout the procurement process.

In an effort to increase transplantable organs, advances have enabled the utilization of organs following cardiac death. In these cases, the donors, who often sustain irreversible neurologic injury, must lose cardiopulmonary function to allow declaration of death. Following family wishes, ventilatory and circulatory support are withdrawn, either in the ICU or the operating room. The patient is declared dead by the caring physician upon cessation of circulation. Each hospital establishes policies and procedures for retrieval of DCD donor organs and it is critical that members of the transplant teams are not involved in the process of declaration of death. After declaration, 2 to 5 minutes must elapse prior to organ retrieval surgery. If the patient does not reach criteria for death within 60 to 90 minutes, kidney recovery is not pursued. For liver, the maximal acceptable agonal time (time from withdrawal to death) is 20 to 30 minutes. While much rarer, if pancreas or lung are recovered, agonal time should be less than 30 minutes. The transplant surgeon rapidly recovers the organs. DCD organs have acceptable but inferior outcomes due to the hypoxia during the agonal phase.[9,10]

Table 35.1 Five-Year Graft Survival of Kidney and Liver Transplant by Donor Type

	Deceased Donor (%)	Living Donor (%)
Liver	71.9	77.3
Kidney	74.4	85.6

OPTN National Data Report: Survival Rates for Transplant Performed 2008–2015. Available at https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/. Accessed January 20, 2020.

Table 35.2 Efforts to Increase Living Donation in the Last Decade

- Improved public education from transplant centers
- Utilization of social media to connect potential pairs
- Transplant center participation on local and/or national paired exchange programs
- Development of protocols for immunologically high-risk transplants

Consent for Donation

Permission for organ donation is obtained from the patient's next of kin prior to organ donation. Organized efforts over the past 25 years have resulted in more than 60% of the U.S. adult population registered as an organ, eye, or tissue donor, often associated with driving licensure.[11] A signed and witnessed organ donor card is sufficient indication of the decedent's wishes to allow organ donation. Despite this declaration, the family's consent is routinely obtained even when a valid organ donor card is present. In conjunction with the OPO, many hospitals have trained specialists who approach families to consent for donation. Explanation of the organ donation process by a trained and empathetic party not directly involved in the care of the deceased patient yields the highest consent rates.

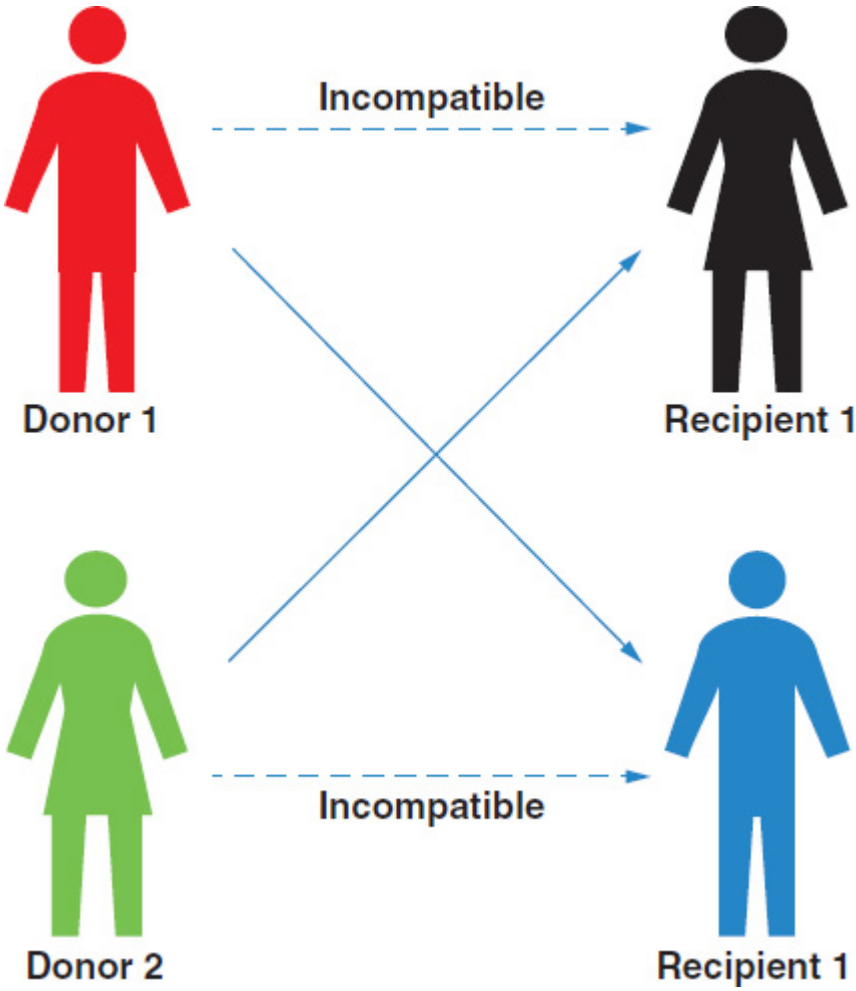

Figure 35.3 Schematic for paired exchange kidney transplant.

Table 35.3 Criteria for Brain Death

- All reversible causes of coma excluded
  - Hypothermia
  - Shock
  - Severe electrolyte abnormality
  - Pharmacologic sedation or paralysis
- Loss of all function of the entire brain, including brain stem[a]
  - No response to noxious stimuli
  - No pupillary light reflex
  - No corneal reflex
  - No oculocephalic reflex
  - No gag reflex
  - No spontaneous respirations
- Preferred confirmatory diagnostic tests (one must be completed)
  - Cerebral angiogram (gold standard)
  - EEG
  - Nuclear medicine perfusion scan

[a]In the United States, one neurologic examination is sufficient in most states.

Data from Wijdicks E, Varelas P, Gronseth G, et al. Evidence-based guideline update: determining brain death in adults. *Neurology* 2010;74(23):1911–1918.

ORGAN SELECTION

3 Organ quality is closely linked to recipient outcomes. A careful balance must be maintained between using every viable organ and ensuring the best possible outcome for each recipient. The transplant team should assess general demographic, health, and social issues of the donor as well as organ-specific function.

Donor History of Cancer

Potential organ donors should be free of cancer as transmission to the organ recipient may result in rapid death related to cancer progression in the setting

systemic immunosuppression. Criteria and guidelines for suitability for donation among cancer survivors are well detailed in the literature.[12]

Donors with a history of melanoma, leukemia, lymphoma or small-cell carcinoma are excluded from donation. For most major cancers associated with systemic progression, organ donors should be disease free for 5 years. Some donor cancers have been shown to have minimal risk of transmission to the recipient. These include nonmelanoma skin cancers without nodal involvement, small renal cell and prostate cancers, and many intracranial malignancies that have not recently had intracranial surgical intervention.

Donor History of Infectious Disease

All donors are screened for transmissible disease and the DHHS has further defined "increased-risk" donors which require nucleic acid testing and the recipients must be tested accordingly after transplant. Potential recipients are required to sign a consent which details the reasoning for determination of high risk.[13]

Donors may spend days prior to donation in the hospital, increasing risk for acquired infections. Treated systemic bacteremia is acceptable while donors with recent fungemia are not donors with undiagnosed viral illnesses. The transplant center needs to follow donor cultures and make sure that the recipient is appropriately treated.

Donors with active HBV (surface antigen positive) are excluded from transplant; however, those with a previous history of hepatitis B infection (core antibody positive) can be used in recipients who have been immunized against HBV. Depending on the organ (hepatic vs. extrahepatic) and the recipient serology, they will require either short- or long-term antiviral therapy.

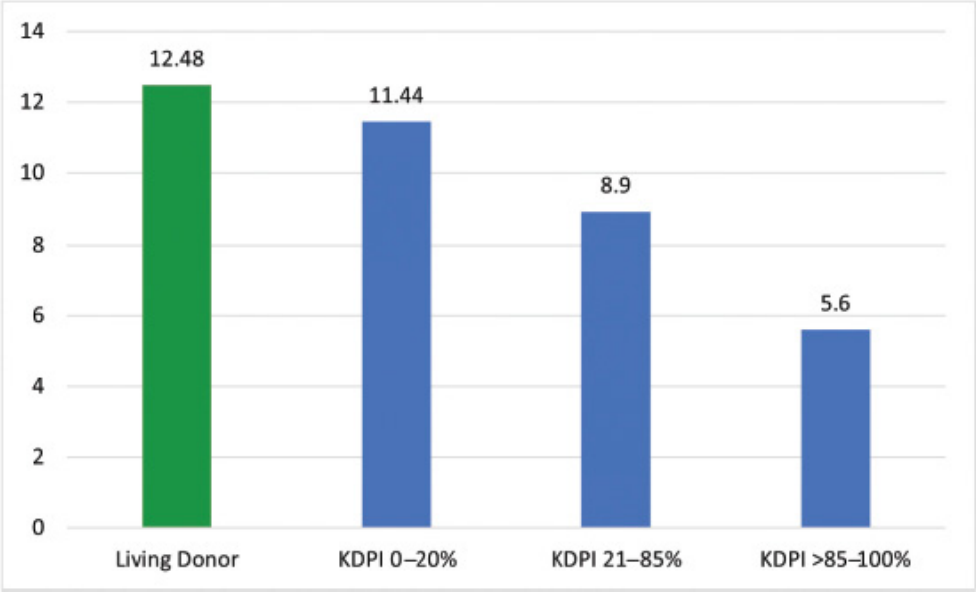

Figure 35.4 Estimated graft half-lives (years) by KDPI as compared to living donor transplant.

Donors with HCV viremia have traditionally been reserved for recipients who are HCV positive. With the development of highly effective antiviral regimens over the last decade, and current literature supporting the utilization of HCV viral positive donors in patients who are HCV naïve, most transplant programs have begun to accept these organs for transplant. Detailed informed consent is essential.[14]

Donors positive for HIV have historically been discarded until the HOPE Act was passed in 2015 allowing their use as part of IRB-approved research protocols. This legislation allowed the transplantation of these organs into HIV-positive recipients exclusively and at centers that meet the specific transplant hospital criteria defined by the NIH and approved by the OPTN.[13]

Other rare but important infectious pathogens such as rabies and encephalitis should raise a red flag and should be discussed with a transplant infectious disease expert prior to accepting any questionable organs.

Organ-Specific Issues

All donors are subject to a global assessment including age, medical history, social history, and cause of death. Each organ has specific considerations:

Kidney

In 2014, the kidney allocation system was significantly revised and began to include a more refined, continuous metric known as the Kidney Donor Profile Index (KDPI). This number combines a variety of donor factors to estimate the likelihood of graft failure after deceased donor transplant (**Fig. 35.4**).

Informed consent is required to be listed for high KDPI organs and both renal biopsy, assessing for glomerular fibrosis, and organ preservation pumping, assessing for circulatory resistance, can aid in graft selection. Kidneys may be preserved for up to 36 hours, though efforts should be made to keep the cold ischemia time (CIT) to less than 24 hours.

Liver

Current liver function and graft size are essential considerations as preterminal liver injury is associated with primary nonfunction of the allograft. A liver biopsy is frequently available from donors with risk factors for liver disease. Greater than 30% macrosteatosis and/or parenchymal fibrosis may preclude transplantation. More than a grade 2 liver laceration generally precludes transplantation. Efforts should be made to keep the CIT to less than 12 hours.

Pancreas

Selection of pancreas allografts must be done with care since recipient complications are common. Donors ideally should be less than 40 years and be free of major comorbidities. On inspection, the pancreas should be soft without significant fat infiltration. Donor iliac vessels used for the vascular conduit should be free of atherosclerotic disease. Pancreatic branches from the splenic and superior mesenteric arteries must be intact (**Fig. 35.5**). Injury to pancreatic parenchyma precludes use of the organ. Efforts should be made to keep the CIT to less than 12 hours.

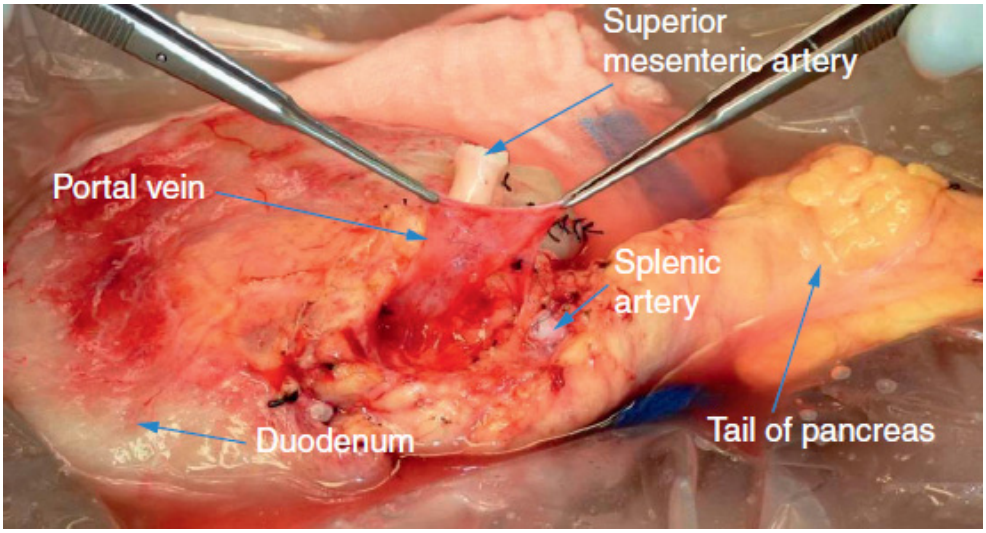

Figure 35.5 Pancreas allograft following procurement, with ample length of portal vein, superior mesenteric artery, and splenic artery.

Heart

Selection of heart allografts includes assessment of an echocardiogram as significant structural cardiac disease or abnormal cardiac function precludes donation. Donors with risk factors for cardiac disease undergo cardiac catheterization to rule out significant coronary artery disease. The relationship between the donor and recipient body size should be considered. Prior to retrieval, the procuring surgeon should examine the beating heart for size and function before the recipient surgeon begins the heart transplant operation. Efforts should be made to keep the CIT to less than 4 hours.

Lungs

Initial assessment of lung donors must determine if there is a history of smoking or pulmonary disease and must consider the events surrounding death (i.e., aspiration or accident with chest injury). Predonation workup includes chest x-rays, arterial blood gases, CT scan, and a bronchoscopy with airway cultures. Lung contusions or pneumonia may preclude transplantation. Donors are ventilated on 100% oxygen to assure high blood oxygen levels. The relationship between the donor and recipient body size is considered. At the time of retrieval, the donor surgeon performs a repeat bronchoscopy and a median sternotomy to physically inspect the lungs for

damage, infection, underlying lung disease, or masses. Efforts should be made to keep the CIT to less than 6 hours.

THE ORGAN RETRIEVAL OPERATION

4 The organ retrieval operation requires coordination of a multidisciplinary team including surgeons, anesthesiologists, nurses, and organ perfusion technicians. By convention, transplant centers send their own teams to procure the heart, liver, lungs, and pancreas. The kidneys are procured by one of the abdominal teams and are shipped to the appropriate transplant center. In most cases, retrieval teams travel to the hospital where the donor is admitted; both air and ground transportation is usually required. In some regions, the donors are transported to a centralized retrieval facility. This has been shown to reduce costs, travel time, and CITs.[15] The recipient liver, lung, and heart operations usually begin before organs return to the transplant center; thus continuous communication and coordination are needed between transplant centers and the retrieval teams.

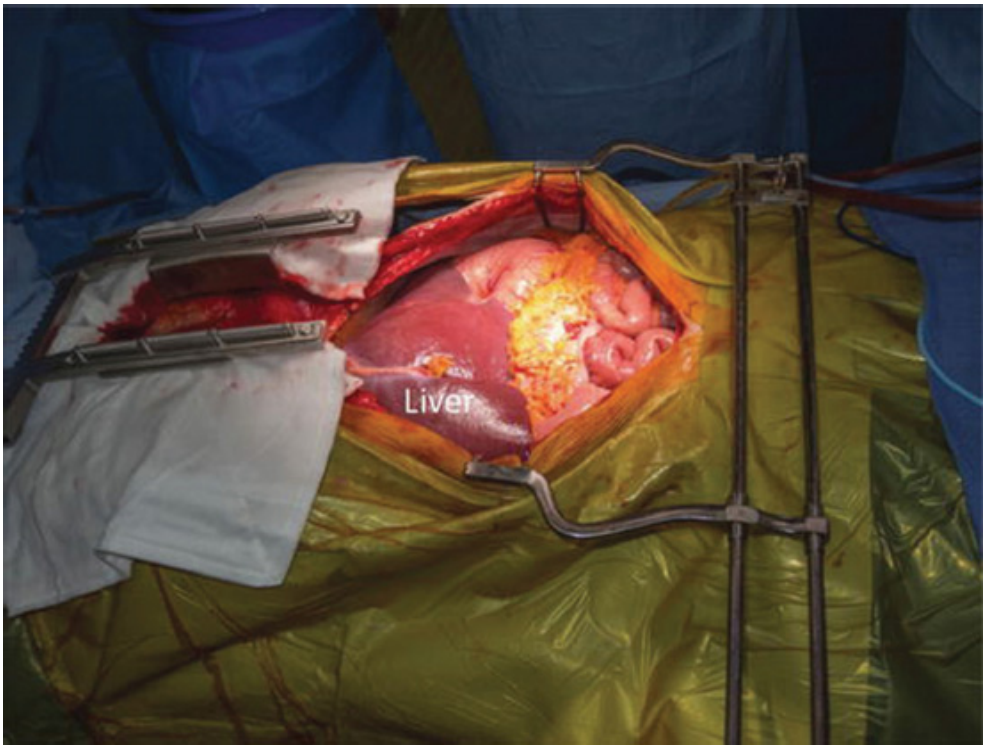

Figure 35.6 Procurement incision/exposure allowing for inspection of thoracic and abdominal cavities.

Upon arrival to the donor operating room, the transplant surgeon must check the appropriate documentation. This includes identification of the donor, consent for donation, and the donor medical chart. The surgery team should discuss hemodynamic and anticoagulation management with the anesthesia team. The donor is placed supine with the arms tucked to facilitate multiple teams working on the donor simultaneously. Prior to incision, it is common to observe a moment of silence to honor the donor and the magnitude of the act of giving. An incision is made from the sternal notch to the symphysis pubis; the abdomen and sternum are opened and the cavities inspected for gross pathologic disease that would contraindicate donation (**Fig. 35.6**). The key organ-specific steps are detailed below.

Heart and Lung Retrieval

A bronchoscopy is done to examine anatomy, remove secretions, and rule out pneumonia. The sternum is opened and a chest retractor placed. The thymus gland is dissected and the innominate vein is identified. The pericardium is

incised and stay sutures are placed. The aorta is mobilized, freeing it from the main pulmonary artery and the right pulmonary artery. The superior and inferior vena cavae are mobilized. The chest and abdominal teams must agree on where to drain the IVC.

When all teams are ready, systemic heparin is administered and the organs are perfused and removed (**Fig. 35.7** and Table 35.4).

Liver Retrieval

Prior to perfusion, the right colon and small bowel are mobilized to expose the entirety of the retroperitoneum, including the infrahepatic vena cava and aorta. The IMV is identified and cannulated for eventual portal perfusion. The superior mesenteric artery is identified and may be encircled at the root of the mesentery close to the aorta (**Fig. 35.8**). The gallbladder is opened and the bile is removed. The left lateral segment of the liver is mobilized and the gastrohepatic ligament is inspected for a replaced or accessory left hepatic artery. If an artery is noted, the surgeon must carefully dissect all of the branches from the proximal left gastric artery, staying close to the lesser curvature of the stomach. Failure to properly manage these small branches will result in a postreperfusion hematoma around this artery, potentially causing arterial thrombosis. The porta hepatis is palpated to assess the location of the arteries. If present, a replaced right hepatic artery is noted to the right and posterior to the common bile duct (**Fig. 35.9**).

The aorta is dissected at its bifurcation to facilitate proximal and distal control (**Fig. 35.10**). The surgeon should assure that there are no renal arteries from the distal aorta or iliac arteries. If there are, the cannulation should occur distal to these arteries to make sure they are flushed. The supraceliac aorta is exposed by retracting the caudate lobe and the left lateral segment of the liver to the right, grasping the crux of the diaphragm, and dividing it with electrocautery. Circumferential control of the supraceliac aorta is not needed, though sufficient exposure for occlusive clamping is a necessity (**Fig. 35.11**). When all teams are ready and heparin is administered, the aorta is clamped and ice is placed into both cavities. The abdominal surgeon works simultaneously with the thoracic surgeon (**Table 35.5**).

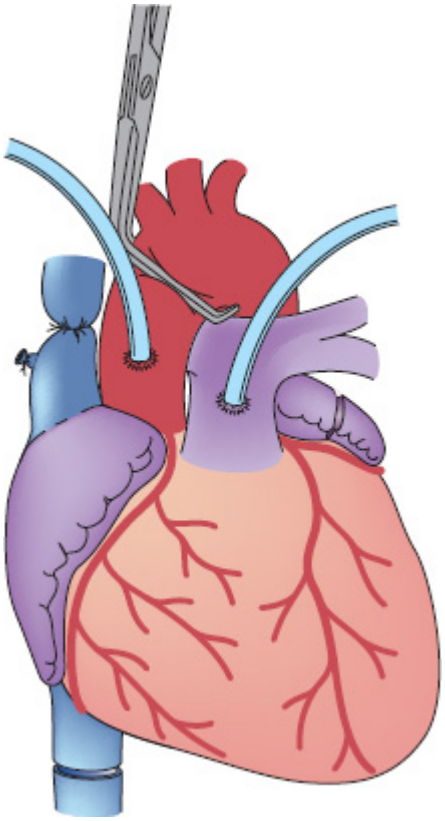

Figure 35.7 Cannulation for flushing and removal of heart then lungs.

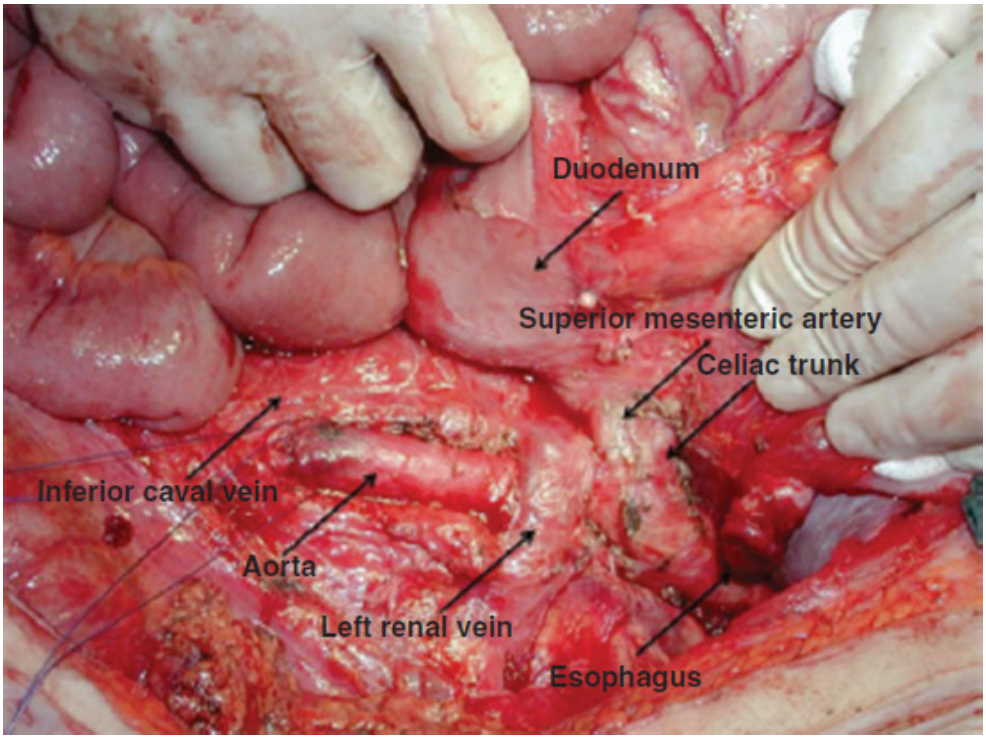

Figure 35.8 Exposure of retroperitoneum following Kocher and Cattell maneuvers.

Table 35.4 Steps for Flushing and Removal of Heart Then Lungs

- The aortic root is cannulated with a standard needle-tipped cannula.
- A purse-string suture is placed on the distal main pulmonary artery through which an "L"-shaped cannula is placed in the pulmonary artery. Prostaglandin is administered into the pulmonary artery.
- The superior vena cava is ligated; the inferior vena cava is incised at the level agreed upon by the liver surgeon.
- An incision is made to vent the heart and the aortic cross clamp is placed distal to the coronary perfusion cannula.
- The heart and lung cold perfusion is started and the organs are surrounded by ice.
- After the flush, the left atrium is divided, leaving an oval cuff of atrial tissue for the pulmonary veins on each lung.
- The pulmonary artery is divided, taking care not to damage the left main pulmonary artery. The aorta is divided just distal to the aortic arch and the heart is removed.
- The lateral and posterior borders of the pericardium are divided.
- The innominate vein is divided and the anterior trachea is identified and encircled as high in the chest as possible.
- The lungs are inflated and the main bronchus and left main bronchus are stapled. The trachea is divided proximal to the stale line and the inflated lungs are removed.

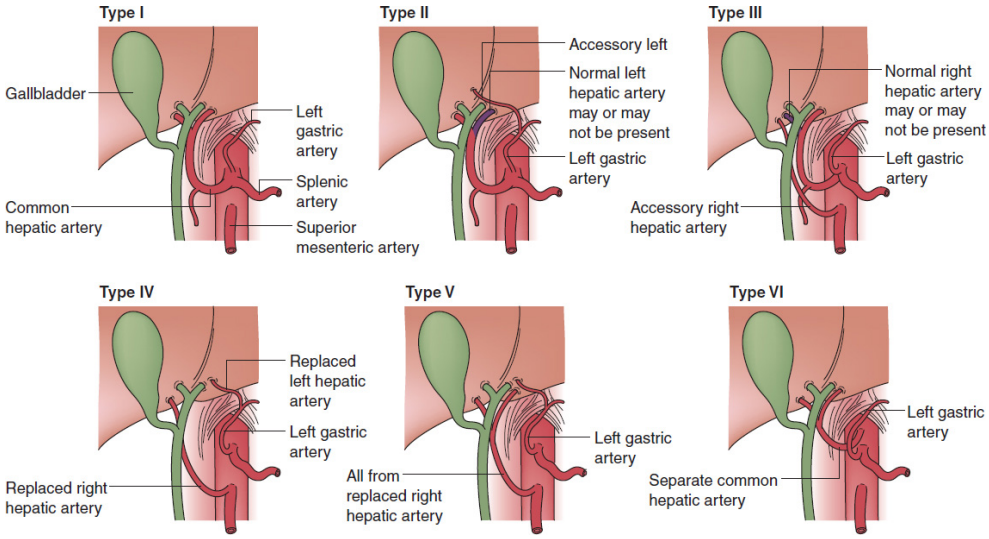

Figure 35.9 Variations in hepatic arterial anatomy. Lack of identification of this anatomy may jeopardize the transplant operation.

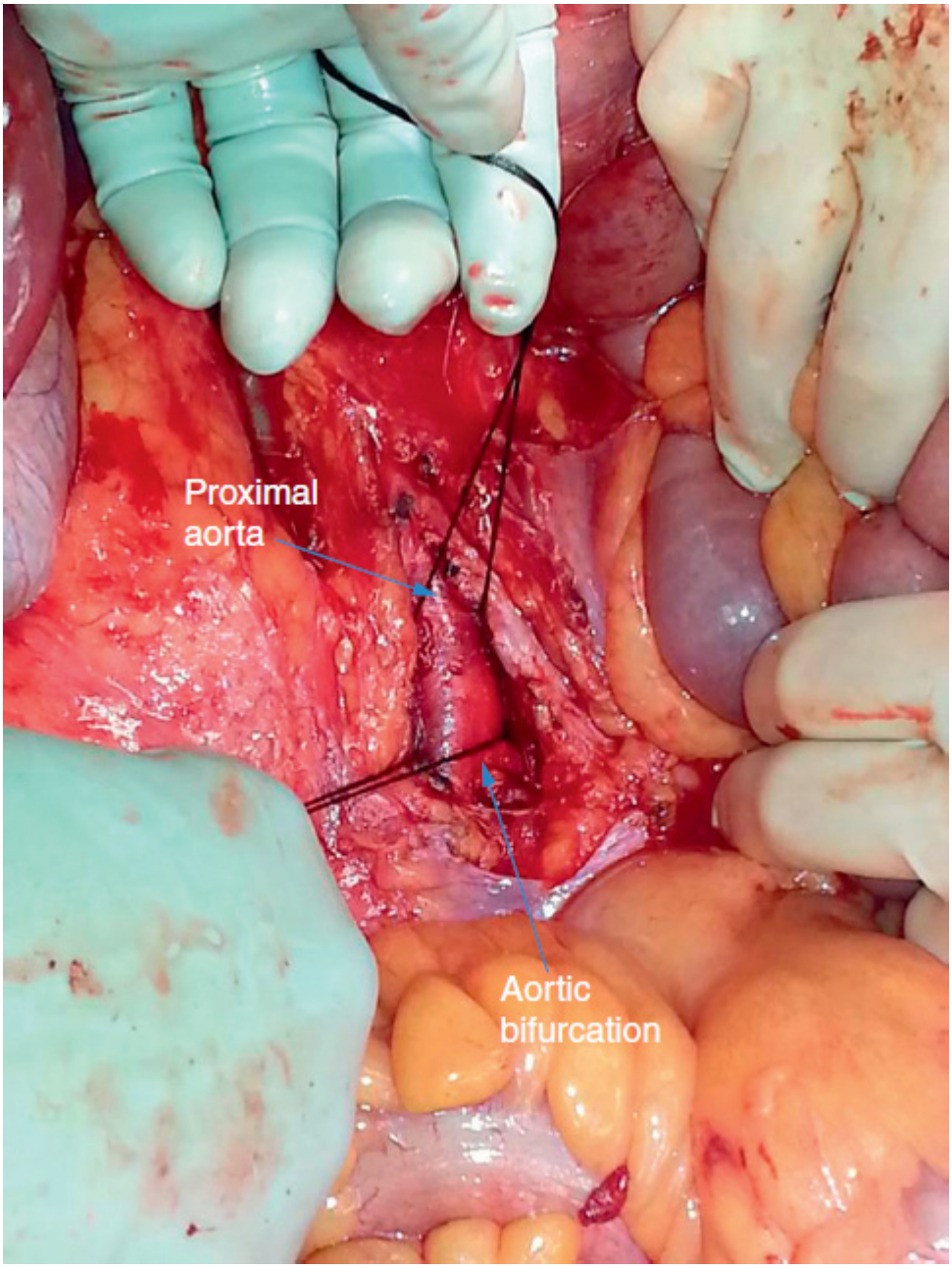

Figure 35.10 Exposure of the distal abdominal aorta in preparation for aortic cannulation.

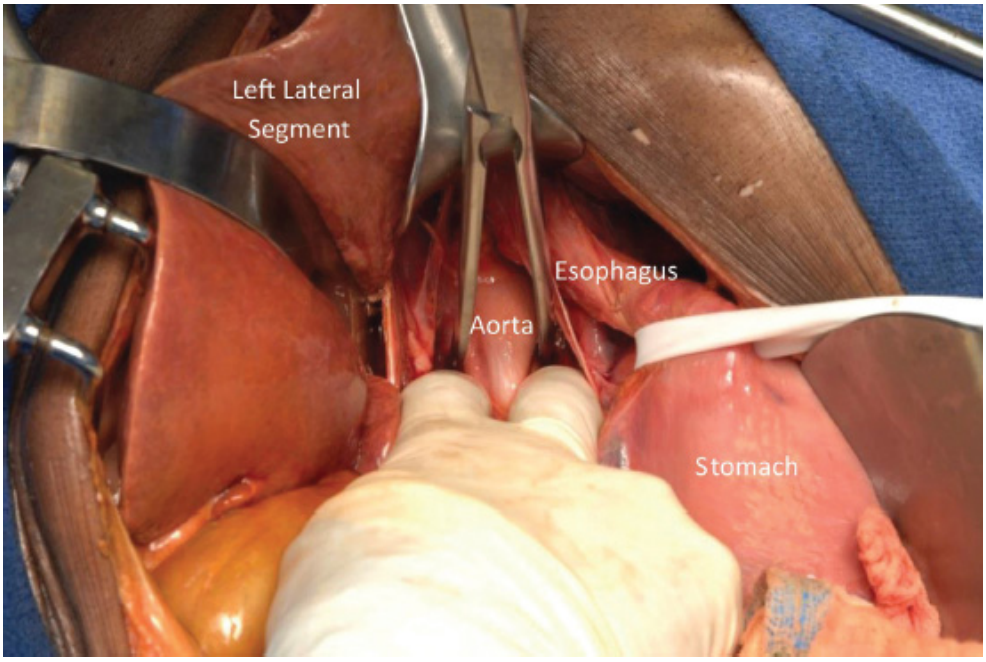

Figure 35.11 Vascular control of the supraceliac aorta in preparation for perfusion. (From Teixeira P, Magee G, Rowe V. Abdominal aorta and splachnic vessels. In: Demetriades D, Inaba K, Velmahos G, eds. *Atlas of Surgical Techniques in Trauma*. Cambridge: Cambridge University Press; 2020:268–285.)

Arterial anatomy has many variations and failure to identify the variation may jeopardize the transplant operation (**Fig. 35.9**). On occasion, dissection of the replaced right hepatic artery can jeopardize the pancreas allograft, but usually both teams can agree to an acceptable dissection plane. The reconstruction of the replaced right hepatic artery can be done in many ways; most common is an anastomosis to the splenic artery with the celiac artery as inflow.

Kidney Retrieval

Kidney retrieval is the final step in the procurement operation. Kidney procurement is significantly easier if the liver has been removed. If the liver has not been removed and will not be used to transplantation, the portal triad and the right diaphragm should be divided. This results in the liver falling into the right chest, greatly facilitating the kidney procurement.

Table 35.5 Steps for Flushing and Removal of Abdominal Organs

- The aorta is cannulated, the supraceliac aorta is clamped, and the abdominal organs are flushed with cold preservation solution.
- The liver is surrounded with ice and flushed with approximately 5 L of preservation solution in the aortic cannula and 2 L in the portal cannula.
- After the flush, the diaphragm is divided with a cuff around the suprahepatic inferior vena cava.
- The infrahepatic inferior vena cava is divided just above the renal veins.
- The bile duct and portal vein are divided.
- The aorta is divided between the SMA and the renal arteries.
- The liver is removed and the portal vein is flushed on the back table if not done in situ and placed in cold storage.

Prior to perfusion, the kidneys are mobilized posteriorly to facilitate packing with ice at the time of the cold perfusion. After flushing, the ureters are divided bilaterally in the pelvis and mobilized upward toward the kidney. The periureteral tissue should be left intact in order to maintain the blood supply to the ureter. The inferior vena cava and the aorta are divided at the bifurcation and the two vessels, along with the ureters are retracted superiorly, and the tissue posterior to the vessels is incised. The left renal vein is divided at the level of the inferior vena cava, leaving the entire inferior vena cava with the right kidney to allow for extension of the short right renal vein utilizing the cava. The kidneys are placed in cold storage or on a perfusion pump.

Pancreas Retrieval

All of the steps necessary for the liver retrieval up to the point of perfusion are completed. The pancreas must be mobilized out of the retroperitoneum with care. This can be done in the cold following perfusion, but mobilization prior to this allows for a careful examination of the organ as well as ensuring that the vasculature is ligated.

The short gastric vessels are divided to widely expose the pancreas. The gland is assessed for fatty infiltration or firmness, both of which may preclude transplantation. The retroperitoneal tissue inferior to the pancreas and behind the spleen is incised. The spleen is retracted both anteriorly and medially. The tissue behind the spleen and pancreas is divided until the aorta is reached. The duodenum is divided distal to the pylorus. A vessel loop is placed around the splenic artery and cold perfusion is initiated.

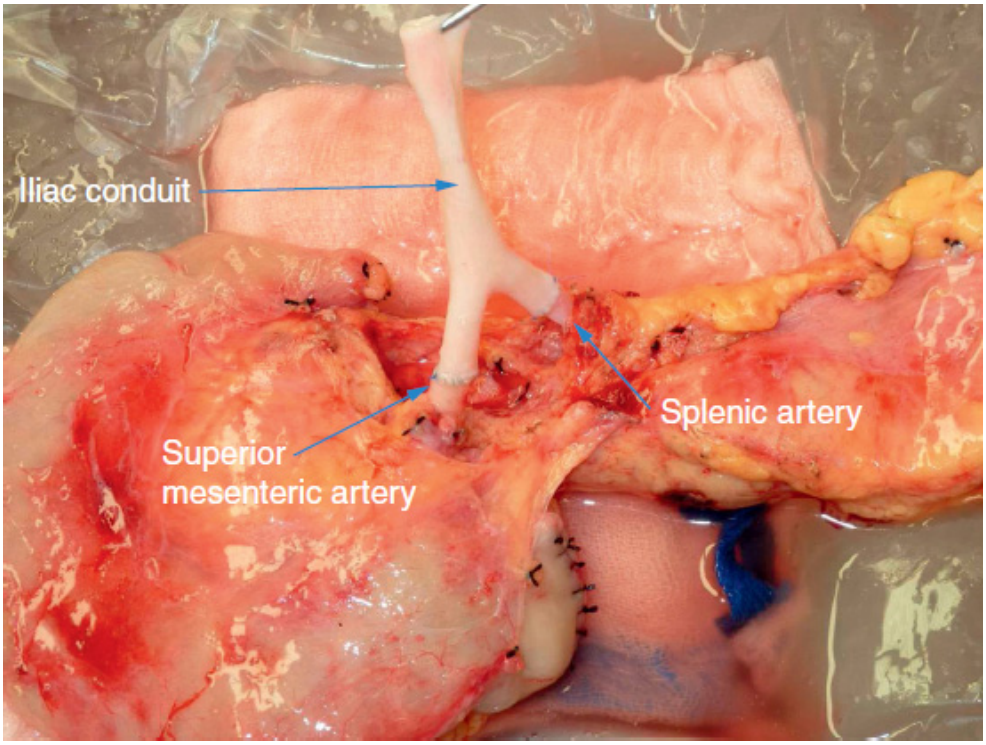

Figure 35.12 Donor superior mesenteric artery and splenic artery with arterial conduit created from the donor iliac artery.

Table 35.6 Key Concepts in Organ Preservation

Prevent thrombosis	▪ Anticoagulation of donor ▪ Rapid and complete organ flush
Maintain organ structural integrity	▪ Maintenance of cell membrane lipid bilayer ▪ Cold storage results in conformational changes of cell membrane resulting in cell swelling ▪ Hypertonic preservation solutions mitigate some of these effects
Maintain ionic composition	▪ Preservation solution electrolyte composition is similar to intercellular composition of Na^+ and K^+ ▪ H^+ accumulated as a result of anaerobic glycolysis ▪ Preservation solution buffers H^+ effects
Maintain cellular energy	▪ Hypothermia reduces metabolism 12-fold ▪ Hypothermia affects the activity of mitochondrial enzymes ▪ Mitochondrial dysfunction results in changes in cellular energy
Reperfusion injury—oxygen-free radicals	▪ The majority of organ injury happens at reperfusion and not during cold ischemia ▪ The sudden availability of O_2 results in the production of reactive oxygen intermediates (O^{2-} and OH^-)

	▪ Free radicals cause cellular injury, largely through lipid peroxidation ▪ Glutathione protects against peroxidation and is useful in preservation solutions
Reperfusion injury—cytokines	▪ Tissue injury results in the release of cytokines ▪ Tumor necrosis factor, interferon gamma, interleukin-1, and interleukin-8 are released at reperfusion ▪ Cytokine exposure results in the upregulation of adhesion molecules, resulting in platelet plugging and leukocyte adherence to the endothelium

After perfusion, the pancreas is removed in situ or en bloc along with the liver. The proximal jejunum is divided as it exits the retroperitoneum. It is critical that the root of the mesentery is securely divided with a vascular stapler. Division of the portal vein, the SMA, and splenic artery should be done in communication with the liver surgeon (**Fig. 35.5**). The iliac artery is retrieved for creation of the Y graft for the transplant operation. The iliac vein is retrieved in case an extension graft is needed for the portal vein (**Fig. 35.12**).

NEW METHODS IN ORGAN OPTIMIZATION AND PRESERVATION

5 Organ retrieval and storage result in significant alterations in the homeostasis of the organ. The degree of organ preservation injury contributes to the degree to which normal organ function is delayed or prevented following transplantation. Organ preservation injury is largely mediated by

ischemia and hypothermia. The duration when the organ is in cold storage is termed "cold ischemic time." Minimizing this time as well as carful organ preservation is critical for successful outcomes (**Table 35.6**).

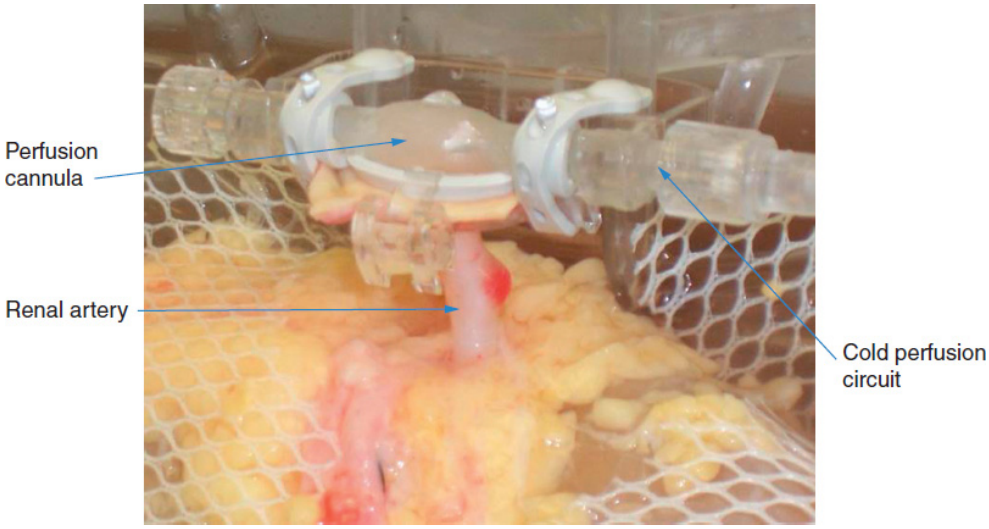

Figure 35.13 Renal machine-cold perfusion circuit with renal artery cannula.

Cold ischemia and subsequent warm reperfusion cause much of the cellular organ damage. As a result, novel strategies for warm perfusion of organs are being used. These techniques involve perfusion with blood or a bloodlike analog with or without oxygenation. Trials of ex vivo liver perfusion machines appear to enhance preservation of donor organs, extending viability and potentially evaluating function in organs previously considered too marginal for transplant.[16] These perfusion techniques remain investigational at this time but offer promise of optimized organ function and potentially expanded donor pool as marginal organs may be rehabilitated.

Machine-cold perfusion is now commonly done in renal transplantation and in some regions is the standard of care for renal preservation. Some of the injury during cold ischemia and reperfusion is related to the accumulation of metabolites; perfusion may mitigate these effects by washing out deleterious metabolites and by maintaining patency of the microvasculature of the organ (**Fig. 35.13**).[17]

Several strategies have been developed to mitigate the effects of ischemia on organs obtained following DCD retrieval procedures. These include the infusion of antifibrinolytics into the donor organ at the time of transplant.[18]

Early reports suggest these strategies result in fewer post liver transplant biliary complications.

Another approach is to resume normothermic perfusion of the abdominal viscera following death using extracorporeal membrane oxygenation (ECMO) circuit. This strategy has several benefits including enabling withdrawal of support in the ICU with the family present, resuscitation of the organs following the agonal period, and avoidance of urgency in the retrieval operation.

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36

Kidney Transplantation

Jayme E. Locke and Peter G. Stock

Key Points

1. The presence of antidonor HLA antibodies is a relative contraindication to kidney transplantation, and is screened by a "virtual cross-match" with increased frequency.
2. Methods to expand living kidney donation include kidney paired exchange and incompatible kidney transplantation.
3. Methods to expand the deceased-donor pool of kidneys include the use of donation after cardiac death donors, high kidney donor profile index kidneys, hepatitis C+ kidneys, and HIV+ kidneys.
4. The etiology of kidney disease resulting in end-stage failure, and the necessity for transplantation is led by glomerulonephritis, diabetes, and hypertension.
5. As a result of the increasing wait times across the United States, the presence of a cardiovascular system which will tolerate a major operation is the biggest barrier to successful transplantation.
6. The kidney transplant is heterotopically placed in the extraperitoneal iliac fossa.
7. Surgical complications of kidney transplantation include vascular, urologic, lymphocele, and wound problems.
8. Hyperacute rejection is humorally mediated by preformed anti-HLA antibodies. Hyperacute rejection occurs within minutes to hours following reperfusion of the kidney.
9. Acute cell-mediated rejection most typically occurs between 1 week and 3 months following transplantation.
10. Chronic rejection leads to loss of graft function over the course of months to several years.

INTRODUCTION

Kidney transplantation has evolved to become the preferred therapeutic modality for patients with end-stage renal failure. Improved patient survival and quality of life as compared with dialysis has been established, with cost-effectiveness achieved after a minimum of 18 months of allograft function. The importance of minimizing time on dialysis, compounded by the exponential growth of patients on the wait list, has led to several strategies to increase the number of deceased- and living-donor organs in an effort to decrease waiting time and mortality on the wait list. These new strategies have been the focus of clinical research in kidney transplantation and will be discussed in this chapter. Other important topics that will be reviewed include immunologic considerations specific to kidney transplantation; preoperative assessment of kidney allograft recipients; the standard surgical approach in kidney transplantation and advances in laparoscopic technology for the donor; current strategies in immunosuppression; management of the technical and immunosuppressive complications; new kidney allocation policies affecting wait list management; and future trends.

IMMUNOLOGY OF RENAL TRANSPLANTATION

The immunologic response to allografted tissue is well defined and under the influence of both T- and B-cell–derived reactions. The cells and cytokines responsible for rejection vary with time post transplant (hyperacute, acute, and chronic rejection) and have a differential response to currently available immunosuppressive agents.

The HLA system is made up of well-defined antigens present on most cell types that are genetically determined for each patient and are termed the *major histocompatibility complex*. These genes reside on chromosome 6 and are distributed in a mendelian fashion to offspring. The HLA system includes several loci, but the most commonly characterized are the HLA-A, HLA-B, and HLA-D regions. Given that each human has two alleles for each locus, there are six potential HLA antigens of clinical significance. These are characterized using tissue-typing techniques and can be used to determine the degree of matching between a donor and potential recipient, that is, one- to

six-antigen match. Improved graft survival is seen when the degree of matching reaches the six-antigen level.

Class I antigens include the HLA antigens A, B, and C, whereas class II antigens include the DP and DR loci. Class I antigens act as targets for cytotoxic T lymphocytes, and class II antigens are important for antigen presentation. Class II antigens are also responsible for triggering lymphocyte proliferation in the mixed lymphocyte culture system.

1 Before a kidney transplant is undertaken, histocompatibility of the donor and recipient is determined. HLA matching is not a prerequisite for proceeding with transplantation. However, the presence of recipient antibodies directed against the donor HLA usually precludes transplantation. Standard pretransplant workup consists of several assays that will help to determine future compatibility with a potential donor. First, donors and recipients undergo tissue typing, which involves characterization of their respective HLA type. Secondly, recipient serum is tested against a panel of antigens that contains the known HLA types, to identify anti-HLA antibodies. The sensitivity for detecting anti-HLA antibodies continues to improve and newer technology uses single antigen beads to detect antibodies against a specific HLA antigen. The amount of reactivity that a potential recipient has against a panel of HLA antigens is indicative of the degree of sensitization. Based on the number of anti-HLA antibodies detected, a calculated percent reactive antibody (cPRA) can be estimated. A cPRA of 70% would suggest that the potential recipient would have anti-HLA antibodies against 70% of the potential-donor pool. Sensitization to HLA antigens occurs as a result of previous exposure to foreign HLA antigen either from pregnancy, previous blood transfusion, or a previous organ transplant. A patient who is highly sensitized is more difficult to transplant because of the greater likelihood of having antibodies to a potential donor.

The last critical test performed prior to transplantation is commonly known as the *final cross-match*. This final cross-match can be performed in several ways. Recipient serum samples collected at different times are mixed with donor lymphocytes in a culture system. This assay will detect preformed cytotoxic antibodies that would result in a hyperacute rejection if the transplantation were performed (see Rejection, later). A more sensitive method of detecting these antibodies uses a fluorescent-activated cell scanner cross-match and is commonly used when evaluating potential recipients who

are highly sensitized or receiving second transplants. Many transplant centers have adopted "virtual cross-matching" based on the detection of anti-HLA antibodies present in a given recipient. The most sensitive technology will be used to detect the presence of anti-HLA antibodies in a given recipient. Based on these antibodies, each recipient will have a list of unacceptable donor antigens. Compatibility with each donor will be determined in the absence of the serum-based final cross-match by eliminating a potential donor based on the presence of unacceptable antigens. This strategy facilitates an expedited transplant and minimization of cold ischemia times, as it avoids the additional time and expense associated with the serum-based final cross-match. The use of the virtual cross-matching is particularly beneficial for determining potentially compatible kidneys allocated to highly sensitized recipients, a scenario occurring with increasing frequency as a result of the new kidney allocation algorithm initiated in December 2014.[1]

In general, kidney transplantation is done between ABO-compatible donor and recipients using the same guidelines as for blood transfusion. However, several groups have reported successful kidney transplantation across ABO blood group barriers, using aggressive pretransplant immunosuppression, plasmapheresis to decrease anti-ABO titers, and in some cases splenectomy.[2,3] This strategy has been implemented in the United States as a result of the marked increases in the waiting times for blood group O and B recipients.[4] However, ABO-incompatible transplants in the United States have not enjoyed the same success as in Japan, where ABO-incompatible living-related donor transplants are the only option for transplantation. Based on the better results observed in ABO-compatible transplants in the United States, most centers have opted to participate in the paired exchange program (see below) rather than proceed with ABO-incompatible transplants. The exception to this is transplantation of blood type A2 and A2B–deceased-donor allografts to blood type B recipients, provided the anti-A titers are acceptably low. In this circumstance, outcomes are comparable to ABO-compatible transplants, and this exception has become part of the United Network for Organ Sharing (UNOS) allocation system in order to decrease the length of waiting times for Blood Type B recipients.[5]

THE DONOR POOL: LIVING DONORS, DECEASED DONORS, AND DONATION AFTER CARDIAC DEATH

There is marked improvement in graft survival for both living and deceased donors when a transplant can be completed before the initiation of dialysis.[6] The significantly better outcomes achieved with preemptive transplantation and minimizations of dialysis times have given rise to several strategies to increase the number of available kidneys.

Living Donors

The first long-term success in kidney transplantation over 60 years ago involved a live-donor transplant between twin brothers. Introduction of laparoscopic donor nephrectomy further revolutionized the field. Despite initial concerns about the safety and efficacy of the laparoscopic technique for the donor procedure, morbidity and mortality rates (0.03%) remain low and comparable with those of the open technique.[7,8]

The evaluation of a potential living kidney donor includes a comprehensive medical, surgical, and psychosocial evaluation. Diabetes, hypertension, and cardiovascular disease generally rule out a potential donor.[9] Testing of a potential donor also involves anatomic definition of the two kidneys and is typically done with either a computed tomography angiogram or MR angiogram, both of which avoid the arterial needlestick and catheters associated with a conventional angiogram. The results of these studies are used to detect any anatomic abnormalities that would exclude a donor and to decide which kidney will be removed. In general, the left kidney is favored for transplant because it has a longer renal vein.

2 Several strategies are currently being considered to increase the frequency of living donation. Potential donors with well-controlled hypertension on a single antihypertensive agent are being considered, although this remains controversial. A national exchange system is currently being designed that matches living donors who were incompatible with their intended recipient (either because of ABO incompatibility or a positive cross-match test) with other recipients with incompatible living donors. Such

exchange systems have already been successful on a regional and national level, and extending this to a single national system will permit many more successful exchanges and further expand the living-donor pool.[10] In addition for those pairs unable to identify a compatible transplant via paired exchange, an important strategy currently being implemented in the United States, as well as internationally, involves the use of desensitization protocols to facilitate transplantation across a known positive anti-HLA cross-match. These protocols may involve pretransplant infusion of gamma globulin in the recipient to bind circulating antibody, plasmapheresis of the recipient to remove circulating antibody, and/or the use of agents, such as rituximab, to decrease antibody production.[11] Lastly, a hybrid approach for the highly sensitized recipient with a cross-match–incompatible donor could involve finding a kidney that is "less incompatible" through an exchange program, and then converting the positive cross-match to a compatible cross-match with desensitization techniques.

Deceased Donors

Procurement of kidneys from brain-dead deceased donors has not increased at the same pace as the rapid growth of the national wait list. Although most deceased donors are brain-dead, there has been an increased use of kidneys from donors who do not meet the strict definitions of brain death but have cardiopulmonary support withdrawn because of a severe brain injury or high spinal cord injury, with little hope of living without the use of ongoing mechanical ventilation and/or the possibility of existing in a persistent vegetative state. Organs are recovered after withdrawal of support, once the heart stops beating, hence the terminology of *donors by cardiac death* or *DCD donors*. Usually support is withdrawn in a controlled setting so that the time of warm ischemia and poor organ perfusion can be minimized. Minimizing the time from cessation of the heart to perfusion of organs with preservation fluid requires an experienced procurement team, and the successful use of these organs is dependent on rapid procurement. [3] Kidneys procured from DCD donors are proving to be an important source of donor kidneys, and studies have demonstrated comparable graft success between kidneys procured from DCD donors and brain-dead donors, although the incidence of initial delayed graft function is higher in DCD

kidneys. The percentage of DCD donors in the United States has progressively increased over the last decade and presently represents about 10% of deceased donors.[12]

Placement of deceased-donor kidneys is guided by a series of complex allocation rules established by the UNOS. Donor kidneys are now assigned a kidney donor profile index (KDPI) score which is used to define donor organ longevity with a lower score corresponding to better-predicted survival of the kidney (better-quality kidney). The new allocation system attempts to match the predicted longevity of the deceased-donor organ quantified by the KDPI with the estimated posttransplant survival (EPTS) of the recipient. The top 20% of kidneys (KDPI scores less than 20%) will be transplanted to recipients with longest EPTS. In the new allocation scheme, the highest KDPI kidneys (KDPI >85%) will be allocated to recipients who have consented to receive an expanded criteria donor (ECD). Highly sensitized patients will receive a significant number of allocation points, so if in the rare event that a compatible kidney becomes available, that kidney will be allocated to the compatible highly sensitized recipient. Highly sensitized recipients with cPRAs of 99% or 100% will get access to the regional and national lists, respectively, to increase the chances of finding a compatible kidney. Finally, waiting times will be backdated to the time of the initiation of dialysis, although patients can still be listed when the glomerular filtration rate drops below 20 mL/min.[13]

Further Strategies for Increasing the Number of Donor Kidneys

Many of the unique approaches for increasing the number of potential living donors, including kidney paired exchange and incompatible transplantation, have been previously discussed in the chapter. Additional strategies include programs aimed at separating the advocacy role from the recipient and including programs such as the Johns Hopkins Champion Program and the University of Alabama at Birmingham Living Donor Navigator Program. Both programs have demonstrated early success, but widespread adoption of such programs remains limited.[14,15]

Further strategies have recently been implemented to expand the number of kidneys procured from deceased donors. In addition to the use of kidneys from DCD donors described earlier, transplant centers have considered using kidneys from donors that are less than optimal (KDPI ≥85%), previously designated as ECDs. These kidneys clearly had a shorter survival compared to younger, healthier donors and therefore potential recipients are required to give consent to receive these kidneys before transplant. The advantage to certain patient groups who were predicted to do poorly on dialysis (i.e., older patients or patients with diabetes) was an increased overall patient survival if they received a timely transplant rather than wait a prolonged time on the list. As mentioned above, the new allocation system also affords the opportunity for blood group–incompatible kidney transplantation in select scenarios, specifically blood group A, subtype A2 donors into blood group B recipients, with the overall goal to increase access to transplantation for ethnic minorities, which have a disproportionate number of blood group B donors. Most recently, in the era of direct-acting antiviral therapy with 99% sustained viral response, kidneys from hepatitis C donors are being offered to select hepatitis C–naive recipients.[16] Initial results are promising, but future work is needed. Finally, an additional source of potential deceased-donor kidneys is now available to HIV+ candidates. With the passage of the HIV Organ Policy Equity Act, HIV+ individuals may donate their organs upon their death. HIV+ to HIV+ kidney transplantation, which is still performed under research protocols in the United States, has met with good success and excellent long-term outcomes abroad.[17]

THE TRANSPLANT PROCEDURE

Recipient Preoperative Assessment

4 The etiologies of kidney disease resulting in end-stage failure and the necessity for transplantation are led by glomerulonephritis, diabetes, and hypertension (**Table 36.1**).[12] Because of the high incidence of cardiovascular disease associated with many of these conditions, most notably diabetes, a careful assessment of the cardiovascular status of the potential recipient is critical. 5 As a result of the increasing wait times across the United States,

the presence of a cardiovascular system which will tolerate kidney transplantation is the biggest barrier. For patients at risk, this assessment should include at a minimum an echocardiogram and an exercise or pharmacologic stress test as a screen for reversible ischemia requiring cardiac catheterization. Controversy remains with regard to the accuracy of noninvasive studies in terms of identifying significant disease of the coronary arteries, particularly in diabetic patients. Nonetheless, for most centers this remains the standard screening strategy, and updated studies should be obtained within 1 year of the transplant procedure. If either coronary artery bypass or stenting has taken place in preparation for renal transplantation, follow-up angiograms and/or stress tests should be repeated within 1 to 2 years of the actual transplant. If stenting of the coronary arteries is required, patients with drug-eluting stents will commonly require clopidogrel (Plavix) for an extended period of time. Although controversial, many centers will proceed with transplantation while recipients are on Plavix, after a waiting period of 6 months following the stenting procedure.

Although the evaluation of potential recipients is focused on the assessment of cardiovascular status, further studies must exclude malignancies and infections that would contraindicate transplantation and immunosuppression. Potential kidney recipients who are infected with hepatitis C should be evaluated by a hepatologist to determine the risks of immunosuppression causing progression to end-stage liver disease. Potential kidney recipients with evidence of advanced liver disease should be evaluated for a combined liver and kidney transplant. For patients with less advanced liver disease, consideration could be given to treatment with newer antiviral drugs before proceeding with kidney transplantation to provide the opportunity for viral clearance.[18] Kidney transplantation was previously contraindicated in people with HIV infection secondary to concerns of exacerbating an already immunologically compromised state. Recent advances in antiretroviral therapy and the ability to provide effective prophylaxis against opportunistic infections have prompted several centers to perform transplantation in people with end-stage renal disease and HIV infection. Early results suggest that progression of HIV to AIDS has not been seen following transplantation and immunosuppression, with early allograft success rates comparable to those in non–HIV-positive recipients.[19] Potential

patients with a previous history of tuberculosis or conversion to purified protein derivative positivity should be evaluated for active disease.

Colonoscopy, mammography, and Pap smear should be performed as dictated by age-specific standard guidelines. For most malignancies, a disease-free interval of 5 years is recommended before kidney transplantation. Controversy exists about pretransplant waiting times for certain malignancies, such as early-stage breast cancer or prostate cancer, and some centers will not require any pretransplant waiting. Similarly, pretransplant wait times are probably not necessary for nonmelanoma skin cancers and early-stage renal cancers. For patients with congenital abnormalities as the cause of renal failure, a complete workup of the genitourinary systems is necessary, including urodynamics and voiding cystourethrograms. These studies are particularly important in children with end-stage disease resulting from posterior urethral valves, to ensure that the bladder will serve as an adequate conduit for the kidney transplant. For patients with severe reflux disease and chronic pyelonephritis, native nephroureterectomy may be required to prevent posttransplant infection secondary to chronic reflux into the native ureters. For patients with inadequate bladder capacity and function, pretransplant-reconstructive procedures such as ileal augmentation or ileal conduits may be required.

Table 36.1 Etiology of Renal Disease as Indications for Renal Transplantation, Ranked in Order of Prevalence

Diabetes mellitus (types I and II)
Hypertension
Polycystic kidney disease
IgA nephropathy
Chronic glomerulonephritis
Focal sclerosis
Systemic lupus
Membranous glomerulonephritis
Pyelonephritis
Focal segmental glomerulosclerosis
Congenital obstructive uropathy
Nephritis
Alport syndrome
Hypoplasia, dysplasia
Wegener granulomatosis
Postinfectious glomerulonephritis
Obstructive uropathy
Hemolytic uremia
Membranoproliferative glomerulonephritis
Goodpasture syndrome
Membranous nephropathy
Analgesic nephropathy
Prune belly syndrome
Medullary cystic disease

Henoch–Schönlein purpura
Nephronophthisis
Scleroderma
Sickle cell anemia
Amyloidosis
Oxalosis

Adapted from Cecka JM. The OPTN/UNOS renal transplant registry. In: Cecka JM, Terasaki PI, eds. *Clinical Transplants 2003*. Los Angeles, CA: UCLA Immunogenetics Center; 2004:1–12, with permission.

For patients with suspected clotting disorders based on a previous history of thromboembolic events (frequent clotting problems with dialysis access) or diseases associated with an increased frequency of clotting disorders (i.e., lupus), a hematologic workup is necessary to determine the necessity for anticoagulation at the time of the transplant. The length of time for anticoagulation is dependent on the severity of the clotting disorder and a history of a previous thrombotic event. This workup should include a determination of serum levels of protein C, protein S, anticardiolipin antibody, factor V Leiden, antithrombin III levels, and the G20210 A prothrombin gene mutation.

Living-Donor Nephrectomy: Open and Laparoscopic

A living kidney donor operation is a unique surgical procedure for two reasons. First, the donor has no medical reason to be in the operating room, and the process is driven only by his or her willingness to help another person with the gift of donation. Second, the removed tissue must be in perfect condition because it will be reimplanted into the recipient. These two features, therefore, necessitate that the donor operation is done safely and well. The original donor operation was done through a generous flank incision, allowing for good exposure and careful dissection of the renal vessels. Unfortunately, this flank approach generally left a large incision,

with its accompanying morbidity, pain, and sometimes adverse cosmetic result. The development of the laparoscopic procedure to remove kidneys has revolutionized the field. With the explosive growth and dissemination of this procedure, it has now become the standard for donor nephrectomy.

The procedure is most commonly done through a transperitoneal approach, although some surgeons prefer to remain retroperitoneal. Once the operative space is expanded with carbon dioxide gas and the scope is inserted, most commonly two to three additional ports are placed to allow for the passage of instruments to dissect the kidney (**Fig. 36.1**). Some centers also favor the use of a gastight "hand port," which allows placement of the surgeon's hand in the operative space to assist in exposure and to have available if sudden bleeding is encountered. Once the kidney vessels are transected and the vessel stumps are controlled by laparoscopic staples, the kidney can be removed through a 2- to 3-in incision, which can be placed in a position that leaves minimal scarring and avoids cutting muscle tissue. Most commonly this is via a Pfannenstiel incision, and recently the use of natural orifice approaches has been described. Additionally, some centers have adopted the use of a robotic-assisted technique, to facilitate the dissection of important vascular structures. Donors who undergo the laparoscopic procedure typically have reduced pain medicine requirements, have a slightly shorter hospital stay, and are able to return to their usual activities sooner.[7,8]

The safety of this relatively new procedure has been established, in addition to the demonstration that kidneys recovered through a laparoscopic approach function as well as kidneys removed in an open operation. There has been an increased interest in live donation, coincident with the introduction of the laparoscopic procedure, suggesting that this procedure has removed some of the disincentives of the donation process.

Recipient Operative Procedure

6 The kidney transplant is heterotopically placed in the extraperitoneal iliac fossa. Attention to detail is imperative to optimize immediate graft function and avoid technical complications resulting in loss of the kidney transplant.

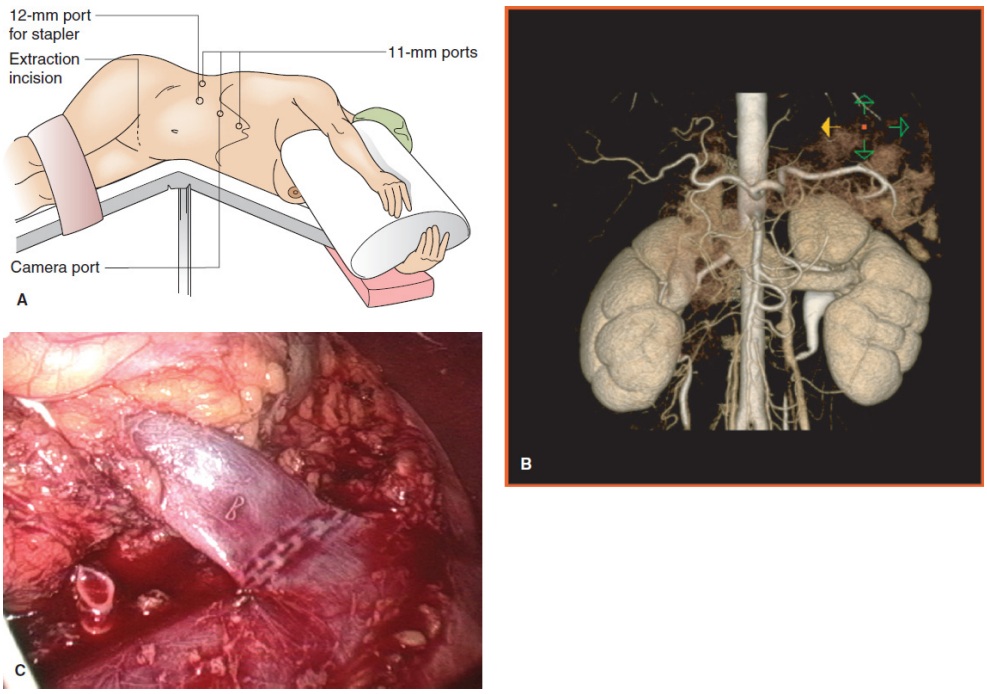

Figure 36.1 **A:** The laparoscopic donor procedure is performed with the donor in a lateral position, typically using three to four ports, with extraction of the kidney through a 6- to 8-cm incision. **B:** Preoperative computed tomography angiogram revealing the arterial and venous anatomy. **C:** Intraoperative photograph of laparoscopic view of right kidney just prior to transection of the renal vein. The artery has already been divided.

The operation is initiated by exposure of the iliac fossa through a curvilinear incision and can be done on either the right or left side. The incision extends from 1 cm above the symphysis pubis to approximately 2 cm medial to the anterior iliac spine (**Fig. 36.2**). The fascia is divided along the lateral border of the rectus sheath, and the contents of the peritoneal cavity are reflected cephalad and medially, exposing the iliac vessels in the retroperitoneum. Lymphatics overlying the iliac vessels are ligated and divided to prevent the development of lymphoceles. In males, the spermatic cord is secured with a vessel loop and can be retracted away from the operative field. In females, the round ligament is suture ligated and divided. The inferior epigastric artery and vein are typically divided to prevent potential compression of the transplanted ureter. Placement of a mechanical retractor should avoid compression of the iliac artery and vein as well as the femoral nerve to prevent neuropraxias.

The living- or deceased-donor kidney is inspected for the presence of multiple vessels, duplication of the urinary collecting system, and parenchymal abnormalities. The artery and vein are dissected from surrounding structures to provide the necessary length for transplantation. In the case of multiple arteries, a decision must be made as to whether to perform ex vivo reconstruction to achieve a single implantable conduit versus implanting the vessels separately. This decision is in part dependent on the quality of the recipient vessels and an assessment as to whether the anastomosis of multiple vessels directly into the recipient would require an unacceptable period of warm ischemia to the kidney. In general, in an adult the anastomosis of the renal artery and vein are performed in an end-to-side fashion to the external iliac vessels, although occasionally the presence of atherosclerotic disease requires transplantation to the common iliac vessels. In children who weigh less than 20 kg, or for third transplants in adults, an intraperitoneal approach is used and the vascular anastomoses are frequently performed to the aorta and inferior vena cava. For kidneys from deceased donors, a Carrel patch of aorta is used to prevent stenosis and to provide a common patch for multiple arteries. Warm ischemia time should be minimized to prevent delayed graft function. Ensuring adequate intravascular volume and stable hemodynamics at the time of reperfusion is extremely important to achieve optimal function of the transplant.

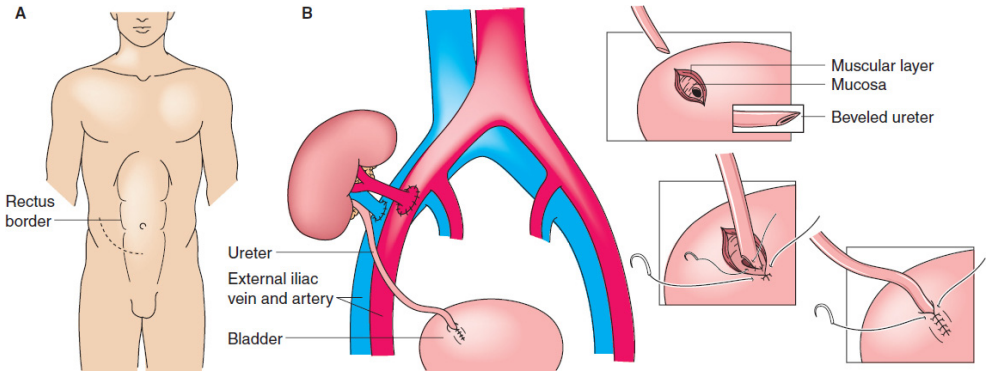

Figure 36.2 **A:** Curvilinear iliac fossa incision used for the kidney-transplant recipient procedure. **B:** Vascular anastomoses completed between the recipient external iliac artery and vein and donor renal artery and vein. *Insets:* ureteral anastomosis performed using the external ureteroneocystostomy technique.

The reimplantation of the ureter is most frequently performed through an extravesicular technique. Following positioning of the revascularized kidney

in the iliac fossa and assurance of hemostasis, the ureter is shortened to permit a tension-free anastomosis with adequate blood supply to the distal ureter. In men, the ureter is placed under the spermatic cord to prevent ureteral obstruction. The bladder is distended to identify a suitable area for ureteral implantation on the dome of the bladder, and a cystotomy is made at this site. An anastomosis between the mucosa of the bladder and transplanted ureter is constructed using an absorbable suture to prevent stone formation. A second layer of the bladder musculature is closed over the distal portion of the ureter to prevent reflux during micturition.

There are alternative techniques to reimplant the ureter, including the Politano–Leadbetter transvesical ureteroneocystostomy. This technique involves tunneling the ureter through the bladder wall from the inside of the bladder. This technique is still preferred by some surgeons who believe the long-term prevention of reflux is superior with the transvesicular approach. However, this technique requires a second cystotomy, and posttransplant hematuria is more common than with the extravesicular technique. A third technique for ureteral implantation in recipients with normal native ureters is ureteroureterostomy over a double-J stent. In general, this technique is reserved as a salvage procedure for reimplantation of transplanted ureters with distal strictures secondary to ischemia. It can also be used as a primary technique if there are questions regarding the blood supply to the distal ureter at the time of transplant. This technique is preferred if the donor ureter was damaged or inadvertently stripped of its blood supply at the time of procurement but is dependent on the availability of normal native ureters to serve as an adequate conduit. The routine placement of a double-J stent is center dependent, with some centers reserving placement of the stent for challenging extravesicular anastomosis to poor-quality bladders.

The surgical procedure has changed little over the last 60 years, with the exception of limited reports of implantation of the kidney with the use of a robotic-assisted laparoscopic approach. The purported advantage is smaller incisions, which appear to have an advantage in obese patients, avoiding some of the frequent wound complications. Widespread adaptation of this technique has not occurred.[20]

COMPLICATIONS

Early Graft Dysfunction

Most kidneys begin to function immediately after implantation, especially in the case of a living donor. When the initial function results in only a slow drop in serum creatinine, the diagnosis of slow graft function is made. When dialysis is needed in the first week because of poor function, the diagnosis of delayed graft function is made. Delayed graft function typically occurs in 15% to 30% of deceased-donor transplants. The diagnosis of slow graft function or delayed graft function is important to establish because other problems, such as rejection, vascular occlusion, or ureteral obstruction, can also result in low urine output and need for dialysis. These other causes must be eliminated before the diagnosis of slow graft function or delayed graft function can be made.

In the immediate postoperative period, careful attention to fluid status is critical. In cases of immediate graft function, fluid orders should include replacement for urine output as well as a maintenance fluid rate. This approach ensures that the patient does not become volume depleted and compromise perfusion to the new kidney. In cases of delayed graft function, fluid should be restricted and dialysis instituted when electrolyte imbalance or fluid overload are evident.

A decrease in urine output in the early postoperative period requires immediate diagnostic and therapeutic intervention. A stepwise algorithm to assist in diagnosing the etiology of oliguria is shown in **Figure 36.3**. Once mechanical obstruction of the indwelling Foley catheter has been excluded by irrigation, the volume status of the patient should be assessed. Fluid replacement to restore intravascular volume should be initiated in the volume-depleted patient.

Radiologic evaluation using various imaging techniques is required if urine output remains low in the face of adequate volume status. Ultrasonography is most helpful to diagnose ureteral obstruction caused by technical complications at the anastomosis or fluid collections that may be obstructing the ureter by extrinsic compression. With the addition of duplex and color Doppler imaging, blood flow to the kidney can be evaluated and technical problems with the vessels can be assessed. Nuclear medicine

techniques are also valuable for assessing renal function. Technetium-99m diethylenetriamine pentaacetic acid (DTPA) and iodine-131 iodohippurate (Hippuran) are the two major radionuclides used in the evaluation of renal allograft function. DTPA renal scans evaluate the vascular flow pattern of the kidney as well as the gross anatomy of the ureter and bladder. Scans are performed over 30 minutes, with uptake of contrast within 6 seconds indicating adequate flow to the graft. Peak activity in the parenchyma should be reached within 2 minutes, followed by a gradual decline in radioactivity in the renal parenchyma and an increase in radioactivity in the urinary collecting system and bladder. Iodine-131 iodohippurate scans are more sensitive in evaluating renal function. Peak activity is also reached in 2 to 4 minutes, with gradual decline over the next 30 minutes. In rejection, acute tubular necrosis and drug toxicity poor uptake and poor excretion are the typical findings with a nuclear medicine scan.

If these imaging techniques do not provide an explanation for poor urine output, the diagnosis of delayed graft function is made. Immunosuppression can then be adjusted to minimize or avoid the calcineurin inhibitors, which can prolong the recovery from delayed graft function, and also to initiate antibody therapy to protect the kidney from rejection. The combination of delayed graft function and early rejection is clearly associated with worse outcome in the long term, and an early biopsy of the kidney that is functioning poorly is helpful to diagnose rejection and guide therapy.

Technical Complications

7 Most surgical complications are experienced in the immediate postoperative period. The two main types of complications can be classified as vascular and urologic.

Renal artery thrombosis is a rare complication occurring in about 1% of transplants. The risk of this complication is higher with size mismatch of donor renal artery and recipient internal iliac artery when an end-to-end anastomosis is performed, in kidneys with multiple renal arteries, in kidneys traumatized because of rough handling, and in the presence of an unidentified renal artery intimal flap. Sudden loss of urinary output, not the result of an obstructed Foley catheter or inadequate vascular volume, should necessitate a workup with duplex Doppler ultrasound. Loss of signal is indicative of no

flow to the kidney. Alternatively, a nuclear medicine renal scan is informative, with lack of isotope uptake by the kidney indicating no blood flow. Prompt return to the operating room for correction of a technical problem is imperative, but often the diagnosis is not made quickly enough to salvage the kidney.

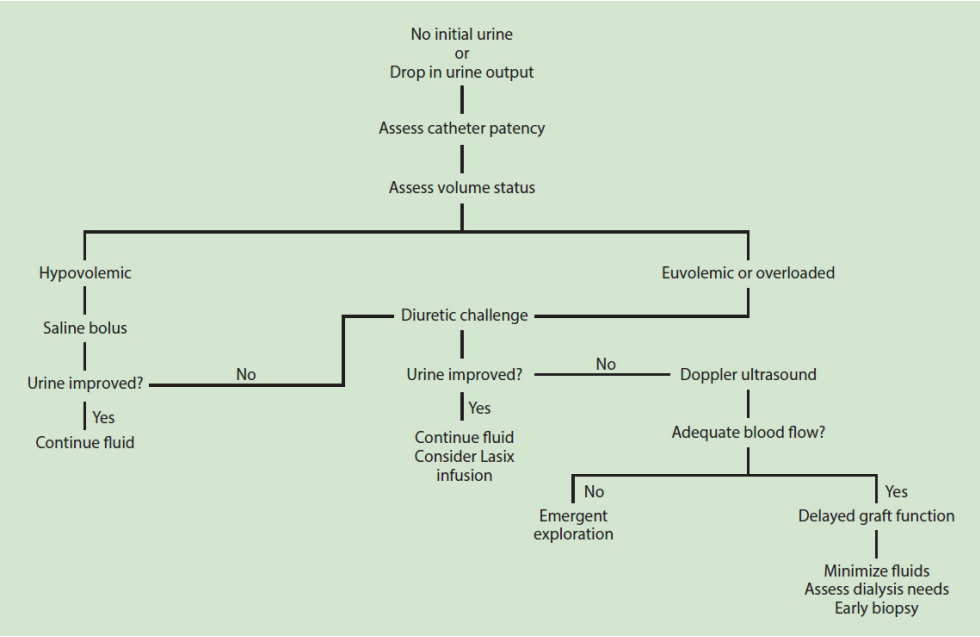

Figure 36.3 Stepwise approach to the management of decreased low urine output post transplant.

Renal artery stenosis occurs in up to 15% of transplanted kidneys. Difficult-to-control hypertension should suggest the possibility of stenosis. Diagnosis with renal duplex ultrasound followed by arteriography to better define the anatomy and degree of stenosis should be done before operative repair or angioplasty. Initial success rates for both methods are similar (75% to 80%), but the restenosis rate following angioplasty is not well defined. Anastomotic strictures respond less well to angioplasty and probably should be repaired by operative intervention.

Aneurysms that occur in the renal artery are either pseudoaneurysms at the anastomotic site or mycotic aneurysms secondary to bacterial or fungal infection. A rapidly expanding, tender pulsatile mass in the region of the kidney suggests a mycotic aneurysm. Arteriography is confirmatory for diagnosis. Treatment consists of appropriate antibiotics and removal of the transplanted kidney.

Venous complications are less frequent, with thrombosis occurring in 1% to 4% of transplants. Causative factors include intimal damage during retrieval, kinking at the iliac vein anastomosis, or pressure secondary to a lymphocele, urinoma, or hematoma. Occasionally, severe rejection can result in venous occlusion. Heparin infusion for incomplete occlusion and transplant nephrectomy for complete occlusion are the indicated therapies. Occasionally, graft salvage is possible if the diagnosis is made before progression of clot into the kidney itself. The classic sign of new-onset hematuria may be an early hint of a renal vein problem and should lead to an ultrasound.

Urologic complications include ureteral obstruction, urinary fistula, or bladder leak. These complications all present with decreased urine output and a rise in serum creatinine. With a urine leak, pain in the region of the transplant may be severe. Mechanical obstruction of the Foley catheter must first be eliminated. Ureteral obstruction occurs in 1% to 9% of transplants, and diagnosis can be made with ultrasonography demonstrating hydronephrosis. A leak is usually diagnosed with a nuclear medicine renal scan. Further definition of a leak or stricture can be obtained via an antegrade pyelogram (**Fig. 36.4**). Early obstruction of the transplant ureter at the site of the bladder anastomosis may respond to internal stenting. Late strictures usually require reoperation, and urine and blood polymerase chain reaction for the polyoma virus should be done in that circumstance, because polyoma viral infection can lead to ureteral stricture. The surgical correction of a ureteral stricture may require reimplantation of the ureter into the bladder, the creation of a Boari flap, or the use of the recipient's native ureter for a ureteroureterostomy (**Fig. 36.5**).

IMMUNOSUPPRESSION, REJECTION, AND IMMUNOSUPPRESSIVE COMPLICATIONS

Immunosuppression

Major advances in the ability to block immune-mediated destruction of the kidney have taken place in the past few years, resulting in a significant decrease in the incidence of acute rejection and improvement in long-term

allograft survival rates.[19] This advance is the result of numerous agents that have been added during the past decade to the immunosuppressive armamentarium of prednisone, azathioprine, and cyclosporine A. These agents include tacrolimus, mycophenolate mofetil, sirolimus, and everolimus (mTOR inhibitors), anti–interleukin-2 receptor blockers, antithymocyte globulin (a polyclonal anti–T-cell agent), rituximab (an anti-CD20 monoclonal agent), and most recently costimulatory blockade with CTLA4-Ig. The addition of various newer drugs targeting different pathways in the alloimmune cascade has permitted the development of regimens that are less dependent on the calcineurin inhibitors or prednisone.[21]

Figure 36.4 Percutaneous nephrostogram revealing a urine leak (*arrow*) from the ureterovesical anastomosis.

Newer strategies in the immunosuppressive pipeline are targeted to block costimulatory pathways; signaling pathways that activate T cells and T-cell proliferation; and trafficking and recruitment of immune cells. The most promising biologic agents targeted to block the costimulatory pathways include a second-generation CTLA4Ig (LEA29Y), a humanized anti-CD11a (anti-LFA1), and a humanized anti-B7.1/B7.2. Promising agents designed to

block T-cell activation and proliferation are the inhibitors of the Janus protein tyrosine kinase (JAK3) and the leflunomide analog FK778. Finally, drugs to block the trafficking and recruitment of immune cells are antagonists against the chemokine receptors CCR1, CXCR3, and CCR5. The chemokine antagonists have been effective in experimental transplantation and will likely be transitioned to clinical trials in the near future.[22]

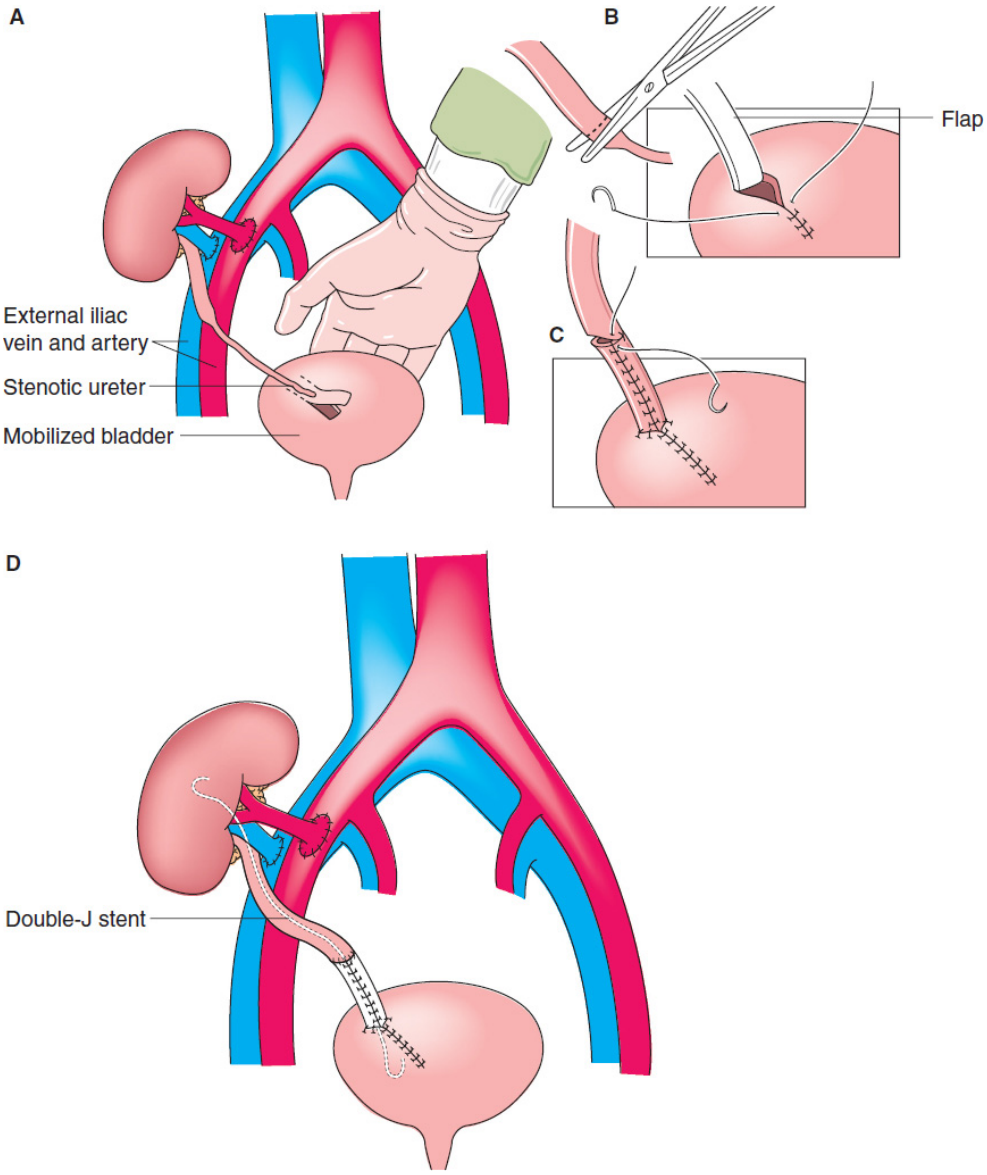

Figure 36.5 **A:** Reconstruction of a stenotic donor ureter, showing resection of the stenotic segment and mobilization of the bladder. **B–D:** A Boari flap is constructed from a tabularized segment of bladder wall and anastomosed end-to-end to the proximal donor ureter.

Rejection

8 Hyperacute rejection is extremely rare and is humorally mediated by preformed anti-HLA antibodies. Hyperacute rejection occurs within minutes to hours following reperfusion of the kidney, whereas classic cell-mediated rejection typically does not occur until 1 to 2 weeks after the transplant. In hyperacute rejection, the anti-HLA antigens bind to the vascular endothelium of the kidney transplant, resulting in activation of the complement cascade and rapid graft thrombosis. The kidney appears blue-black with poor tissue turgor despite adequate blood flow. The characteristic histologic appearance includes the triad of polymorphonuclear leukocytes in the glomerular capillary loops, fibrin deposition, and platelet thrombi. The kidney cannot be salvaged, and a transplant nephrectomy is necessary. The presence of anti-HLA antibodies should be detected in the pretransplant cross-match, and with the sensitivity of current immunologic assays, hyperacute rejection is usually a result of technical or clerical errors in the cross-match procedure. A more common and less intense form of humoral rejection occurring within a few days of transplantation is a result of reactivation of memory B cells following reexposure to alloantigen. The histologic findings are defined by positive C4d staining on vascular endothelium, although lymphocytic infiltrates consistent with classic cell-mediated rejection can be present. Treatment of this aggressive rejection can include plasmapheresis, the anti–B-cell agent rituximab (anti-CD20 monoclonal antibody), and polyclonal antilymphocyte preparations (antithymocyte globulin).

9 Classic acute cell–mediated rejection typically occurs between 1 week and 3 months following transplantation. Most patients with rejection episodes present with decreasing urine volumes and increases in serum creatinine values. Low-grade fever and allograft tenderness may be present, but significant physical symptoms frequently are absent. Immediate workup of increasing serum creatinine should be initiated, beginning with an ultrasound to rule out ureteral obstruction or technical vascular complications as the cause of the deteriorating function. Similarly, toxicity from calcineurin inhibitors needs to be determined by checking drug levels. A percutaneous kidney biopsy is performed to confirm rejection. The severity of the rejection episode is based on the presence of lymphocytes in renal tubules (tubulitis) and vascular endothelium (vasculitis). Mild rejection

is generally treated with pulse corticosteroids and maximizing the maintenance immunosuppression to ensure therapeutic levels of calcineurin inhibitors. More severe rejection with both tubulitis and vasculitis, as well as steroid-resistant rejection, is treated with antilymphocyte antibody preparations, most frequently with rabbit polyclonal antilymphocyte preparations. If the rejection episode occurred while the patients had therapeutic drug levels, maintenance therapy is frequently altered following the antibody therapy. For example, if maintenance therapy consisted of cyclosporine A, the calcineurin inhibitor could be switched to tacrolimus. Other potential strategies include the addition of an mTOR inhibitor to the immunosuppressive regimen, particularly for cases where there is evidence of calcineurin inhibitor toxicity on biopsy.

Each rejection episode takes a toll on long-term function of the kidney transplant. Even well-controlled acute rejection episodes initiate a cascade of events leading to interstitial fibrosis and proliferative changes affecting the vascular endothelium. 10 These histologic and progressive degenerative changes are classified as chronic rejection or chronic allograft nephropathy. These changes lead to loss of graft function over the course of months to several years. Current strategies minimizing calcineurin inhibitor nephrotoxicity are being used to prolong function in kidneys with these chronic changes and involve the addition of TOR inhibitors to replace the calcineurin inhibitors. It remains unclear whether the marked decrease in acute rejection episodes, from greater than 50% to less than 20% observed in the past 5 years, will translate to better long-term function of transplants. Nonetheless, it is evident that immunosuppression strategies minimizing prednisone and calcineurin inhibitors are providing safer and more effective immunosuppression for kidney-transplant recipients while decreasing long-term toxicities associated with immunosuppression.

Immunosuppressive Complications

It would be naive to assume that the intensification of immunosuppressive regimens resulting in decreased acute and chronic rejection rates can be accomplished without sequelae. Infections and malignancy remain significant complications associated with long-term immunosuppression and are the driving force for drug-minimization strategies. Early infections during the

perioperative period are commonly iatrogenic and involve bladder infections or intravenous catheter use. Higher doses of immunosuppressive drugs used in the early postoperative period predispose patients to these infections and emphasize the importance of maintaining sterility during Foley catheter placement and insertion of intravenous catheters. Pneumonia related to mechanical ventilation and poor postoperative inspiratory effort can occur in the early postoperative period, and early incentive spirometry should be encouraged to decrease the potential for this infection. Wound infections are relatively uncommon, although diabetes and obesity are both associated with a much higher incidence of wound complications. Weight reduction to achieve a body mass index of less than 40 kg/m^2 is strongly recommended to facilitate the operative procedure and minimize the risks of wound complications, particularly in the recipient with diabetes mellitus.

Cytomegalovirus (CMV), a herpesvirus, remains a problematic infection in the immunosuppressed patient and can become symptomatic 1 to 2 months following the transplant. CMV-seronegative patients who receive a kidney from a CMV-seropositive donor are at the highest risk for infection, although prophylaxis with acyclovir or ganciclovir is generally provided for all recipients for a period of 3 to 6 months following the transplant. Despite prophylaxis, activation of CMV can occur, accompanied by fever, malaise, pneumonia, gastrointestinal distress, or dysfunction of the kidney transplant. The effective treatment of blood- or tissue-invasive CMV has been one of the major advances in the management of kidney-transplant patients within the past two decades. What was a life-threatening disease in the early era of solid organ transplantation can today be effectively managed with oral antibiotics.

Prophylaxis against *Candida albicans* with fluconazole and *Pneumocystis carinii* with trimethoprim–sulfamethoxazole is also part of most management strategies post transplant. Other potentially life-threatening opportunistic organisms that can affect the chronically immunosuppressed transplant recipient include *Aspergillus, Cryptococcus, Listeria, Nocardia,* and *Mycobacterium.*

More potent immunosuppression regimens used in the current era have been associated with the emergence of polyoma or BK virus, a previously rare infection that may cause graft loss in up to 5% of infected patients. Reduction in immunosuppression is necessary to prevent progression of viral

tubulitis. There has been some experience with the use of leflunomide, ironically an immunosuppressive agent, but with an active metabolite, A77 1726, that has substantial antiviral activity in vitro and in animals. Another potential medication, cidofovir, is a nucleotide analog that inhibits viral DNA polymerase but unfortunately is also nephrotoxic, and its in vivo efficacy has not been proved. Probably the best method to prevent graft loss due to polyoma is the use of monitoring of urine and serum levels of BK virus, with lowering of immunosuppression when early evidence of polyoma is detected.

Patients with a previous history of active tuberculosis or conversion to purified protein derivative positivity should receive appropriate prophylaxis for 6 months to 1 year following the transplant procedure.

More potent immunosuppression regimens will also have an impact on the development of neoplasms following transplantation.[23] Skin cancers are the most common malignancy following transplantation, with more than 90% being squamous or basal cell cancers. The incidence of skin cancers is staggering, with 50% or more of white recipients ultimately developing lesions. The immunosuppressed patient also has a higher incidence of nodal spread, and educating the patient about the importance of avoiding direct sun exposure is essential. Other malignancies that have a particularly high incidence in transplant recipients include non-Hodgkin lymphomas and carcinomas of the anogenital areas. The etiology of anogenital carcinoma is related to the presence of human papillomavirus. Although there have been no prospective trials to date, there is some evidence that TOR inhibitors are advantageous in the setting malignancies as the preferred immunosuppressive agent based on their antiproliferative qualities. Conversion to mTOR inhibitors and minimization of calcineurin inhibitors is a strategy that has been used with increasing frequency in the scenario of malignancies following transplantation.

Posttransplant lymphoproliferative disease is the second most common form of malignancy in transplant recipients and is associated with Epstein–Barr virus. These lymphoproliferative syndromes present as a spectrum of pathology, extending from polyclonal lymphoproliferation to monoclonal B-cell lymphomas. Polyclonal disease has been managed by decreasing or withdrawing immunosuppression, whereas progression to monoclonal lymphomas has required chemotherapy. CD20-positive lymphomas have

been successfully managed with rituximab, an anti-CD20 antibody, with no significant side effects.

CURRENT RESULTS AND FUTURE TRENDS

Over the past three decades, progressive improvement has been made in patient and graft survival, independent of donor source. Overall graft survival, as well as the half-life of the graft, improved incrementally for live-donor transplants, standard deceased-donor transplants, and even deceased-donor transplants using suboptimal or expanded criteria donors.[12] This change is related to improved organ preservation, perfected operative technique, and most important, improved immunosuppressive agents. Current 1-year graft survival rates for living- and deceased-donor transplants are 97.5% and 93.2%, respectively.[24] These remarkable 1-year results continue to be overshadowed by the specter of late graft loss due to chronic rejection. This problem remains unsolved in renal transplantation, and future improvement in long-term survival will be achieved only when the mechanisms of this process are understood.

The exponential growth in waiting lists compounded by the ongoing critical shortage of organs will continue to stimulate creative means of increasing both the living- and deceased-donor pools. Expansion in the number and types of immunosuppressive agents has resulted in marked decreases in the incidence of acute rejection, which it is hoped will translate to prolongation in the long-term function of kidney transplants. Newer strategies in immunosuppressive regimens that minimize nephrotoxic cyclosporine and tacrolimus by adding nonnephrotoxic agents will also benefit the long-term function of transplanted kidneys. The effect of ischemia-reperfusion injury on both early and late graft function, as well as its impact on the development of chronic rejection and transplant glomerulopathy, is an area of active research, and potential therapeutic interventions to minimize this injury are being evaluated. The induction of tolerance to foreign antigen remains the “holy grail” of transplantation. A paucity of tolerizing regimens have been applied clinically, although the use of donor bone marrow or stem cells will likely have a future role in achieving the elusive goal of transplantation tolerance.

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37

Hepatic Transplantation

Benjamin Samstein and Christopher J. Sonnenday

Key Points

1. Liver transplantation remains the only definitive therapy for patients with end-stage liver disease.
2. The three primary indications for liver transplantation in the United States are alcohol-related liver disease, nonalcoholic fatty liver disease (NAFLD), and hepatocellular carcinoma (HCC).
3. Transplantation for early-stage HCC is associated with low recurrence rates and excellent survival, driving interest in expanding criteria for liver transplantation to patients with more extensive but localized tumor burden.
4. The multidisciplinary evaluation of a patient for liver transplantation involves thorough scrutiny of medical, surgical, and psychosocial domains to ensure the benefits of transplant are realized.
5. Recipient, donor, and technical factors dictate the likelihood of major posttransplant complications, which tend to occur in a predictable continuum.

1 Over the past 50 years, liver transplantation has evolved from an experimental procedure to the definitive treatment for patients with end-stage liver disease (ESLD), specific metabolic diseases, and select hepatic malignancies. Dr. Thomas Starzl reported the first three cases of orthotopic liver transplantation in 1963, for a child with biliary atresia, a man with alcohol-related cirrhosis and hepatocellular carcinoma (HCC), and a man with hilar cholangiocarcinoma.[1] None of these patients survived more than 22 days after the operation, but the foundation for the donor and recipient operations was established. Each of those diagnoses remains indications for liver transplantation today, and the survival of liver transplant recipients has improved dramatically. Current 1-year patient survival rates following liver transplantation are 90% to 97%, with median life expectancy for recipients of more than 15 years posttransplant.[2]

As is true of all solid organ transplantation, advances in immunosuppression strategies have had an equivalent or greater impact on outcome as advances in surgical technique. Following the discouraging initial experience in liver transplantation in the 1960s in the United States and the United Kingdom, a relative moratorium on liver transplantation was established by Dr. Starzl and his contemporaries. Very few liver transplants occurred worldwide until the 1980s, following the development of the calcineurin inhibitor cyclosporine by Sir Roy Calne in 1979.[3] This discovery transformed the field, and cyclosporine quickly became the primary maintenance immunosuppression drug for all solid organ transplant recipients. Over the ensuing decade, liver transplantation rapidly expanded such that more than 2,000 cases were performed in the United States in 1989. In 1991, liver transplantation of adults with decompensated cirrhosis was approved for Medicare coverage by the Centers for Medicare & Medicaid Services.[4]

While substantial challenges remain in refining all aspects of liver transplant care including immunosuppression, arguably the greatest barrier in all of solid organ transplantation today is the profound deficit of donor organs to meet the demand of this lifesaving therapy. In recent years, more than 12,000 candidates await liver transplantation in the United States while annual transplant volume is only 8,000 to 9,000.[2] This disparity in supply of donor livers, and the lack of an alternative life-sustaining therapy for ESLD, translates to approximately 2,000 deaths on the waiting list annually. Many of

the recent innovations in liver transplantation over the last 20 years have focused on expanding the number of available donors for liver transplantation, including use of elderly deceased donors, use of grafts with significant steatosis, use of organs from donors with risk of transmission of donor disease (e.g., donors with hepatitis B, hepatitis C, HIV, or malignancy), novel preservation techniques, use of livers from donation after cardiac death (DCD) donors, and living donor liver transplantation (LDLT).

INDICATIONS FOR LIVER TRANSPLANTATION

2 One of the most noticeable changes in liver transplantation over the past three decades has been the significant change in the patients undergoing transplantation—recipients are older, have more comorbidities, and have different primary diagnoses as their indication for liver transplantation. For more than two decades, decompensated cirrhosis related to chronic hepatitis C infection was leading indication for liver transplantation in the United States. The development of direct acting antiviral agents that can effectively eradicate hepatitis C viremia in greater than 95% of treated patients has led to a rapid fall in the number of patients with hepatitis C–related cirrhosis referred for liver transplantation.[5] This change, accompanied with the substantial rise in number of patients with nonalcoholic steatohepatitis (NASH)-related cirrhosis, alcohol-related cirrhosis, and hepatic malignancy referred for liver transplantation, has significantly changed the recipient population (**Fig. 37.1**).

Nonalcoholic Fatty Liver Disease

The epidemic of obesity, metabolic syndrome, and associated nonalcoholic fatty liver disease (NAFLD) have begun to dramatically change the epidemiology of liver disease in the United States and other Western nations. Projections are that ESLD secondary to NAFLD will continue to rise as a primary indication for liver transplantation, advancing a patient population with other substantial comorbidities toward transplant.[6] The incidence of

hepatic steatosis and NAFLD has also begun to affect the health of the deceased donor organ pool, with steatotic donor livers recognized as higher-risk organs particularly as it relates to the risk of early allograft dysfunction. The obesity and comorbid disease associated with NAFLD patients have raised concern that posttransplant outcomes will be inferior in this patient group, but published studies to date do not appear to validate that concern.[7] Clearly though, NAFLD can recur in the transplanted liver, and programs to engage patients in improving their overall health and nutrition posttransplant will be critical to achieving durable outcomes in this patient population. Combining liver transplantation with bariatric procedures to achieve durable weight loss has been demonstrated to be feasible and effective in select patients.[8]

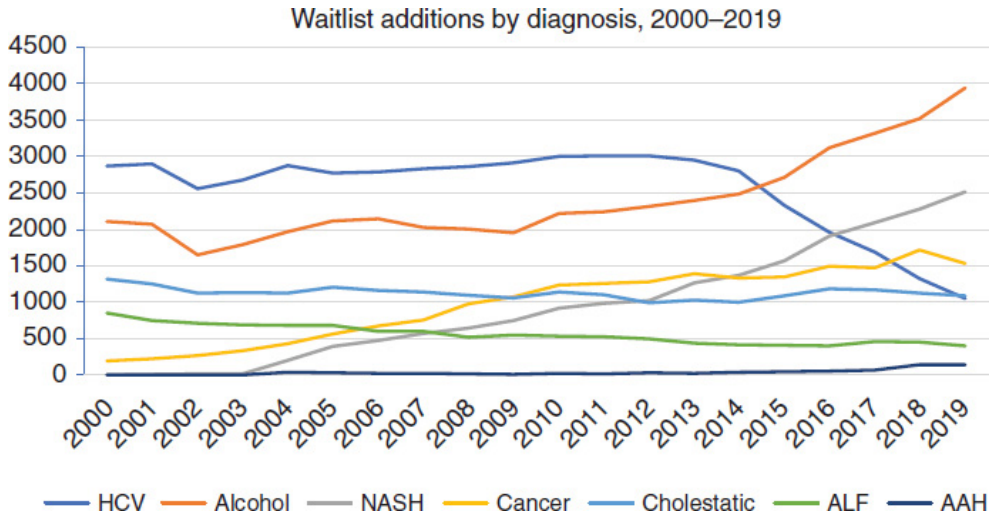


Figure 37.1 Liver transplant waitlist additions by diagnosis, United States, 2000–2019. ALF, acute liver failure; AAH, acute alcoholic hepatitis. (Source: Based upon UNOS Organ Procurement and Transplant Network data as of June 30, 2020. https://optn.transplant.hrsa.gov/)

Alcohol-Related Liver Disease

Alcohol-related liver disease (ALD) remains a primary indication for liver transplantation, and recent data suggest a substantial rise in the incidence of alcohol-use disorder and associated transplant referrals in the United States.[9] In addition, the utilization of liver transplantation for select patients with alcoholic hepatitis has emerged as a growing indication for liver transplantation.[10] This practice, which violates traditional arbitrary policies

about length of sobriety necessary to be considered a liver transplant candidate, suggests that select patients without concomitant untreated mental illness and possessing adequate social support can be transplanted for alcoholic hepatitis, a highly lethal condition, with outcomes similar to other diagnosis groups. In general, the ALD patient population is younger and otherwise healthier than other liver transplant candidates but pose substantial psychosocial challenges in evaluation and posttransplant management for centers.[11]

Of note, ALD and NAFLD together appear to account for approximately 50% of HCC cases in the United States,[12] and epidemiologic evidence exists that obesity and type 2 diabetes mellitus increase the risk of HCC among ALD patients. There are, however, distinctions between the presentation of patients with HCC in the setting of ALD versus NAFLD. ALD patients most often develop HCC in the setting of cirrhosis (~80% of cases), have a higher incidence of vascular invasion, and appear to have worse overall survival than patients with NAFLD-related HCC. As many as 50% of HCC cases in NAFLD patients may not yet have cirrhosis at the time of diagnosis and appear to more often present with a large solitary HCC as opposed to multifocal disease. NAFLD-related HCC also may more often be well-differentiated tumors, and less prone to alfa-fetoprotein (AFP) production, which poses additional challenges to screening protocols.[13]

Transplant for Malignancy

3 As the incidence of primary hepatic malignancies has increased, and outcomes of patients transplanted for hepatobiliary malignancies have improved, the indications for transplant have expanded (**Fig. 37.2**), new challenges in recipient selection, immunosuppression management, and cancer surveillance have emerged. Liver transplantation has been established as definitive therapy for select patients with HCC, for the rare neoplasm hepatic epithelioid hemangioendothelioma, for pediatric patients with unresectable hepatoblastoma, and for a select population of patients with hilar cholangiocarcinoma and metastatic neuroendocrine tumor. More uncertainty exists about the role of liver transplantation, and specifically the selection of appropriate patients, in the treatment of patients with intrahepatic cholangiocarcinoma and metastatic colorectal cancer.

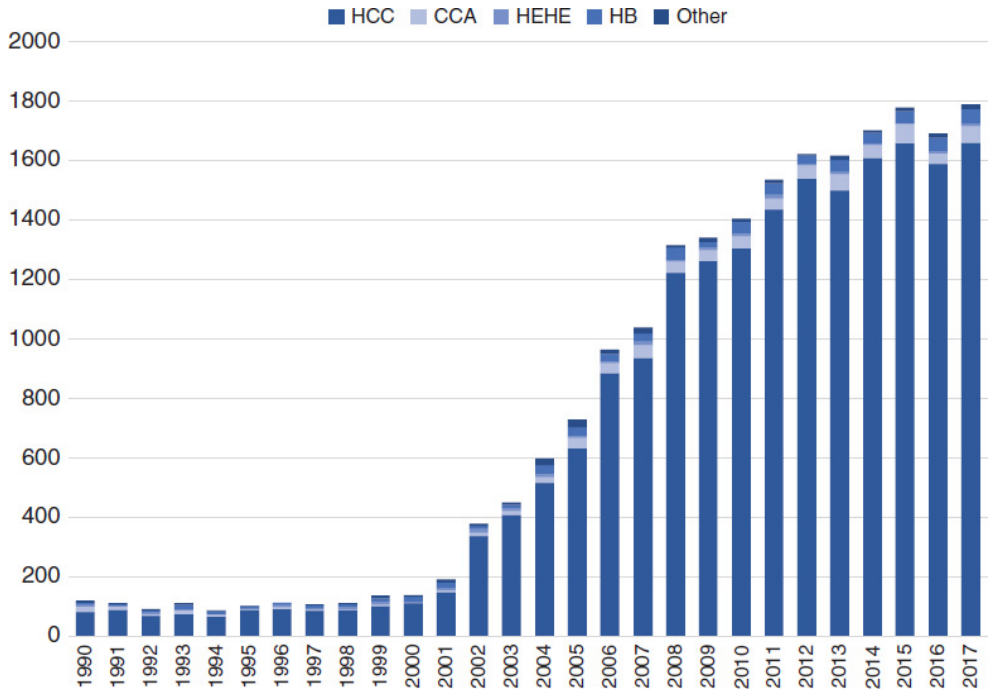


Figure 37.2 Liver transplants performed for malignancy, United States, 2000–2017. HCC, hepatocellular carcinoma; CCA, cholangiocarcinoma; HEHE, hepatic epithelioid hemangioendothelioma; HB, hepatoblastoma. (Source: Based upon UNOS Organ Procurement and Transplant Network data as of January 15, 2018. https://optn.transplant.hrsa.gov/)

Table 37.1 UNOS Modified TNM Staging for Hepatocellular Carcinoma

T stage	T1	Solitary tumor <2 cm
	T2	Solitary tumor 2–5 cm; 2–3 nodules all <3 cm
	T3	Solitary tumor >5 cm; 2–3 nodules with at least one >3 cm
	T4a	4 or more tumors
	T4b	T2, T3, or T4b tumor with gross vascular involvement
N stage	N1	Regional lymph node involvement
M stage	M1	Any extrahepatic metastatic disease beyond regional nodes

Selection of patients with HCC appropriate for liver transplantation has been the seminal challenge in the field, and in fact early series of HCC patients documented excessively high recurrence rates (75%+) with expedited cancer-related mortality.[14] It was not until Mazzaferro's seminal series of patients with early-stage HCC undergoing successful liver transplantation that the primacy of patient selection and tumor burden was established.[15] The Milan criteria established in this study have been stretched and challenged since that time, but they remain the standard for low recurrence risk in this patient population. Cirrhotic patients with T2 tumors (**Table 37.1**), who do not have a resection option either due to tumor burden or severity of liver disease, are considered optimal candidates for liver transplantation.

Numerous efforts have been made to expand eligibility criteria for liver transplantation beyond Milan criteria, although none have been universally accepted in a manner to drive organ allocation. Alternative criteria may be evaluated on the balance between expanding eligibility for transplant to additional patients with HCC with the increased risk of recurrent disease. Consensus in the transplant community has generally established 60% 5-year overall posttransplant survival as the lowest acceptable survival to balance the utility of transplant for HCC with other diagnoses.[16] Among alternative criteria for transplant eligibility among HCC patients, only the University of California San Francisco (UCSF) criteria have been prospectively validated with acceptable outcomes.[17,18] UCSF criteria extend Milan criteria by modestly extending tumor volume criteria (one tumor ≤6.5 cm, three nodules at most with the largest ≤4.5 cm, and total tumor diameter ≤8 cm). These criteria were generated retrospectively based on explant pathology, but prospective validation using preoperative imaging documented a low overall recurrence rate of 10% at 5 years, with only 15% of patients found to exceed UCSF criteria on explant pathology.[18] Despite these excellent outcomes, there has not been national support in the United States to change United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) policy to extend selection criteria for HCC candidates.

While extension of HCC eligibility criteria at the time of transplant has not been endorsed broadly in the United States, liver-directed therapy to downstage patients beyond Milan criteria such that they meet UNOS T2 criteria at the time of transplant has been increasingly utilized. Despite this increasing experience and expert opinion supporting the use of downstaging to expand access to transplantation, there is no consensus about the most effective modality for liver-directed therapy.[19,20] A recent systematic review of published series of downstaging suggested that up to 60% of candidates will be successfully downstaged to within Milan criteria, but no clear advantage was demonstrated according to liver-directed therapy modality (transarterial chemoembolization vs. transarterial radioembolization).[21] Critically important to the establishment of uniform downstaging strategies is the utilization of standard criteria for measuring response to therapy by imaging. The modified RECIST (mRECIST) criteria were created by expert consensus convened by the American Association for the Study of Liver Diseases (AASLD) and remain the gold standard for evaluating response to

therapy on contrast-enhanced CT or MRI.[22] The extent of residual viable tumor, rather than measurement of treatment cavity or previous tumor size, is utilized to determine the amount of residual disease. Response to therapy should be observed for at least 3 months prior to consideration of active listing for transplant. Patients who maintain residual tumor volume within Milan criteria or less after downstaging therapy are appropriate for listing and should be monitored for intrahepatic and extrahepatic progression every 3 months until transplant.

In the case of deceased donor liver transplantation, allocation policy must balance the survival benefit of liver transplantation for HCC patients against the needs of patients with noncancer diagnoses. Furthermore, evidence exists that "expedited" transplant of HCC patients may lead to inferior outcomes, as patients with HCC with shorter waiting times for transplant actually have higher recurrence rates relative to HCC patients with longer wait times for transplant.[23] Current UNOS allocation policy delays assignment of HCC exception points for 6 months (with restaging imaging and serum AFP required every 3 months). After 6 months listing with their natural Model of End-Stage Liver Disease (MELD) score, patients with T2 HCC are granted an exception score near the median MELD at transplant in their area. The delay in granting of the HCC exception for 6 months allows for observation of tumor biology and dropout of patients who progressed beyond T2 criteria.

Given the principle that waiting time may actually help select the most appropriate patients for transplantation for HCC, the use of LDLT for HCC recipients poses interesting challenges. While among patients with non-HCC diagnoses, LDLT offers equivalent or superior survival outcomes to deceased donor liver transplantation,[24] LDLT for HCC patients appears to be associated with an increased risk of tumor recurrence.[25] Explanations for inferior outcomes among HCC patients treated with LDLT include differences in pretransplant therapies (such as decreased use of liver-directed therapy), differences in patient selection (potential tendency to consider patients beyond Milan criteria for LDLT), and expedited transplant via LDLT such that a period of observation of tumor behavior does not occur.[26] The most appropriate selection criteria for selection of HCC patient appropriate for LDLT have not been established, but utilization of some observation period (3 to 6 months) after diagnosis of HCC prior to LDLT

may eliminate the possibility of transplanting patients with particularly unfavorable tumor biology and increased recurrence risk.

Patients with ALD, NAFLD, and HCC account for ~60% of patients currently transplanted in the United States, with the remainder accounted for with the diagnoses in **Table 37.2**. Biliary atresia is the most common indication for liver transplantation in infants and children. The cholestatic liver diseases (primary sclerosing cholangitis, primary biliary cirrhosis, Alagille syndrome) and autoimmune hepatitis tend to occur in younger adults and occasionally in adolescents requiring transplant. Viral hepatitis (chronic B and C) remain important causes of cirrhosis and HCC in the United States, although their prevalence as a primary indication for transplant have declined with effective antiviral therapy.

Table 37.2 Indications for Liver Transplantation by Diagnosis	
Nonalcoholic fatty liver disease	
Alcohol-related liver disease	
Hepatic malignancy	Hepatocellular carcinoma Hilar cholangiocarcinoma Metastatic neuroendocrine tumor Hepatoblastoma
Viral hepatitis	Hepatitis B Hepatitis C
Cholestatic liver disease	Primary sclerosing cholangitis Primary biliary cirrhosis Biliary atresia Alagille syndrome
Autoimmune hepatitis	
Budd–Chiari syndrome	
Fulminant hepatic failure	
Metabolic liver disease	Amyloidosis Ornithine transcarbamylase (OTC) deficiency Maple syrup urine disease Crigler–Najjar syndrome Tyrosinemia Cystic fibrosis Wilson disease Alpha-1 antitrypsin deficiency Hemochromatosis

END-STAGE LIVER DISEASE AND EVALUATION FOR LIVER

TRANSPLANTATION

Regardless of their primary diagnosis, the vast majority of patients referred for liver transplantation have ESLD, defined as decompensated cirrhosis with symptoms of hepatic synthetic failure and complications of portal hypertension. Since many of the complications of ESLD are driven by portal hypertension, replacement of healthy hepatocytes alone (such as through a cellular-based therapy, or heterotopic or auxiliary transplant) would not cure patients of portal hypertension. Orthotopic liver transplantation addresses not only the synthetic failure by replacement with a healthy mass of hepatocytes but serves to correct portal hypertension by replacing the scarred, fibrotic liver that serves as a high-resistance circuit to portal blood flow with a healthy, low-resistance liver. Patients without significant hepatic synthetic failure but with significant complications of portal hypertension (refractory ascites or recurrent variceal hemorrhage) might be treated effectively with procedures to address portal hypertension, such as a transjugular intrahepatic portosystemic shunt (TIPS) procedure or a surgical therapy for portal hypertension (splenorenal or mesocaval shunt).

While laboratory measures of hepatic function exist, and the MELD score serves as a helpful predictor of mortality of ESLD,[27] patients referred for liver transplantation should have clinical symptoms that justify transplantation rather than just abnormal laboratory studies. The most common symptoms include jaundice, fatigue, loss of muscle mass and cachexia, and hepatic encephalopathy. Complications of portal hypertension include ascites, hepatic hydrothorax, variceal hemorrhage, and splenomegaly with thrombocytopenia. The development of hepatorenal syndrome, a clinical entity associated with a poor prognosis among patients with ESLD, should also prompt consideration of liver transplantation.[28] The clinical trajectory of patients with chronic liver disease can be variable and difficult to predict and may depend on whether the cause of liver injury can be treated or removed, such as antiviral therapy for chronic hepatitis or alcohol cessation in alcohol-related liver disease. Medical therapies to manage symptoms of decompensated cirrhosis have improved substantially over the past decades, but ultimately no definitive therapies for ESLD exist other than liver transplantation.

In addition to these classic indications for transplant, patients with cirrhosis may develop other rare complications of liver disease that can be cured with transplantation. These include hepatopulmonary syndrome (HPS), characterized by the development of progressive hypoxia caused by the development of intrapulmonary vascular dilations. These acquired vascular anomalies may develop out of proportion to other complications of portal hypertension, and lead to arterial hypoxia by creating a mismatch between alveolar perfusion and ventilation. HPS may be cured by liver transplantation, especially when offered soon after the development of clinically significant hypoxia. Patients with HPS are granted additional MELD exception points to achieve adequate priority on the waiting list, as HPS may occur prior to more significant clinical decompensation otherwise. A room air PaO_2 less than 60 mm Hg is considered as the benchmark indication for liver transplantation and qualification for MELD exception.[29,30] Patients with HPS are considered higher-risk candidates for liver transplantation, but recent outcomes have improved as MELD exceptions have allowed an earlier pathway to liver transplantation.[29]

Portopulmonary syndrome is another more uncommon indication for liver transplantation, defined by the development of pulmonary arterial hypertension in the setting of portal hypertension. Patients typically present with progressive dyspnea and right heart catheterization establishes a definitive diagnosis. Evaluation of these complex patients requires diagnostic evaluation to rule out other causes of pulmonary hypertension. Liver transplantation may also be curative in this patient population, and patients with portopulmonary hypertension may receive MELD exception points after pretransplant medical therapies to optimize the management of their pulmonary hypertension prior to transplant. Similar to HPS, patients with portopulmonary hypertension face higher perioperative mortality but can have acceptable long-term outcomes after liver transplantation.[31]

Acute Liver Injury and Fulminant Hepatic Failure

Currently, less than 5% of liver transplants in the United States are performed for fulminant hepatic failure, a profound clinical syndrome that

may be precipitated by diverse etiologies. Common causes of acute liver injury among liver transplant candidates include acetaminophen toxicity, autoimmune hepatitis, drug-induced injury, viral disease, hepatic ischemia, and idiopathic causes.[32] Fortunately, the majority of patients with acute liver injury will recover with supportive care, but patients who develop fulminant hepatic failure may be considered for urgent liver transplantation. Patients with fulminant hepatic failure may present with jaundice and hepatic encephalopathy and develop multisystem organ failure. However, the urgency of liver transplantation is driven by the development of cerebral edema and brain injury including herniation that occurs in patients with fulminant hepatic failure. Decisions to list appropriate patients for liver transplantation should be made in 24 hours, and patients meeting criteria for fulminant hepatic failure are granted special expedited priority for liver transplantation (Status 1) with the goal of transplantation within 48 to 72 hours of presentation. Outcomes in the select patients with this diagnosis who are able to be transplanted rapidly can be quite good, similar to other diagnosis groups in more recent studies.[33]

Medical and Surgical Evaluation for Liver Transplantation

4 The medical and surgical evaluation of patients referred for liver transplantation must focus on identifying patients whose benefit from the procedure outweighs the substantial risks of the liver transplant procedure and the need for chronic immunosuppression. In addition, given the lack of sufficient donor organs to meet demand, transplant centers must choose candidates for transplant who have a high likelihood of posttransplant survival, as any patient transplanted competes to some degree with other needy candidates. The evaluation therefore must determine the presence and impact of medical comorbidities, psychosocial fitness for transplant, and any technical factors that would increase surgical risk. In addition, given the need for immunosuppression posttransplant, the evaluation must identify risk factors for conditions that could be exacerbated with chronic immunosuppression (e.g., chronic infections and malignancy). While the specific risk–benefit analysis for any individual patient is subject to

transplant center practices, guidelines do exist to guide standard evaluation processes.[34]

As the success of liver transplantation has increased, medical conditions previously thought to be contraindications to transplant have diminished. Broadly speaking, conditions with limited life expectancy, and/or those that compromise short-term transplant outcomes, are still considered relative contraindications to transplant. Examples include end-stage cardiac or pulmonary disease, metastatic malignancy, active substance abuse, untreated mental illness, or active sepsis. A MELD score less than 15 has also been considered a relative contraindication to transplant, as prior studies indicate that below that MELD score the perioperative risks of transplant may exceed the mortality of ESLD.[35] However, it is important to realize that certain patient populations may have conditions where MELD does not reflect their mortality risk (i.e., HPS, portopulmonary syndrome, cancer, metabolic disease). In addition, LDLT may be appropriate and provide a survival benefit for lower MELD patients with significant clinical decompensation refractory to medical management.[36]

The most challenging elements of the liver transplant evaluation in current practice often focus on the evaluation of older candidates with obesity and medical comorbidities, particularly cardiac disease. Obese patients have been shown to have increased perioperative complications and diminished long-term outcomes following liver transplantation in older studies.[37] However, traditional measures of obesity, such as body mass index (BMI), may be difficult to interpret in liver transplant candidates with ascites and anasarca, and more recent studies suggest similar outcomes in selected obese patients relative to nonobese recipients.[38] Obesity and metabolic syndrome are common among liver transplant candidates, particularly those with NASH-related cirrhosis, which has markedly increased the demand for transplant among obese candidates. A BMI over 40 is considered by many centers a relative contraindication to transplant, although recent innovations such as combining sleeve gastrectomy with liver transplantation may show pathways to expanding transplantation to more obese candidates.[8]

Pretransplant cardiac evaluation focuses primarily on identifying risk factors that would compromise perioperative outcomes. The hemodynamic changes experienced during the liver transplant period, associated with the challenges of total hepatectomy, the systemic vasodilation of cirrhosis, and

the circulatory collapse that can be associated with reperfusion injury and early graft dysfunction require that liver transplant candidates have acceptable cardiac function. All liver transplant candidates should undergo noninvasive cardiac testing, typically with echocardiography and some test for inducible ischemia (dobutamine echocardiography or nuclear medicine perfusion scan). Patients with concern for inducible ischemia should be evaluated with coronary angiography if otherwise appropriate transplant candidates and considered for revascularization when treatable lesions are identified.[39] In addition, the cardiac evaluation should carefully scrutinize valvular dysfunction, ventricular dysfunction, and for evidence of pulmonary hypertension, all of which would require further evaluation to determine appropriateness for transplant.

Waitlist Management and Organ Allocation

Once the decision has been made to list a patient for transplant, the patient's priority for transplant is established by United Network for Organ Sharing (UNOS) policy. Current liver transplant allocation in the United States is based upon the MELD-Na score, an adaptation of the MELD-based allocation first adopted in 2002. MELD-based allocation is predicated on the ability of MELD to predict waitlist mortality, and the addition of MELD-Na recognizes the profound effect of significant hyponatremia on outcomes of patients with ESLD.[40] MELD-Na is a relatively sensitive indicator of changes in clinical condition, allowing the sickest patients to rise to the top of the waiting list. Current liver transplant allocation distributes livers according to proximity circles determined by distance of the candidate transplant center from the donor hospital, allowing broader sharing of livers in an attempt to limit geographic variation in transplant rates.

As the MELD system does not represent the waitlist mortality or dropout rate for all patients, a system of MELD exception scores has been created to assign additional points to patients who meet established criteria for specific diagnoses. Patients being transplanted for HCC represent that largest group of MELD exception candidates, though other standard criteria exist for other diagnoses (HPS, portopulmonary syndrome, polycystic liver disease, etc.). Current UNOS policy dictates that exception applications are reviewed by a national review board, with standardized appeal policies when necessary.

This system aims to assign appropriate waitlist priority to patients awaiting transplant. Current UNOS policy prioritizes children, who are allocated livers from young donors preferentially before adults. This policy attempts to overcome the disadvantage children on the waitlist may face due to size mismatch between pediatric candidates and available donor organs. Pediatric waitlist mortality remains low in the current system, although the smallest infants continue to face challenges in identifying appropriate donors.[41]

SURGICAL PROCEDURE: LIVER TRANSPLANTATION

Anesthetic Management

An anesthesiologist with experience in liver transplantation is invaluable to the transplant team. Proper anesthetic management and effective communication between the surgery and anesthesiology teams is necessary to optimize patient care during the surgical procedure. For adult patients, cardiac monitoring is often performed either by pulmonary artery catheterization or intraoperative transesophageal echocardiography. An arterial catheter is placed for blood pressure monitoring. Adequate vascular access, often including central venous catheters, is required for the administration of blood products and the potential for rapid resuscitation in the case of massive blood loss. A device for rapid infusion and the ability to warm blood products or intravenous fluids is required. Low central venous pressures maintained during the hepatectomy phase of the procedure may help avoid excess bleeding.

Intraoperative Management of Coagulopathy

Liver transplantation has the potential for massive blood loss for several reasons. Liver transplant candidates with cirrhosis often have synthetic deficiencies in circulating coagulation factors as well as severe portal hypertension associated with thrombocytopenia and extensive venous collaterals. Intraoperative coagulopathy may be worsened during the

anhepatic phase of the procedure and immediately after reperfusion when hepatic function may be impaired. Finally, liver transplantation involves extensive dissection of major vascular structures including the inferior vena cava, portal vein, and hepatic artery, all with an inherent risk for bleeding. Intraoperatively, coagulation can be monitored by conventional coagulation tests including prothrombin time, partial thromboplastin time, platelet count, and fibrinogen. Viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) assess global coagulation and clot dynamics.[42] Use of these point-of-care tests may reduce transfusion requirements.[43] Normal coagulation is also helped by maintaining normal pH, calcium levels, and normothermia. Following reperfusion of the donor liver, a fibrinolytic state may be encountered. This is related to the global reduction of all coagulation factors and simultaneous generation of tPA.[44] As long as graft function is not significantly impaired, fibrinolysis gradually resolves.

Surgical Technique

Transplantation of the liver is among the most technically demanding surgical procedures. The donor liver must be prepared on the back table for implantation (**Fig. 37.3A**). Bench preparation includes resection of the donor diaphragm and adrenal gland off of the bare area of the liver and vena cava. Meticulous ligation of tributaries from the vena cava (adrenal vein, phrenic vein, and lumbar branches) is performed. The artery is dissected free from the Carrel patch of the aorta up to the gastroduodenal artery. Dissection near the right or left hepatic arteries is avoided to prevent unnecessary injury. The portal vein is circumferentially dissected free. The gallbladder may be removed at this stage or following reperfusion. Tissues surrounding the common bile duct are left intact to avoid injury of the blood supply.

The most commonly used incision is a unilateral or bilateral subcostal incision with a midline extension to the xiphoid process (**Fig. 37.3B**). After dividing the fascia, ascites, which can occasionally be present in a large volume, is evacuated. The ligamentum teres hepatis is carefully divided between clamps and ligated because a large recannulized umbilical vein is often present in patients with severe portal hypertension. After dividing the falciform ligament, a mechanical retractor is used to retract the bilateral

costal margins anteriorly and superiorly for excellent exposure of the upper abdomen. The abdominal cavity and liver are then inspected for any abnormalities including unsuspected malignancy. Following this, liver transplantation occurs in three stages: recipient hepatectomy, anhepatic phase, and postrevascularization.

Recipient Hepatectomy

During the recipient hepatectomy phase, the liver is mobilized from its ligamentous attachments and the porta hepatis is skeletonized. Attention is first directed to dissecting and skeletonizing the structures of the portal triad. The peritoneum overlying the portal triad is divided with electrocautery. The right and left hepatic arteries are dissected free, ligated, and divided leaving adequate length to provide options for the arterial anastomosis. The proper hepatic artery is also dissected free to the level of the gastroduodenal artery allowing enough length for clamping during the anastomosis. A replaced or accessory right hepatic artery, which arises as a branch of the superior mesenteric artery and travels in a posterior position to the common bile duct and lateral to the portal vein. When the replaced right hepatic artery is relatively large and the proper hepatic artery is diminutive in size, the replaced right hepatic artery can be left long and used for arterial inflow for the donor liver. A replaced or accessory left hepatic artery is rarely adequate for arterial inflow.

Conceptually, the common bile duct and common hepatic duct should be dissected free with as much length as possible and without injuring the blood supply to the bile duct. Leaving the recipient bile duct as long as possible allows the length of the donor bile duct, which may have a tenuous blood supply, to be shorter and still avoid tension at the time of anastomosis.

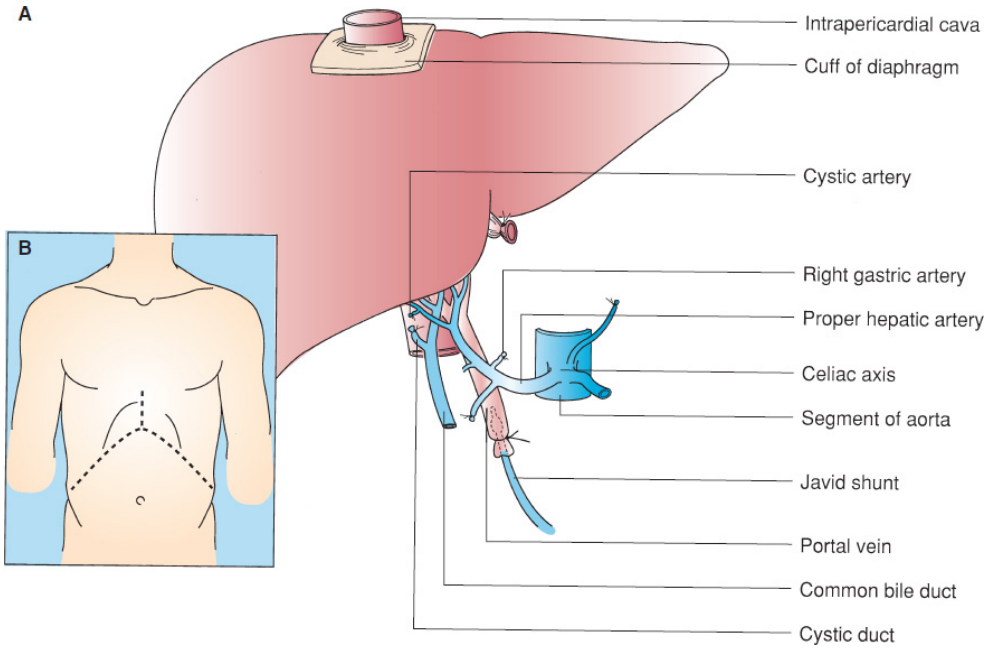


Figure 37.3 **A:** The donor liver after excision and before transplantation. **B:** Bilateral subcostal incision with a subxiphoid extension.

Once the bile duct and the hepatic artery are freed from surrounding tissues, the portal vein can be easily approached from its anterior, medial, and lateral aspects. In general, the portal vein is freed circumferentially from the edge of the duodenum up to its bifurcation of the right and left portal veins. Most patients with severe portal hypertension will not develop hypotension, small bowel edema, or ischemia if the portal vein is clamped and divided because of the presence of portal venous collaterals. However, patients without portal hypertension such as those undergoing liver transplantation for fulminant hepatic failure, metabolic deficiency, or those who have had a TIPS for a prolonged period of time, may develop extensive small bowel edema or hypotension when the portal vein is clamped. Small bowel edema can lead to limited exposure in the right upper quadrant making implantation of the liver extremely difficult. In these situations, the portal vein should be left in continuity for as long as possible, particularly when the use of venovenous bypass is not intended.

For those patients with portal vein thrombosis, portal venous flow can be restored in most cases. A mature portal vein thrombosis may require an eversion endovenectomy. If these maneuvers are unsuccessful, the junction of the splenic vein and superior mesenteric vein may be patent. Dissection of

the portal vein behind the pancreas to this junction can then be performed to allow for future anastomosis. Dissection to the confluence of the splenic and superior mesenteric veins is sometimes necessary in pediatric recipients because of the small caliber of the portal vein within the porta hepatis. In rare cases, all of these maneuvers may be unsuccessful and a venous bypass graft from the superior mesenteric vein may be necessary (**Fig. 37.4**). If the superior mesenteric vein is also occluded, the inferior vena cava or left renal vein can be used for portal inflow, procedures termed cavoportal or renoportal transposition (**Fig. 37.5**). These procedures are associated with acceptable outcomes despite the fact that portal hypertension may not be alleviated.[45] A fourth option for management of portal vein thrombosis is arterialization of the portal vein, using a conduit created by anastomosing donor iliac vessels to the recipient aorta and connecting this to the donor portal vein.[46]

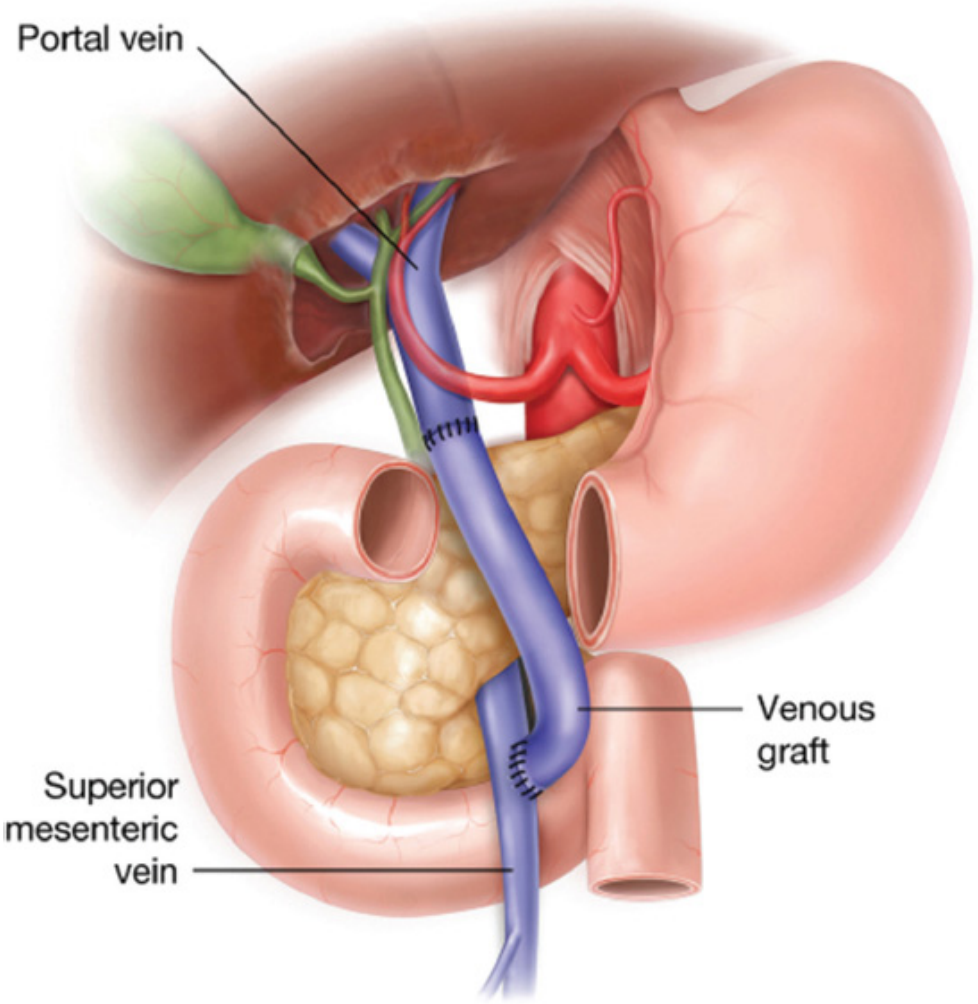


Figure 37.4 Mesoportal venous jump graft in the setting of portal vein thrombosis. The venous conduit is sewn to the superior mesenteric vein and tunneled retrogastric to anastomosis end to end to the donor portal vein.

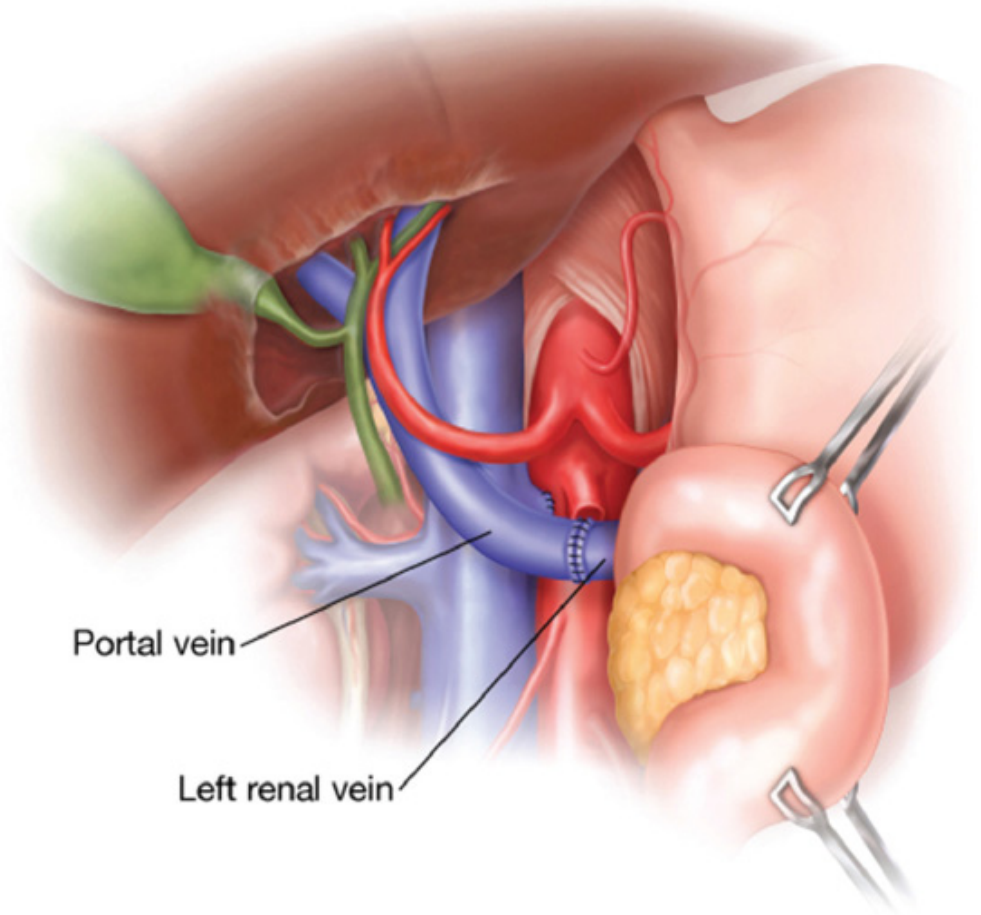


Figure 37.5 Renoportal anastomosis in the setting of portal vein thrombosis. The duodenum and pancreatic head have been mobilized to expose the left renal vein, which is divided at its drainage to the IVC and anastomosed end to end to the donor portal vein.

During mobilization of the liver, the left and right triangular and coronary ligaments are divided using electrocautery. The bare area of the liver is dissected along a plane just superficial to the capsule of the liver. Care must be taken to avoid injury to the phrenic or hepatic veins when freeing the suprahepatic inferior vena cava where it traverses the diaphragm. If a bicaval venous anastomosis technique is used, the vena cava can be circumferentially mobilized near the diaphragm above the hepatic veins as well as in an infrahepatic position. However, if a piggyback or cavocavostomy (side-to-side caval anastomosis) technique is intended, the dissection of the posterior aspect of the vena cava should be avoided to prevent encountering unnecessary bleeding from collateral or lumbar venous branches in this area. The hepatocaval ligament along the right lateral aspect

of the vena cava can be divided using a combination of cautery and ligation as a phrenic venous branch is often present within this ligament. If caval preservation is being performed, the liver is then dissected off the anterior aspect of the inferior vena cava. Small venous branches from the inferior vena cava to the caudate lobe are ligated and divided. Larger branches, such as an inferior hepatic vein, are clamped, divided, and oversewn. Division of the portal vein facilitates exposure for this dissection but is not required. The liver may be gradually retracted and dissected from either the right or left aspects until the right, middle, and left hepatic veins are reached.

Anhepatic Phase and Implantation of the Donor Liver

At this point, the liver has been completely mobilized except for its attachments of the hepatic veins to the inferior vena cava and in some cases, the portal vein. Most patients will tolerate clamping of both the portal vein and the inferior vena cava without difficulty.[47] At this point, communication with the anesthesiologist is essential and the vena cava should be test clamped before division to make sure that adequate cardiac filling and blood pressure can be maintained. If the patient becomes hypotensive during test clamping, the clamp should be removed and additional volume or vasopressor support can be administered. Occasionally, patients will require venovenous bypass, but its use is no longer routine at most centers.

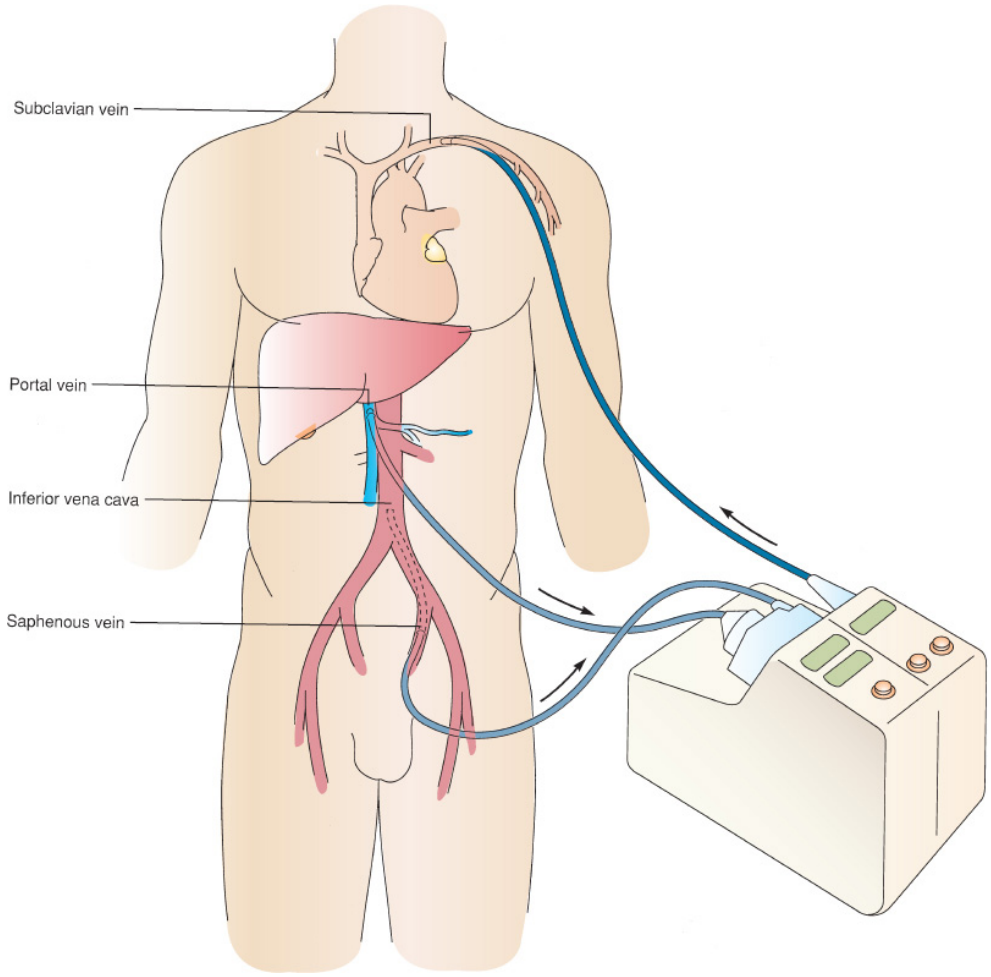


Figure 37.6 Setup for venovenous bypass during hepatic transplantation. Cannulas are placed into the portal vein and inferior vena cava (through the greater saphenous vein). A centrifugal pump is used to deliver bypassed blood to the central circulation by means of a cannula passed into the axillary vein.

If necessary, venovenous bypass can be accomplished from both the portal vein and inferior vena cava simultaneously, or a single cannula in either the portal vein or the inferior vena cava may be used (**Fig. 37.6**). There are several accepted methods of placing cannulas for venovenous bypass. Cannulas may be placed percutaneously in the internal jugular vein and femoral vein prior to beginning the procedure. These cannulas are advanced into the superior and inferior vena cava, respectively. Alternatively, one or both of the bypass cannulas may be placed by cutdown on the axillary and/or the greater saphenous vein. Inferior vena caval and mesenteric blood is delivered to the superior vena cava by a centrifugal pump. The cannulas, tubing, and centrifugal pump head are heparin bonded to reduce the chance of

thrombus formation and subsequent embolism without the use of anticoagulation. Flow rates of 1 to 2 L/min are typical. Once venovenous bypass has been established or the decision to forego bypass has been made, the recipient hepatectomy is completed. If still intact, the portal vein is divided as high in the hilum as possible. Three methods are commonly used for orthotopic liver transplantation: the bicaval technique, the piggyback technique, cavocavostomy (side-to-side caval technique).

For the **bicaval** technique, the recipient liver is excised en bloc with the retrohepatic inferior vena cava after caval clamps have been placed in a suprahepatic and infrahepatic position. The hepatic veins are divided within the substance of the liver to allow the creation of a large suprahepatic cuff compromising the left, middle, and right hepatic veins (**Fig. 37.7**). This technique has the disadvantages of: (a) occluding inferior vena cava flow resulting in renal ischemia and decreased cardiac filling with associated hypotension, (b) requires two vena caval anastomoses prolonging the warm ischemic time, (c) requires increased dissection of the recipient vena cava possibly leading to bleeding. However, complete dissection of the caudate lobe off the vena cava is not necessary in this technique, making the recipient hepatectomy phase somewhat easier and faster.

For the **piggyback** technique, a clamp is placed transversely, partially occluding the vena cava at the level of the hepatic veins. The vena cava is left in continuity and the hepatic veins are divided within the substance of the liver allowing the creation of a common patch of the right, middle, and left hepatic veins for a wide anastomosis. While the intention is to only partially occlude the vena cava allowing venous return to the heart, often a clamp placed for the piggyback technique either occludes or nearly occludes the inferior vena cava. This technique does have the advantage of only requiring a single vena caval anastomosis helping to limit warm ischemic time.

For the **cavocavostomy** technique, liver is excised and the hepatic veins are stapled or oversewn (**Fig. 37.8**). Advantages of the cavocavostomy anastomosis include the following: (a) minimal time that the vena cava is clamped, (b) the vena caval clamp is placed longitudinally only occluding the anterior third of the vena cava leading to minimal or no changes in the recipient's hemodynamics, (c) a broad anastomosis is performed limiting the likelihood of caval stenosis.

The donor liver is then brought onto the operative field. The vascular anastomoses are performed using a running monofilament polypropylene suture. If a bicaval technique is planned, two caval anastomoses are required. The suprahepatic vena caval anastomosis is first performed by suturing the posterior walls from within the lumen using an imbricating technique (**Fig. 37.7**). The anterior wall is then completed. The infrahepatic anastomosis is then completed in a similar fashion. Redundancy in the donor vena cava is avoided to prevent the potential for kinking. The completion of the anastomosis may be left until the time of hepatic revascularization to provide a vent or blood, and for washout of residual preservation solution.

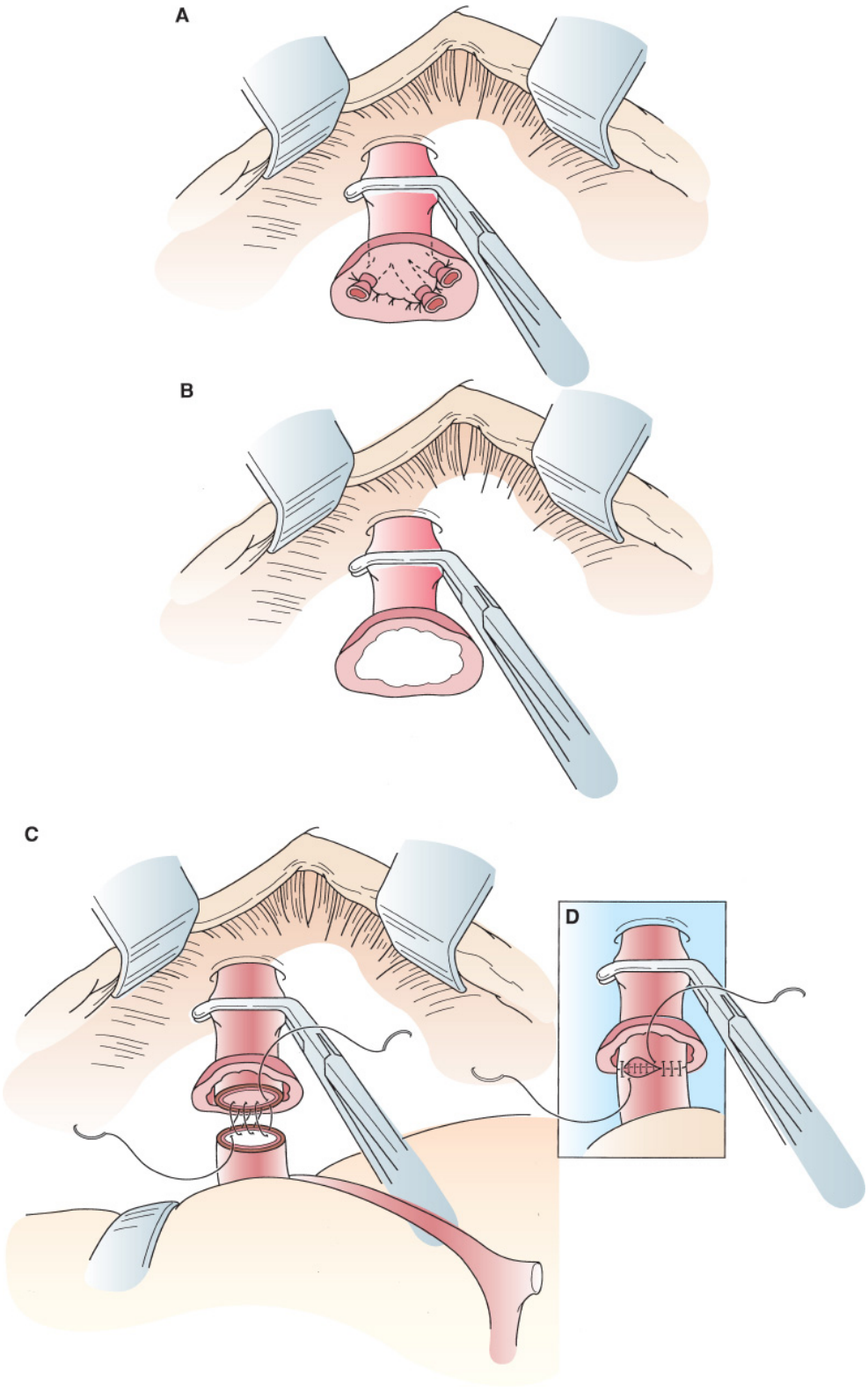


Figure 37.7 Bicaval liver transplant. **A:** The diseased recipient liver is removed by incising the liver below the level of the hepatic veins. **B:** The hepatic veins are then

opened to form a large suprahepatic cuff for the anastomosis. The suprahepatic vena caval anastomosis: posterior suture line (**C**); anterior suture line (**D**).

For the piggyback technique, the donor suprahepatic vena cava is then sewn in an end-to-side fashion to the recipient hepatic vein cuff (**Fig. 37.9**). As described above, an imbricating suture technique is often helpful to prevent gaps in the anastomosis and to compensate for size discrepancies. Venting at the time of reperfusion can either be performed through the suprahepatic anastomosis or at the donor infrahepatic vena cava. The donor infrahepatic vena cava is either oversewn or stapled. For the side-to-side caval technique, a clamp is placed longitudinally on the anterior third of the recipient vena cava. A longitudinal venotomy is made on the anterior surface of the recipient vena cava. The donor supra- and infrahepatic vena cava are either oversewn or stapled closed. A longitudinal posterior venotomy is then made matching the length of the recipient venotomy. The liver then placed in the right upper quadrant in the left lateral segment is elevated. The two vena cavae are then sutured in a side-to-side fashion with the lateral wall sutured from within the lumen and the medial wall sutured from outside the lumen (**Fig. 37.8**). During the caval anastomosis, the donor liver may be perfused with cold fluid via a cannula placed within the donor portal vein to wash out the preservation solution and to help maintain the cold temperature of the liver. This step is not required but may be considered if the liver was preserved with a solution containing a high concentration of potassium or if a prolonged warm ischemic time is anticipated. Once the caval anastomosis or anastomoses are completed, the portal venous anastomosis is completed, and the liver is reperfused. If portal bypass has been used, the portal limb of the venovenous bypass circuit is removed. The portal anastomosis is usually performed in an end-to-end fashion using a running technique. To avoid narrowing and allow for expansion under venous flow, a small air or "growth" knot is used when the suture is tied.

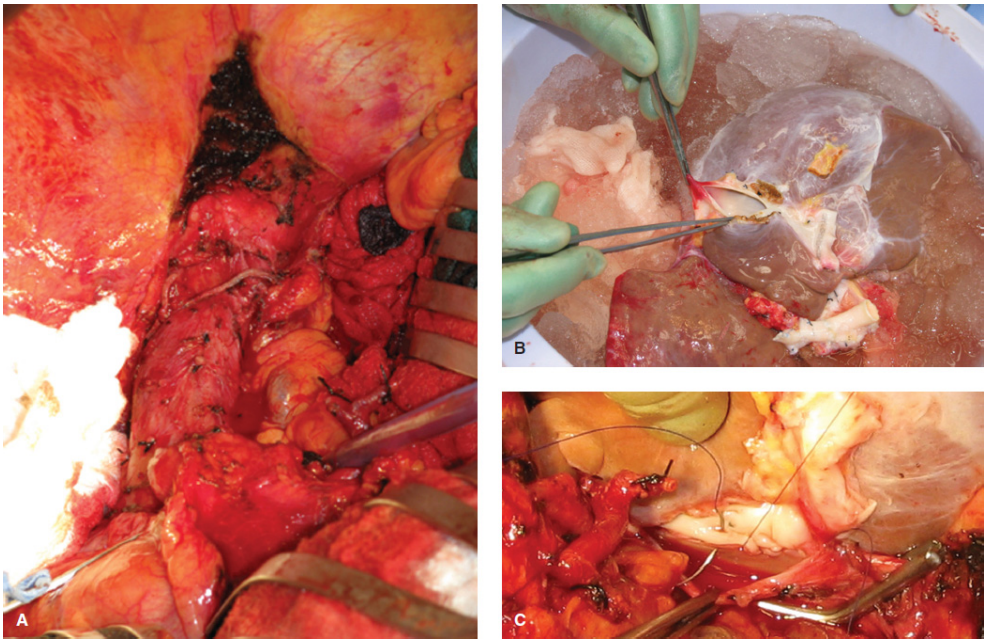


Figure 37.8 Cavocavostomy. **A:** The recipient right and junction of the middle and left hepatic veins are stapled and the inferior vena cava is left in continuity. **B:** The supra- and infrahepatic vena cavae are stapled and a venotomy is made longitudinally on the posterior aspect of the donor liver. **C:** A side-to-side caval anastomosis is performed with a running suture.

At the time of revascularization, flow is restored to the liver through the portal vein and/or the hepatic artery. The first several hundred milliliters of blood may be vented through the infrahepatic vena cava and the knot can be tied completing the caval anastomosis. Alternatively, the caval clamp can be briefly opened and the anastomosis inspected for bleeding and repaired if present. If blood is not vented through the infrahepatic cava, portal blood should be restored gradually to minimize cardiac irritability, bradycardia, and hypotension, all of which routinely result from cold blood circulating through the donor liver and going directly into the right atrium. Close coordination between the surgeon and anesthesiologist is necessary during this phase as hypotension and bradycardia are routinely encountered and cardiac arrest may rarely occur. If venovenous bypass has been used during the anhepatic phase, it can now be discontinued.

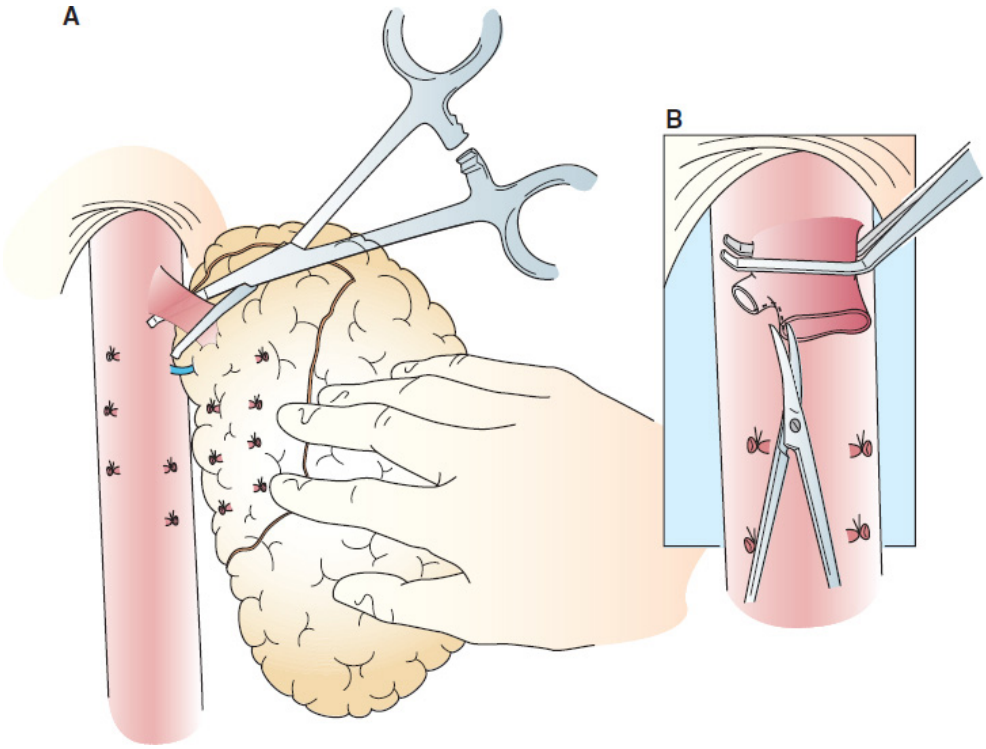
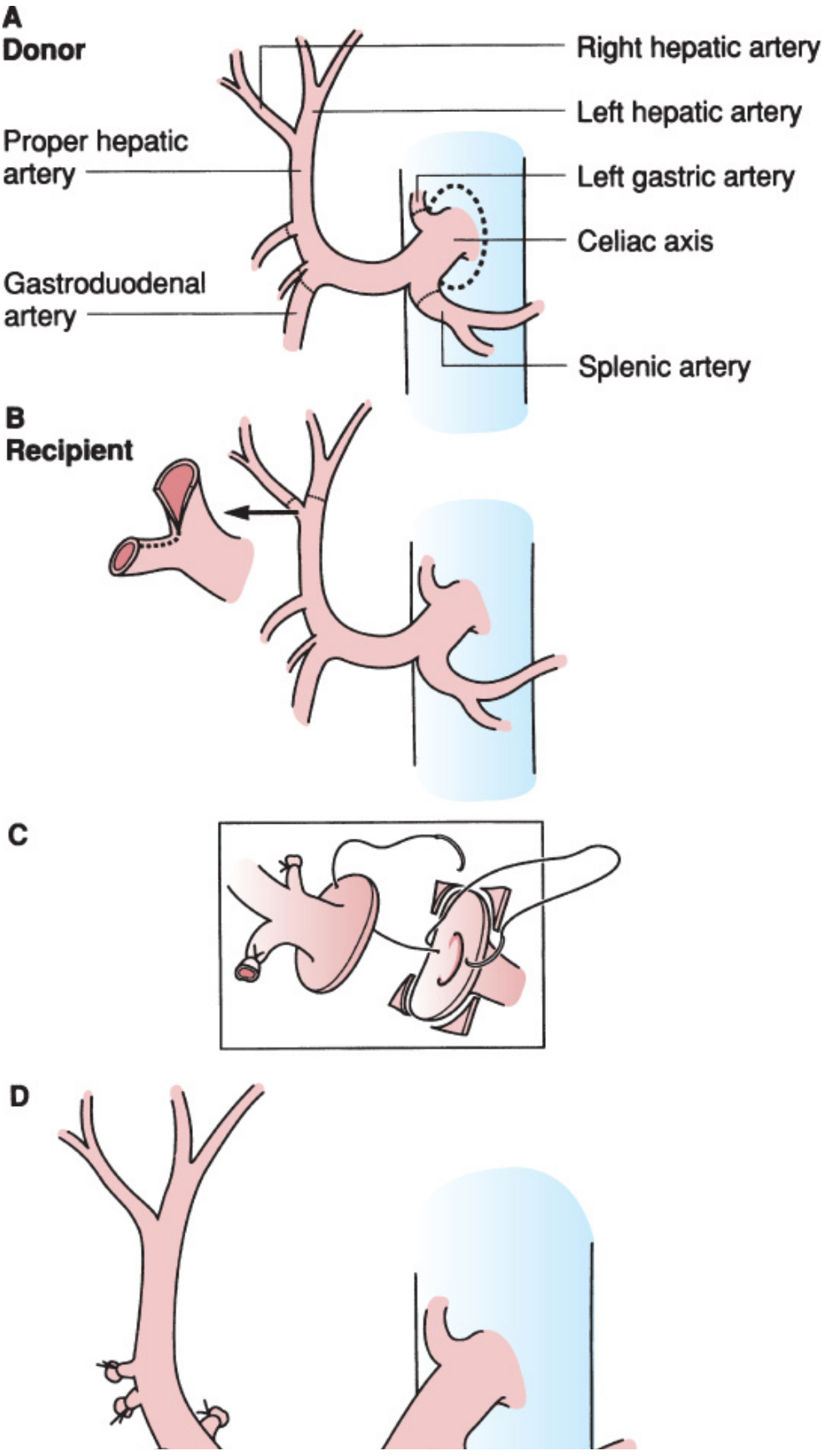


Figure 37.9 Piggyback technique. **A:** Recipient liver is dissected off native inferior vena cava by dividing veins draining directly into the inferior vena cava up to the level of the hepatic veins. **B:** Clamp placed on recipient hepatic veins in preparation of excision of the recipient's native liver and performance of a piggyback anastomosis.

Once hemostasis is obtained and the patient has stabilized, attention can now be turned toward the arterial anastomosis if it has not already been performed. The anastomosis can be performed distally on the donor artery or more proximally leaving the artery long, which allows the artery to lie with a smooth and gentle curve or loop. For this technique, all branches on the donor artery are ligated and the donor aortic Carrel patch, celiac artery, or branch patch of the celiac and splenic artery are anastomosed in an end-to-end fashion to a branch patch of the recipient right and left hepatic arteries (**Fig. 37.10**).


A
Donor
Right hepatic artery
Left hepatic artery
Proper hepatic artery
Left gastric artery
Celiac axis
Gastroduodenal artery
Splenic artery
B
Recipient
C
D

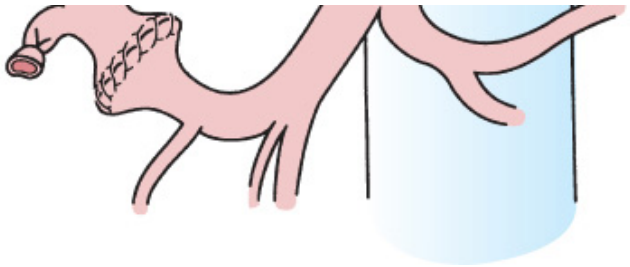


Figure 37.10 Hepatic artery anastomosis. **A:** The donor hepatic artery is procured with a Carrel patch of aorta. **B:** The recipient hepatic artery bifurcation is used to fashion a branch patch for a larger anastomosis. **C:** The anastomosis is carried out using continuous monofilament suture material. **D:** The completed anastomosis.

If the recipient arterial inflow is inadequate, an aortic conduit may be constructed. This is often performed using a graft consisting of the donor common and external (or internal) iliac artery. A partially occluding aortic clamp can either be placed in a supraceliac or infrarenal position and the common iliac artery is sutured in an end-to-side fashion to the recipient aorta. The donor Carrel patch can then be sutured in an end-to-end fashion to the external iliac artery of the conduit.

Post-revascularization Phase

Following revascularization, the liver should assume a normal color and consistency within several minutes. If the liver remains pale or is overly soft, problems with portal inflow should be considered. Alternatively, if the liver becomes edematous and overly firm, outflow obstruction should be excluded. Bile production should be seen while in the operating room and is among the first evidence for liver function. Inspection for surgical bleeding should be performed and entails examination of the vascular anastomoses as well as a search for branches of the major vessels that may not have been ligated. If bleeding continues after all surgical bleeding has been resolved, attention should be directed toward correction of coagulopathy as described above.

While biliary reconstruction does not carry the same risk for intraoperative complications when compared to the recipient hepatectomy and reperfusion, it is associated with considerable postoperative morbidity and mortality and requires the same diligence and attention as other steps of the operation. Because of the relatively high complication rate associated

with biliary reconstruction, it has been referred to as the Achilles heel of liver transplantation. The simplest and most common technique is currently an end-to-end choledochocholedochostomy from the donor to the recipient bile duct (**Fig. 37.11**). If a size discrepancy exists, the narrower duct can be spatulated. Running or interrupted sutures can be used. Absorbable monofilament suture is most commonly used to avoid a nidus for future stone formation within the bile duct. Alternative biliary reconstruction methods may be necessary for those with a bile duct of inadequate quality or size or in those whose primary disease is biliary pathology that prevents use of the native recipient duct. The most common option employed in these situations includes a standard Roux-en-Y choledochojejunostomy. Placement of drains may be considered to monitor for biliary leak. Abdominal wall and skin closure are then performed in the standard fashion.

Technique for Partial Liver Transplantation

The remarkable success of liver transplantation has led to challenges with liver availability. In part, motivated by need for more organs, techniques for split and living donor grafts based on Couinaud segmental anatomy (**Fig. 37.12**) were developed.[48,49] Techniques have now developed so that both sides of the liver can be transplanted into two recipients, either a child and an adult or two adults.[50,51] Split liver transplantation has been associated with a decreased survival rate and the potential for increased risk of complications, including primary nonfunction, hepatic artery thrombosis, and biliary complications. Because of this, while widespread adoption of allocation policies to encourage greater utilization of split liver grafts in the adult population has been suggested, split liver transplantation only accounts for a small proportion of transplants performed. In addition, only grafts from "ideal donors" are thought to be suitable to this form of transplantation. Criteria supported by the UNOS for splitting currently include donor age less than 40 years of age, on limited or no vasopressors, transaminases no greater than three times normal, and a BMI of 28 or less.

Living Donor Liver Transplantation

Experiences with deceased donor split liver transplantation and ongoing shortages of deceased donor allografts led to the adoption of the techniques utilized in split liver transplantation for LDLT. While, LDLT now accounts for approximately 5% of all liver transplants performed in the United States, it is the predominant pathway to liver transplantation in many countries. Although initially used in the pediatric recipients, adult LDLT rapidly became more frequent. Early in the LDLT experience, adult recipients with left lobe grafts developed severe hyperbilirubinemia, coagulopathy ascites.[52] This syndrome termed small-for-size syndrome led to increased utilization of larger, primarily right lobe grafts.

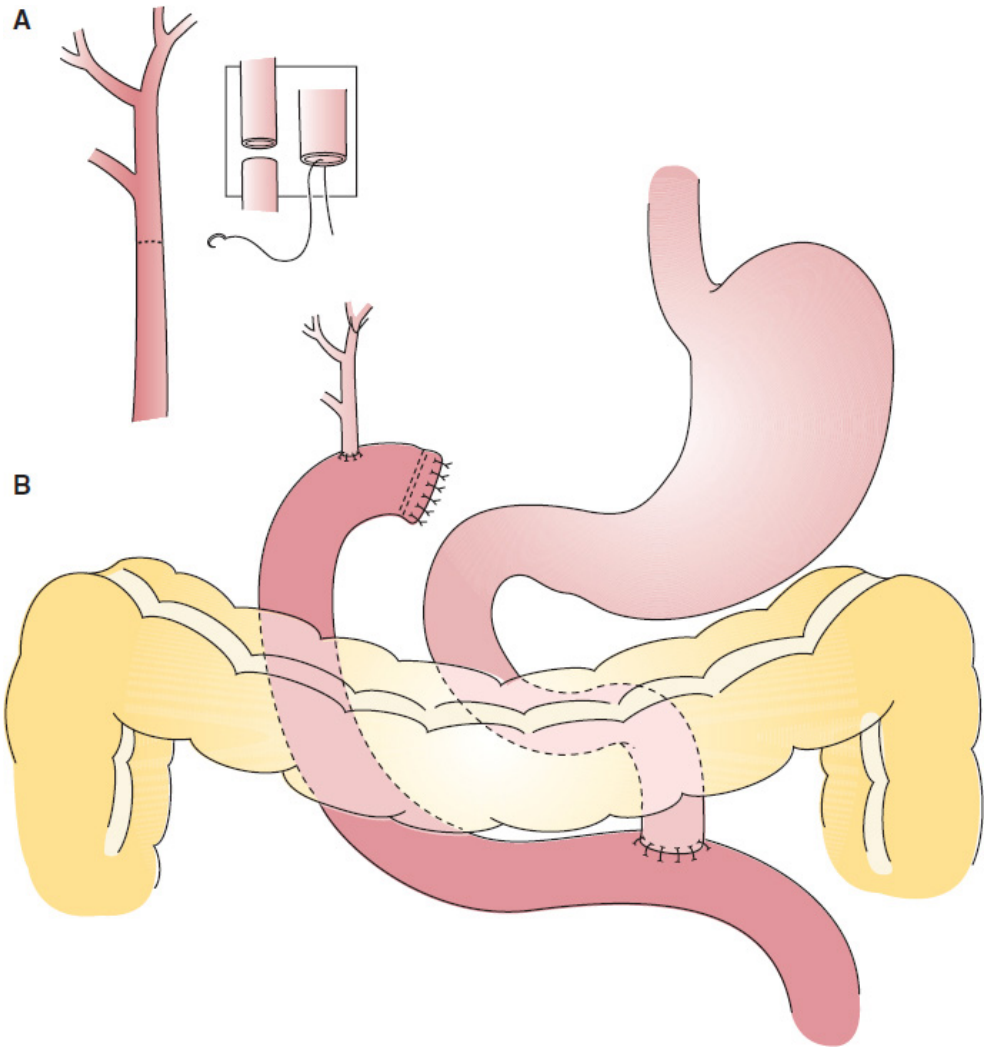


Figure 37.11 Biliary anastomosis. **A:** In most cases, a choledochocholedochostomy is performed, possibly over an internal stent. **B:** Patients with a diseased or unsuitable common bile duct may require biliary reconstruction with a Roux-en-Y choledochojejunostomy.

In many respects, transplantation of a graft from a living donor is similar to transplantation of a whole liver from a deceased donor. However, the recipient vena cava must be left intact. A direct hepatic vein to vena caval anastomosis is used. Establishing adequate outflow of hepatic venous blood is necessary to help prevent congestion of the anterior segment of the right lobe. Therefore, any vein draining segment 5 or 8 greater than 3 to 5 mm in diameter should be reconstructed either by direct anastomosis to the vena cava or using an interposition graft (**Fig. 37.13**). In addition, the length of the portal vein, hepatic artery, and bile duct on the donor graft is considerably

shorter than that available from a deceased donor. Therefore, during the recipient hepatectomy, considerable care should be given to preserving the length of the recipient bile duct as well as the right and/or left hepatic artery and portal vein which are intended for future anastomosis. Advantages of LDLT include lower recipient mortality compared to waiting for a deceased donor, less medical complications, and optimization of timing of transplant.[53,54] However, due to the technical complexity, there are more biliary and vascular complications.

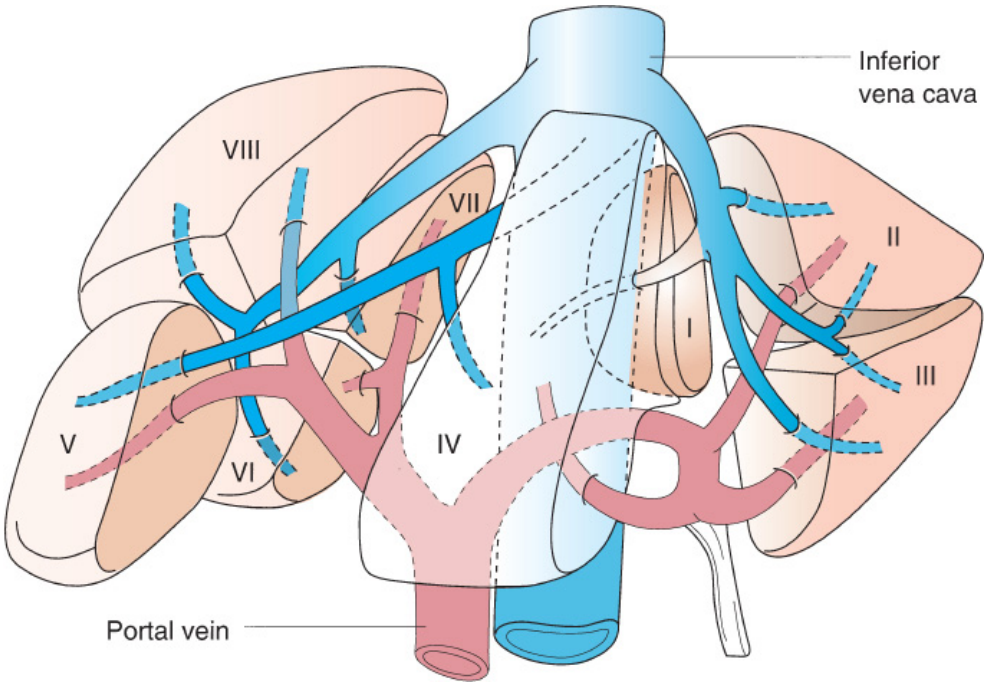


Figure 37.12 Segmental anatomy of the liver as based on Couinaud nomenclature.

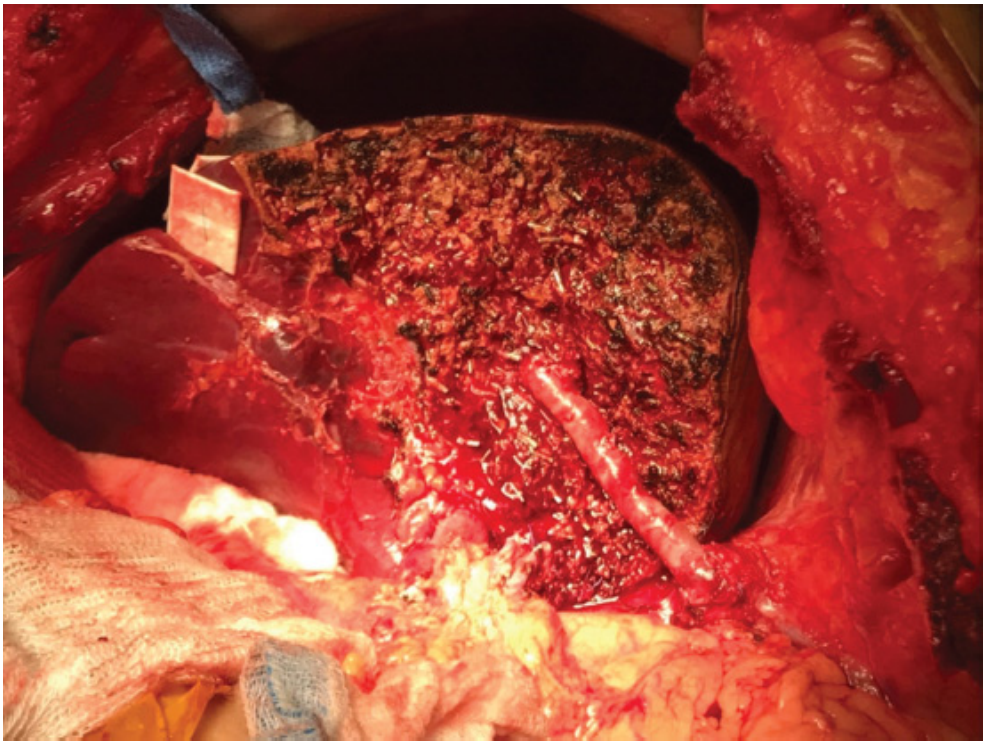


Figure 37.13 Living donor right hepatic lobe allograft demonstrating reconstructed V5 with cryopreserved femoral vein. (Photo belongs to Dr. Samstein.)

POSTTRANSPLANT CARE AND COMPLICATIONS

5 Management of the post-liver transplant patient requires understanding of the continuum of care from acute perioperative issues to long-term health maintenance and management of immunosuppression. While transplant patients may be challenging to manage, they develop complications across a predictable timeline, and the best clinicians anticipate complications such that rescue may occur (**Table 37.3**).

Recipient Factors

Early posttransplant complications occur in the first 30 to 90 days posttransplant and are typically the most immediately threatening to the survival of the graft and patient. Three critical elements dictate the immediate posttransplant course: recipient health and comorbidity at time of

transplant, donor organ quality, and technical details of the transplant operation. Comprehensive care of the transplant recipient requires detailed knowledge of all three and can guide perioperative care. The clinical status of the recipient at the time of operation can have a profound effect on the perioperative course. Given the current MELD-Na based allocation system, recipients may often have significant renal dysfunction and hyponatremia at the time of transplant. This factor, coupled with an aging recipient population with a higher burden of comorbid disease, explains the high incidence of posttransplant renal dysfunction, with acute kidney injury occurring in up to 50% of recipients, with up to 15% of patients requiring some duration of renal replacement therapy following transplant.[55] Other aspects of recipient clinical status at the time of transplant beyond renal dysfunction, such as frailty, obesity, and malnutrition, can increase recipient vulnerability to posttransplant complications, particularly sepsis. Clinical pathways to promote early extubation, mobilization, and optimization of nutrition act in part to mitigate these recipient-challenges in the early posttransplant period.[56]

Table 37.3 Continuum of Post-Liver Transplant Complications

Time	Event
0–90 d	Primary nonfunction Acute kidney injury Vascular complications Biliary complications Sepsis; surgical site infections Medication adverse reactions Perioperative cardiac events Acute rejection Donor-derived disease
90 d to 1 yr	Acute rejection Atypical/Opportunistic infections Biliary complications
Beyond 1 yr	Chronic kidney disease Cardiovascular disease Cancer Chronic allograft failure

Donor Factors

Donor quality has long been associated with risk of perioperative complications and early graft loss.[57] With increasing demand, transplant centers have increasingly used more marginal grafts (older donors, more steatosis, DCD donors) at risk of early allograft dysfunction. Donor livers of lesser quality, and particularly DCD donor livers, are associated with more robust reperfusion injury and associated downstream consequences for the recipient, including but not limited to coagulopathy and need for more transfusions, prolonged ICU and hospital length of stay, prolonged ventilation, acute kidney injury, and early mortality.[58,59] Given that early graft dysfunction can often be predicted based upon donor characteristics, surgeons may choose to avoid grafts of lower predicted quality for more complex or frail recipients. Improvement in preservation technique,

particularly machine perfusion of donor livers, may help to mitigate some of the reperfusion injury associated with more marginal donor organs, and allow more refined selection of donor livers based upon functional metrics while on machine perfusion systems.[60,61] Primary nonfunction, defined as lack of graft function without associated vascular compromise, is a rare (~1% of liver transplants in most series) occurrence but requires immediate retransplant for rescue as patients can develop sequelae of acute liver failure including cerebral edema and multisystem organ failure.

Technical Factors

In addition to recipient health and donor quality, the difficulty of the transplant operation has a significant impact on the initial perioperative course. Risk factors for more increased perioperative risk include retransplantation, previous abdominal surgery, and portal vein thrombosis. In addition, patients in specific diagnosis groups may pose greater technical challenges including candidates with Budd–Chiari syndrome, polycystic liver disease, and acute alcoholic hepatitis. Technical factors that complicate vascular inflow or outflow to the transplant liver are of particular consequence, with portal vein thrombosis being the most common vascular challenge among liver transplant candidates, occurring in up to 15% of candidates and associated with increased risk of graft loss and patient death.[62,63]

Vascular Complications

Vascular complications in the early posttransplant period can be catastrophic and may lead to the need for immediate retransplantation. Hepatic artery thrombosis, occurring in 1% to 2% of deceased donor whole grafts, may occur at increased frequency with higher-risk grafts including DCD donor livers, partial allografts, and pediatric donor livers. The diagnosis of hepatic artery thrombosis may be suspected by an unexpected rise in serum transaminase levels and confirmed by Doppler ultrasonography and/or CT angiography. When recognized immediately, hepatic artery thrombosis may be rescued with surgical revision and thrombectomy, but given the hepatic artery's preferential blood supply to the biliary epithelium, biliary

complications including ischemic cholangiopathy may be predictable sequelae. Hepatic artery thrombosis that occurs in the first-week posttransplant and is not able to be surgically corrected is an indication for immediate retransplantation. Hepatic artery thrombosis may occur more indolently in a delayed fashion, weeks to month posttransplant, and in that setting, the consequences to graft function and biliary tree may be less severe.

Portal vein thrombosis occurs less commonly than hepatic artery thrombosis in the acute posttransplant setting. The most important risk factor for posttransplant portal vein thrombosis is portal vein thrombosis at the time of transplant. Inadequate thrombectomy, and/or inadequate flow due to robust collaterals that divert mesenteric venous return away from the transplant portal vein may predispose recipients to portal vein thrombosis and persistent or recurrent portal hypertension. Portal vein thrombosis that occurs in the immediate posttransplant period should prompt operative exploration and revision to ensure there is not a technical error in construction of the anastomosis. Management of posttransplant portal vein thrombosis that occurs more indolently requires understanding of mesenteric venous anatomy, such that a venous-phase CT or more formal mesenteric angiography with venous runoff is needed. Ligation or embolization of collateral venous channels may be necessary to ensure adequate flow to keep the transplant portal vein patent.

Hepatic venous outflow stenosis is a rare complication that can be complicated to diagnose and treat. When outflow stenosis presents in the immediate posttransplant period, or even in the primary operation, graft congestion and dysfunction can develop immediately. Surgical revision of the outflow may be necessary, which is a high-risk and difficult procedure that can cause significant graft injury during a time of vascular exclusion. When outflow stenosis develops in the posttransplant period, it is typically characterized with a clinical syndrome that may include persistent ascites, lower extremity edema, and renal dysfunction. Cross-sectional imaging studies and ultrasonography can be suggestive but not definitive for outflow stenosis, so direct caval venography with manometry is needed to make and localize the diagnosis of outflow stenosis. Balloon angioplasty and stenting can fortunately address most subacute venous stenoses without the need for operative revision.

Biliary Complications

Biliary complications are among the most common posttransplant complications, affecting 15% to 30% of recipients.[64] Patients with partial allografts are at highest risk for biliary complications, particularly when reconstruction of segmental ducts is required. Biliary complications are likely multifactorial, related to technical factors, duct size, donor liver quality, and ischemia. Approximately 4% to 12% of patients will experience biliary leaks, which typically present in the first days to weeks posttransplant. Biliary leaks can present with sepsis and peritonitis and should be suspected in any posttransplant patient who develops infectious symptoms, ileus, or other evidence of clinical decline. In the absence of a direct evidence of bile from a surgical drain or peritoneal aspirate, direct cholangiography via ERCP or percutaneous cholangiography is needed to make a diagnosis (**Fig. 37.14**). Management of biliary leaks should be catered to the clinical context and patient condition. Early leaks, particularly when associated with evidence of intra-abdominal sepsis, should prompt consideration of reoperation, washout, and surgical revision. Less acute leaks in stable patients can be managed with drainage of peritoneal bilomas or ascites and endoscopic stenting. Percutaneous transhepatic cholangiography and placement of an external biliary drain may be necessary with a biliary enteric anastomosis.

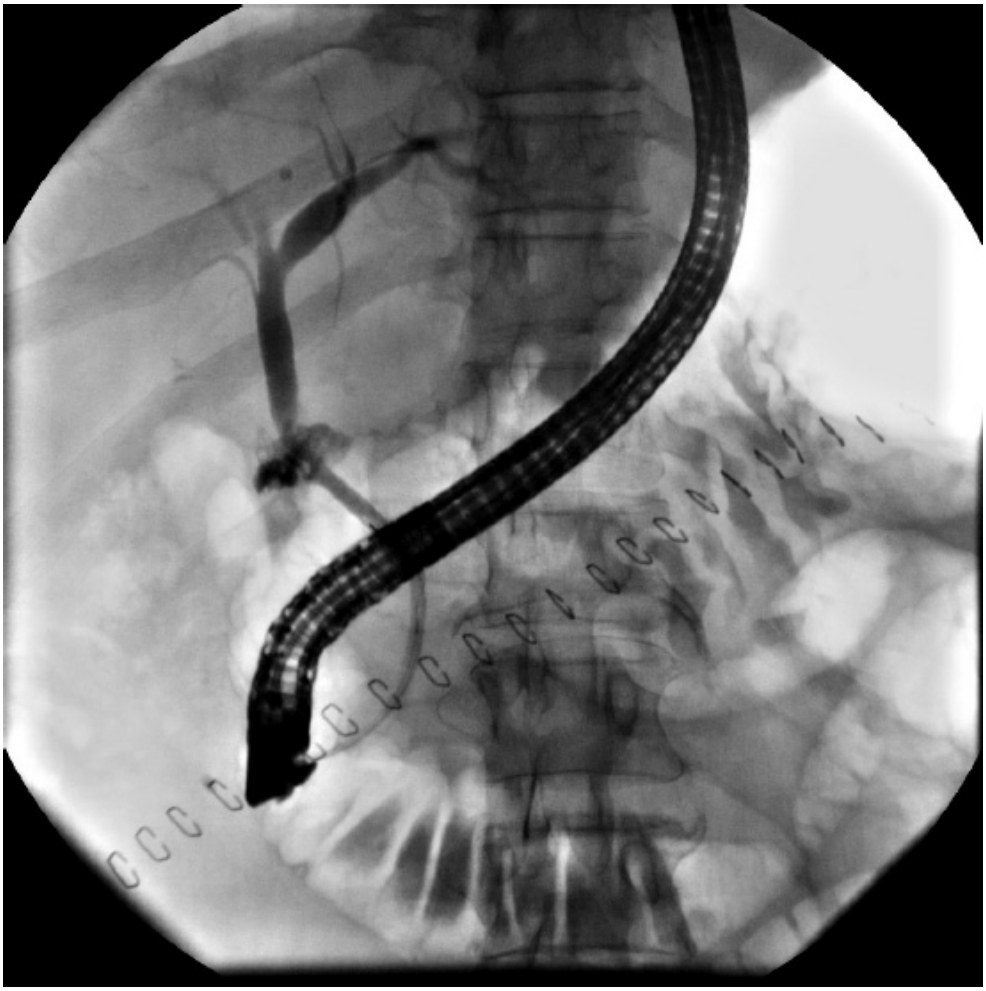


Figure 37.14 Endoscopic retrograde cholangiogram demonstrating a biliary anastomotic leak. (Photo belongs to Dr. Sonnenday.)

Biliary stricture occurs in 10% to 20% of liver transplant recipients and may present months or even years posttransplant. Recipients with a previous leak are at risk for stricture development, as well as patients who receive DCD donor livers and patients with hepatic artery complications.[65] The majority of biliary strictures are anastomotic and can be dealt effectively with endoscopic or percutaneous dilatation and stenting. Use of self-expanding fully covered metal stents has further expanded nonoperative management options with fewer endoscopic procedures.[66] Surgical revision should be reserved for patients who fail endoscopic management.

Immunologic Complications

For reasons that are not fully elucidated, liver transplant recipients require less immune suppression than patients with other types of allografts, such as heart, lung, and kidney recipients. This is somewhat surprising given that the mass of the liver is so great compared with the mass of the other organs. With current immunosuppressive therapy, graft loss from rejection is rare.

Antibody-Mediated Rejection

The liver is relatively resistant to injury from recipient antibodies, regardless of whether they are present at the time of transplant or develop later. This is very different compared with renal and cardiac recipients who experience rapid graft destruction, termed hyperacute rejection, if performed in a patient who has complement-fixing antibodies directed against the donor organ in significant concentrations at the time of transplantation. Hepatic graft injury from pre-existing antibodies directed at donor ABO determinants does occur, but in a much less pronounced fashion than in the context of renal transplantation. The overall results of ABO-incompatible liver transplants are somewhat inferior to those of ABO-compatible transplantations, but only by about a 10% to 20% decrease in 1-year graft survival rates compared to ABO-compatible grafts. Some of this decrease in graft survival rate may be due to the fact that ABO-incompatible transplants are usually performed only in dire circumstances where the patient is so ill that he or she may not survive the wait for a compatible organ. Because preformed antibodies do not seem to be clinically important, most transplantation programs do not perform prospective crossmatch between recipient serum and donor cells before transplantation, and determination of recipient and donor HLA type is no longer considered mandatory.

Why the liver is less susceptible to antibody-mediated destruction than the kidney is not clearly understood. One factor may be the vastly different microcirculation that the liver has compared to the kidney, with a preponderance of sinusoidal channels and a smaller capillary network. It is probable that antibody-mediated injury affects blood flow through the delicate capillary network of the kidney more than it does to the liver sinusoids. In addition, each hepatocyte is exposed to two sinusoidal channels, presumably permitting survival if only one sinusoid is occluded. Finally, differences in HLA antigen expression are known to exist in the two

organs, with the kidney the more antigenic of the two. The clinical impact of antibody-mediated injury in liver transplantation is still being deciphered, with evidence to suggest cumulative injury may compromise allograft function.[67,68]

Cellular Rejection

Typically, acute rejection in liver transplant recipients is cell mediated and occurs frequently but is effectively blunted by antirejection therapy. Acute rejection occurs most commonly in the first two postoperative months and occurs in up to 25% of patients in the first-year posttransplant. In modern practice, cell-mediated rejection is a less common cause of graft loss than are primary nonfunction or hepatic artery thrombosis. Still, the effectiveness of antirejection treatment assumes a relatively early diagnosis and treatment of acute rejection, which is in turn the result of careful monitoring by the transplantation physician and compliance by the patient with frequent laboratory testing. Treatment of acute rejection with enhanced immunosuppressive therapy is highly effective, and an episode of rejection does not affect long-term graft survival. This is very different from renal transplantation, where an episode of rejection decreases long-term graft survival markedly. The diagnosis of cell-mediated rejection is made primarily on a histologic basis. Clinical features can include low-grade fever and malaise, but frequently the patient is completely asymptomatic. Laboratory evaluation of peripheral blood may demonstrate leukocytosis and occasionally eosinophilia. Biochemical changes associated with rejection include elevated and rising levels of serum transaminases and alkaline phosphatase. A prolonged serum prothrombin time and an abnormal serum bilirubin also suggest the possibility of rejection, but frequently these parameters are normal if rejection is detected early. Any of these findings should prompt a biopsy.

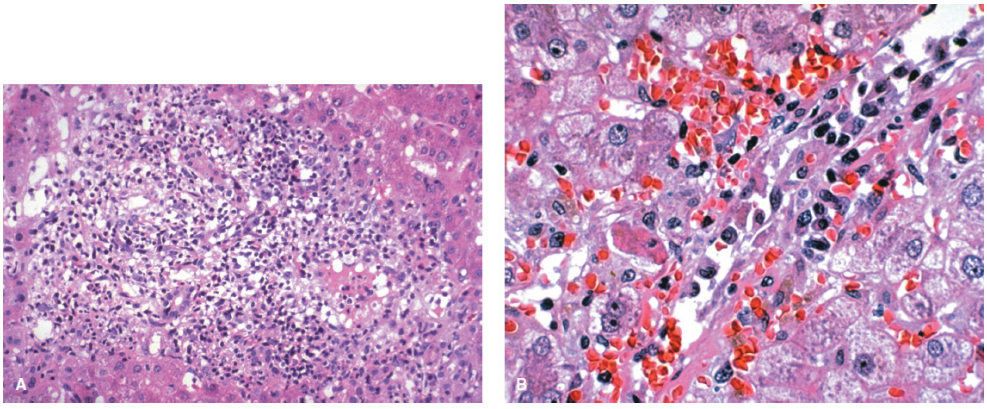


Figure 37.15 Acute rejection of a liver transplant. **A:** A portal tract is expanded by a polymorphous inflammatory infiltrate consisting of large and small lymphocytes, plasma cells, macrophages, and neutrophils. The bile ducts (*arrows*) are damaged and inflamed. **B:** A central vein from the same biopsy exhibits endothelialitis, characterized by swollen endothelial cells and infiltrating lymphocytes. (From Thung SN, Gerber MA. Histopathology of liver transplantation. In: Fabry TL, Klion FM, eds. *Guide to Liver Transplantation*. New York: Igaku-Shoin Medical Publishers; 1988.)

The diagnosis of cell-mediated rejection rests on the finding of a triad of portal lymphocytosis, endotheliitis (subendothelial deposits of mononuclear cells), and bile duct infiltration and damage (**Fig. 37.15**). Various classification schemes have been devised to grade the severity of the rejection process based on the degree of cellular involvement or injury in these areas. Cell characterization studies have documented that the cells in the portal triads are primarily T cells, with fewer macrophages and neutrophils. Bile duct epithelial cells appear to be a prime target of immune attack, and they are known to express large amounts of class II HLA antigen.

If the recipient has hepatitis C, it is critical that recurrent hepatitis C is differentiated from acute rejection. At times, the difference can be subtle, and a pathologist with experience in the interpretation of allograft biopsies is extremely valuable. Enhanced immunosuppression is associated with accelerated rates of hepatitis C viral replication; it is, therefore, important that immunosuppression is kept to a minimum for these patients.

Chronic Rejection

Chronic rejection is characterized by ongoing and often subacute immune injury, with particular impact on small bile ducts. Clinically, the pattern is

one of gradual elevation of alkaline phosphatase and bilirubin, in the absence of obstruction of the large bile ducts. Histologically, small bile ducts are obliterated or completely absent, with a less pronounced cellular infiltrate than is seen with acute rejection. This finding has been termed vanishing bile duct syndrome when bile ducts are absent in 15 of 20 portal triads examined. The loss of small bile ducts is partly the result of lymphocyte-directed attack on biliary epithelium. Relative to other cells in the liver, biliary epithelium tends to express more class I antigen. Thus, biliary epithelial cells are vulnerable targets for host attack because of their antigenicity. Loss of bile ducts may also occur indirectly as the result of ischemia secondary to immune-mediated obliteration of small to medium arteries. While the biliary injury and ductopenia may not improve significantly histologically, patients may stabilize clinically with increased tacrolimus-based immunosuppression.[69]

Immunosuppression Induction and Maintenance

Multiple immunosuppressive protocols achieve acceptable suppression of allograft rejection for liver transplant recipients. Induction with antithymocyte globulin or other induction agents is no longer considered to be mandatory but is used at some centers. Similarly, prednisone therapy, once considered a mainstay of a successful immunosuppressive protocol, is often tapered off rapidly. Treatment with a calcineurin inhibitor, either cyclosporine or tacrolimus, is still considered to be imperative for most liver transplant recipients. These agents are associated with significant long-term morbidity, particularly the development of chronic renal failure. Dosages of these agents have gradually been reduced both to prevent renal insufficiency and to avoid the rapid and aggressive recurrence of hepatitis C infection. Induction antibody therapy with either polyclonal antilymphocyte preparations or with inhibitors of the receptor for IL-2 are still used commonly in the perioperative setting to avoid the nephrotoxicity associated with the immediate use of calcineurin inhibitors.

Because immunosuppression predisposes to infection, prophylactic anti-infective drugs are usually administered. Trimethoprim-sulfamethoxazole,

dapsone, or pentamidine is recommended to prevent *Pneumocystis carinii* infection. Oral mycostatin or fluconazole therapy is used to prevent fungal infections, particularly esophageal *Candida albicans*. Either ganciclovir or valganciclovir is prescribed for patients who are at risk for CMV infection, which includes any patient exposed to CMV in the past and any patient transplanted with organs from a donor who has been exposed to CMV. Patients who are CMV negative who receive CMV-negative organs are not at high risk for CMV infection but should still receive prophylaxis against disseminated herpes simplex infections with acyclovir therapy. The duration of prophylactic anti-infective therapy has not been rigorously defined by evidence-based trials and is therefore dependent on each center's experience with the prevalence of these infections in its patient population.

Treatment of Acute Rejection

Despite the overall effectiveness of the regimen described, acute rejection does occur and must be treated promptly. Several options are available for treatment of acute rejection, depending on the clinical circumstances. Traditionally, high doses of methylprednisolone are administered (usually 500 mg to 1 g) intravenously on a daily basis for 3 days. This treatment is effective in reversing most acute rejection episodes. Alternatively, increased doses of oral prednisone, a calcineurin inhibitor, or the addition of an antimetabolite drug, such as mycophenolate mofetil, will also reverse most episodes of rejection, particularly if the rejection is mild. Rejection that is resistant to these maneuvers or severe is treated with antilymphocyte therapy, typically a polyclonal antilymphocyte therapy such as Thymoglobulin. These treatments are typically administered daily for 3 to 7 days. These agents are highly effective, and it is unusual to lose an allograft secondary to acute rejection. However, these treatments are associated with profound and long-lasting immunosuppression, and it is usually advisable to restart prophylactic anti-infective therapies when they are initiated.

Liver transplantation remains the definitive therapy for patients with ESLD and select metabolic diseases and hepatic malignancies. Despite an aging patient population with more comorbid disease, short- and long-term outcomes after transplantation continue to improve. Graft loss due to immunologic causes is rare, and long-term threats to graft and patient

survival include chronic kidney disease, cardiovascular disease, and malignancy, all of which are associated with the need for lifetime immunosuppression. Given the success of liver transplantation as a durable therapy for ESLD, the primary challenge in the field remains expanding donor organ availability to allow expansion of this lifesaving therapy to more patients with chronic liver disease.

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38

Cardiac Transplantation

Ahmet Kilic and Robert S. D. Higgins

Key Points

1. Heart transplantation is the gold standard of biologic replacement for end-stage heart failure; however, its long-term success and growth is limited by donor availability, perioperative infections, and cellular rejection and the development of malignancies and transplant allograft vasculopathy.
2. Patients with end-stage myocardial dysfunction refractory to conventional methods, including advanced heart failure therapies and revascularization, may require mechanical circulatory support (MCS) as bridge to transplantation (BTT).
3. MCS using left ventricular assist devices (LVADs) has developed as an effective means of circulatory support and end organ perfusion; however, complications of LVADs are common including driveline infection, pump thrombosis, strokes, allosensitization, and gastrointestinal bleeding.

HISTORICAL PERSPECTIVE

The original technique described by Lower and Shumway and perfected in the laboratory at Stanford in the 1960s confirmed that the denervated heart could function to support the circulation in the transplant recipient (**Fig. 38.1**).[1] This technique has evolved over the past 50 years to be the ultimate biologic 1 replacement and surgical intervention for patients with advanced heart failure, refractory to medical therapies. During that time, a number of extraordinary advancements continued to enhance the ability to overcome inherent obstacles imposed by the body's immunologic response to biologic replacement by a foreign organ. In addition to demonstrating the technical aspects of successful transplantation, the development of a technique to perform transvenous endomyocardial biopsies for immunologic surveillance was also a breakthrough milestone at Stanford. This innovation provided tissue to characterize the nature of acute cellular rejection and enable earlier rejection detection, leading to treatment with augmented immunosuppression.[2] One of the most influential advances in the field of modern transplantation was the development and application of cyclosporine, a powerful immunosuppressant used as part of the triple immunosuppression protocol in solid organ transplant programs around the world and a breakthrough clinical application led by the Stanford Group and Roy Calne at Cambridge University.[3] Cyclosporine reduced the activity of the immune system by interfering with the activity and growth of T cells and its immunosuppressant activity is manifest by binding to a cytosolic protein cyclophylin of the lymphocyte. This complex of cyclosporine and cyclophylin then inhibits calcineurin that under normal circumstances is responsible for activating the transcription of interleukin-2 (IL-2). The success of cyclosporine in preventing organ prevention was shown in kidney transplants by Calne et al. at the University of Cambridge and in liver transplants by Thomas Starzl at the University of Pittsburgh. Cyclosporine was subsequently approved for use in 1983.[4]

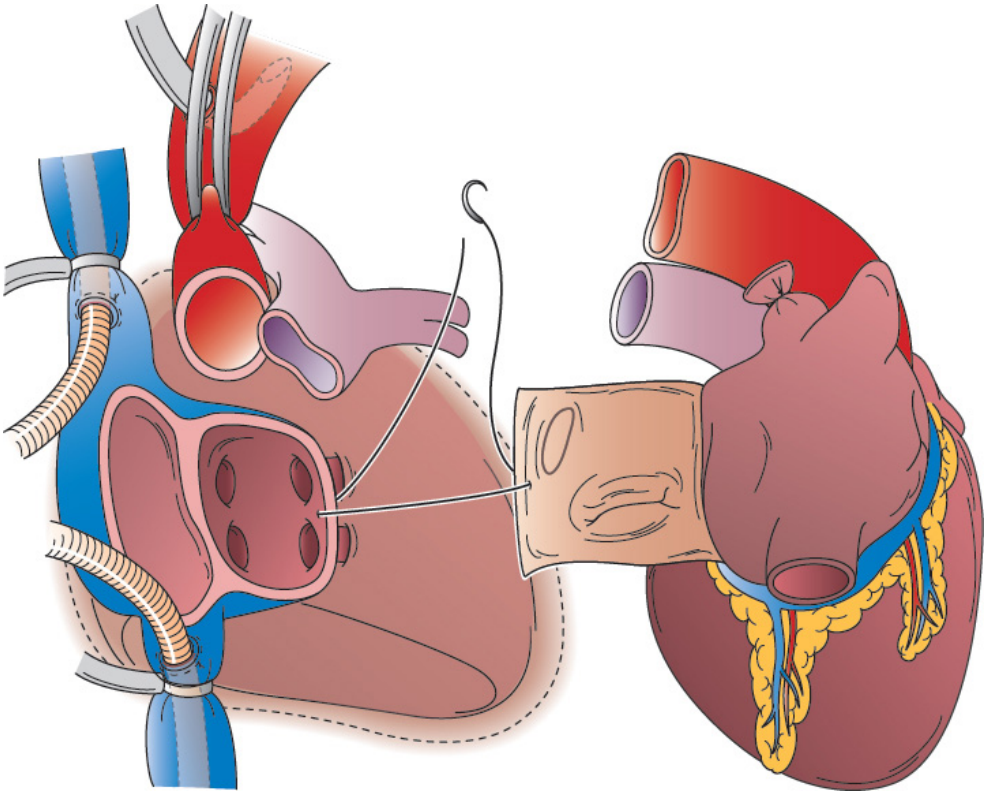
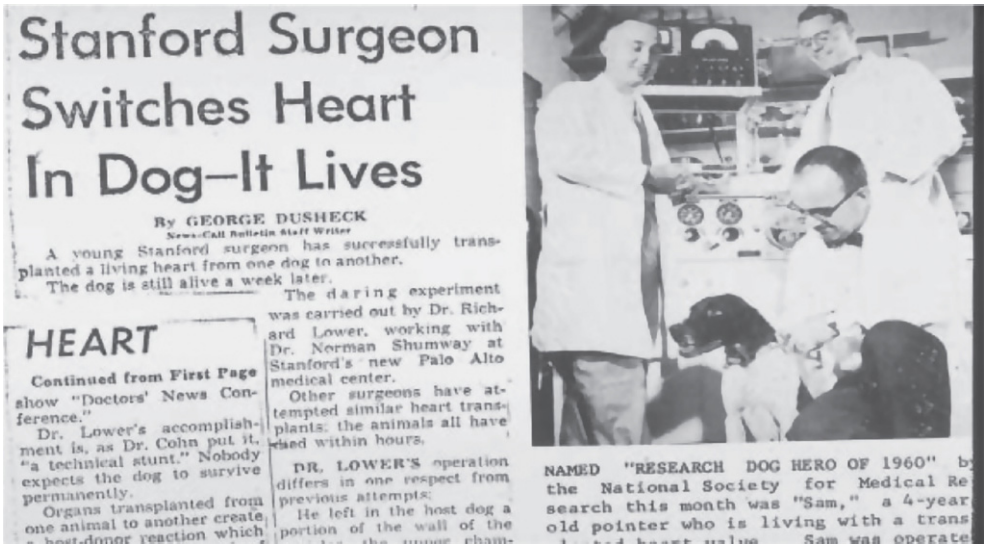


Figure 38.1 The implantation procedure is begun with the left atrial anastomosis.



Stanford Surgeon Switches Heart In Dog–It Lives

By GEORGE DUSHECK

A young Stanford surgeon has successfully transplanted a living heart from one dog to another.

The dog is still alive a week later.

The daring experiment was carried out by Dr. Richard Lower, working with Dr. Norman Shumway at Stanford's new Palo Alto medical center.

Other surgeons have attempted similar heart transplants; the animals all have died within hours.

DR. LOWER'S operation differs in one respect from previous attempts:

He left in the host dog a portion of the wall of the

HEART

Continued from First Page

show "Doctors' News Conference."

Dr. Lower's accomplishment is, as Dr. Cohn put it, "a technical stunt." Nobody expects the dog to survive permanently.

Organs transplanted from one animal to another create

NAMED "RESEARCH DOG HERO OF 1960" by the National Society for Medical Research this month was "Sam," a 4-year old pointer who is living with a trans

Figure 38.2 Hypothermia preservation research in the dog highlights human heart transplant potential at Stanford.

While the history of heart transplantation as documented above highlights a relatively uneventful path from concept to reality, the actual evolution toward human heart transplantation was a much more exciting journey with many

extraordinary twists and turns. Over the course of close to a decade of innovative research and laboratories in Minneapolis, Palo Alto, New York, and other laboratories around the world, the field of heart transplantation exploded in what can only be characterized as an extraordinary human drama.[1]

On the brink of successful transplantation in 1967, four very different surgeons and their groups were on the cusp of medical immorality, including Norman Shumway, who many believe was the father of the modern technique of midatrial excision of the heart and reimplantation developed in his laboratory while studying hypothermia and myocardial protection with his laboratory partner and future competitor Richard Lower (**Fig. 38.2**). Adrian Kantrowitz pushed the process in the hopes of saving neonates and babies with developmental anomalies in New York. Dr. Kantrowitz performed the first pediatric transplant in New York. He also laid the foundation for formulating the brain death criteria, which later was developed by the Ad Hoc Committee on Brain Death Criteria of the Harvard Medical School. However, the ultimate winner of the race to immortality was Barnard, who gained worldwide recognition by capitalizing on the application of this innovative technique to perform the first human heart transplant in Cape Town on December 3, 1967.[5] Although the patient died 18 days later from infectious complications, history was made and the future was defined as advancements in surgical technique, immunosuppression, and patient selection led to improvements in outcomes leading to peaks in heart transplantation performance in the early 1990s.

INDICATIONS FOR TRANSPLANTATION

Over 5 million Americans suffer from heart failure and more than 250,000 die annually. Current therapeutic interventions are focused on the appropriate assessment of myocardial dysfunction as a means to select the right patient for the appropriate procedure using state of the art myocardial viability testing and metabolic testing to determine if patients with advanced heart failure are candidates for conventional interventions, mechanical devices, or transplant. Heart transplantation is the treatment of choice for selected patients with advanced heart failure who have extraordinary limitations in

terms of their overall physical well-being and limited life expectancy, approaching less than 2 years.[6]

Cardiopulmonary stress testing is the most reliable and objective criterion, in addition to clinical criteria, to determine the extent of the critical advanced heart failure and the likely morbidity and mortality associated with class for heart failure (**Fig. 38.3**). The measurement of peak oxygen consumption (VO_2) has been shown to correlate with functional capacity and mortality. Mancini et al. were the first to demonstrate a relationship between peak oxygen consumption and outcomes (**Fig. 38.4**).[7] More recently, other measurements obtained during a metabolic exercise test have been shown to predict mortality in patients with end-stage heart failure. Peak oxygen consumption per unit time (VO_2) of less than 10 to 15 mL/kg/minute with respiratory exchange ratio greater than 1.05 is predictive of severely poor outcome. This value has been used as criterion for transplant waitlist selection.[8] These measurements include the slope of the relationship between ventilation and carbon dioxide production (Ve/VCO_2 slope), end-tidal carbon dioxide (CO_2), the oxygen uptake efficiency slope, and the rate of heart rate recovery.[9] Based on this data, metabolic exercise testing is now routinely performed in the assessment of patients for heart transplantation.[10]

2 Additional criteria of a clinical nature include repeated hospitalizations for heart failure therapy, progressive increases in heart failure medications, and the need for mechanical circulatory support (MCS), such as an intra-aortic balloon pump or MCS with a left ventricular assist device (LVAD). Selection criteria for heart transplantation have been well-defined and suggest that evaluation by a multidisciplinary team of healthcare professionals, nurses, and physical therapists, is the best means to determine those at greatest risk for high mortality and potential benefit for transplantation (**Fig. 38.5**).

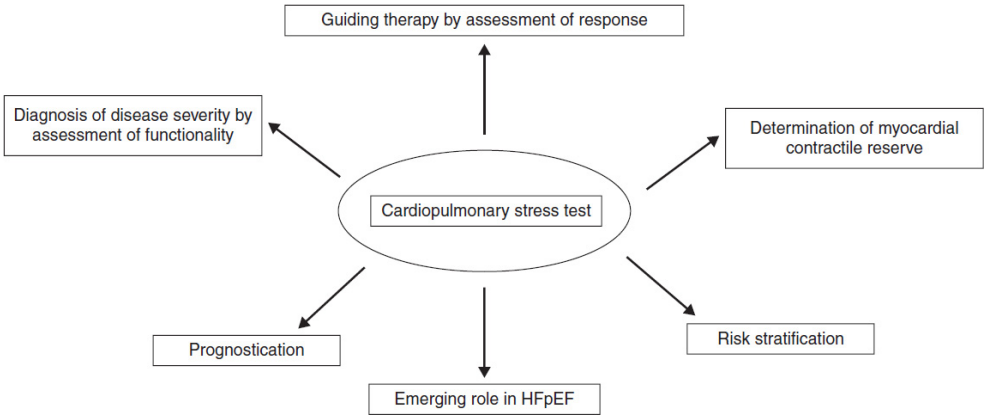


Figure 38.3 Uses of cardiopulmonary stress tests in heart failure.

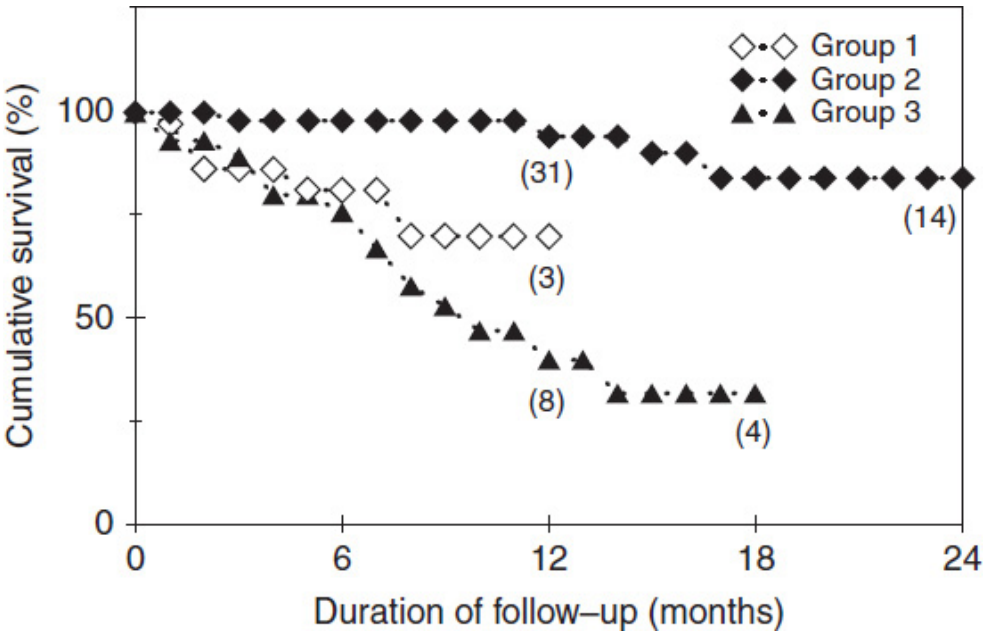


Figure 38.4 Survival curves comparing groups 1, 2, and 3. Survival curves for groups accepted (1) and rejected for transplant (3) are similar but are significantly reduced compared with group 2 ($p < 0.001$).

PRETRANSPLANT MANAGEMENT

During the past decade, there have been significant advancements in the therapy of heart failure. The use of beta adrenergic blockers, aldosterone antagonists, implantable cardioverter defibrillators (ICDs), and biventricular pacemakers (CRT devices) have all been shown to improve mortality in patients with advanced heart failure.[11,12] Despite demonstrated improvement

in mortality, only biventricular pacemakers have led to improved exercise capacity.[13–15]

The majority of patients with advanced heart failure have secondary end-organ dysfunction, including reductions in renal perfusion leading to renal failure, evolution of secondary pulmonary hypertension, and eventual irreversible pulmonary hypertension leading to the risk of right ventricular failure in the immediate perioperative period after transplantation. Therefore, selection criteria related to assessments of pulmonary vascular bed resistance and irrevocable pulmonary hypertension can often eliminate patients from consideration for transplantation. Perioperative assessment of the pulmonary vascular bed is then necessary to avoid patients with irreversible pulmonary hypertension and multiple therapies can be used to mitigate the impact of advanced heart failure, including nitroprusside, nesiritide, dobutamine, and inhaled nitrous oxide. Milrinone, a phosphodiesterase inhibitor, has been highly effective over the years and is often used to determine if pulmonary hypertension is irreversible and/or treatable. If pulmonary hypertension is controlled, then the patient may be considered for transplantation. Other end-organ dysfunction, which may result from advanced heart failure and compromise perioperative success, include:

NYHA Class	Patients with Cardiac Disease (Description of HF Related Symptoms)
Class I (Mild)	Patients with cardiac disease but without resulting in limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation (rapid or pounding heart beat), dyspnea (shortness of breath), or anginal pain (chest pain).
Class II (Mild)	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III (Moderate)	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
Class IV (Severe)	Patients with cardiac disease resulting in the inabiltiy to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Figure 38.5 NYHA functional classification. (The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, MA: Little, Brown & Co; 1994:253–256.)

American Heart Association Heart Failure Stages

- **Stage A:** Presence of heart failure risk factors but no heart disease and no symptoms
- **Stage B:** Heart disease is present but there are no symptoms (structural changes in heart before symptoms occur)
- **Stage C:** Structural heart disease is present AND symptoms have occurred
- **Stage D:** Presence of advanced heart disease with continued heart failure symptoms requiring aggressive medical therapy

Figure 38.6 AHA heart failure stages.

- Renal failure
- Diabetes or complications of end-organ diabetes
- Previous malignancy within 5 years of transplant consideration
- Hepatic insufficiency
- Psychosocial noncompliance
- Active substance abuse, including smoking and illicit drug use
- Lack of social support sufficient to address the perioperative needs of the patient

All of these factors serve to limit the success of transplantation in the modern era.

Right heart catheterization is often used to determine the suitability of the transplant patient and allows direct measurement of right atrial pressure, pulmonary capillary wedge pressure, pulmonary artery pressure, and mixed venous artery saturation. It can also be used to guide optimal medical therapy in patients with advanced heart failure and elevated filling pressure despite optimal treatments. Other biomarkers, such as natriuretic peptide levels, can be predictive of prognosis in those with advanced heart failure and used as a marker for improvements with medical therapy.[16] A number of prognostic heart failure scores have been developed, including the Seattle Heart Failure Model and the Heart Failure Survival Score in advanced heart failure populations.[17] These estimates can correlate with American Heart Association Heart Failure Stages to guide additional therapies and improvements in outcomes over time (**Fig. 38.6**).

PRETRANSPLANT ASSESSMENT

A number of pretransplant investigations are necessary as part of the selection process and can often identify contraindications of transplantation as listed. Blood group and tissue typing are also necessary in patients being considered for transplantation, as well as the presence of secondary infection, such as hepatitis B, hepatitis C, HIV, Epstein–Barr virus, hemoglobin A1c, diabetes, herpes simplex, and cytomegalovirus (CMV).

Patients who have been ill and requiring multiple transfusions can often be allosensitized to human leukocyte antigens (HLAs). This sensitization may also occur in women who have been pregnant or previously transplanted. This can have an impact on the chances of successful donor-recipient matching and is factored into the time of listing of heart transplantation.[10,18] Active contraindications include active infection, peripheral vascular or cerebral vascular disease, diabetes with end-organ damage, current neoplasm within 5 years, severe lung disease, irreversible renal dysfunction with a glomerular filtration rate (GFR) estimated less than 30 mL per minute, irreversible liver dysfunction and cirrhosis, recent pulmonary embolism, pulmonary hypertension with systolic arterial pressure greater than 60 mm,

transpulmonary gradient greater than 15, or a pulmonary vascular resistance greater than 5 Wood units. Physiologic manipulation with pharmacologic drugs may unload the ventricle and demonstrate reversibility of pulmonary hypertension.[19]

ORGAN AVAILABILITY AND ALLOCATION

The Organ Procurement and Transplantation Network (OPTN) brings together medical professionals, transplant recipients, and donor families to develop organ transplantation policy. Organ Procurement and Transplant Network (OPTN) policies affect all U.S. transplant centers, organ procurement organizations (OPOs), and candidates waiting for an organ transplant. OPTN maintains data on over 120,000 potential transplant recipients of all organs including heart, lung, liver, kidney, liver, and pancreas. The current OPTN system has identified four major limitations:

- Too many status 1A heart transplant candidates;
- Too many exception requests required for allocation of transplant organs;
- Increased use of MCS devices for patients with advanced heart failure not accommodated by current system; and a geographic sharing scheme that is not equitable for those waiting on the list.[20]

In 2018, the OPTN/UNOS Thoracic Organ Transplantation Committee proposed modifications to the adult heart allocation system to better stratify the most medically urgent heart transplant candidates, reflect the increased use of mechanical circulatory support devices (MCSDs) and prevalence of MCSD complications, and address geographic disparities in access to donors among heart transplant candidates. Concerned that the former three-tier system did not prioritize enough urgency for these patients, UNOS has implemented a six-tier system with more specific guidelines for each tier. The new allocation system assigns patients on extracorporeal membrane oxygenation (ECMO) devices the highest priority.[21] This may evolve as a heart allocation score similar to the Lung Allocation Score (LAS) and the model for end-stage liver disease (MELD) scores utilized for lung and liver transplantation.

In a different approach to enhance organ allocation in EUROTRANSPLANT countries, a cardiac allocation score was developed

and then revised in Germany.[22] The idea behind the cardiac allocation score, similar to the established LAS in lung transplantation, is to provide middle ground between risk and benefit. Risk of mortality on the waiting list is based on the Seattle Heart Failure Model and posttransplant outcomes are predicted by the Index for Mortality Prediction After Cardiac Transplantation score (IMPACT score). Patients who have a high urgency and a high chance of a successful posttransplant outcome will have the highest cardiac allocation score and are assigned the highest priority in the allocation process.[23]

MCS has been employed for advanced heart failure since the 1990s, when the Federal Drug Administration approved volume displacement pumps (LVADs). Two general indications to support the failing heart have evolved since then: to act as a bridge to transplant (BTT) and to be a destination therapy (DT) to support cardiac function for the remainder of the patient's life.[24] Some patients may require support until their general medical condition improves or until they become a better candidate eligible for transplantation (bridge to decision or eligibility).[25]

3 Continuous flow pumps have emerged as the preferred MCS for patients with left ventricular failure awaiting heart transplantation or as DT. LVADs restore cardiac output and tissue perfusion, therefore improving end-organ function. The two currently approved LVADs have inlet and outflow ports with a single rotary element that rotates to propel blood to the aorta, leading to increased arterial blood pressure and flow. Blood is drawn into the pump impeller from the left ventricular apex and delivered to the aorta. There are two LVAD blood flow configurations: axial and centrifugal flow pumps. In the centrifugal flow pump, blood is captured between the blades, which spin at right angles to the outflow. In the axial flow pump, the rotating impeller operates like a propeller in a tube. The three commercially approved LVADs are the Heartmate II and III (Thoratec/St. Jude Corp.) and the Heart Ware HVAD (Heart Ware/Medtronic Inc.) (**Fig. 38.7A–C**). Through documentation and reporting in clinical databases like INTERMACS and the International Society of Heart and Lung Transplantation (ISHLT) Registry, LVADs have demonstrated effective performance profiles, improved systemic perfusion, and enhanced outcomes. The databases also show that complications of MCSDs are common—the most common complications being driveline infections, cannula obstruction, gastrointestinal bleeding, and

device can lead to inflow or outflow obstruction and subsequent device power surges (**Fig. 38.8**). Predisposing factors include shear stresses in blood flow, cannula malposition, disturbances in von Willebrand factor levels (deficiency), and heparin-induced thrombocytopenia. Starling et al. reported an increase in the rate of device thrombosis in patients with HeartMate II in 2014.[26] Based upon data from three institutions with experience in 837 patients, a total of 72 pump thromboses were confirmed in 66 patients. They reported that elevated lactate dehydrogenase (LDH) levels presaged thrombosis. The majority of patients underwent pump replacement and 11 patients underwent urgent transplantation. In the most recent clinical study of 366 patients comparing survival of patients using the HeartMate 3 LVAD to those using the HeartMate II LVAD, they reported that 77.9% of the HeartMate 3 patients, as compared to 56.4% of the HeartMate II patients, survived to 2 years without a disabling stroke and without the need to replace the pump.[27] About 1.6% of the HeartMate 3 patients needed the pump replaced within 2 years, compared to about 12.2% of the HeartMate II patients.

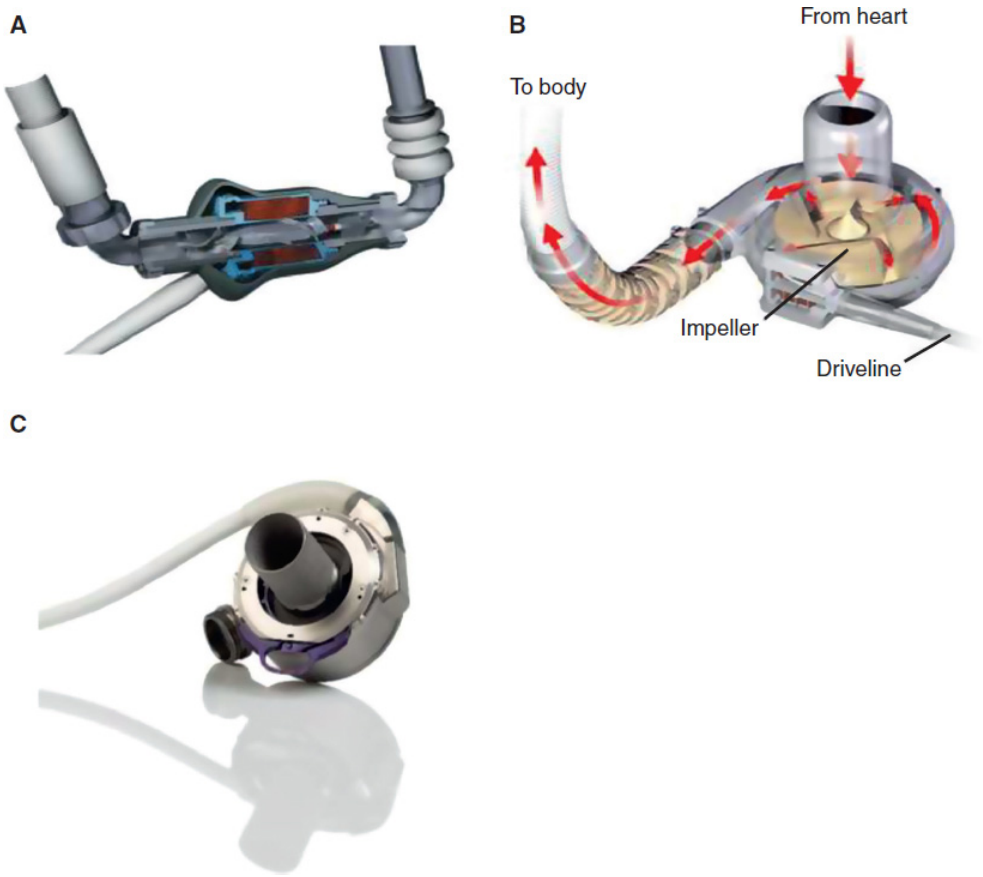


Figure 38.7 **A–C:** Heartmate II and III (Thoratec/St, Jude Corp.) and the Heart Ware HVAD (Heart Ware/Medtronic Inc.).

LVADs can stimulate the development of alloreactive antibodies.[18] Panel reactive antibody (PRA) screening is done in all heart transplant candidates and further evaluation is needed if PRA levels are elevated above 10% to 20%. The factors involved leading to sensitization are homograft use in congenital surgery, female sex, prior pregnancies, Black race, VAD surface exposure, retransplantation, perioperative blood products usage, and infections. Acute antibody-mediated rejection (AMR) occurs in about 10% and this is usually due to antibodies driven by T cells to donor vascular antigens. This leads to B-cell activation and production of plasma cells. While difficult to diagnose, this rejection is typically associated with detection of immunoglobulins, complement fragments, CD 68 positive cells, and de novo anti-HLA antibodies.

Significantly improved survival is associated with treatment of PRA levels greater than 10%, aggressive desensitization with plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab.[28] IVIG is used to

neutralize preformed antibodies before and after transplantation, however the effectiveness is variable. Plasmapheresis is fast, short-lived, and can be done immediately before transplantation. Rituximab (anti-CD20) is frequently used and is effective in the long term. Immunoabsorption and splenectomy are rarely used as the rate of infection is very high with these therapies.

IMMUNOSUPPRESSION

Current immunosuppressive regimens can be classified as induction, maintenance, or antirejection. Induction regimens provide intense early postoperative immune suppression while maintenance regimens are used throughout the patient's life to prevent both acute and chronic rejection. Three general principles govern induction and maintenance immunosuppressive therapy regimens. The first principle is that immune reactivity and tendency toward graft rejection are highest early (within the first 3 to 6 months) after graft implantation and decrease with time. The second principle is to use low doses of several drugs with nonoverlapping toxicities in preference to higher (and more toxic) doses of fewer drugs whenever feasible. The third principle is to avoid overimmunosuppression, because it leads to a myriad of undesirable effects including susceptibility to infection and malignancy.

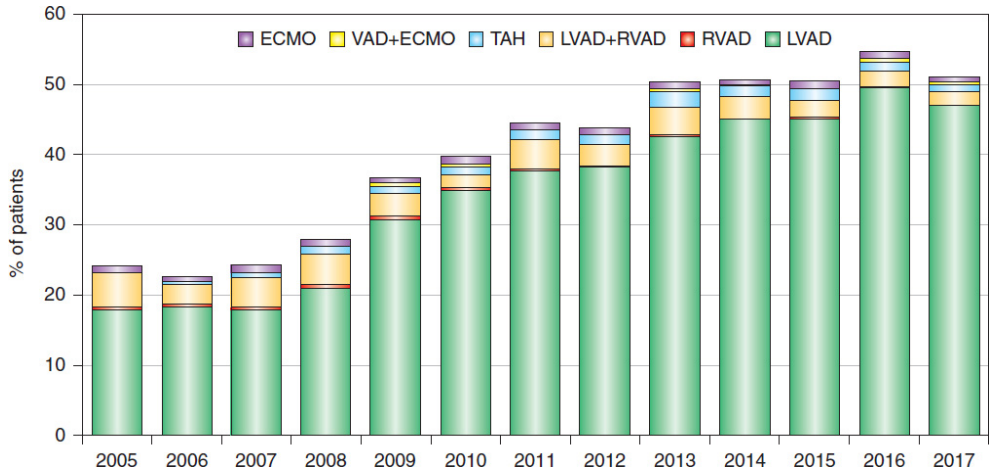


Figure 38.8 Percent of patients bridged with mechanical circulatory support by year and device type. (Adult heart transplants: 2005–2017.) ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; RVAD, right ventricular assist device.

Most modern immunosuppressive regimens consist of a two- or three-drug regimen, including a calcineurin inhibitor (typically tacrolimus), an antimetabolite agent (typically mycophenolate mofetil), and tapering doses of glucocorticoids over the first year. Although tacrolimus and cyclosporine are both highly effective agents, evidence from clinical trials suggests that tacrolimus-based immunosuppression may offer an advantage over cyclosporine-based regimens with respect to decreased rates of acute rejection and an overall more favorable metabolic derangement profile (decreased incidence of hypertension and hyperlipidemia but higher incidence of posttransplant diabetes). The proliferation signal inhibitors sirolimus and everolimus are typically used in patients with cardiac allograft vasculopathy (CAV) or renal insufficiency. Due to their inhibitory effects on smooth muscle proliferation and absence of intrinsic nephrotoxicity, they have been useful for slowing disease progression in these settings.

Current regimens use IL-2 receptor antagonists for induction therapy and these drugs are now used in 30% of patients undergoing heart transplantation. The currently available agent, basiliximab (Simulect), is a monoclonal antibody that selectively binds to the IL-2 receptor of T lymphocytes, blocks binding of IL-2 to the receptor complex, and exhibits its immunosuppressive effects by inhibiting IL-2-mediated T-lymphocyte proliferation.[29] There was a reduction in the incidence of acute rejection among patients treated with IL-2 receptor antagonists compared with no induction. There were fewer

rejection episodes among patients treated with polyclonal antibody induction compared with IL-2 receptor antagonist therapy, though the numbers of events were small.[30] In a retrospective analysis, antithymocyte globulin (ATG) was associated with better long-term survival at 5 and 10 years as compared to basiliximab.[31]

The absolute indications for induction therapy are not clearly defined, however, those patients at high risk for rejection (>5% at 1 year), younger patients, Black race, patients with a high number of human leukocyte antigen mismatches, and patients supported with ventricular assist devices with high levels of preformed antibodies, may get benefit from the induction therapy.[32]

DONOR SELECTION AND MANAGEMENT

Donor Selection

It is stated that if you have a good donor and a good recipient, you should always have a good outcome. Although this is a somewhat overgeneralization, it is paramount to match the individual recipient with the ideal donor. Particular attention should be paid to the age of the donor, function and quality of the donor heart, donor–recipient compatibility (gender, height, and body mass index), ischemic time, and preformed antibodies.[33] The ideal age for a donor is between 11 and 39 years old according to Kaplan–Meier survival stratified by age group in the UNOS database with a median survival for this age group of 11.5 years posttransplant. Following this, the donor age group of 0 to 10 years has a median survival of 10.6 years, that of 40 to 59 years 9.7 years, and those donors above age of 60 having a 7.4-year median survival. It is interesting to note that despite the scarcity of organs, over the past 30 years, the median donor age in the United States has remained between 25 and 30 years of age whereas in Europe the median age is around 45.[16]

Gender discordance has been recognized as a posttransplant risk particularly when female hearts are transplanted to male recipients.[34–36] In addition to gender matching, the importance of height, weight, body surface area, predicted heart mass, and body mass index have all been reported to potentially play a factor in success.[37–40] Another major influence in outcomes

following heart transplantation has been the ischemic time between the donor cross clamp and recipient reperfusion. This plays heavily in the decision making between donor availability and suitability for organ acceptance with the ideal ischemic time being less than 4 hours with most centers having a cap of around 6 hours. Indeed there is evidence of worse survival and higher rejection episodes within the first year post transplant, as well as higher chance of long-term CAV in those recipients having a longer than 6-hour ischemic time.[16]

Perhaps the single most important variable in donor selection is the quality or function of the donor heart. Oftentimes, the cause of death is secondary to a catastrophic event, such as an anoxic brain injury, stroke, or trauma that can lead to dynamic changes in the heart function. The body's response to the variety of neurohormonal changes are complex and a spectrum of physiologic effects can result including variations in blood pressure, volume status, and metabolic derangements, which all lead to conflicting reports of outcomes following transplantation utilizing these organs.[41,42] An important component of donor management has been the recognition of the sick thyroid syndrome, with most OPOs utilizing continuous thyroxine infusion during the periprocurement brain death period.

As a general rule, the function of the donor heart can be assessed in a step-wise fashion with the first step being the cause of death. Most clinicians would avoid the use of a donor heart where the mechanism of death was attributable to the heart like a lethal arrhythmia, a myocardial infarction, or a traumatic injury. In patients where there is a question as to the underlying cause, an electrocardiogram at admission and serially can help exclude coronary pathology, as well as serial troponin values. In patients with hypertensive stroke as the cause of death, careful evaluation must be made to ensure that the left ventricle is not overly hypertrophied (ideal left ventricular interventricular septum is <1.3 cm), as this can be a predictor for restrictive dysfunction of the allograft in the long term, as well as difficulty in myocardial preservation during the period of organ recovery in the immediate transplant period.

An essential part of the evaluation of the potential donor is an echocardiogram, which gives important information such as the ejection fraction, anatomic and physiologic abnormalities, ventricular hypertrophy, right heart function, the exclusion of masses or vegetation, and regional wall

abnormalities. Care should be taken to look at the amount of inotropic infusion during times of echocardiographic assessment. Whereas pressor requirement does not necessarily affect heart function, the number of and the dosage of inotropic support can serve as an important prognostic measure for the posttransplant primary graft dysfunction (PGD).

In patients with risk factors for coronary arterial disease (age >40, smoking, hypertension, diabetes mellitus, regional wall motion abnormality on echocardiogram), a left heart catheterization can provide information of coronary anatomy as well as left ventricular function and left ventricular end diastolic pressure. A right heart catheterization can be an adjunct test in patients where right heart function is in question. In combination with a central venous pressure, pressures obtained from a right heart catheterization can aid the clinician in deciding to use a potential donor heart.

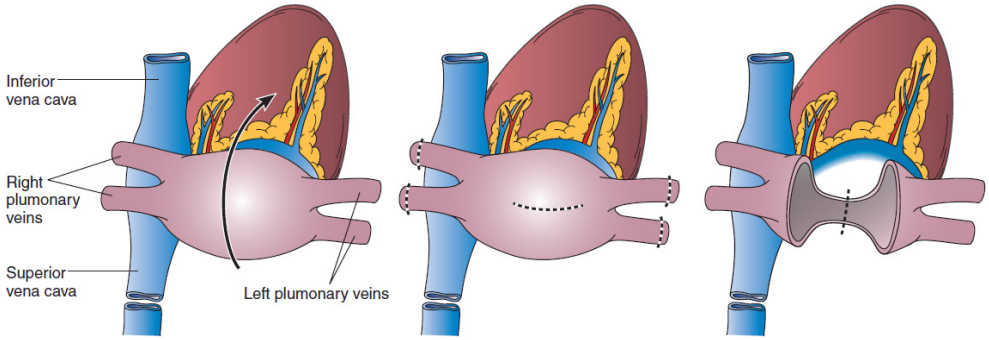


Figure 38.9 Steps to excise the donor heart with emphasis on adequate atrial cuffs (if lung procurement is also performed). (This image was produced by medical illustrator from Johns Hopkins–Timothy Phelps.)

Heart Procurement

After a donor is assessed to be appropriate for a given recipient, the goals of the procurement is to minimize ischemic time of the allograft, ensure no technical procurement injury to important structures, and to ensure optimal myocardial protection during the procurement and transportation. The acceptable ischemic time should have already been discussed prior to accepting an organ by members of the donor and implanting surgical team and constant communication between the procurement team and the recipient team can anticipate any delays or changes in either procedure.

Postprocurement function and myocardial protection during this time relies on ensuring that there is no distension of the heart, immediate induction of a diastolic arrest of the donor heart and avoidance of warm ischemia. During the donor procedure, after the systemic administration of heparin, an aortic cardioplegia line is placed in the midascending aortic portion as to allow safe placement of an aortic cross clamp. Once this is placed and the preservation solution is flushed, the process of organ procurement is started in coordination with the rest of the procurement team. The first steps in the procurement of the heart is to interrupt the systemic return of warm blood back into the heart and to avoid warm distension. To enable this, the superior vena cava (SVC) is ligated or clamped, followed by transection of the inferior vena cava (IVC). Then the aortic cross clamp is applied above the cardioplegia line and the infusion of the hypothermic (−4°C), preservation solution. The preservation solution may or may not contain free radical scavengers, but has a hyperkalemic content to ensure diastolic cardiac arrest for optimal myocardial preservation. It is imperative at this time to ensure appropriate delivery of the cardioplegia solution to the coronary arteries by manually checking the aortic root to make sure it is pressurized. In an expedited fashion and to avoid left ventricular distension, a venting cut must be made in the left side of the heart during this time. Potential sites, pending status of simultaneous lung recovery, are the left atrial appendage, the right superior pulmonary vein, or halfway between the distance of the circumflex artery and the left inferior pulmonary vein. Once again, it is of utmost importance at this time to avoid left ventricular distension and to get tactile and visual feedback to ensure a well-vented and decompressed heart. Simultaneously, topical ice and expeditious topical cooling is critical to check for the color of the effluent solution to turn clear, indicating circulation through the coronary system. Focusing on the technical aspects of the procedure ensure a donor cardiectomy that has appropriate cuffs for safe anastomosing into the recipient without compromise of blood flow (**Fig. 38.9**). The procurement of the heart is orchestrated with other organs—in particular, the lungs if they are to be utilized and to a lesser degree, the liver. The technical goals of the operation are to procure the following: a heart with aorta to the level of the great vessels, a pulmonary artery at the pulmonary bifurcation to not impinge on the pulmonary valve, as much length on the SVC as possible, enough length on the IVC as to be a safe distance

away from the coronary sinus without compromising the suprahepatic cava for the liver team, and most importantly, enough of a left atrial cuff that allows safe course for the left circumflex artery and the coronary sinus without damaging the pulmonary venous drainage for the lung team (**Fig. 38.10**). After ensuring no anatomic damage and the quality of the arrest, the organ is placed in a series of sterile plastic bags, labeled with the appropriate blood type and identification, and readied for transportation on ice.

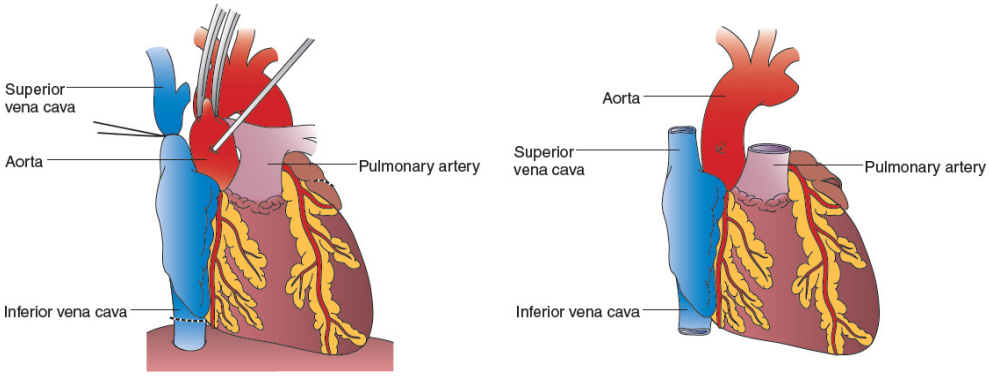


Figure 38.10 Donor heart with preservation canula in aortic root and occlusion of SVC with venting of heart at the IVC level during and after procurement in preparation for bicaval reimplantation. (This image was produced by medical illustrator from Johns Hopkins–Timothy Phelps.)

Key Concept

In summary, donor selection, management, and procurement requires experience, skill, and judgment that is often acquired over a period of time and is best managed in a multidisciplinary decision-making concept. The complex interplay between recipient and donor physiology, the neurohormonal derangements of the donor, and the optimization of the donor allograft before procurement, in transport, and early reperfusion are all key steps in optimizing success.

RECIPIENT MANAGEMENT AND PROCEDURE

There are a variety of indications for heart transplantation and each carries with it a different set of special anatomic and physiologic considerations.[10] Before entering the operating room for the recipient procedure, it is important to ensure one is as knowledgeable about the recipient as possible. Of note, about 50% of heart transplant recipients have had previous cardiac operations and up until the new heart allocation system the previous operation was an LVAD to act as a BTT.[43,44] In patients with a prior sternotomy, a preoperative computed tomography of the chest can help plan reentry as well as safe cannulation strategies.[45]

Patients who either have been maintained on anticoagulation with Coumadin or have other types of coagulopathy should have their effects reversed. This is essential for transplant success especially patients who have had a prior sternotomy and in particular in patients with an LVAD, given their acquired von Willebrand deficiency. The risk of bleeding must be weighed with the risk of thrombosis and this is paramount with early reports showing increased use of short-term mechanical support devices prior to transplantation.[46–48]

After optimization of the recipient before the operating room and in coordination with the donor procedure, the recipient is brought to the operating room with induction of anesthesia, vascular access for rapid volume infusion, venous access with ability to perform invasive hemodynamic monitoring of the new heart, transesophageal echocardiogram, and arterial line monitoring.

The recipient procedure is performed with the major principle of not taking on undue risks while minimizing warm ischemic time.[49] The commencement of the operation occurs after confirmation that the donor heart is of appropriate quality and match. The most common orthotopic techniques for the recipient portion are to utilize either the biatrial, bicaval, or total atriocaval technique of transplantation. In order to accomplish this, safe entry into the mediastinum needs to be achieved to perform a recipient cardiectomy. It should be noted that in cases of patients with LVADs, one must be weary of injury to the outflow graft, as well as the driveline, when trying to achieve safe entry. Likewise, previous patent grafts, coronary anatomy, systemic and pulmonary venous drainage, and other anomalies should be noted.

In order to establish cardiopulmonary bypass (CPB), venous drainage from the body to the circuit needs to utilize drainage from the upper and lower body. Bicaval cannulation is most commonly achieved via a cannula in the SVC and one in the IVC. In some cases, a femoral venous can be advanced into the junction of the IVC and right atrium as to allow safe drainage of the venous blood from the lower part of the body. Return of blood through the CPB circuit back to the body is achieved via arterial access with utilization of the ascending aorta, femoral artery, subclavian artery, and innominate artery all being viable options. Establishment of arterial access is paramount in protecting the patient from harm, especially in cases of prior operations.

CPB is initiated in anticipation of the arrival of the donor organ with some degree of hypothermic circulation. Once appropriate drainage and perfusion to the rest of the body is ensured, the heart is isolated by the use of caval snares. An aortic cross-clamp is applied and a recipient cardiectomy is carried out with the reimplantation technique in mind (**Fig. 38.11**). In general, unimpeded blood flow needs to be established from the systemic and pulmonary venous systems with outflow to the lungs and body being preserved. Prior to the start of the reimplantation, careful assessment and preparation of the donor heart is carried out on the back table.

The implantation procedure starts with the common left atrial anastomosis being the first connection performed using a running nonabsorbable suture for the most posterior structure to allow for clear visualization of all four of the pulmonary veins. This also allows the surgeon to avoid the potential complication of obstruction of the pulmonary venous drainage or an injury to the left circumflex artery that runs in the atrioventricular groove. The sequence of anastomoses can vary from surgeon to surgeon, however in general after completing the superior and inferior vena caval anastomoses, the aortic anastomosis can be performed to minimize the ischemic time, followed by the pulmonary arterial anastomosis. In general this sequence is selected to avoid distension of the nonbeating heart with return of pulmonary venous blood with either a left ventricular vent via the right superior pulmonary vein or by leaving open the left atrial appendage vent site from the procurement procedure.

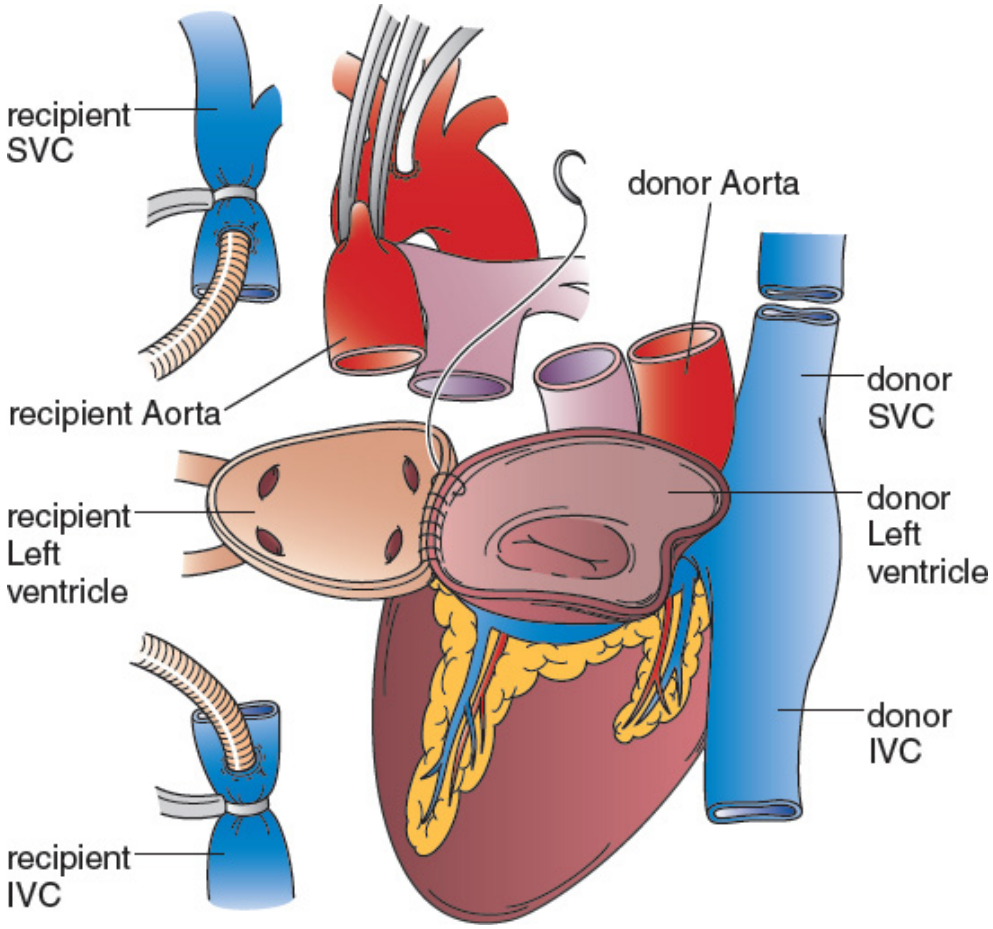


Figure 38.11 Bicaval implantation technique starting with left atrial anastomosis followed by inferior/superior vena cava anastomosis, pulmonary artery and aortic anastomosis. (This image was produced by medical illustrator from Johns Hopkins–Timothy Phelps.)

The systemic venous return anastomosis can either be performed with each cava separately or in a common chamber (biatrial) manner. For the inferior vena caval anastomosis, care must be taken with not only the Eustachian valve, but also the orifice of the coronary sinus. The SVC anastomosis cannot be narrowed by purse stringing the anastomosis, as it can lead to SVC syndrome. In addition, this is the preferred route of access for subsequent endomyocardial biopsies through the SVC to detect graft rejection.

The aorta or pulmonary artery are anastomosed next, but one needs to take care to avoid right ventricular distension if the pulmonary artery anastomosis is performed first. For this reason, if the pulmonary artery is anastomosed first, the anterior suture line is not completed to allow for decompression of the right heart until the aortic anastomosis is established and the heart is

allowed to beat with coronary perfusion. The ischemic time of the heart is deemed completed when the aortic cross clamp is released and coronary arterial blood flow is reestablished. A dose of steroids (500 mg) are often administered just prior to the release of the cross clamp to allow for maximal immunosuppression right before the donor heart is reperfused by the recipient's circulation. In addition, an aortic root vent is placed prior to the cross-clamp coming off and the patient is placed in Trendelenburg position (head down) to ensure that no air is embolized into the systemic circulation and also to aid with deairing of the coronary circulation. In cases of both the aortic and pulmonary anastomosis, the surgeon should be prepared to modify the anastomosis to perform an invagination technique when a large size discrepancy exists between the donor and the recipient vessels. Lastly, the surgeon must avoid excess tension on the anastomosis as well as overt redundancy to avoid kinking particularly of the pulmonary anastomosis.

Upon completion of the anastomosis for the heart, a period of reperfusion is carried out commensurate with the duration of ischemic time while rewarming the recipient to euthermia. During this time of reperfusion, care is taken not to distend the denervated heart with establishment of extrinsic rhythm via atrial and ventricular wires. In principle, tachycardia is welcomed as it avoids myocardial distension by keeping the volume low. To minimize myocardial distension, particularly the right heart which is more prone to dysfunction, a concoction of inhaled pulmonary vasodilators, chronotropic, inotropic, and vasopressor agents can be utilized. In addition to these and the extended time for reperfusion, hyperventilation is used to drive the PCO_2 down and hyperoxygenation can aid the freshly transplanted right ventricle. If these maneuvers are failing and there is evidence of PGD, early institution of MCS such as an intra-aortic balloon pump or even ECMO should be considered.

CURRENT OUTCOMES

Heart transplantation continues to evolve and improve, with major changes in allocation systems and the increasing use of extended-criteria donor hearts, including hearts from donation after circulatory death (DCD) donors, hearts supported with *ex vivo* perfusion, and hearts from hepatitis C viremic

donors. Ironically, the first human heart transplant donor came from a donor after cardiac death before modern legal criteria for brain death determination were developed in 1968.[5] The current use of such nontraditional donor hearts has made transplantation available to a larger number of recipients, but the demand continues to outpace the supply for recipients who are critically ill and waiting for advanced heart failure treatment around the world.

The annual ISHLT adult heart transplant report is based on data submitted to the ISHLT Thoracic Organ Transplant Registry of 146,975 heart transplants in recipients of all ages (including 131,249 adult heart transplants).[40] Since the registry's inception in 1982, a total of 481 heart transplant centers have submitted data, which is estimated to represent approximately 80% of the worldwide transplant activity (**Fig. 38.12**).

Survival

Outcomes following heart transplantation have improved significantly since the report of the first technically successful heart transplant in 1967.[50] The first decade of heart transplantation saw dismal postoperative outcomes with about 60% of patients surviving to 1 year post transplant.[51] The current 1-year survival now exceeds 90% and can be attributed to advancements in every aspect of heart transplantation. Indeed among the many improvements in clinical care has been patient selection (both recipient and donor), myocardial preservation, immunosuppression, importance of graft surveillance, and refined techniques in suppressing rejection episodes with patient-specific immunomodulation. The improvements in survival by era can clearly be seen with the current median survival of a heart transplant exceeding 12 years (**Fig. 38.13**). The median survival after adult heart transplants performed between 2002 and 2009 is 12.5 years extending to 14.8 years among 1-year survivors. As posttransplant survival has improved over time, survival within the first year post transplant and overall survival vary by primary diagnosis. For instance, patients transplanted for nonischemic and ischemic cardiomyopathy have the highest 1-year survival, while retransplants have the lowest survival rate.

Another improvement for outcomes may be the increasing number of patients who are transplanted after the placement of a durable LVAD. Posttransplant survival does not appear to be adversely affected by the

pretransplant use of an LVAD, alone or in combination with right ventricular support in univariate analyses. This strategy has led to improvements in patient survival while on the wait list, as well as equivalent outcomes post transplantation in patients bridged with LVAD to transplantation, as compared to those patients that were not bridged with a durable device.[52,53] However, it is important to recognize that selection bias may affect outcomes, since sicker patients on mechanical support may not survive through transplantation. Survival is notably lower in patients bridged to transplant with ECMO, particularly in the early posttransplant period. This observation is of interest given the recent change to the heart transplant allocation policy in the United States that prioritizes candidates supported with ECMO and other forms of acute MCS.[54]

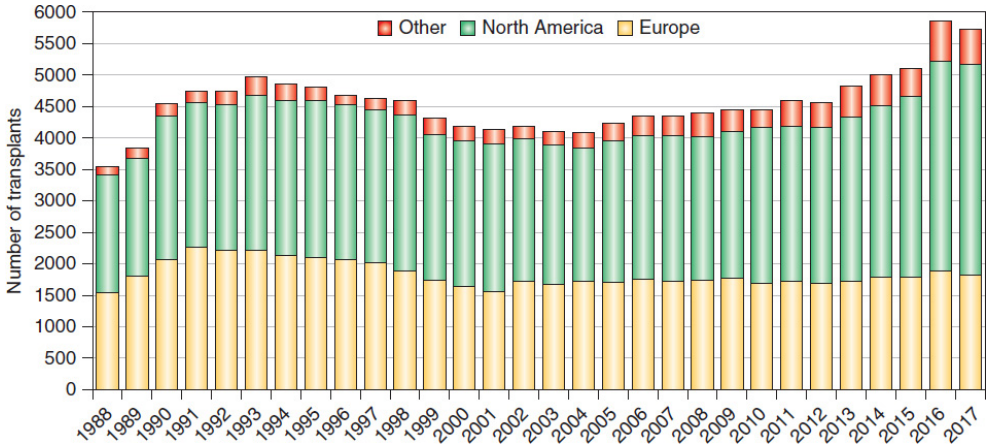


Figure 38.12 Number of heart transplants (adult and pediatric) by year (transplants: 1988–2017) and geographic region. (Khush KK, Cherikh WS, Chambers DC, et al. The international thoracic organ transplant registry of the international society for heart and lung transplantation: thirty-sixth adult heart transplantation report—2019; focus theme: donor and recipient size match. *J Heart Lung Transplant* 2019;38(10):1056–1066.)

In many regards, the quality of life and functional capacity that is restored after heart transplantation is as important as the time of survival post transplantation. Indeed, there is a significant improvement in the quality of life reported after heart transplantation.[55–57] The improvement in quality of life allows for patients to resume full activity, lead productive lives as part of the workforce, and have a higher perception of themselves with improved self-esteem. These metrics are adversely affected by the presence of and

severity of rejection episodes, highlighting the importance of reduction and management of complications for heart transplant recipients.

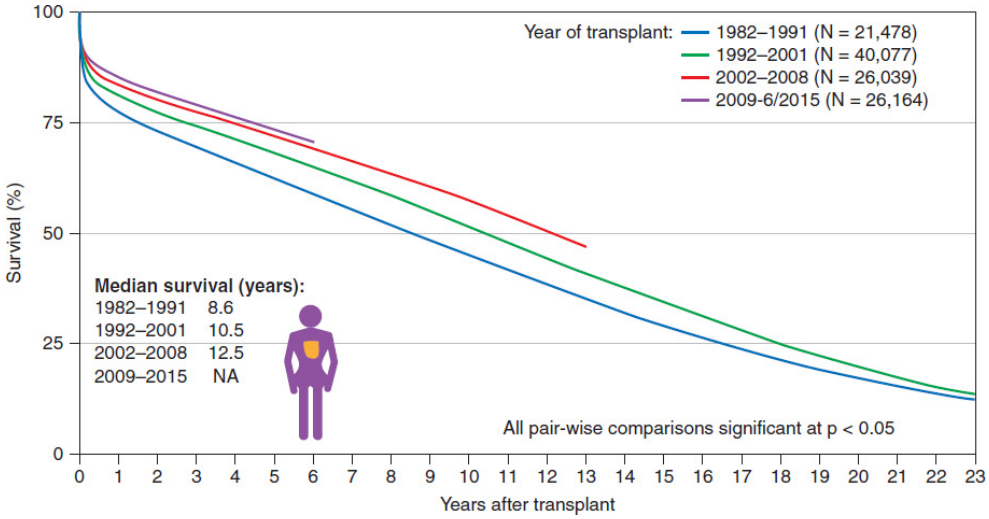


Figure 38.13 Kaplan–Meier survival graph following heart transplantation based on era.

Complications

The most immediate and morbid complication following heart transplantation is PGD. Reports of PGD have been quite varied with a multitude of definitions, diagnostic criteria, and therapeutic options which have been debated. Given these discrepancies, a consensus statement with clear definitions was established stating that PGD must be diagnosed within 24 hours of completion of surgery and that is should be divided into PGD-left ventricle and PGD-right ventricle with PGD-left ventricle being graded as mild, moderate or severe.[58] It was estimated that the incidence of PGD was approximately 7% with an accompanying 30-day mortality of 30% and a 1-year mortality of nearly 35%. Treatment modalities ranged from prophylactic maneuvers to avoid PGD to support of the allograft for recovery with MCSDs, such as intra-aortic balloon pump and ECMO, with hopes for recovery or retransplantation (**Fig. 38.14**). Following PGD, most complications can be divided into early (<3-month posttransplant) and late (>3-month posttransplant) time periods. A major component to all outcomes is the complex balance and management required to prevent rejection by tricking the body into believing that the heart is its own, while simultaneously

avoiding the inherent effects of immunosuppression on infections and neoplastic changes. In addition to early and late time periods, acute episodes of rejection following heart transplantation can be categorized by the mechanism of rejection—cellular, antibody mediated, or mixed rejection.

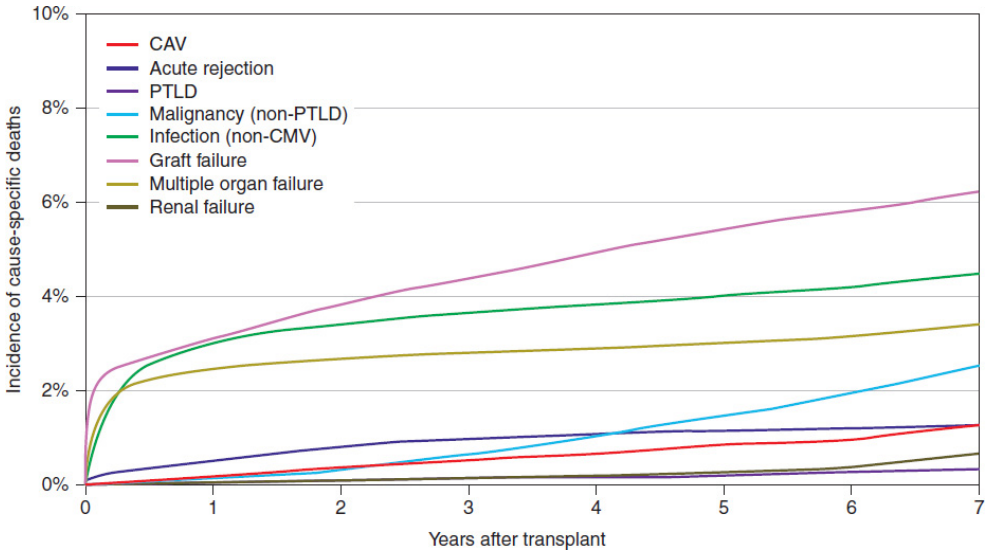


Figure 38.14 Cumulative incidence of leading causes of death (adult heart transplants: January 2010–June 2017). CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; PTLD, posttransplant lymphoproliferative disorder.

In 2004, the ISHLT revised the cardiac biopsy grading system to ensure a more consistent grading across centers for cardiac allograft rejection.[59] The differences between this system and the previous definitions from 1990 are highlighted in **Table 38.1**. In brief, grade 0 R is no rejection, 1 R—mild rejection, grade 2 R—moderate rejection, and grade 3 R—severe rejection. A 1 R represents interstitial and/or perivascular infiltrate with one focus of myocardial damage; a 2 R represents two or more foci of infiltrate with accompanying myocardial injury; and a 3 R has diffuse infiltrate with multifocal myocardial damage with or without edema hemorrhage or vasculitis (**Fig. 38.15A,B**). AMR, similar to the definition of PGD, was controversial with multiple iterations. A final consensus has been reached abandoning clinical criteria in favor of a pathologic diagnosis.[60] The pathologic diagnosis of AMR depends on the following: morphologic aspects, primary and secondary antibody panels, immunohistochemistry, and immunofluorescence with a combination of these serving as the basis of the grading system (**Table 38.2**).[61]

In general, all three types of rejection—cellular, AMR, and mixed rejection—have been associated with increased risk of mortality and loss of graft function.[61] It is estimated that during the first year, roughly 25% of all patients will have an episode of acute rejection.[62] In the more chronic form of rejection, CAV can develop. CAV is the abnormal coronary endothelial inflammation, injury, fibrosis, and dysfunction that occurs as a result of chronic rejections, as well as nonimmune insults. Unlike acute rejection, which has surveillance diagnosis by endomyocardial biopsies, CAV is usually evaluated by invasive coronary angiography (**Fig. 38.16**). By 5 years post transplant, a third of heart transplant recipients develop CAV and this is the most common cause of death in the long term.[63]

Table 38.1 ISHLT Standardized Cardiac Biopsy Grading: Acute Cellular Rejection

2004		1990	
Grade 0 R[a]	**No Rejection**	**Grade 0**	**No Rejection**
Grade 1 R, mild	Interstitial and/or perivascular infiltrate with up to one focus of myocyte damage	Grade 1, mild A—Focal B—Diffuse Grade 2 moderate (focal)	Focal perivascular and/or interstitial infiltrate without myocyte damage Diffuse infiltrate without myocyte damage One focus of infiltrate with associated myocyte damage
Grade 2 R, moderate	Two or more foci of infiltrate with associated myocyte damage	Grade 3, moderate A—Focal	Multifocal infiltrate with myocyte damage
Grade 3 R, severe	Diffuse infiltrate with multifocal myocyte damage ± edema, ±	B—Diffuse Grade 4, severe	Diffuse infiltrate with myocyte damage Diffuse, polymorphous infiltrate with extensive

	hemorrhage ± vasculitis	myocyte damage ± edema, ± hemorrhage + vasculitis

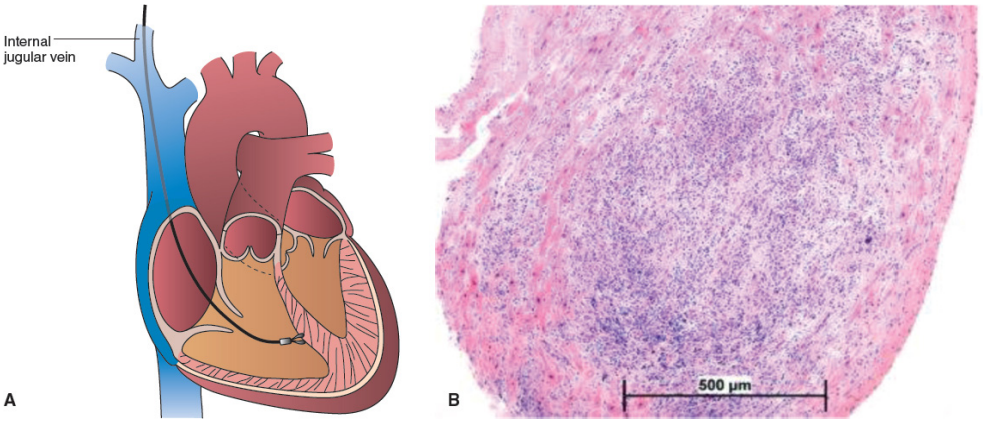


Figure 38.15 **A:** Endomyocardial biopsy via internal jugular vein to detect acute cellular rejection. **B:** Severe acute cellular rejection. This photomicrograph exhibits diffuse myocardial inflammation with associated myocyte damage (ISHLT 1990 grade 3B or ISHLT 2004 grade 3R). (From Maleszewski JJ, Burke AP. Heart Transplant Rejection Pathology. TheHeart.org Medscape.) (This image was produced by medical illustrator from Johns Hopkins–Timothy Phelps.)

In addition to complications from rejection and PGD, other causes of complications following heart transplantation can arise from a variety of different types of issues. Technical issues usually arise in the immediate peritransplant period (anastomotic narrowing, damage to coronary arterial blood flow, infections, bleeding or inappropriate patient–donor matching). Complications can also arise from chronic immunosuppression which can include infectious complications such as viral, bacterial, or fungal infections. Particular attention should be paid to recipients who are CMV negative who receive donor CMV-positive organs. CMV prophylactic therapy during the early postoperative course is routinely employed when immunosuppression is greatest during the first 6 months post transplant. Another complication from immunosuppression can be the development of malignancies such as skin cancer, posttransplant lymphoproliferative disease, and visceral cancers.[64] Lastly, patients on chronic immunosuppression can develop diabetes mellitus, hypertension, and renal failure.

Table 38.2 The 2013 ISHLT Working Formulation for Pathologic Diagnosis of Cardiac Antibody-Mediated Rejection

Grade	Definition	Substrates
pAMR 0	Negative for pathologic AMR	Histologic and immunopathologic studies are both negative.
pAMR 1 (H+)	Histopathologic AMR alone	Histologic findings are present and immunopathologic findings are negative.
pAMR 1 (I+)	Immunopathologic AMR alone	Histologic findings are negative and immunopathologic findings are positive (CD68+ and/or C4d+).
pAMR 2	Pathologic AMR	Histologic and immunopathologic findings are both present.
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis, and marked edema and immunopathologic findings are present. These cases may be associated with

	profound hemodynamic dysfunction and poor clinical outcomes.

AMR, antibody-mediated rejection.

Berry GJ, Burke MM, Andersen C, et al. The 2013 International Society for Heart and Lung Transplantation Working Formulation for the standardization of nomenclature in the pathologic diagnosis of antibody-mediated rejection in heart transplantation. *J Heart Lung Transplant* 2013;32(12):1147–1162.

FUTURE DIRECTIONS

The future of heart transplantation is undoubtedly bright. The annual number of heart transplants in the United States has continued to rise within the last 5 years with improvements in expansion of the donor pool and postoperative success rates. As stated earlier, these incremental improvements are multifactorial with meticulous patient selection, donor selection, careful operative technique, regimented posttransplant immunosuppression, protocol driven surveillance biopsies to detect early, nonclinical rejection and maintenance of long-term health care needs all contributing to great outcomes. In light of these improvements, numerous areas can continue to be enhanced.

Immunosuppression in its present state is not perfect. Although effective in the immediate period, induction therapy is associated with increased infective complications and a tailored regimen to each specific recipient–donor situation would be ideal. The reliance on triple therapy for maintenance immunosuppression in the early period likewise comes with certain drug-induced toxicities and their unwanted side effects. The development of graft tolerance is the penultimate goal and progress will be made in this arena with an ever growing list of targeted immunosuppressive medications.

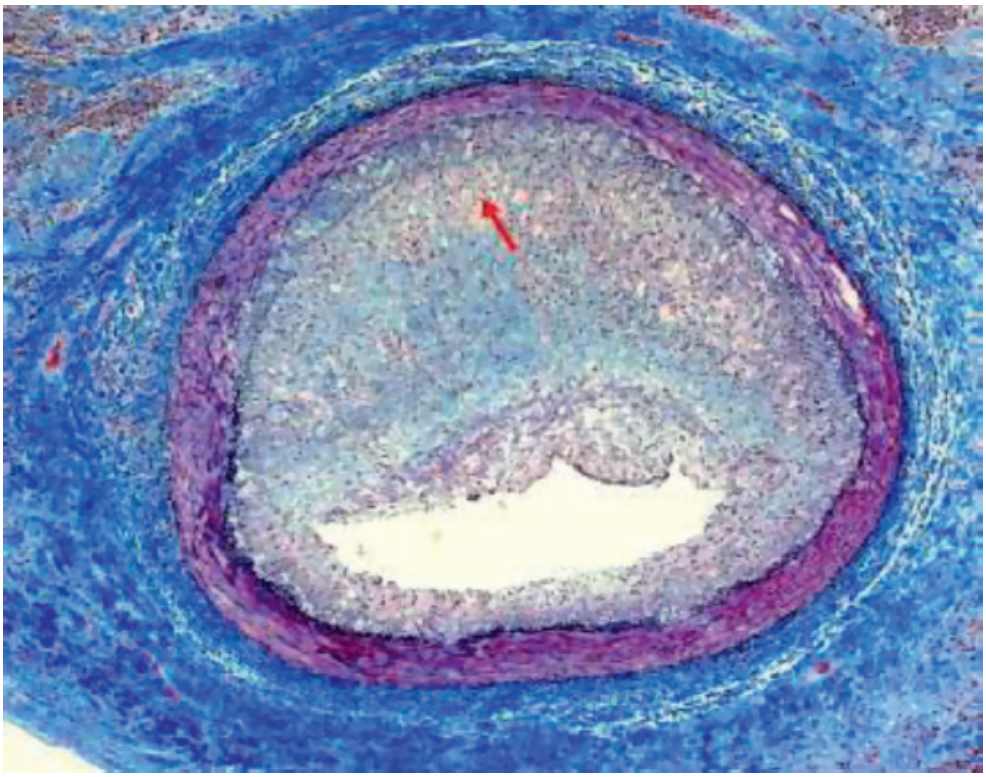


Figure 38.16 Lipid-laden foam cell macrophages in TCAD. Trichrome elastic stain of a coronary artery demonstrating progressive arterial occlusion with lipid-laden foam cell macrophages (*arrow*) in a patient with transplant coronary artery disease (TCAD). (Used with permission from Zimmer R, Lee M. *JACC Cardiovasc Interv* 2010;3(4):367–377. doi: 10.1016/j.jcin.2010.02.007.)

The early detection and treatment of rejection will continue to be refined. Currently, there is a reliance on serial, surveillance endomyocardial biopsies to assess for rejection, as well as yearly cardiac angiography for accelerated chronic rejection leading to atherosclerotic coronary disease. There is increasing data that noninvasive methods such as AlloMap testing can look at genetic expression to detect early rejection.[63] In addition, our understanding of the differences between AMR and acute cellular rejection will enable for more targeted treatment options based upon the specific type of rejection in the future.

From a patient selection perspective, the field had seen a rapid expansion of the use of durable MCS as a bridging option to get patients to transplantation. More recently with the changing of the allocation system and the downgrading of the status of stable patients with LVADs, the role of temporary MCS has increased. Indeed, in the early reports evaluating the

allocation change, there were more patients being transplanted on temporary MCS devices than durable devices.[48] The increased use of ECMO will allow early transplantation of patients that are the most critically ill, preventing the allocation of precious donors to a subset of sick recipients who may not receive the greatest benefit from transplantation.

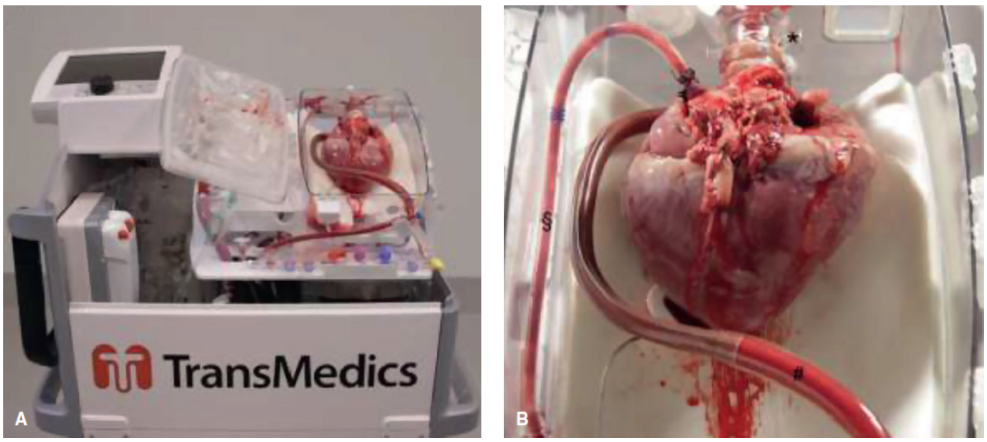


Figure 38.17 **A:** The transport unit of the Organ Care System (Transmedics) with ex vivo perfusion of a porcine heart. The ascending aorta is connected to an artificial circulation circuit filled with donor blood. An inserted oxygenator ensures gas exchange. During warm pump run with controlled perfusion pressure and flow, the heart function is assessed visually together with hemodynamic and laboratory parameters. **B:** The heart is connected to the perfusion line with a connector at the ascending aorta (*). A venous return cannula (#) is placed into the right ventricle via the pulmonary artery with the caval veins being closed. The left ventricle is vented additionally (§). (Photos courtesy of Transmedics.)

There has already been an increased awareness of the utilization of nontraditional donors. Indeed with available medications to treat and potentially cure hepatitis C, donors with hepatitis C are being used increasingly with good early results from this donor population.[65] Human immunodeficiency virus (HIV) is another virus that currently has been effectively treated in the donor population that could be used for heart transplantation. A number of recent studies have reported an acceptable 5-year survival in HIV-positive recipients (88%) in a selected group of recipients.[66]

Perhaps, a bigger impact for the future of heart transplantation will be the inclusion of the nontraditional donor. The traditional donor at this time is the brain-dead donor where a procurement procedure can occur in a

semielective manner while the c still has a functioning circulatory system on mechanical ventilation. In Australia and the United Kingdom, increasing experience is being achieved in DCD.[67,68] The early outcomes following DCD heart transplants has shown some promise with a 1-year survival of 86% as compared to the traditional donors where a 1-year survival was 88%.[69] This technique may allow for more liberal heart organ donation in patients with families who do not believe in brain death donation.

A significant technical hurdle in DCD patients is to ensure a working graft after urgent heparinization following circulatory death followed by a hastily performed preservation of the heart. Another technique that could serve as a litmus test for the use of these hearts could be the utilization of normothermic *ex vivo* perfusion for assessment and potential repair of these organs prior to transplantation. The currently available platform is the Organ Care System from Transmedics that allows continuous normothermic ex-vivo heart perfusion immediately after the procurement of the heart to aid in the reduction of static, cold ischemic time of the organ (**Fig. 38.17**). The added benefit of this device is the ability of the clinician to assess organ function with parameters such as coronary blood flow and lactate clearance in addition to potential resuscitation to recovery for utilization in transplantation.[70,71] Early randomized, multicenter trials (PROCEED II) between this system and the standard hypothermic, standard solution have shown no difference in short-term outcomes.[72]

CONCLUSION

Over the past 50 years, heart transplantation has come a long way, going from a romantic ideal with dismal early outcomes to the gold standard biologic cure for patients suffering from end-stage heart failure. It has developed after decades of innovation, perseverance, and commitment by thousands of dedicated heart failure physicians and surgeons, immunologists and scientists, procurement technicians and professionals, drug development experts, nurses, regulatory and administrative policy experts, and infectious disease clinicians. It is impressive to think there have been over 70,000 heart transplants in the UNOS registry at this time, with 1-year survival surpassing 90%. The careful attention to patient and donor selection, meticulous surgical

technique, surveillance, and early detection of rejection, combined with emerging technologies, is sure to push the field into even greater heights in the future.

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39

Lung Transplantation

Errol L. Bush

Key Points

1. Annual numbers of lung transplants in the United States have been increasing and in 2018, 2,562 lung transplants were performed in the United States, the highest annual number to date and over 15,000 lung transplant recipients were alive.
2. While systematic allocation changes have correlated with sicker candidates being listed, overall there have been improved transplantation rates, lower mortality rates, and fewer days on the waitlist with a median wait time of 2.5 months.
3. Candidacy for lung transplantation should utilize each center's multidisciplinary candidate selection committee to carefully weigh candidates' individual underlying disease severity, medical comorbidities, psychosocial factors, and surgical risk.
4. Idiopathic pulmonary fibrosis (IPF) is the most common subtype of interstitial lung disease and since 2007, IPF has replaced COPD as the most common indication for lung transplantation in the United States. In 2018, restrictive lung diseases represented 60% of all lung transplants performed in the United States.
5. The donor recovery lung evaluation is as important to the success of the lung transplant recipient as the implantation, and an expert recovery surgeon is facile with the multiple required steps, understands their relationship to the success of organ preservation, and able to articulately communicate and troubleshoot abnormalities that arise during the organ evaluation process.
6. Seventy five percent of recipients received a bilateral lung transplant. The technique of double-lung transplantation has evolved considerably since the late 1980s from an en bloc technique to a bilateral, sequential technique. With the patient in the supine position, this operation can be performed through a median sternotomy, bilateral thoracosternotomy (clamshell) incision, bilateral anterior thoracotomies without sternal division, or bilateral muscle-sparing axillary thoracotomies.
7. Most transplant centers attempt to limit organ ischemic time to less than 6 total hours, however, many centers have vast experience comfortably extending cold ischemic time with careful donor selection, organ preservation, and utilization of ex vivo lung perfusion (EVLP) to evaluate extended criteria donors.
8. Primary graft dysfunction (PGD) is an acute lung injury syndrome occurring within the first 72 hours following lung transplantation and is characterized by inexplicable diffuse allograft infiltrates and hypoxemia defined as a PaO_2/FiO_2 ratio (P/F) <300, and results in significant short- and long-term morbidity and mortality.
9. Donor availability remains a limiting factor to successful and timely transplantation, which has led to innovative utilization of techniques that result in increased donor utilization, such as utilization of EVLP, donation after cardiac death donors, and hepatitis C virus--infected organs.

INTRODUCTION

Early Years of Lung Transplantation

In 1963, Dr. James Hardy, Chair of surgery at the University of Mississippi, reported the first human lung transplant in a 58-year-old male incarcerated patient who had end-stage emphysema, an obstructive left mainstem carcinoma and chronic renal disease, utilizing a donor who had suffered a massive myocardial infarction and unsuccessful cardiopulmonary resuscitation.[1] While the surgery was regarded as a success, the recipient died 18 days later of renal failure and with a reported functioning allograft. Over the next 20 years, less than 40 attempts at lung or heart–lung transplantation were performed, all but one dying in less than a month of bronchial dehiscence, and only one midterm survivor, 10.5 months.[2] With the advent of improved

surgical technique, better recipient selection, and the availability of cyclosporine, in 1982, the Toronto Lung transplant group would go on to perform the first long-term successful lung transplant[3] and the recipient survived for 7 years.[2]

Current Status of Lung Transplants in the United States

1 Since 2012, annual numbers of lung transplant in the United States have been increasing and in 2018, 2,562 lung transplants were performed in the United States, the highest annual number to date and over 15,000 lung transplant recipients were alive.[4] These transplants were performed in 67 centers; 55 adult-only centers. The median number of transplants performed per program was 26, although three programs performed more than 100 transplants, which represented 20% of national cases; 75% of candidates received a bilateral lung transplant, and 97.4% of candidates received a primary lung transplant.[4] While allocation changes have correlated with sicker 2 candidates being listed, overall there have been improved transplantation rates, lower mortality rates, and fewer days on the waitlist with a median wait time of 2.5 months. In 2018, 3,134 recipients were added to the waitlist, continuing a trend of donor shortage and resulting in 12% of recipients dying or becoming too sick for transplant while on the list.[4] While still the worst outcome of solid organ transplants, progressive improvements in survival have been realized in lung transplantation; 89.4% of recipients survived to 1 year, 73.5% to 3 years, and 59.4% to 5 years.[4]

THE FINAL RULE

The Organ Procurement and Transplantation Network (OPTN) links all professionals involved in the U.S. donation and transplantation system with the goals to increase the number of and access to transplants, improve survival rates after transplantation, and to promote patient safety and efficient management of the system. The United States Department of Health and Human Services established the regulatory framework to support the OPTN on March 16, 2000, by implementing the Final Rule. The Final Rule states that allocation polices shall be based on sound medical judgment; shall seek to achieve the best use of donated organs; shall preserve the ability of a transplant program to decline an offer of an organ or not to use the organ; shall be specific for each organ type transplanted; shall be designed to avoid wasting organs, to avoid futile transplants, to promote patient access to transplantation, and to promote the efficient management of organ placement; shall be reviewed periodically and revised as appropriate; shall include appropriate procedures to promote and review compliance; and shall not be based on the candidate's place of residence or place of listing, except to the extent required by other aforementioned requirements.[5] In an effort to assure equitable and medical necessity based allocation of donor organs, two major changes to lung allocation have occurred since the implementation of the Final Rule: development of the lung allocation score (LAS) and broader geographic organ allocation.

Lung Allocation

Prior to 2005, lung allocation priority for lung transplantation was based upon wait times, geography, and blood type, which resulted in significantly prolonged wait times and high waitlist mortality. The LAS was implemented in 2005 as a weighted combination of the predicted risk of death on the waiting list and the predicted likelihood of survival during the first year after transplantation.[6] Variables included in the LAS are listed in **Table 39.1**, with addition of BMI <20 kg/m^2. Greater weight is given to waitlist survival and medical urgency than posttransplant survival. Four disease diagnosis groups are utilized and considered in the LAS: group A: obstructive; group B: pulmonary vascular; group C: cystic fibrosis and immunodeficiency; and group D: restrictive (**Table 39.2**). Reevaluation and revision of the criteria utilized to calculate LAS may occur after a substantial evaluation period and has resulted in several influential changes. 2012 noted the addition of cardiac index, CVP, and serum creatinine and their relative weights to other variables. More recently, in February 2015, variables were updated to more accurately reflect disease severity for all candidates, especially those with pulmonary vascular disease. Finally, in November 2017, in an effort to reduce geographic

disparities, the first geographic unit of allocation was changed to a 250 nautical mile radius from the donor circle, eliminating local donor service areas as a unit of allocation.

Despite allocation changes, the median LAS at transplant, 42.3 in 2018, has been relatively stable over the last decade, but represents a 2 point increase from 2017.[4] About 25% of candidates are hospitalized prior to transplant; 13.6% required care in the intensive care unit. Proportions of candidates requiring support with mechanical ventilation (vent) were 1.6%, extracorporeal membrane oxygenation (ECMO) 3.3%, and vent + ECMO 3.1%.[4]

Table 39.1 Selected Components of the Lung Allocation Score

Age
Bilirubin
Cardiac index, CVP
Diagnosis group
Functional status
Diabetes
Assisted ventilation
Supplemental oxygen
FVC% predicted (Group D)
PA systolic
PA mean
PA wedge
$PaCO_2$ (≥40 or increase ≥15%)
6-min walk
Creatinine

FVC, forced vital capacity; PA, pulmonary artery.

INDICATIONS

3 Ultimately, each center's multidisciplinary candidate selection committee will need to carefully weigh candidates' individual underlying disease severity, medical comorbidities, psychosocial factors, and surgical risk. In 1998, the International Society for Heart and Lung Transplantation (ISHLT) produced the multiorganizational consensus document, International Guidelines for the Selection of Lung Transplant Candidates.[7] The document has since been updated twice, most recently in 2015,[8] and is generally considered by lung transplant programs in their selection criteria (**Table 39.3**). The statement recommends that in general, lung transplantation should be considered for adults with end-stage lung disease who have:

1. High (>50%) risk of death from lung disease within 2 years if lung transplantation is not performed.
2. High (>80%) likelihood of surviving at least 90 days after lung transplantation.
3. High (>80%) likelihood of 5-year posttransplant survival from a general medical perspective provided that there is adequate graft function.

Table 39.4 lists disease-specific listing considerations for the most common disease diagnoses undergoing lung transplantation.

Idiopathic Pulmonary Fibrosis

Table 39.2 Pulmonary Disease Diagnosis Groups

Group A: Obstructive	Group B: Pulmonary Vascular	Group C: Cystic Fibrosis and Immunodeficiency	Group D: Restrictive
Allergic bronchopulmonary aspergillosis	Congenital malformation	Common variable immune deficiency	ABCA3 transporter mutation
Alpha-1 antitrypsin deficiency	CREST—pulmonary hypertension	Cystic fibrosis	Alveolar proteinosis
Bronchiectasis	Eisenmenger syndrome	Fibrocavitary lung disease	Amyloidosis
Bronchopulmonary dysplasia	Portopulmonary hypertension	Hypogammaglobulinemia	Acute respiratory distress syndrome or pneumonia
Chronic obstructive pulmonary disease/emphysema	Primary pulmonary hypertension/pulmonary arterial hypertension	Schwachman–Diamond syndrome	Bronchioloalveolar carcinoma (BAC)
Ehlers–Danlos syndrome	Pulmonary capillary hemangiomatosis		Carcinoid tumorlets
Granulomatous lung disease	Pulmonary telangiectasia—pulmonary hypertension		Chronic pneumonitis of infancy
Inhalation burns/trauma	Pulmonary thromboembolic disease		Constrictive bronchiolitis
Kartagener syndrome	Pulmonary vascular disease		CREST—restrictive
Lymphangioleiomyomatosis	Pulmonary veno-occlusive disease		Eosinophilic granuloma
Obstructive lung disease	Pulmonic stenosis		Fibrosing mediastinitis
Primary ciliary dyskinesia	Right hypoplastic lung		Graft versus host disease (GVHD)
Sarcoidosis with mean pulmonary artery pressure of 30 mm Hg or less	Scleroderma—pulmonary hypertension		Hermansky–Pudlak syndrome
Tuberous sclerosis	Secondary pulmonary hypertension		Hypersensitivity pneumonitis
Wegener granuloma—bronchiectasis	Thromboembolic pulmonary hypertension		Idiopathic interstitial pneumonia
			Idiopathic pulmonary hemosiderosis
			Lung retransplant or graft failure
			Lupus mixed connective tissue disease
			Obliterative bronchiolitis: nonretransplant
			Occupational lung disease
			Paraneoplastic pemphigus associated Castleman disease
			Polymyositis
			Pulmonary fibrosis: other

	Pulmonary hyalinizing granuloma Pulmonary lymphangiectasia (PL) Pulmonary telangiectasia—restrictive Rheumatoid disease Sarcoidosis with mean pulmonary artery pressure higher than 30 mm Hg Scleroderma—restrictive Secondary pulmonary fibrosis Silicosis Sjogren syndrome Surfactant protein B or C mutation Teratoma Wegener granuloma—restrictive

Adapted from the U.S. Organ Procurement and Transplantation Network Policy 10.1.F.i (Effective February 27, 2020).

4 Idiopathic pulmonary fibrosis (IPF) is a progressive fibrosing interstitial lung disease with less than 5 years expected survival following diagnosis, though is improved at younger ages.[9] IPF is the most common subtype of interstitial lung disease and since 2007, mostly secondary to the implementation of the LAS, IPF has replaced chronic obstructive pulmonary disease (COPD) as the most common indication for lung transplantation in the United States.[10] In 2018, restrictive lung diseases represented 60% of all lung transplants performed in the United States.[4]

Chronic Obstructive Pulmonary Disease

COPD is the second most common indication for lung transplantation. It is the most common disease indication in the obstructive diagnosis group, which represented 24% of all lung transplants in the United States.[4] Recipients with COPD share the best 1-year survival with those with cystic fibrosis (CF), but a lower 10-year survival compared to all except IPF.[11]

Table 39.3 ISHLT General Recommendations for Consideration for Lung Transplantation[3]

High (>50%) risk of death from lung disease within 2 yrs if lung transplantation is not performed
High (>80%) likelihood of surviving at least 90 days after lung transplantation
High (>80%) likelihood of 5-year posttransplant survival from a general medical perspective provided that there is adequate graft function

Cystic Fibrosis

CF is the third most common indication for lung transplantation, but the proportion of patients transplanted for CF continues to slowly fall, now representing 13% of total adult lung transplants worldwide,[11] and 10% in the United States.[4] Recipients with CF share the best 1-year survival with those with COPD, and highest overall survival, even up to 20 years.[11] Colonization of the airway with multi- or pan-resistant organisms is common in CF, and some transplant programs consider colonization with pan-resistant strains of *Pseudomonas aeruginosa* or *Burkholderia* species as contraindications to transplantation because of poorer demonstrated posttransplant outcomes. A comprehensive review by Morrell et al. found that patients with pan-resistant *Pseudomonas* seem to have poorer outcomes than sensitive patients with CF undergoing transplantation, but comparable to overall UNOS registrants, and only patients infected with *Burkholderia gladioli* and specific nonepidemeic *Burkholderia cenocepacia* strains demonstrate excess mortality in the first 6 months after transplant.[12]

Table 39.4 Disease-Specific Considerations for Listing for Lung Transplantation[3]

Interstitial Lung Disease—Early Referral Following Radiologic or Histologic Diagnosis, Regardless of Lung Function
Decline in FVC ≥10% during 6 mo of follow-up (note: A 5% decline is associated with a poorer prognosis and may warrant listing)
Decline in DLCO ≥15% during 6 mo of follow-up
Desaturation to <88% or distance <250 m on 6-min walk test or 450 m decline in 6-min walk distance over a 6-mo period
Pulmonary hypertension on right heart catheterization or 2-dimensional echocardiography
Hospitalization because of respiratory decline, pneumothorax, or acute exacerbation
Chronic Obstructive Pulmonary Disease (COPD)
BODE index ≥7
FEV_1 <15–20% predicted
Three or more severe exacerbations during the preceding year
One severe exacerbation with acute hypercapnic respiratory failure
Moderate to severe pulmonary hypertension
Cystic Fibrosis—Early Referral When FEV_1 That Has Fallen to 30% or a Patient with a Rapidly Falling FEV_1 Despite Optimal Therapy (Particularly in a Female Patient) or Increasing Frequency of Life-Threatening Lung Disease Complications
Chronic hypoxic or hypercapnic respiratory failure
Long-term noninvasive ventilation therapy
Pulmonary hypertension
Frequent hospitalization
Rapid lung function decline
World Health Organization Functional Class IV
Pulmonary Hypertension
NYHA functional class III or IV despite a trial of at least 3 mo of combination therapy including prostanoids
Cardiac index of <2 L/min/m^2
Mean right atrial pressure of 415 mm Hg
6-min walk test of <350 m
Development of significant hemoptysis, pericardial effusion, or signs of progressive right heart failure

Pulmonary Hypertension

Pulmonary vascular diseases are included in the group B diagnostic group and in 2018, represented only 6% of the U.S. transplants.[4] The median LAS is highest for this diagnostic group,[4] but considerable debate arises around whether the LAS accurately characterize the clinical urgency of these patients while on the waitlist.

Natural history registry data reported a 3-year median survival,[13] which has improved with optimal medical therapies to 75% at 3 years.[14] Because of the relative success and good response with medical therapies, timing for referral to transplant is variable among centers, as institution and optimization of therapies may delay the need for transplant for some time. However, clinical deterioration may do so rapidly enough to not allow time for a full evaluation, therefore earlier referral for evaluation is recommended. Recipients with IPAH have the lowest 1-year survival, but their 10-year conditional 1-year median survival approaches the best of all recipients, 12 years.[11]

Contraindications to Lung Transplantation

Table 39.5 lists absolute consensus and relative contraindications to lung transplantation.[8] The list represents common comorbid patient concerns and a complex balance between transplant benefit, organ stewardship, and expected recipient and allograft survival. An individualized candidate evaluation should ensue with careful consideration of candidates' individual underlying disease severity, medical comorbidities, psychosocial factors, and in the context of surgical risk for perioperative morbidity and mortality based on the program's relevant experience and expertise. Ultimately, candidate selection is the decision of the transplant program's selection committee. Therefore, a patient may be a suitable or unsuitable candidate at any particular center, and patients are free to be evaluated and/or listed at more than one program, if the recipient finds it beneficial to do so. If a candidate is deemed not a candidate at one particular center for a relative contraindication, then referral to a center with relevant expertise or prior considerations should be made.

Table 39.5 Contraindications to Lung Transplant

Absolute Contraindications
Recent history of malignancy
Multiorgan dysfunction unless combined multiorgan transplant considered correctable
Uncorrected atherosclerotic disease
Acute medical instability, including, but not limited to, acute sepsis, myocardial infarction, and liver failure
Uncorrectable bleeding diathesis
Chronic infection with highly virulent and/or resistant microbes that are poorly controlled pretransplant
Evidence of active Mycobacterium tuberculosis infection
Significant chest wall or spinal deformity expected to cause severe restriction after transplantation
Class II or III obesity (body mass index [BMI] ≥ 35.0 kg/m^2)
Current or history of nonadherence to medical therapy
Psychosocial barriers to posttransplant care adherence
Severely limited functional status with poor rehabilitation potential
Substance abuse or dependence
Relative Contraindications
Age >65 yrs in association with low physiologic reserve and/or other relative contraindications
Class I obesity (BMI 30.0–34.9 kg/m^2), particularly truncal (central) obesity
Progressive or severe malnutrition
Severe, symptomatic osteoporosis
Extensive prior chest surgery with lung resection
Mechanical ventilation and/or extracorporeal life support (ECLS)
Colonization or infection with highly resistant or highly virulent bacteria, fungi, and certain strains of mycobacteria
For patients infected with hepatitis B and/or C, a lung transplant can be considered in patients without signs of cirrhosis or portal hypertension
For patients infected with human immunodeficiency virus (HIV), a lung transplant can be considered in compliant patients with controlled disease with undetectable HIVRNA
Infection with *Burkholderia cenocepacia*, *Burkholderia gladioli*, and multi-drug–resistant *Mycobacterium abscessus*
Prior chest surgery, particular pleurodesis (surgical or chemical)
Patients requiring a mechanical (ventilator or circulatory) bridge to transplant

Adapted from ISHLT Consensus Statement.[8]

OPERATIVE PROCEDURES

Donor Recovery Operation

5 The donor recovery lung evaluation is as important to the success of the lung transplant recipient as the implantation, and is summarized in **Table 39.6**. The experienced recovery surgeon will review the donor's ABO blood group, history, and imaging and then perform a bronchoscopy and manual inspection of the lung(s) to assure no contraindications or problematic anatomy before acceptance communication with the implant team.

Table 39.6 Sequential Steps in Donor Lung Recovery	
1	Review donor blood group, history and imaging
2	Perform bronchoscopy
3	Perform median sternotomy
4	Intraoperative inspection of lungs and thoracic cavity
5	Lung recruitment maneuvers and assessment of lung function and suitability for transplantation
6	Dissection of great vessels as needed
7	Systemic donor heparinization
8	Cannulation of main PA
9	Prostaglandin E1 (500 mg) injected into main pulmonary
10	Division of systemic venous return to decompress right heart
11	Aortic cross-clamp
12	Left atrial division to decompress left heart
13	Initiation of cold lung preservation flush
14	Topical cooling of ventilated lungs
15	Cardiectomy
16	Retrograde lung flush
17	Recovery of lung

A median sternotomy is performed, often concomitant with a laparotomy by the abdominal team. The sternal retractor is often placed toward the head to minimize interference with the abdominal operation. If there is no urgency for cardiac evaluation, the pericardium should be left closed during the lung evaluation to decrease hemodynamic instability with excessive lung manipulation. Bilateral pleura are opened widely with care to avoid damage to the lung parenchyma. Visual and manual inspection then ensues of the pleural cavity and lungs for nodules, masses, consolidation, atelectasis and/or infarction. Compliance is checked by temporarily disconnecting the ventilator, which should result in an immediate collapse of the lungs. If necessary, positive pressure lung recruitment maneuvers are performed, while minimizing risk of barotrauma by restricting peak pressures to 20 to 30 cm H_2O. If an intraoperative systemic arterial blood gas (ABG) is satisfactory, usually a PaO_2/FiO_2 >300 on PEEP 5 with normal CO_2 levels, then proceeding with intended lung recovery and transplantation is applicable. However, if the ABG is not satisfactory, or there is a clinical concern about the independent function or suitability of the lung, individual pulmonary vein gas may be sampled to further evaluate lobar contributions to total pulmonary function.

If no contraindications arise, in preparation for organ recovery, the pericardium is opened, and exposure optimized with the use of stay sutures. The SVC is encircled caudal to the azygous vein while care is utilized to separate the right PA from the back of the SVC and ascending aorta. The paratracheal tissue is accessed between the SVC and the ascending aorta with gentle retraction of both vessels. The trachea is then manually exposed circumferentially. The author prefers to wait on circumferential exposure until after cross-clamp in order to minimize bleeding risk and/or airway injury.

Once all teams have completed dissection, the donor is heparinized as per protocol; usually 250 to 300 units/kg. A purse string suture is placed in the main PA near its midpoint and a perfusion cannula secured. Preferably, to achieve equal distribution of preservation solution, the cannula is oriented in a retrograde fashion toward a competent pulmonary valve. 500 μg of prostaglandin E1 (PGE1) is injected into the main PA directly with less than 1 minute prior to intended cross-clamp as systemic vasodilation and potentially hemodynamic compromise may ensue. Next, the SVC is ligated and the IVC divided at an appropriate level to facilitate intended heart and/or liver transplant. The aorta is cross-clamped. The left atrial appendage is then amputated to allow left heart decompression, prior to beginning pulmonary flush. Three to 4 L of cold Perfadex flush is initiated under pressure by gravity, and the chest cooled with iced saline and with care to avoid thermal injury by direct ice contact with the organ. Ventilation is continued throughout the duration of the flush to facilitate even distribution of perfusate. At completion of the flush, ventilation may be temporarily ceased until just prior to lung extraction. The heart is now extracted by sharply mobilizing the IVC to the level of the right inferior pulmonary vein. While lifting the heart, an incision is made in the left atrium in the midpoint of the left and right inferior pulmonary veins. The atriotomy may now be retracted with a suction device to allow visualization and utilization of scissors to extend the opening superiorly while visualizing the vein orifices. The remaining left atrium is now divided. The great vessels are now divided by dividing the SVC distal to the ligature, the ascending aorta proximal to the head vessels, and the main PA at the level of cannulation. With the heart now removed, a Foley or self-inflating retrograde perfusion catheter is utilized to provide 500 mL of Perfadex flush into each vein orifice until clear of residual blood and clots. Now, the en bloc lungs may be removed by division of bilateral inferior pulmonary ligaments and herniating the left lung toward the right chest, to visualize and develop an anterior paraesophageal plane. Division of the mediastinal pleura just anterior to the esophagus completely into the right chest during gentle upward retraction of the lungs, protects the lung and its vasculature, while avoiding enteric contamination with esophageal injury or division. Finally, the only remnant connection is the trachea. The endotracheal tube is then withdrawn into the proximal trachea, a gentle Valsalva maneuver is performed until atelectasis is resolved, and then the Valsalva is released just before the proximal trachea is divided with a linear stapler, distal to the endotracheal tube. To minimize air leak, two staple firings are usually placed on the extracted trachea. If the lungs will be split for two different recipients, the proximal left main bronchus is divided with a liner stapler to maintain inflation before dividing the left atrium and PA at the midline. The lungs are then bagged in a cold preservation solution and transported on ice.

Recipient Preparation

Before anesthetic induction, patients have epidural catheters placed to aide in perioperative pain management and to facilitate faster extubation and ambulatory rehabilitation. If cardiopulmonary bypass (CPB) is needed intraoperatively, intraoperative use of ECMO is planned, which limits the requirement for heparinization usually to less than 5,000 total units. Double-lumen endotracheal intubation is routine with an appropriately sized tube, but large enough to allow vigorous suctioning of purulent secretions through an adult fiberoptic bronchoscope. Routinely, two internal jugular central venous lines are placed for both volume and medication administration. Also inserted a Foley catheter with bladder temperature monitor, both radial and femoral arterial lines, and a transesophageal echocardiography probe. In my practice, with these adjuncts, I have not needed a Swan-Ganz catheter placed for perioperative management and have therefore avoided intendent risks that arise with the catheter in place during pneumonectomy or with fresh anastomoses. The patient is placed either in a supine position with all extremities padded, shoulders medially rotated and arms tucked at sides for bilateral lung transplants or in the lateral recumbent position for single-lung transplants. A heating blanket may be utilized.

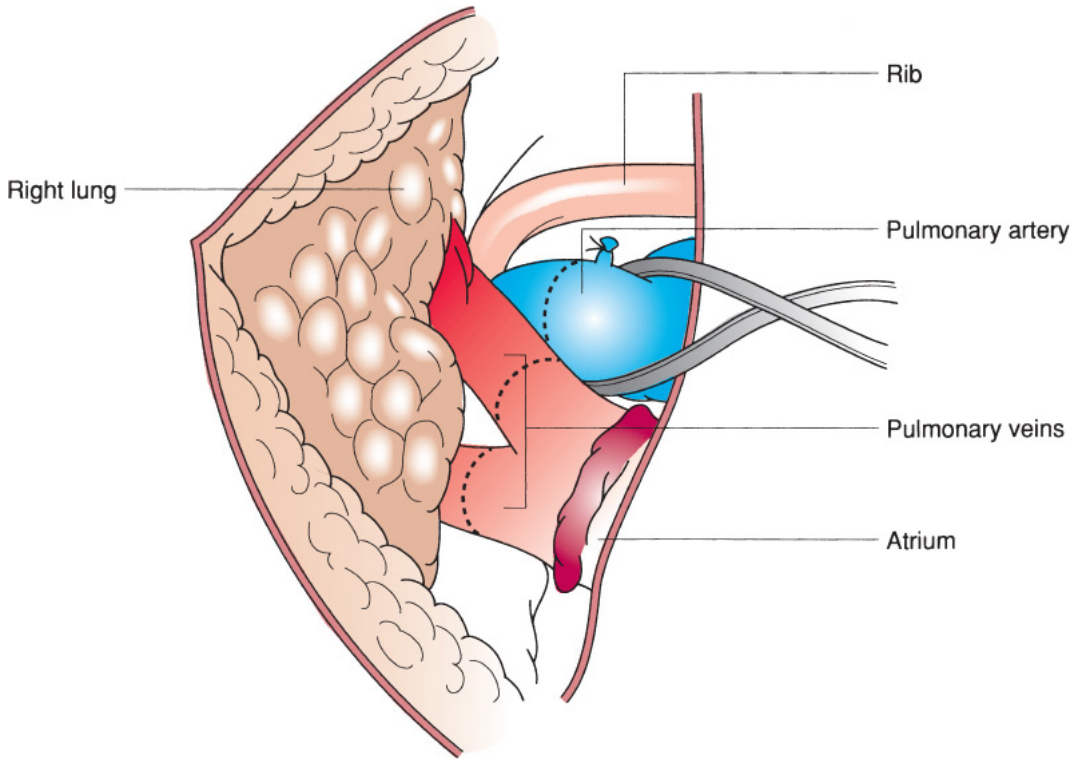

Figure 39.1 Mobilization of the hilum of the right lung. The pulmonary artery is encircled, and the first branch is ligated and divided. The superior and inferior pulmonary veins have been exposed. Both the artery and veins are taken as close to the lung as possible. The bronchus is divided at the level of the takeoff of the upper lobe to minimize ischemia of the airway.

Single Lung Transplantation

In the recipient operation, a standard fifth intercostal space posterolateral thoracotomy is preferred. The groin should always be included in the sterile field. If necessary, CPB can be performed by cannulating the femoral vessels in the groin. The hilar dissection (**Fig. 39.1**, shown with stapler) differs from that of a pneumonectomy in that the main pulmonary artery and the pulmonary veins should be divided within the pulmonary hilum at the level of the lung parenchyma, to allow as great of a vascular stump as possible, for later ease of reconstruction. The pericardium is opened around the left atrial cuff allowing the left atrium to be clamped centrally to the branch point of the superior and inferior veins. On the right, the veins are elongated by mobilizing Waterston's groove. The artery and vein stumps are gently retracted with a 2-0 silk suture through the staple line, away from the bronchus to provide exposure. Care should be taken to preserve the peribronchial lymphatic and areolar tissue in order to maintain the vascular supply of the mainstem bronchus just proximal to the origin of the upper lobe bronchus. However, care should be utilized to clip any divided bronchial or lymphatic vessels during the dissection. In addition, injury to the phrenic nerve must be avoided, especially in the setting of pleural adhesions from previous surgery, severe emphysema, or pulmonary fibrosis, to avoid diaphragmatic dysfunction, which can adversely affect posttransplant functional recovery.

The donor lung is prepared by dissecting the left atrial cuff and the proximal pulmonary artery from the surrounding tissues. Retrograde perfusion is then administered by perfusing the superior and inferior pulmonary veins with cold Perfadex while the lung is still inflated. The bronchial cuff is prepared by transecting the mainstem bronchus approximately two cartilaginous rings from the orifice of the upper lobe bronchus to maximize retrograde perfusion to the bronchial anastomosis.

Implantation of the donor lung progresses from posterior to anterior, with the anastomosis between the donor and recipient bronchus, first. An end-to-end anastomosis is performed with a running 4-0 polydioxanone suture at the cartilagino-membranous junction, continuing along the membranous airway, before reapproximation of the cartilaginous airway. Care to not pursestring the anastomosis is undertaken by the assistant maintaining equal

tension along the suture until completion. Absorbable sutures are used rather than polypropylene to reduce the risk of suture granuloma formation.

The vascular anastomoses are then performed sequentially using running 4-0 and 6-0 nonabsorbable polypropylene sutures for the venous and arterial anastomoses, respectively. Our preference has been to perform the left atrial anastomosis followed by the pulmonary arterial anastomosis. The recipient pulmonary vein stumps are prepared by unifocalization into one left atrial cuff to reduce the risk of pulmonary venous obstruction. In constructing the pulmonary arterial anastomosis, care must be taken to trim the donor pulmonary artery to the appropriate length to avoid kinking of the low-pressure vessel. Once the vascular anastomoses are completed, the lungs are gently ventilated as the vessels are deaired with the patient in the Trendelenburg position, removing the left atrial clamp followed by the pulmonary arterial clamp prior to tying the anastomotic sutures. A 500 mg dose of methylprednisolone is usually given prior to reperfusion to minimize an expected systemic inflammatory response. It is also standard in our institution to initiate inhaled nitric oxide prior to reperfusion of the lung to theoretically minimize risk and complications of primary graft dysfunction (PGD).[15] Progressive reperfusion to the allograft is manually controlled. Both anterior and posterior chest tubes are secured and the chest is then closed in standard fashion.

Bilateral Lung Transplantation

6 The technique of double-lung transplantation has evolved considerably since the late 1980s from an en bloc technique to a bilateral, sequential technique.[16,17] With the patient in the supine position, this operation can be performed through a median sternotomy, bilateral thoracosternotomy (clamshell) incision (**Fig. 39.2**, shown with arms tucked at sides), bilateral anterior thoracotomies without sternal division, or bilateral muscle-sparing axillary thoracotomies. The bilateral thoracosternotomy incision is the author's preference for bilateral lung transplantation and provides the widest exposure facilitating dissection and mobilization of the hilar structures as well as cannulation of the right atrium and ascending aorta if CPB is necessary. This exposure is particularly important in recipients with diffuse dense pleural adhesions as is often seen in patients with chronic infections with bronchiectasis or CF, previous pleurodesis, or with severe apical adhesions after lung volume reduction in patients with emphysema.

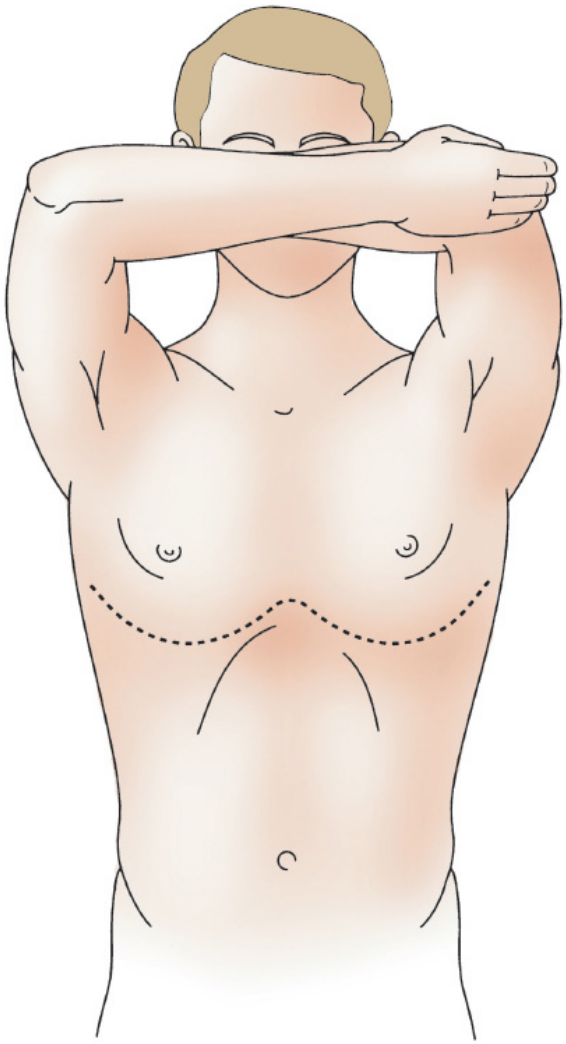

Figure 39.2 Patient positioning for a bilateral, sequential lung transplant. Bilateral anterior thoracotomies are made in the fourth intercostal space with a transverse sternotomy when needed for exposure (clamshell incision).

Although both lungs are replaced, the operation can often be performed without CPB unless the recipient has significant pulmonary hypertension or severely limited gas exchange. By replacing the lung with the least function first, based on the quantitative ventilation perfusion scan or intraoperative pulmonary arterial test clamping, oxygenation and ventilation can be maintained by the native lung. If the patient is unable to tolerate single-lung ventilation due to inadequate gas exchange or worsening right ventricular dysfunction with increasing pulmonary hypertension (near or suprasystemic), then CPB is initiated. If recipient hemodynamics are significantly impaired during retraction and exposure of the left atrial anastomosis, particularly during left lung recipient pneumonectomy and implantation, CPB should be utilized to facilitate the operation. In patients with severe mediastinal shift due to volume loss from pulmonary fibrosis, CPB may be necessary to provide sufficient cardiac decompression in order to obtain adequate exposure to complete the anastomoses.

The donor lungs are prepared leaving a cuff of left atrium around the pulmonary veins on each side. The recipient pneumonectomy is performed one side at a time with the patient maintained using single-lung ventilation of the contralateral lung. Each donor lung is implanted using the same technique as described for single-lung transplantation. The bronchial anastomosis is completed first, followed by the left atrial and pulmonary arterial anastomoses. Once perfusion and ventilation are restored to the first implanted lung, this lung then supports the patient while the remaining lung is removed and the second lung is implanted.

OPERATIVE CONSIDERATIONS

Allograft Ischemic Time

7 Most transplant centers attempt to limit organ ischemic time to less than 6 total hours, however, multiple institutions, including our own, have vast experience comfortably extending cold ischemic time with careful donor selection. Conflicting evidence using older registry data found increased 2-year mortality with donor age >50 years and ischemic times 7 hours or more,[18] yet another analysis demonstrated that prolonged ischemic time was not an independent predictor of mortality.[19] In the current era of widening donor shortages and improved organ preservation techniques, 10% of recipients were reported to have ischemic times >8 hours, and ischemic times up to 12 hours was demonstrated to not be associated with primary graft failure nor survival.[20]

Unilateral versus Bilateral Lung Transplant

Despite almost 30 years of bilateral lung transplant being the predominant lung transplant operation and 75% of candidates currently receiving a bilateral lung transplant,[4] an omnipresent debate over the best strategy to utilize for lung transplantation still exists. While institutional preferences, including ours, favor bilateral lung transplant for recipients without technical and comorbid contraindications to bilateral transplant, single-lung transplants are suggested to be a better utilization strategy for such a limited resource. A recent comprehensive review of literature during the LAS era concluded that the level of evidence supporting either conclusion is conflicted, limited, and varied enough by disease and patient factors that without a randomized trial, which will likely never happen, considerations for the technique should be made on a case-by-case basis.[21]

Intraoperative Cardiopulmonary Support

Traditionally, during implantation in recipients who demonstrate inadequate pulmonary reserve during single-lung ventilation or inadequate cardiovascular reserve, evidenced by hemodynamic instability or progressive right ventricular dysfunction, intraoperative CPB is utilized. However, the risks and side effects of full heparinization resulting in perioperative bleeding and PGD are concerning and desired to avoid if possible. There has been a shift of intraoperative support toward the use of intraoperative ECMO, as the benefits of less heparinization, absence of a venous reservoir, less circuit component interfaces, and ease of conversion to postoperative support as needed, invite consideration of first line deployment over full CPB, when safe to do so. Several institutions have reported their results and experience utilizing the technique with consistent benefits of fewer postoperative complications, such as bleeding, inhospital mortality, prolonged ventilation requirements, and incidence in PGD.[22–26] We have also adopted use of intraoperative ECMO when cardiopulmonary support is necessary, which is only 25% of double-lung transplants and rarely needed for single-lung transplants. Some programs even now advocate routine intraoperative ECMO for all lung transplant procedures, based on demonstrated excellent early allograft function and midterm survival utilizing the technique.[27]

Special Patient Populations

While patient safety and surgical team efficiency are important and improved by standardizing common procedures, it is prudent to review each recipient's specific history preoperatively to recognize patient-specific factors that may complicate or alter the course of the operation or predispose them toward postoperative complications. Those patients with severe pulmonary hypertension and RV failure are at risk for hemodynamic collapse with induction of general anesthesia and the surgical team and perfusionist should be immediately available for emergent institution of CPB or ECMO if needed. In the case of near or suprasystemic PA pressures, preinduction establishment of ECMO should be considered. In patients with severe peripheral vascular disease, history of Raynaud disease or digital ischemia, consideration of avoiding the radial arterial line or minimizing the duration of its insertion should be undertaken. It is also reasonable to consider the application of local heating devices or topical vasodilators to an at-risk extremity, as tolerated.

Surgical Complications

Primary Graft Dysfunction

8 PGD is an acute lung injury syndrome occurring within the first 72 hours following lung transplantation and is characterized by inexplicable diffuse allograft infiltrates and hypoxemia, defined as a PaO_2/FiO_2 ratio (P/F) <300 (**Table 39.7**). The definition has been standardized by ISHLT consensus[28] and later validated and clarified[29] in order to promote improved clinical and scientific progress and potential development of therapeutic strategies. PGD is also characterized by low pulmonary compliance, interstitial/alveolar edema, pulmonary infiltrates on chest radiographs, increased pulmonary vascular resistance, intrapulmonary shunt, and acute alveolar injury, as revealed by diffuse alveolar damage (DAD) on pathology.[30] Recipients who suffer from severe PGD have been reported to have 3 to 5× increased short-term mortality, 30-day, 23%, 1-year, 34%, and long-term mortality.[31,32] Risk of PGD development is thought to result from complex immunomechanistic interactions between donor and recipient characteristics and the conduct of the donor and recipient operations. While no specific pathomechanism has been identified, Diamond et al. published a multicenter prospective multivariate analysis identifying risk factors for severe PGD as donors with any smoking history, FiO_2 >0.4 during allograft reperfusion, preoperative sarcoidosis or pulmonary arterial hypertension, use of CPB, single-lung transplant, large-volume blood product transfusion, elevated pulmonary arterial pressures, and overweight or obese recipient body habitus.[32]

Airway Complications

The lung has a dual blood supply from both the pulmonary and bronchial arteries. Conventional lung transplantation operative techniques interrupt the bronchial artery supply and do not revascularize the bronchial anastomosis, so postlung transplant airway complications remain of concern. Airway complication rates have ranged from 2% to 18% in larger contemporary studies.[33] The current bronchial anastomotic complication rate represents a significant improvement over early lung transplant experience where 55% of recipients were noted to have airway complications,[34] most likely a result of improved operative technique, organ preservation, and patient care protocols.

Table 39.7 Grading of Primary Graft Dysfunction Severity

Grade	PaO_2/FiO_2	Radiographic Infiltrate Consistent with Pulmonary Edema
0	>300	Absent
1	>300	Present
2	200–300	Present
3	<200	Present

Early strategies to minimize airway complications such as tracheal anastomosis for bilateral lung transplant, anastomotic flaps from omentum, intercostal muscle, or pedicled internal mammary artery or pericardial fat pads either significantly worsened, as in the case of the tracheal anastomosis, or did not show any significant reduction in complications.[34,35]

In 1970, Haglin et al. performed the first lung transplant with bronchial artery revascularization (BAR), using an aortic vascular cuff, and proposed the technique as a method to restore bronchial artery circulation. The technique is infrequently described and utilized secondary to concerns for added complexity, operative time, lack of acceptance of improved postoperative airway, and other complications. The largest reported clinical results of BAR was by a group in Denmark reporting 65 patients, 47 undergoing double-lung transplant with the left mammary artery used as BAR conduit and demonstrated excellent success and long-term survival,[36]

superior to their more recent series of non-BAR lung transplants.[37] A recent pilot study at the Cleveland Clinic in 27 bilateral lung transplant recipients demonstrated that BAR resulted in similar operative time and hospitalization, but resulted in reduced airway ischemia and complications, lower biopsy tissue grades, fewer infections, and delay of BOS.[38] Together, these results raise the consideration for the field to investigate more in depth the success and potential impact of more routine use of the technique and if supported, then development of a pathway to disseminate the technique to other centers.

DONOR CONSIDERATIONS

In 2018, 2,407 deceased lung donors were utilized; 4.8% from donation after circulatory death donors, 7.9% from donors with a smoking history of 20 pack-years or more.[4] While the goal of the transplant community should be to improve donor utilization efficiency, be better stewards of organ, and to maintain or improve posttransplant outcomes and quality of life, there remains concern that increased donor utilization strategies may result in higher rates and complications of PGD. Therefore, effective strategies to minimize or treat PGD will remain of utmost importance.

Ex Vivo Lung Perfusion

The circumstances or mechanisms leading to a donor's death often results in pulmonary injury or dysfunction prompting concerns for further postoperative allograft dysfunction or severe PGD. Because of this, lung donor utilization remains around only approximately 20% of multiorgan donors; this is in stark contrast to that of liver and kidney utilization rates of almost 75%.[39] Ex vivo lung perfusion (EVLP) has been proposed as a technique to allow the safe and timely assessment of underutilized donor lungs prior to transplantation. Since the original EVLP description for the evaluation of a DCD lung donor,[40] three basic EVLP techniques have been reported,[41] but the premise is the same; normothermic perfusion and ventilation of donor lungs with the ability to recondition lungs and assess physiologic parameters. The three systems are differentiated based upon four concepts: blood-based perfusate, pulsatility, portability, and atrial reconstruction. A recent meta-analysis demonstrated no differences in outcomes between the use of marginal lungs resuscitated using EVLP compared to standard lungs transplanted without EVLP.[42] The Toronto Lung Transplant program, which has been influential in leading the field in EVLP utilization and experimental therapies recently shared their long-term EVLP results. Since the inception of their EVLP program in 2008, 497 lungs were evaluated with EVLP and 25% of their lung transplants have resulted from EVLP evaluation; representing an almost 70% EVLP to transplant conversion rate, with comparable short- and long-term results.[43]

While the use of EVLP may be more readily accepted for marginal or nonutilized lungs, the benefit of use of EVLP for standard lungs may raise questions. Slama et al. demonstrated that EVLP can safely be used in standard donor lungs, with comparable perioperative outcomes as using standard donor lung preservation techniques, with the added potential to exclude lungs with functional impairment and safely extend total preservation time.[44]

EVLP Clinical Trials

Several informative prospective trials have been completed including the NOVEL trial (United States; XVIVO), the HELP trial (Toronto; XVIVO), the INSPIRE and EXPAND trials (Europe and the United States; Transmedics), the Perfusix trial (United States; Perfusix), the Vienna trial (Vienna; XVIVO), and the DEVELOP trial (United Kingdom; Vivoline). Other than the INSPIRE trial, all studies have demonstrated noninferiority to traditional cold storage methods, even with the use of marginal donor organs after EVLP.[45–50] The international, multicenter randomized controlled trial, INSPIRE, demonstrated that use of the OCS device in standard donor lungs resulted in slightly poorer 30-day survival that normalized at later timepoints, but also demonstrated superiority in reduction of severe PGD at 72 hours and in combination with 30-day survival compared to our traditional cold static storage.[45] The results of this trial resulted in FDA approval of the OCS device as standard of care, and remains the only EVLP device FDA approved as such.

All prior studies have utilized positive pressure ventilation; thus the University of Alberta has proposed in the UA NP-EVLP currently active pilot study (NCT03293043, Canada) to more closely mimic lung physiology by utilizing negative pressure ventilation during EVLP. Preliminary results were just released and demonstrated in 12 extended criteria donor human lungs, that negative pressure ventilation EVLP allows for preservation and evaluation of donor lungs with all grafts and patients surviving to 30 days and recovered to discharge without any patients demonstrating PGD grade 3 at 72 hours nor requiring post-operative ECMO.[51]

While all of these aforementioned options include the use of significant resources and staff from the recipient hospital to recover, resuscitate, monitor, and evaluate organs during EVLP, Lung Bioengineering (Silver Spring, MD) is currently investigating the ability of a centralized facility to evaluate marginal donor lungs utilizing the Toronto EVLP system, usually for targeted recipients, in the EVP-DEV-301 trial (NCT02234128).

Hepatitis C Virus-Infected Organs (HCV)

Prior to 2016, only five HCV+ donor lung transplants had been performed, however, in 2017, willingness of patients to accept and programs to perform HCV+ transplants resulted in 100 total anti-HCV+ (45 nucleic acid test+) lung transplants being performed in 2018.[52] This rise is in direct response to earlier success in abdominal transplant organs and the advent of more effective and less challenging therapeutic regimens in very complex patients, with the FDA approval of second-generation direct-acting antivirals (DAAs) that demonstrate more than a 90% sustained HCV cure rate.[52] In 2019, the DONATE clinical trial investigators published the results of a nonrandomized, open label phase IV clinical trial at Brigham and Women's Hospital in 36 lung transplant recipients, who received organs from donors with hepatitis C viremia and were treated with a DAA regimen for 4 weeks beginning within a few hours after transplantation, prevented the establishment of HCV infection.[53] The findings and potential impact of this study has resulted in progressive adoption of HCV protocols at many institutions. Our institution has also developed experience and success with utilizing HCV+ donor lungs, which so far has not only improved our donor utilization rate, but has also resulted in decreased wait time as well.

CONCLUSIONS

While lung transplant outcomes continue to lag behind other solid organ transplants, improvements in technique, perioperative care, and allocation adjustments continue to advance survival 9 and volume benchmarks. Donor availability remains a limiting factor to successful and timely transplantation, which has led to innovative utilization of techniques that result in increased donor utilization. However, PGD is still of concern with the use of underutilized donor populations and several clinical trials are ongoing, but it is currently unclear the effect that these increased donor utilization strategies will have on the incidence or severity of PGD or if effective therapies will arise to minimize or eliminate the effects of PGD.

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Pancreas and Islet Transplantation

Randall S. Sung

Key Points

1. The Diabetes Control and Complications Trial (DCCT) demonstrated that tight control of blood glucose and minimization of hemoglobin A1C delays the progression of secondary complications of diabetes.
2. Recipients with functioning pancreas transplants have normal glycemic control without the need for exogenous insulin, and pancreas transplantation has a beneficial impact on diabetic complications.
3. Pancreas graft survival rates are 90% at 1 year.
4. Most pancreas transplants are performed in patients with end-stage renal disease (ESRD), either concomitant with or following a kidney transplant.
5. In general, eligibility criteria for pancreas transplantation are more stringent than for kidney transplantation alone.
6. Pancreas transplant outcome is dependent on the careful selection of donors and on meticulous pancreas recovery technique.
7. Immunosuppression for pancreas transplantation is similar to that for kidney transplantation.
8. In contrast to kidney transplants, the effect of a pancreas transplant on patient survival is only modest.
9. Islet transplantation does not require an operative procedure.
10. Islet transplant outcomes vary by center; overall, insulin independence is less frequent and less durable than whole-pancreas transplants, but continues to improve.

INTRODUCTION

Diabetes mellitus is a spectrum of impaired glucose tolerance that ranges from gestational glucose intolerance to severe hyperglycemia and

ketoacidosis. Diabetes, which affects approximately 34 million people, or 10.5% of the U.S. population, can be divided into two major classifications.[1] Type 1, previously referred to as insulin-dependent diabetes, is an autoimmune disease characterized by the eventual loss of all pancreatic β-cell function. Type 2 diabetes, previously referred to as non–insulin-dependent diabetes or adult-onset diabetes, characteristically presents in obese patients over age 40.[1] Many of these individuals eventually require insulin therapy. The prevalence of type 2 diabetes is increasing as the prevalence of obesity increases, especially in younger age groups. Overall, the age-adjusted incidence of diabetes peaked in 2009 and has actually declined since then, although the incidence of both type 1 and type 2 diabetes in those under age 19 continues to increase. Prevalence of diagnosed diabetes for 2017 to 2018 was highest among American Indians/Alaska Natives (14.5%), people of Hispanic origin (12.5%), and non-Hispanic blacks (11.7%).

While the mean age of onset is in the early teenage years, the disease may present as early as the first year of life. Type 1 diabetes afflicts approximately one in every 400 to 500 children and adolescents.[2] Patients may present as late as the fourth decade of life, and these patients may be misclassified as type 2 diabetics, despite clearly possessing the physiology of type 1 diabetes. The disease classically presents in a lean patient with polyuria, polydipsia, and polyphagia. It may present at the time of a concurrent illness. While there may be a brief "honeymoon" period after presentation where insulin is not required, exogenous insulin is always required to replace that lost by the complete destruction of β-cell mass. While hyperglycemic episodes from poorly controlled diabetes, or hypoglycemic events from insulin, may be life threatening, the major morbidity of type 1 diabetes stems from the myriad long-term manifestations of the disease, particularly those that are due to accelerated atherosclerosis.

PATHOPHYSIOLOGY

The classic pathophysiology of diabetes is that of insulin secretory failure in type 1 diabetes and peripheral insulin resistance in patients with type 2 diabetes. The etiology, epidemiology, and pathogenesis of diabetes are much

more complex than is reflected in early characterizations of the disease. Type 1 diabetes is classically described as an autoimmune disorder manifested by destruction of β-cells, with proinsulin being the most likely primary target.[3] Although there are rare monogenic, immune-mediated forms of type 1 diabetes, the common form is thought to be determined by multiple genetic and environmental factors. The concordance for type 1 diabetes in monozygotic twins is less than 100%, and although type 1 diabetes aggregates in some families, it does not segregate with any clear mode of inheritance.[4]

There is multigenic susceptibility to type 1 diabetes. Genes within the HLA region, especially those that encode antigen-presenting molecules, confer the greatest part of the genetic risk of type 1 diabetes. The likelihood that these many genes may individually only have weak effects make them more difficult to identify precisely, and may explain the heterogeneity of inheritance of type 1 diabetes. This genetic susceptibility background is thought to interact with environmental triggers, perhaps infectious, that lead to autoimmunity and insulitis, the characteristic pathologic lesion of type 1 diabetes, although definitive proof of these triggers is lacking.

The incidence of type 1 diabetes has been progressively increasing during the past several decades, particularly among children younger than 5 years. In children at genetic risk, diabetes-related autoantibodies appear, followed by the evolution of metabolic abnormalities and the eventual clinical appearance of the disease. If individuals identified by genetic markers subsequently undergo seroconversion and develop two or more diabetes-related autoantibodies, their risk of progression to type 1 diabetes is 75% over 10 years and appears to be almost certain over 20 years.[5] A recent study of patients with diabetes-related autoantibodies who were treated with teplizumab, a monoclonal antibody that reduces the actions of CD8+ T lymphocytes on targets such as beta cells, showed significant reductions in annualized rates of type 1 diabetes and an increase in the median time to diagnosis of type 1 diabetes.[6]

Mucosal tolerance has been exploited in secondary prevention studies using nasal insulin and in secondary prevention and recent-onset type 1 diabetes studies using oral insulin.[7] However, these studies have not been successful in altering the course of the disease. In the Diabetes Prevention Trial–Type 1 (DPT-1), a secondary prevention study of oral insulin, those

with high levels of insulin autoantibodies at baseline had a projected 4.5- to 5-year delay in the development of clinical diabetes. A subsequent analysis showed continued beneficial effects even after oral insulin was discontinued.

In type 2 diabetes, while β-cell hypersecretion initially may exist, ultimately loss of β-cell mass ensues. β-Cell apoptosis is mediated by glucotoxicity from insulin resistance, and is exacerbated by fatty acids, lipoproteins, leptins, and cytokines, all of which are elevated in type 2 diabetes and obesity.[8] Because of peripheral insulin resistance, many patients require insulin in amounts that exceed one unit per kilogram, far greater than typically required by type 1 diabetics.

The observation that type 1 and type 2 diabetes frequently occur in the same family has raised the possibility that they are opposite ends of the same disease spectrum, and ample evidence suggests the two are more similar than initially believed.[9,10] Families with mixed diabetes histories tend to have an intermediate diabetes phenotype: insulin resistance in type 1 and lower BMI and C-peptide concentrations in type 2 patients. β-Cell destruction is common to both types, and obesity and insulin resistance have both been shown to be risk factors for childhood type 1 as well as type 2 diabetes. The "accelerator hypothesis" of diabetes proposes three determinants of disease in all types of diabetes: the intrinsic rate of β-cell apoptosis, insulin resistance, and autoimmunity (which would apply only to a subset). Genetic studies suggest there may be a common predisposition. However, the cytokines, signal transduction pathways, and other soluble mediators of apoptosis are quite different between the insulitis of type 1 diabetes and the lipotoxic or glucotoxic processes of type 2 diabetes, and thus at minimum represent distinct mechanisms of β-cell destruction.[11]

The relatively recent discovery of the replicative potential of a variety of adult tissue types, and their roles in the pathogenesis of disease, has relevance to the pathogenesis of diabetes. In such a model, diabetes occurs due to a failure of regeneration of β-cells, and individual variation in the ability to regenerate β-cells is an important determinant of diabetes development. This hypothesis is partially supported by the finding of associations of type 2 diabetes with genes having identified roles in cellular development. While it is broadly agreed that failure of β-cell replication is an important contributor to diabetes development, increased susceptibility of replicating β-cells to apoptosis in a proapoptotic environment may also lead

to loss of β-cell mass. There is also evidence that deficits of β-cell secretion are as important as those of replication. Furthermore, the range of β-cell mass in adult diabetic and nondiabetic humans is very wide, and exceeds the apparent capacity for expansion of β-cell mass in response to regenerative stimuli. Thus it appears more likely that insufficient growth of β-cell mass during development may be more likely to have a role in the predisposition to diabetes than specific deficits in regeneration.[12]

Alternatively, β-cell dedifferentiation, rather than death, may be the mechanism responsible for β-cell failure in type 2 diabetes.[13] When normal β-cells are challenged by mild hyperglycemia or insulin resistance, they produce and secrete more insulin, thus maintaining euglycemia. Current thinking suggests that oxidative stress and/or endoplasmic-reticulum stress results in β-cell dysfunction, leading to increased secretion of incompletely processed proinsulin, which may trigger apoptosis. Stressed β-cells may undergo dedifferentiation, decreasing expression of β-cell–specific genes, including the enzyme that processes proinsulin; this may explain increased proinsulin secretion in type 2 diabetes. Dedifferentiation may also promote expression of embryonic progenitor-cell markers, and these cells may later secrete non–β-cell hormones such as somatostatin and glucagon.

SECONDARY COMPLICATIONS OF DIABETES

Diabetes mellitus is responsible for tens of thousands of deaths each year in the United States. The high incidence of cardiovascular complications in diabetics is primarily responsible for the twofold increase in the risk of death in diabetics compared with those without diabetes.[2] Clinical complications of diabetes include end-stage renal disease (ESRD), retinopathy, peripheral vascular disease, coronary artery disease, and neuropathy. Diabetic nephropathy is responsible for nearly 40% of all cases of ESRD; diabetes is also the leading cause of blindness and amputations in the United States.[1] The total direct estimated costs of diagnosed diabetes increased from $188 billion in 2012 to $237 billion in 2017.[1]

Improvements in diabetes care have reduced the long-term impact to some extent. Rates of all five major diabetes complications (acute myocardial infarction, hyperglycemic crisis, stroke, amputations, and ESRD) have

declined since 1990, with the smallest decline in ESRD. However, when expressed as rates for the overall population, in which a change in prevalence also affects complication rates, there was a decline in rates of acute myocardial infarction and death from hyperglycemic crisis, but not in rates of amputation, stroke, or ESRD. Thus, while rates of diabetes-related complications have declined substantially in the past two decades, a large burden of disease persists because of the continued increase in the prevalence of diabetes.[14]

While diabetic complications have a multifactorial etiology, they are ultimately secondary to structural alterations in nerves, blood vessels, and connective tissue. Excess glucose is converted to sorbitol by aldose reductase, leading to the reduction of cellular content of myoinositol, abnormal phosphoinositide metabolism, and reduction in Na^+-K^+-ATPase activity. In experimental animals, aldose reductase inhibitors prevent diabetic neuropathy, cataracts, and retinopathy.[15] The accumulation of advanced glycosylation end products (AGEs), due to abnormal nonenzymatic glycosylation of proteins, and extensive crosslinking of these proteins, is likely to be pathogenic.[16] Ligation of endothelial cell receptors by AGEs results in the release of proinflammatory cytokines and activation of the coagulation cascade. Microangiopathy is characterized by thickening of capillary basement membranes, which increases with the duration of disease, and altered capillary permeability.

1 The Diabetes Control and Complications Trial (DCCT) demonstrated that tight control of blood glucose prevents and delays the progression of secondary complications of diabetes.[17,18] This study, in which patients with type 1 diabetes were randomized to conventional treatment with one or two doses of daily insulin versus intensive treatment with three or more injections per day, demonstrated a dramatic reduction in the risk of progression of retinopathy, microalbuminuria, albuminuria, peripheral neuropathy, and cardiovascular disease in the subjects randomized to intensive treatment. However, the major side effect of intensive treatment was a threefold increase in the risk of severe hypoglycemic episodes; approximately 10% of patients in the intensive insulin therapy cohort experienced five or more episodes of seizure or coma during the study period. Even in the absence of overt brain injury, multiple episodes of severe hypoglycemia have been associated with cerebral perfusion abnormalities

and poor neuropsychiatric performance. In addition, there is a significant risk of accident during hypoglycemic episodes. Frequently, as hypoglycemia becomes more frequent and autonomic neuropathy worsens, patients may develop a syndrome of unawareness to hypoglycemia where the typical symptoms of tremor and anxiety do not occur. Such patients with hypoglycemic unawareness may develop profound hypoglycemia, especially if left unsupervised, and risk severe neurologic and traumatic injury.

In a similar trial, patients randomized to intensive insulin therapy, compared to those randomized to conventional therapy, had lower all-cause mortality. The most common causes of death were cardiovascular disease (22%), cancer (20%), and acute complications (18%).[19] The long-term risk of an impaired glomerular filtration rate (GFR) was significantly lower among persons treated early in the course of type 1 diabetes with intensive diabetes therapy than among those treated with conventional diabetes therapy.[20] Notably, all-cause mortality was significantly higher among those with higher mean hemoglobin A1C (HbA1C) levels and with renal disease during the 20-year follow-up.[19]

The overall management of diabetes is focused upon maintaining blood glucose as close to normal range as possible while attempting to minimize significant hypoglycemic episodes. Although the frequency and extent of hyperglycemia is important in the assessment of glucose management, long-term glycemic control is best assessed by evaluation of blood levels of HbA1C which measures the extent of glycosylation of hemoglobin. Although the incidence of diabetes is increasing, the overall treatment efficacy has improved. The use of subcutaneous insulin pumps is being increasingly employed, inhaled insulin has been used in selected patients, and infusion devices which also assess serum glucose and automatically adjust insulin dose accordingly are being developed.[21,22] Fully automated artificial-pancreas systems have been developed which link glucose sensors with insulin pumps through computerized control algorithms, which dictate insulin delivery in response to real-time sensor data.[23] Recent studies that have been carried out both in hospitals and in outpatients have shown that such systems can improve glucose control and reduce the risk of nocturnal hypoglycemia in children, adolescents, and adults.[24,25]

Nevertheless, until such systems are widely adopted, many diabetics still have difficulty maintaining tight glucose control without hypoglycemic

complications.[26] In addition, most type 1 diabetics, even if on optimal insulin therapy, are unable to maintain HbA1C levels in the normal range, and most will ultimately develop progressive diabetic complications.

PANCREAS TRANSPLANTATION

Overview

Pancreas transplantation, while not technically a cure, represents an important therapeutic insulin replacement option 2 for many type 1 diabetics. Recipients with functioning pancreas transplants have normal glycemic control without the need for exogenous insulin. Initial experience with pancreas transplantation, from the first pancreas transplant performed by Kelly and Lillehei in 1966 until the 1980s, was marked by low success rates and high mortality.[27] In 1980 the 1-year graft survival rate for pancreas transplantation was only 21%, and there was tremendous skepticism about the utility of the procedure. 3 Advances in surgical technique and immunosuppression dramatically improved graft survival rates to the current rate of around 90% at 1 year. In addition to the development of cyclosporine, the introduction of bladder drainage of the donor pancreas, first introduced by Sollinger in 1985 using a button of donor duodenum, and subsequently modified by Corry in 1986 using an entire segment of duodenum anastomosed to the urinary bladder, dramatically improved the results of pancreas transplantation (**Fig. 40.1**).[28,29] Graft survival continued to improve throughout the 1980s and 1990s, especially for isolated pancreas transplantation (pancreas transplant alone [PTA], or pancreas after kidney transplantation [PAK]), the results of which have been historically inferior to simultaneous kidney–pancreas transplants (SPK). Both short- and long-term survival of pancreas transplants have improved much more slowly over the past decade. Because bladder drainage is associated with significant morbidity, most pancreas transplants are currently performed with enteric exocrine drainage and venous drainage into the systemic circulation. However, pancreas transplantation may also be performed by draining pancreatic venous blood into the recipient portal circulation, usually via the superior mesenteric vein.

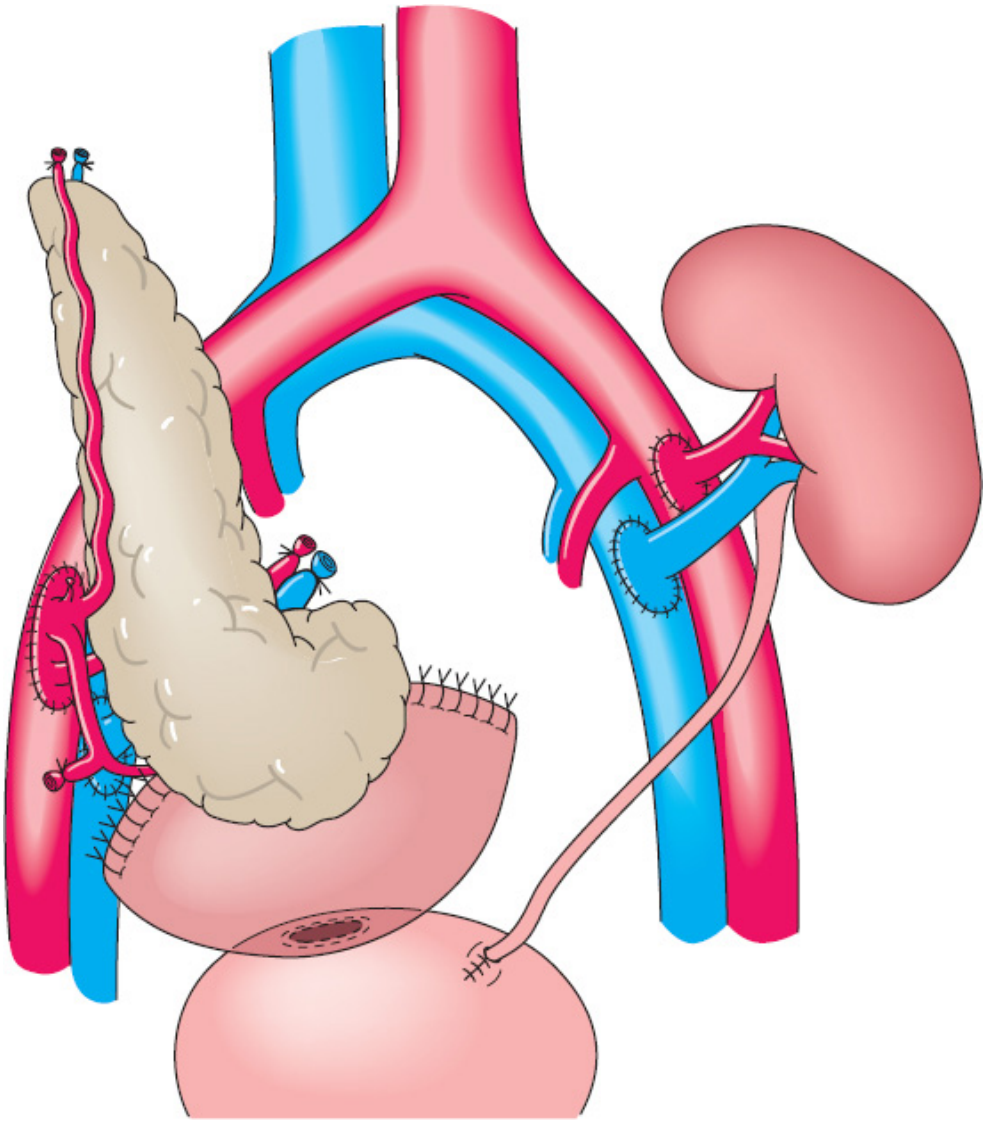


Figure 40.1 Simultaneous pancreas kidney transplantation performed with drainage of the pancreatic exocrine secretions into the urinary bladder (bladder drainage). This technique has been predominant until recently. Note that a segment of the second portion of the duodenum is left attached to the pancreas. Despite its heterotopic location, the transplanted pancreas responds to gastrointestinal hormones with a marked increase in secretion of pancreatic juice that has very high bicarbonate content. Also note that the portal vein drains into the iliac vein (i.e., systemic venous drainage). In healthy individuals 50% of the secreted insulin is extracted from the circulation in the first pass through the liver. Transplant recipients with systemic venous drainage have peripheral insulin levels two to two and one half times higher than normal.

Patient Selection

Pancreas transplantation is usually performed in patients with type 1 diabetes. The diagnosis of type 1 diabetes is relatively straightforward for most individuals. A history of juvenile or young adult onset, diabetic ketoacidosis, a lean body habitus, and a low insulin requirement (<0.7 units/kg) all support the diagnosis of type 1 diabetes. In contrast, older age of onset, obesity, an interval of treatment with diet or oral agents, or high insulin requirements are all suggestive of type 2 diabetes. A subset of adult-onset diabetics will display characteristics otherwise associated with type 1 diabetes, including absence of insulin production. Whether these individuals are properly classified as type 1 or type 2 diabetics may be subject to debate, but these individuals may certainly benefit from pancreas transplantation. Individuals with type 1 physiology but adult age of onset and who make low levels of endogenous insulin may also be considered for pancreas transplantation. Outcomes for these recipients are similar to those with type 1 diabetes. Recognition of these excellent outcomes has resulted in an increase in pancreas transplant recipients classified as having type 2 diabetes up to 14%.[30] As these are typically highly selected individuals without significant insulin resistance, most type 2 diabetics would not be considered candidates. Some type 1 diabetics may develop insulin resistance as a result of years of insulin therapy; this is frequently accompanied by increased body weight and insulin requirements. While insulin resistance may improve after transplantation in such patients, or may be managed with additional oral hypoglycemic agents, these patients are at higher risk for remaining on insulin after pancreas transplantation.[31] While provocative tests for insulin resistance exist, they are not commonly employed.

A small percentage of pancreas transplant recipients do not have type 1 or type 2 diabetes, but have diabetes from other causes. Several have undergone pancreatectomy for chronic pancreatitis or other conditions.[32] Some pancreas transplants (<1%) are performed as part of a multivisceral transplant that includes liver and small intestine in patients who do not have diabetes; in these transplants, the pancreas is included in the graft to facilitate the technical conduct of the operation and to reduce complications.[33]

4 Most individuals evaluated for pancreas transplantation have chronic renal disease. These patients may present prior to onset of dialysis, while currently receiving dialysis, or following kidney transplantation. For individuals without a functioning kidney transplant, potential options include

simultaneous deceased donor kidney/pancreas transplantation (SPK), living donor kidney transplantation followed by PAK, simultaneous living donor kidney–deceased donor pancreas transplantation (SPLK), or simultaneous living donor kidney–pancreas transplantation. Of these options the former two are by far the most common.

Simultaneous Kidney–Pancreas Transplantation

SPK from a deceased donor is the most commonly performed pancreas transplant option, with the number exceeding all other types combined. An SPK transplant has the advantage of requiring only one operation for both transplants. Since alloreactivity against the transplanted pancreas tends to be concordant with activity against the kidney, pancreas rejection may be heralded by signs of kidney rejection, which are more sensitive and present earlier. Consequently, SPK pancreas outcomes have been historically superior to those of solitary pancreas transplants.

Pancreas after Kidney Transplantation

If a living kidney donor is available, candidates have the option of receiving a living donor transplant, followed by a deceased donor pancreas transplant. This approach has the disadvantage of requiring two separate operations, but the recipient enjoys the benefit of a living donor kidney transplant that in many circumstances occurs sooner than would an SPK from a deceased donor. Since the primary survival benefit of the kidney–pancreas transplant comes from the restoration of renal function, this is a significant advantage. However, since a PAK is essentially a solitary pancreas transplant immunologically distinct from the kidney transplant, pancreas outcomes are worse than for SPK.

Simultaneous Living Donor Kidney–Deceased Donor Pancreas Transplantation

SPLK is another option previously performed at a few centers, but now done rarely.[34] Candidates with identified living donors are listed for deceased donor pancreas transplantation. When a deceased donor pancreas becomes available, the living kidney donor transplant is performed at the same time as the pancreas transplant. This approach has the advantages of sequential living donor kidney followed by PAK transplants while requiring only one operation. It does require that the potential living donor be available to donate at any time, a requirement that excludes some donors from this approach. It also has the disadvantage of potentially delaying a kidney transplant for the recipient if the waiting time for a deceased donor pancreas is long.

Living Donor Kidney–Pancreas Transplantation

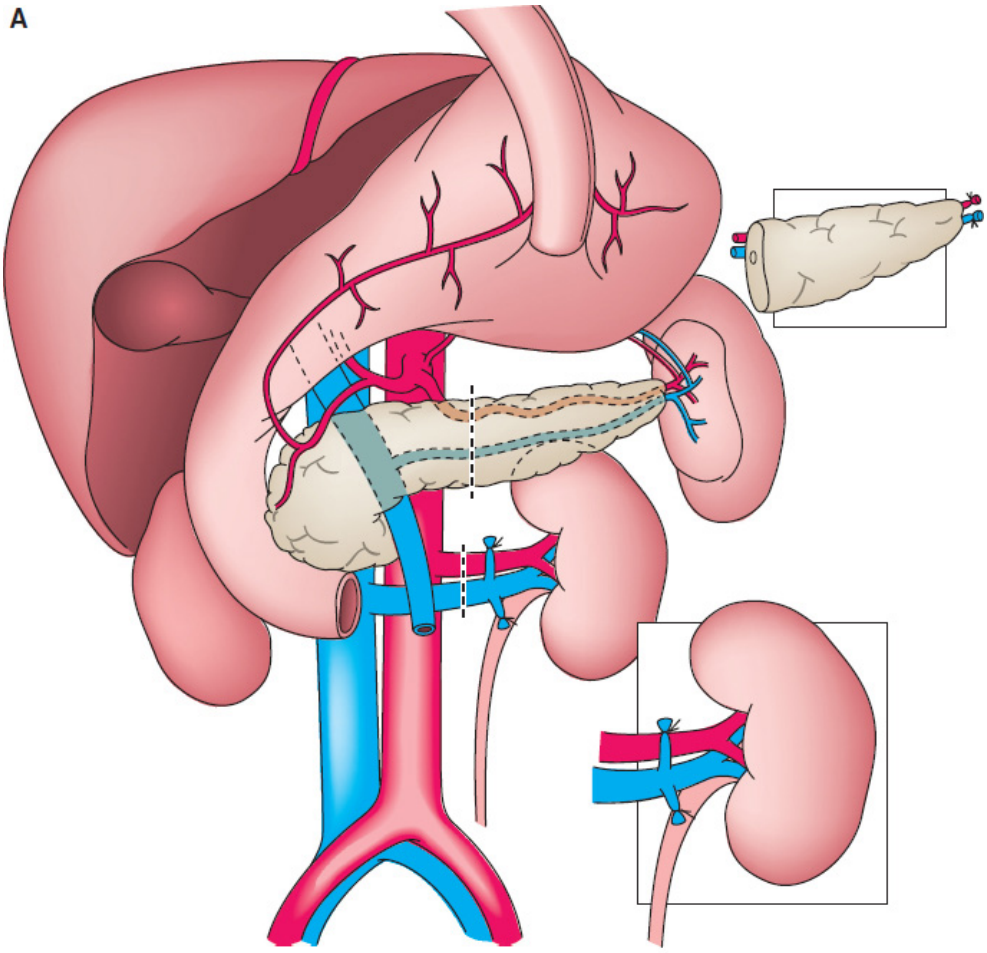
A few centers perform living donor kidney–pancreas transplantation, with a single living donor donating the tail of the pancreas as well as the kidney (**Fig. 40.2**). This approach has all the advantages of a single operation, a single donor, and no waiting time. Results have been comparable to deceased donor SPK transplants.[35,36] Widespread adoption of this approach has been limited by concerns about donor morbidity from the pancreatectomy. Serious complications such as pancreatitis, fistula, abscess, or pseudocyst can occur. Glucose intolerance and frank diabetes have occurred, although this problem has been nearly eliminated with more stringent donor selection criteria.[36,37]

Pancreas transplant candidates with renal failure may be counseled in a variety of ways depending on the availability of a living donor. How individuals are counseled depends in part on factors particular to the potential living donor and recipient, and also on the expected waiting time for SPK and PAK transplantation, which vary greatly by geographic region. Since the mortality benefit of a kidney–pancreas transplant derives primarily from the kidney transplant, priority is generally given to achieving kidney transplantation expeditiously. In geographic regions where the waiting time for SPK is longer (3 years is not unusual), living donor kidney transplantation is advised. Recipients of living donor kidney transplant can then be listed for PAK which can be performed following recovery from the

living donor kidney transplant. Individuals without living donors or those with borderline living donors in areas with short waiting times can be listed for SPK. Interestingly, there does not appear to be the same adverse impact in outcome with a limited interval of pretransplant dialysis (less than 2 years) in SPK recipients that is observed in kidney-alone recipients, whether deceased or living donor.[38] Therefore, even candidates with living donors may reasonably opt for SPK if anticipated waiting times are short.

Pancreas-Alone Transplantation

A small number of type 1 diabetics are evaluated for PTA. These individuals are generally extremely labile diabetics who have progressive complications but do not have nephropathy. In these individuals the risk–benefit equation is quite different than those uremic diabetics evaluated for kidney–pancreas transplantation. For nonuremic diabetics evaluated for pancreas transplantation the risk of immunosuppression in addition to the surgical procedure must be weighed against the potential benefits from transplantation. This contrasts to uremic diabetics, for whom the risk of immunosuppression is already assumed by virtue of the need for a kidney transplant. This risk includes renal failure due to chronic calcineurin inhibitor use. This is commonly cited as justification to not perform PTA, and recent evidence suggests the 10-year risk is at least 20% and is related to pretransplant GFR.[39] Whether PTA for type 1 diabetes results in a significant survival benefit is controversial. PTA in most centers is generally offered only in the most exceptional cases, the most common indication being frequent life-threatening hypoglycemic events. However, several transplant programs have a different philosophical outlook on the risks and benefits of PTA, and these referral centers generally perform large numbers of PTA. Most PTAs are from deceased donors, with a small number of centers offering living donor PTA. Living donor pancreas transplants carry a higher rate of technical failure but a lower rate of immunologic failure.[40,41]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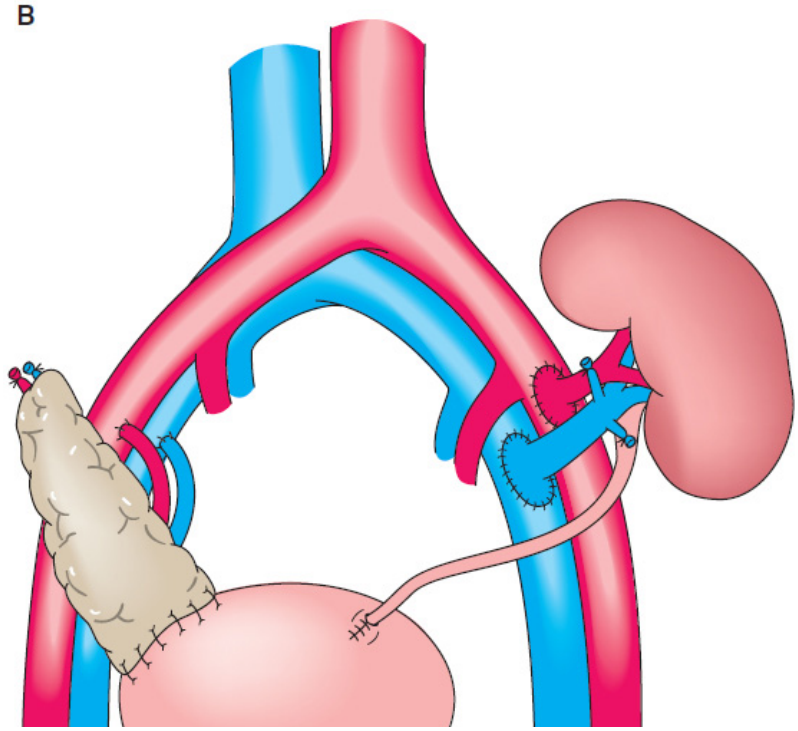
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Figure 40.2 Live donor pancreas and kidney transplantation. **A:** Provided that the donor has a normal glucose tolerance test, a living donor may donate the segment of the pancreas that is to the left of the superior mesenteric vessels. **B:** Transplantation of tail of the pancreas is based on the splenic artery and vein.

Evaluation and Screening

5 In general, eligibility criteria for pancreas transplantation are more stringent than for kidney transplantation alone, since the operation and recovery are more rigorous, the potential complications more serious, and the benefits less pronounced compared with kidney transplantation. Candidates should have excellent functional status in anticipation of the more extensive surgery and more frequent complications. Age is not tightly related to outcome, but patients over the age of 60 are carefully scrutinized.[42] A detailed history of the patient's diabetes and treatment is obtained, including current glycemic control, hypoglycemic events, secondary complications, insulin requirements, and overall quality of life. Obesity in and of itself is not a contraindication, as outcomes for carefully selected obese (BMI >30) recipients are similar to nonobese recipients, although surgical complications and the likelihood of remaining insulin dependent may be slightly higher.[43] Selection practices vary widely—for some centers, pancreas transplantation is reserved for those with significant complications and poor glycemic control who have failed alternative treatments, while for others the presence of type 1 diabetes and a full understanding of the risks and benefits are sufficient, with patient preferences playing a significant role. Because of the added need for immunosuppression in PTA, these diabetes-related criteria are often more stringent than for SPK or PTA, where the risk of immunosuppression is already assumed by virtue of the kidney transplant.

All candidates should have at the least noninvasive cardiac stress testing such as dobutamine stress echocardiography or adenosine thallium stress scintigraphy. Potential candidates with reversible myocardial defects undergo coronary angiography, and many centers perform angiography on all candidates. The decision to perform pretransplantation coronary revascularization must be made with consideration of both peritransplant mortality and long-term survival. Although survival outcomes are diminished

in recipients with coronary artery disease,[44] a history of coronary revascularization is not necessarily a contraindication; individuals with extensive myocardium at risk and without revascularization options are frequently excluded.

Screening for peripheral vascular occlusive disease is often performed. Although distal peripheral vascular occlusive disease is characteristic of long-standing diabetes, aortoiliac disease and femoral popliteal vascular disease may also be present. Femoral popliteal disease is generally not a contraindication to transplantation, unless there are clinical signs of arterial insufficiency such as severe claudication or nonhealing ulcers. The presence of iliac disease is more problematic, as it can compromise inflow to the transplanted organs or increase the risk for postoperative arterial complications. In addition, diabetics may have significant vascular calcification which could preclude transplantation even in the absence of flow abnormalities. Screening for peripheral vascular occlusive disease, in addition to a thorough physical examination, may include noninvasive flow studies and/or CT scanning to evaluate vascular calcification. Candidates with a history or examination findings suggestive of cerebrovascular disease should be screened for hemodynamically significant carotid occlusive disease.

Other evaluations, as with other types of organ transplants, are tailored to the individual medical history, and differ among centers. Screening for malignancy commonly includes mammography and pap smears for women, and colonoscopy, generally in accordance with established screening guidelines for the general population. Individuals with a prior history of treated cancer and who are judged to be at low risk for recurrence are usually candidates following an appropriate disease-free interval. This interval is decreasing as greater experience with transplantation in individuals with a history of cancer has accumulated, and can be as little as 2 years for many solid epithelial tumors to none for carcinoma in situ or early prostate cancer.[45] Screening for chronic viral infections such as hepatitis B, hepatitis C, and HIV is commonly performed, and pancreas transplants in selected individuals with chronic hepatitis are being performed with increasing frequency.[46,47] As with liver and kidney transplantation, early experience with pancreas transplantation in carefully selected individuals with HIV infection has been encouraging.[48] Social work and/or psychiatric

evaluation is performed to rule out psychiatric disease, inadequate social environments, and other issues that may impact the recipient's ability to participate in posttransplantation management.

The Waiting List and Recipients

The number of patients on the waiting list for pancreas transplant has gradually decreased from over 3,500 in 2007 to approximately 2,500 in 2018.[49] The majority of patients are white (58%), though the percentages of white candidates is decreasing, while the percentage of minority candidates (black, Asian, Hispanic) patients continues to increase. The number of patients on the waiting list has decreased since 2000 for all adult age groups except those in 50 to 64, and the age distribution has shifted upward. While the majority are ages 35 to 49 (52% in 2018), the percentage who are older (ages 50 to 64) and younger are increasing slightly. The annual death rate on the pancreas waiting list was 58 per 1,000 patient years in 2018, compared with 45 per 1,000 in 2017 and 69 per 1,000 in 2007.

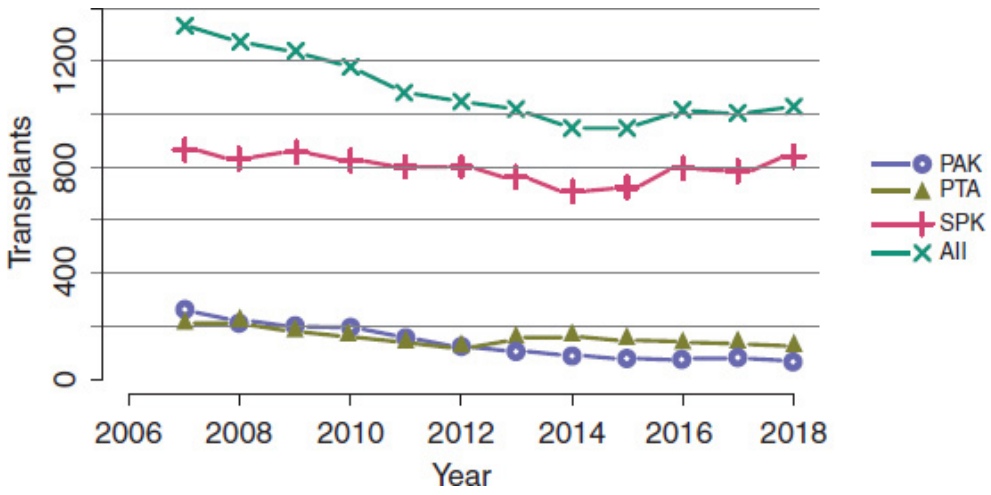

Figure 40.3 Number of U.S. simultaneous pancreas–kidney (SPK), pancreas after kidney transplantation (PAK), and pancreas transplantation alone (PTA) pancreas transplants performed by year. (Data from Scientific Registry of Transplant Recipients. 2018 *Annual Data Report.* Rockville, MD: Health Resources and Services Administration, Department of Health and Human Services; 2020.)

The overall number of pancreas transplants performed has increased over the last several years after a decade long decline. There were 1,027 pancreas

transplants performed in 2018, compared with 1,002 in 2017 and a low of 947 in 2015. The increase has been due to increases in SPK transplants, as a slight downward trend continued in numbers of PAK and PTA transplants (**Fig. 40.3**). Median times to transplant have declined over the past 3 years for SPK (13.5 months in 2017–2018) and PTA (19.7 months). Time to transplant is longer for African American and Hispanic recipients. While the majority of SPK recipients are white and males, the percentage of nonwhite recipients is increasing. The age distribution of recipients generally parallels that of the waiting list.

Deceased Donor Pancreas Allocation

As with many organs, deceased donor pancreas allocation is determined primarily by geography, with most organs offered to centers in the donation service area (DSA) of donor origin. The base organ allocation unit is the organ procurement organization (OPO) which serves the population within the DSA. The 58 DSAs are organized into 11 regions, which serve as the second-tier of organ allocation. As with other organs, pancreata are allocated according to nationally determined policies.[50] There is mandatory sharing of pancreata to highly sensitized candidates that are completely matched to the donor; beyond this, pancreata are allocated to these pancreas candidates first locally, then regionally, then nationally based primarily on waiting time.

If the pancreas candidate is an SPK candidate, then a kidney from the same donor is usually also allocated to the SPK candidate, regardless of the candidate's place on the kidney waiting list. While such a policy promotes pancreas utilization, it has been somewhat controversial, since preferential allocation of kidneys to simultaneous kidney–pancreas (SPK) candidates prevents allocation to kidney-alone candidates who have generally been waiting longer. Solitary pancreata can be difficult to place compared with SPK because their outcomes are slightly worse, but are more easily shared voluntarily since OPOs are obligated to share kidneys along with pancreas for outside SPK candidates only under certain circumstances (highly sensitized or 0-HLA antigen mismatch candidates). Thus, shared pancreata are usually restricted to PTA or PAK candidates.[51]

Pancreas allocation is also complicated by the fact that the pancreas donor selection criteria for islet transplant and whole-organ transplant overlap, leading to competition among certain types of organs. In determining whether a given pancreas will be allocated to a solid organ or islet transplant candidate, donor age and BMI are considered. Donors under age 50 and with BMI <30 are allocated for whole-organ pancreas transplant locally. If there is no local acceptance, the pancreas is offered regionally and then nationally. If there is no candidate for whole pancreas, the pancreas is then allocated for islets. For donors older than age 50 or with BMI >30, whose pancreata are rarely used for whole-organ transplant, the organ is first offered for pancreas transplant locally; if there are no local candidates, the pancreas is then offered for islets.[50]

Pancreata are significantly underutilized compared to other solid organs such as liver and kidney. As discussed below, donor selection criteria are more rigorous. Restrictions on cold ischemia time for whole-pancreas transplantation and particularly for islet transplantation make the placement of pancreata that are not used by the recovering center difficult. There is significant geographic variation in pancreas use, which correlates with activity by local transplant centers.[52] A recently approved change in organ distribution for abdominal organs designed to address this disparity will eliminate the use of DSA in allocation, relying instead on distance of the transplant center to the donor hospital. The principles of local, regional, and national allocation still apply but instead are represented by increasing distances (<250, 250 to 500, and >500 miles).[53]

Donor Evaluation

6 The selection of appropriate pancreas donors is perhaps the most important determinant of successful pancreas transplantation. Many of the early complications of pancreas transplantation are thought to be secondary to processes related to organ quality and preservation, rather than the technical conduct of the recipient operation. While the ideal donor is young, nonalcoholic and nonobese, very few donors meet this description, and the surgeon frequently needs to consider pancreata from imperfect donors. Donor selection criteria may vary among surgeons and transplant centers, and may depend upon past experience, waiting time, and recent outcomes. Primary

criteria are the age of the donor, donor BMI, donor cause of death, and the gross appearance of the organ at the time of recovery. Additional information that may influence the decision include aspects of the medical and social history, donor hemodynamics, laboratory values, HLA matching, and anticipated preservation time. As with donor selection with other organs, the decision-making process often involves consideration of multiple factors in aggregate.

The importance of donor age on graft outcomes has been confirmed by multiple studies, and the maximum age threshold is significantly lower than for liver and kidney transplantation.[54,55] Many centers use an age threshold, which may range from 40 to 50, above which donors are selected very carefully. The mechanism by which age affects outcomes is not firmly established: age appears to influence both early technical and late graft loss.[55,56]

Donor BMI has been found to be a determinant of graft failure by single-center and transplant registry analyses.[57,58] Very few pancreata from donors with BMI greater than 30 are used for solid-organ transplant, and are more likely to be recovered for islet transplant.[51] More recent registry data suggest that carefully selected donors with BMI up to 35 can successfully be used as pancreas donors.[59] It is not known whether associations with BMI relate to fatty infiltration of the pancreas or by a separate mechanism.

The circumstances of death and the condition of the donor influence donor selection. Pancreata from donors with stroke as a cause of death have reduced graft survival. Although experience from donors after cardiac death (DCD) remains relatively limited (<5% of all pancreas transplants), outcomes have been good with careful donor selection.[49,60,61] Laboratory values, including serum amylase and lipase, play a relatively minor role in donor selection. Insulin administration is generally not considered a contraindication to pancreas donation. While the presence of donor hyperglycemia may raise concerns about latent diabetes, in most donors this reflects the rapid administration of dextrose-containing solutions, corticosteroids for cerebral edema, and high-dose catecholamines for blood pressure support rather than latent pancreatic endocrine insufficiency. Abnormal HbA1C has been utilized as a relative contraindication, but recent single-center data suggest that levels up to 6.2 mg/dL are not associated with graft outcomes.[62] Evidence of injury to other organs such as liver and

kidneys, as a marker of abdominal ischemia, while not ordinarily a contraindication, may be considered in marginal cases.

Donors with a history of type 2 diabetes, excessive alcohol use or pancreatitis may be used. A history of cardiovascular disease or cardiac risk factors are also not contraindications but may influence decision making or be associated with mesenteric atherosclerotic disease. A social history which suggests an increased risk of transmission of hepatitis or HIV should be evaluated, as with other organs, in the context of the degree of perceived risk relative to the benefit of the transplant.

Intraoperative evaluation of the donor organ is said to be the most important determinant of donor selection. Evidence of inflammation or fibrosis, which may manifest as focal or diffuse firmness to palpation, is considered to be a contraindication. Fatty infiltration of the pancreas, trauma and pancreatic edema are also adverse findings, although the latter may be correctable with donor management. Traumatic injury to the pancreas or hematoma within the substance of the pancreas would preclude transplantation. However, a prior splenectomy is not a contraindication, provided that the tail can be dissected atraumatically.

Factors not intrinsic to the donor may bear on the decision to perform a transplant. The higher risk of graft failure associated with solitary pancreas transplants leads some centers to have more stringent selection criteria for PTA and PAK. While cold ischemia is a risk factor for graft survival, pancreata from selected donors can be transplanted with cold ischemic times approaching 24 hours with good outcomes. Attention to HLA matching varies by center; the many analyses performed suggest that any relationships between matching and graft outcome that may exist are not likely to be very significant.[56,58,63]

As for deceased donor livers and kidneys, a Donor Risk Index for pancreas has been described.[52] The pancreas DRI (PDRI) is based on 10 factors demonstrated to have significant impact on pancreas transplant outcomes. These include age, gender, race (black or Asian), BMI, height, CVA as cause of death, cold ischemia time, DCD, and terminal creatinine greater than 2.5 (**Table 40.1**). There is great variation in outcome by PDRI: the difference in graft survival at 1 year between the lowest 20% of PDRI (best outcomes) and the highest 20% is about 11% for SPK transplants and 16% to 17% for solitary transplants (**Table 40.2**). In addition to predicting

outcomes for individual patients, indices like the PDRI are useful in assessing trends in pancreas utilization, which is variable by geography and by transplant center.[52]

Recovery Technique

The importance of the pancreatic recovery cannot be overstated. It is thought by many pancreas transplant surgeons to be more critical to the success of the transplant than the recipient procedure. Because the pancreas is susceptible to traumatic injury, it must be carefully dissected and manipulated to avoid injury to the pancreatic parenchyma. Typically, the pancreas is recovered along with the liver and kidneys. This is performed in standard fashion through a midline incision which extends from the sternal notch to the pubic symphysis. After a generous Kocher maneuver, mobilization of the right colon, and isolation of the distal and supraceliac aorta to prepare these vessels for clamping, the pancreas is mobilized. This is most commonly achieved by entering the lesser sac, dividing the gastrocolic omentum. This dissection continues with division of the short gastric vessels and the avascular gastrosplenic ligament. The pancreas is dissected from the pancreatic bed using the spleen as a handle. The tail is lifted from the pancreatic bed using blunt dissection and the occasional use of electrocautery. The proximal jejunum is dissected at the ligament of Treitz. An antibiotic and/or a betadine-containing solution are frequently instilled into the duodenum through a nasogastric tube for decontamination. The duodenum is divided both at the ligament of Treitz and at the pylorus using a stapler. Division of the middle colic vessels permits exposure of the proximal small bowel mesentery, which is divided distal to the pancreas with a vascular stapler. The mobilization of the pancreas may be performed either prior to or following the aortic perfusion procedure described below.

Table 40.1 Summary of Pancreas DRI

Donor Characteristics	Reference Donor (DRI = 1.00)	Change Factor Value to	DRI
Gender	Male	Female	0.87
Age	28	45	1.56
Black race	No	Yes	1.27
Asian race	No	Yes	1.17
BMI	24	30	1.17
Height (cm)	173	190	0.9
Cause of death: CVA/stroke	No	Yes	1.23
Cause of death: CVA/stroke in PAK	No	Yes	0.93
Pancreas preservation time (hrs)	12	20	1.13
DCD	No	Yes	1.39
SCr >2.5	No	Yes	1.22

Equation: pDRI = exp(−0.13792 × I[Female Donor]) – 0.034455 × I[Donor Age <20] × [Donor Age – 20] + 0.026149 × [Donor Age – 28] + 0.19490 × I[Donor Creatinine > 2.5] + 0.23951 × I[Donor Black Race] + 0.15711 × I[Donor Asian Race] – 0.000986347 × [Donor BMI – 24] + 0.033274 × I[Donor BMI > 25] × [Donor BMI – 25] − 0.006073879 × (Donor Height – 173) + 0.21018 × I[Donor COD CVA] – 0.28137 × I[Donor COD CVA for PAK txp] + 0.014678 × [Preservation Time – 12] + 0.33172 × I[DCD]).[40]

Perfusion of the pancreas is generally achieved through an intra-arterial cannula placed in the distal aorta following clamping of the supraceliac aorta and the aortic bifurcation. This is typically achieved with approximately 1 to

3 L of University of Wisconsin or HTK (histidine–tryptophan–ketoglutarate) solution while the entire abdominal organs are packed in saline slush. Preservation solutions are generally regarded to be equivalent.[58,64,65] A minority of centers will also perfuse the abdominal viscera with a portal perfusion cannula, typically through the inferior mesenteric vein, although some surgeons maintain that overperfusion of either the arterial or the venous circulation may result in pancreatic edema and an increased risk of complications.

The pancreas can be removed either en bloc with the liver and kidneys, en bloc with the liver, or separately, following removal of the liver. Whatever the technique, the portal triad is dissected out in cooperation with the liver recovery team. Typically the portal vein is shared by dividing it at the level of the coronary vein. Only in the rarest of circumstances should there be any difficulty using both the liver and the pancreas from the same donor even in the presence of hepatic arterial anomalies. In the presence of a replaced right hepatic artery, the superior mesenteric artery (SMA) can be divided just distal to the replaced right hepatic artery, leaving a very short cuff of SMA on the pancreas. Alternatively, the replaced right hepatic artery, if large enough to be safely reconstructed by the liver transplant team without a cuff of SMA, can be transected as it exits superiorly from behind the head of the pancreas. This is also true in the rare case where a completely replaced hepatic artery emerges from the superior aspect of the head of the pancreas; usually the artery in this case is long enough and large enough to be used for liver transplant without a celiac axis or aortic cuff. The bile duct and gastroduodenal artery are ligated on the pancreas side and divided on the liver side. Dissection then proceeds along the superior aspect of the pancreas along the proper hepatic artery. The splenic artery, which constitutes the other arterial blood supply to the pancreas, is divided a few millimeters from its origin to allow for adequate length on the pancreas while allowing the stump to be oversewn without compromising flow to the liver. Once the pancreas is removed or split from the liver, the pancreas is packed in preservation solution; the entire common iliac artery and its two main branches, the internal and external iliac arteries, are packaged along with the pancreas for back-table reconstruction. A graft of donor iliac vein is also included in case the portal vein needs to be extended, which is done by some surgeons. Although most centers transplant the pancreas as soon as possible,

up to 24 hours of cold ischemia time (time between perfusate infusion and organ reperfusion) has not been associated with reduced graft survival in carefully selected donors.[53,56]

Table 40.2 Unadjusted 1-Year Pancreas Allograft Survival by DRI and Transplant Type

	SPK		PAK		PTA	
DRI Group	Adjusted% Graft Survival	95% Confidence Limits	Adjusted% Graft Survival	95% Confidence Limits	Adjusted% Graft Survival	95% Confidence Limits
0.64–0.85	88	(87, 90)	84	(81, 87)	84	(76, 89)
0.86–1.15	87	(86, 89)	77	(73, 79)	82	(77, 87)
1.16–1.56	82	(79, 84)	75	(70, 79)	70	(61, 77)
1.57–2.11	78	(75, 81)	69	(61, 75)	68	(57, 77)
2.12–2.86	77	(70, 82)	67	(46, 81)		

Back-Table Preparation of the Pancreas

The pancreas is placed on ice and remains cold at all times on the back table. The spleen is removed by dividing all vessels near the spleen, either by ligature or stapling, taking care to avoid injury to the tail of the pancreas which should be clearly identified. Some surgeons elect to wait until reperfusion of the pancreas in the recipient to remove the spleen. Significant peripancreatic fat, if left on at the time of recovery, should be trimmed. Both ends of the distal duodenum are shortened to the point where they are immediately adjacent to the head of the pancreas. Both stapled ends of the duodenum may be oversewn with silk or polypropylene sutures. Some surgeons elect to reinforce the mesenteric staple line by oversewing with polypropylene suture. The iliac artery Y-graft is typically attached by anastomosis of the internal iliac artery to the splenic artery and anastomosis of the externally iliac artery to the SMA (**Fig. 40.4**). In the absence of a Y-graft, the splenic artery may be implanted in end-to-side fashion to the SMA. The portal vein is mobilized by freeing from surrounding adventitial tissue to the confluence of the splenic vein and superior mesenteric vein. This should allow an adequate length of portal vein for anastomosis, as only 1 to 2 cm of portal vein length is generally needed. However, some surgeons routinely

add an end-to-end venous extension graft from donor iliac vein to lengthen the portal vein on the back table.

Recipient Operation

The pancreas transplant is typically performed through a midline incision, although a lower quadrant incision similar to a kidney transplant incision may be used. The recipient should receive broad-spectrum antibiotics preoperatively. The pancreas transplant, for systemic venous drainage, is placed preferably on the right side, and can be oriented either head up or head down. After dissection of the recipient artery and vein, the portal vein is anastomosed in end-to-side fashion to the systemic vein. The distal inferior vena cava, common iliac vein, or external iliac vein may be used; the recipient vein segment should be mobile enough for the portal vein to reach without tension. The common iliac artery component of the donor Y-graft is then anastomosed in end-to-side fashion to either the recipient external iliac artery or common iliac artery; the distal aorta can also serve as the site of anastomosis. A pancreas placed on the left side in the recipient may be placed either medial or lateral to the sigmoid colon. Multiple variations have been described.

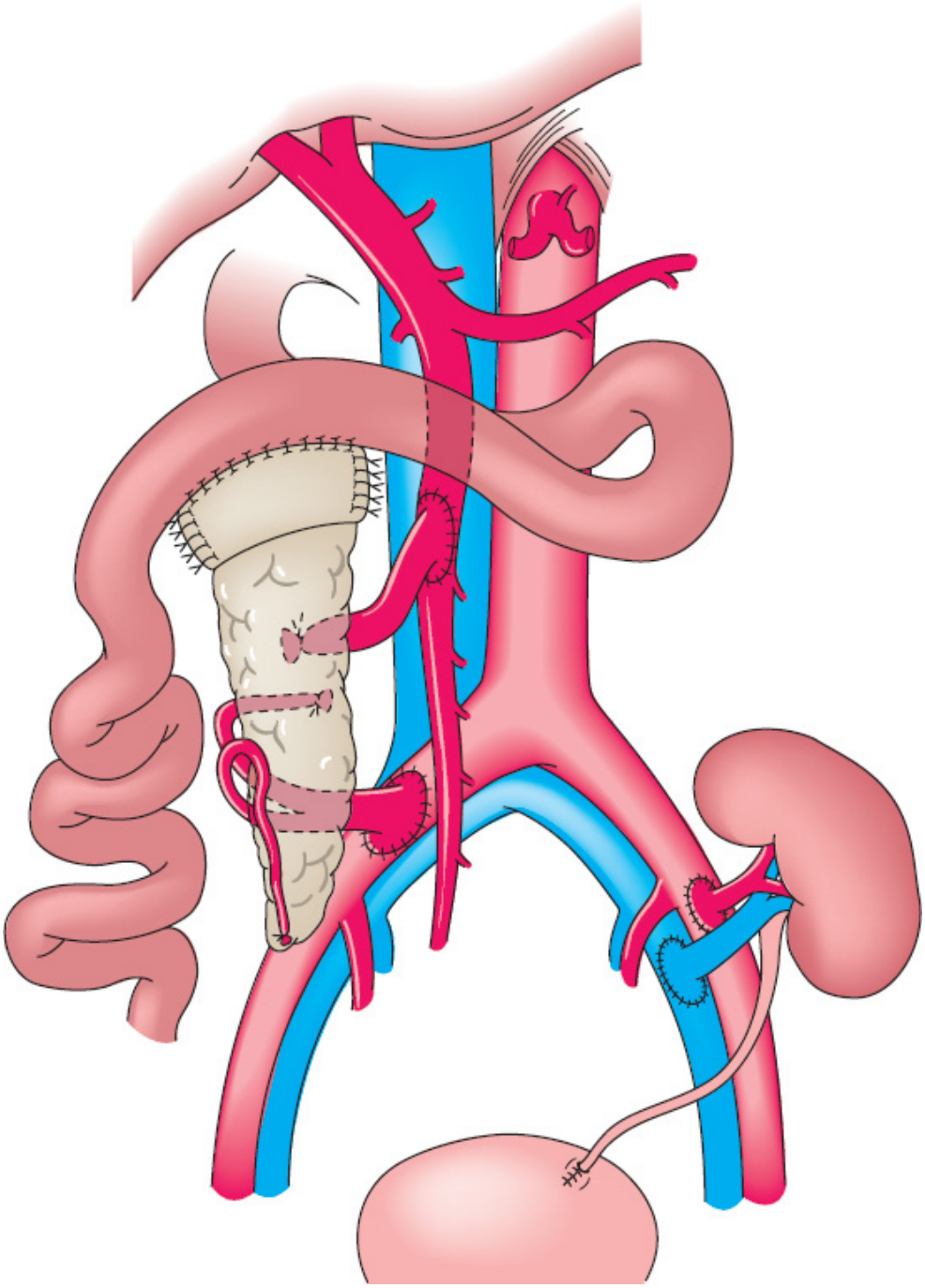

Figure 40.4 Simultaneous pancreas–kidney transplantation performed with drainage of the pancreatic exocrine secretions into the proximal jejunum (enteric drainage). This technique has been adopted by most transplant centers in the United States for simultaneous pancreas–kidney transplants. For solitary pancreas transplantation, some centers still utilize bladder drainage to allow monitoring of the urinary amylase. Note that the donor portal vein drains into the recipient superior mesenteric vein (portal venous drainage), preventing peripheral hyperinsulinemia. Many centers continue to place the pancreas in the pelvis, combining enteric

drainage and systemic venous drainage. This placement requires enteric anastomosis to a more distal segment of jejunum or ileum.

Because of concerns about the systemic hyperinsulinemia that invariably develops with systemically drained pancreas transplants, portal venous drainage is also utilized (**Fig. 40.5**). As 50% of insulin is removed with the first pass through the liver, systemic drainage leads to elevated peripheral insulin levels, which is not observed following portal venous drainage. Since hyperinsulinemia has been associated with dyslipidemia and accelerated atherosclerosis, portal venous drainage theoretically ought to decrease cardiovascular risk compared with systemic drainage.[66] Portal drainage is associated with stimulation of the IGF-I/GH axis, contributing to glucose control despite lower insulin levels.[67] However, despite a nearly 10-year experience with the procedure, no difference in cardiac morbidity or mortality has been observed between the two techniques, and graft and patient survival are essentially equivalent.[68–70]

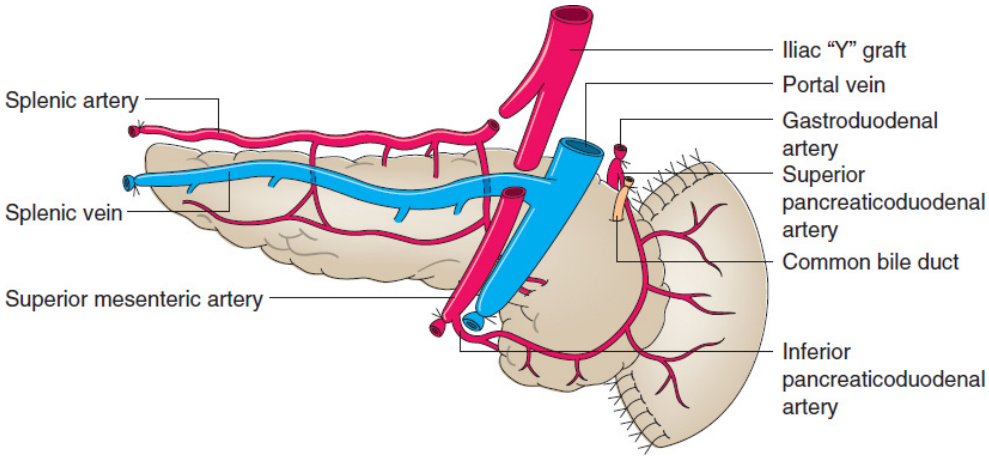

Figure 40.5 Back-table preparation of the pancreas. Before transplantation, the pancreas must be prepared in a slush-filled basin to maintain cold preservation. Preparation includes unifying the arterial blood supply of the pancreas by anastomosis of the donor external iliac artery to the superior mesenteric artery and the donor internal iliac artery to the splenic artery. The donor common iliac artery is used for anastomosis to the recipient iliac artery. During back-table preparation, donor splenectomy is performed.

Although the type of venous drainage typically depends on the preferences of individual surgeons or transplant centers, the decision to perform portal or systemic drainage may also depend upon the anatomy of an individual

patient. Patients with multiple previous abdominal operations or who have a thickened mesentery may be more suited for systemic venous drainage. Alternatively, patients who have had multiple transplants or other operations on the iliac vessels may be candidates for portal venous drainage.

For portal venous drainage the superior mesenteric vein is dissected out just below the transverse mesocolon.[71] The right common iliac artery is almost completely dissected. An end-to-side anastomosis of the donor portal vein to the recipient superior mesenteric vein is performed with the duodenum oriented superiorly and the tail pointed inferiorly. The iliac artery graft of the donor is then passed through a hole created in the small bowel mesentery, and anastomosed to the recipient common iliac artery.

Most centers currently use enteric exocrine drainage for simultaneous kidney/pancreas transplant and some centers use enteric drainage for all transplants including solitary pancreas transplantation. This shift to enteric drainage occurred as a result of the significant morbidity associated with bladder-drained pancreas transplants. Morbidity includes recurrent urinary tract infections, hematuria, chemical urethritis, severe bicarbonate wasting, and dehydration. Historically, approximately 25% of individuals who receive a bladder-drained pancreas transplants require enteric conversion because of persistent complications,[72] but an additional percentage endure significant morbidity early after transplant. The major advantage of bladder drainage is the ability to monitor urinary amylase, a decrease in which can be associated with rejection. This can be helpful in solitary pancreas transplants, but is perhaps less important for simultaneous pancreas/kidney transplants where graft function may be monitored by serum creatinine. Improved immunosuppression and an increased utilization of biopsy to diagnose rejection have led to a decreased reliance on urinary amylase.[73]

Enteric drainage is achieved by creating a side-to-side or end-to-side anastomosis of donor duodenum to recipient jejunum. This may be a loop of jejunum, or a Roux-en-Y configuration may be created. For bladder drainage a side-to-side anastomosis between the donor duodenum and the bladder is performed. Enteric drainage is always used for pancreas transplants with portal venous drainage or those with systemic venous drainage oriented head-up, because the orientation of the pancreas precludes anastomosis of the duodenum to the bladder.

If a simultaneous kidney–pancreas transplant is performed, the kidney transplant is usually placed in the left iliac fossa, although some surgeons place both organs on the right side, with the pancreas anastomoses to the common iliac vessels, and the kidney to the external iliac vessels. The anastomoses, as with a kidney transplant via a retroperitoneal incision, are typically to the external iliac artery and external iliac vein. The kidney is typically placed in an intraperitoneal location, which increases the potential for torsion of the kidney on its vascular pedicle compared with kidney-alone transplants which are usually placed in a retroperitoneal location. Some surgeons prefer to raise a retroperitoneal flap to place the kidney retroperitoneally after implantation. Advantages to this approach include improved percutaneous access should biopsy be required, and a decreased risk of postbiopsy hemorrhage.

Following revascularization of the pancreas, attention is paid to bleeding from the pancreas which can be quite brisk. This is controlled with ties or suture ligatures. Since thrombosis is a common complication of pancreas transplantation, anticoagulation in the perioperative period may be employed, particularly for solitary pancreas transplantation. Thrombosis is less frequent in simultaneous pancreas–kidney transplantation, where uremic platelet dysfunction is protective. The extent of anticoagulation may range from the intraoperative administration of heparin prior to clamping of vessels, followed up by low-dose heparin infusion and warfarin anticoagulation, to more conservative approaches such as the use of low-dose heparin for a limited interval postoperatively, or the use of aspirin or other antiplatelet agents.[74] Hypercoagulability states may predispose to graft thrombosis in a significant number of individuals, although definitive data are lacking; anticoagulation is individualized based on risk.[75] Whatever the approach, patients should be monitored for bleeding, since as many as 10% of patients experience postoperative hemorrhage requiring reoperation.[76]

Following revascularization serum glucose levels are obtained hourly. It is common for the blood glucose to decline significantly following revascularization, and it is not uncommon for it to fall to normal levels soon after the patient's arrival in the recovery room. At some point intravenous fluids should be converted to dextrose-containing solution in order to prevent hypoglycemia. Pancreas transplant recipients with enteric drainage require only maintenance fluid with consideration of third-space losses.

Simultaneous kidney–pancreas transplant recipients may require the additional fluid replacement that would be administered following kidney transplantation alone. Individuals who receive bladder-drained pancreas transplants require replacement of pancreatic exocrine losses, which can be quite profound in the early postoperative period.

Immunosuppression

7 Immunosuppression for pancreas transplantation is similar to that for kidney transplantation. The immunogenicity of a pancreas transplant is considered to be greater than the majority of solid-organ transplants because of the extensive lymphoid component of the gland. In addition, the difficulty in diagnosing rejection compared to other solid-organ transplants makes the choice of immunosuppression more significant for pancreas transplants. Most centers use some forms of triple maintenance therapy utilizing a calcineurin inhibitor, an antiproliferative agent, and steroids, although steroid-free regimens are not uncommon. According to data from the Scientific Registry of Transplant Recipients, over 90% of pancreas transplant recipients receive tacrolimus.[49] Mycophenolate mofetil is the antiproliferative agent of choice in pancreas transplantation, with over 90% of recipients in 2018 receiving it. About two-thirds of recipients are on steroid-containing regimens.

The use of induction therapy to inhibit lymphocyte function is common. Several large randomized multicenter trials utilizing either T-cell–depleting antibody induction (OKT3, ATGAM, and thymoglobulin) or interleukin-2 (IL-2) receptor antibody inhibition (daclizumab and basiliximab) showed a reduction in the incidence of acute rejection but failed to demonstrate a significant effect on patient or graft survival.[77,78] Despite this modest impact on overall graft outcome, about 90% of pancreas transplant recipients received induction therapy in 2018, 81% T-cell–depleting agents, and around 10% IL-2 receptor antibody.[49] The International Pancreas Transplant Registry (IPTR) demonstrated a lower risk of pancreas graft loss in all categories of pancreas transplantation with the use of tacrolimus, and also demonstrated similar associations with the use of mycophenolate mofetil.[56] Consistent with the multicenter trials, IPTR analyses also fail to demonstrate a beneficial effect of induction therapy on patient and graft survival.

Several groups have reported excellent intermediate-term patient and graft outcomes utilizing steroid minimization protocols.[79–81] These protocols generally employ an induction agent (usually a depleting T-cell antibody), tacrolimus, and either MMF or sirolimus. Steroids are given for a maximum of 3 days. These steroid minimization protocols, as in kidney transplantation, aim to avoid the significant short- and long-term side effects associated with corticosteroids. Regimens employing maintenance monotherapy have also been successfully employed but are currently rarely used.[48,82]

Complications

Thrombosis of the pancreas transplant is the most common cause of graft loss in the early postoperative period, occurring in 5% to 10% of transplants. Why pancreas transplants are more prone to thrombosis than other solid-organ transplants is uncertain. The most likely mechanism is that ischemia reperfusion injury in the pancreas, characterized by the release of cytokines and activation of pancreatic enzymes, leads to accelerated injury and a procoagulant state. Diabetic patients have impaired fibrinolysis and are, therefore, relatively hypercoagulable. The relatively low venous flow through the portal vein, which leads to diminished flow velocity, may be contributory. Thrombosis is slightly more common in solitary pancreas transplantation than in SPK, probably due to the absence of uremic platelet dysfunction present in SPK recipients. The risk of thrombosis has been associated with donor factors such as older patient age, renal dysfunction, cold ischemic time, body mass index, DCD status, and cerebrovascular cause of death.[55,83,84]

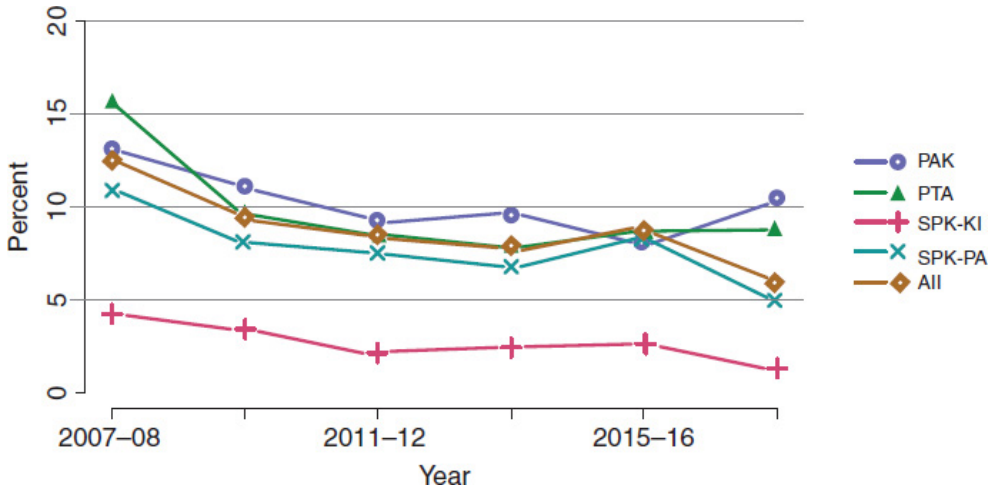

Figure 40.6 Graft failure within the first 90 days posttransplant among adult pancreas transplant recipients by year. (Data from Scientific Registry of Transplant Recipients. 2018 *Annual Data Report.* Rockville, MD: Health Resources and Services Administration, Department of Health and Human Services; 2018.)

Pancreas transplant thrombosis is usually heralded by a sudden rise in blood glucose in a pancreas that was previously functioning. Confirmation of the diagnosis is usually obtained with duplex ultrasound. Although anecdotal reports have described successful surgical and angiographic thrombectomy or thrombolysis in restoring flow to the pancreas,[85,86] the usual treatment is removal of the infarcted pancreas. While this usually occurs immediately after diagnosis, some centers opt to relist the patient urgently and wait until another pancreas transplant becomes available. Depending on the waiting time for another pancreas, the added morbidity of delaying the graft pancreatectomy is usually not significant. In contrast, asymptomatic thrombosis, whether partial or even complete, has been successfully managed with anticoagulation, especially if late in onset.[87,88] Because of the high risk of thrombosis, some degree of anticoagulation is frequently employed after pancreas transplantation.[89] It is likely due to these efforts and improvements in immunosuppression that the thrombosis rate for simultaneous pancreas–kidney transplants has decreased to less than 5% for simultaneous pancreas–kidney transplant and to less than 10% for isolated pancreas transplants (**Fig. 40.6**).

Bleeding is another frequent cause for reoperation in the early postoperative period. Because of the large number of vessels that enter and exit the pancreas, bleeding following reperfusion is not unusual. While

readily controllable, it is not uncommon for bleeding points to emerge later in the procedure, and postoperatively. This can be minimized by meticulous attention to ligating vascular structures during pancreas recovery. The use of anticoagulation in the perioperative period, as described above, adds to the bleeding risk. Pancreas transplant recipients are monitored carefully in the early postoperative period for signs and symptoms of intra-abdominal hemorrhage.

The other major early complication is leak from the donor duodenum. Duodenal leaks occur in approximately 5% to 10% of cases, usually 1 to 2 weeks after the transplant.[90] A leak may present as fever, abdominal pain, leukocytosis, lower abdominal tenderness, and persistent ileus. The diagnosis may be supported by the finding of a focal fluid collection near the head of the pancreas on CT scanning or ultrasound. Alternatively, diffuse peritonitis may reflect disseminated contamination. For bladder-drained pancreas transplants, the diagnosis may be made by cystography.

The management of a suspected duodenal leak is operative. This is caused by the growth of organisms transmitted into the peritoneal cavity during performance of the duodenal anastomosis. The peritoneum should be lavaged and all necrotic debris removed. If a leak is present it is usually at the stapled end of the duodenum rather than at the anastomosis. The likelihood of success for repair of a duodenal leak depends on the viability of the duodenum at the point of the leak, the patient's overall hemodynamic stability, and the degree of surrounding inflammation. Usually one attempt at repair is made, but failure may necessitate removal of the pancreas in order to control life-threatening sepsis. Some surgeons have adopted a practice of managing leaks from duodenal enteric anastomoses by conversion to bladder drainage. This minimizes the risk of recurrent contamination of the peritoneal cavity with enteric contents and allows for Foley catheter decompression of the duodenum, but has the morbidity associated with bladder drainage. Drainage of infection without primary repair of the duodenal leak has been successfully employed in situations where inflammation is so profound that the leak could not be primarily repaired. However, the morbidity associated with these duodenal fistulas dictates that these options be employed only when definitive repair is not possible. Peripancreatic abscess also can occur in the absence of a frank duodenal leak. Those patients with abscess and

without systemic sepsis can be treated with percutaneous CT-guided drainage.[91]

In contrast to renal transplantation, the complications of pancreas transplantation can be severe and life threatening if not properly managed. Even in the most experienced centers, occasional patients who suffer extended intensive care unit stays are not unusual. This is a consequence of both the tenuous medical status of long-standing diabetics and the substantial morbidity of pancreas transplant complications. Nevertheless, the risk of death form perioperative complications is low (0.5% in the first month after transplant). Given the limited survival benefit of pancreas transplantation, particularly compared with kidney transplantation, patients should be counseled frankly about the potential magnitude of these complications so that they have a realistic expectation of outcomes. Even with honest discussion and informed consent, most individuals will elect pancreas transplantation, and many will pursue multiple pancreas transplants even with a history of complications from previous pancreas transplants.

Diagnosis and Treatment of Rejection

The timely and accurate diagnosis of pancreas transplant rejection is one of the most important and challenging aspects of posttransplant management. As with kidney transplant rejection, pancreas rejection, whether acute cellular rejection or antibody-mediated rejection, is associated with inferior graft survival.[92] Furthermore, both pre- and posttransplant donor-specific antibodies (DSAs) are associated with antibody-mediated rejection and reduced pancreas and kidney graft survival.[92,93] The incidence of pancreas rejection was about 13% in the first year for transplants performed in 2016–2017. The incidence is higher (20%) in PTA recipients.[49] Therefore, the implications of delayed or missed antirejection treatment can be profound.

There is no single laboratory abnormality capable of diagnosing rejection. Amylase and lipase serum levels are commonly elevated, and can arouse suspicion, but are not specific. Hyperglycemia is also nonspecific. If hyperglycemia is due to rejection, it occurs late in the process and reflects significant pancreatic endocrine injury and a dismal prognosis. While imaging modalities including ultrasound may identify abnormalities in parenchyma or perfusion, they are neither sensitive nor specific.[94] Hence, the

diagnosis of rejection is best made with histologic examination of a pancreatic biopsy specimen.[95] The pancreas graft in SPK transplants benefits by monitoring of the kidney transplant by serum creatinine, as there is some degree of concordance rate for rejection between kidney and pancreas grafts. However, isolated pancreas rejection clearly occurs, and neither a normal creatinine nor a normal kidney biopsy can rule out pancreas rejection.[96,97] Improvements in the outcome of solitary pancreas transplants are attributable to improvements in overall quality of immunosuppression, and to more accurate diagnosis and treatment of pancreas rejection.

The technique of pancreas transplant biopsy has evolved over the years. In the era of bladder-drained pancreas transplants, cystoscopic biopsy of both the pancreas and transplant duodenum was common.[98] As more enteric-drained pancreas transplants have been performed, a greater reliance on percutaneous biopsy has developed, using either ultrasound or CT-guided techniques.[99] Laparoscopic-assisted or open pancreas biopsy may be utilized for patients whose pancreas transplant is not accessible to percutaneous approaches, although the need for operative biopsy is decreasing as the percutaneous procedure has become more routine.[100] Enteroscopic biopsy has been described, and a high jejunal anastomosis can facilitate utilization of this method.[101] The indications for pancreatic biopsy include hyperamylasemia, hyperlipasemia, hyperglycemia, or unexplained pain in the vicinity of the pancreas transplant. The differential diagnosis includes pancreatitis, cytomegalovirus (CMV) infection, and toxicity from calcineurin inhibitors and, in the early postoperative period, peripancreatic infection. The histologic grading system developed at the University of Maryland for determining rejection grade in pancreas biopsies is generally used (**Table 40.3**).[102] Indeterminate rejection may be treated with increases in calcineurin inhibitor dose or pulse corticosteroids. More substantial rejection is generally treated with depleting antilymphocyte antibody therapy.

As long-term survival of pancreas transplants becomes more commonplace, chronic rejection is now an important problem.[103] Unfortunately, as with kidney transplantation, while newer agents have improved short-term survival by preventing acute rejection, improvement of short-term survival has not translated into improved long-term graft survival.[104] Chronic rejection is histologically characterized as expansion of fibrous septa within the pancreatic parenchyma. This may progress to lobular

atrophy or loss of both acini and β-cells. Although there are parallels to chronic allograft nephropathy, whether chronic calcineurin inhibitor toxicity contributes to chronic pancreas rejection is unknown.

Recurrent Autoimmunity

Selective β-cell destruction in pancreas transplants may occur in a pattern similar to the insulitis seen in type 1 diabetes. This pattern is histologically distinct from cellular rejection. Although recurrent autoimmunity has been documented in both immunosuppressed pancreas transplant recipients and nonimmunosuppressed living donor recipients from identical twin siblings, well-documented case series have been infrequent. A variety of associations have been suggested with autoantibodies to glutamic acid decarboxylase (GAD-65) and islet cells (IA-2), but patterns of autoantibody expression have not proven reliable enough to establish their etiologic relevance or prognostic value.[105,106]

Posttransplant Viral Infections

The higher level of immunosuppression given to pancreas transplant recipients compared with kidney transplant recipients, particularly with respect to lymphocyte-depleting induction therapy, places pancreas transplant recipients at risk for conditions known to be influenced by overall immunosuppressive exposure. While rates of CMV infection are generally higher than for kidney recipients, especially when the donor is known to carry the virus, the use of intravenous and oral ganciclovir has reduced the incidence of significant CMV-associated disease.[107,108] The incidence of CMV disease may also be lower in those recipients receiving steroid-free immunosuppression.[108] Data are mixed with respect to the incidence of polyoma-associated, or BK, nephropathy, with some analyses suggesting a higher rate and other an equivalent incidence in SPK recipients compared with kidney-alone recipients.[109,110] As with kidney-alone recipients, those SPK recipients with BK nephropathy have inferior kidney graft survival. Posttransplant lymphoproliferative disorder (PTLD), often associated with Epstein–Barr virus (EBV) infection, has a 5-year incidence of approximately 2%, which is similar to or higher than kidney recipients.[111,112] Pancreas

recipients with PTLD have a worse prognosis than other abdominal organ transplants recipients with PTLD.

Table 40.3 Revised Banff Classification for Diagnosis and Grading Pancreas Allograft Rejection[102]

Category	Findings
1. Normal	Absent inflammation *or* inactive septal, mononuclear inflammation not involving ducts, veins, arteries or acini. There is no graft sclerosis. The fibrous component is limited to normal septa and its amount is proportional to the size of the enclosed structures (ducts and vessels). The acinar parenchyma shows no signs of atrophy or injury.
2. Indeterminate	Septal inflammation that appears active but the overall features do not fulfill the criteria for mild cell-mediated acute rejection.
3. Acute T-cell–mediated rejection	Grade I/Mild acute T-cell–mediated rejection—Active septal inflammation (activated, blastic lymphocytes and ±eosinophils) involving septal structures: venulitis (subendothelial accumulation of inflammatory cells and endothelial damage in septal veins), ductitis (epithelial inflammation and damage of ducts), *and/or* focal acinar inflammation. No more than two inflammatory foci per lobule with absent or minimal acinar cell injury. Grade II/Moderate acute T-cell–mediated rejection (requires differentiation from AMR)—Multifocal (but not confluent or diffuse) acinar inflammation (≥3 foci per lobule) with spotty (individual)

	acinar cell injury and dropout *and/or* mild intimal arteritis (with minimal, <25% luminal compromise). Grade III/Severe acute T-cell–mediated rejection (requires differentiation from AMR)—Diffuse (widespread, extensive) acinar inflammation with focal or diffuse multicellular/confluent acinar cell necrosis *and/or* moderate or severe intimal arteritis, >25% luminal compromise *and/or* transmural inflammation—necrotizing arteritis.
4. Antibody-mediated rejection	Confirmed circulating donor-specific antibody (DSA)—Morphologic evidence of tissue injury (interacinar inflammation/capillaritis, acinar cell damage swelling/necrosis/apoptosis/dropout, vasculitis, and thrombosis). C4d positivity in interacinar capillaries (IAC, ≥5% of acinar lobular surface). Acute AMR 3 of 3 diagnostic components—Consistent with acute AMR 2 of 3 diagnostic components. Requires exclusion of AMR 1 of 3 diagnostic components. Chronic active antibody-mediated rejection—Combined features of categories 4 and 6 in the absence of features of category 3.
5. Chronic allograft arteriopathy	Arterial intimal fibrosis with mononuclear cell infiltration in fibrosis.

6. Chronic allograft rejection/graft fibrosis	Stage I (mild graft fibrosis)—Expansion of fibrous septa; the fibrosis occupies less than 30% of the core surface but the acinar lobules have eroded, irregular contours. The central lobular areas are normal. Stage II (moderate graft fibrosis)—The fibrosis occupies 30–60% of the core surface. The exocrine atrophy affects the majority of the lobules in their periphery (irregular contours) and in their central areas (thin fibrous strands criss-cross between individual acini). Stage III (severe graft fibrosis)—The fibrotic areas predominate and occupy more than 60% of the core surface with only isolated areas of residual acinar tissue and/or islets present.
7. Islet pathology	Recurrence of autoimmune DM (insulitis and/or selective β-cell loss). Islet amyloid (amylin) deposition.
8. Other histologic diagnosis	Pathologic changes not considered to be due to acute and/or chronic rejection. For example, CMV, pancreatitis, PTLD.

Results of Kidney–Pancreas Transplantation

Current kidney graft survival at 1 and 5 years following SPK transplantation is 96% and 85%, respectively.[49] African Americans have historically had

somewhat poorer 5-year graft survival than whites. Kidneys from older donors have the poorest graft survival. As opposed to previous decades, 5-year kidney graft survival is not associated with HLA matching.

In 2018, the OPTN and SRTR codified definitions of pancreas graft failure to make reporting more consistent. Since return to insulin can occur due to pancreas dysfunction or insulin resistance, and there was previously no defined threshold of C-peptide level or insulin use for graft failure, center reporting had been variable for events other than pancreatectomy, relisting, or death.[49] Prior to that, pancreas graft survival at 1 and 5 years following SPK transplantation was 86% and 73%, respectively. Worse 5-year graft survival has been seen in African American recipients compared with whites. Recipients with a previous transplant (kidney, pancreas, or both) have worse pancreas graft survival. As with SPK kidney survival, there is no difference in 5-year pancreas graft survival with increasing levels of HLA mismatch. While contemporary estimates of long-term graft survival cannot yet be made under the current definition of 0.5 units/kg/d of insulin use, 90-day survival in SPK transplants appears to be improved, presumably owing to a reduction in technical graft loss (**Fig. 40.6**).[49] Recent studies suggest a relationship between center volume and graft failure.[113]

Registry analyses demonstrate a mortality benefit of SPK transplantation compared with dialysis[114] or deceased donor kidney transplantation alone.[115] These benefits diminish with higher-risk donors, particularly older donors.[116] Patient survival at 1 year and 5 years following SPK transplantation is 98% and 92%, respectively (**Fig. 40.7**). Race, ethnicity, gender, and transplant center volume are not associated with decreased patient survival at 5 years, and patient survival has improved since 1995 but not appreciably in the past 15 years.[49]

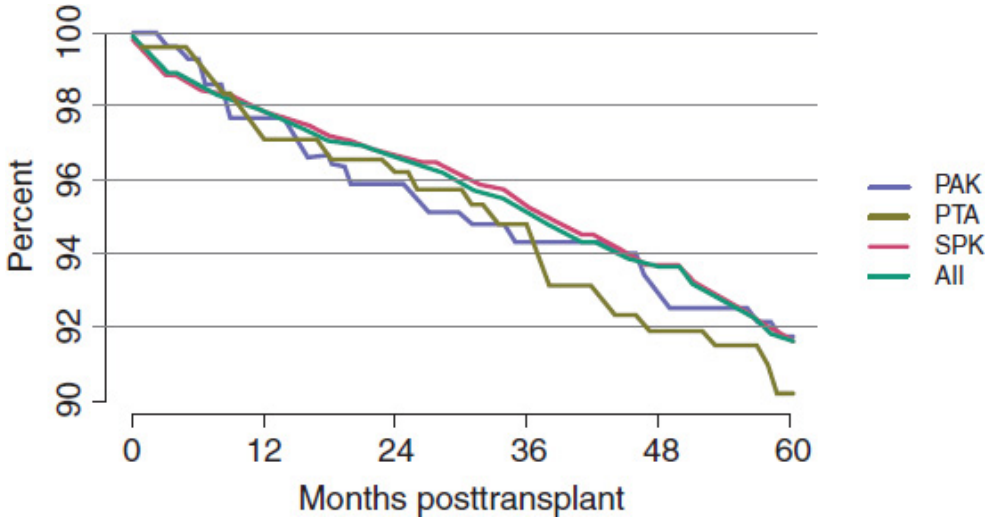

Figure 40.7 Patient survival among adult deceased donor pancreas transplant recipients, 2011–2013 by transplant type. (Data from Scientific Registry of Transplant Recipients. 2018 *Annual Data Report.* Rockville, MD: Health Resources and Services Administration, Department of Health and Human Services; 2018.)

Results of Solitary Pancreas Transplantation

Over time, the 1-year reported pancreas graft survival for recipients of a PAK transplant improved from 78% for PAK transplants performed in 2005 to 88% for transplants performed in 2011.[49] The last reported graft survival for PAK at 5 years was 53% in 2011. One-year pancreas graft survival for PTA was 80% at 1 year and 53% at 5 years. Graft survival rates for PTA are better than PAK early, but the rate of graft failure in the long term is greater for PTA than for PAK. Patient survival for both PAK and PTA recipients is excellent, around 98% at 1 year and >90% at 5 years for recipients transplanted in 2011–2013 (**Fig. 40.7**).

Whether pancreas transplantation positively impacts patient survival is controversial. One study reported that registrants on the waiting lists for PAK and PTA had better survival rates than recipients who underwent these procedures.[114] Subsequently, another group, using a similar cohort but different analytical methods, reported better survival rates for recipients of solitary pancreas transplantation than registrants on the waiting list.[117] These discrepancies are in part related to the differing methodologies used in the two studies with respect to deaths among those removed from the waitlist and also to variability in the year-to-year death rates on the waiting list. In

contrast, both studies demonstrated a conclusive benefit for SPK recipients compared with remaining on the waiting list, which illustrates the importance of restoration of kidney function in this population, as with kidney-alone transplant. 8 While opinions on the specific benefit of the pancreas transplant differ in light of the differing conclusions of these two studies, together the studies indicate any survival benefit conferred by the pancreas transplant is likely to be modest. In fact, most studies do not demonstrate a graft or patient survival advantage of SPK over living donor kidney transplant.[115,118] The survival benefit of SPK over deceased donor kidney transplant alone has been recently further quantified, and while statistically significant, the survival benefit was not considered clinically meaningful.[119]

Effect of Pancreas Transplantation on Secondary Complications of Diabetes Mellitus

There are data that clearly demonstrate the impact of pancreas transplantation on the course of secondary complications of diabetes. This could be predicted from the results of the DCCT, in that pancreas transplantation leads to a complete normalization of blood glucose and glycosylated hemoglobin levels that are vastly superior to those achievable by intensive insulin therapy. Therefore, it should not be surprising that pancreas transplantation has an impact on diabetic complications.

For example, while type 1 diabetic recipients of kidney transplants alone show typical findings of diabetic nephropathy following transplantation, SPK transplantation prevents the development of recurrent diabetic nephropathy.[120] In addition, native diabetic nephropathy, including microvascular structural abnormalities has been demonstrated to reverse 10 years following successful isolated pancreas transplantation.[121,122] These reports demonstrate convincingly that pancreas transplantation has a significant impact on diabetic nephropathy.

Effects on diabetic neuropathy have also been documented using nerve conduction studies, which are significantly improved following pancreas transplantation and SPK.[123] Small corneal nerve fiber regeneration can be detected.[124,125] Furthermore, clinical progression of diabetic neuropathy is

significantly diminished compared to nontransplanted controls. However, no study has been able to demonstrate symptomatic clinical improvement in existing diabetic neuropathy following transplantation. There is also an impact on autonomic neuropathy, with clinical improvement in epinephrine responses to hypoglycemia.[126]

While the DCCT demonstrated a relationship between glycemic exposure and retinopathy, the effect of pancreas transplantation on retinopathy is only modest. While stabilization of moderate retinopathy has been demonstrated, long-term graft function (>3 years) is required.[127,128] Many pancreas transplant candidates have advanced retinopathy, and an effect has not been demonstrated in these individuals. Early acceleration of retinopathy, a phenomenon that has been noted with other methods of improving glycemic control, can occur in the first 6 to 12 months following transplant.

Pancreas transplantation also appears to have a modest impact of cardiovascular disease parameters. Despite the findings of the DCCT trial, assessment of the clinical impact of pancreas transplantation on the progression of cardiovascular disease lacks a definitive large-scale study. Positive effects on lipid profiles, hypertension, carotid intimal thickness and left ventricular ejection fraction have been demonstrated.[129–131] Some centers have demonstrated a positive impact on peripheral vascular occlusive disease.[132,133] One recent study showed similar progression of coronary artery disease in SPK recipients as in recipients of living door kidney-alone.[134]

Regardless of the magnitude of objectively demonstrable benefits of pancreas transplantation, most recipients enjoy a dramatic improvement in quality of life.[97,135–137] While many diabetics can adapt quite well to the dramatic glucose fluctuations and the associated morbidity of diabetes, the freedom from insulin and the avoidance of hyper- and hypoglycemia offered by a functioning pancreas transplant is a primary motivator for many recipients. The fervor with which many candidates pursue pancreas transplantation, especially retransplantation, is an indication of the significant benefit on quality of life for these individuals.

ISLET TRANSPLANTATION

Overview

The notion that insulin-producing–β-cells could be physically separated from the pancreas and transplanted for the treatment of diabetes has long been recognized. Islet transplantation, as a cellular transplant, has significant potential 9 advantages over whole-organ pancreas transplantation. Islet transplantation does not require an operative procedure.[138] In addition, the potential ability to preserve islets opens up possibilities with regard to distribution, allocation, transportation, and preparation of the islet recipient. Pretreatment of the graft to reduce immunogenicity or enhance survival and function is also possible.[139] Recipients of successful islet transplants can have glucose metabolism and insulin secretion profiles that are close to normal, and maintain metabolic control in a manner equivalent to whole-pancreas transplantation.[140] Although effects on long-term mortality and progression of diabetic complications are unproven, these benefits are also anticipated. From a long-range perspective, the development of islet transplantation sets some of the procedural, technical, and regulatory groundwork for the eventual establishment of stem-cell–derived β-cell transplantation. Furthermore, technologic advances in islet isolation for allotransplantation have been very successfully utilized in autotransplantation following pancreatic resection.

History

The development of islet transplantation was historically limited by poor graft survival. The first human islet allograft in a type 1 diabetic was performed in 1974 by the University of Minnesota.[141] The first islet autograft for the treatment of chronic pancreatitis was performed at Minnesota in 1977. Despite intense research in islet transplantation over three decades, until 2000 clinical islet transplantation met with minimal success.[142] While transplanted islets were capable of physiologic function, as evidenced by the 66% rate of insulin independence at 1 year in the 163 recipients of islet autografts from 1974 to 1995, even these recipients had significantly reduced functional β-secretory reserve.[143] Allotransplantation presented an even greater hurdle; in the 96 islet allograft recipients with type 1 diabetes from 1990 to 1994, C-peptide production and insulin independence at 1 year were

25% and 7%, respectively.[142] Of the 270 recipients until 1999, only 6 had achieved insulin independence for greater than 2 years.

The dramatic improvement in islet transplant outcome reported by the Edmonton Group in 2000 stimulated an increase in islet transplant activity.[144] Several important refinements in islet isolation and immunosuppression were credited for the improvement, including careful attention to pancreas recovery; minimization of cold ischemia time of the pancreas prior to islet isolation; avoidance of xenoproteins in the isolation process; and avoidance of steroids in the immunosuppressive regimen. The use of sequential infusions to achieve insulin independence has been critical to success for many centers. Subsequently, the enthusiasm that accompanied this success was tempered by the inability for many new centers to replicate the success of more established centers,[145] the disappointing long-term survival of the transplants,[146] and the costs associated with islet transplants, which are still not reimbursed by third-party payers and Medicare.[147] As a result, the volume of islet transplants and the number of centers performing transplants contracted over the next decade, and are currently at a steady state of low volume; in 2015, 4 North American centers performed islet transplants in 10 recipients.[148] Nevertheless, incremental improvement in efficacy and long-term outcomes in selected centers, as well as progress toward a biologic license from the U.S. Food and Drug Administration (FDA) has sustained optimism that this procedure will ultimately be reimbursed by Medicare and thus be regarded as a realistic alternative to pancreas transplantation.[149,150]

Islet Isolation

The precise separation of the islets from the other tissues of the pancreas (exocrine cells, lymphatics, and vascular structures) is the most important determinant of successful islet transplantation. One of the limitations of islet isolation is the difficulty in getting a large number of high-quality islets, and consistent success in islet isolation is a combination of science, art, and experience. Although a variety of methods have been utilized, most currently employ some modification of the semiautomated method described by Ricordi in 1988.[151] This method combines mechanical distension with enzymatic digestion of the pancreas. After cleaning the pancreas of surrounding fat, the pancreatic duct is cannulated with an angiocatheter and

the pancreas is distended and loaded with warm collagenase solution, which digests the pancreas.[152] The pancreas is then placed into a sterile chamber, which also contains a number of stainless steel or glass spheres. Additional collagenase solution is added, and the chamber is attached to a shaking apparatus or agitated by hand. The collagenase solution is recirculated and kept at 37°C as the chamber is agitated. Agitation of the chamber allows the spheres to continue to disrupt the structural integrity of the pancreas as it digests. Following digestion, the separation of islets from nonislet tissue is performed via density gradient centrifugation. After suspension in culture media, islets are counted and assessed for sterility, purity, viability, and functional capacity. As islet isolation in the United States is regulated by the FDA, stringent product release criteria are in place to ensure the quality of the transplanted islets.

The percentage of islet isolations that result in a transplantable preparation varies widely among centers, between 25% and 70%, and depends both on donor selection practices and the experience and expertise of the particular center. Many elements of the process, such as collagenase batch or type, gradient preparation, the use of culture and culture conditions, and additives to prevent islet loss, are not standardized. This variability reflects both the need for improvements in isolation efficiency and the art/science currently inherent in the process. The ultimate goal is to develop a reproducible process with enough fidelity to allow islet preparations to be biologically licensed, which appears to be a major barrier to federal funding for the procedure, which will be necessary for broader application.

Patient Selection

Candidates for islet transplantation are selected in a similar manner as for whole-organ pancreas transplantation. Islet transplantation is currently limited to adult type 1 diabetics with progressive diabetic complications who have failed intensive insulin therapy. Because islet transplantation remains experimental therapy with limited availability, the procedure is generally offered only to ideal candidates with minimal medical conditions other than diabetes. Most centers require evaluation and/or a period of treatment by an experienced endocrinologist specializing in diabetes. Candidates with coronary artery disease, chronic infections, including

hepatitis B and C, or a prior solid-organ transplant are excluded. Nonuremic candidates must be free of renal insufficiency, due to concerns about aggravation of nephropathy by calcineurin inhibitors. Since efficacy of the islet transplant appears to be related to the number of islets transplanted per kilogram of recipient body weight, only lean (<70 kg or BMI <28) recipients are selected. Although most islet transplants are currently performed in nonuremic diabetics, islet transplants either concurrent with or following kidney transplantation are also performed.[153,154]

Donor Selection/Recovery/Preservation

Donor selection for islet isolation differs from that for whole-pancreas transplantation in several respects. While the ideal donor for islet isolation is still young and healthy, the age and weight criteria are less stringent than for whole-pancreas transplantation. Donors greater than age 50, donors on vasopressors, and especially obese donors are all perfectly suitable for islet isolation. Since the ideal pancreas is easily distensible and digestible, fatty pancreata are felt to be especially suitable, whereas fibrotic pancreata are not. As previously mentioned, pancreata from older and obese donors (which are infrequently used for whole pancreas) are preferentially allocated for islet transplantation rather than for regional and national sharing for whole-pancreas transplantation.[50]

The pancreas is recovered in a manner similar to whole-pancreas transplantation. However, less attention to preservation of vascular structures is required. Attention is paid to surface cooling following flushing of preservation solution, and avoidance of pancreatic injury. A number of reports have highlighted the importance of a dedicated team trained in pancreas recovery in the success of islet isolation.[155,156] Expanded use of the two-layer technique of pancreas preservation, using both standard preservation solution (UW solution or HTK) and oxygenated perfluorocarbon solution, has resulted in increased islet yields.[157–160] The two-layer technique also permits the successful use for islet transplantation of pancreata subjected to prolonged cold ischemia as long as 18 hours. Success with pancreata from DCD has been reported.[161]

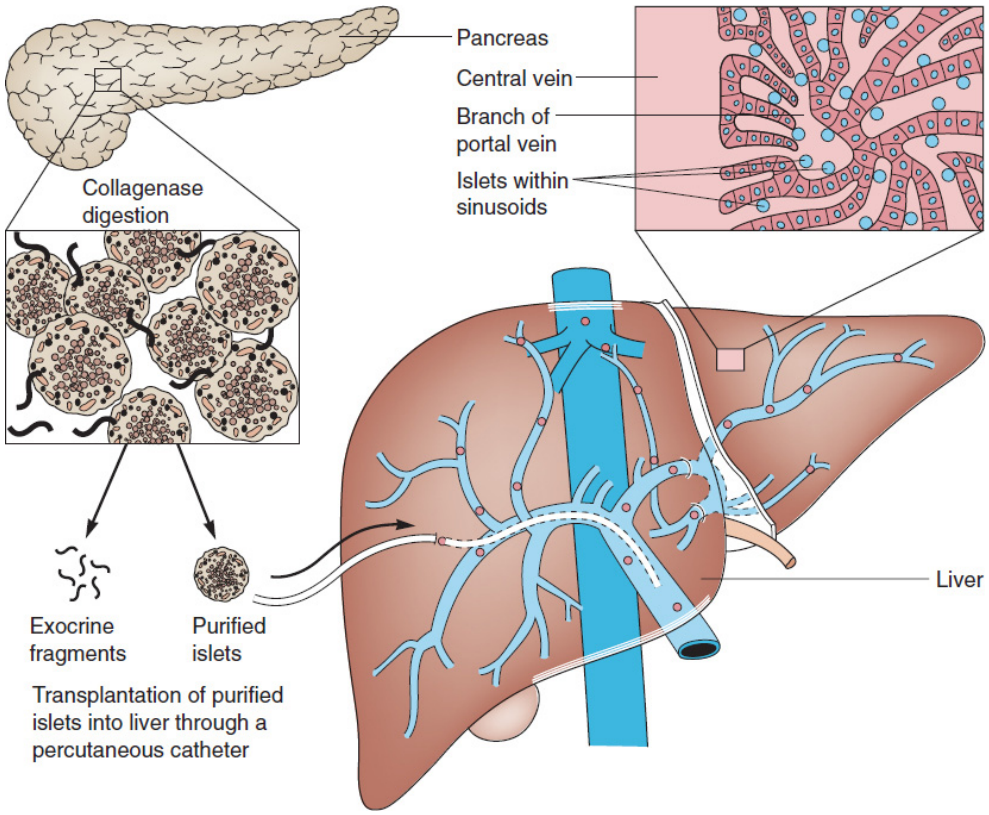

Figure 40.8 Islet transplantation. The pancreas is recovered as a whole organ from the donor. The islets are isolated from the pancreas and are purified and infused into a cannula placed in a branch of the recipient's portal vein.

Transplant Techniques

The portal circulation of the liver is currently the preferred site for islet transplantation (**Fig. 40.8**).[162] This can be performed by a minilaparotomy, with infusion of the islets into a peripheral mesenteric vein. However, most centers utilize interventional radiology techniques, avoiding both a surgical incision and general anesthesia. Percutaneous transhepatic portal vein catheterization is done under ultrasound and fluoroscopic guidance, with usually a small gauge (4-French) catheter. The islets are infused into the portal vein through the catheter by either gravity from an infusion bag or by hand injection, and the islets lodge in the hepatic parenchyma. Portal vein pressure is monitored intermittently throughout the procedure. Following infusion of the islets, hemostasis is usually achieved using a combination of coils and gelfoam. Recipients receive heparin in the islet preparation, systemically during the procedure, and in the perioperative period as

prophylaxis against portal vein thrombosis, a now rare but serious complication.

Perioperative Care

Although islet transplantation is in theory an outpatient procedure, it is not uncommon for recipients to receive a few days of inpatient care for monitoring purposes. Immediately following the islet transplant, patients are maintained on bed rest for a short interval and monitored for bleeding. Liver function tests are monitored, and a liver ultrasound is frequently done to assess portal venous flow and to check for hematoma. It has been demonstrated that intensive glycemic control with insulin in the immediate posttransplant period is beneficial for islet function.[163] Hence, many centers will give insulin postoperatively to keep the serum glucose tightly controlled, in order to "rest" the islets. Additional adjuncts to prevent the instant blood-mediated inflammatory reaction (IBMIR), which results in early islet loss and reduced β-cell mass in the recipient, may include antioxidants such as vitamin E, etanercept (anti-TNFα antibody), anakinra (IL-1β antagonist), reparixin (CXCR1/2 inhibitor), pentoxifylline, and others.[164]

Immunosuppression

Immunosuppresssive regimes for islet transplantation have evolved in the 21st century. Earlier regimens used basiliximab induction, and maintenance therapy with low-dose tacrolimus and sirolimus. However current regimens more commonly used T-cell–depleting antibody therapy for induction, and calcineurin inhibitors and IMPDH inhibitors such as mycophenolate mofetil.[148] The best results for islet–kidney transplantation are cases where steroids are avoided or eliminated at the time of islet transplantation. While long-term effects of either the islet transplant or steroid elimination on kidney function are not known, steroid avoidance in kidney transplant recipients is now routine.[49] Regimens that avoid both steroid and calcineurin inhibitors have also been successfully used.[165]

Metabolic Control

Islet recipients show significant improvement in metabolic function and glycemic reserve, although hormonal counter regulation to hypoglycemia is diminished, actual hypoglycemic events are rare.[166] Data from the Collaborative Islet Transplant Registry show that nearly 80% of islet-alone transplant recipients maintained HbA1C level of <7.0% at 1 year, and over 60% at 5 years after transplant.[148] These rates are approximately 10% lower in islet-after-kidney recipients. Over 90% of are free of severe hypoglycemic episodes at 1 year, and this is maintained over 5 years. Islet recipients also demonstrate a reduction in behaviors adopted in avoiding hypoglycemia and attenuation in concerns about hypoglycemic episodes.[167] Islet transplantation also results in improved insulin sensitivity mediated by effects at both the liver and skeletal muscle.[168] However, islet recipients have significantly diminished β-cell reserve than do recipients of whole-pancreas transplants, which may account for their reduced long-term survival.[169] Acute insulin response to intravenous glucose is commonly used to determine islet engraftment, and is a robust early metabolic marker to predict return to insulin therapy.[170] Analyses of the impact on diabetic complications and mortality await further experience.

Complications

Morbidity from islet transplantation is substantial but much less than for whole-pancreas transplantation. The most common serious complication is bleeding (1% to 5%). Most cases of bleeding can be managed nonoperatively with adjustments in anticoagulation, though occasionally laparotomy is required. The side effects of immunosuppression, such as hyperlipidemia and mouth ulcers in sirolimus-containing regimens, are much more common and can significantly affect quality of life.[171] Renal insufficiency is an uncommon but serious consequence.[148] Transient elevations of portal venous pressure during islet infusion and elevations of liver function tests following infusion are common and usually well tolerated.[172,173] However, reduction in liver perfusion during the islet infusion has been linked to premature graft failure.[174] The demonstration of late steatosis has raised concerns about chronic liver disease; to date this has not been reported.[175] CMV infection is rare. Mortality is virtually nil.

Sensitization and the development of posttransplant DSA, which was originally thought not to occur following allogenic islet transplantation, are now recognized as a significant challenge. Recent experience has shown that most recipients have increases in DSA or autoantibody (de novo expression or titer increase) after islet transplantation. Recipients who have an increase in posttransplant antibody have similar initial performance but significantly lower graft survival than patients without an increase.[176] Patients with complete graft loss who discontinue immunosuppression had significantly higher levels of anti-HLA antibodies than those with functioning grafts still on immunosuppression.[177] Ways to minimize sensitization in these recipients includes minimizing the number of islet donors used per recipient, and in the absence of donor-specific anti-HLA antibodies, repeating HLA mismatches with subsequent islet infusions.

Results

10 The short-term results of islet transplantation at high-volume centers are approaching that of whole-pancreas transplantation. The most successful centers achieve insulin independence rates of 80% to 90% at 1 year.[145,178,179] In the Immune Tolerance Network multicenter trial of the Edmonton Protocol, success rates at the most successful centers (Edmonton, Minnesota, and Miami) were significantly higher than at the other centers.[145] However, long-term rates of insulin independence are worse than whole-pancreas transplants, but continue to improve. Overall, insulin independence is 50% at 1 year and 20% to 30% at 5 years after the last infusion for those transplanted in the years 2010 to 2013. In experienced centers the 5-year insulin independence rate approaches 50% which approaches the graft survival of PTA.[145,148,149] Generally, long-term outcomes are more favorable in recipients older than 35.

One of the shortcomings of islet transplantation compared with whole-pancreas transplantation is the inability to reverse diabetes with the islets from one pancreas. This is due to extensive early beta-cell loss from recipient inflammatory responses to the transplanted islets. Most recipients in the modern era have required two or more islet infusions to achieve insulin independence. However, some centers have successfully employed single-donor islet transplantation by utilizing careful donor and recipient

selection, usually by transplanting islets from pancreata from large donors into small recipients.[178,180,181] As long-term outcome appears to be related to β-cell mass, which is likely to be lower for single-donor infusions, these recipients may return to insulin or require retransplants earlier.[182] At the recipient level, administration of anti-inflammatory agents, whether nonspecific or directed at specific molecular targets, has become the mainstay of perioperative treatment. The ability to maximize the use of islets and minimize islet requirements and pancreas utilization for an individual recipient is critical if islet transplantation is to compare favorably with whole-pancreas transplantation.

Graft Failure

Graft failure appears to occur earlier than for whole-pancreas transplants. This may be related to a lower initial islet mass or the inability to histologically diagnose and treat islet rejection, since the islets are scattered about the liver parenchyma. As with pancreas graft failure, there is no true agreement on what constitutes graft failure; recipients may require insulin yet still make C-peptide and have improved glycemic control compared with before transplant. Most outcome measures focus on insulin independence as the most stringent, and C-peptide production as the least stringent. Recent findings indicate that immunologic markers of rejection or recurrent autoimmunity, and metabolic indicators may identify recipients at risk for inferior outcomes and impending graft failure, although treatment algorithms based on these predictors are not standardized.[170,176,183,184] A number of investigators have demonstrated the ability to label and identify islets in vivo in recipients in order to monitor functional islet mass—an example of this is ferucarbotran-labeling of islets, which enables their long-term noninvasive visualization by MRI and correlates with sustained C-peptide production.[185]

Recipients with prior graft function who have returned to insulin are candidates for retransplantation. In fact, some centers have used transplanted islets from isolations where yields are insufficient for a primary transplant as retransplants, where the islet requirement may be less if there is still sufficient residual graft function.

Alternative Methods

As islet allotransplantation has progressed toward wider clinical application over a long period of time, other alternative methods have also advanced. There continues to be interest in the use of encapsulated islets. These capsules can be made from a variety of materials designed to be permeable enough to permit the passage of insulin and glucose, but to isolate the islet from the immune system. Several pilot clinical trials in humans, with transplantation into the peritoneal cavity without immunosuppression have been reported, which confirms the safety of the procedure and the demonstration of graft function, if not insulin independence.[186,187] No allo- or autoantibody has been detected in this small number of recipients. Encapsulated human islets can also be shipped safely for long distances after encapsulation and culture without compromising viability and function.[188] The major barriers to graft function and longevity have been the tendency of the capsules to cluster and fibrose, which limits their efficacy.

Artificial delivery systems that contain beta-cells or islets have been developed that can be implanted either in the abdomen or subcutaneous tissue. These artificial pancreata have semipermeable barriers that allow diffusion and neovascularization but afford immunoprotection, and have the advantage of being reloadable and less prone to fibrosis. Other devices are vascularized, which are more complex to implant and can be complicated by thrombosis, but provide better oxygenation and fast exchange of nutrients. They also better maintain concentration gradients by preventing local buildup of molecules, which is a potential limitation of nonvascularized systems. However, these technologies have still not advanced to human clinical trials.

Animal studies suggest that bone marrow precultured with human islets may enhance the survival and function of transplanted islets, thus significantly improving the therapeutic efficacy of islet transplantation.[189] Other investigators have cotransplanted mesenchymal stem cells with islets, which may be beneficial for islet engraftment by promoting cell survival/angiogenesis and reducing inflammation.[190,191]

The emergence of pancreatic beta-cells as potential renewable source of insulin-producing cells to treat diabetes has shifted interest and funding somewhat away from islet transplantation. Beta-cells can be isolated from mature islets but can also be derived from either mature or embryonic stem cells, as the biology of beta-cell development and differentiation has been well established. These engineered beta-cells produce insulin and exhibit

glucose responsiveness in vitro. They also reverse diabetes in animal models. Despite this promise, technical hurdles with scalability and bulk production have limited progress toward clinical application, and the cells still require protection from allioimmune and inflammatory host responses. Pilot studies in humans have not been conducted to date.

More recently, decellularization of organs and recellularization with islets is an emerging approach in bioartificial pancreas development.[192] This preserves important extracellular matrix components that enhance viability of implanted islets. Other approaches utilizing 3-D bioprinting of islets or beta-cells into an organ-like scaffolding are early in development.[193]

THE FUTURE OF PANCREAS AND ISLET TRANSPLANTATION

Many challenges remain in determining the ideal insulin replacement therapy for type 1 diabetics. While the current allocation system designed to maximize whole-pancreas transplantation ensures the most efficient use of donor pancreata, improvements in the efficiency of islet isolation may require that further refinements be made to allocation policy. Current outcomes support the prioritization of whole-pancreas transplantation over islet transplantation, and sufficient long-term survival reproducible among a larger number of centers is required to move islet transplantation into the mainstream. If this occurs, the reduced morbidity of islet transplantation may mean that a large number of candidates who are not surgical candidates for pancreas transplantation may be islet candidates in the future. Many centers have taken the philosophical step to offer islet transplantation primarily to diabetics who would not otherwise receive immunosuppression, that is, nonuremic diabetics. This is somewhat in contrast to PTA transplantation, which is offered to only the most exceptional candidates. Taken further, islet transplantation could theoretically be open to a large number of type 1 diabetics that would surely exhaust the limited supply of human donor pancreata. However, the experience gained by the development of islet transplantation would apply to technologies not affected by human donor supply, such as islet xenografts or engineered β-cells, which could have a

profound impact on the devastating effects of diabetes on the public health worldwide.

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Section C: HEAD AND NECK

41

Head and Neck

Kelly Michele Malloy

Key Points

1. Patients with new onset hoarseness of 2 weeks or greater duration should be evaluated via flexible fiberoptic laryngoscopy.
2. Airway obstruction is a potential concern in many head and neck conditions, be they infectious or neoplastic. Assessment of the airway with nasopharyngolaryngoscopy (NPL) is crucial to safe management of these patients and should be considered early in the evaluation of patients with stridor or other signs of airway compromise.
3. A cystic neck mass in an adult represents a cervical metastasis until proven otherwise; this should be worked up with imaging and fine needle aspiration (FNA) biopsy and should not be incised and drained.
4. Thoughtful, functional reconstruction of the oral cavity and pharynx is equally important as sound oncologic resection in head and neck surgery.

INTRODUCTION

The head and neck comprises one of the most functionally sensitive anatomic regions of the human body. Disorders of hearing, sight, speech, swallowing, smell, and taste are some of the most frustrating and life altering. Cosmetic and self-image concerns also arise when the head and neck is affected by disease. There is a great breadth and depth of disease that impacts the head and neck, from infectious abscesses and congenital cysts to rare tumors. This chapter provides a high-level review of the presentation, assessment and management of more common head and neck disorders, as well as a template for consultation and collaboration with multidisciplinary specialists when needed.

PATIENT EVALUATION

History and Physical Examination

A thorough patient history is critical to accurate diagnosis of head and neck disease. Symptoms such as mass/swelling, pain, drainage, and changes in breathing, swallowing, or speech need to be further explored with questions about timing of onset, pace of progression, and relationship to any constitutional symptoms like weight loss and fevers. Social history is particularly meaningful in head and neck patients. Habitual tobacco and alcohol use increases the risk of head and neck malignancy, with increasing pack years augmenting risk in dose-dependent fashion.[1] Sexual history has become important as increasing number of oral sexual partners is associated with an increased risk of human papilloma virus (HPV)-related oropharyngeal cancer (OPC).[2]

A complete head and neck examination includes systematic inspection of the head and neck, including each mucosal subsite (**Table 41.1**) via otoscopy, anterior rhinoscopy, and often flexible fiberoptic nasopharyngolaryngoscopy (NPL). Dentures should be removed prior to inspection and bimanual palpation of the oral cavity and oropharynx. Gross craniofacial and/or neck deformity, skin lesions, previous scars, and any radiation sequelae should be noted. Complete cranial nerve examination is critical as even subtle changes in function can guide diagnosis. [1] The head and neck examination also relies

on auditory cues: hoarseness, garbled voice, stridor, stertor, and hyper- or hyponasality are all important features of head and neck disease.

Indirect mirror laryngoscopy to visualize the larynx and hypopharynx requires practice, skill, and specialized office equipment to perform well; moreover, patients with active gag reflexes or with larger tongues may be difficult to examine adequately via mirror examination. NPL examination provides improved visualization of the nasal cavity, nasopharynx, larynx and pharynx, including assessment of airway patency, dynamic function of the vocal folds, and sensation of the pharynx; NPL also affords the ability to record images and video when coupled with appropriate equipment, critical to assessing treatment response in cases of malignancy and for enhanced medical record keeping. **Figure 41.1** demonstrates the view of the larynx provided by office NPL.

The neck should be inspected and palpated carefully with particular attention to both salivary glands and cervical lymph nodes. Location of adenopathy or neck mass should be described by level, from I to VI as described by Robbins et al. (**Fig. 41.2**)[3]; tenderness and mobility should also be described. Lymph nodes tend to be mobile in all directions early in disease, but fixation to deep tissues or invasion of overlying skin indicates more advanced disease. A lateral neck mass that is mobile in the anteroposterior dimension, but not superior–inferiorly raises suspicion of paraganglioma or schwannoma. A pulsatile mass suggests a vascular pathology and should not be biopsied without imaging. The larynx and trachea should be palpated to determine any disruption to the normal architecture, tenderness, or deviation due to neck or thyroid masses. The thyroid gland is also palpated as part of every head and neck examination, the specifics of which are addressed in a separate chapter.

Cranial neuropathies deserve special attention and the clinician must be vigilant for subtle neurologic signs of underlying disease. Hyposmia may be a sign of sinonasal pathology, either due to nasal obstruction or to direct involvement of the olfactory nerve. Extraocular movement abnormalities are presenting symptoms of orbital or skull base pathology. Facial numbness or progressive facial pain raises concern for trigeminal nerve involvement by malignancy. Facial weakness or twitching in the setting of a parotid mass suggests malignancy. Bell palsy, like trigeminal neuralgia, are diagnoses of exclusion and underlying malignancy must be considered during workup of

these cranial neuropathies. Ipsilateral vocal fold paresis or impaired palatal elevation suggests involvement of the vagus nerve by neoplasm. Shoulder weakness in the setting of cervical lymphadenopathy indicates spinal accessory nerve invasion by tumor, and would prompt preoperative discussion of radical neck dissection over nerve- and muscle-sparing techniques. Tongue weakness/deviation raises concern for hypoglossal nerve involvement by primary tumor or by level I/II neck disease. Horner syndrome in the context of head and neck malignancy prompts suspicion for sympathetic chain invasion of deep cervical lymphatics.

Table 41.1 Anatomic Subsites of the Head and Neck

Subsite	Anatomy
Anterior skull base	Nasal cavity Paranasal sinuses Orbit
Oral cavity	Anterior 2/3 tongue/floor of mouth Lip/buccal mucosa/teeth/gingiva/retromolar trigone Hard palate
Pharynx	Nasopharynx Oropharynx (soft palate, palatine tonsils, posterior 1/3 tongue/lingual tonsils, posterior pharyngeal wall above the hyoid to level of palate) Hypopharynx (piriform sinuses, postcricoid space, posterior pharyngeal wall below the level of the hyoid)
Larynx	Supraglottis Glottis Subglottis
Salivary	Parotid Submandibular gland Sublingual gland Minor salivary glands
Lateral skull base	Parapharyngeal space Infratemporal fossa Temporal bone

Figure 41.1 Office NPL demonstrates a normal larynx with glottis open.

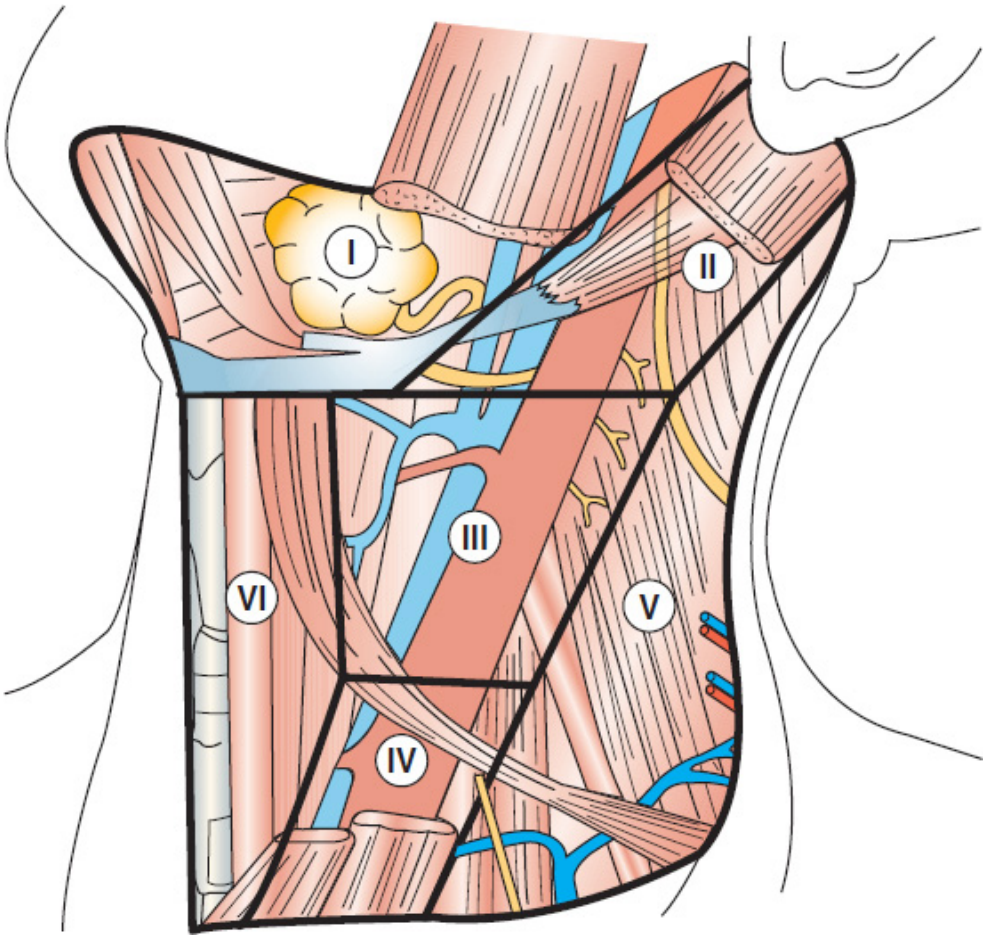


Figure 41.2 The anatomic levels of the cervical lymph nodes.

Workup

In the setting of an accessible tumor (e.g., oral tongue, tonsil), biopsy may be performed in the office under local anesthesia. For more distal tumors or in the presence of severe pain, trismus, or brisk gag, operative direct laryngoscopy is warranted. For palpable salivary or cervical masses, fine-needle aspiration (FNA) biopsy is easily performed without image guidance; however, in office ultrasound guidance may prove useful for smaller lesions. Obtaining imaging prior to needle biopsy is reasonable in any circumstance when vascular pathology or proximity of pathology to vascular structures is of concern. CT with contrast is the preferred imaging modality for most head and neck pathologies. MRI is useful to evaluate for perineural spread of tumor and for orbital and dural assessment. When malignancy is diagnosed, metastatic workup with PET/CT or chest CT should be performed.

Airway Concerns

2 The presence of head and neck disease may impact the patient's airway on presentation, but it may also complicate safe airway management during planned surgery. This requires a thoughtful, multidisciplinary approach. A number of patient factors have been described in the anesthesia literature as predictors of difficult direct laryngoscopy, including sternomental distance, thyromental distance, Mallampati score, and mouth opening.[4] Imaging may assist with assessment and NPL examination by an expert practitioner is critical to evaluate airway patency. A large laryngeal or oropharyngeal mass may lead to failure of mask ventilation and difficulty passing an orotracheal tube; lesions prone to bleeding may cause similar problems. Trismus secondary to advanced tumor or radiation fibrosis may also impede orotracheal intubation. Extrinsic compression or deviation of the airway by thyroid or neck nodal mass is another situation where head and neck surgeons can assist in airway assessment and management. A prospective study of intubation in patients with head and neck pathology found that a diagnosis of cancer, particularly of the supraglottis or glottis, as well as history of radiation, predicted difficult airway.[5] Surgeon and anesthesiologist thus must communicate clearly about the airway plan prior to induction.

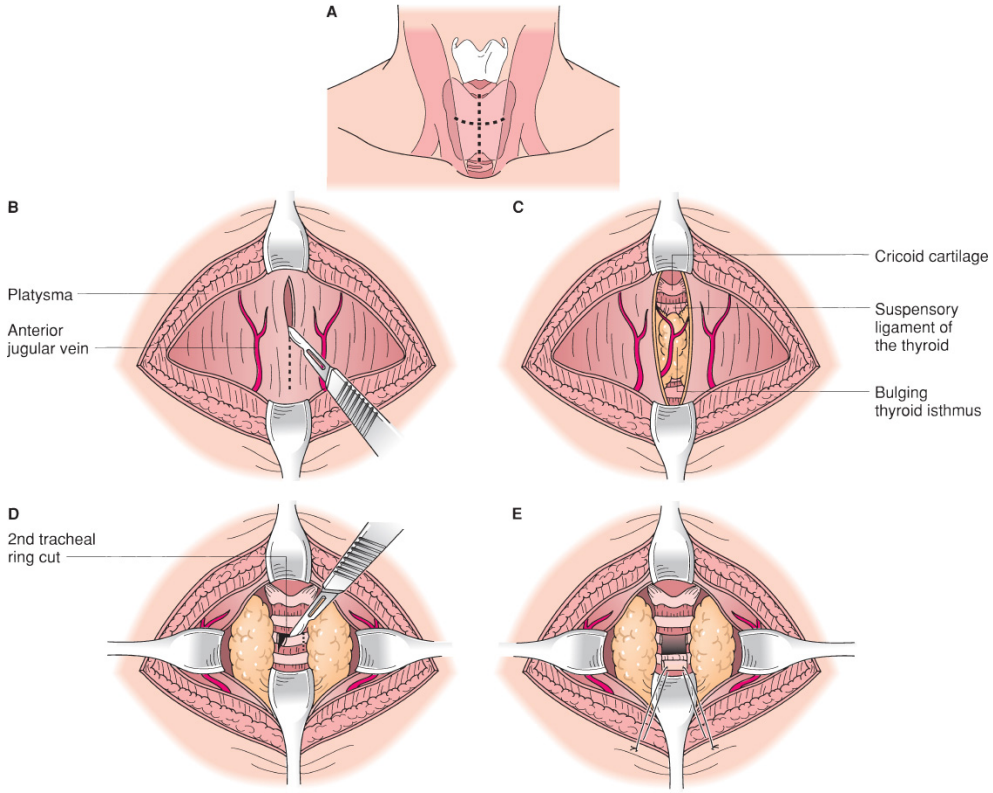


Figure 41.3 Tracheostomy. **A:** The incision for an elective tracheostomy is typically placed on a horizontal axis, approximately two-finger breadths above the sternal notch. A vertical incision allows for less bleeding when the procedure must be performed emergently. **B:** The strap muscles are separated in the midline. **C:** The thyroid isthmus is then encountered and may require division with cautery and/or inferior retraction. **D:** The trachea is entered horizontally, preferably between rings 2 and 3. **E:** An inferiorly based flap (i.e., Bjork flap) is developed in the tracheal wall and sutured to the skin or subcutaneous tissues. This allows for easy access to the trachea while the tract is maturing.

Awake fiberoptic intubation (FOI) may be safely performed in many such cases with the patient spontaneously breathing, using topical anesthesia and mild sedation to intubate via the nasotracheal or orotracheal route. A tracheotomy kit should always be available for emergent cricothyrotomy or tracheotomy should FOI prove impossible or the airway becomes further compromised. In cases where NPL examination indicates imminent airway collapse, planned awake tracheotomy is the safest option. Early consultation with otolaryngology-head and neck surgery is strongly encouraged in difficult airway cases. **Figure 41.3** demonstrates the steps of a tracheotomy.

INFECTIOUS AND INFLAMMATORY DISEASE OF THE HEAD AND NECK

Neck Abscesses

The most common head and neck abscess is the peritonsillar abscess (PTA). A complication of untreated bacterial pharyngitis, it may lead to bacterial invasion of the parapharyngeal space if not adequately drained. Trismus is a hallmark of PTA, alongside symptoms of dysphagia, odynophagia, and a muffled "hot potato" voice. Physical examination reveals soft palate and tonsillar bulging with uvula deviation toward the unaffected side. CT neck is typically unnecessary but may have a role in equivocal cases. Drainage is performed at bedside under local anesthesia. An 18-gauge needle can be used to localize the pus collection and plan an incision. An 11 or 15 blade is then used to make a cruciate incision superolaterally, and a hemostat or Yankauer suction used to probe the space and drain the collection (**Fig. 41.4**). Antibiotics with broad coverage (e.g., amoxicillin–clavulanate or clindamycin) should be thereafter prescribed for 10 to 14 days. Patients with a history of multiple PTAs should be considered for subsequent tonsillectomy.[6,7]

Patients with epiglottitis may present similarly to PTA with odynophagia, muffled voice, and drooling; trismus, however is usually absent, and epiglottitis patients have impending airway compromise. Lateral neck plain films demonstrate a classic "thumbprint sign" of an edematous epiglottis. NPL examination can be used to confirm the diagnosis, but early securing of the airway in the operating room via FOI or awake tracheotomy is paramount.

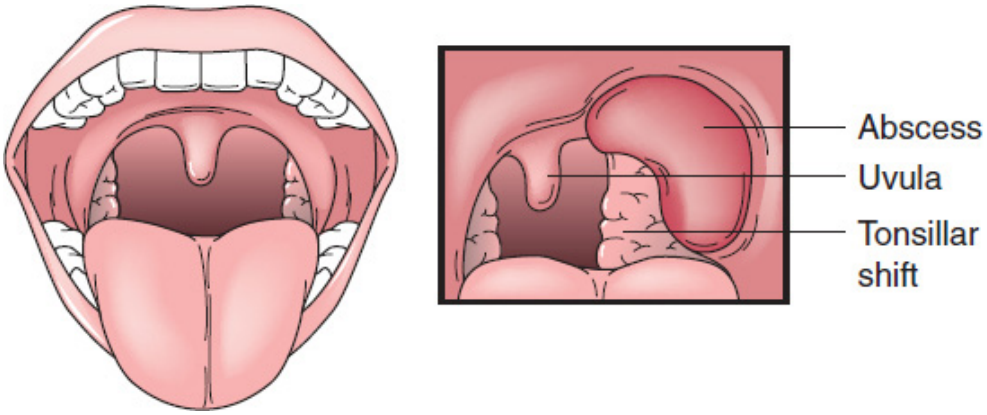


Figure 41.4 Schematic representation of a peritonsillar abscess. Purulence develops between the tonsillar capsule and the superior pharyngeal constrictor muscle. As a result, the palate bulges and the tonsil are deviated medially. Inflammation in the region of the pterygoid muscles results in pain and trismus which may be significant.

Odontogenic and pharyngeal infections can progress to deep neck space infections, particularly in diabetic patients. Early evaluation of the patient's airway is critical as airway compromise may evolve rapidly. Elective intubation should be considered and tracheotomy may be necessary in the setting of prolonged airway edema. Of particular concern are infections involving the floor of mouth, or Ludwig angina, which cause airway compromise via posterior displacement of the base of tongue. Infections in other neck spaces, including retropharyngeal, parapharyngeal, and prevertebral spaces, may spread quickly and cause rapid decompensation via mediastinitis. **Figure 41.5** lists the relevant deep neck spaces and paths of spread.

Incision and drainage with copious irrigation and placement of dependent drains is the treatment of choice for deep neck space infection, and reexploration is occasionally needed. Culture-guided antibiotics and control of blood glucose levels are also indicated. If odontogenic in origin, the source tooth should also be addressed.

Complications of Rhinosinusitis

Acute rhinosinusitis may be viral or bacterial and presents with fever, facial pressure, pain, nasal obstruction, and purulent or discolored nasal discharge. The American Academy of Otolaryngology-Head and Neck Surgery Clinical

Practice Guideline for adult sinusitis notes that the vast majority of upper respiratory tract infections (URIs) are viral, and that bacterial rhinosinusitis should be suspected when symptoms persist after 10 days or worsen after a period of initial improvement.[8,9] Surgery is not indicated for patients with acute sinusitis unless orbital or intracranial involvement occurs. Complicated acute bacterial rhinosinusitis (**Table 41.2**) should be suspected when visual, mental status, or neurologic changes are present. Proptosis, chemosis, and periorbital edema may signify orbital abscess (**Fig. 41.6**). Contrast-enhanced CT and MRI are warranted in most cases. Prompt consultation with otolaryngology, ophthalmology, and/or neurosurgery is imperative.

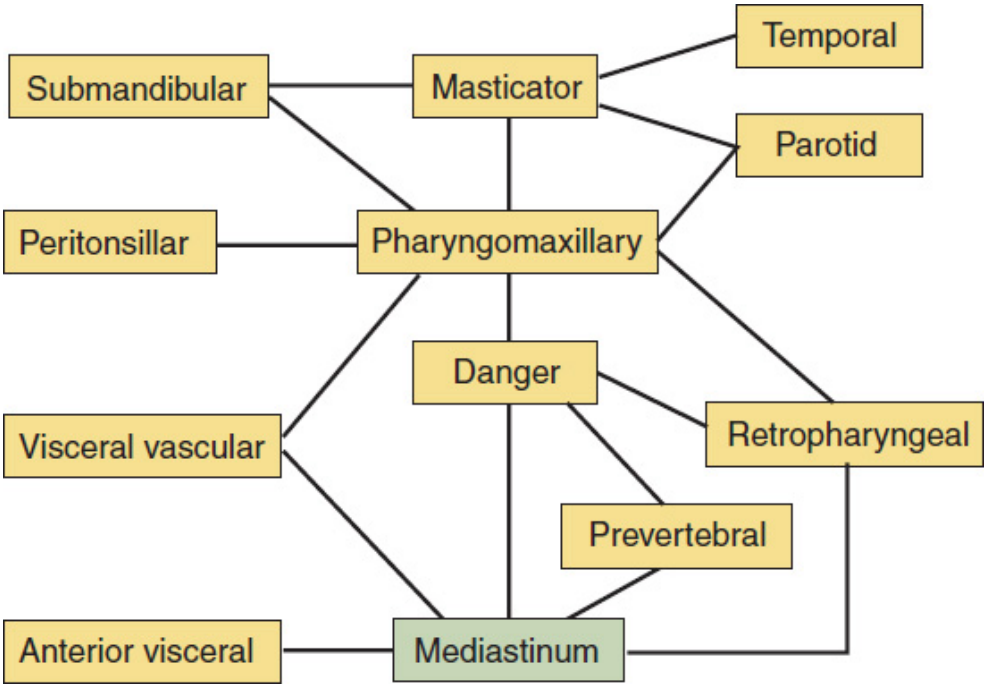


Figure 41.5 The deep spaces of the neck are distinct but interconnected compartments. Infections in any one of these may spread to involve other potential spaces and critical structures contained therein.

Table 41.2 Complications of Sinusitis

Local
Mucocele
Pott puffy tumor
Osteomyelitis
Orbital
Preseptal cellulitis
Orbital (postseptal) cellulitis
Subperiosteal abscess
Orbital abscess
Cavernous sinus thrombosis
Intracranial
Meningitis
Epidural abscess
Subdural abscess
Intracerebral abscess
Cavernous sinus thrombosis
Superior sagittal sinus thrombosis

From Epstein VA, Kern RC. Invasive fungal sinusitis and complications of sinusitis. *Otolaryngol Clin North Am* 2008;41(3):497–524; with permission.

Rapid onset, severe rhinosinusitis in the immunocompromised (neutropenic, HIV, poorly controlled diabetic or transplanted patients) prompts concern for acute invasive fungal sinusitis. Rapidly progressive and fatal if untreated, the organisms most commonly associated are from the genera *Aspergillus, Rhizopus, Mucor, Rhizomucor,* and *Absidia*.[10] Nasal endoscopy demonstrates pale or black necrotic mucosa of the turbinates or septum. Frozen section biopsy is performed as immediate diagnosis is imperative. The patient should be emergently and aggressively debrided to bleeding tissue in the operating room, tissue sent for cultures, and antifungal therapy initiated in consultation with Infectious Disease specialists. Reversal of the underlying immunocompromised state (i.e., aggressive control of blood glucose) improves prognosis as well.

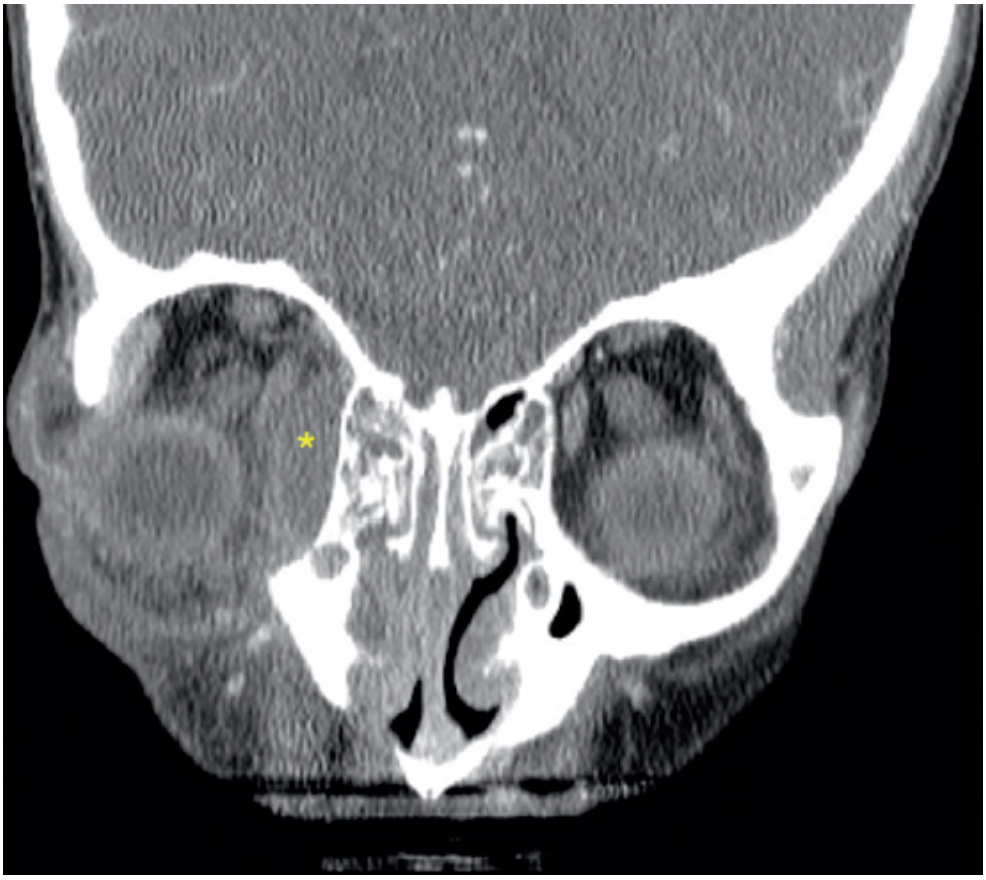


Figure 41.6 Coronal CT sinuses with contrast demonstrates a right-sided periorbital abscess (*asterisk*) arising in a child with acute bacterial ethmoid sinusitis. Urgent ophthalmologic consultation was obtained, which revealed increased intraocular pressure. The child was taken for endoscopic ethmoidectomy and orbital decompression.

Sialadenitis

Patients who are debilitated, dehydrated, or have decreased salivary flow due to medications or xerostomia are predisposed to salivary gland infections. Sialadenitis is a clinical diagnosis, based on tense, tender swelling of the affected gland(s), fevers, and presence of purulence from Warthin or Stensen duct. Viral sialadenitis tends (mumps, HIV) tends to be bilateral. Bacterial sialadenitis is most often caused by *Staphylococcus aureus,* although a variety of anaerobes and other oral pathogens may be cultured.[11]

Patients with uncomplicated sialadenitis should be treated with hydration, sialogogues, gland massage, and broad-spectrum antibiotics if bacterial

pathogens are suspected. Worsening of symptoms after initiation of therapy should prompt consideration of abscess development, and imaging with ultrasound or contrast-enhanced CT should be performed. Recurrent or chronic salivary infections should prompt suspicion for structural or inflammatory disorders. Structural disease includes salivary stones or strictures, while connective tissue disorders, such as Sjögren syndrome, rheumatoid arthritis, and sarcoidosis may present with or develop sialadenitis. When sialadenitis recurs, CT imaging should be undertaken to evaluate for stones or underlying duct-obstructing tumor. Abscess drainage must be thoughtful of the course of the facial nerve, with carefully placed incisions and dissection parallel to its branches.

NECK MASSES: CYSTIC NECK INFECTION OR MALIGNANCY?

3 A neck mass, solid or cystic, should be presumed malignant until definitive expert evaluation proves otherwise. Congenital cystic neck masses and infectious/inflammatory adenopathy remain on the differential diagnosis for adult neck masses (**Table 41.3**), but they are rare and the first thought must be of neoplastic etiologies. HPV-related oropharyngeal squamous cell carcinoma (SCC) frequently presents with a cystic neck mass as the only symptom (**Fig. 41.7**); central necrosis with hemorrhage or superinfection can cause pain and rapid growth, thus mimicking an infected congenital mass or suppurative node. Incision and drainage must be avoided in cases of possible malignancy, as this seeds the neck soft tissues with tumor and may limit treatment options and efficacy. In cases where there is doubt, initiation of antibiotics with close monitoring for improvement may be considered, but prompt imaging with contrast-enhanced CT, FNA biopsy, and referral to a head and neck surgical oncologist will avoid delays in cancer diagnosis and treatment. If FNA does not yield sufficient material for diagnosis, open *excisional* biopsy may be considered provided the surgeon sends for frozen section analysis and is prepared to perform completion neck dissection at the time of surgery for the appropriate diagnosis.

Table 41.3 Differential Diagnosis of a Neck Mass	
Congenital	Branchial cleft cyst Vascular malformation Thyroglossal duct cyst Dermoid
Infectious	Tuberculosis Atypical mycobacteria Cat scratch disease Mononucleosis Odontogenic Sialadenitis
Inflammatory	Sarcoidosis Sialadenosis
Trauma	Hematoma Laryngocele
Neoplasm	Epithelial (SCC, melanoma, adenocarcinoma) Salivary Neurogenic (schwannoma, paraganglioma) Sarcoma Lipoma Lymphoproliferative

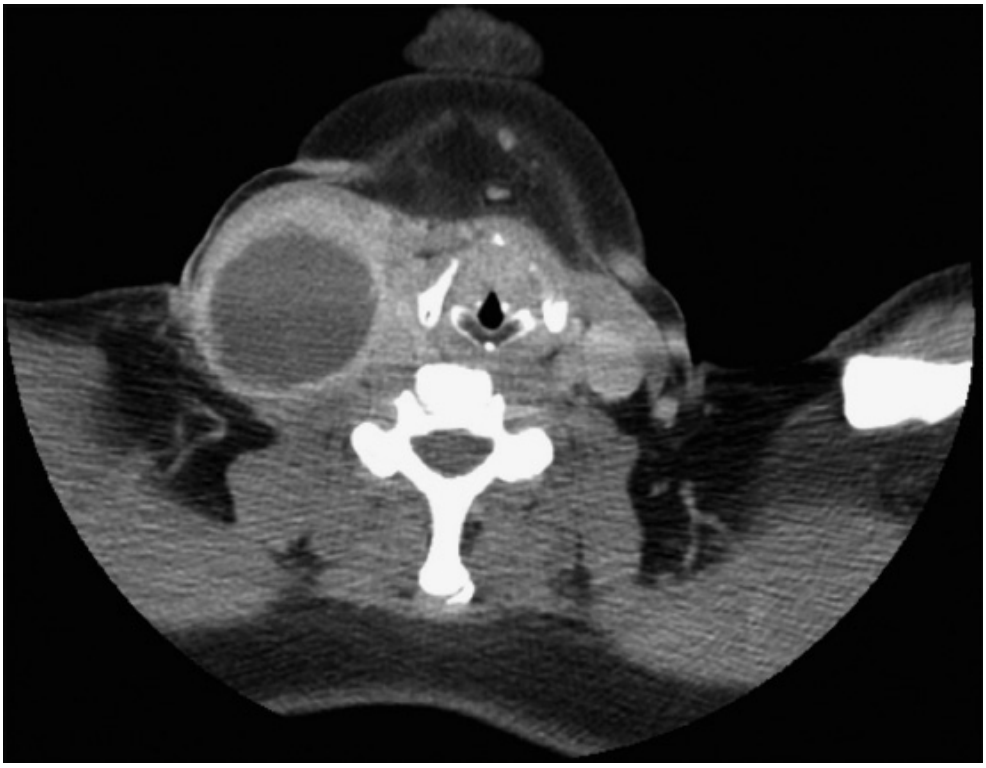


Figure 41.7 Axial CT neck with contrast shows a large cystic mass involving the right level III/IV neck. Image-guided FNA confirmed HPV-positive squamous cell carcinoma.

Algorithm 41.1 is a suggested approach to the adult with a lateral neck mass.

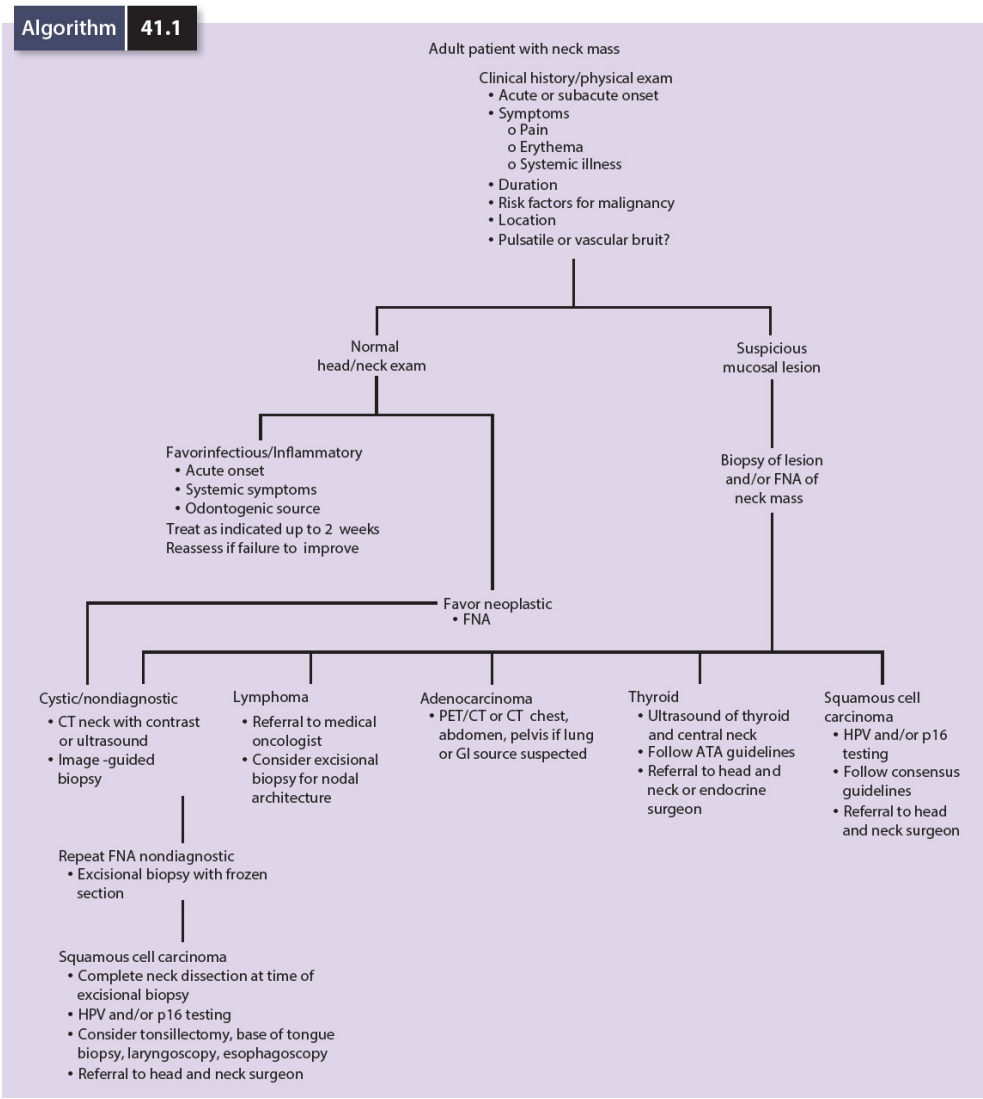
HEAD AND NECK NEOPLASMS

Whenever possible, patients with head and neck cancer should be referred to a multidisciplinary center with specialized head and neck surgeons, radiation oncologists, medical oncologists, dentists, pathologists, radiologists, speech therapists, and social workers. Both surgery and radiation may impact speech, swallowing, and taste, and anticipatory treatment of these consequences of treatment is critical.

Salivary Neoplasms

Salivary tumors include a diverse array of benign and malignant pathologies (**Table 41.4**). The parotid is the most commonly affected gland and ~80% of parotid tumors are benign. Pleomorphic adenoma, or benign mixed tumor, is the most common benign tumor. Warthin tumor, or papillary cystadenoma lymphomatosum, another common pathology noted predominantly in male smokers, may be bilateral and tends to locate in the tail of the parotid gland. These and other benign salivary tumors present as a painless firm mass of the affected gland, though those arising in the deep lobe of the gland or in the parapharyngeal space may grow quite large before they are noted clinically.[12–15]

Figure 41.8A,B demonstrates MRI characteristics of a pleomorphic adenoma on MRI.



Algorithm 41.1 Workup of a neck mass in an adult patient.

A salivary mass that presents with pain, rapid growth, or facial nerve weakness must prompt immediate suspicion for malignancy. There is an inverse relationship between size of the gland and rate of malignancy: ~20% of parotid tumors harbor malignancy, 50% for the submandibular gland, and as high as 86% for the sublingual gland. Mucoepidermoid carcinoma (MEC) is the most common malignant salivary tumor, followed by adenoid cystic carcinoma (ACC) and adenocarcinoma.[12] **Table 41.5** lists the American Joint Committee on Cancer (AJCC) T-staging for salivary cancer.[14]

FNA biopsy should be considered prior to surgery alongside imaging (contrast-enhanced CT or MRI). The surgeon should be aware that the specificity of FNA for neoplasia and malignancy is high, however the

sensitivity is lower.[16] That said, proper workup can direct the surgeon toward more aggressive surgery in the presence of known malignancy, avoid surgery in cases of lymphoma or inflammatory disease, and even to help counsel patients in the presence of benign tumors. FNA of the parotid demonstrating SCC indicates metastatic disease to parotid lymph nodes, and would further direct investigation to locate a primary skin cancer of the scalp or face.

Some benign tumors, like Warthin tumors, may be observed, while a pleomorphic adenoma should be excised due to the long-term risk of malignant transformation to carcinoma ex pleomorphic adenoma. The risk of this transformation is around 6%, and increases with time.[20] Superficial parotidectomy is typically adequate in these circumstances, taking care to dissect and preserve facial nerve branches.[17–19] Pleomorphic adenomas may have "tumor pseudopodia," thus resection with a margin of normal gland where possible is favored.[21] Often the tumor is sitting directly on nerve branches at its deep margin, however, and meticulous dissection to preserve the nerve and avoid tumor spillage is critical. Tumor spillage may lead to multifocal recurrence in the operative bed. Surgical salvage is recommended in these cases, but radiation may provide local control in multiply recurrent cases.

Table 41.4 Salivary Tumors

Benign	Malignant	Malignant Nonsalivary and Metastatic
Pleomorphic adenoma	Mucoepidermoid carcinoma	Lymphoma
Warthin tumor (papillary cystadenoma lymphomatosum)	Adenoid cystic carcinoma	Squamous cell carcinoma
Basal cell adenoma	Adenocarcinoma	Melanoma
Oncocytoma	Acinic cell carcinoma	
Hemangioma	Carcinoma ex-pleomorphic adenoma Salivary duct carcinoma	

Figure 41.9 demonstrates the steps performed in superficial parotidectomy with facial nerve dissection.

Total parotidectomy may be required in cases of malignancy, however, a diagnosis of malignancy may not be confirmed until final pathology; an en bloc resection of tumor with good margins is adequate in most small cancers.[19] Total parotidectomy is more challenging to perform en bloc with respect to the facial nerve, which should always preserved if functional or not grossly invaded by a pathology-confirmed malignant tumor. If nerve sacrifice is warranted, it should be immediately reconstructed with a nerve graft.

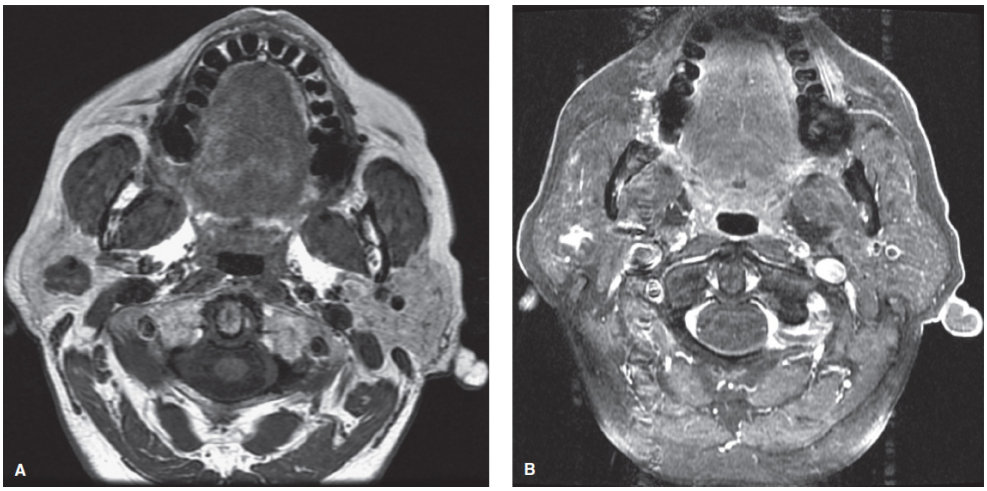


Figure 41.8 Precontrast (**A**) and postcontrast (**B**) T1 MRI demonstrate a lobulated, heterogeneous mass within the right parotid gland just posterior to the retromandibular vein, consistent with a pleomorphic adenoma.

Parotidectomy alone is adequate in low-grade malignancy (ACC and polymorphous low-grade adenocarcinoma), but in high-grade cancers (salivary duct carcinoma, high-grade MEC, most adenocarcinomas, and carcinoma ex-pleomorphic adenoma), the regional lymphatics must be addressed via ipsilateral neck dissection. Adjuvant radiation should be considered for stage III/IV disease, high-grade pathology, and perineural invasion.

Sinonasal Neoplasms

Sinonasal neoplasms are rare, and often present with nonspecific symptoms like unilateral nasal obstruction or drainage, epistaxis, or decreased smell. The most common pathology is benign inverted papilloma, but there are over 70 different pathologies that may arise in the paranasal sinuses, over half of which are malignant.[22] The maxillary sinus is the most common subsite, followed by the ethmoid, sphenoid, and frontal sinuses.[23]

Surgery is the standard of care for most sinonasal tumors, and is usually undertaken by a multidisciplinary surgical team that includes otolaryngology, neurosurgery, and ophthalmology depending on the extent of disease. Inverted papilloma is typically resected via endoscopic sinus surgery and requires drilling out of the site of tumor origin for an essential en bloc resection; this is to prevent recurrence as there is an ~10% malignant transformation rate to

SCC. SCC is the most common malignant sinonasal tumor (40% to 50%), followed by adenocarcinoma and ACC.[24–26] "Round blue cell" tumors are less common, but represent numerous different pathologies, including esthesioneuroblastoma, sinonasal undifferentiated carcinoma (SNUC), neuroendocrine carcinoma, small cell carcinoma, mucosal melanoma, lymphoma, and various sarcomas. As such, consultation with a head and neck pathologist is critical because high-grade pathologies (SNUC, small cell) tend to metastasize early and are also often treated with induction chemotherapy and radiation or concurrent chemoradiation over primary surgery. Sinonasal rhabdomyosarcoma, most frequently noted in the pediatric population, is also treated with primary or induction chemotherapy with radiation over initial surgery.[27,28]

Table 41.5 Staging of Major Salivary Gland Tumors

T1	Tumor ≤2 cm without extraparenchymal extension
T2	Tumor >2 cm but ≤4 cm without extraparenchymal extension
T3	Tumor >4 cm or with extraparenchymal extension
T4a	Any size tumor with involvement of skin, mandible, ear canal, or facial nerve
T4b	Any size tumor with carotid artery encasement or pterygoid plate/skull base invasion

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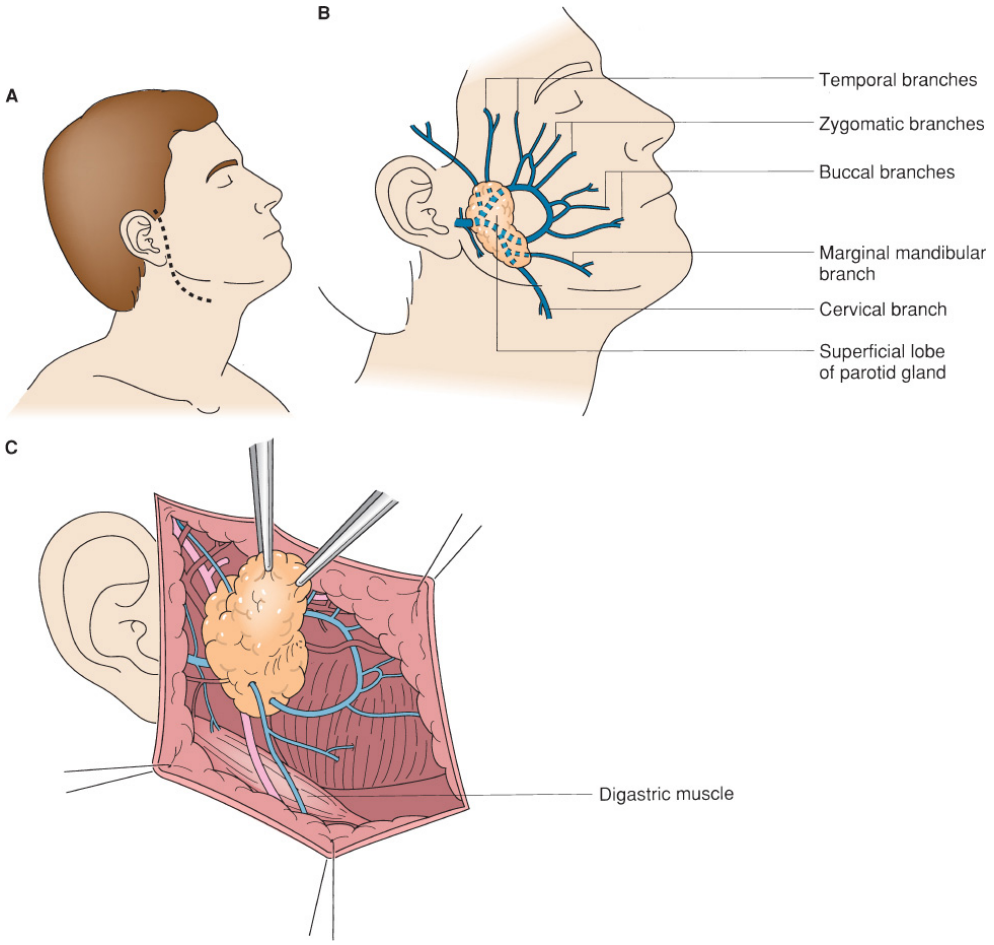
HEAD AND NECK SQUAMOUS CELL CARCINOMA

SCC is the most common malignancy of the upper aerodigestive tract. AJCC 8th edition TNM staging is provided in **Tables 41.6** to **41.8** for oral cavity, oropharynx, and larynx cancer, while **Tables 41.9A** and **41.9B** provide the new nodal staging that accounts for the prognostic differences of nodal disease in HPV-positive versus HPV-negative SCC.[14] Generally speaking, patients with AJCC stage I/II tumors are often considered for single-modality treatment, either primary surgery or primary radiation in most cases. Patients with stage III/IV require multimodality treatment, often including systemic therapy; as such, most patients will benefit from evaluation and treatment in a multidisciplinary head and neck cancer program.


A
B
Temporal branches
Zygomatic branches
Buccal branches
Marginal mandibular branch
Cervical branch
Superficial lobe of parotid gland
C
Digastric muscle

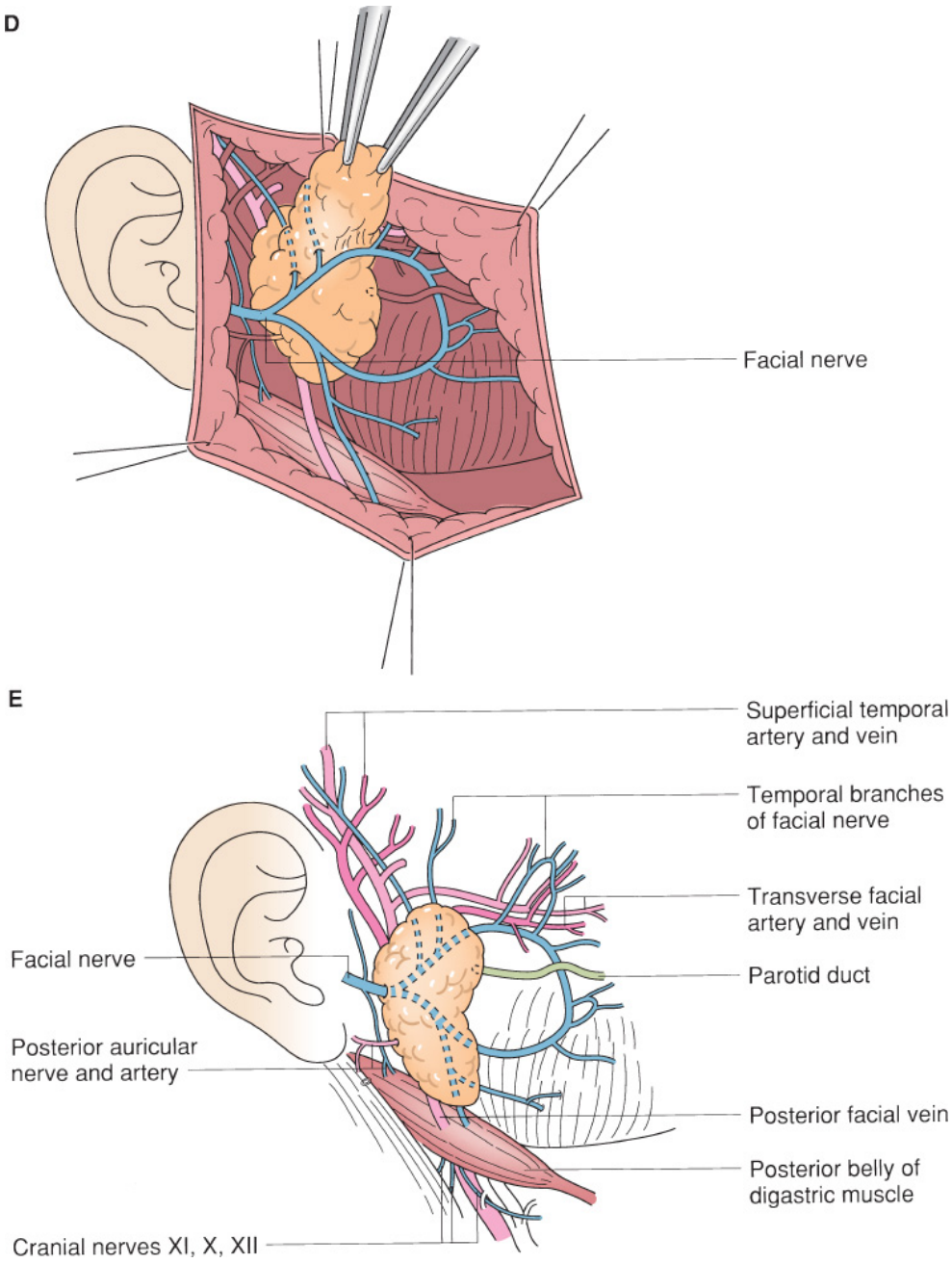


Figure 41.9 Superficial parotidectomy. **A:** Either a modified Blair incision or the cosmetically superior rhytidectomy incision may be employed. **B:** Branches of the facial nerve course between the superficial and deep lobes of the parotid. **C:** The main trunk of the facial nerve is located 3 to 4 mm deep and inferior to the tympanomastoid suture line and at the same level as the posterior belly of the digastric muscle. **D:** The nerve and its branches are then dissected distally, carefully reflecting the superficial lobe off of the nerve. **E:** Schematic representation of the relationship between the parotid and surrounding structures.

Oral Cavity

Cancers of the oral cavity should be considered for primary surgery to optimize oncologic outcomes and to avoid complications of definitive radiation or chemoradiation (i.e., osteoradionecrosis of 4 the mandible) whenever possible. Given the sensitive functional nature of the structures of the oral cavity, thoughtful reconstruction is as important as oncologically sound resection of malignancy for these patients to achieve quality survivorship. Microvascular free tissue reconstruction is a mainstay of oral cavity malignancy surgery as it restores structure and function of the oral cavity to maintain speech and swallowing.

Table 41.6 Lip and Oral Cavity Cancer Staging

T1	Tumor ≤2 cm with DOI ≤5 mm
T2	Tumor ≤2 cm with DOI >5 mm **OR** tumor >2 cm and ≤4 cm with DOI ≤10 mm
T3	Tumor >2 cm and ≤4 cm with DOI >10 mm **OR** tumor >4 cm with DOI ≤10 mm
T4a	Tumor >4 cm with DOI >10 mm **OR** tumor invades cortical bone or skin of face
T4b	Tumor involves masticator space, pterygoid plate or skull base, and/or encases internal carotid artery

DOI, depth of invasion, NOT tumor thickness.

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Table 41.7A HPV-Positive (p16+) Oropharyngeal Cancer Staging	
T0	No primary tumor identified
T1	Tumor ≤2 cm
T2	Tumor >2 cm and ≤4 cm
T3	Tumor >4 cm or extension to lingual surface epiglottis
T4	Tumor invades larynx, extrinsic muscles of tongue, medial pterygoid muscle, mandible, hard palate or beyond

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Table 41.7B HPV-Negative (p16−) Oropharyngeal Cancer Staging	
T1	Tumor ≤2 cm
T2	Tumor >2 cm and ≤4 cm
T3	Tumor >4 cm or extension to lingual surface epiglottis
T4a	Tumor invades larynx, extrinsic muscles of tongue, medial pterygoid muscle, mandible, hard palate
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, nasopharynx, skull base or encases internal carotid artery

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Table 41.8 Larynx Staging

Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside supraglottis (base of tongue, vallecular, medial wall piriform) without fixation of larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: pre-epiglottic, paraglottic space, postcricoid area, and/or inner cortex of thyroid cartilage
T4a	Tumor invades outer cortex of thyroid cartilage and/or invades tissues beyond larynx (trachea, soft tissues, neck including deep extrinsic tongue muscles, strap muscles, thyroid, esophagus)
T4b	Tumor invades prevertebral space, mediastinal structures, or encases carotid artery
Glottis	
T1a	Tumor limited to one vocal cord, with normal mobility
T1b	Tumor involves both vocal cords, with normal mobility

T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of thyroid cartilage
T4a	Tumor invades through outer cortex of thyroid cartilage and/or invades tissues beyond larynx (trachea, cricoid, soft tissues, neck including deep extrinsic tongue muscles, strap muscles, thyroid, esophagus)
T4b	Tumor invades prevertebral space, mediastinal structures, or encases carotid artery

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Table 41.9A Clinical Nodal Staging for Salivary, Oral Cavity, HPV-Negative Oropharynx, Hypopharynx, and Larynx Cancers	
N0	No regional lymph node metastases
N1	Single ipsilateral lymph node metastasis ≤3 cm and ENE (−)
N2a	Single ipsilateral lymph node metastasis >3 cm and ≤6 cm and ENE (−)
N2b	Multiple ipsilateral lymph node metastases ≤6 cm and ENE (−)
N2c	Bilateral or contralateral lymph node metastases ≤6 cm and ENE (−)
N3a	Metastasis in a lymph node >6 cm and ENE (−)
N3b	Metastasis in any node(s) with clinically overt ENE (+)

ENE, extranodal extension.

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Lip carcinomas pose both functional and cosmetic concerns. Lower lip cancer is more common than upper lip cancer and is most often caused by sun exposure; it has a very low incidence of occult cervical metastases (<15%) thus the bilateral necks may be observed in cT1–2 N0 disease as noted in consensus guidelines. The upper lip has unilateral nodal drainage but a higher incidence of occult nodal involvement compared to cancers of the lower lip. Reconstruction of the lip ranges from primary closure (after wedge resection of the primary) to local advancement or rotational flaps to free flap reconstruction for larger and more complex lip defects.[30]

Depth of invasion (DOI) in oral tongue and floor of mouth cancer is important for prognosis, so much so that the AJCC 8th edition added DOI to

the staging system (**Table 41.6**). Thin tumors (<2 mm) have less regional lymphatic metastatic potential compared to thick tumors (>8 to 9 mm). Many head and neck surgeons recommend elective neck dissection for patients with T1 tumors and DOI >4 mm; sentinel node many be considered in experienced hands for tumors 2 to 4 mm DOI.[31,32] T1–T2 tongue tumors may be resected and closed primarily or with a skin or acellular dermis graft; larger defects and those involving the floor of the mouth require microvascular reconstruction to restore the tongue mound and facilitate recovery of articulation and swallowing. Similarly, small floor of mouth resections may be closed primarily or skin grafted, but free tissue is needed for larger defects, particularly when simultaneous neck dissection is performed.

Table 41.9B Clinical and Pathologic Nodal Staging for HPV-Positive Oropharynx Cancer

cN0	No regional lymph node metastases
cN1	One or more ipsilateral nodes, none >6 cm
cN2	Contralateral or bilateral nodes, none >6 cm
cN3	Lymph node(s) >6 cm
pN0	No regional lymph node metastases
pN1	Metastasis in four or fewer nodes
pN2	Metastasis in more than four nodes

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SCC of the retromolar trigone and buccal mucosa/buccal space often demonstrates early involvement of the muscles of mastication. Pterygoid or masseter invasion causes trismus and pain, and may make preoperative examination a challenge for both patient and surgeon. Marginal mandibulectomy is necessary when a retromolar trigone tumor is attached to mandibular periosteum. Composite resection of a segment of mandible

should be performed when tumor invades bone (noted clinically or on preoperative CT) or when tumor surrounds a tooth root. Osteocutaneous free tissue reconstruction is the gold standard for segmental defects. While an unreconstructed lateral mandible defect ("mandibular swing") causes malocclusion and cosmetic asymmetry, failure to reconstitute the anterior mandibular arch leads to swallowing and airway compromise; once known as the "Andy Gump deformity," loss of the anterior mandibular arch causes the lip and chin to migrate posteriorly and inferiorly into the neck, releases the tongue posteriorly, and thus adversely impacts oral competence, deglutition, speech, and airway. Tempting as it may be to place a titanium reconstruction plate across a segmental defect of the mandible, this should be avoided due to inevitable delayed hardware extrusion that occurs with mere plating and soft tissue coverage alone. This reinforces the need to refer complex oral cavity cancer patients to a center where microvascular free tissue reconstructive surgery of the head and neck is available.

Nasopharynx

Nasopharyngeal carcinoma (NPC) is endemic to certain parts of Asia, particularly southern China. The most important causal factor is Epstein–Barr virus (EBV).[33–35] The World Health Organization classifies NPC into three types: keratinizing SCC (I), nonkeratinizing SCC (II), and undifferentiated carcinoma (III).[22] Endemic NPC is 95% type III, which is associated with the best prognosis, and types I and II are more common in nonendemic areas.

NPC most commonly presents with bulky cervical adenopathy. Primary tumors do not typically cause symptoms until quite advanced. Unilateral otitis media in an adult should prompt a scope examination of the nasopharynx as this may be due to Eustachian tube obstruction by tumor. More advanced tumors may present with nasal obstruction or changes in speech due to palatal involvement. Cranial neuropathies are a hallmark of skull base invasion. Interestingly, large-volume lymphadenopathy alone is less prognostic in NPC than in other head and neck malignancies; it is the involvement of the supraclavicular nodes that portends a worse prognosis. This is reflected in a separate nodal staging paradigm for NPC.[14]

Endoscopic biopsy of the nasopharynx or FNA of lymph nodes confirms NPC; staining for EBV is also performed, and is key to making the diagnosis from a neck node. Imaging should include contrast-enhanced CT and MRI to evaluate the skull base and infratemporal fossa. PET/CT is also obtained for complete staging and planning of radiation fields. The primary treatment for NPC is chemoradiation which has been shown to be superior to radiation alone in advanced disease.[36,37] Surgery is reserved for recurrent/persistent localized disease in select cases; small tumors may be amenable to an endoscopic approach, but may require an open transfacial approach with maxillary disarticulation for adequate exposure and protection of the carotid artery.[38–40]

Oropharynx

The overall incidence of head and neck SCC in the United States has decreased in concert with the decrease in tobacco abuse in recent decades; a notable exception to this trend is in cancers of the oropharynx. OPC incidence has risen over the past two decades due to the increase in HPV transmission and chronic infection. HPV, particularly subtypes 16 and 18, appears to be responsible for approximately 80% of OPC.[41] Interestingly, HPV-associated OPC is associated with a more favorable prognosis compared to the tobacco-related "classic" HPV-negative cancers of the head and neck, even in advanced local and regional disease states.[42,43] This difference in prognosis led to changes in the AJCC staging system that account for the differences between HPV-positive and HPV-negative tumors (**Tables 41.7A and 41.7B**). These include the findings that nodal metastases are less impactful on survival for HPV-positive OPC patients, and extranodal extension of tumor does not appear to impart the same poor prognosis as in HPV-negative SCC disease (**Tables 41.9A and 41.9B**).[14]

T1 and T2 tumors of the palatine tonsils are typically amenable to transoral resection, but radiation and chemoradiation have been used since the 1990s to treat less accessible (i.e., lingual tonsil) and larger tumors due to equivalent effectiveness and decreased morbidity and mortality compared to open surgical approaches (i.e., mandibulotomy/transmandibular approach, transcervical and transpharyngeal approaches).[44] Both the increasing prevalence of HPV-positive OPC patients with favorable prognoses and the

advent of transoral, minimally invasive approaches to the oropharynx, have led to increased interest in primary surgery to avoid the long-term sequelae of chemotherapy and even radiation in these younger patients. Transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) have emerged in the past 10 to 15 years as viable treatments for T1–T3 OPC with acceptable oncologic and functional outcomes.[45–48]

Hypopharynx

The hypopharynx is the area between the oropharynx and cervical esophagus. Cancers of the hypopharynx usually present in advanced stages as symptoms are delayed until the tumor is large enough to impede swallowing or invade the larynx. Patients report gradually increasing dysphagia, hoarseness, neck mass, and referred otalgia via Jacobson and Arnold nerves (branches of cranial nerves IX and X, respectively).

Hypopharyngeal SCC has the poorest prognosis of the head and neck subsites, with an overall survival of only 30% to 35% in early-stage cancer,[49] and a rate of distant metastases of up to 60%.[50] Surgical resection usually requires total laryngectomy with partial or complete pharyngectomy due to the intimate proximity of the piriform sinuses/postcricoid mucosa and the larynx; as such primary chemoradiation approaches predominate initial treatment algorithms. Small tumors of the posterior pharyngeal wall may be amenable to resection via transoral laser or robotic techniques.[51,52] Due to the rich lymphatics of the hypopharynx, bilateral neck treatment is required for regional control. Recurrent hypopharyngeal SCC following chemoradiation typically requires salvage total laryngopharyngectomy; free tissue reconstruction is critical to reconstitute the pharynx, either with a tubed fasciocutaneous free flap or an enteric flap such as the gastro-omental free tissue transplant.

Larynx

The glottic larynx, composed primarily by the true vocal folds, is the most common site of origin of laryngeal SCC, involved, followed by the supraglottis (tip of the epiglottis to the laryngeal ventricle), and subglottis (just below the true vocal folds to the inferior border of the cricoid

cartilage). The glottis consists of nonkeratinizing stratified squamous epithelium overlying a complex lamina propria over the thyroarytenoid ligament and muscle. Early glottic tumors have a low rate of metastasis to regional lymphatics due to the investing fibroelastic structure of the conus elasticus and quadrangular membrane. By way of contrast, supraglottic and subglottic are known for their risk of nodal metastasis even in early disease.

Early (T1–T2) glottis cancers may be managed with single modality treatment—either radiation or endolaryngeal surgery—with long-term control rates of approximately 90% for T1 and 75% for T2 tumors. Surgical treatment is performed via transoral resection, often using CO_2 laser. Surgery has no statistically significant difference in local control, overall or disease-free survival compared to narrow-field radiation, although laryngeal preservation rates appear to be higher in surgical patients based on retrospective studies.[53–55] Supraglottic carcinoma has a high incidence of occult nodal metastasis and is an anatomic subsite with bilateral lymphatic drainage. Thus for both surgical and radiation based treatments of the supraglottis, bilateral level 2–4 neck nodes must be addressed alongside the primary tumor.

Advanced laryngeal cancer (T3–T4, N positive) requires multimodality treatment. This may be primary surgery followed by radiation or concurrent chemoradiation. The landmark "VA Larynx Trial" demonstrated equivalent survival between surgery followed by radiation versus induction chemotherapy followed by radiation, with 64% laryngeal preservation in the nonsurgical arm.[56] The RTOG 91–11 trial demonstrated the superiority of concurrent chemoradiation compared to radiation alone or after induction chemotherapy for laryngectomy-free survival and local control.[57] However, the 10-year follow-up to this study did not demonstrate an advantage of concurrent chemoradiation versus induction chemotherapy and radiation in overall survival, local control, or overall laryngeal preservation.[58]

Surgical treatment for advanced-stage laryngeal cancer is typically total laryngectomy with bilateral neck dissections. Speech is restored via esophageal speech training, tracheoesophageal puncture with prosthesis, or electrolarynx. These patients are permanent neck breathers and education for patients and caregivers on the implications of a separated airway and digestive tract is critical to ongoing safety. Open partial laryngectomy,

including supraglottic or supracricoid partial laryngectomy, may be used in selected cases based on tumor anatomy but has long-term impact on swallowing and airway protection that requires both surgical and speech language pathology expertise to manage.

While the aforementioned chemoradiation trials have led to the term "laryngeal preservation" treatment, there are instances where caution should be used when considering this approach. High-dose radiation may cause chondroradionecrosis and osteoradionecrosis, and it is less effective in tumor-invading cartilage and bone. As such it is felt to be inferior to total laryngectomy in T4 laryngeal cancers[59]; moreover, even if the tumor is eradicated, the secondary and long-term changes from chemoradiation may render the larynx dysfunctional. Tumors with extensive paraglottic spread and vocal cord fixation may present with airway compromise necessitating tracheostomy and dysphagia requiring gastrostomy tube placement. These patients may not regain vocal fold mobility posttreatment, and are likely to remain tracheostomy-dependent postradiation.[60] Permanent gastrostomy tube is also a risk due to dysfunctional larynx after chemoradiation.

NECK DISSECTION

Given the risk of nodal metastasis in SCC of the head and neck, even in early T stages for many subsites, decision making regarding treatment of the neck is critical. In most cases, the cervical lymph nodes are treated via the same modality as the primary tumor. In the example of oral cavity cancer, neck dissection is performed alongside primary tumor extirpation and reconstruction. In the same vein, the radiation oncologist contours their treatment fields to incorporate draining lymphatic basins in oropharyngeal or laryngeal cancers selected for definitive radiation. Elective neck dissection or elective neck radiation is performed in the N0 neck when the risk of occult nodal metastasis is greater than 15%.

First described by George Crile in 1906, the radical neck dissection includes comprehensive removal of cervical lymphatics with sacrifice of the sternocleidomastoid (SCM) muscle, internal jugular vein, and spinal accessory nerve. The modified radical neck dissection removes levels I to V nodes with preservation of one or more of the aforementioned three

structures. Eventually, head and neck surgeons migrated to the concept of selective oncologic lymphadenectomy, based on tumor subsite drainage patterns, with decreased morbidity.[61] Known as selective neck dissection, careful but comprehensive removal of the at-risk nodal basins with preservation of normal structure is now the standard of care.[62] "Node plucking" or random sampling of neck nodes is inappropriate and should be avoided.

Head and neck patterns of lymphatic drainage are well described by Lindberg and Shah, and these studies allow for thoughtful subsite-based surgical planning.[63,64] As a general rule, oral cavity cancers require dissection of levels I–III, and possibly IV depending on nodal burden, while dissection of levels II to IV is performed for cancers of the oropharynx, larynx, and hypopharynx (**Fig. 41.10**). Level V is rarely involved except in NPC and some advanced skin cancers. Sentinel lymph node biopsy may be considered in early T-stage, clinically N0 oral cavity cancer, but does require technical experience, and one should be prepared to complete the neck dissection at the time of biopsy[65]; this technique is under investigation in OPC as well.

The boundaries of the "lateral neck dissection," encompassing levels II to IV, extend from the posterior belly of the digastric muscle's insertion on the mastoid where it meets with the SCM superiorly to the plane of the clavicle inferiorly, and from the posterior edge of the SCM to the strap muscles anteriorly. The depth of the dissection is defined by the cervical sensory rootlets in level III and the deep layer of deep cervical fascia that invests the deep musculature in level II (levator scapulae) and level IV (anterior and middle scalenes). Care should be taken to preserve the deep layer of deep cervical fascia in order to protect the phrenic nerve and brachial plexus. As the dissection completes inferiorly in level IV, attention must be paid to controlling the lymphatics as they course towards the thoracic duct on the left and the lymphatic duct on the right. When level IB is dissected, the marginal mandibular nerve must be identified and preserved to allow for safe resection of the submandibular gland and perifacial nodes. Level V neck dissection requires identification of the spinal accessory nerve just above Erb's point, followed by meticulous dissection to its entry into the trapezius. The nodes are then removed from the trapezius superiorly, the posterior edge

of the SCM anteriorly and the clavicle inferiorly, all while preserving the accessory nerve.

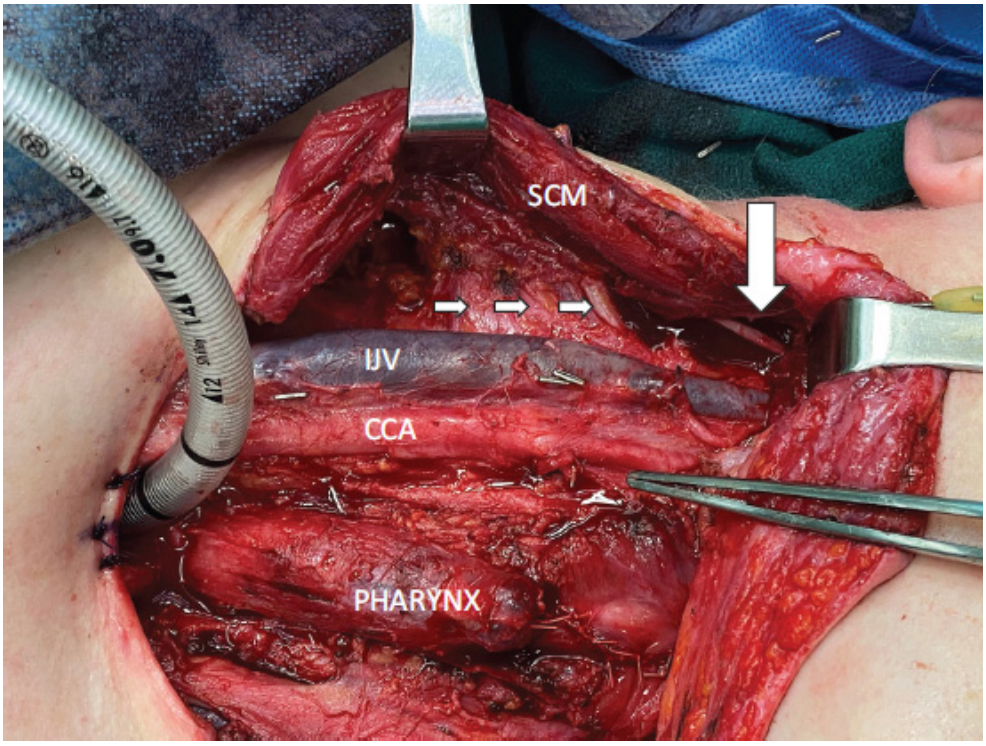

Figure 41.10 Intraoperative photograph demonstrating the right neck after performance of a selective, level II-IV neck dissection. Selective neck dissection is generally a low-morbidity procedure. Vital structures such as the internal jugular vein (IJV), common carotid artery (CCA), and spinal accessory nerve (*large arrow*) are carefully preserved. Also preserved and noted here are the sternocleidomastoid muscle (SCM), and cervical sensory rootlets (*small arrows*). The forceps is highlighting the external carotid artery. This patient also underwent laryngectomy for laryngeal cancer; the endotracheal tube is positioned in the permanent tracheostomy and the pharyngeal reconstruction is noted superior to the stoma (PHARYNX).

Table 41.10 Complications of Head and Neck Surgeries
Tonsillectomy/Adenoidectomy
Hemorrhage
Velopharyngeal insufficiency
Lingual neuropraxia
Endoscopic Sinus Surgery
Intranasal adhesions
Hyposmia
Epistaxis
Orbital injury/hematoma
Cerebrospinal fluid leak
Internal carotid artery injury
Parotidectomy
Great auricular nerve injury
Hematoma/seroma
Frey syndrome (gustatory facial sweating)
Facial nerve injury
Submandibular Gland Removal
Hematoma/seroma
Marginal mandibular nerve injury
Lingual nerve injury
Neck Dissection
Spinal accessory nerve injury
Marginal mandibular nerve injury
Hypoglossal nerve injury
Great vessel injury
Chyle leak
Total Laryngectomy
Pharyngocutaneous fistula
Parathyroid injury with hypocalcemia
Hypoglossal nerve injury
Esophageal stricture

COMPLICATIONS OF HEAD AND NECK SURGERY

Table 41.10 lists both common and rare complications of various head and neck procedures. Knowledge of these potential adverse outcomes, avoidance thereof, and disclosure of risk to patients during informed consent is crucial.

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Section D: ESOPHAGUS

42

Esophageal Anatomy and Physiology and Gastroesophageal Reflux Disease

Yulia Zak, Micaela Esquivel, and Mary T. Hawn

Key Points

1. Esophageal anatomy: the cervical, thoracic, and abdominal esophagus each have distinct physiologic and pathologic differences.
2. The three layers of the esophageal wall: mucosa, submucosa, and muscularis propria. There is no serosa of the esophagus.
3. During a swallow, the lower esophageal sphincter (LES) relaxes at the initiation of the swallow and remains open until the peristaltic waves passes down through the body and through the LES.
4. The LES retains its competence as a barrier to gastric reflux by three factors: length, resting pressure, and position.
5. Diagnostic modalities of the esophagus include: endoscopy, fluoroscopy, manometry, ambulatory pH monitoring, and impedance planimetry.
6. Ambulatory pH monitoring remains the gold standard for confirming gastroesophageal reflux.
7. Endoluminal functional lumen imaging probe (EndoFLIP) is an impedance planimetry system used to evaluate real-time pressure, diameter, and distensibility of the esophagus and gastrointestinal sphincters.
8. Barrett esophagus is defined as having the presence of both endoscopic mucosal changes and microscopic findings of cardiac mucosa with goblet cells or intestinal metaplasia.
9. Preoperative functional assessment of the esophagus and LES are pivotal to determining which type of antireflux operation is most appropriate.
10. Surgical treatment options for gastroesophageal reflux disease (GERD) include total and partial fundoplication repair and magnetic sphincter augmentation. Concurrent hiatal hernia repair must be performed.
11. Two main endoscopic approaches for treating GERD include the Stretta procedure and transoral incisionless fundoplication (TIF

2.0).

ESOPHAGEAL ANATOMY AND FUNCTION

1 The esophagus is an approximately 25- to 30-cm muscular tube that connects the pharynx to the stomach. It starts at cricopharyngeus or upper esophageal sphincter (EUS) and travels from the superior mediastinum to the posterior mediastinum, ending at the lower esophageal sphincter (LES) as it enters to stomach (**Fig. 42.1**). The esophagus has specific anatomical relationships to critical structures and organs within the mediastinum, and requires a detailed knowledge to these relationships to not only workup esophageal pathology, but to also manage and expose the esophagus intraoperatively. The cervical, thoracic, and abdominal esophagus each have distinct physiologic and pathologic differences.

Cervical Esophagus

The cervical esophagus begins just below the cricopharyngeus muscle and is an apparent continuation of the inferior constrictor muscle of the pharynx. The cervical esophagus is the first 3 to 5 cm of the esophagus. A Zenker diverticulum occurs in the cervical esophagus at a natural area of weakening at Killian triangle. This is the space between the posterior left and right inferior constrictor muscles and immediately above the cricopharyngeus muscle (**Fig. 42.2**). The carotid sheaths lie laterally, and the recurrent laryngeal nerves lie in the grooves between the trachea and esophagus, important landmarks for thyroid and parathyroid operations. The cervical esophagus is more frequently approached surgically from the left due to the more variable course of the right recurrent laryngeal nerve. The trachea and larynx are immediately anterior to the cervical esophagus, and posteriorly is the prevertebral space, with the cervical esophagus immediately anterior to the vertebral bodies. The cervical esophagus passes from the retropharyngeal space superiorly to the posterior mediastinum superiorly, allowing mediastinitis from oropharyngeal infections. When evaluating x-ray or CT

imaging, the cervical esophagus is located from C6 to the lower border of T1.

Thoracic Esophagus

The thoracic esophagus begins at the thoracic inlet and is approximately 18 to 20 cm long (**Fig. 42.1**). In the upper thorax the esophagus is immediately posterior to the trachea, and just above the level of the tracheal bifurcation the esophagus lies to the right of the aortic arch and descending aorta. It then courses to the left as it passes behind the tracheal bifurcation and left main bronchus. The esophagus remains on the left in the lower thorax as it passes through the diaphragmatic hiatus. The thoracic esophagus can be constricted as it passes behind the aortic arch and left mainstem bronchus. The thoracic duct and azygos vein are both closely related to the esophagus and require particular consideration during esophagectomy (see Chapter 42).

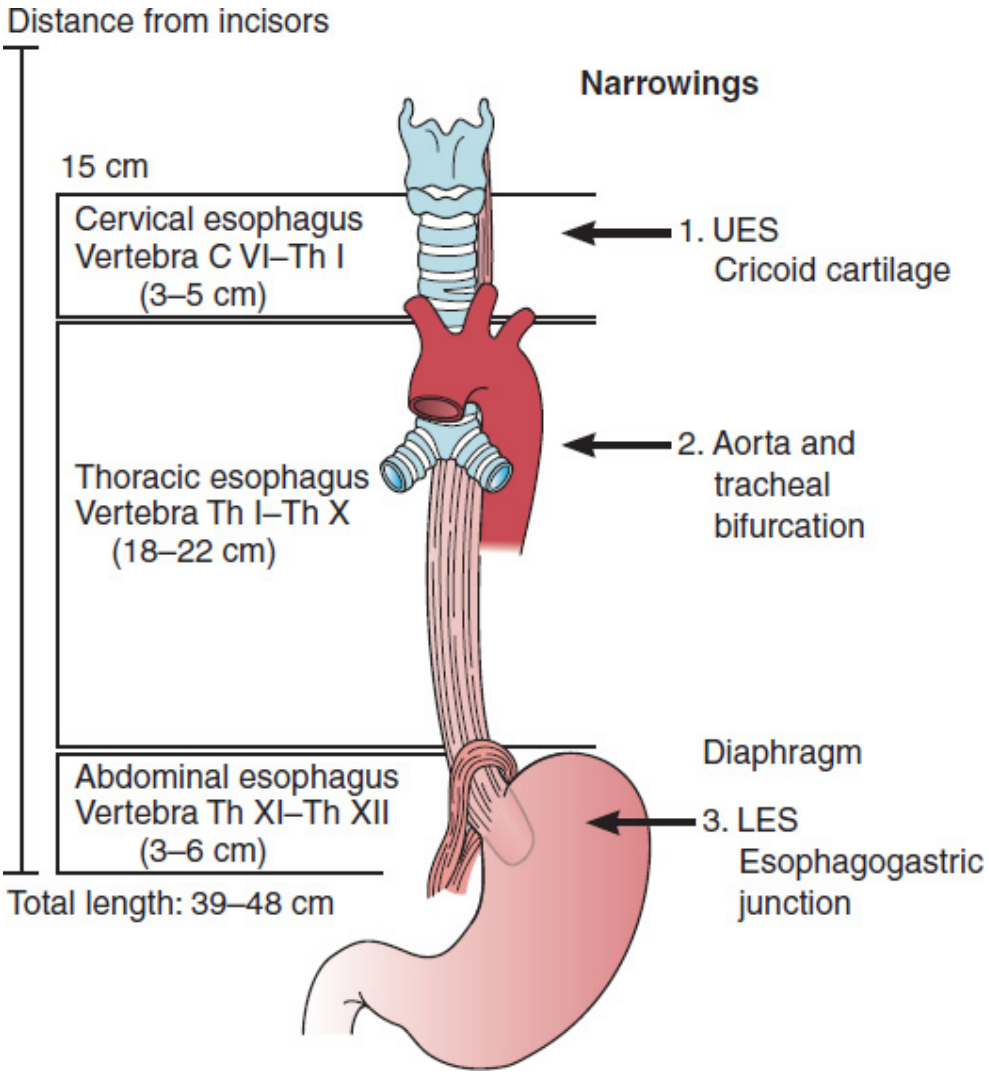


Figure 42.1 Anatomy of the esophagus.

Abdominal Esophagus

The abdominal esophagus starts at the diaphragmatic hiatus is approximately 3 to 6 cm in length and consists of the abdominal portion of the LES. The phrenoesophageal membrane surrounds this section of the esophagus circumferentially and courses to approximately 1 to 2 cm above the level of the hiatus at its upper leaf. Its lower leaf merges with the serosa of the stomach, and in this area there is a notable fat pad, marking the location of the gastroesophageal junction (GEJ) (**Fig. 42.3**).

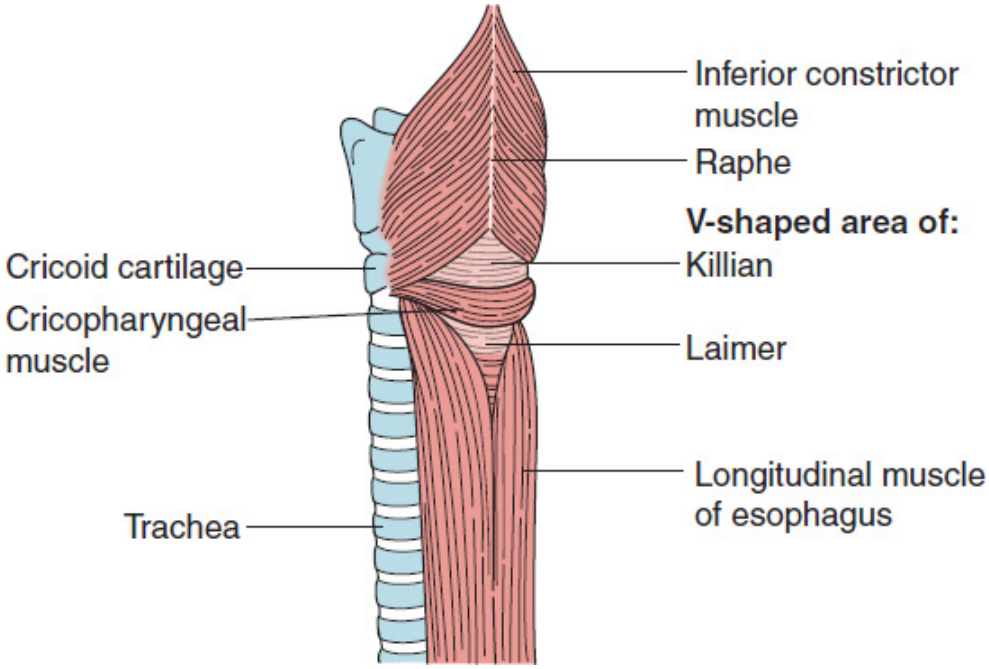


Figure 42.2 Posterior view of cervical esophagus.

The LES is a high pressure zone about 3 to 4 cm in length at the distal esophagus.[1] The LES has no visible macroscopic appearance changes on the inner mucosal lining or the outer surface of the esophagus. The left and right crura form the esophageal hiatus, and together they form a "sling" of diaphragmatic skeletal muscle around the esophagus.

These muscles originate from tendinous bands attached to the anterolateral surface of the first lumbar vertebra (**Fig. 42.4**). The median arcuate ligament, a tendinous arch, lies immediately anterior to the aorta, and attaches the crura posterior to the esophagus.

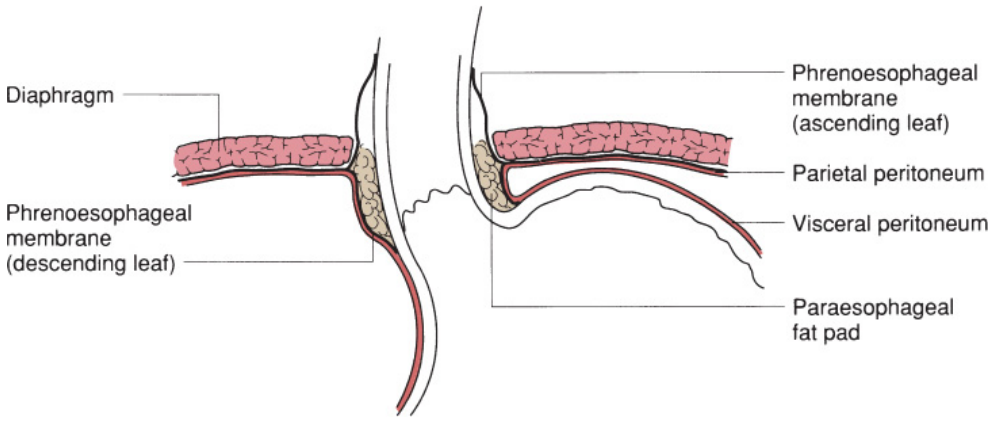


Figure 42.3 Anatomy of the esophageal hiatus and relationship to the phrenoesophageal membrane.

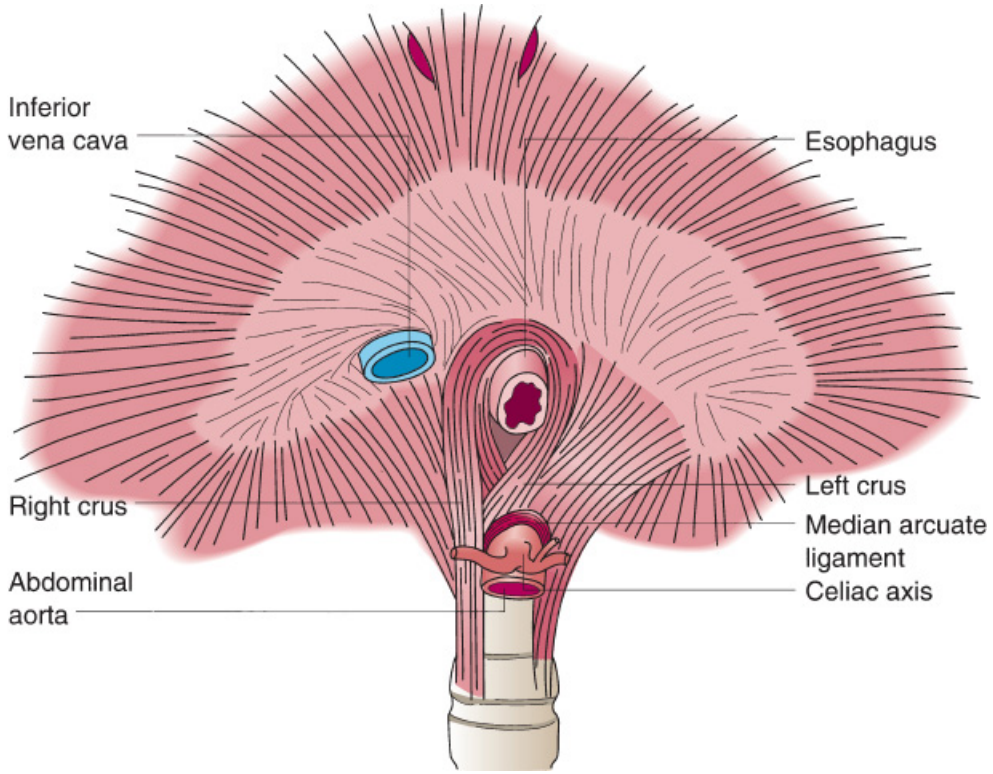


Figure 42.4 Inferior view of diaphragm and anatomy of the esophageal hiatus.

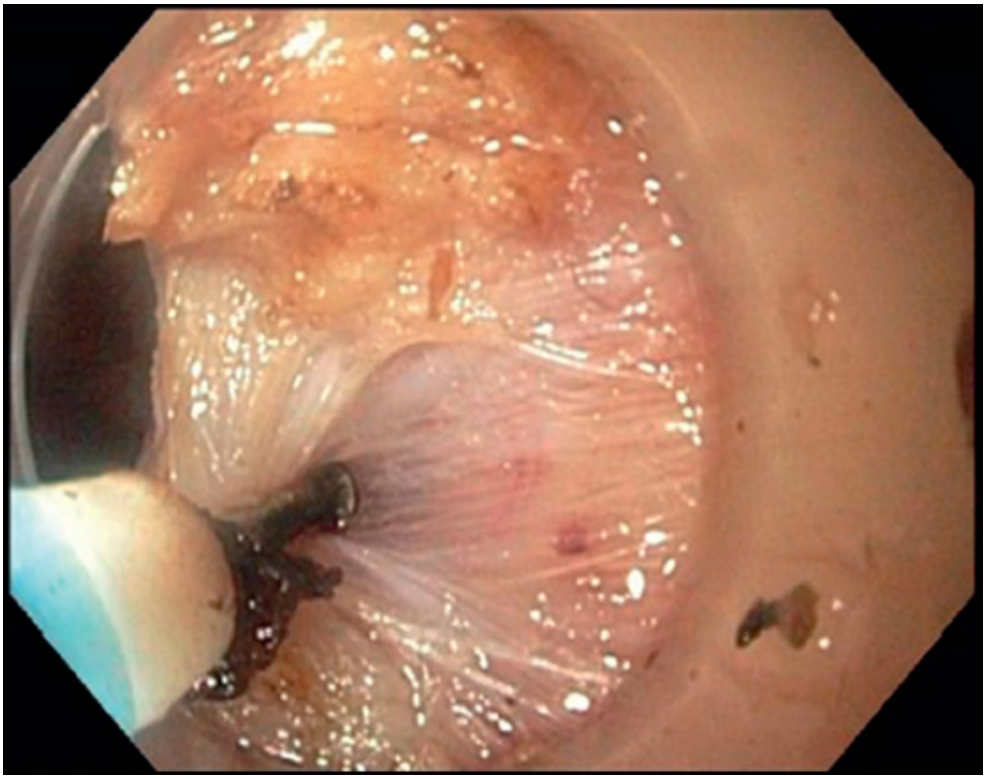


Figure 42.5 Endoscopic view of esophageal muscle layers during a peroral endoscopic myotomy (POEM) for achalasia. The endoscopic knife is lifting and cutting the circumferential circular muscle fibers, leaving the longitudinal muscle fibers intact.

Structure of the Esophageal Wall and Mucosa

2 The mucosa, submucosa, and muscularis propria are the three principal layers of the esophageal wall. In contrast to the rest of the gastrointestinal tract, there is no serosal layer, making the mucosa the strength layer of the esophagus. The mucosal layer is composed of nonkeratinized stratified squamous epithelium. The muscularis mucosa is located immediately below the basement membrane and above the submucosa. Tumors that penetrate this layer and into the submucosa carry a higher likelihood of lymph node metastases.[2] The submucosa contains the extensive lymphatic plexus throughout the esophagus, with collecting branches that penetrate the muscularis propria to connect with the thoracic duct and regional lymph nodes. This lymphatic web is the reason esophageal cancers can spread longitudinally and produce skip metastases.

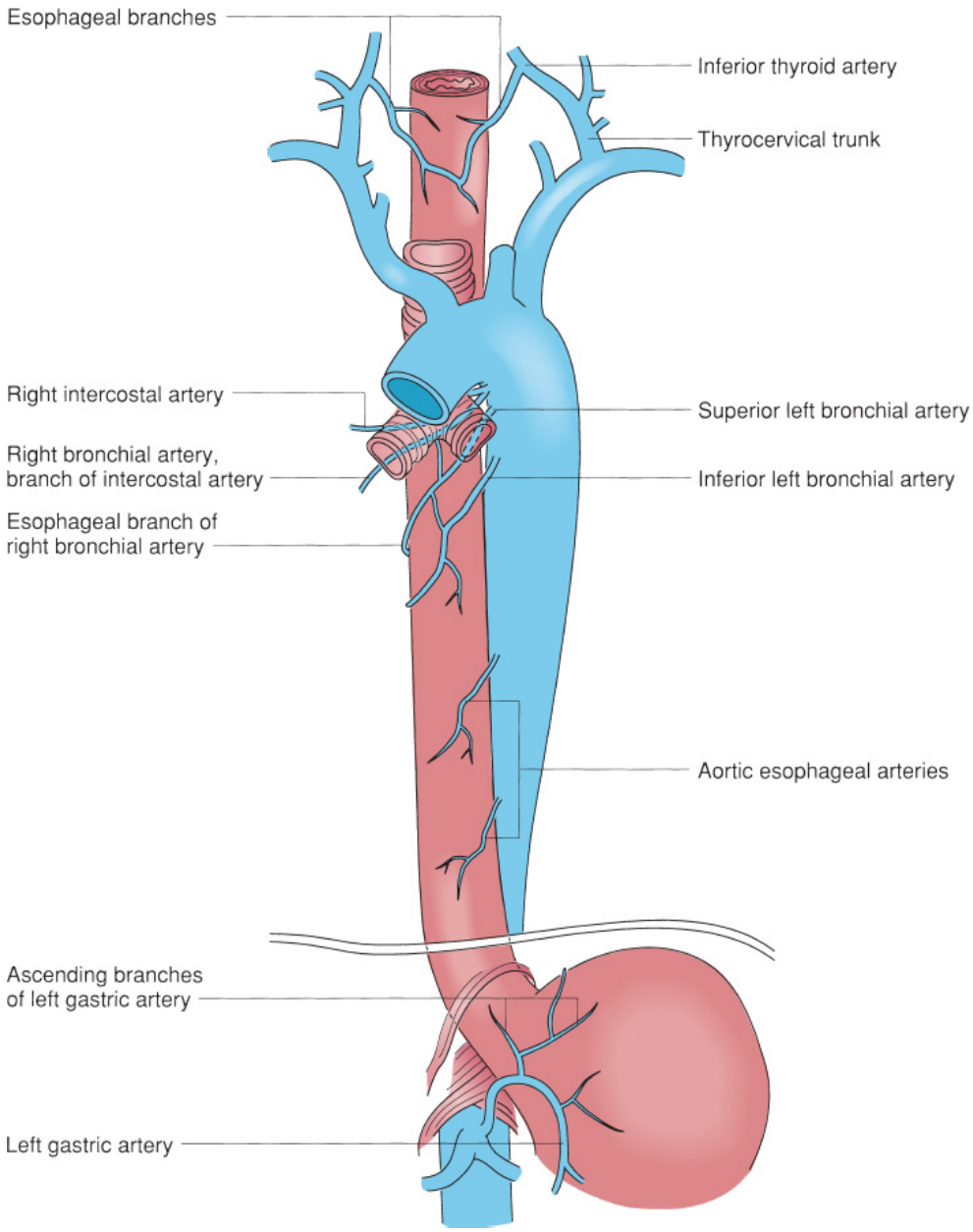


Figure 42.6 Arterial anatomy of the esophagus.

Intramucosal tumors have a rate of regional lymph node metastases of <5%, compared to 20% to 50% for submucosal tumors.[3] Additionally, the mucous glands of the esophagus are also located in the submucosal layer and drain into the esophageal lumen. The muscularis propria has an outer longitudinal muscle layer and a thicker inner circular muscle layer, composed of striated muscle in the uppermost portion that transitions to smooth muscle near the junction of the upper and middle third of the

esophagus. Both the muscle layers have a spiraling orientation, with the longitudinal rotating nearly 90 degrees as it courses down to the stomach (**Fig. 42.5**). This organization of the two muscle layers allows for the esophageal waves of peristalsis.

Blood Supply, Lymphatics, and Innervation

The cervical, thoracic, and abdominal portions of the esophagus each have a specific blood supply (**Fig. 42.6**):

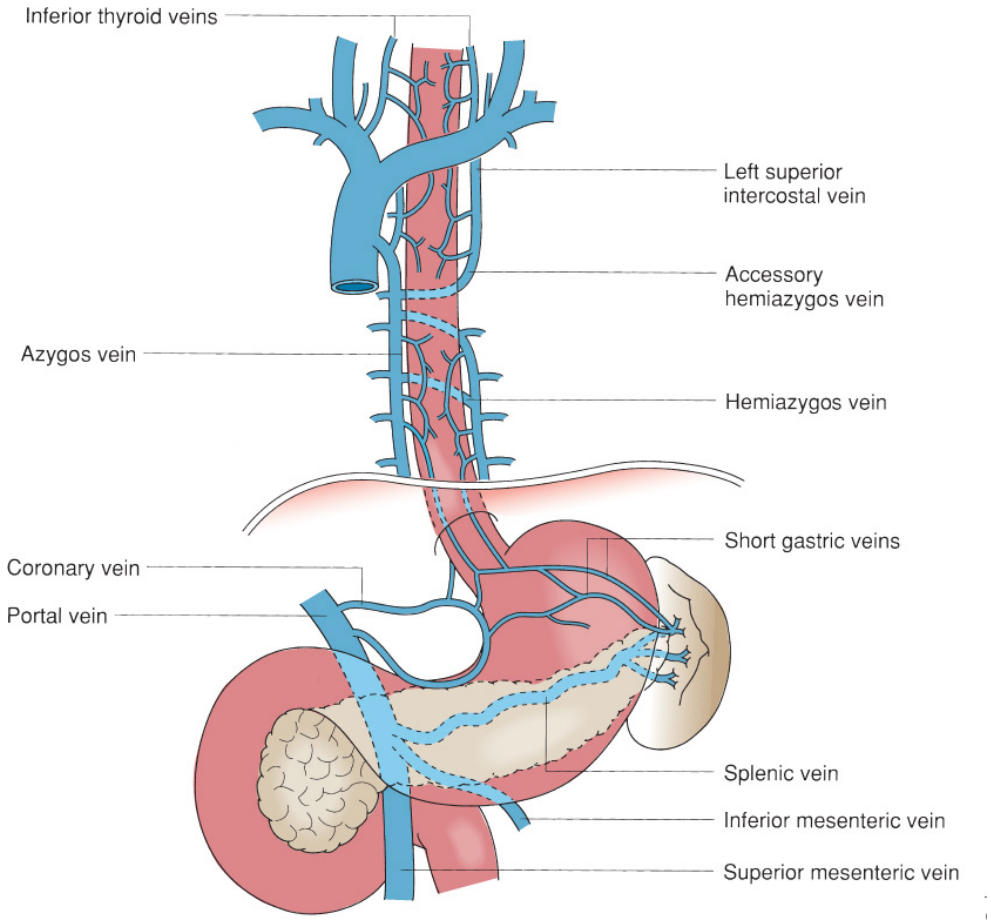


Figure 42.7 Venous anatomy of the esophagus.

- Cervical: inferior thyroid artery
- Thoracic: bronchial (frequently two right sided and left one left sided) and esophageal arteries (frequently two directly from the aorta)
- Abdominal: ascending branch of left gastric artery and bilateral inferior phrenic arteries

In the muscular layer of the esophagus these vessels branch extensively to make an extensive longitudinal vascular plexus, allowing for esophageal mobilization to the aortic arch with no ischemia.[4] The venous drainage of the esophagus is as follows (**Fig. 42.7**):

- Cervical: empties into inferior thyroid vein
- Thoracic: empties into the bronchial, azygos, and hemiazygos vein
- Abdominal: empties into the coronary vein

Esophageal lymphatic channels form a very dense plexus located in the submucosa, just below the muscularis mucosa. Lymph flows primarily in the longitudinal direction, and particularly in the thoracic esophagus, can travel a long distance prior to penetrating the muscle layer to enter the lymphatic channels and lymph nodes. It is for this reason that esophageal tumors in this region have a higher rate of skip metastases. See **Figure 42.8** for lymph channels and nodal drainage.[5] (See Chapter 42: Esophageal Tumors and Injury for more detail.)

The vagus nerve, or cranial nerve X, is the primary innervation of the pharynx and the esophagus. The right and left recurrent laryngeal nerve, branches from the vagus nerves, innervate the cricopharyngeal sphincter and cervical esophagus (**Fig. 42.9**). Injury to these nerves causes impaired movement of the vocal cords as well as impaired function of the cricopharyngeal sphincter and cervical esophageal motility, thus significantly increasing aspiration risk during swallowing. The left recurrent laryngeal nerve and both vagus nerves innervate the upper thoracic esophagus. As the right and left vagus nerves descend into the mediastinum they lie immediately on the outer surface of the esophagus, and rotate in a counter-clockwise fashion. Thus, the left vagus nerve rotates to be anterior vagal trunk, while the right rotates to become posterior vagal trunk.[6] Esophageal and cardiac symptoms are similar, as they share the same afferent visceral sensory pathways, and end in the first four segments of the thoracic spinal cord.

PHYSIOLOGY

The Swallowing Mechanism

Swallowing can be intentional or reflexive secondary to stimulation of the tonsillar pillars or the posterolateral walls of the hypopharynx. The glossopharyngeal nerves and the superior laryngeal branches of the vagal nerves are the afferent sensory nerves of the pharynx. Once these are simulated, the swallowing center (or the medulla) then triggers neurons via cranial nerves V, VII, X, XI, and XII and the motor neurons of C1 through C3 to complete a swallow. This swallowing impulse follows an incredibly coordinated pattern that once started, cannot stop, and lasts for about 0.5 seconds. Swallowing occurs in six distinct steps (**Fig. 42.10**):

1. Elevation of tongue
2. Posterior movement of tongue (propels food bolus into hypopharynx)
3. Elevation of soft palate (this closes the passage between the oropharynx and nasopharynx)
4. Elevation and anterior movement of hyoid
5. Elevation and anterior movement of larynx (thus enlarging the retropharyngeal space)
6. Tilting of epiglottis (thus closing the laryngeal inlet to prevent aspiration)

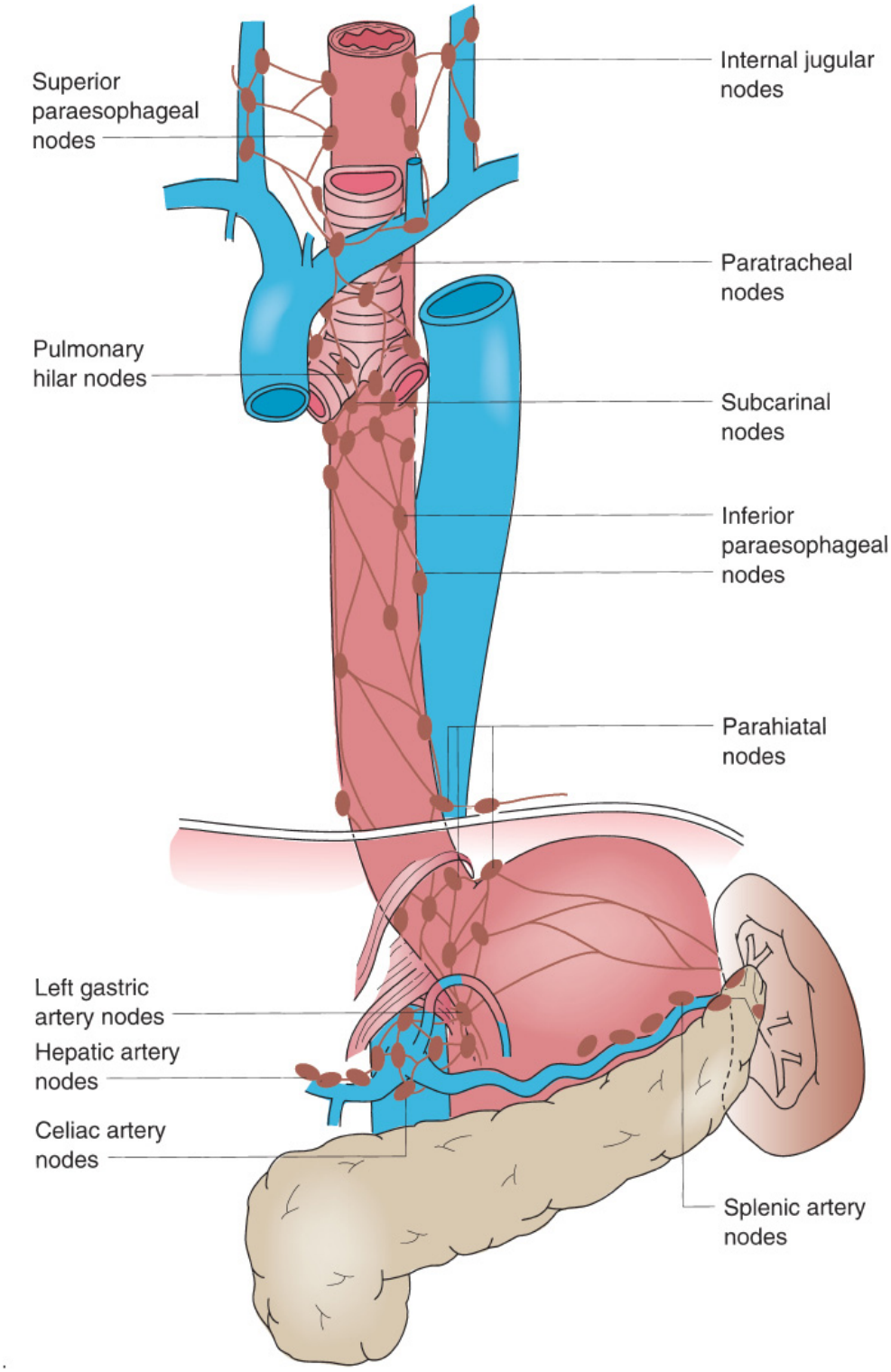


Figure 42.8 Lymphatic anatomy of the esophagus.

Pressure gradients starting in the hypopharynx helps propel the movement of food from the hypopharynx into the esophagus as the cricopharyngeus, or

EUS, relaxes.

The timing of relaxation of the UES and compliance of the cervical esophagus is pivotal to accepting the bolus. Deviations from this function may result in pharyngeal dysphagia. Step 5 above, the elevation of the larynx, pulls the hyoid bone by attached muscles and pulls the EUS open at the same time the EUS muscle is relaxing. The relaxation of the EUS is a neurologically mediated reflex that results in decreased tone of the cricopharyngeal muscle. The EUS then closes within half a second after the swallow is initiated, and the postrelaxation pressure is nearly two times the resting pressure (of 30 mm Hg). This high closing pressure of the EUS prevents reflux back into the pharynx. This postrelaxation contraction flows down the esophagus to form a peristaltic wave (**Fig. 42.11**). At the conclusion of a swallow, the EUS returns to its baseline resting pressure.

When a swallow is initiated, the longitudinal muscles of the esophagus contract, or shorten, to then enlarge the lumen of the esophagus to better accept a bolus. The circular smooth muscle contraction is responsible for the peristaltic wave. The 3 peristaltic waves produce an occlusive pressure of 30 to 120 mm Hg. The rise and fall of these contracts can engage one point in the esophagus for 3 to 5 seconds, as the wave rising peaks by 1 second, maintains peak pressure for 0.5 seconds, and subsides in about 1.5 seconds.[7,8] After the initiation of a swallow, the peak of the primary peristaltic contraction waves down the esophagus 2 to 4 cm per second, and will reach the distal esophagus about 9 seconds later. The LES will relax at the start of the peristaltic wave and will remain open and relax until the wave passes through the LES. Similar to the UES, there is then a distinct postrelaxation contraction of the LES. This esophageal wave will be reproduced with a consecutive swallow 20 seconds after the first, though if a swallow occurs sooner, the esophagus will be functionally unresponsive (deglutitive inhibition).

These peristaltic contractions must have sufficient amplitude or pressure to effectively occlude the esophageal lumen and be organized to successfully propel a bolus distal toward the stomach. There are three primary categories that cause impaired peristalsis. The first is a result of a neural abnormality resulting in defective organization of the peristaltic wave, resulting in a primary motility disorder, such a diffuse esophageal spasm. The second is noted by a decrease in the amplitude with maintenance of peristalsis, most

frequently due to muscle damage and fibrosis, often seen in longstanding gastroesophageal reflux disease (GERD) or connective tissue disorders (e.g., scleroderma). The third is caused by altered anatomy of the esophagus, most often seen with large hiatal hernias where the distal esophagus is not anchored.

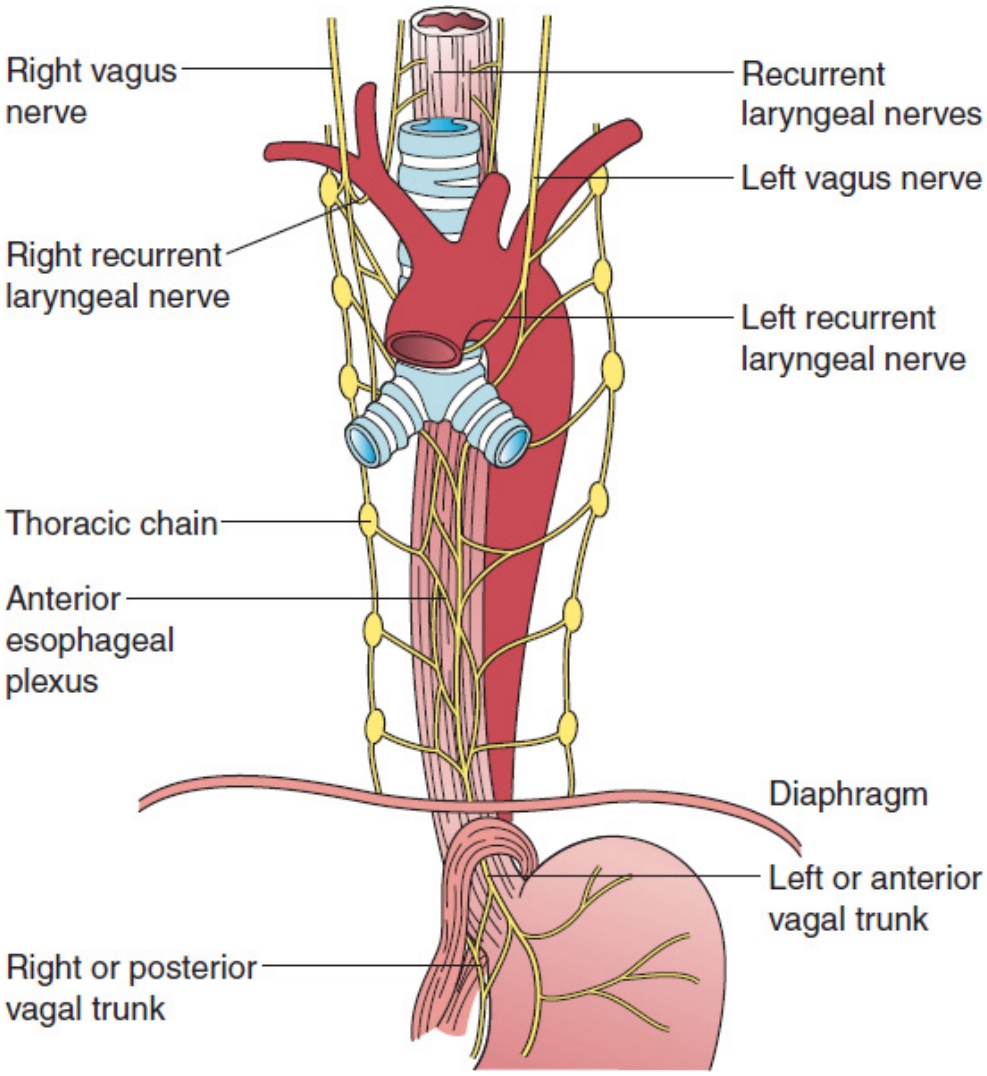


Figure 42.9 Relationship of the esophagus to the vagus nerves and their branches.

The Gastroesophageal Barrier: Lower Esophageal Sphincter

The LES functions as the barrier that prevents the esophageal mucosa from injury from refluxed gastric contents. Failure of the LES to open, or relax

appropriately, prevents the esophagus from effectively pushing a bolus into the stomach and if severe, can lead to achalasia. Failure of the LES to close effectively can lead to GERD, or increased exposure of the esophageal squamous epithelium to acidic gastric contents. Though the LES has no anatomical landmarks endoscopically, on manometry, it can be localized due to an area of pressure over the baseline gastric pressure. At baseline it is a "high-pressure zone" except during swallowing to allow a bolus to pass, or during belching to allow gas to be released. Passage of gastric juice from the higher-pressure area of the stomach to the lower pressure area of the esophagus is prevented due to the barrier of a competent LES. In early GERD, this is often due to a transient loss of the barrier, while in advanced GERD it is frequently a permanent loss of LES barrier.[9]

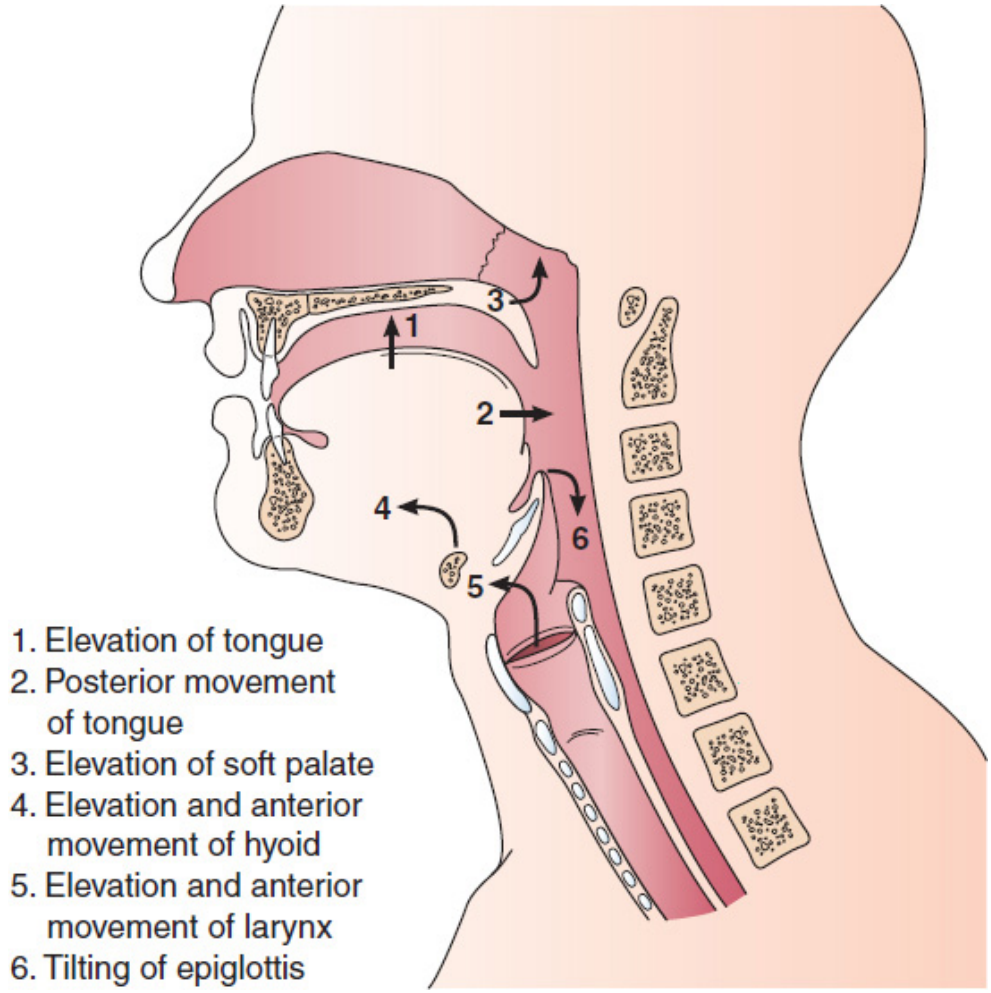


Figure 42.10 Overview of the act of swallowing.

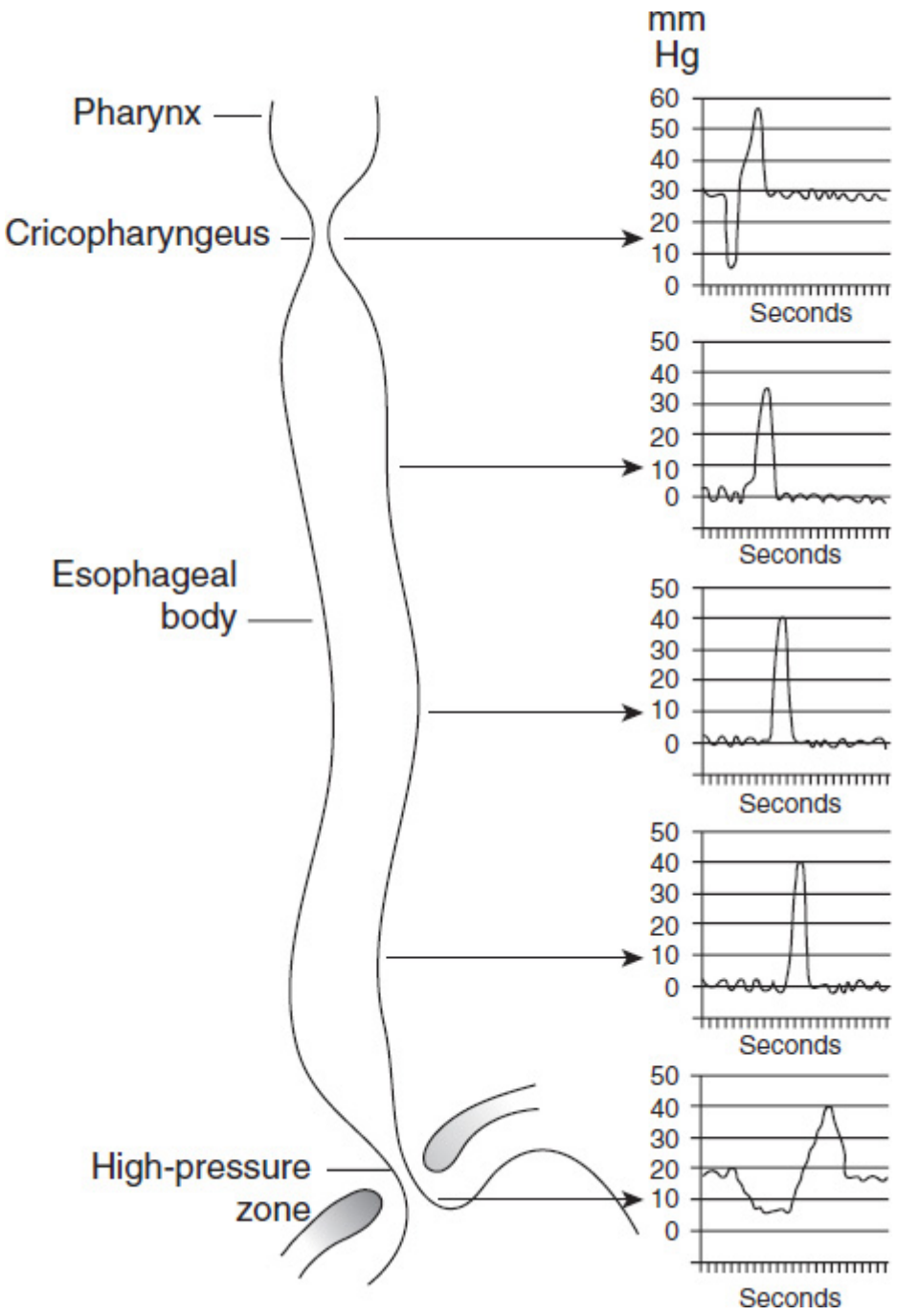


Figure 42.11 Overview of esophageal body peristalsis. (From Waters PF, DeMeester TR. Foregut motor disorders and their surgical management. *Med Clin North Am* 1981;65[6]:1235–1268, with permission.)

There are three primary characteristics of the LES to allow it to maintain its function, even with high intragastric and intra-abdominal pressures. These LES characteristics include:

1. 4 Length
2. Pressure
3. Position

The LES length and pressure work closely together to maintain LES effectiveness. The shorter the LES length, the higher the LES pressure must be to maintain competence.[10] Additionally, the impact of a normal LES pressure can be negated by a short LES length and the impact of a normal LES length can be negated by a low LES pressure (**Fig. 42.12**).

The LES shortens due to gastric filling, as the terminal esophageal length is reduced by the expanding fundus—the greater the gastric volume, the shorter the LES length (**Fig. 42.13**).[11] Overeating causes excessive gastric distension which in turn critically shortens the LES to the point of impairing its ability to close. The LES pressure then abruptly drops and reflux occurs (**Fig. 42.14**).[12] Additionally, if the LES is already permanently shortened, even normal-sized meals can cause postprandial reflux. The abnormal anatomy of the cardia, such as a sliding hiatal hernia, also impacts the ease in which the LES is shortened due to gastric distension. Less gastric distension is required to open the LES barrier in patients with a hiatal hernia.[13] The funnel or dome shape of a hiatal hernia changes the wall tension and allow the barrier to be pulled open more easily, accounting for the frequent association of hiatal hernia with GERD.[14] The position of the LES is also pivotal to its function. A segment of the LES is intra-abdominal and exposed to the higher intra-abdominal pressures. If these pressure were only applied to the stomach, the barrier of the LES would be easily overcome (and therefore reflux would occur) if the intra-abdominal LES were not also experiencing those same pressures.[15] A minimum of 1 cm of abdominal LES is critical to its proper function.

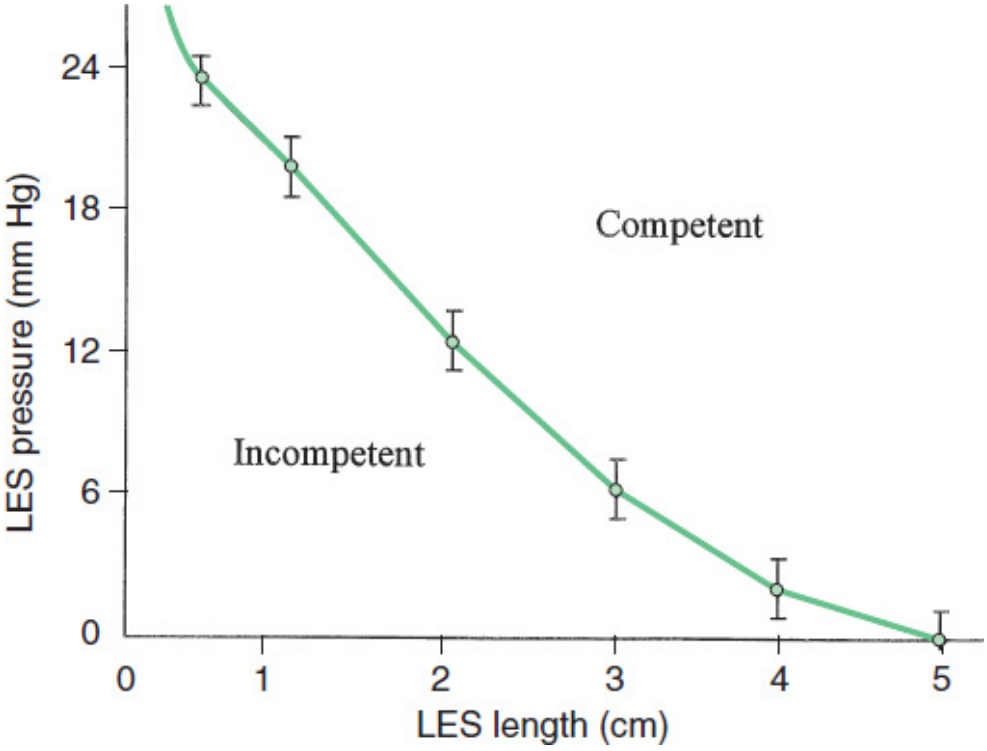


Figure 42.12 Relationship of the length and pressure of the lower esophageal sphincter in maintaining competence of the gastroesophageal barrier.

When LES length, pressure, and position are not adequate, this will lead to an incompetent LES. In these cases, even when fasting continued reflux can occur leading to chronic esophageal injury (**Fig. 42.15**).

5 EVALUATION OF ESOPHAGEAL FUNCTION

Thorough assessment of esophageal anatomy and function is imperative to both medical and surgical management of esophageal disease. There are four core diagnostic tests commonly utilized, these include: upper endoscopy, barium esophagram, ambulatory pH monitoring, and high-resolution esophageal manometry. We also recommend esophageal impedance planimetry (endoluminal functional lumen imaging probe or Endoflip) for assessment of esophageal distensibility and function.

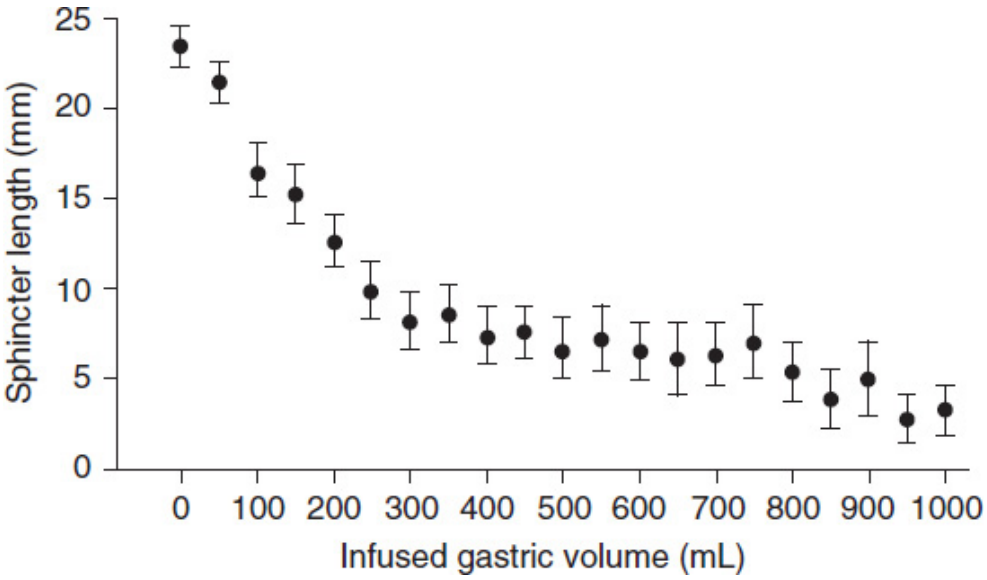


Figure 42.13 Effect of increasing gastric volume on the shortening of the lower esophageal sphincter length. As the stomach expands, the gastric body takes up the inferior aspect of the sphincter causing its length to shorten. (From Mason RJ, Lund RJ, DeMeester TR, et al. Nissen fundoplication prevents shortening of the sphincter during gastric distention. *Arch Surg* 1997;132[7]:719–724; discussion 724–726, with permission.)

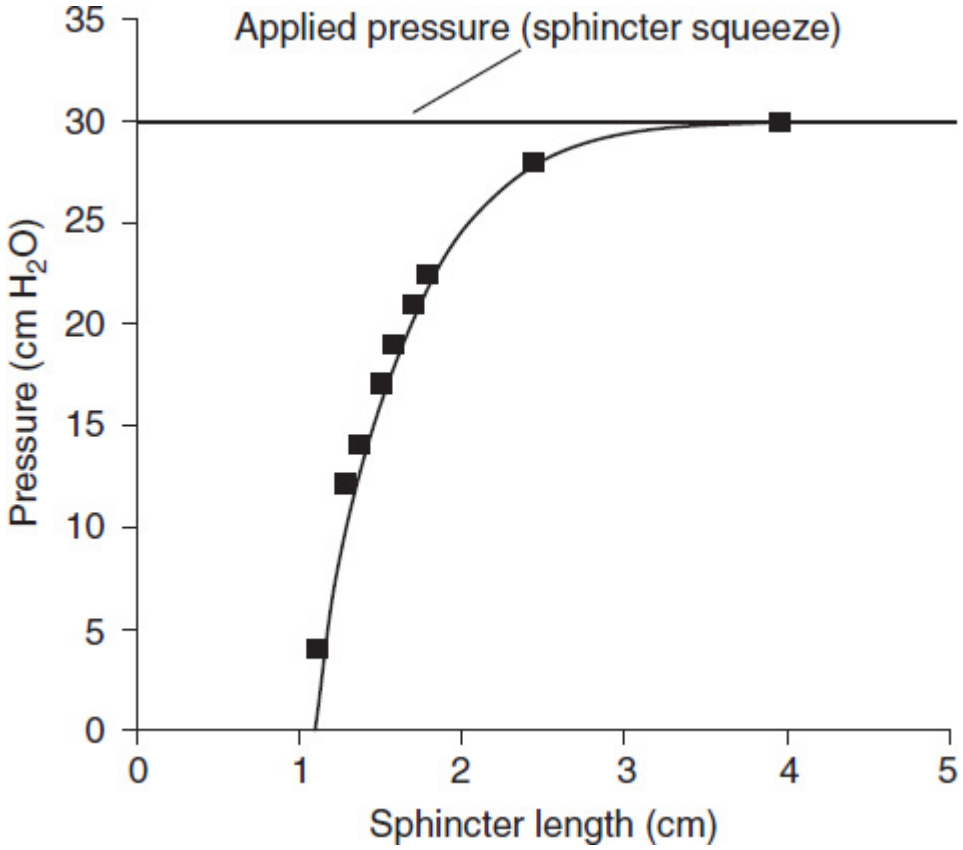


Figure 42.14 Representation of the loss of competence of the lower esophageal sphincter with shortening of its length. As a critical length is reached, there is a precipitous drop in sphincter pressure reflecting loss of competence. (From Pettersson GB, Bombeck CT, Nyhus LM. The lower esophageal sphincter: mechanisms of opening and closure. *Surgery* 1980;88[2]:307–314, with permission.)

Upper Endoscopy

An esophagogastroduodenoscopy (EGD) is indicated in every patient being evaluated for GERD, and is a critical physical examination of the foregut. A thorough visual evaluation of the entire foregut is necessary with particular attention to the location and appearance of the squamocolumnar junction. This junction is noted by the transition of the lighter squamous epithelium and the darker rose (or velvet)-colored columnar epithelium. Narrow band imaging (NBI) is particularly helpful in distinguishing these two cellular types. If erosive esophagitis is encountered, application of the Los Angeles classification system should be applied (**Table 42.1**).[16]

Table 42.1 Modified Los Angeles Classification of Esophagitis

Grade	Lesion
A	One (or more) mucosal break of longer than 5 mm that does not extend between the tops of two mucosal folds
B	One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds
C	One (or more) mucosal break that is continuous between the tops of two or more mucosal folds but that involves <75% of the circumference
D	One (or more) mucosal break that involves at least 75% of the esophageal circumference

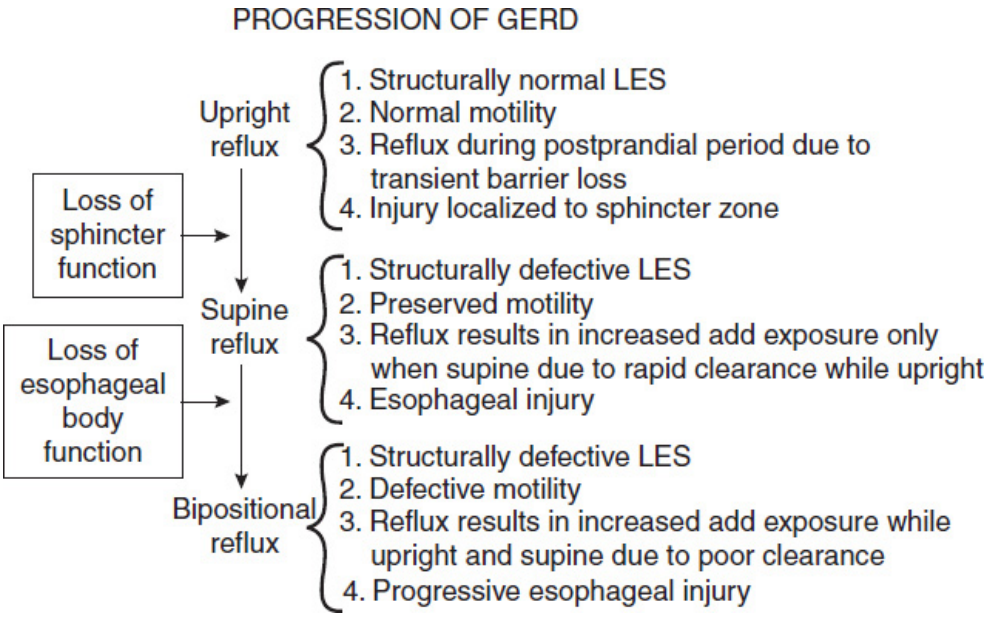


Figure 42.15 Overview of the progressive nature of GERD and the effect of the lower esophageal sphincter and esophageal body on reflux in the upright and supine positions.

If columnar metaplasia is observed during endoscopy, this raises a concern for Barrett esophagus and the area must be biopsied (four-quadrant every 2 cm of columnar metaplasia). The cardia and GEJ should be visualized for abnormalities by retroflexion as this will also assess the competency of the gastroesophageal barrier. The Hill grading system is commonly used to categorize the appearance and competence of the gastroesophageal barrier (**Fig. 42.16**). The grading is I to IV, a higher grade with worsening architecture and thus higher likelihood of acid exposure through the GEJ.[17]

A hiatal hernia is seen when there is a separation of the GEJ from the crura, and by definition is present when a minimum of 2 cm of rugal folds are above the pinch of the diaphragmatic crura. GERD is frequently associated with a notable sliding hiatal hernia. It is important to assess for presence of gastritis or Cameron ulcers within the hiatal hernia. During the removal of the endoscope it is important to again slowly examine the esophagus. The larynx and vocal cords should also be visualized to assess inflammation and movement, as chronic acid reflux can injure these structures.

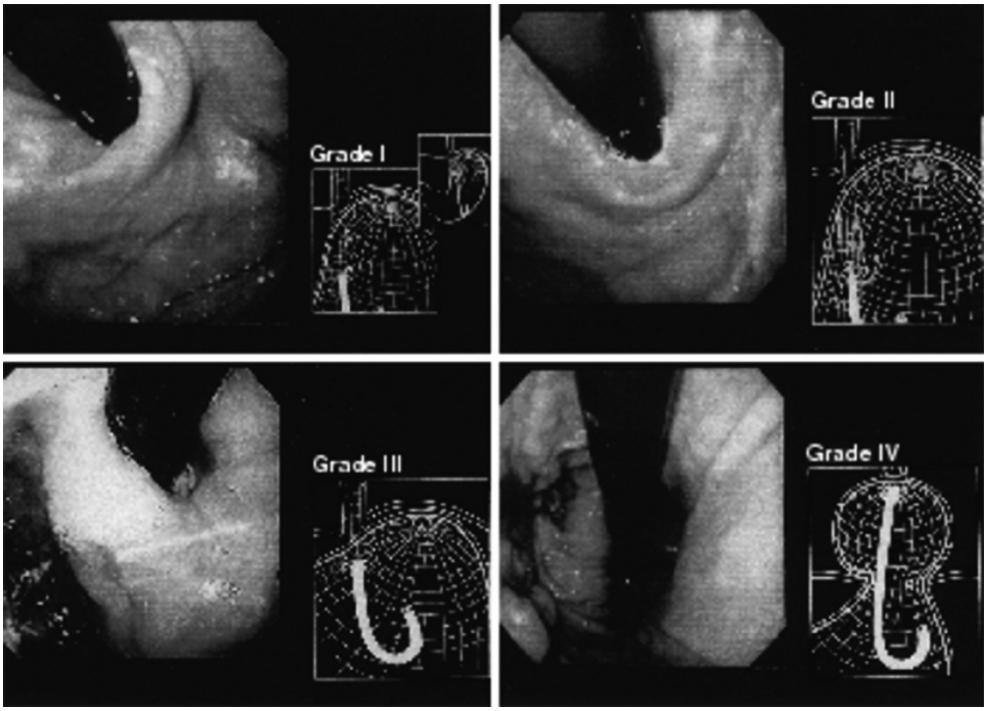


Figure 42.16 Endoscopic grading of the gastroesophageal junction during the retroflex view. (From Oberg S, Peters JH, DeMeester TR, et al. Endoscopic grading of the gastroesophageal valve in patients with symptoms of gastroesophageal reflux disease [GERD]. *Surg Endosc* 1999;13(12):1184–1188, with permission.)

Radiologic Evaluation

A barium esophagram is one of the first critical diagnostic tests to assess the anatomy and function of the esophagus and upper stomach. Historically, the barium esophagram has been used as the "road map" of the esophagus as it can provide real-time visualization of bolus transport, esophageal motility, size of hiatal hernia, and structural abnormalities. The first part of the esophagram includes an assessment of the UES and pharynx in the upright position, to evaluate the coordination of pharyngeal transit. Bolus transit on esophagram complements information from esophageal manometry and clearance can be assessed with both liquids and solids (tablet), and is done in the upright and supine positions. A primary peristaltic wave strips the bolus through the esophagus and into the stomach during a normal swallow and adequate contractility is shown by full lumen approximation. Disorders of esophageal motility result in a segmented appearance of barium within the esophagus. This can be due to disorganized peristalsis or simultaneous

esophageal contraction, resulting in a beading or corkscrew appearance. A 13-mm barium tablet is a useful proxy to determine how solid material transits through the esophagus, and assists in identifying areas of clinically significant narrowing as well as functional obstructions, as luminal narrowing below 13 mm frequently results in dysphagia.

Hiatal hernias are best visualized in the prone position as the increased intra-abdominal pressure pushes the hernia above the diaphragm. Hiatal hernias >5 cm or hernias that do not reduce are more likely to be associated with chronic reflux and esophageal foreshortening. Though reflux of contrast can be seen on UGI, it is not always consistent with a true diagnosis of reflux. Evoked reflux and spontaneous reflux to the distal esophagus are not correlated to a positive pH, though spontaneous reflux to the thoracic inlet more frequently does correlate. Additionally, the absence of reflux seen on an UGI does not exclude the disease.

Esophageal Manometry

High-resolution manometry (HRM) provides a detailed assessment of esophageal contractility, coordination, and sphincter function. The most common HRM system utilizes 36 circumferential sensors spaced at 1-cm intervals, with each transducer able to detect pressure over a length of 25 mm in 12 radially dispersed sectors (**Fig. 42.17**).

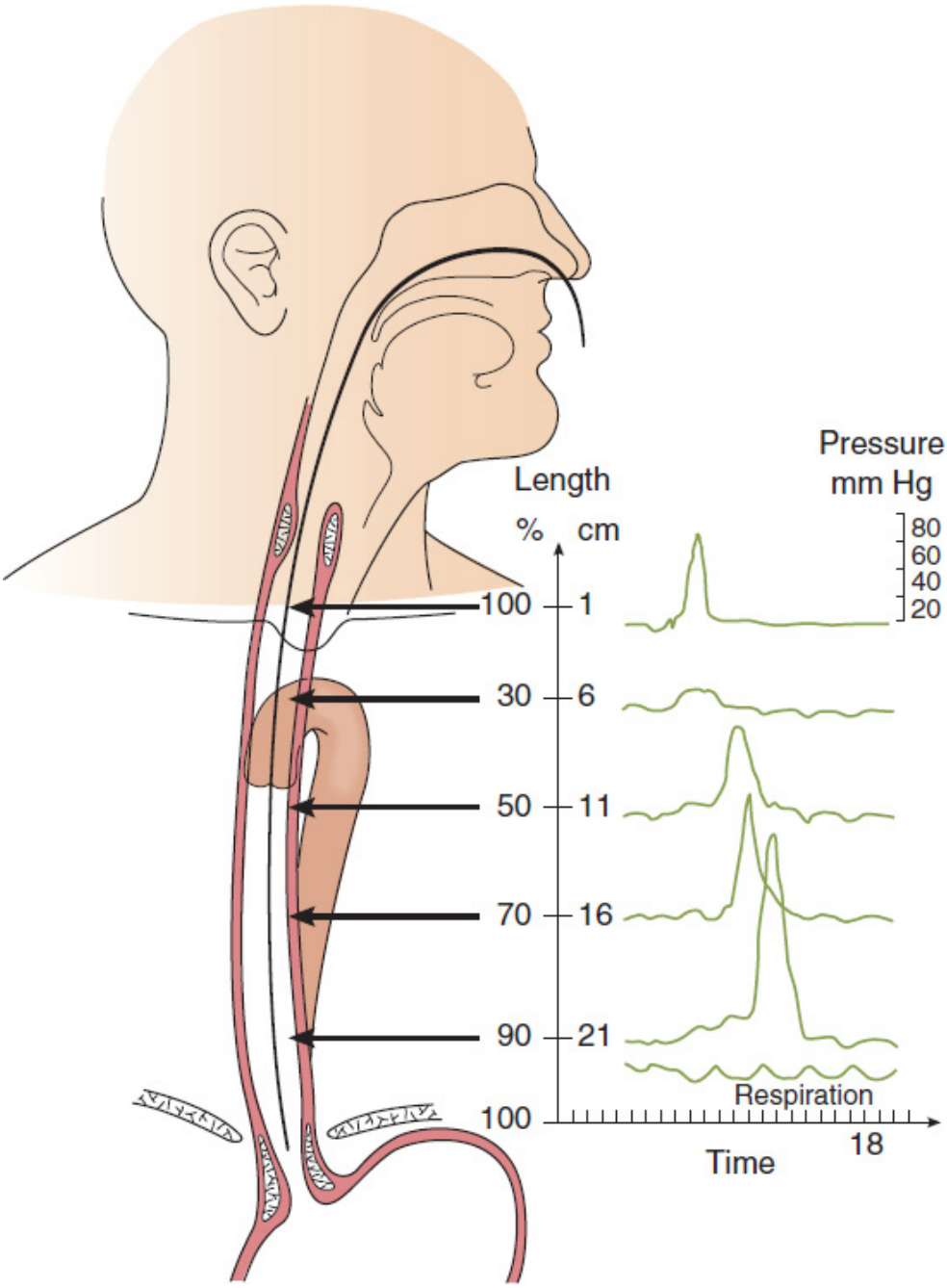


Figure 42.17 Illustration of the position of a five-channel esophageal motility catheter during the esophageal body portion of the study.

The pressures at each sector are averaged, providing a large amount of data that is then converted via a topographic plotting algorithm to a Clouse plot, or esophageal pressure topography (**Fig. 42.18**). HRM is generally performed by passing a lubricated catheter through the nasopharynx, into the esophagus and stomach, though endoscopic guidance is recommended in

large paraesophageal hernias and achalasia to confirm no coiling within the esophagus. The patient then completes 10 swallows (supine with head elevated), with at least 30 seconds between swallows (to prevent deglutitive inhibition) and quiet breathing between for better assessment of baseline resting pressures of UES and LES. The full HRM assessment includes contraction amplitude, waveform, esophageal body coordination, UES function, structural characteristics of the LES, and LES relaxation.

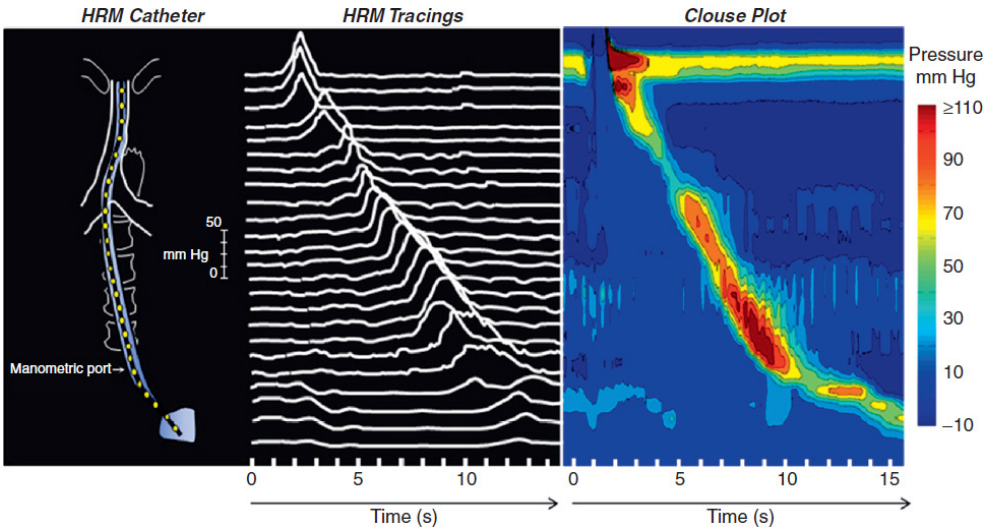


Figure 42.18 High-resolution manometry with line tracings and converted pressure topography or Clouse plot view. (From Pandalfino JE, Roman S. High-resolution manometry: an atlas of esophageal motility disorders and findings of GERD using esophageal pressure topography. *Thor Surg Clin* 2011;21[4]:465–475, with permission.)

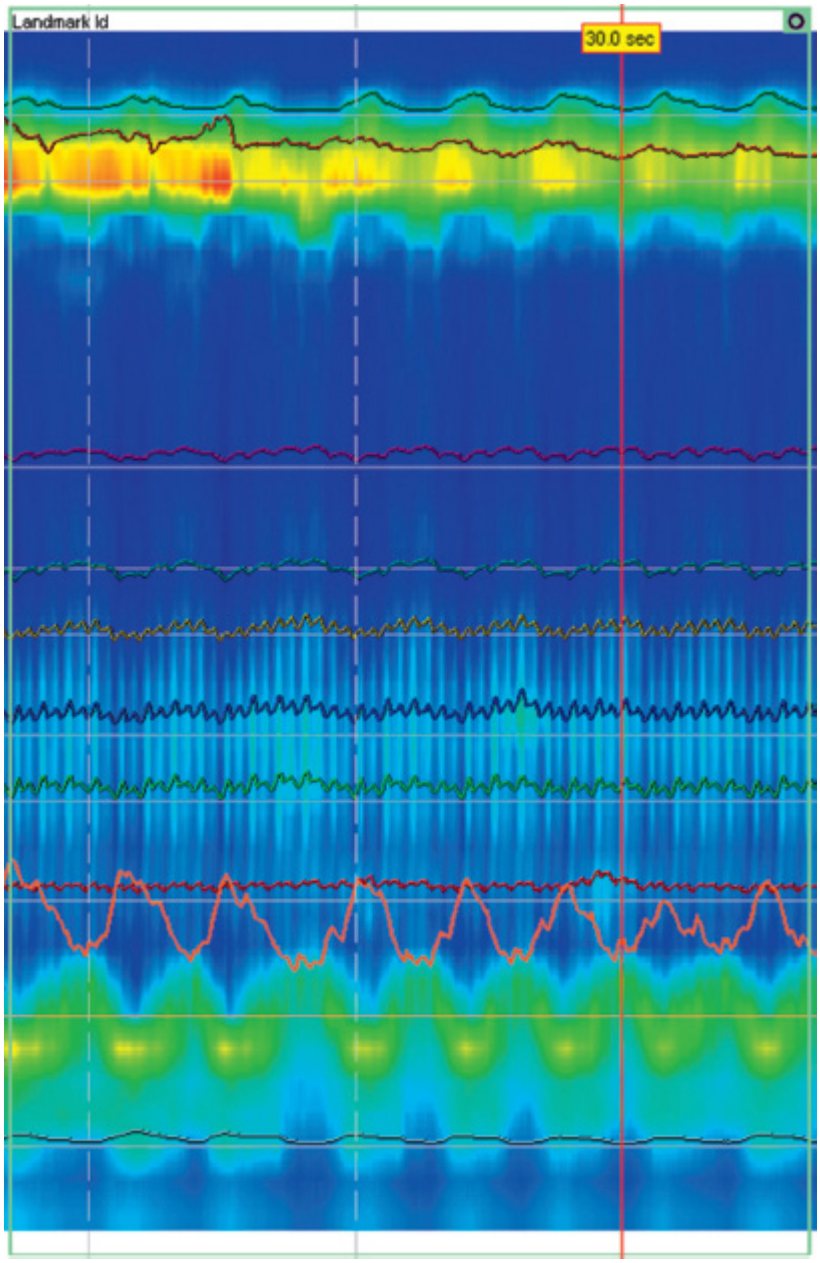


Figure 42.19 High-resolution esophageal manometry showing the landmark frame. The upper and lower esophageal sphincters are observed at the **top** and **bottom** of the frame, respectively. Resting pressure and length measurements of the sphincters can be determined in this portion of the study while the patient is refraining from any swallowing. (From Pandalfino JE, Roman S. High-resolution manometry: an atlas of esophageal motility disorders and findings of GERD using esophageal pressure topography. *Thor Surg Clin* 2011;21(4):465–475, with permission.)

HRM is indicated in symptoms of dysphagia, odynophagia, regurgitation, and heartburn. HRM plays a critical role in confirming and differentiating

primary esophageal motility disorders including diffuse esophageal spasm, nutcracker esophagus, achalasia, and a hypertensive LES. Systemic diseases (including scleroderma, polymyositis, and dermatomyositis) as well as long-standing GERD can result in ineffective esophageal motility (IEM). HRM can identify a noncompetent LES and determine its location for placement of an ambulatory pH monitor.

Lower Esophageal Sphincter

The LES is initially assessed with the landmark frame, which lasts for 30 seconds without swallowing and is calculated as an average over this time period (**Fig. 42.19**). The proximal border of the LES is where the sphincter pressures equals the esophageal baseline, and the distal border is where its resting pressure rises above the gastric baseline.[18]

Utilizing the HRM technique, expected LES measurements compared to noncompetent LES measurements are shown in **Table 42.2**.

Generally, the LES pressure drops to the baseline gastric pressure immediately after a swallow is initiated, and will remain open and relaxed until the peristaltic wave reaches the stomach. After the passage of the bolus, the postrelaxation contraction of the LES is observed to ensure LES closure and prevention of reflux. The LES relaxation is assessed by the integrated relaxation pressure (IRP), which is a 4-second time period between initiation of swallow and when peristalsis reaches the LES. An IRP over 15 mm Hg is elevated and can result in resistance of flow through the LES.

Table 42.2 Normal and Abnormal Lower Esophageal Sphincter Measurements on HRM

Overall Length	**2.7–4.8 cm**	**<2 cm**
Pressure	13–43 mm Hg	<6 mm Hg

Esophageal Body Motility

HRM assesses esophageal body motility by quantifying contraction amplitude, duration, velocity, slope, and even morphology (type of peak of amplitude). Pathologic gaps in peristalsis occur if there are >2 cm long

breaks in isobaric contour along the esophagus or any break at the LES. The distal contractile integral (DCI) provides a global assessment of esophageal contractile function, and calculated by: amplitude (mm Hg) duration (sec) × length (cm). Normal values for DCI range between 500 and 4,300 mm Hg · s · cm (**Fig. 42.20**). Current clinical practice recommends a DCI >500 to prevent postoperative dysphagia after an antireflux procedure, as a pressure above that is required to overcome the resistance produced from such a procedure.

Ambulatory pH Monitoring

The development of ambulatory pH monitoring was pivotal to obtaining 6 an objective assessment of acid exposure in a continuous setting, and can correlate symptoms to high acid exposure.[19] It has the highest sensitivity and specificity for confirming the diagnosis of GERD and is indicated in patients with GERD who require ongoing therapy or have atypical symptoms of GERD. The test is performed in two ways, one with a transnasal catheter and one with an endoscopically placed capsule (Bravo capsule, Medtronic Inc., Minneapolis, MN).[20] Both are positioned ~5 cm above the upper border of the LES. Both communicate with a portable device that is kept with the patient and records the pH continuously for a set period of time, often 24, 48, or even 96 hours. This test is ideally done off acid suppression therapy; 2 weeks for proton pump inhibitors (PPIs), and 2 days for H_2 blockers. During the study the patient is asked to remain upright during the day and to avoid highly acidic or basic foods which can impact the reliability of the results. The patient is to note timing of meals, timing of sleep and wake, as well as document the presence and duration of symptoms. The pH tracing can be seen in **Figure 42.21**. Several key measurements include percentage of time the pH is less than 4, the number of reflux episodes and their duration.[21] DeMeester and Johnson developed a composite scoring system that assesses six different components of the pH measurements into a single score, the DeMeester Score. These include: number of refluxes per day, number of long refluxes per day (over 5 minutes), longest reflux, total time below pH of 4.0, upright time below pH 4.0, and supine time below pH 4.0. A normal DeMeester Score is <14.7, and the normal total time spent in reflux is

<4%.[20,22] The ambulatory pH study is the most reliable way to quantitively measure the degree and pattern and of esophageal acid exposure, which can have an impact on the decision to operate for GERD.

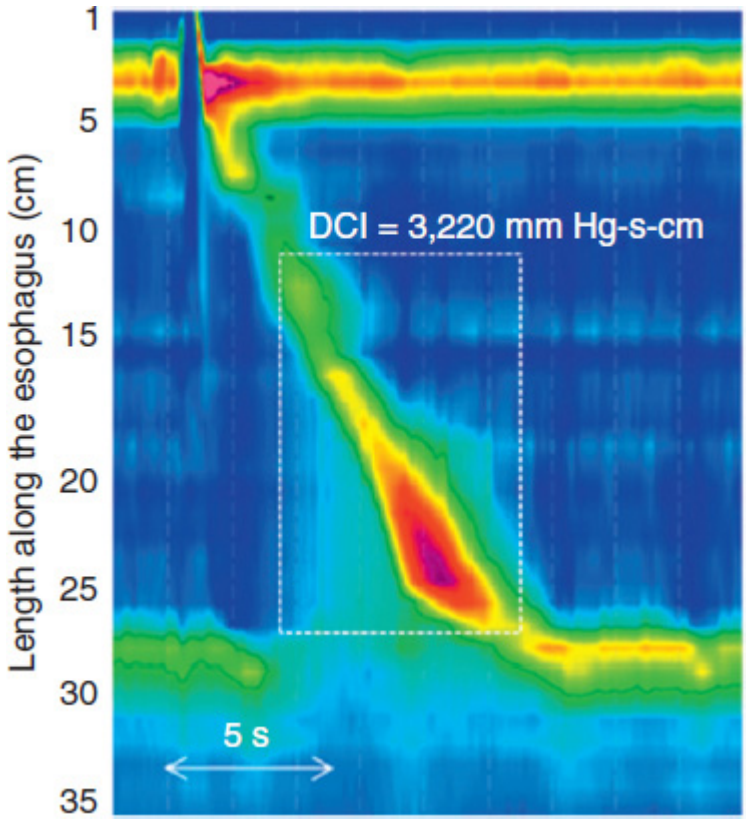


Figure 42.20 High-resolution esophageal manometry during a swallow. The initiation of swallowing is reflected by transient relaxation of the UES followed by a peristaltic pressure wave progressing down the esophageal body. Note the LES relaxes at the initiation of swallowing. A characteristic peristaltic break is observed in the upper third of the esophageal body at the transition zone between the striated and smooth muscle. (From Pandalfino JE, Roman S. High-resolution manometry: an atlas of esophageal motility disorders and findings of GERD using esophageal pressure topography. *Thor Surg Clin* 2011;21[4]:465–475, with permission.)

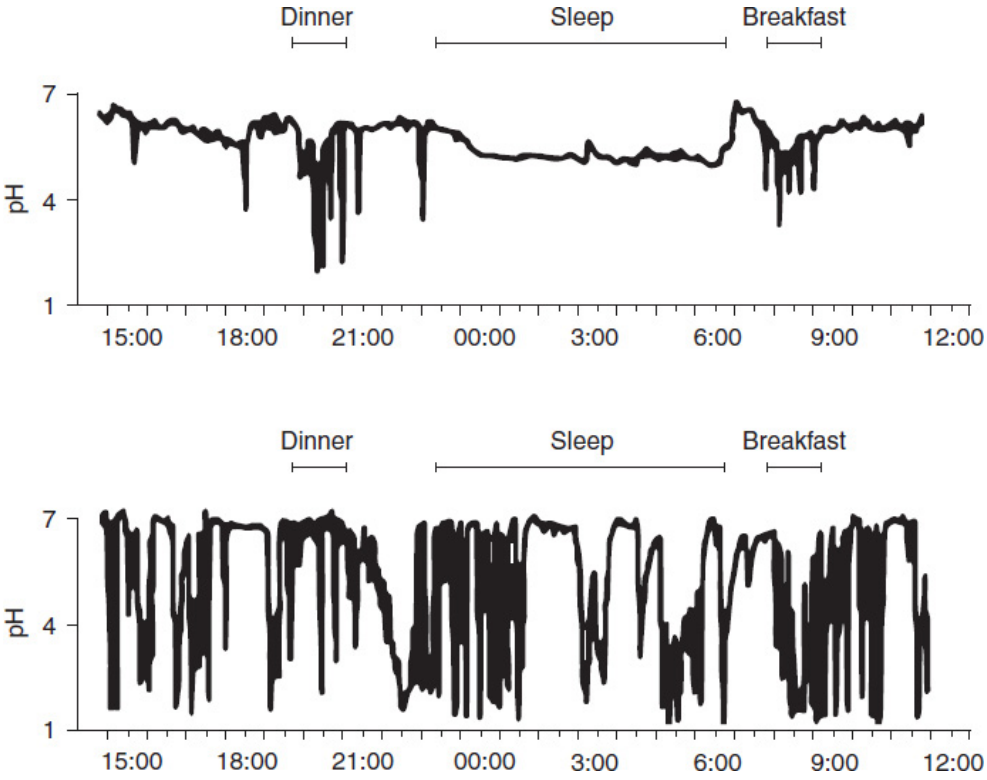


Figure 42.21 Dual-probe 24-hour pH tracing of patient. The top tracing is of the pH sensor located below the upper esophageal sphincter and the bottom tracing is of the pH sensor located 5 cm above the top of the lower esophageal sphincter. Episodes of pH <4 are considered acid events. In this example, the patient has abnormal acid exposure in the distal esophagus with several reflux events extending into the proximal esophagus.

Multichannel Impedance Testing

Multichannel intraluminal impedance (MII) uses a catheter with multiple pressure and impedance sensors separated by 1 to 2 cm, which allows evaluating the direction and effectiveness of bolus transit in addition to esophageal pressure abnormalities. It also permits the detection of both acid and nonacid gastroesophageal reflux when combined with pH testing, and can be done both on and off PPIs. This method is preferred for the assessment of patients with atypical symptoms and those with incomplete or no response to acid-suppressive therapy. MII-HRM classifies swallows as "complete bolus transit," "incomplete bolus transit" (no bolus exit identified at any one of the distal impedance-measuring sites), and "esophageal transit abnormality" (30% of liquid swallows or 40% of viscous swallows with incomplete bolus transit). MII-pH can establish the association of the

patient's symptoms with reflux episodes by providing the symptom index (SI; 50% indicates symptomatic reflux on PPI therapy) and the symptom association probability (SAP; 95% is considered indicative of a good temporal association between the patient's symptoms and reflux).

Impedance Planimetry

7 Endoflip is an impedance planimetry system used to evaluate real-time pressure, diameter, and distensibility of the esophagus and gastrointestinal sphincters.[23] The balloon catheter can be passed with transorally with endoscopic guidance or through the endoscope. There is an 8-cm long and a 16-cm balloon catheter, both of which can be used to assess the GEJ and LES, as well as the pylorus if indicated. The 16 cm is better suited for assessment of the esophagus proximal to the LES. The balloon is then filled with 30 cc, 40 cc, 50 cc, 60 cc, or 70 cc and the metrics documented (note, the 8-cm balloon should only be filled to 50 cc). There are several primary metrics and these include the maximum diameter (mm) of the narrowest luminal area, the cross-sectional area (mm^2), balloon pressure (mm Hg), the distensibility index (mm^2/mm Hg), and esophageal contractile pattern categories (repetitive antegrade contractions, repetitive retrograde contractions, absent contractile response, or disordered/diminished contractile response). Endoflip can be easily completed with upper endoscopy to immediately assess the competence of the LES, in workup for dysphagia, esophageal motility disorders such as achalasia, or symptoms of GERD. Endoflip allows an improved functional assessment of the LES, with detailed diameter assessment of the GEJ and of notable clinical importance, its distensibility, or ability to open at varying pressures (**Fig. 42.22**).

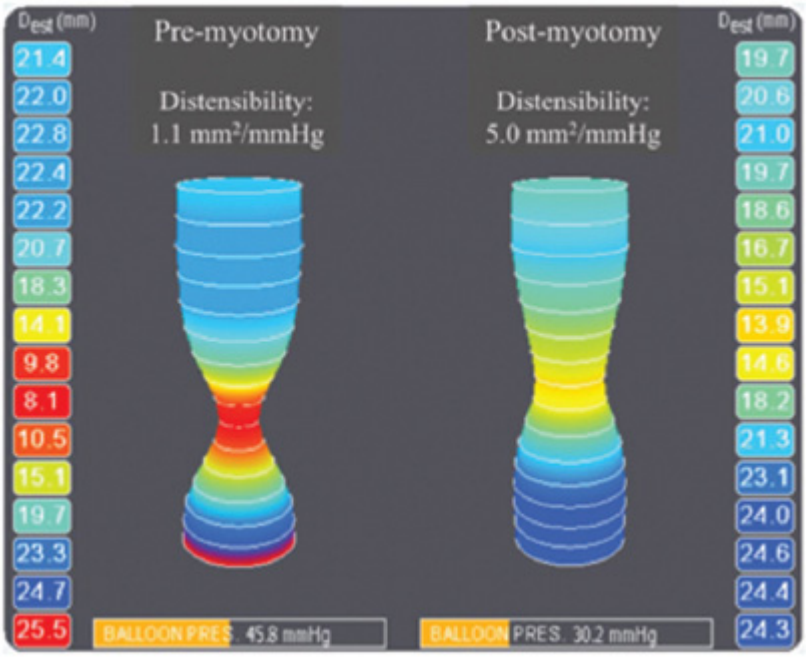


Figure 42.22 Visual representation of changes in the lower esophageal sphincter before and after myotomy for achalasia using Endoflip with a 40-mL volume fill.

CONCLUSIONS

The anatomy and physiology of the esophagus is unique and requires a detailed understanding to ensure safe workup and management. A deep appreciation of the anatomic relationships to other critical structures is pivotal to safe operations on the esophagus. The anatomic and functional studies outlined guide clinical decision making and surgeons should mater their use and interpretation.

GASTROESOPHAGEAL REFLUX DISEASE

Definition and Epidemiology

The most widely used definition for GERD is "a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications."[24] It is difficult to accurately estimate the prevalence of GERD due to heterogeneity in the design of published studies, but

approximately 20% of people in the United States experience GERD symptoms at least weekly.[25] Worldwide, GERD is most prevalent in South Asia and Southeast Europe (>25%) and lowest in Southeast Asia, Canada, and France (<10%).[26] Its prevalence was increasing into the early 2000s but appears to have now leveled off.[25] However, it is still responsible for 110,000 hospital admissions annually in the United States, and deaths from end-stage benign esophageal disease are on an upward trend,[27] despite dramatic improvements in the efficacy of treatment options.

Two epidemiologic trends may be contributing to the increasing prevalence and severity of GERD over the past several decades. The first is the increasing prevalence of obesity, which is a significant risk factor for GERD. Jacobson et al. have shown that compared to normal-weight women, underweight women (BMI <20) were one-third less likely and overweight women (BMI 25 to 27.4) two times more likely to have frequent GERD symptoms. Obese women (BMI >30) had a nearly three times higher risk of frequent GERD symptoms.[28] Recent meta-analyses confirm this association between increasing BMI and the presence of GERD.[26] High-resolution motility studies have shown a significant correlation with BMI and both increased intragastric pressure and abnormal gastroesophageal pressure gradients, providing a physiologic explanation for the BMI–GERD association.[29] Specifically, central obesity has been shown to be especially associated with erosive esophagitis (OR 1.87), Barrett esophagus (OR 1.98), and esophageal adenocarcinoma (OR 2.51).[30]

The second risk factor is *Helicobacter pylori*, which has an inverse relationship with GERD. Epidemiologic data show that the decline of *H. pylori* infection is one of the reasons behind the increasing incidence of GERD-related diseases, including Barrett esophagus and esophageal and cardia adenocarcinoma in the Western world. Barry Marshall and Robin Warren from Perth, Australia, were awarded the Nobel Prize for their demonstration of the pathogenic role of *H. pylori,*[31] which induces a significant inflammatory and immune response in the affected host, resulting in persistent inflammation in infected subjects. It has been postulated that *H. pylori*–induced chronic corpus gastritis may protect against the development of GERD and its malignant transformation. Available evidence shows that the prevalence of *H. pylori* infection in patients with GERD or Barrett esophagus is lower than in healthy control populations.[32–35] The cagA+

strains of *H. pylori* have been specifically implicated in this correlation,[36,37] and studies have confirmed an inverse relationship between the presence of cagA positivity and adenocarcinoma of the esophagus and the GE junction.[38] As the incidence of duodenal ulcers and distal gastric cancer has decreased, the incidence of erosive esophagitis and gastric cardia cancer has increased, further supporting the theory that there is likely an inverse epidemiologic relationship between GERD and *H. pylori*. There are two main categories of GERD: nonerosive disease (NERD) and erosive disease (ERD).

Up to 70% of patients have NERD, but over time, patients may progress from NERD to erosive esophagitis and from ERD to Barrett esophagus.[39,40] The progression or regression of GERD complications was assessed in a cohort of nearly 4,000 patients with predominant heartburn who were treated with antisecretory medications over a 2-year period. After 2 years, 25% of patients with nonerosive GERD progressed to ERD, 1.6% with mild erosive esophagitis worsened to more severe esophagitis, and nearly 8% progressed to Barrett esophagus; the latter predominantly in patients with Los Angeles grade C/D ERD at baseline. On the other hand, 50% to 60% of patients with baseline esophagitis improved to a milder grade or no ERD and 22% were off medications at 2 years. A follow-up study at 5 years on 2,721 of the originally enrolled patients reported that while in most the disease was stable or esophagitis had improved, a minority of patients progressed despite pharmacologic treatment. At 5 years, 6% of patients with NERD, 12% with LA grade A/B esophagitis, and 20% of those with LA grade C/D esophagitis had developed Barrett esophagus. Risk factors for progression of disease included family history of GERD, baseline esophagitis or remaining unhealed after initial treatment, alcohol intake, and regular use of PPIs.[41]

Clinical Presentation

The most common symptoms in patients with GERD are heartburn, regurgitation, and dysphagia. Dysphagia may be an indication of more serious underlying pathology, including esophageal carcinoma, and should prompt an upper endoscopy. Heartburn is typically characterized as a substernal “burning” discomfort often radiating from the epigastrium to sternal notch. Occasionally patients will refer to it as chest or epigastric pain or indigestion. Typically, heartburn occurs postprandially and is exacerbated

by acidic foods, chocolate, coffee, and alcohol. It is commonly relieved by antacids, histamine-2 blockers, or PPIs. Importantly, the severity of symptoms is not necessarily related to the severity of the underlying disease as characterized by endoscopic findings (**Fig. 42.23**).

Regurgitation is the spontaneous return of gastric contents proximal to the GE junction, without necessarily reaching as high as the pharynx or mouth. It is typically worse at night in the recumbent position or when bending over or lying down after a meal. Patients commonly compensate by not eating late at night or by sleeping partially upright with several pillows or in a chair. This symptom is less often improved with antacid treatment. Dysphagia is generally described as the sensation of food being temporarily "stuck" in the esophagus. Dysphagia that is limited to solid food with normal passage of liquids is suggestive of a mechanical problem, such as a hiatal hernia, benign esophageal stricture, or tumor. Dysphagia with both solids and liquids is more typical of a functional or motor disorder such as achalasia. Patients usually adjust their eating habits as dysphagia progresses without realizing it, and dietary history including questions regarding the consistency of consumed food is an important component of patient assessment.

Many patients with GERD often also manifest extraesophageal symptoms, such as cough, asthma, hoarseness, and noncardiac chest pain. Atypical symptoms are the primary complaint in 20% to 25% of patients with GERD and are secondarily present in association with heartburn and regurgitation in many more. It is considerably more difficult to prove a cause-and-effect relationship between atypical symptoms and GE reflux than it is to do so for the typical symptoms, and the etiology of these symptoms is often multifactorial. Often a trial of high-dose PPIs is helpful, but it takes several months to evaluate the full impact of the therapy since it takes time for that inflammation to improve or resolve with medications. Antireflux surgery can provide symptom relief in these patients, but careful testing to document GERD is critical particularly in those with little or no response to medical therapy.

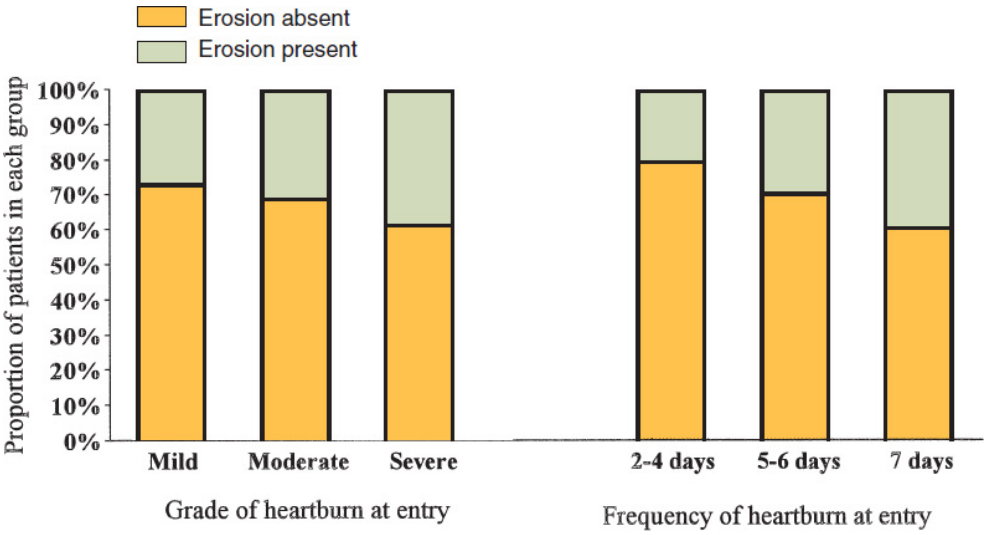


Figure 42.23 Prevalence of erosive esophagitis in 994 patients with varying severity and frequency of reflux symptoms. (Reproduced with permission from Venables TL, Newland RD, Patel AC, et al. Omeprazole 10 mg once daily, omeprazole 20 mg once daily, or ranitidine 150 mg twice daily, evaluated as initial therapy for the relief of symptoms of gastro-oesophageal reflux disease in general practice. *Scand J Gastroenterol* 1997;32[10]:965–973.)

The symptoms above are not specific to GERD and the differential diagnosis includes achalasia, diffuse spasm, esophageal carcinoma, pyloric stenosis, cholelithiasis, gastritis, gastric or duodenal ulcer, and coronary artery disease. In fact, the diagnosis of GERD based on symptoms alone is correct in only approximately two-thirds of patients.[42] This underlines the importance of objective diagnosis before the decision is made for surgical treatment.

Physiology of the Antireflux Barrier

The common feature of both physiologic or pathologic gastroesophageal reflux is the loss of the normal gastroesophageal high-pressure zone and the resistance it imposes to the flow of gastric juice from an environment of higher pressure (the stomach), to an environment of lower pressure (the esophagus). This barrier, composed of both anatomic (flap valve and diaphragm) and physiologic (LES) components, acts to prevent reflux. The key determinants of the barrier include:

1. The frequency of swallow- and non–swallow-induced transient relaxations of the LES
2. The structural integrity of the LES
3. Anatomic alterations of the diaphragmatic crura and gastroesophageal flap valve represented by the angle of His

The presence or absence of pathologic esophageal acid exposure (i.e., abnormal 24-hour pH studies) is not only influenced by the degree of barrier loss but also by esophageal and gastric functional characteristics including esophageal clearance, intra-abdominal pressure, and gastric emptying abnormalities.

Transient Relaxation of the Lower Esophageal Sphincter

Non–swallow-induced transient relaxations of the lower esophageal sphincter (TLESRs) are a major mechanism of belching and physiologic reflux in individuals with normal LES and hiatal anatomy, but a less significant contributor to GERD.[43] These spontaneous relaxations occur without pharyngeal contraction and are associated with relaxation of the diaphragmatic crura. Gastric distention, upright position, and meals high in fat have all been shown to increase the frequency of TLESRs.[44,45] The latter observations suggest that unfolding of the sphincter may be responsible for the loss of sphincter pressure.

Structural Integrity of the Lower Esophageal Sphincter

The pressure, overall length, and the length exposed to the positive pressure environment of the abdomen are the three characteristics of the LES that maintain its resistance or barrier function to intragastric and intra-abdominal pressure increases. The resistance of the LES is a function of its pressure and the length over which this pressure is exerted. The shorter the overall length of the high-pressure zone, the higher the pressure must be to maintain sufficient resistance to remain competent (**Fig. 42.12**). If the overall length of the sphincter is abnormally short, then with minimal gastric distention there

will be insufficient sphincter length for the existing pressure to maintain sphincter competency, and reflux will occur even in the presence of "normal" resting sphincter pressure.[10]

The third characteristic of the LES is its position, specifically the length of the high-pressure zone that is exposed to positive intra-abdominal pressure. If the abdominal length is inadequate, the sphincter cannot respond to an increase in applied intra-abdominal pressure by collapsing, and reflux is more likely. This usually occurs as a result of a hiatal hernia, and is the most common cause of a permanently defective sphincter.

If the LES has an abnormally low pressure, a short overall length, or minimal exposure to the abdominal pressure environment in the fasting state, then uninhibited reflux of gastric contents into the esophagus occurs. Such a *permanently defective sphincter* is identified by having one or more of the following:

- high-pressure zone with an average pressure of less than 6 mm Hg
- average overall length of 2 cm or less
- an average length exposed to the positive pressure environment of the abdomen of 1 cm or less[46]

A permanently defective sphincter is commonly associated with esophageal mucosal injury, difficulty to control symptoms with medical therapy, and esophageal dysmotility.

Anatomic Alterations

Hiatal Hernia

Hiatal hernia is a common abnormality in patients with GERD, although its contribution to the pathophysiology of this disease has been debated through the years. It has now been demonstrated that the diaphragmatic crura are important in preventing reflux during periods of loss of LES pressure,[47] and that the physiologic flap valve created by the angle of His is a contributing barrier to gastroesophageal reflux.[17] The presence of a normal acute angle of His or the abnormal dome architecture of a sliding hiatus hernia influences the ease with which the sphincter is pulled open, and a higher intragastric pressure is needed to open the sphincter in patients with an intact angle of His when compared to patients with a hiatal hernia (**Fig. 42.24**).

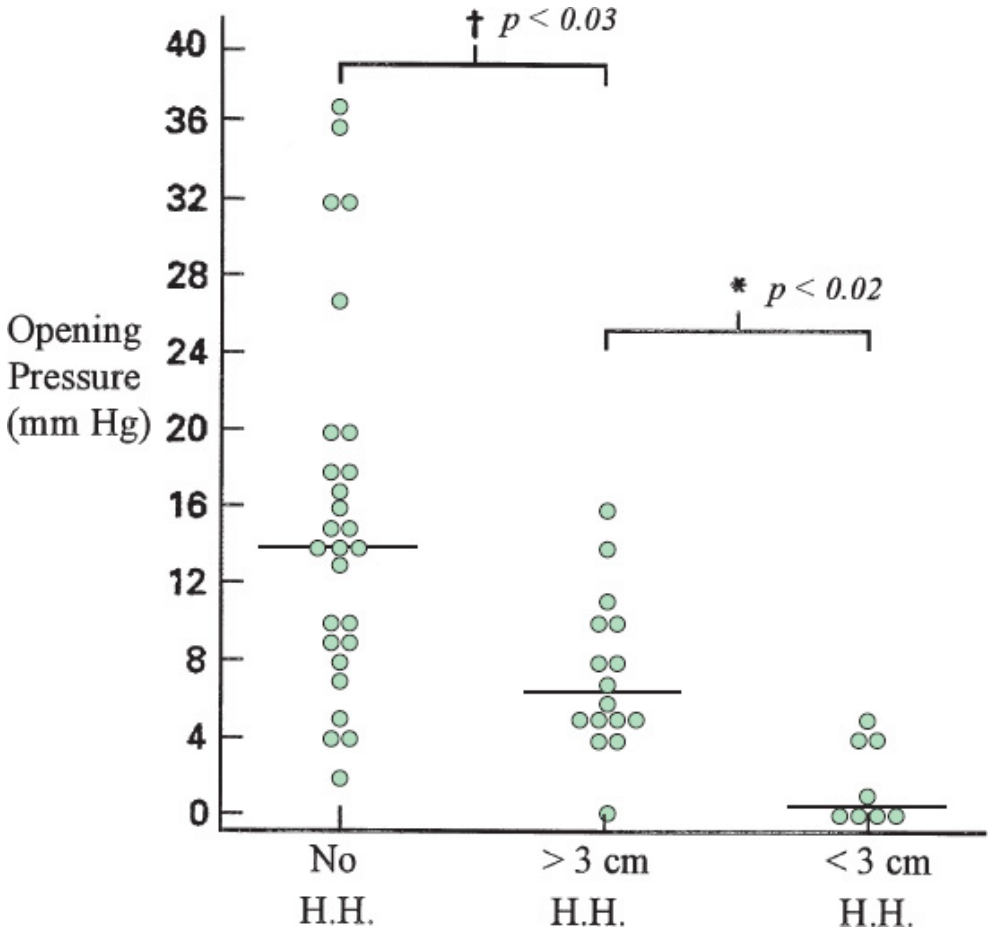


Figure 42.24 The intragastric pressure at which the lower esophagus endoscopically opened in response to gastric distention by air during endoscopy. Note that the dome architecture of a hiatus hernia (HH) influences the ease with which the sphincter can be pulled open by gastric distention. (Reproduced with permission from Ismail T, Bancewicz J, Barlow J. Yield pressure, anatomy of the cardia and gastro-oesophageal reflux. *Br J Surg* 1995;82[7]:943–947.)

The presence of a hiatal hernia also leads to impaired esophageal clearance due to loss of anchorage of the esophagus in the abdomen. Kahrilas et al. have shown that complete esophageal emptying was achieved in 86% of swallows in control subjects without a hiatal hernia, 66% in patients with a reducing hiatal hernia, and only 32% of patients with a nonreducing hiatal hernia.[48] Thus, there is overwhelming evidence that hiatal hernia does indeed play a significant role in the pathophysiology of GERD.

Gastric Distension

When the stomach is distended from overeating, aerophagia, or delayed gastric emptying secondary to the high-fat Western diet, the vectors produced by gastric wall tension pull on the GE junction with a force that varies according to the geometry of the cardia. Thus, when increased intragastric pressure occurs in the presence of a hiatal hernia, the force is applied more directly. This pulls on the terminal esophagus, reducing the length of the sphincter until a critical length of 1 to 2 cm occurs, when the pressure drops precipitously and reflux occurs. This results in postprandial reflux, which is a common complaint in the initial stages of GERD. After gastric venting, the length of the high-pressure zone is restored and competence returns until the next episode of distention. This sequence results in the common complaints of repetitive belching and bloating in patients with GERD. The patients' repetitive swallowing in an effort to neutralize the refluxed acid then contributes to repeat gastric distension.

Fletcher et al. identified an area of acid at the GE junction unaffected by the buffering action meals, which extends across the squamocolumnar junction an average of 1.8 cm into the lumen of the esophagus. The authors concluded that this was the source of postprandial esophageal acid exposure. The same process was shown to occur in patients with endoscopy-negative dyspepsia and normal conventional esophageal pH monitoring 5 cm above the upper border of the LES.[49] Importantly, dietary nitrate was also shown to result in potentially mutagenic levels of concentration of nitric oxide at the GE junction (**Fig. 42.25**).[50] These observations provide the fundamental basis for the observations of inflammation and other alterations in the epithelium known to occur at the squamocolumnar junction in both overt and unrecognized GERD.

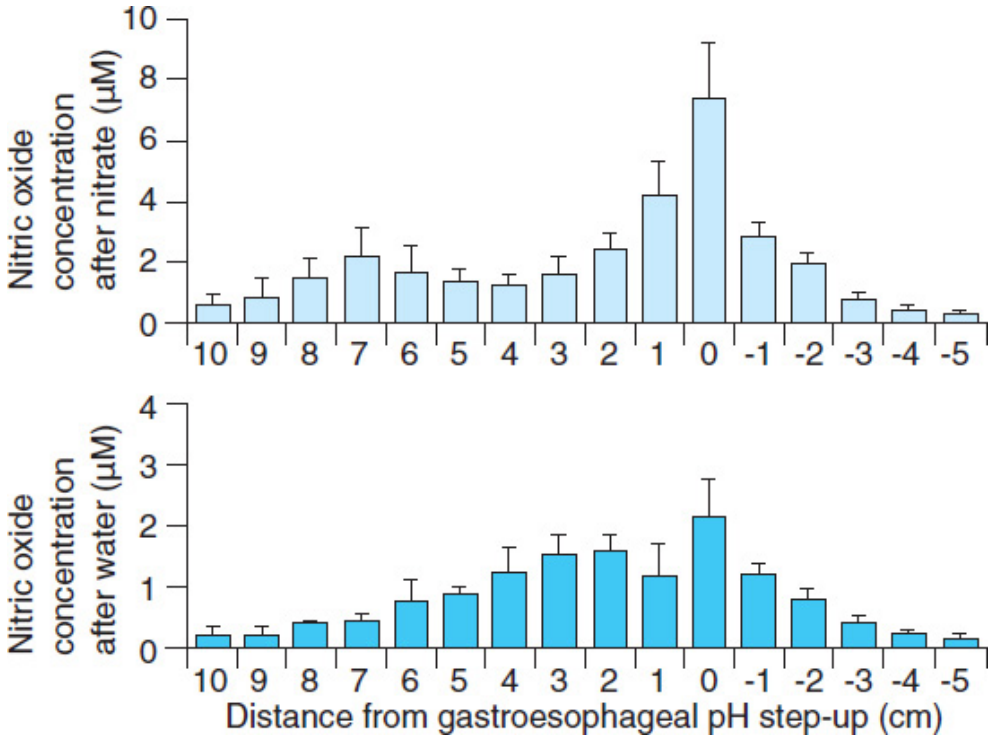


Figure 42.25 Mean (±SEM) nitric oxide concentrations in the upper stomach and lower esophagus after administration of water with 2-mmol nitrate (upper tracing) and water alone (lower tracing) (**$p < 0.01$, *$p < 0.05$ compared with value at gastroesophageal junction pH step-up). (Reproduced with permission from Iljima K, Henry E, Moriya A, et al. Dietary nitrate generates potentially mutagenic concentrations of nitric oxide at the gastroesophageal junction. *Gastroenterology* 2002;122[5]:1248–1257.)

Repeated exposure of the squamous epithelium of the distal esophagus to gastric juice causes inflammation, columnarization, and carditis. In early disease the esophagitis is mild and commonly limited to the very distal esophagus. The patient compensates by increased swallowing, allowing saliva to bathe the injured mucosa and alleviate the discomfort induced by exposure to gastric acid. Increased swallowing results in aerophagia, bloating, and repetitive belching. The distention induced by aerophagia leads to further exposure and repetitive injury to the terminal squamous epithelium and the development of cardiac-type mucosa (carditis). The process can lead to a fibrotic mucosal ring at the squamocolumnar junction (Schatzki ring). Extension of the inflammatory process into the muscularis propria causes a progressive loss in the length and pressure of the distal esophageal high-pressure zone associated with an increased esophageal exposure to gastric juice and the symptoms of heartburn and regurgitation. The loss of the barrier

eventually results in the permanent loss of LES resistance and the extension of the disease into the esophagus with progression to severe esophagitis. Intestinalization of the cardiac-type mucosa can occur at any time during this process, setting the stage for malignant degeneration.

Implications

Implications of recognizing anatomic alterations as component of GE barrier:

1. Transient LES relaxation is likely a consequence of sphincter shortening by gastric distention and is the underlying mechanism for belching and physiologic reflux. It does not play a major role in patients with symptomatic gastroesophageal reflux, particularly those with ERD, Barrett esophagus, or those referred for surgery.
2. Efforts to augment the gastroesophageal barrier either pharmacologically or endoscopically will commonly fail when a hiatal hernia is present.
3. Patients with abnormal esophageal acid exposure in the presence of normal LES characteristics and no hiatal hernia have an uncommon reason for reflux and these patients require additional evaluation since gastric or esophageal clearance failure may be present and may impair the outcome of a fundoplication.
4. Both reduction of hiatal hernia and augmentation of the LES are necessary to maximally restore gastroesophageal barrier competence.
5. Although acid control without regard to barrier incompetence will improve heartburn and heal esophageal ERD, it results in increasing numbers of patients with pulmonary manifestations of GERD.

Complications of Gastroesophageal Reflux Disease

The complications of gastroesophageal reflux result from the damage caused by the reflux of gastric juice onto the esophageal mucosa or laryngeal or respiratory epithelium (**Fig. 42.26**). Complications can be conceptually divided into (a) mucosal complications such as esophagitis and stricture; (b) extraesophageal or respiratory complications such as chronic cough, asthma, and pulmonary fibrosis; and (c) metaplastic (Barrett esophagus) and

neoplastic (adenocarcinoma). The prevalence and severity of complications is related to the degree of loss of the gastroesophageal barrier, defects in esophageal clearance, and the content of refluxed gastric juice (**Fig. 42.27**).

Mucosal Complications

The potential injurious components that reflux into the esophagus include gastric secretions, such as acid and pepsin; biliary and pancreatic secretions that regurgitate from the duodenum into the stomach, and toxic compounds generated in the mouth, esophagus, and stomach by the action of bacteria on dietary substances.

Acid alone does minimal damage to the esophageal mucosa, but the combination of acid and pepsin is highly deleterious. Similarly, the reflux of duodenal juice alone does little damage to the mucosa, while the combination of duodenal juice and gastric acid is particularly noxious. The components of duodenal juice thought to be most damaging are bile acids, which have been found in the esophagus of GERD patients in abnormally high concentrations when supine and during the upright period following meals. Reflux of bile and pancreatic enzymes into the stomach can either protect or augment esophageal mucosal injury. For instance, the reflux of duodenal contents into the stomach may prevent the development of peptic esophagitis in a patient whose gastric acid secretion maintains an acid environment, because the bile salts would inhibit pepsin and the acid would inactivate the trypsin. Such a patient would have bile-containing acid gastric juice that, when refluxed, would cause less esophagitis than if the refluxate contained acidic gastric juice with pepsin or alkaline gastric juice, where trypsin is not uninhibited. The latter patient may have minimal heartburn because of the absence of hydrogen ions in the refluxate but have endoscopic esophagitis because of the bile salt potentiation of trypsin activity on the esophageal mucosa.[51]

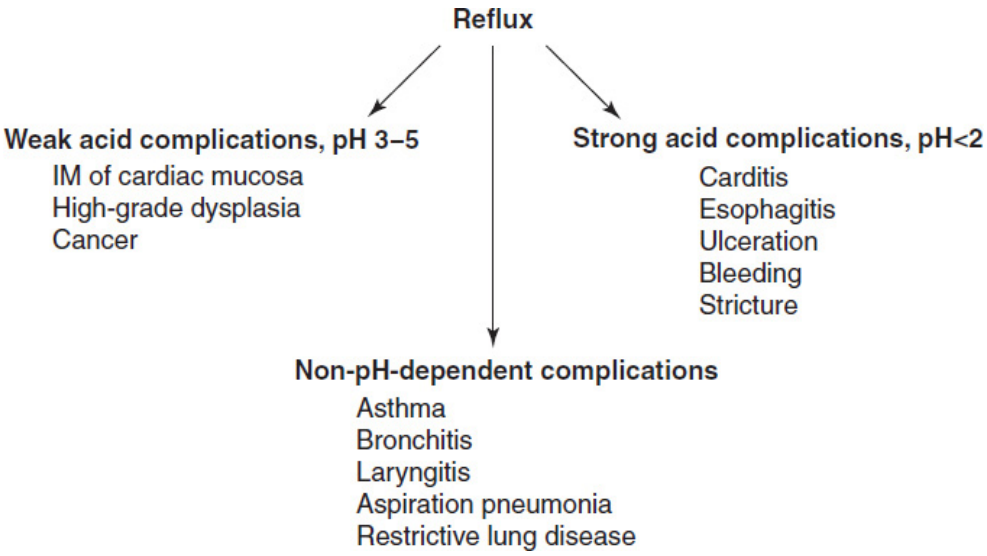


Figure 42.26 Schematic representation of the types of complications of gastroesophageal reflux disease.

In addition to acid and bile injury to the GEJ mucosa, dietary nitrate (e.g., present in green vegetables) has been shown to be potentially mutagenic.[50] Approximately 25% of ingested nitrate is resecreted into the mouth via the salivary glands, where it is transformed to more toxic nitrite, swallowed, and later converted to nitric oxide and other toxic compounds in the stomach.

Respiratory Complications

Reflux has been implicated as causative of asthma and idiopathic pulmonary fibrosis (IPF), with 35% to 50% of asthmatics shown to have abnormal esophageal pH, esophagitis, and a hiatal hernia.[52] Others have shown that the prevalence of reflux symptoms exceeded 50% in patients with asthma and CF.[53,54] In addition, patients with COPD and gastroesophageal reflux are twice as likely to have significant COPD exacerbations than their nonreflux counterparts,[55] and reflux symptoms correlate with airway obstruction in COPD patients.

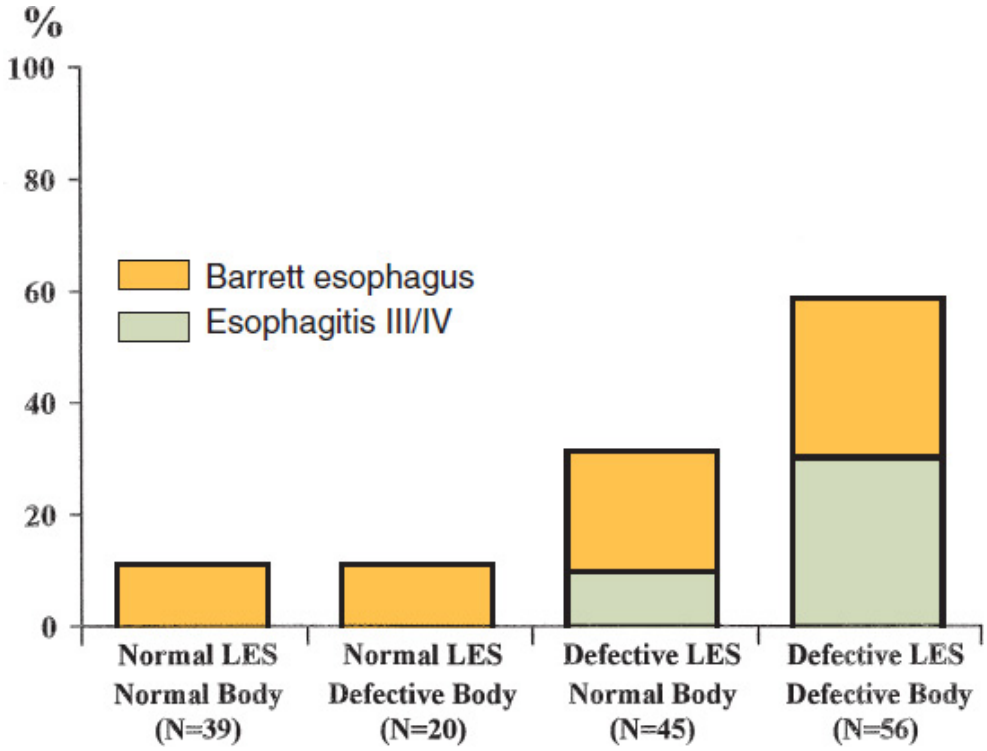


Figure 42.27 Prevalence of esophageal mucosal injury related to the presence of a defective lower esophageal sphincter, esophageal body motility, or both.

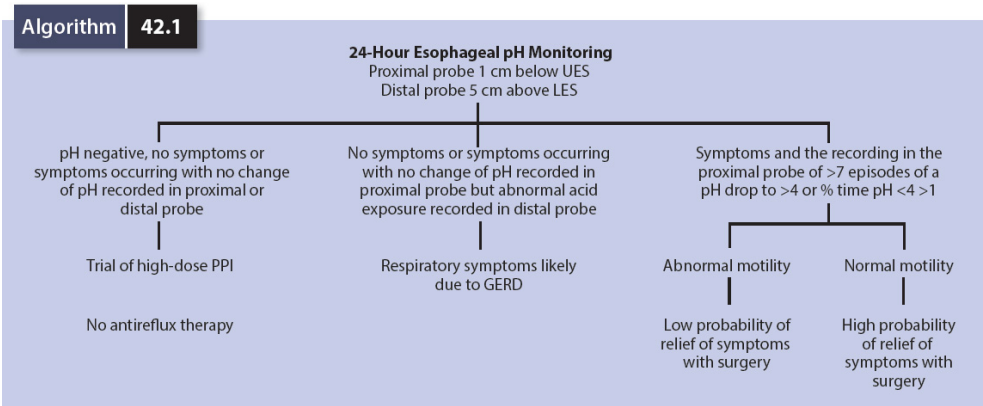
Pathophysiology of Reflux-Induced Respiratory Symptoms

Two mechanisms have been proposed as the pathogenesis of reflux-induced respiratory symptoms. The *reflux* theory postulates that respiratory symptoms are the result of the aspiration or microaspiration of gastric contents which results in pneumonitis, epithelial damage, and airway resistance. The *reflex* theory maintains that vagally mediated bronchoconstriction follows acidification of the lower esophagus via a reflex neurologic arc. The evidence supporting a *reflux* mechanism includes the findings that patient with pulmonary fibrosis have an increased prevalence of hiatal hernia on upper GI series,[56,57] while elderly patients with large hiatal hernias have a significantly increased frequency of pleural scarring on chest CT scans.[58] In addition, erosive esophagitis is found at a high frequency in patients with asthma, pneumonia, chronic bronchitis, and pulmonary fibrosis.[52] Third, patients with chronic lung diseases have a significantly higher frequency of positive 24-hour pH studies,[58,59] and simultaneous tracheal and esophageal acidification have been documented on pH monitoring in these patients.[60]

Finally, medications used to treat chronic lung diseases, in particular, bronchodilators, relax esophageal sphincter tone.[61]

A *reflex* mechanism is primarily supported by the fact that bronchoconstriction occurs following the infusion of acid into the lower esophagus.[62–64] This can be explained by the common embryologic origin of the tracheoesophageal tract and its shared vagal innervation.

The primary challenge in implementing treatment for reflux-associated RSs lies in establishing the diagnosis because in a substantial number of patients with reflux-induced RSs, gastroesophageal reflux is silent and respiratory symptoms dominate the clinical scenario. For example, D'Ovidio et al.[65] found that 72% of patients awaiting lung transplant for IPF, scleroderma, COPD, or CF had a hypotensive LES, 33% abnormal esophageal body motility, and 38% abnormal 24-hour pH testing. A high index of suspicion is therefore required in patients with poorly controlled respiratory diseases despite appropriate medical therapy. These patients should be investigated with upper endoscopy, manometry, and dual-probe pH monitoring, often combined with multichannel intraluminal impedance (MII-pH), where the proximal probe is positioned in the proximal esophagus close to (but not above) the UES. Loss of the normal alkalinity in the cervical esophagus has been shown to be a sensitive indicator of proximal reflux.[66] If the initial 48-hour Bravo pH is normal, the addition of the Restech pH probe to evaluate pharyngeal reflux exposure has been recommended.[67]



Algorithm 42.1 24-Hour esophageal pH monitoring.

Laryngopharyngeal Reflux

The term *LPR* is used for a broad category of atypical symptoms that may be secondary to gastroesophageal reflux. These may include laryngitis, pharyngitis, hoarseness, sinusitis, sleep disturbance, dental erosions, and globus.[68,69] Mechanisms for these symptoms are difficult to prove and available clinical studies are heterogeneous and frequently of low quality.[70]

Treatment of Extraesophageal Complications

Once gastroesophageal reflux is suspected or thought to be responsible for extraesophageal symptoms, treatment may be with either prolonged PPI therapy or antireflux surgery. Initially, a 3- to 6-month trial of high-dose PPI therapy may help confirm (by virtue of symptom resolution) the fact that reflux is partly or completely responsible for the symptoms. If symptoms are improved, patients can be treated with maintenance medical therapy or may be offered surgical treatment to control the reflux. The persistence of symptoms despite PPI treatment, however, does not necessarily rule out reflux as being a potential contributor. In patients with laryngopharyngeal reflux whose symptoms that are not relieved by acid suppression, small case series suggest that neuromodulating agents (tricyclic antidepressants, gabapentin, pregabalin) can provide some benefit.[71,72] **Algorithm 42.1** bases clinical decisions on the results of dual-probe 24-hour pH monitoring and is a useful starting point.

Based on reported observations, relief of RSs can be anticipated for 25% to 50% of patients with reflux-induced asthma treated with antisecretory medications,[73–75] although patients with pulmonary fibrosis in particular may have an inherent resistance to standard-dose PPIs.[76] Fewer than 15% of asthmatics with symptom relief, however, have been shown to have objective improvements in their pulmonary function. Antireflux surgery has better outcomes, improving RSs in nearly 90% of children and 70% of adults with asthma and reflux disease.[75,77] Improvements in pulmonary function were demonstrated in around one-third of these patients. It is important to note that patients with non–reflux-induced esophageal dysmotility have inferior outcomes after antireflux surgery.

The lung transplantation literature shows that there is a benefit of antireflux surgery in improving both symptoms and pulmonary function tests in patients with bronchiolitis obliterans pre- and post–lung transplant patients, with acceptable morbidity outcomes.[78–80]

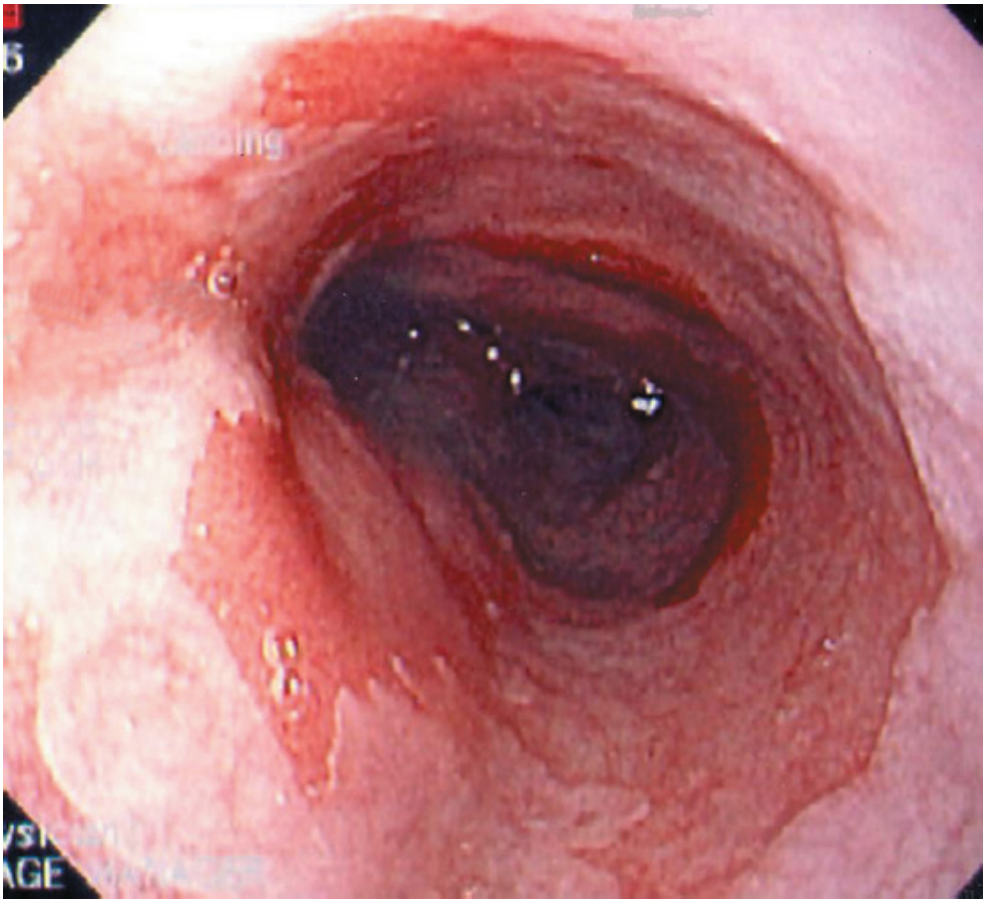


Figure 42.28 Endoscopic appearance of Barrett esophagus. Note the pink metaplastic mucosa as opposed to the normal whitish squamous lining of the esophagus.

Metaplastic (Barrett) and Neoplastic (Adenocarcinoma) Complications

8 Barrett esophagus occurs in 7% to 10% of patients with GERD, and represents the end stage of the natural history of this disease (**Fig. 42.28**).[81] Diagnosis of Barrett esophagus is made from any length of endoscopically visible tissue that is intestinal metaplasia on histology (**Fig. 42.29**) or columnar replacement of the esophagus of 3 cm or more.

Factors predisposing to the development of Barrett esophagus include early-onset GERD, abnormal LES, and esophageal body physiology, and mixed reflux of gastric and duodenal contents into the esophagus.[82] In fact, increased esophageal exposure to duodenal juice in patients with GERD is most dramatically related to Barrett esophagus.[83]

Pathophysiology of Barrett Metaplasia

Recent studies suggest that the metaplastic process at the GEJ may begin by conversion of distal esophageal squamous mucosa to cardiac-type epithelium due to exposure of the distal esophagus to excess acid and gastric contents via prolapse of esophageal squamous mucosa into the gastric environment. This results in inflammatory changes at the GEJ and/or a metaplastic process, both of which may result in the loss of muscle function and a mechanically defective sphincter allowing free reflux with progressively higher degrees of mucosal injury.

Treatment

The goals of treatment in this patient population are the relief of symptoms, healing of esophageal mucosal injury, and the prevention of disease progression. Antireflux surgery should be considered when patient factors suggest severe disease or predict the need for long-term medical management, both of which are almost always true in patients with Barrett esophagus. PPI therapy, is an acceptable treatment option in patients with Barrett esophagus. Once initiated, however, most patients with Barrett esophagus will require lifelong treatment. Complete control of reflux with PPI therapy can be difficult, and 40% to 80% of patients continue to experience abnormal esophageal acid exposure despite PPI administration.[84,85] An important consideration is that patients with Barrett esophagus generally have severe GERD, with its attendant sequelae such as large hiatal hernia, stricture, shortened esophagus, and poor motility. Compared to mild and nonerosive reflux disease, severe ERD and Barrett esophagus are associated with significantly greater loss of the mechanical antireflux barrier because of associated hiatal hernias and a hypotensive LES. Antireflux surgery likely results in more reproducible and reliable elimination of reflux of both acid and duodenal content than medical treatment. Studies focusing on the symptomatic outcome following antireflux surgery in patients with Barrett esophagus document excellent results in 79% to 92% of patients at up to 12 following surgery.[86–90] Objective outcome studies suggest that histologic regression of Barrett metaplasia is seen in 22% to 41% of surgical patients post fundoplication, though as many as 25% of them will have persistent pathologic esophageal acid exposure confirmed by 24-hour pH studies.[86–88]

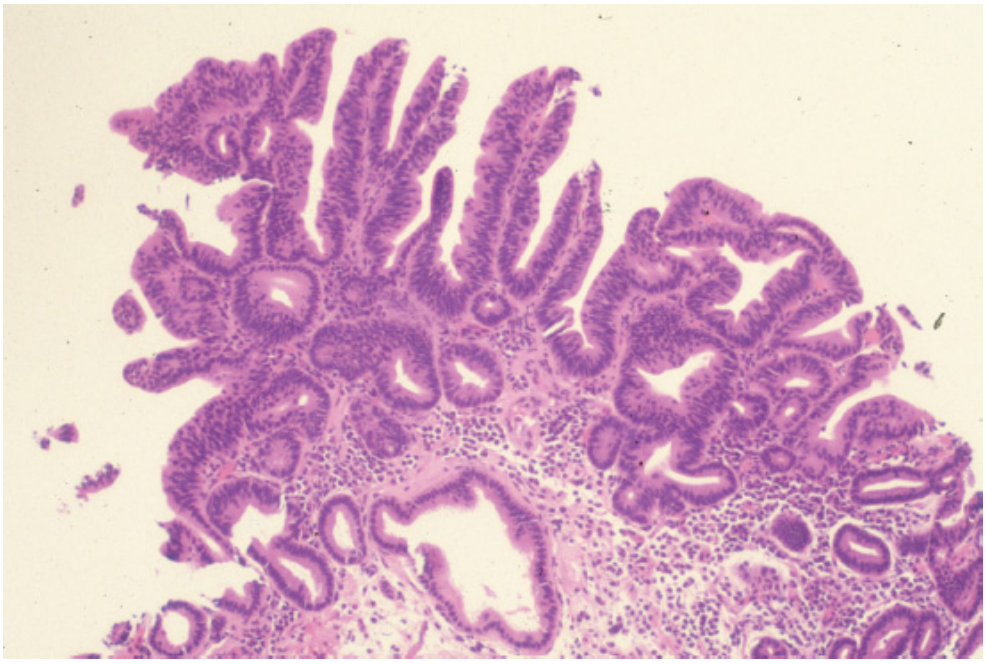


Figure 42.29 Histologic appearance of Barrett esophagus. To the left of the photograph, columnar mucosa with abundant goblet cells is seen. This is intestinal metaplasia, which is the histologic hallmark of Barrett esophagus. To the right of the photomicrograph, cardiac epithelium is present.

In addition to symptomatic and physiologic improvement in reflux after surgery, there is evidence that mediators of esophageal inflammation implicated in carcinogenesis are decreased as well. Cyclooxygenase-2 (COX-2) gene expression is elevated in the distal esophagus of reflux patients, but the expression of COX-2 and another inflammatory mediator, interleukin 8, can be decreased in the distal esophageal mucosa after a fundoplication.[91–93]

Dysplasia in Barrett Esophagus

The prevalence of dysplasia at diagnosis in patients presenting with Barrett esophagus ranges from 15% to 25%, and approximately 5% of patients will develop dysplasia each year. Barrett metaplasia is currently classified into four broad categories:

1. No dysplasia
2. Indefinite for dysplasia
3. Low-grade dysplasia
4. High-grade dysplasia (HGD)

The overall annual risk of progression to esophageal adenocarcinoma among patients with Barrett esophagus is 0.29%, and the risk of progression is significantly higher in patients with low-grade dysplasia than in those without it at baseline.[94] Therefore, Barrett esophagus complicated by dysplasia should undergo aggressive therapy. Patients whose biopsies are interpreted as indefinite for dysplasia should be treated with a medical regimen consisting of 60 to 80 mg of PPI therapy for 3 months and rebiopsied. The presence of severe inflammation makes the microscopic interpretation of dysplasia difficult, and the purpose of acid suppression therapy is to resolve inflammation that may complicate the interpretation of the biopsy specimen. Persistent indefinite or low-grade dysplasia should be a relative indication for a Nissen fundoplication given the evidence that in most patients, low-grade dysplasia reverts to nondysplastic intestinal metaplasia after a fundoplication. Radiofrequency ablation or cryotherapy are acceptable alternative treatments to reduce the risk of progression to cancer in these patients.

Approximately 50% of patients thought to have only HGD will harbor a focus of invasive carcinoma somewhere in the columnar mucosa.[95–97] Any patient with dysplasia, particularly HGD, requires careful endoscopic evaluation with high-definition white-light endoscopy to look for any nodules or lesions. If no lesion is present then ablation therapy should be performed to reduce the risk of progression to cancer in patients with HGD. If a lesion is present, endoscopic mucosal resection should be performed to determine if it is malignant and allow assessment of the depth of invasion and tumor characteristics. Endoscopic resection is preferred over esophagectomy for BE patients with intramucosal esophageal adenocarcinoma (T1a) given a significantly better safety profile, 96% complete response rate, and similar rates of recurrence. The remaining Barrett epithelium should be ablated after all visible lesions are resected. Risk factors for failure of endoscopic therapy include ultra–long segment (>8-cm) Barrett, poorly controlled reflux disease, and high-grade tumor differentiation. Metachronous lesions and local recurrences are treated following the same algorithm.[98] Treatment of more advanced esophageal cancers is discussed in Chapter 43.

Treatment of Gastroesophageal Reflux Disease

Medical Treatment

GERD is one of the most prevalent conditions encountered in general medical practice. As a result, medications for control of GERD comprise one of the largest pharmaceutical markets in the United States and abroad. Omeprazole is the seventh most commonly prescribed medication, and there are over 100 million PPI prescriptions given yearly, accounting for over $10 billion in expenditures.[99] GERD is such a common condition that most patients with mild symptoms self-medicate with over-the-counter H_2-receptor antagonists (H_2RAs) and PPIs. When first seen with symptoms of heartburn or regurgitation without obvious complications, patients can reasonably be placed on 8 to 12 weeks of acid suppression therapy before extensive investigations are carried out. This is done in addition to counseling on dietary and lifestyle modification with avoidance of acidic foods, alcohol, tobacco, and weight loss for those with a BMI >25. In many situations, symptoms will successfully resolve. Patients should be advised to elevate the head of the bed; avoid tight clothing; eat small, frequent meals; avoid eating their nighttime meal shortly before retiring; lose weight; and avoid alcohol, coffee, chocolate, and peppermints, which may aggravate the symptoms.

Patients with persistent symptoms should be given PPIs, such as omeprazole, which result in up to 80% to 90% reduction in gastric acidity and up to 95% reduction in esophageal acid exposure. H_2RAs are less effective in decreasing esophageal acid exposure (80%). PPI doses of 40 mg/d will usually heal mild esophagitis, though healing occurs in only three-fourths of patients with severe esophagitis. It is important to realize that in patients who reflux a combination of gastric and duodenal juice, inadequate acid suppression therapy may give symptomatic improvement while still allowing mixed reflux and persistent mucosal damage in an asymptomatic patient. Unfortunately, within 6 months of discontinuation of any form of medical therapy for GERD, 80% of patients have a recurrence of symptoms.[100]

Despite their effectiveness, periods of acid breakthrough occur in 75% to 80% of patients taking PPIs, primarily at nighttime.[101,102] This is particularly pertinent because it is during the nighttime and early morning that asthma symptoms are most pronounced and that peak expiratory flow rate is at its lowest. Ranitidine 300 mg at bedtime appears superior to omeprazole 20 mg at bedtime in preventing acid breakthrough, likely due to the abolition of histamine-mediated acid secretion in the fasting state.

While PPIs are very well tolerated in the short term, there is increasing evidence suggesting potential adverse consequences to their long-term use. Increased relative risk of bone fractures due to calcium malabsorption, pneumonia, chronic kidney disease, dementia, myocardial infarction, renal disease, GI malignancies, B_{12} deficiency, hypomagnesemia, *Clostridium difficile* infection, and interactions with antiplatelet medications have all been reported. Most of the evidence is weak and obtained from observational studies. However, special attention should be given to elderly patients with significant comorbidities, those on many other medications, and patients with known osteoporosis when considering maintenance PPI therapy.[103,104]

Failure of acid suppression to control symptoms or immediate return of symptoms after stopping treatment suggests that either the diagnosis is incorrect or the patient has relatively severe disease. Endoscopic examination at this stage of the patient's evaluation provides the opportunity for assessing the severity of mucosal damage and the presence of Barrett esophagus. Both of these findings on initial endoscopy should prompt 24-hour pH monitoring and manometry to assess the LES and the function of the esophageal body. These studies identify features that predict a poor response to medical therapy, frequent relapses, and the development of complications of GERD. Patients who have these risk factors should be given the option of surgery as a primary therapy.

Antireflux Surgery

Indications

Antireflux surgery is indicated for the treatment of objectively documented, relatively severe GERD. Candidates for surgery include patients with erosive esophagitis, stricture, Barrett esophagus, as well as those without

severe mucosal injury who are dependent on PPIs for symptom relief. Patients with atypical symptoms who have a good response to intensive medical treatment are also candidates. The option of antireflux surgery should be given to all patients who have demonstrated the need for long-term medical therapy, particularly if escalating doses of PPIs are needed to control symptoms. Antireflux surgery may be the preferred option in patients younger than 50 years, those who are noncompliant with their drug regimen, those for whom medications are a financial burden, and those who favor a single intervention over long-term drug treatment. It may be the treatment of choice in patients who are at high risk of progression despite medical therapy, such as those with nocturnal reflux on 24-hour esophageal pH study, a structurally deficient LES, mixed reflux of gastric and duodenal juice, and mucosal injury at presentation.[105]

Preoperative Evaluation

9 The preoperative evaluation of GERD is imperative to determining a diagnosis and establishing an optimal treatment plan for each individual patient. **Table 42.3** outlines four important goals in the diagnosis of suspected GERD and those being considered for antireflux surgery. Please refer to the prior section in this chapter for details on preoperative studies, the below will be a summary.

Table 42.3 Goals of the Diagnostic Approach to Patients Suspected of Having GERD and Being Considered for Antireflux Surgery

Establish that GERD is the underlying cause of the patient's symptoms.
Estimate the risk of progressive disease.
Determine the presence or absence of esophageal shortening.
Evaluate esophageal body function and, occasionally, gastric emptying function.

GERD, gastroesophageal reflux disease.

Table 42.4 Predictors of Outcome after Laparoscopic Fundoplication: Stepwise Logistic Regression Results of 199 Patients

Predictor	Status	Adjusted Odds Ratio (95% Confidence Intervals)	Wald p Value
Composite Acid score	Increased	5.4 (1.9–15.3)	<0.001
	Normal	—	—
Symptom	Typical	5.1 (1.9–13.7)	<0.001
	Atypical	—	—
Response to Medical Therapy	Complete/partial	3.3 (1.3–8.7)	0.02
	Minor/none	—	—

Odds ratios and corresponding p values are adjusted for age and for all other factors in the model.

From Campos GM, Peters JH, DeMeester TR, et al. Multivariate analysis of the factors predicting outcome after laparoscopic Nissen fundoplication. *J Gastrointest Surg* 1999;3(3):292–300.

Patient selection is critically important and the studies outlined in the prior section of this chapter increase the degree of certainty of a diagnosis of GERD. In addition, three specific factors have been identified as predictive of a positive outcome after antireflux surgery.[106] These factors include: abnormal score on 24-hour esophageal pH monitoring, present of typical symptoms of GERD (heartburn or regurgitation), and symptomatic improvement in response to acid suppression therapy (**Table 42.4**).

Endoscopic Assessment. Upper endoscopy is the true physical examination of the foregut and is important preoperatively to determine complications of GERD and anatomical landmarks. The location of the diaphragmatic crura, the GE junction, and the

squamocolumnar junction must be identified. The GE junction is located where the tubular esophagus meets the rugal folds, which is often just proximal to the squamocolumnar junction, which is where there is a visible change from the velvety (and darker) columnar epithelium to the lighter squamous epithelium. Additionally, the presence of endoscopic esophagitis must also be classified and the presence of Barrett esophagus must be determined (**Table 42.1**). As mentioned above, identification of the gastroesophageal valve with Hill grading and determination of presence of a hiatal hernia is also imperative to operative planning.

Twenty-four–Hour Ambulatory pH Monitoring. Ambulatory pH testing is widely considered to be the "gold standard" to diagnose GERD, and gives the most direct method for determining the relationship between symptoms and gastric acid exposure. It is highly sensitive and specific and gives an objective assessment of acid exposure. More frequently, the ambulatory pH study is reserved for those patients with atypical symptoms of GERD and/or no evidence of reflux (esophagitis) on upper endoscopy.

Ambulatory Combined Impedance-pH Monitoring. Combined impedance-pH monitoring allows for measurement of both acid and nonacid refluxate. The Sleuth system (Sandhill Scientific, Denver, Colorado) uses a single catheter to measure both (**Fig. 42.30**). This multichannel impedance (MII-pH) has been validated, and has interestingly shown that PPI therapy does not change number of reflux events; it solely converts those events to a neutral pH.[107,108] This modality is generally used in patients who have atypical symptoms of GERD or who are resistant to medical therapy, with one study demonstrating superior accuracy compared to pH monitoring alone.[109]

Radiographic Evaluation. Radiographic evaluation of the esophagus is important for assessment of anatomy and function. These include assessment of presence and size of hiatal hernia, esophageal peristalsis and bolus transit, anatomic abnormalities, as well as

presence of esophageal shortening (**Fig. 42.31**). In addition, the presence of reflux can also be visualized, and is particularly reliable if spontaneous while the patient is upright.

A barium upper GI study or esophagram generally follows a protocol to ensure a complete detailed examination of the esophagus is completed (**Table 42.5**).

Assessment of Esophageal Function. Esophageal body function influences the decision to do a partial or complete fundoplication and can impact the improvement of symptoms after surgery. Esophageal motility is best assessed with esophageal manometry, a study that consists of 10 wet swallows with 5 mL of water that records amplitude, duration, and morphology of esophageal contractions (**Fig. 42.18**).

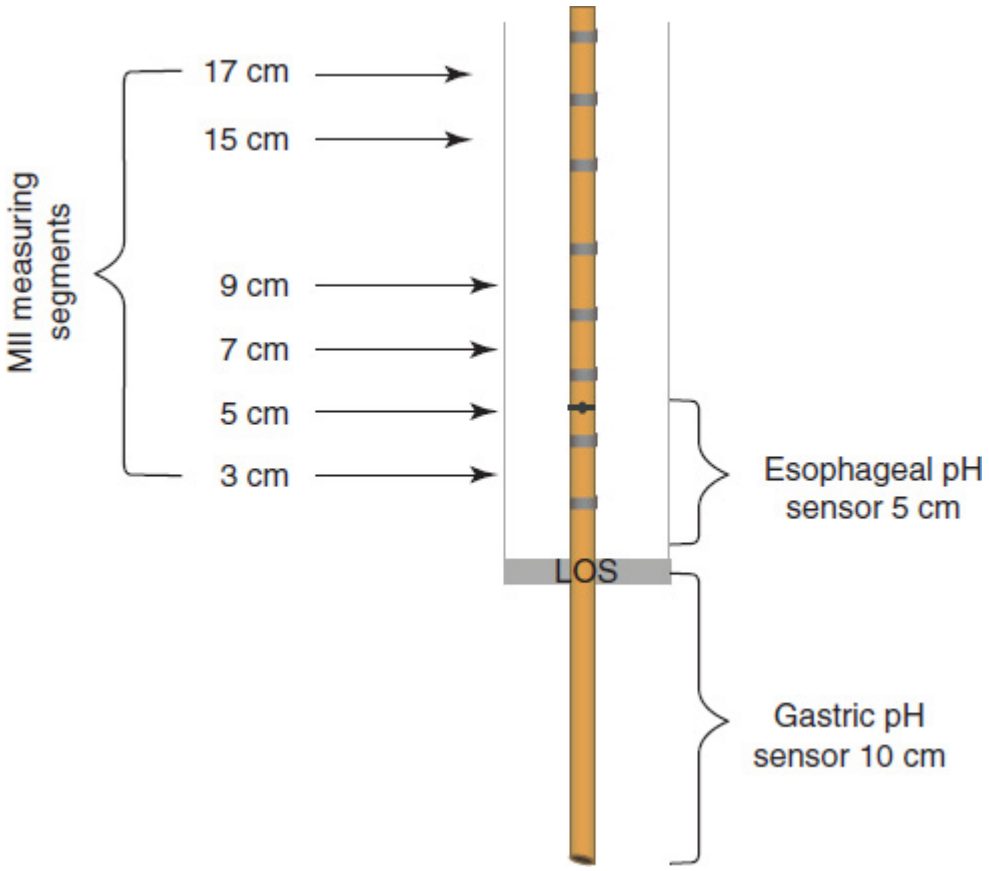


Figure 42.30 Combined multichannel intraluminal impedance–pH catheter. (Reproduced with permission from Mainie I, Tutuian R, Agrawal A, et al. Combined multichannel intraluminal impedance-pH monitoring to select patients with persistent gastro-oesophageal reflux for laparoscopic Nissen fundoplication. *Br J Surg* 2006;93[12]:1483–1487.)

Figure 42.31 Barium-filled esophagogastric segment in a patient with a short esophagus. Note that the gastroesophageal junction is well above the hiatus.

Assessment of Gastric Function. Patients who suffer from nausea, epigastric pain, early satiety, bloating, or burping may have impaired gastric motility. Gastric emptying studies are necessary in these patients and these symptoms should be evaluated for every patient with refractory GERD. Gastric emptying studies are completed with

radionuclide-labeled meals with interval imaging to assess percent and timing of passage of both liquids and solids.

Table 42.5 University of Southern California Protocol for Video Esophagram Studies

Patient Position	Purpose	Technique
Prone RAO	Esophageal body function	Five separate 10-mL swallows, 15 sec between each, follow bolus on videotape Video swallow over thoracic inlet and another over distal third of esophagus without panning
	Esophageal diameter	Rapid swallow of several gulps to distend esophagus maximally
	Gastric function	Video-record activity of stomach and duodenum for 30 sec in prone position
Supine	Relationship of GE junction to hiatus	Two or three individual swallows focused on distal esophagus and GE junction
Erect	Cricopharyngeal function	Lateral and anteroposterior views of oropharynx and upper esophagus
	Mucosal injury	Spot of collapsed esophagus for mucosal detail

	Reducibility of hernia	Video images of one or two swallows focused on distal esophagus and GE junction
	Gas distention of distal esophagus	
Erect	Solid bolus transport	Record video images of passage of two contrast-coated hamburger boluses from oropharynx to stomach

GE, gastroesophageal; RAO, right anterior oblique.

Impedance Planimetry. Endoflip is an impedance planimetry system used to evaluate real-time pressure, diameter, and distensibility of the esophagus and gastrointestinal sphincters.[23] This is particularly useful to assess the LES during workup of achalasia, and can also be used intraoperatively, for fundoplication or myotomy to assess diameter, pressures, and distensibility pre- and postintervention.[110]

Partial versus Complete Fundoplication

10 The decision between partial and complete fundoplication requires considerable judgment. Randomized studies have shown equivalence of these approaches in terms of operative time, perioperative morbidity, and hospital stay.[111,112] Resting and residual LES pressures seem to be greater after complete fundoplication and esophageal clearance prolonged in patients after complete fundoplication compared with after posterior partial fundoplication.[112] In the first 2 years after operation, partial fundoplication was linked to a greater overall level of patient satisfaction, lower incidence of dysphagia, inability to belch, and excessive flatus.[113] Long-term results of randomized trials between Nissen and Toupet fundoplication reveal no significant differences in heartburn, regurgitation, or dysphagia scores.[114,115] Several randomized trials comparing laparoscopic Nissen fundoplication to

an anterior 180-degree partial fundoplication similarly revealed no significant differences between the two groups with regard to reflux symptoms and patient satisfaction in up to 10 years' follow-up, but with some studies showing lower rates of dysphagia and gas-related symptoms.[116]

These observations, however, must be tempered by reports questioning the durability of partial fundoplications. Jobe et al.[117] found that 51% of patients studied by 24-hour esophageal pH monitoring after Toupet fundoplication still had pathologic acid exposure. Disturbingly, only 40% of the refluxers were symptomatic. Broeders et al. found higher total esophageal acid exposure time, more frequent acid reflux episodes, and lower mean LES and relaxation pressures in patients 14 years after anterior 180-degree fundoplication.[118] The presence of a defective LES function, an aperistaltic distal esophagus, and higher grades of esophagitis are risk factors for partial fundoplication failure.[114,117] Bell et al. reported recurrent reflux in 14% after Toupet fundoplication. The presence of mild esophagitis and a normal LES were associated with a 3-year success rate of 96%, whereas the presence of complicated esophagitis or a defective LES lowered this value to 50%.[119]

These findings lead to the question whether total fundoplication should be applied more liberally to patients with severe reflux disease and associated esophageal dysmotility. Patti et al. reported on 357 patients undergoing antireflux surgery, 235 undergoing a "tailored approach" with either a partial or total fundoplication, depending on the results of preoperative manometry and 122 more recent patients undergoing a total fundoplication regardless of the quality of esophageal peristalsis.[120] In the first group, heartburn from pathologic reflux, confirmed by postoperative ambulatory esophageal pH monitoring, recurred in 19% after partial fundoplication and in 4% after total fundoplication. In the latter group, heartburn recurred in 4% after total fundoplication.

Importantly, the incidence of postoperative dysphagia was similar in the two groups. Given this evidence, we believe that partial fundoplication is best reserved for patients with severe esophageal dysmotility approaching aperistalsis, such as occurring in scleroderma, or in combination with a distal esophageal myotomy for achalasia.[121]

Laparoscopic Nissen Fundoplication

Table 42.6 lists the most critical steps in the performance of laparoscopic fundoplication and concurrent hiatal hernia repair as necessary.

Port Placement. Five ports are used. The camera is placed superiorly and to the left of the umbilicus, roughly one-third of the distance to the xiphoid process to optimize the visualization of the hiatus. The liver is retracted with flexible retractor placed through a 5-mm incision in the right subcostal region along the anterior axillary line. A retraction port is placed slightly above the level of the umbilicus, in the left anterior axillary line. The surgeon's right-hand 11-mm port is placed 1 to 2 cm below the costal margin approximately at the lateral rectus border to allow triangulation between the camera and the two working instruments. The surgeon's left hand 5-mm port is placed last, after the left lateral segment of the liver has been retracted, to visualize the best trajectory under the falciform ligament toward the hiatus.

Crural Dissection. In patients without a large hiatal or paraesophageal hernia dissection begins with division of the gastrohepatic omentum and identification of the right crus of the diaphragm. Care is taken to preserve the hepatic branch of the anterior vagus nerve. Alternatively, when a paraesophageal hernia is present, the hernia contents are reduced as much as possible first, and sac excision is started at the 2 o'clock position at the hiatus to avoid injuring the left gastric vessels that are routinely up in the chest on the right side of the hiatus.

Table 42.6 Elements of Laparoscopic Fundoplication

1. Crural dissection with identification and preservation of both vagus nerves
2. Circumferential dissection of the esophagus and mobilization of the gastric fundus
3. Crural closure
4. Creation of a short, loose fundoplication around the distal esophagus

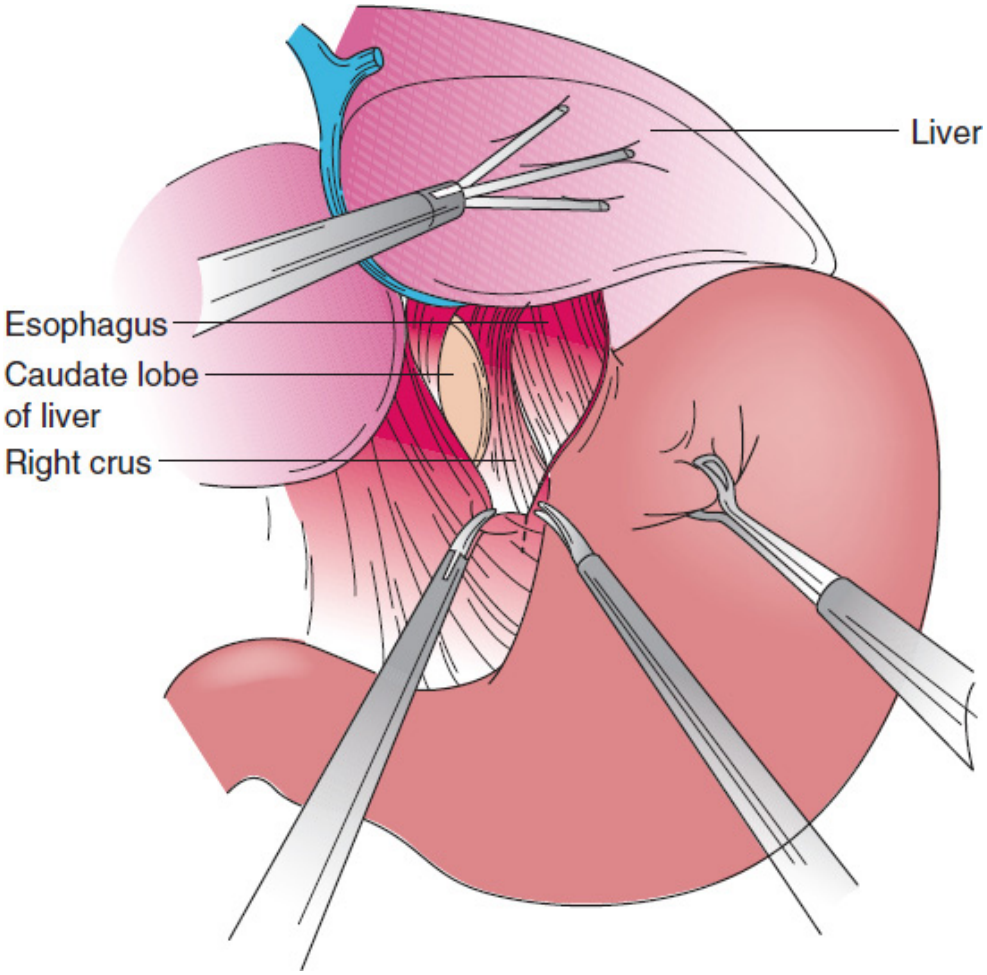


Figure 42.32 Illustration of the initial dissection of the esophageal hiatus. The right crus is identified and dissected toward its posterior confluence with the left crus.

A replaced left hepatic artery arising from the left gastric artery is present in up to 25% of patients; it should be identified and can typically be clipped and divided, but a pulse in the hepatoduodenal ligament should be confirmed first. The peritoneum overlying the anterior aspect of the right crus is incised and the plane between the esophagus and right crus developed (**Fig. 42.32**).

The dissection is then continued anteriorly, and the esophagus and anterior vagus nerve are swept downward away from the phrenoesophageal ligament. The anterior crural tissues are divided and the left crus identified. The anterior vagus nerve often "hugs" the left crus and can be injured in this portion of the dissection if not carefully searched for and protected. The left crus is dissected as completely as possible, including taking down the angle of His and the attachments of the fundus to the left diaphragm (**Fig. 42.33**).

The short gastric vessels are divided along with the posterior pancreatic vessels to completely mobilize the gastric fundus. A window behind the GE junction is then created and a Penrose drain passed around the distal esophagus for retraction.

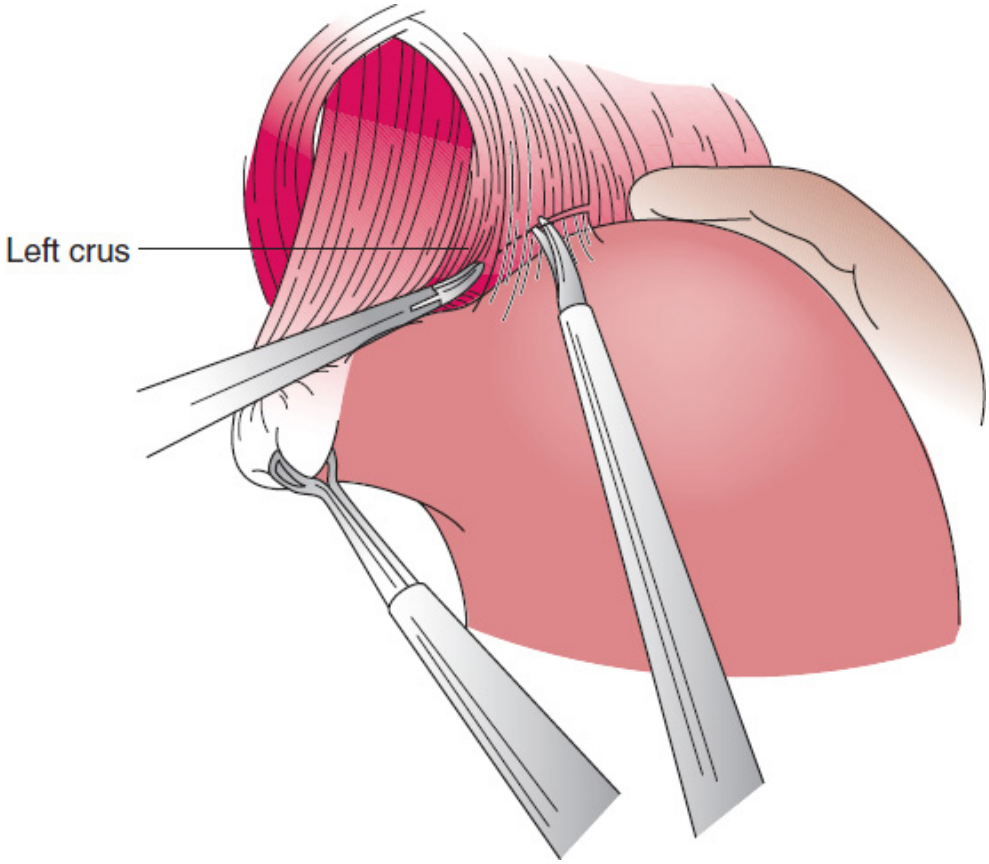


Figure 42.33 Left-sided crural dissection. The left crus is dissected as completely as possible and the attachments of the fundus of the stomach to the diaphragm are taken down.

Esophageal Mobilization and Crural Closure. The esophagus is mobilized circumferentially into the posterior mediastinum centimeters to provide at least 3 cm of intra-abdominal esophageal length. Both the anterior and posterior vagus nerve should be identified and protected. The right and left pleural reflection often come into view and should be avoided, although if a pleural opening is created it is well tolerated provided the hole is made large enough to prevent a ball valve tension pneumothorax from developing. Following mobilization and an assessment of intra-abdominal esophageal

length, the hiatus is closed. The esophagus is retracted anteriorly and to the left, and the crura is approximated with interrupted 0-Ethibond sutures, starting just above the aortic decussation and working anteriorly. The authors prefer using absorbable pledgets to reinforce the repair. Care must be taken to identify the anterior surface of the aorta during this step in order to avoid inadvertent injury to it while suturing the left crus. If the crura cannot be approximated despite maximal mobilization, a right-sided relaxing incision in the diaphragm is recommended to allow the crura to be closed without tension. The defect created in the diaphragm is then repaired with permanent mesh to avoid herniation of abdominal contents into the thorax. The authors prefer a Gore-Tex patch for this purpose and reinforce the primary crural closure with an absorbable or biologic mesh. When the right-sided relaxing incision is inadequate (with a very large hernia or in reoperations), a left diaphragm relaxing incision may be necessary. Synthetic mesh bridging the crura should be avoided because it leads to the highest risk of mesh erosion. There are some studies showing that reinforcement of a primary crural closure with biologic or resorbable mesh may help prevent early hiatal hernia recurrence, but this advantage disappears with long-term follow-up, and may increase the complexity of a reoperation if one is necessary in the future.

Creation of the Fundoplication. A 2-cm loose fundoplication is created after ensuring that there is no twisting of the wrap (**Fig. 42.34**). The mid-posterior fundus is grasped and passed left to right behind the esophagus to ensure that the posterior fundus is used for the posterior aspect of the fundoplication (**Fig. 42.35**). One should gently bring the posterior fundus behind the esophagus to the right side with an upward, rightward, and clockwise twisting motion. A 0-0 silk suture can be placed in the mid-posterior fundus 6 cm down from the GEJ to facilitate this step, and grasping it from the right side helps bring the posterior fundus around to create the fundoplication. The anterior wall of the fundus is then folded over the esophagus to meet the posterior at about the 9 o’clock position such that the

esophagus is imbricated within the fundus rather than having the fundus twisted or spiraled around the esophagus.

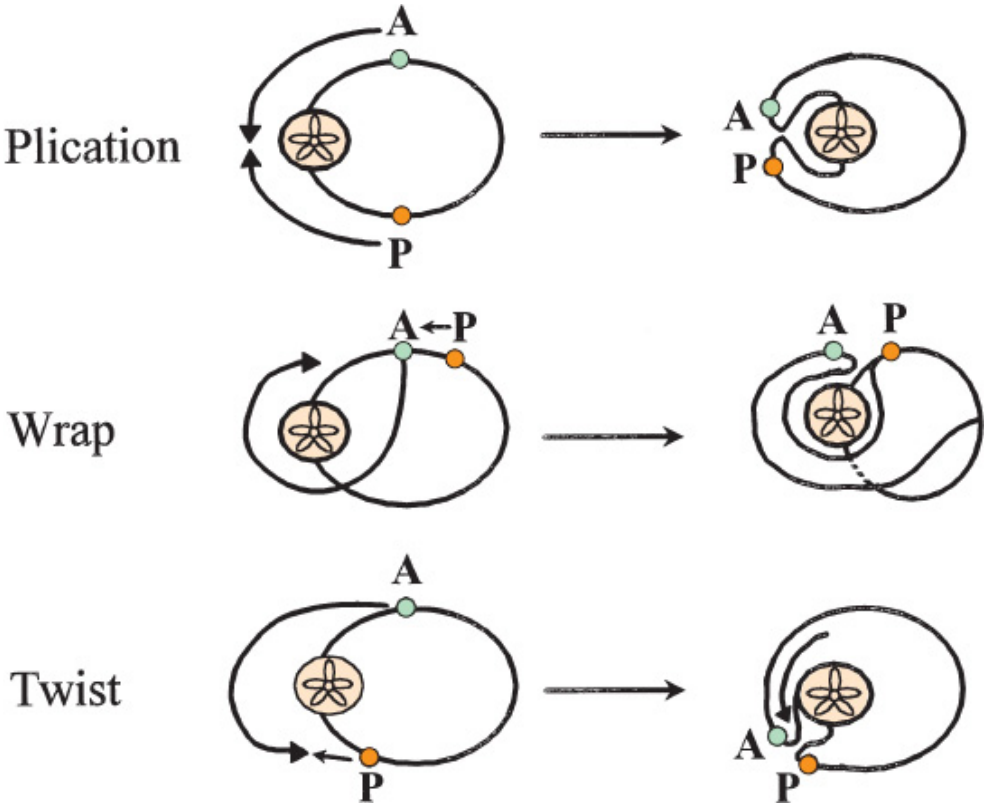


Figure 42.34 Schematic representations of the various possibilities of orientation of a Nissen fundoplication. The **top** set of figures represents the preferred approach, whereas the **bottom** two sets can be seen to result in twisting of the fundoplication.

The posterior and anterior fundic lips should be maneuvered (as in a "shoe shine") to allow the fundus to envelop the esophagus without twisting. The esophagus should comfortably lie in the untwisted fundus prior to suturing. Adequate size of the posterior opening must be ensured to avoid any compression of the posterior fundus, and there must be sufficient mobilization of the posterior fundus to avoid undue tension on the fundoplication. A 60-Fr bougie is passed to properly size the fundoplication, and the "lips" of the fundoplication sutured utilizing three interrupted 2-0 silk sutures buttressed with absorbable pledgets. The middle stitch can incorporate the muscular wall of the esophagus to facilitate a more secure fundoplication. The most common error is an attempt to grasp the anterior portion of the stomach to construct the right lip of the fundoplication rather

than the posterior fundus. When finished, the suture line of the fundoplication should be facing in a right anterior direction (**Fig. 42.36**). One may also consider a single-stitch pexy of the wrap posteriorly to the closed crura at this point to help prevent reherniation.[122]

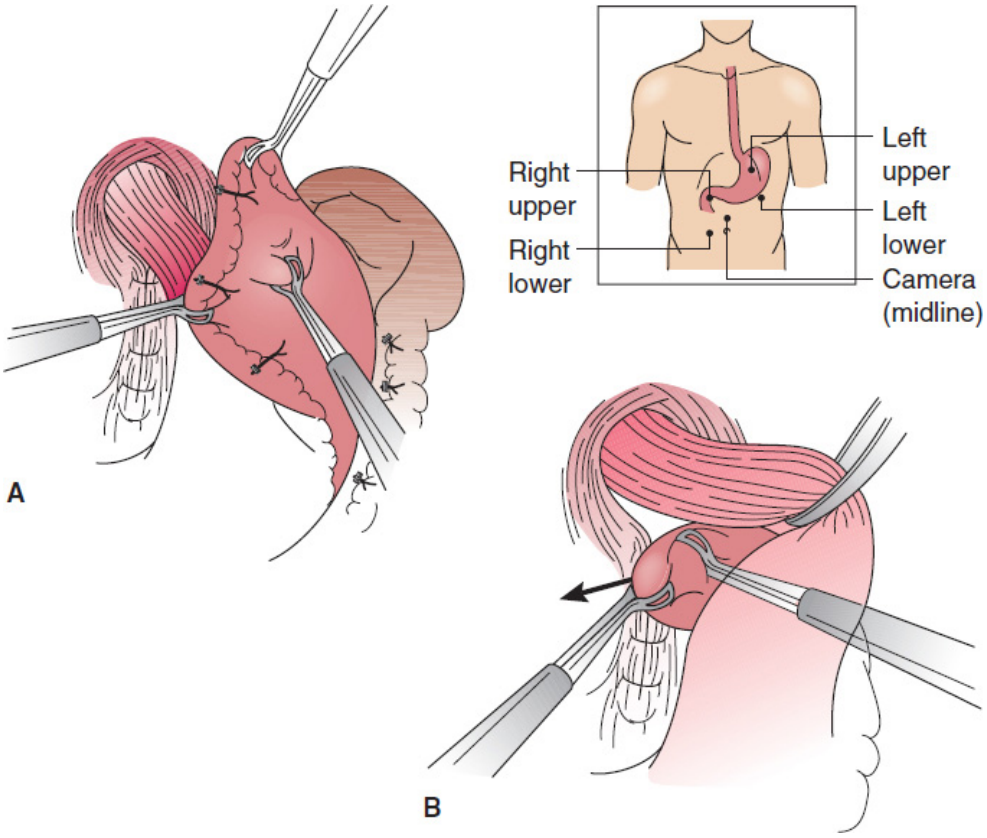


Figure 42.35 Placement of Babcock on the posterior fundus in preparation for passing it behind the esophagus to create the posterior or right lip of the fundoplication. The posterior fundus is passed left to right and grasped from the right through the right upper trocar. **A:** Location of posterior fundus for passage to the right side. **B:** The posterior fundus passed underneath the esophagus and grasped on the right.

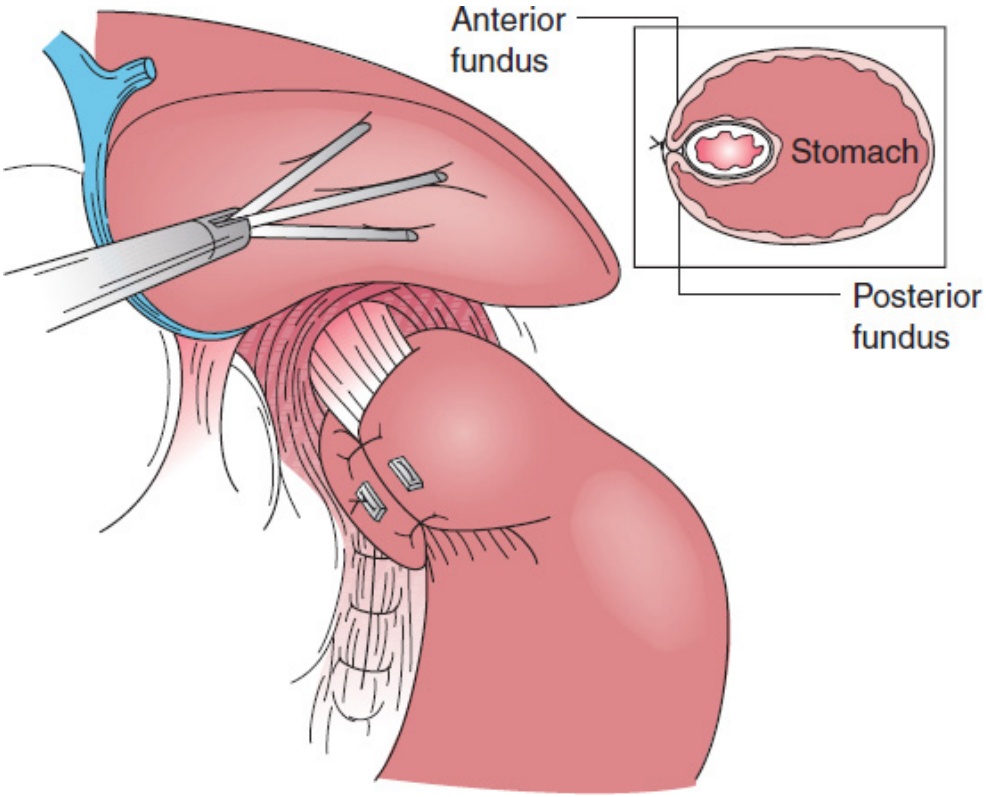


Figure 42.36 Fixation of the fundoplication. The fundoplication is sutured in place with pledgeted interrupted 2-0 silk sutures. A 60-Fr bougie is passed through the gastroesophageal junction prior to fixation of the wrap to ensure a floppy fundoplication. Inset illustrates the proper orientation of the fundic wrap.

Transthoracic Nissen Fundoplication

The indications for performing an antireflux procedure by a transthoracic approach are given in **Table 42.7**.

In the thoracic approach the hiatus is exposed through a left posterior lateral thoracotomy incision in the sixth intercostal space. When necessary, the diaphragm is incised circumferentially 2 to 3 cm from the lateral chest wall for a distance of approximately 10 to 15 cm. The esophagus is mobilized from the level of the diaphragm to underneath the aortic arch. Mobilization up to the aortic arch is usually necessary for repair in patients with a shortened esophagus to prevent undue tension. Failure to do this is one of the major causes for subsequent breakdown of a repair and return of symptoms. The cardia is then freed from the diaphragm. When all the attachments between the cardia and diaphragmatic hiatus are divided, the fundus and part of the body of the stomach are drawn up through the hiatus into the chest. The vascular fat pad that lies at the GEJ is excised. Crural

sutures are then placed to close the hiatus though are not tightened until later. The fundoplication is constructed by enveloping the fundus around the distal esophagus in a manner similar to that described for the abdominal approach. When complete, the fundoplication is placed into the abdomen by compressing the fundic ball with the hand and manually maneuvering it through the hiatus. The previously placed crural stitches are then tightened and knotted.

Collis Gastroplasty

In patients with a short esophagus secondary to a stricture, Barrett esophagus, or a large hiatal hernia, the esophagus can be lengthened with a Collis gastroplasty to allow a tension-free fundoplication around the newly formed gastric tube. Prior to considering a Collis, one must perform an extensive mediastinal mobilization of the esophagus at least 6 cm above the GE junction. If this does not achieve at least 2 cm of intra-abdominal esophageal length, a gastroplasty should be performed. With the bougie in place, a point approximately 3 cm below the angle of His is marked on the stomach with electrocautery. A 45-mm EndoGIA stapler (Universal EndoGIA, USSC, Stamford, Connecticut) is then used to fire horizontally toward the bougie at that level. A vertical staple line is then created alongside the bougie, as the assistant retracts the resected wedge laterally. This results in a 3- to 4-cm neoesophagus, which is then tested with methylene blue or saline to rule out a leak prior to proceeding with the fundoplication.[123]

Table 42.7 Indications for Performing an Antireflux Procedure by a Transthoracic Approach

Indication	Explanation
Previous hiatal hernia repair	In this situation, a peripheral circumferential incision in the diaphragm is made to provide simultaneous exposure of the upper abdomen. This allows safe dissection of the previous repair from both the abdominal and thoracic sides of the diaphragm.
Concomitant procedure	Concomitant esophageal myotomy for achalasia or diffuse spasm.
Short esophagus	This is usually associated with a stricture or Barrett esophagus. In this situation, the thoracic approach is preferred to allow maximum mobilization of the esophagus, the performance of a Collis gastroplasty, or, if necessary, placement of the repair without tension below the diaphragm.
Sliding hiatal hernia that does not reduce below the diaphragm during a roentgenographic barium study in the upright position	This can indicate esophageal shortening and, again, a thoracic approach is preferred for maximum mobilization of the esophagus and, if necessary, the performance of a Collis gastroplasty.
Associated pulmonary pathology	The nature of the pulmonary pathology can be evaluated and the proper pulmonary surgery, in addition to the antireflux repair, can be performed.

Obesity	The abdominal repair is difficult because of poor exposure, whereas the thoracic approach gives better exposure and allows a more precise repair.

Outcomes following Antireflux Surgery

Symptomatic and Objective Outcomes after Antireflux Surgery. Multiple studies of long-term outcomes following laparoscopic fundoplication document its ability to relieve typical reflux symptoms (heartburn, regurgitation, and dysphagia) in more than 90% of patients at follow-up intervals averaging 2 to 3 years and 80% to 90% of patients 5 years or more following surgery.[124–127] The results of laparoscopic fundoplication compare favorably with those of the "modern" era of open fundoplication.[126] Of note, atypical reflux symptoms (cough, asthma, laryngitis) after surgery are relieved in only two-thirds of patients.[128]

When compared to patients on PPIs, laparoscopic fundoplication leads to a better GERD-specific quality of life, fewer heartburn symptoms, but a higher risk of adverse events. The treatment failure rates are significantly lower after antireflux surgery in follow-up of 5 to 12 years,[127] with 5% to 18% requiring revision surgery. The most common reason for reoperation is dysphagia, which occurs in 2% to 16% of the patients. Rates of recurrent hiatal herniation are largely dependent on the size of the underlying hiatal hernia. While the need for reoperation after fundoplication for GERD is only approximately 5% over a patient's lifetime, it can be as high as 42% after repair of a giant paraesophageal hernia.[129]

When assessing some of the unpleasant side effects of antireflux surgery such as hyperflatulence and inability to belch or vomit, these symptoms are significantly more common than in patients on medical therapy. Nevertheless, studies have shown an improvement in quality of life following antireflux surgery, outperforming medical therapy on some parameters.[130–134]

Looking at objective physiologic outcomes, patients after antireflux surgery experience significantly greater reductions in 24-hour esophageal acid exposure when compared to the medical treatment cohort in long-term

follow-up.[135] Laparoscopic fundoplication also results in a significant increase in LES pressure and length, generally restoring these values to normal. Esophageal acid exposure is restored to normal in >90% of Nissen fundoplications versus 50% of patients with a partial fundic wrap.[117] There is still a significant proportion of patients (62%) who continue to take acid suppression medications postoperatively,[136] but only a quarter of these patients have been found to have abnormal pH scores.[137] Based on these data, objective evidence of reflux should be obtained prior to restarting acid suppression medications in patients with symptoms after a fundoplication.

Complications of Antireflux Surgery. Laparoscopic Nissen fundoplication has been extensively studied and its complications are well documented. Postoperative complications occur in approximately 8% of patients, with the rate of conversion to an open procedure of about 4%. The most common perioperative complication is early wrap herniation (1.3%), defined as occurring within 48 hours of surgery.[138]

Both pneumothorax and pneumomediastinum have been reported secondary to the breach of either pleural membrane. Accumulated carbon dioxide usually dissipates following release of pneumoperitoneum by a combination of positive pressure ventilation and absorption, and creating a large pleural defect prevents tension pneumothorax. Intraoperative complications are rare, and include trocar injury, gastric or esophageal perforation, hemorrhage, retractor trauma to the liver, splenic injury, and vascular injury to the aberrant left hepatic vein or inferior vena cava. Generally, immediate recognition and repair of injury is the key to avoiding a major complication. Major vascular injury mandates immediate conversion to an open procedure to achieve hemostasis. Mortality rate has been reported at 0.08%.

Roux-en-Y Gastric Bypass. Bariatric surgery is the procedure of choice in patients with refractory GERD and a BMI ≥ 35.[35] Fundoplication alone in this patient population poses a significant risk of failure or hernia recurrence without significant weight loss. Of the available bariatric procedures, Roux-en-Y gastric bypass (discussed in detail elsewhere in this text) has been demonstrated to be the most

effective at treating GERD, while sleeve gastrectomy carries the potential to exacerbate GERD symptoms and is contraindicated in patients with known esophagitis.

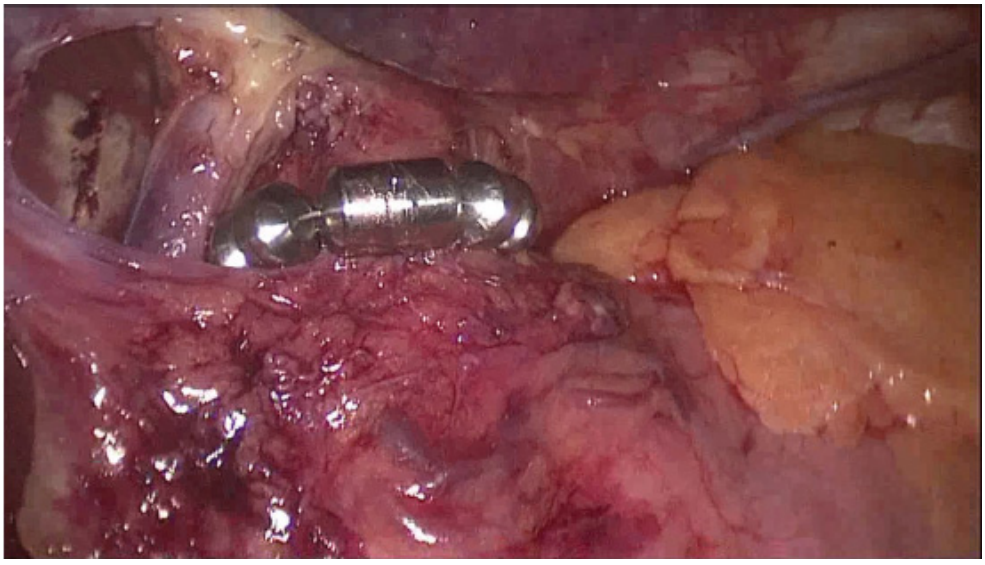


Figure 42.37 Magnetic sphincter augmentation device (LINX) placed around the gastroesophageal junction.

Magnetic Sphincter Augmentation. The LINX Reflux Management System (Torax Medical, Shoreview, MN) is a ring of titanium magnetic beads that is placed around the GEJ laparoscopically to mimic and augment the function of the LES (**Fig. 42.37**). The ring increases the natural resistance of the LES to opening but expands to allow food passage with swallowing. Concurrent hiatal hernia repair is performed during LINX placement, although patients with large hernias (>3 cm) and/or Barrett esophagus have traditionally been excluded from this procedure. Other exclusion criteria include those with allergies to titanium, stainless steel, nickel, or iron. Caution should be taken in those who need ongoing MRI screening, although the newest version of the device is compatible with 1.5-Tesla MRI.

Single-arm studies have shown that 80% to 90% of patients stop PPI use at up to 5 years after LINX placement, with a normalization of esophageal pH in 70%.[139,140] Importantly, all patients retain the ability to belch and vomit. Ganz et al.'s pivotal trial showed that dysphagia is present in about 68% of the patients in the first several months postoperatively, but decreases to 4%

by 3 years. Five percent of patients required endoscopic balloon dilation or removal of the device for severe dysphasia.[141] Subsequent studies have also demonstrated that device erosion occurs in about 1.2% of the patients.[142] Nonrandomized controlled trials have shown comparable outcomes of the LINX to Nissen fundoplication with lower rates of gas bloat and greater ability to belch and vomit in the LINX patients, with comparable safety, rates of PPI suspension, and postoperative GERD-HRQL scores.[143] Long-term data on hernia recurrence in patients with magnetic sphincter augmentation and concurrent large hiatal or paraesophageal hernia repair is missing. However, short-term results are encouraging, with a 10% endoscopic recurrence rate reported at 12 months. Less than a third of these patients were symptomatic and required operative intervention.[144]

Endoscopic Management of GERD

11 Medical therapy for GERD and antireflux surgery both have inherent drawbacks. Major limitations of acid suppressive medications include the inability to prevent regurgitation of weakly acidic or nonacidic refluxate and the need for chronic, continual therapy, not to mention the cost, inconvenience, potential side effects, and need for ongoing dietary and lifestyle modifications. In addition, current therapy does not address the main pathophysiologic contributor to the presence of GERD, the mechanically defective LES Fundoplications, while intended to permanently restore the LES, suffer from the potential for perioperative complications, a high initial cost, the risks inherent in general anesthesia, as well as possible short- and long-term side effects. For all these reasons, there is an interest in developing endoscopic means of restoring LES competence. The two main endoscopic approaches for treating GERD include the Stretta procedure and transoral incisionless fundoplication (TIF 2.0).

Radiofrequency Ablation. Stretta (Curon Medical, Sunnyvale, CA) involves the application of controlled radiofrequency energy (RFA) to the LES region using a four-channel RF generator and catheter system that is introduced endoscopically. Multiple lesions are created in the region 2 cm above and below the z-line, and thermocouples at each needle tip ensure that the lesion temperatures stay below 100°C to minimize collateral tissue damage. Appropriate candidates

for this procedure include patients who have relatively normal esophageal peristalsis and adequate relaxation of the LES, nonerosive reflux, or mild esophagitis (LA grade A or B), and are refractory to or wish to discontinue long-term medical therapy. Those with large hiatal hernias, significant dysphagia or esophageal aperistalsis, or advanced esophagitis are not good candidates for Stretta.

This procedure has been shown to reduce the rate of postprandial transient LES relaxations and esophageal acid exposure.[145,146] Stretta also decreases the compliance of the GEJ and causes a reduction in esophageal acid sensitivity, leading to a decrease in GERD symptoms.[147,148] RCTs and cohort studies show a significant reduction in PPI use at up to 10 years of follow-up.[149–151] One small cohort study has suggested that RFA may also improve gastroparesis via an unknown mechanism.[152]

Nonrandomized studies comparing RFA to fundoplication show that 51% to 58% of the Stretta patients are able to discontinue PPI use at 5 years of follow-up, compared to 91% to 97% of the patients after a Nissen.[153] Although there was a significant improvement in symptoms after RFA, up to 59% of those patients subsequently required antireflux surgery.[154] The complication rate is very low at <1%, with small erosions and mucosal lacerations being the most common adverse events.[155]

Transoral Incisionless Fundoplication (TIF 2.0). TIF is performed using the EsophyX Z+ device (EndoGastric Solutions, Redmond, WA), which creates full-thickness serosa-to-serosa plications with polypropylene H-shaped fasteners to reconstruct a valve that is 200 to 300 degrees in circumference and 3 cm in length,[156] mimicking a partial fundoplication. TIF 2.0 has been shown to reduce GEJ distensibility and increase resting LES pressures, thereby decreasing the number of transient LES relaxation episodes. It is appropriate for patients with a dysfunctional LES without a significant hiatal hernia (Hill grade I or II). Several RCTs comparing TIF 2.0 to PPI therapy showed that the procedure is superior to medical treatment in eliminating regurgitation and extraesophageal symptoms, and allowed 66% to 72% of patients to stay off PPIs for at least 5 years.[157,158] The reported complication rate is 2% to 2.5%, and most commonly

consists of gastrointestinal perforation, bleeding, and pneumothorax.[159] Comparative data to surgical fundoplication is pending.

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Esophageal Tumors and Injury

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Key Points

1. The incidence of esophageal adenocarcinoma is increasing but squamous cell carcinoma is the most common cancer histology worldwide.
2. The latest AJCC esophageal cancer staging system separates the clinical, pathologic, and post-neoadjuvant stage groups and has different staging systems for squamous cell and adenocarcinoma.
3. Resection remains essential to cure of esophageal cancer for most patients who do not have metastatic disease. The mortality of esophagectomy has improved over time, particularly in high-volume centers. Minimally invasive techniques are increasingly used, but the procedure remains complex with relatively high morbidity.
4. Esophagectomy without induction therapy is recommended for superficial tumors that involve the submucosa (T1bN0M0) so that lymph nodes can be removed for diagnostic and therapeutic purposes.
5. Whether to give neoadjuvant therapy before esophagectomy for T2N0M0 esophageal cancer is controversial.
6. Neoadjuvant chemoradiation improves overall survival and disease-free survival over primary surgery in patients with locoregional disease.
7. Esophagectomy is rarely indicated for patients with metastatic esophageal cancer but palliative procedures can improve comfort, possibly restore swallowing ability, and provide nutritional support.
8. Choice of esophagectomy (three-incision, transhiatal, Ivor Lewis, or thoracoabdominal; open or minimally invasive) depends on the tumor location, patient characteristics, and surgeon experience.
9. Leiomyomas are the most common benign esophageal neoplasm and can often be resected by endoscopic submucosal dissection or surgical enucleation.

MALIGNANT ESOPHAGEAL NEOPLASMS

Epidemiology and Histology

Esophageal cancer is the most common indication for esophagectomy. Although relatively uncommon in that it represents only 1% of all new cancer cases, the number of cases of esophageal cancer in the United States has risen from less than 14,000 new cases annually in the 2000s, to almost 17,000 annual new cases in 2012, and now to an estimate of 18,440 in the year 2020.[1–5] Adenocarcinoma and squamous cell carcinoma are by far the most common esophageal cancer 1 histologies. Squamous cell carcinoma is much more common worldwide, with an estimated 398,000 squamous cell carcinoma cases and only 52,000 adenocarcinoma cases in 2012.[6] The epidemiology in the United States has evolved such that adenocarcinoma (64% of esophageal cancer cases) is now more common than squamous cell carcinoma (31% of cases).[1,2,5]

Esophageal cancer in the United States is most frequently diagnosed among people aged 65 to 74 years, with a median age at diagnosis of 68.[1] Tumor histology appears to differ by race: 71.4% of cases diagnosed among Caucasian patients are adenocarcinomas, while 75% of cases diagnosed among Black patients are squamous cell carcinoma.[1] Interestingly, the incidence of esophageal cancer among white men has almost doubled since 1975 while the incidence among black men and women have significantly decreased.[1] Tobacco use and a history of mediastinal radiation are risk factors for both tumor types.[2,7] Other risk factors for adenocarcinoma include male sex, gastroesophageal reflux disease (GERD), obesity, and Barrett esophagus.[2,8,9] Barrett esophagus with high-grade dysplasia is considered a premalignant condition as 13% to 50% are found to harbor intramucosal carcinoma or invasive carcinoma at the time of biopsy or resection.[2] Additional risk factors for squamous cell carcinoma are conditions that cause chronic esophageal irritation and inflammation such as alcohol abuse, achalasia, esophageal diverticuli, and frequent consumption of extremely hot beverages.[2] Approximately three-quarters of all adenocarcinomas are found in the distal esophagus whereas squamous cell carcinomas are more evenly distributed throughout the distal two-thirds.[2]

Clinical Presentation and Diagnostic Evaluation

The Society of Thoracic Surgeons has published guidelines on the diagnosis and staging of patients with esophageal cancer.[10] The workup often starts because patients present with symptoms of dysphagia (74%) and weight loss (57%) with less common symptoms being heartburn, odynophagia, shortness of breath, chronic cough, hoarseness, and hematemesis.[11] The physical examination is usually unremarkable.[2]

Upper gastrointestinal (GI) tract contrast studies and upper endoscopy with biopsy are commonly the initial diagnostic tests. An upper GI contrast study typically shows a stricture or ulceration when malignancy is present. Upper GI endoscopy typically shows a friable, ulcerated mass, and allows identification of tumor location and length and biopsy for pathologic examination. In addition to identifying the cancer and providing tissue for histologic confirmation, the endoscopy should also report detailed information on the location of the tumor as well as the presence of other areas of Barrett esophagus which are particularly important to the selection of surgical approach. For distal tumors that involve the gastroesophageal junction, the extent of gastric involvement should be carefully evaluated. Tumors with epicenters in the lower esophagus that extend to the junction (Siewert Type I) and tumors of the true gastric cardia with epicenter within 1 cm above and 2 cm below the junction (Siewert Type II) should be treated as esophageal cancers. Tumors with epicenter between 2 cm and 5 cm from junction but infiltrate the junction from superior extension (Siewert Type III) should be treated as gastric cancers though surgical approach will likely involve some degree of distal esophageal resection to obtain negative margins and complete resection.[12]

After a histologic cancer diagnosis has been obtained, subsequent studies are performed to determine clinical stage as accurately as possible before treatment is initiated to optimize esophageal cancer outcomes. Accurate staging and appropriate treatment can avoid both inadequate and unnecessary treatment to balance the potential benefits of improving prognosis with risks of treatment-related morbidity. A computed tomographic (CT) scan of the chest, abdomen, and pelvis with oral and intravenous contrast should be

obtained when esophageal cancer is detected. This study is useful in evaluating for distant metastatic disease such as in the liver or lungs, though CTs are not generally useful for detecting nodal disease or identifying or determining the extent of early-stage cancers localized to the superficial aspect of the esophageal wall.[9] Positron emission tomography (PET) scans improve staging and will detect previously unsuspected metastatic disease in up to 15% to 20% of patients. They should be considered in place of CT scans or as an additional study when the CT scan does not show metastatic disease.[13,14] Further studies that evaluate T and N status would not typically impact treatment and therefore are generally unnecessary if distant disease is identified and subsequently confirmed by biopsy.

If CT and PET do not demonstrate distant disease, subsequent evaluation determines the extent of locoregional disease. Endoscopic ultrasound (EUS) is often the next test.[2,3,15] EUS provides more accurate evaluation of the depth of tumor invasion (T stage) and the extent of lymph node involvement (N stage) than both PET and CT.[16,17] However, the specific information obtained from EUS alone does not often change the clinical management of patients with esophageal cancer. For patients with significant symptoms from bulky tumors, the local extent of the tumor is almost certainly at least T3 with a high chance of local lymph node involvement. In these cases, EUS is likely only to confirm the clinical suspicion or to be unable to provide a complete evaluation due to luminal narrowing by the tumor, and therefore not changing the planned management. Conversely, EUS is generally less accurate for early-stage lesions such as T1 or T2 compared to more advanced tumors.[18–22] The accuracy of T staging can also be improved via endoscopic resection, which can be therapeutic in some cases as discussed below.[15,23,24] Finally, most incidences of understaging from EUS are due to missing nodal disease, and the specificity and the sensitivity for identifying lymph node disease are better when EUS is combined with fine-needle aspiration (FNA) compared to EUS alone.[25]

Additional studies prior to treatment may be indicated in certain circumstances. Bronchoscopy should be considered for tumors in the upper and middle esophagus to rule out airway invasion, which would preclude an eventual attempt at surgical resection. Airway evaluation is ideally done prior to starting any therapy in cases where there is a high suspicion due to imaging or clinical symptoms such as cough or pneumonia that could be due

to an esophageal-airway fistula, as distinguishing between treatment changes and definite tumor invasion can be difficult after patients have been treated with chemotherapy and radiation. In addition, distant metastases are unfortunately missed even with completion of the staging evaluation described above. Small liver or lung metastases can be missed by both PET and CT scans, and patients can also have undetected pleural or peritoneal disease.[26] Staging via minimally invasive surgical techniques of thoracoscopy and laparoscopy improves the accuracy of the above noninvasive testing.[26–28] Use of these invasive techniques is relatively uncommon but should be considered in select patients, such as those who may be considered to have a high risk of treatment-related complications. Staging laparoscopy may particularly have a role for patients with adenocarcinoma of the esophagus or gastroesophageal junction.[29]

Staging

Esophageal cancer staging is defined by the American Joint Committee on Cancer (AJCC) Staging System that establishes tumor–node–metastasis (TNM) subclassifications based on the depth of invasion of the primary tumor (T), involvement of regional lymph nodes in the adventitia or periesophageal tissue from the upper esophageal sphincter to the celiac artery (N), and presence of metastatic disease (M).[30] The most recent 8th edition used the Worldwide Esophageal Cancer Collaboration database to expand on the 7th edition and provide distinctive and homogeneous stage groups with monotonically decreasing survival (**Fig. 43.1**).[31] **Figure 43.2** and **Tables 43.1** and **43.2** show the specific 8th edition TNM definitions. Grade is important for pathologic staging of early-stage cancers. Location is important to subgroup pT3N0M0 squamous cell carcinoma. The definition of the gastroesophageal junction was also revised in the new edition, such that cancers involving it with epicenters no more than 2 cm into the gastric cardia are staged as esophageal cancers and those with more than 2-cm involvement of the gastric cardia are staged as stomach cancers.

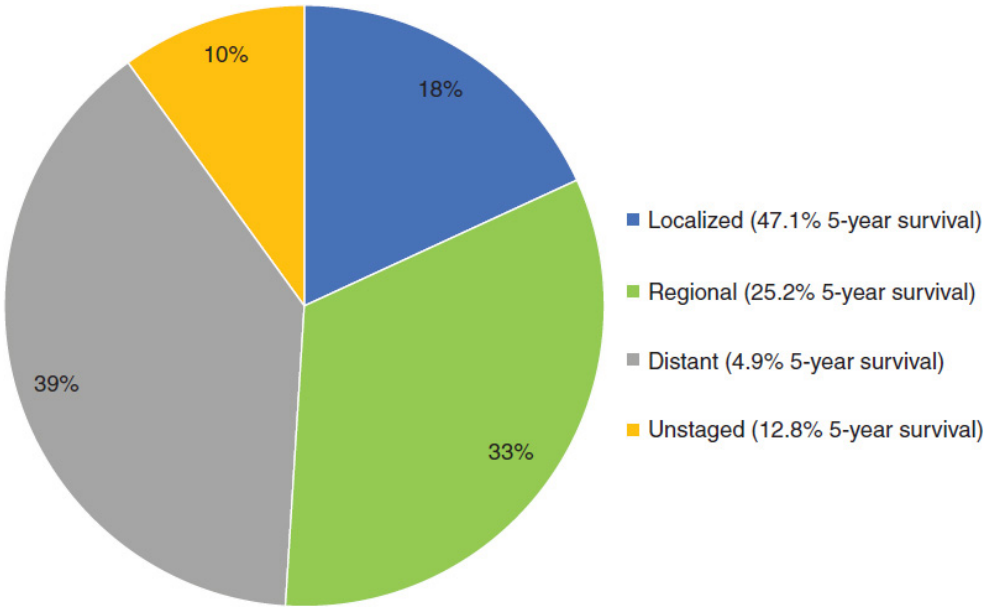


Figure 43.1 Distribution and survival of esophageal cancer by stage. (Adapted from Howlader N, Noone AM, Krapcho M, et al, eds. In: *SEER Cancer Statistics Review, 1975–2017, National Cancer Institute*. Bethesda, MD, https://seer.cancer.gov/csr/1975_2017/, based on November 2019 SEER data submission, posted to the SEER web site, April 2020.)

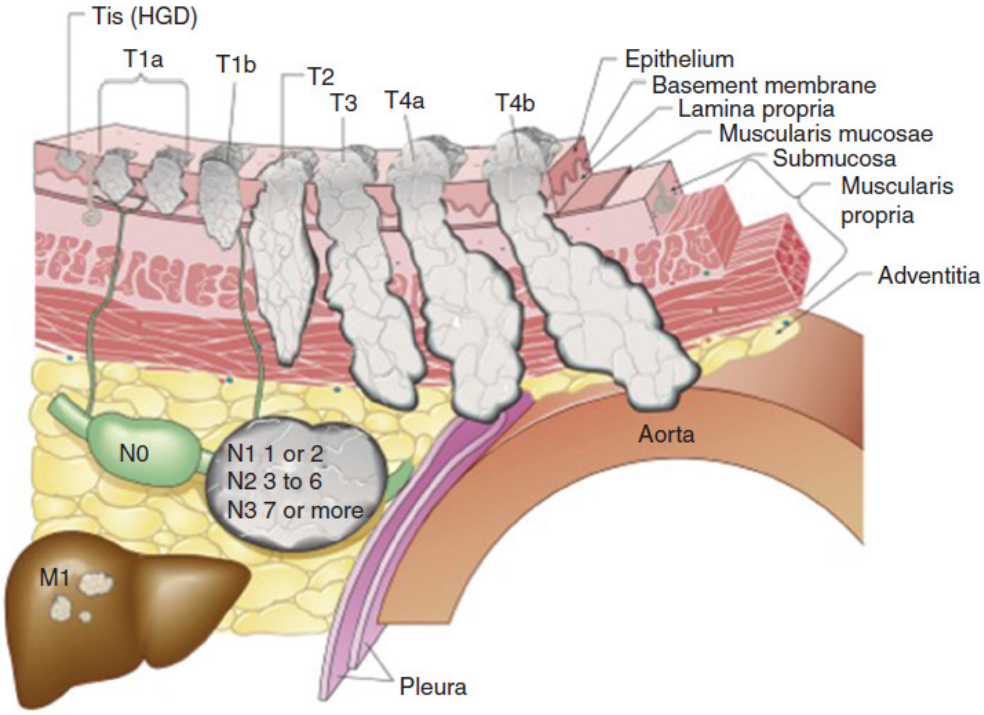


Figure 43.2 TNM categories. T is categorized as Tis: high-grade dysplasia (HGD). T1 is cancer that invades the lamina propria, muscularis mucosae, or submucosa and is subcategorized into T1a (cancer that invades the lamina propria or muscularis mucosae) and T1b (cancer that invades the submucosa); T2 is cancer that invades the muscularis propria; T3 is cancer that invades the adventitia; T4 is cancer that invades the local structures and is subcategorized as T4a (cancer that invades adjacent structures such as the pleura, pericardium, azygos vein, diaphragm, or peritoneum) and T4b (cancer that invades the major adjacent structures, such as the aorta, vertebral body, or trachea). N is categorized as N0 (no regional lymph node metastasis), N1 (regional lymph node metastases involving one to two nodes), N2 (regional lymph node metastases involving three to six nodes), and N3 (regional lymph node metastases involving seven or more nodes). M is categorized as M0 (no distant metastasis) and M1 (distant metastasis). (Reproduced from Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer. *J Thoracic Oncol* 2017;12(1):36–42.)

Table 43.1 T, N, and M Categories for Esophagus and Esophagogastric Junction Cancer in the 8th Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual

Category	Criteria
T Category	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia (malignant cells confined by the basement membrane)
T1a	
T1b	
T2	Invasion into the lamina propria or muscularis mucosae
T3	
T4a	Invasion into the submucosa
T4b	Invasion into muscularis propria
	Invasion into adventitia
	Invades resectable adjacent structures (pleura, pericardium, azygos vein, diaphragm, or peritoneum)
	Invades unresectable adjacent structures (aorta, vertebral body, or trachea)
N Category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	1–2 positive regional lymph nodes
N2	3–6 positive regional lymph nodes
N3	7 or more positive regional lymph nodes
M Category	
M0	No distant metastases
M1	Distant metastases

Adapted from Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer. *J Thoracic Oncol* 2017; 12(1):36–42.

A major change from the 7th edition is that the 8th edition has separate classifications for clinical (cTNM), pathologic (pTNM), and post-neoadjuvant (ypTNM) stage groups (**Tables 43.3** to **43.5**). 2 Clinical and pathologic groups were separated based on survival profiles. A separate post-neoadjuvant pathologic stage group was added to account for pathologic information that may not have been available after induction therapy and different survival profiles across groups.[31]

Treatment

Consensus guidelines provide recommendations for the treatment of esophageal cancer. Treatment options include local mucosal resection or ablation therapies, esophagectomy, chemotherapy, and radiation therapy. Recommended treatment is primarily dictated by stage, tumor location, and patients' medical fitness for receiving a potential therapeutic modality. However, definitive data from randomized trials to guide the treatment of esophageal cancer is lacking for many clinical situations. Consensus guidelines reflect the lack of definitive evidence and often allow a spectrum of potential treatments for many clinical situations. Given both the generally poor overall prognosis and the potential morbidity associated with therapy, multidisciplinary evaluation by surgery, medical oncology, and radiation oncology should be considered for all patients before a treatment strategy is initiated. Treatment that does not follow guidelines should probably only be used in the context of clinical trials. In addition, all treatment strategies should include careful nutritional assessment and counseling, as well as smoking cessation advice if indicated. In some situations, placement of a pretreatment feeding tube can be integral in allowing a patient to adequately start and maintain therapy.

The stage groupings described above are very useful for both providing prognosis and guiding treatment. However, patients can be categorized more simply when considering treatment. When considering treatment for esophageal cancer patients, the approach is initially dictated by whether the patients have been determined to have early-stage superficial cancers, cancers that are locally advanced with locoregional disease but no distant metastases, and cancers with distant disease. The 3 general treatment

guidelines for each of these categories are discussed in the following sections.

Table 43.2 Histologic Grade (G) and Squamous Cell Carcinoma Location (L) Categories for Esophagus and Esophagogastric Junction Cancer in the 8th Edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual

Category	Criteria
Adenocarcinoma G Category	
GX	Differentiation cannot be assessed
G1	Well differentiated, with >95% of the tumor composed of well-formed glands
G2	Moderately differentiated, with 50–95% of the tumor showing gland formation
G3	Poorly differentiated, with tumors composed of nests and sheets of cells with <50% of the tumor showing gland formation
Squamous Cell Carcinoma G Category	
GX	Differentiation cannot be assessed
G1	Well differentiated, with prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells, tumor cells arranged in sheets, and mitotic counts low
G2	Moderately differentiated, with variable histologic features ranging from parakeratotic to poorly keratinizing lesions and pearl formation generally absent
G3	Poorly differentiated, consisting predominantly of basal-like cells forming large and small nests with frequent central necrosis and with the nests consisting of sheets or pavement-like arrangements of tumor cells that

	are occasionally punctuated by small numbers of parakeratotic or keratinizing cells
Squamous Cell Carcinoma L Category	
LX	Location unknown
Upper	Cervical esophagus to lower border of the azygos vein
Middle	Lower border of the azygos vein to lower border of the inferior pulmonary vein
Lower	Lower border of the inferior pulmonary vein to the stomach, including the esophagogastric junction

Adapted from Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer. *J Thoracic Oncol* 2017;12(1):36–42.

Superficial Cancers

Patients with T1-2N0 esophageal cancer typically are recommended to undergo resection without induction therapy as noted in consensus guidelines. The prognosis for patients treated for intra- and submucosal (T1) esophageal cancers is significantly better than the prognosis for all other patients found to have esophageal cancer, even those also found in other relatively early-stage disease.[33] These early-stage cancers are generally either found incidentally during endoscopies done for other reasons or during endoscopies done for Barrett monitoring, though fewer than 15% of esophageal adenocarcinomas are detected during surveillance endoscopies.[9]

Esophagectomy is effective oncologically for these superficial cancers but is associated with considerable morbidity and mortality despite improvements over time and the development of minimally invasive techniques.[34–40] Although recent data from high-volume centers have shown low mortality rates of 1% to 3.5%, studies involving population-based databases or multicenter trials have shown esophageal resection to have perioperative mortality rates as high as 8.8% to 14%.[35,37,40–42] Local

treatments with modalities such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), radiofrequency ablation, cryotherapy, and photodynamic therapy can provide effective cancer treatment for superficial cancers with much less treatment-related morbidity.[43–56] These local treatments are good treatment options for patients with superficial tumors that involve only the mucosa (T1a), but pathologic examination should confirm complete resection with negative margins and close endoscopic surveillance should be planned post treatment.

Table 43.3 AJCC 8th Edition Clinical Stage Groupings

Adenocarcinoma				Squamous Cell Carcinoma			
c Stage	T	N	M	c Stage	T	N	M
0	is	0	0	0	is	0	0
I	1	0	0	I	1	0–1	0
IIA	1	1	0	II	2	0–1	0
IIB	2	0	0		3	0	0
III	2 3–4a	1 0–1	0 0	III	1–2 3	2 1–2	0 0
IVA	1–4a 4b	2–3 Any	0 0	IVA	1–3 4a–b	3 Any	0 0
IVB	Any	Any	1	IVB	Any	Any	1

Adapted from Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer. *J Thoracic Oncol* 2017;12(1):36–42.

Table 43.4 AJCC 8th Edition Pathologic Stage Groupings

Adenocarcinoma					Squamous Cell Carcinoma					
p Stage	T	N	M	Grade	p Stage	T	N	M	Grade	Location
0	is	0	0	Any	0	is	0	0	Any	Any
IA	1a	0	0	1	IA	1a	0	0	1	Any
IB	1a-b	0	0	2	IB	1a	0	0	2-3	Any
						1b	0	0	Any	Any
						2	0	0	1	Any
IC	1a–b	0	0	3						
	2	0	0	1–2						
IIA	2	0	0	3	IIA	2	0	0	2–3	Any
						3	0	0	1	Any
						3	0	0	2–3	Lower
IIB	1a–b	1	0	Any	IIB	1a–b	1	0	Any	Any
	3	0	0	Any		3	0	0	2–3	Upper or middle
IIIA	1a–b	2	0	Any	IIIA	1a–b	2	0	Any	Any
	2	1	0	Any		2	1	0	Any	Any
IIIB	2	2	0	Any	IIIB	2	2	0	Any	Any
	3	1–2	0	Any		3	1–2	0	Any	Any
	4a	0-1	0	Any		4a	0-1	0	Any	Any
IVA	1–3	3	0	Any	IVA	1–3	3	0	Any	Any
	4a	2–3	0	Any		4a	2–3	0	Any	Any
	4b	Any	0	Any		4b	Any	0	Any	Any
IVB	Any	Any	1	Any	IVB	Any	Any	1	Any	Any

Adapted from Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer. *J Thoracic Oncol* 2017;12(1):36–42.

Table 43.5 AJCC 8th Edition Post-Neoadjuvant Pathologic Stage Groupings for Both Adenocarcinoma and Squamous Cell Carcinoma

yp Stage	T	N	M
I	0–2	0	0
II	3	0	0
IIIA	0–2	1	0
IIIB	0–2	2	0
	3	1–2	0
	4a	0	0
IVA	0–3	3	0
	4a	1–3	0
	4b	Any	0
IVB	Any	Any	1

Adapted from Rice TW, Ishwaran H, Ferguson MK, et al. Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer. *J Thoracic Oncol* 2017;12(1):36–42.

Local mucosal therapies at the present time are generally not considered appropriate for superficial tumors that involve the submucosa (T1b) which have occult lymph node involvement in as many as 50% of patients.[57,58] Therefore, esophagectomy without induction therapy rather than endoscopic therapy is recommended for superficial tumors that involve the submucosa (T1b) so that the lymph nodes can be removed for both diagnostic 4 and therapeutic purpose. Patients undergoing esophagectomy without induction therapy should have at least 15 lymph nodes removed during surgery for adequate nodal staging.[59]

The optimal management of esophageal cancer clinically staged 5 as T2N0M0 is somewhat more controversial.[60] Clinical staging modalities for this subset are somewhat unreliable, with significant percentages of patients being both under and over staged.[18,61–64] Perhaps because clinical staging inaccuracies lead to a relatively high incidence of patients actually having nodal disease present at the time of surgical resection, induction therapy use

in this setting has been increasing and was shown recently to exceed 50% for cases that were reported to the Society of Thoracic Surgeons General Thoracic Database in 2011.[61] However, data that proves a survival benefit to induction therapy over surgery alone is still lacking.[65,66] Consistent with the uncertainty of optimal treatment, consensus guidelines for medically fit patients allow a wide spectrum of treatment possibilities that include definitive chemoradiation and esophagectomy with or without induction or adjuvant therapy. One clinical approach to patients with cT2N0 disease is proceeding with primary esophagectomy when the tumor was incidentally found on endoscopy or during workup for very mild symptoms and using induction therapy in cases where patients had symptoms more consistent with a bulky or locally advanced tumor.

Locoregional or Locally Advanced Disease

Approximately 33% of esophageal cancer patients have regional disease at the time of diagnosis, with a 5-year survival of only 10% to 30%.[1,2,33] Surgery is considered integral to achieving cure in patients with esophageal cancer, as one study showed the 5-year survival rates for patients with stages I through III esophageal cancer treated with and without surgery to be 28% and 10%, respectively.[67–69] Definitive chemoradiation is generally reserved for those patients who refuse surgery or are not surgical candidates as noted in consensus guidelines. Areas of esophageal cancer in which definitive chemoradiation is recommended in place of surgical resection are squamous cell carcinoma of the cervical esophagus and patients with T4b (unresectable) tumors.[70–73] Some data suggest that definitive chemoradiation could be adequate for some patients with squamous cell carcinoma in other esophageal locations, but surgery is considered integral to potential cure for adenocarcinoma in which pathologic complete response rates are generally less common.[74–77]

The treatment for locally advanced esophageal cancer that does not have distant metastases and is potentially resectable (T3-4aN0, T1-4aN1M0) is highly variable in practice.[78] The poor survival rate after esophagectomy alone for patients with locally advanced but not metastatic disease led to many studies of multimodality therapy in efforts to improve outcomes.[4] Although not all trials demonstrated a benefit to induction therapy, recent

evidence suggests that induction chemoradiation followed by surgical resection is the optimal treatment for 6 patients with T3-4a tumors or nodal disease.[79–84] Most importantly, the Dutch Chemoradiotherapy for Oesophageal Cancer followed by Surgery Study (CROSS) randomized trial demonstrated a survival benefit to induction chemoradiation followed by surgery compared to surgery alone (47% vs. 33% 5-year survival after an 84-month median follow-up) for esophageal or gastroesophageal junction cancer.[85,86]

Induction therapy is currently used in most patients with locally advanced disease.[87] However, the optimal induction regimen has not been precisely determined. Induction chemotherapy without radiation has also been shown to be beneficial for distal esophageal and gastroesophageal junction adenocarcinomas and is used by some high-volume centers.[88,89] Although combined chemoradiation has the theoretical advantage over chemotherapy alone of providing local benefit in addition to systemic control as well as possibly facilitating resectability, a definitive survival benefit has not been demonstrated.[90] The FLOT chemotherapy regimen (docetaxel, oxaliplatin, leucovorin, and fluorouracil) has recently been shown to have survival advantages over previous standard chemotherapy regimens for gastric and gastroesophageal junction adenocarcinomas.[91] Currently, there are several major ongoing randomized trials comparing induction chemotherapy versus induction chemoradiation.[92,93]

Metastatic or Unresectable Disease

Approximately 40% to 50% of patients have evidence of distant metastatic disease at the time of diagnosis.[1,2] Palliative therapy is recommended for these patients, and can include chemotherapy, clinical trial enrollment if available, or best supportive care. Best supportive care is often the most appropriate treatment option. Patients' performance status should determine whether chemotherapy is added to best supportive care. Specific symptoms that often need palliation include dysphagia, pain, and nausea. Oncologists generally avoid feeding tubes in patients with stage IV cancer but feeding tubes may be reasonable options in some select patients with limited metastatic disease. Radiation or endoscopic management techniques such as dilation and stenting can be used to palliate dysphagia or cases of bleeding

from esophageal tumors. Palliative esophagectomy for patients with metastatic disease may have 7 a role in very few cases and should be considered very selectively given the morbidity of surgery and the poor prognosis with or without surgery.

Prognosis

Survival of esophageal cancer has improved from <5% at 5 years in 1975 to approximately 20% currently.[1,94,95] There are multiple factors responsible for this improvement, including a change in the stage distribution and more diagnoses of early-stage cancers secondary to the recognition of the importance and need for surveillance of Barrett esophagus, development of low-risk but highly effective endoscopic therapies for early-stage superficial cancers, improvements in the knowledge of the importance of multimodality for locally advanced cancers, and improvement in the outcomes associated with esophagectomy in general. As expected, survival correlates with the stage at presentation. Patients with localized disease have a 5-year survival of 47.1%, while patients with regional disease and distant disease have 5-year survival of 25.2% and 4.9%, respectively.[1] Specific survival is obviously impacted by not only stage, but therapy as discussed above. Survival curves after esophagectomy for various specific stage presentations are shown in **Figure 43.3**.[96]

ESOPHAGECTOMY

Surgery is recommended as possible treatment for most cases of esophageal cancer that do not have invasion of unresectable structures or distant metastatic disease. Several studies have provided evidence that complete surgical resection provides the best chance for cure for these patients.[67–69] However, surgery for locoregional esophageal cancer is utilized in less than half of potentially resectable cases, perhaps because esophagectomy is historically associated with significant morbidity and mortality and disappointing long-term results.[68,97,98] Mortality following esophagectomy has decreased over time but still exceeds that of most surgical procedures, and long-term survival generally remains poor. Consequently, minimizing

perioperative morbidity in any manner possible is critically important, such that primary nonsurgical treatment is reserved for those who refuse surgery, have unresectable cancers, or are not thought to be surgical candidates for other reasons.

Techniques of Esophagectomy

Resection of the esophagus for malignancy is a technically complex procedure. The esophagus traverses three body regions (neck, chest, and abdomen) and the anatomy of the esophagus in the posterior mediastinum is such that its accessibility is very different at various positions in the chest. In addition, an appropriate conduit must be prepared in order to reestablish GI continuity, and this conduit must be placed in a location such that its blood supply will remain viable. Esophageal resection generally requires access to at least two body cavities, and often requires at least two incisions as well as patient repositioning and lung isolation with single-lung ventilation. Structures at risk of intraoperative injury include the spleen, trachea, and mainstem bronchi as well as major vascular structures in the chest such as the aorta.

Esophageal resection can be performed via several different techniques, with the most appropriate technique for any specific individual patient being dependent on both patient and surgeon factors. The most common surgical techniques used for esophagectomy are listed in **Table 43.6**. Minimally invasive techniques with either laparoscopy and/or thoracoscopy have been reported for all approaches except the left thoracoabdominal approach.

Specifics for each surgical technique are described below, with advantages and disadvantages listed in **Table 43.7**. The approach chosen for a patient depends on personal surgical experience and preference, institutional tradition, and patient characteristics. [8] Relevant factors include stage of disease, associated lesions such as Barrett esophagus or achalasia, other medical comorbidities, pulmonary function, and previous surgical history. In general, proximal and distal margins of at least 5 cm are desired; thus, the location of the tumor is a critical factor in determining surgical approach.[99,100] Also, the importance of the total number of lymph nodes involved and removed during surgery is increasingly recognized, so transthoracic approaches may be preferred over others that do not provide as

optimal access to the relevant nodes.[59,101–106] Interestingly, an individual surgeon's skills are probably more critically important than variations in surgical approach in optimizing the long-term survival after esophagectomy for esophageal cancer.[107]

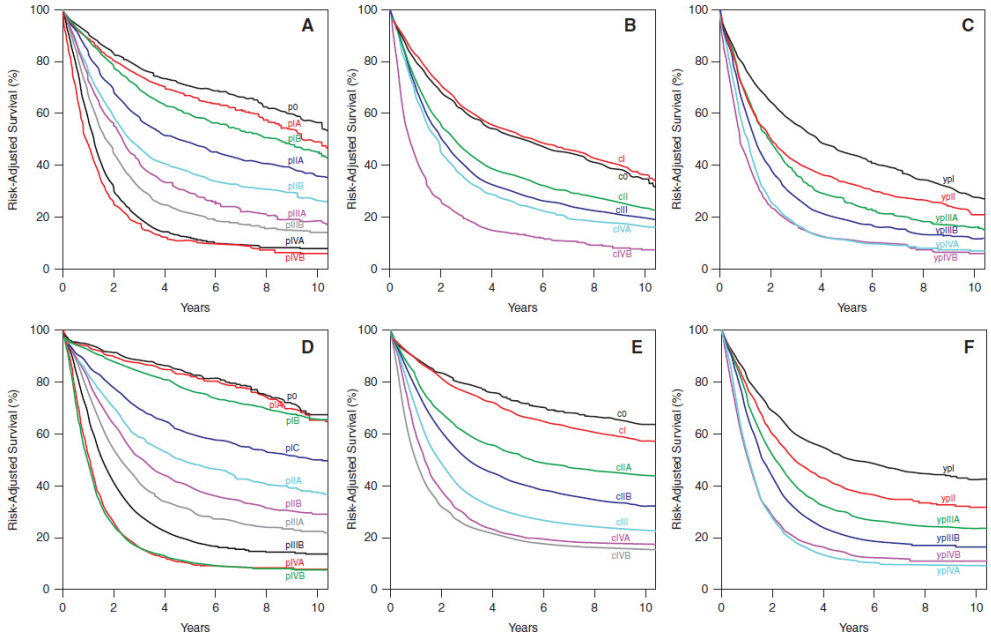


Figure 43.3 Risk-adjusted survival for squamous cell carcinoma (**A**) pathologic, (**B**) clinical, and (**C**) post-neo adjuvant stage groups, as well as adenocarcinoma (**D**) pathologic, (**E**) clinical, and (**F**) post-neoadjuvant stage groups. (Reproduced from Rice TW, Gress DM, Patil DT, et al. Cancer of the esophagus and esophagogastric junction-Major changes in the American Joint Committee on Cancer eighth edition Cancer Staging Manual. *CA Cancer J Clin* 2017;67(4):304–317.)

For all approaches, patients undergo preoperative upper endoscopy to confirm tumor location prior to resection to ensure the planned approach is appropriate. Patients with tumors in the mid-esophagus or more proximal esophagus should have bronchoscopy to evaluate for airway involvement. Most surgeons place an orogastric or nasogastric (NG) tube prior to the start of the procedure to assist in esophageal mobilization. These tubes are manipulated during the procedure as requested and guided by the surgical team. Jejunostomy feeding tubes are routinely placed in many patients because there may be a delay in the return of normal eating during the postoperative period. However, feeding tubes themselves are associated with complications and some surgeons selectively place feeding tubes.[108,109]

Surgeons overwhelmingly choose to use the stomach as the final conduit and most of these patients have good or excellent functional results.[110] Patients generally express good satisfaction with their life after esophageal replacement with a gastric conduit, but post-esophagectomy patients do fare worse in some physical and social functioning factors compared to the general population.[111] Patients who have had prior gastric surgery or another chronic condition such as diabetic gastroparesis may require a colon or jejunal interposition to reestablish GI continuity.[112–114]

Table 43.6 General Operating Room Set-Up for Different Esophagectomy Approaches

Procedure	Position	Order of Operation	Anastomosis	One-Lung Ventilation
Three-incision	1) Left lateral 2) Supine	1) Right thoracic 2) Abdominal with left cervical	Left cervical	Yes
Transhiatal	Supine	Abdominal with left cervical	Left cervical	No
Ivor Lewis	1) Supine 2) Left lateral	1) Abdominal 2) Right thoracic	Right chest	Yes
Left thoracoabdominal	Supine with chest bumped 45 degrees	Left thoracoabdominal	Left chest	Yes

Table 43.7 Advantages and Disadvantages of Different Esophageal Approaches

Esophagectomy Approach	Advantages	Disadvantages
Three-incision	All tumors Good nodal access Maximal margins ↓ risk of GERD Access to thoracic duct No thoracic anastomosis	Thoracic incision ↑ risk of pulmonary complications Requires intraoperative repositioning ↑ risk of RLN injury
Transhiatal	No thoracic incision No thoracic anastomosis Maximal margins Minimally invasive approach possible ↓ risk of GERD	Poor access to nodes Blunt thoracic dissection ↑ risk of RLN injury Risk of hemorrhage, dysrhythmia, tracheal injury, hemodynamic instability
Ivor Lewis	Good access to nodes ↓ risk of RLN injury Access to thoracic duct No cervical incision Minimally invasive approach possible	Thoracic anastomosis Thoracic incision Not good for tumors in proximal third of esophagus Requires intraoperative positioning
Thoracoabdominal	Easier access to hiatal area of patient has extensive abdominal adhesions secondary to previous surgeries	Only for tumors beyond 30–35 cm Very large incision ↑ rate of residual positive margins

	↑ risk of GERD due to low thoracic location of anastomosis

RLN, recurrent laryngeal nerve; GERD, gastroesophageal reflux disease.

The optimal location for the esophageal anastomosis after resection (cervical vs. intrathoracic) is controversial, although the majority (almost 60%) in the past were placed in the cervical region.[110] The advantages of a cervical anastomosis include better access for a wider primary esophageal resection, avoidance of potentially morbid thoracotomy incisions, and less severe postoperative symptoms of reflux due to less residual esophageal mucosa.[99,115] Conversely, advantages of an intrathoracic anastomosis include a lower incidence of anastomotic leaks and injuries to the recurrent laryngeal nerves as well as a lower risk of postoperative stricture formation.[99,115,116] In the current era, mortality associated with cervical and intrathoracic leaks are similar, although intrathoracic leaks are more likely to require surgical intervention.[99,115,117,118]

Three-Incision Esophagectomy (McKeown)

The three-incision esophagectomy or McKeown approach combines left cervical, right thoracic, and abdominal incisions (**Fig. 43.4A**). This approach is especially useful for tumors of the mid and upper esophagus and for tumors when a long Barrett segment is present. The patient is initially positioned in the left lateral decubitus position for a right thoracotomy or thoracoscopy and one-lung ventilation is required for the thoracic portion of the case. The esophagus is mobilized from the thoracic inlet to the esophageal hiatus and a lymph node dissection performed. The azygos vein is routinely ligated in this approach, and recurrent laryngeal nerve injury can occur during this portion of the procedure. The thoracic incisions are closed after placement of a chest tube and the patient is repositioned in the supine position with a roll placed under the scapula to extend the neck. The head is turned to the right to maximally expose the left neck. An upper midline laparotomy or laparoscopy is then performed, and the gastric conduit is mobilized and created. Surgeons

selectively place jejunostomy feeding tubes and perform pyloroplasty to enhance gastric emptying.

A left cervical incision is then made, and the cervical esophagus is dissected free in the neck. The recurrent laryngeal nerve is at risk of injury during this dissection. The NG tube is withdrawn to a specific depth under direct supervision of the surgeon, and the cervical esophagus is divided. A suture or a rubber drain is fastened to the distal end of the divided esophagus and the distal esophagus is withdrawn through the esophageal hiatus into the abdominal incision. The prepared gastric conduit is then pulled back through the hiatus and up into the neck with care to avoid torsion. The cervical anastomosis is then performed, and the NG tube is guided through the anastomosis under direct supervision by the surgical team.

Transhiatal Esophagectomy

The transhiatal esophagectomy combines abdominal and left cervical incisions (**Fig. 43.4B**). This approach is probably ideal for patients with Barrett's and high-grade dysplasia where lymph node dissection is not as critical for staging purposes. The abdominal portion of this procedure is performed as described above for the three-incision technique. The hiatus is dilated, and the surgeon's hand is inserted into the mediastinum to bluntly dissect the esophagus free from other intrathoracic structures. A left cervical incision is then made, and the esophagus is dissected in a similar manner from the neck into the chest but with special care to avoid injury to the recurrent laryngeal nerve. After complete esophageal mobilization, the esophagus is divided, and the anastomosis is performed in the neck as described above for the three-incision technique.

Excellent surgical outcomes for this technique have been reported by high-volume surgeons.[42] However, the use of this technique has decreased in the United States. An esophagectomy analysis of the American College of Surgeons-National Surgical Quality Improvement Project of the years 2005–2011 showed 52.5% of patients had a transhiatal approach, but a subsequent study that included the years 2005–2014 found that only 41.7% had the transhiatal approach.[119,120] The decrease in the utilization of this technique was probably influenced by both the recognition of the importance of lymph node resection to prognosis as well as the increasing use of minimally

invasive techniques that also provides the transhiatal advantage of avoiding the morbidity of a thoracotomy.[59,121]

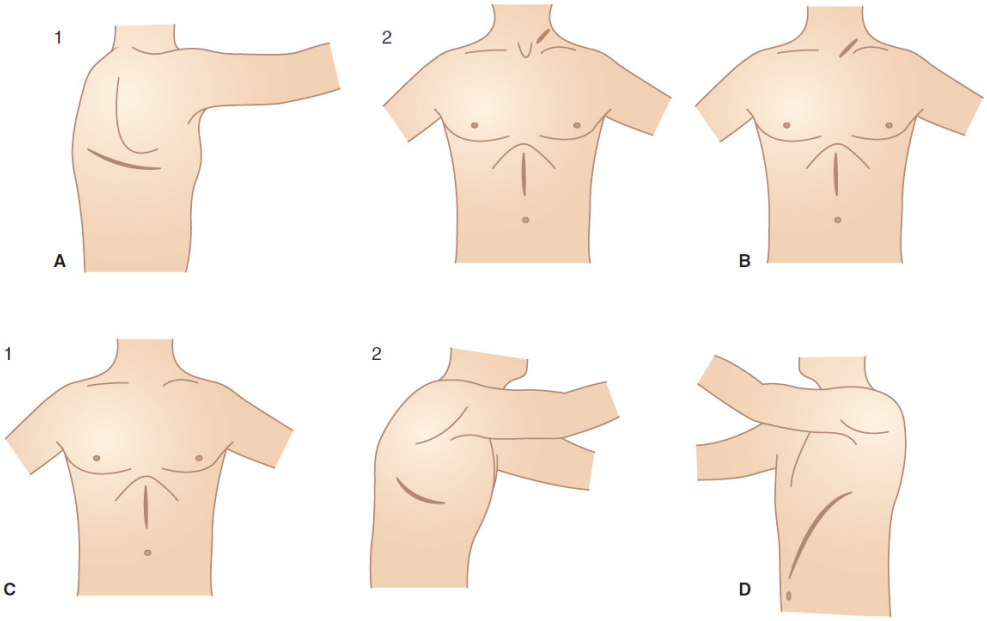


Figure 43.4 Incisions used for (**A**) three-Incision or McKeown, (**B**) transhiatal, (**C**) Ivor Lewis, and (**D**) left thoracoabdominal esophagectomies.

Ivor Lewis Esophagectomy

The Ivor Lewis esophagectomy resembles the modified McKeown approach, but involves only two incisions: right thoracic and upper abdominal (**Fig. 43.4C**). Although it also requires one-lung ventilation, the Ivor Lewis begins with the patient in the supine position for laparotomy or laparoscopy for preparation of the gastric conduit. The gastric tube is then advanced into the chest as far as possible and the abdomen is closed. The patient is then repositioned in the left lateral decubitus position for right thoracotomy or thoracoscopy. In the chest, the esophagus is mobilized and divided. The gastric conduit is pulled further into the chest and the anastomosis performed. The thoracotomy or thoracoscopy incisions are closed after placement of a chest tube.

Left Thoracoabdominal Esophagectomy

The left thoracoabdominal approach (**Fig. 43.4D**) can be performed with acceptable morbidity and mortality but is generally only considered for

patients with tumors limited to the distal esophagus, and even in those cases is associated with high rates of residual disease.[122] This approach necessitates one-lung ventilation, and the patient is positioned in the right lateral decubitus position but with the abdomen rolled back approximately 45 degrees. A thoracoabdominal incision is made along the 7th intercostal interspace across the costal margin, and the diaphragm is taken down circumferentially from the chest wall (**Fig. 43.4D**). Esophageal and gastric mobilization and resection are performed as described for the Ivor Lewis technique but with reconstruction of the diaphragm prior to closure. This approach is not often utilized due to the limited amount of esophageal resection that can be achieved, and also the postoperative pain and morbidity associated with this approach. However, a thoracoabdominal option may be optimal for patients who have previous abdominal surgeries that could make a midline abdominal approach more difficult.

Minimally Invasive Esophagectomy

Minimally invasive techniques to achieve esophagectomy have been utilized for decades and are becoming increasingly more common.[123,124] Essentially, the chest and the abdominal components of the different esophagectomy approaches described above can all be done using minimally invasive techniques via laparoscopic, thoracoscopic, and robotic approaches. Considering the multiple approaches that can be used to achieve an esophagectomy, specifically defining a minimally invasive esophagectomy (MIE) not surprisingly is problematic. One proposed MIE definition is "an operation that removes part or all of the esophagus, does not retract, lift, spread or remove any part of the chest or abdominal wall and the surgeon's and assistant's vision of the operative field is via a monitor, the patient's tissue is manipulated only by instruments that are controlled by the operating surgeon or team, except for during the neck portion if used."[125] Procedures that are done with not all but at least one component minimally invasively are generally considered to be "hybrid" procedures.[126]

A MIE can be performed by experienced surgeons with low conversion rates and a median reported hospital stay of 7 days.[123,127] These techniques can be associated with longer operative times early in surgeon experiences, and morbidity and mortality rates can still be as high as 46% to 61.5% and

3.3% to 6%, respectively.[123,128–130] However, MIE has been associated with less major morbidity, particularly pulmonary-related, and shorter postoperative recovery times.[126,131,132] Studies have also shown mortality rates to be as low as 2.1% in multi-institutional settings, and as low as 0.9% in very experienced centers.[121,133] Multiple studies have shown that a minimally invasive approach does not compromise the oncologic efficacy of the procedure.[124,126,132,134] The improved results and benefits seen with minimally invasive techniques are probably due not only to the differences in surgical approach, but also to the fact that they are being performed by experienced and highly trained esophageal surgeons at high-volume centers. Robotic techniques are feasible, though use of the robot may be more important for the surgeon rather than the patient, as a recent NSQIP analysis found no significant difference in the incidence of 30-day postoperative outcomes between robotic and other minimally invasive approaches.[135,136]

Intraoperative Complications

Cardiac dysrhythmias occur in up to 65% of patients undergoing esophagectomy.[137,138] These occur commonly during transhiatal procedures during the blunt dissection portion of the case but are mostly well tolerated. Most are atrial tachydysrhythmias, but more than 50% of these are of combined atrial and ventricular origin. Interestingly, in a closely monitored observational study, there was no correlation between the incidence of dysrhythmias and that of hypotension, but there was a strong correlation between hypotension and the duration of manipulation.[137]

Other serious intraoperative events that can occur are hemorrhage and airway injury. While massive bleeding is rare, it may require rapid conversion from a minimally invasive to an open technique, or even an emergent change in patient position to facilitate surgical exposure of the involved vessel. In general, if severe bleeding occurs in the mid- or upper esophagus, it may require conversion to a right thoracotomy for approach to the azygos vein; and if from the lower third of the esophagus, a left thoracotomy may be required to access a bleeding esophageal branch from the aorta. Fortunately, such vascular injuries occur in less than 2% of transhiatal esophagectomy cases.[139] Similarly, airway injury is rare, <1%.[140] These injuries are mostly limited to the distal membranous trachea or

proximal bronchi and may be detected by the smell of inhaled anesthetic in the field or a feeling of airflow by the surgeon with each ventilator-delivered breath. Injuries are rarely large enough to be detected by loss of ventilator volume. If an airway injury is detected, deflation of the endotracheal tube cuff and advancement of the tube past the injury with manual guidance by the surgeon should be performed. An airway injury can be amenable to primary repair, though an intercostal muscle flap to buttress the repair is advisable. If the patient remains stable when an airway injury occurs, completing the procedure as planned should be accomplished. In any case of airway injury, though, extubating the patient immediately postoperatively is critically important to minimize pressure on or manipulation of the repair.

Immediate and Long-term Outcomes Following Esophagectomy

Even with advances in surgical technique, anesthetic, and critical care, esophagectomy continues to be a source of significant morbidity and mortality in both the immediate perioperative period and for long-term survivors. Perioperative mortality rates have historically been reported as 8.8% to 14% but was still 2.7% to 3.4% in a recent Society of Thoracic Surgeons General Thoracic Surgery Database and Targeted esophagectomy NSQIP studies; major morbidity is still 25% to 33%.[11,35–40,42,115,117,127,128,141–145] Patients undergoing esophageal surgery have long hospital stays and prolonged overall recovery periods, which are more than doubled when significant complications occur.[39,115,142,146] It is perhaps for these reasons that surgical resection is pursued for less than half of all potentially resectable stage I, II, and III esophageal cancers.[68,98]

Interestingly, clinical studies have shown that surgical and center experience is much more important in determining ultimate outcome than choice of procedure. Prospective trials have failed to demonstrate any significant differences in short- or long-term survival or quality of life between transthoracic and transhiatal esophagectomies, although some evidence suggests that the transhiatal approach has a slightly lower rate of perioperative complications and these patients may achieve better activity levels postoperatively.[36–38,146–148] However, centers and surgeons that

perform high volumes of esophageal surgery report mortality rates that are significantly lower for both transhiatal and transthoracic procedures than those reported in multicenter studies or national databases.[41,42,99,149,150] In fact, it appears that the mortality rate for low versus high-volume centers and surgeons may differ by as much as 50%. Interestingly, high volume has been defined as >12 or >5 cases/year for centers and surgeons, respectively, and low volume as <5 or <2 cases/year for centers and surgeons.[38,151–153] Similarly, improvements reported in long-term surgical outcomes are significantly better for high-volume centers and surgeons, with some centers reporting recent mortality rates as low as 1%.[39,42,149,154–157] Specialty training also appears to have a significant effect on outcome, with surgeons without specialty training having 37% to 50% higher mortality than those with specialty training.[142,151,158]

Morbidity Following Esophagectomy

A summary of complications following esophagectomy is listed in **Table 43.8**. Risk factors for major morbidity are pulmonary disease, older age, Black race, congestive heart failure, coronary artery disease, peripheral vascular disease, malnutrition, decreased functional status, hypertension, insulin-requiring diabetes, higher American Society of Anesthesiology rating, and use of tobacco or steroids.[35,37,141,142] Preoperative predictors of mortality based on multivariable analysis include higher Charlson score (a measure of comorbid conditions), older age, renal dysfunction, diabetes, alcohol abuse, decreased functional status, intraoperative transfusion, and ascites.[35,40] Tumor location and histology are also important, with squamous cell carcinomas and upper third esophageal tumors being associated with worse outcomes.[141,159,160] As noted above, undergoing surgery at a center where less than 12 esophagectomies are performed per year is also a risk factor for postoperative mortality.[40] Neoadjuvant therapy has been variably identified as a predictor of significant morbidity and mortality in the postoperative period.[35,142]

Considering the overall poor prognosis for esophageal cancer patients, the impact of surgical complications on survival and quality of life cannot be overstated.[99,161] However, surgical technique and perioperative care has implications beyond immediate perioperative survival. Improved long-term

survival and quality of life are often directly related to avoidance of postoperative complications.[162] Measures that have been successful in reducing perioperative morbidity include aggressive preoperative conditioning, minimizing intensive care unit stays, aggressive pain management, early ambulation, involvement of a dedicated intensivist in the perioperative care team, and an overall multidisciplinary, multimodal approach to management.[42]

Table 43.8 Perioperative Morbidity and Mortality After Esophagogastrectomy

Complication	Incidence
Technical	
Anastomotic stricture	16–48%
Anastomotic leak	6–14%
Conduit necrosis	0.5–2%
Vocal cord palsy	2–14%
Wound infection	5.3–12%
Fascial dehiscence	2–5%
Delayed gastric emptying	1.8–3.7%
Chylothorax	0.8–9%
Pulmonary (total)	28.5–29.7%
Pneumonia	8–26%
Reintubation	6–17%
Respiratory failure	1.8–16%
Aspiration	7%
Atelectasis requiring bronchoscopy	4.5%
Miscellaneous	
Deep venous thrombosis	0.9–2%
Myocardial infarction	0.7–1.2%
Pulmonary embolism	0.7–1.7%
Atrial fibrillation	14–17.5%
Renal failure	0.9–3.4%

Anastomotic and Conduit Complications

Anastomotic leaks occur in 6% to 14% following esophagectomy and traditionally were associated with extremely high mortality. However, with improvements in surgical technique and critical care, mortality rates as low as 3.3% have been achieved.[117,163,164] Clinical features commonly associated with leaks include fever, leukocytosis, pleural effusion, and sepsis, although small leaks are often identified in asymptomatic patients.[165] Many leaks (57%) can be managed nonoperatively although operative alternatives include stent placement, primary anastomotic repair, anastomotic tissue reinforcement such as with a muscle flap, and esophageal diversion.[166–168] Early leaks (within 5 days) and those associated with gastric tip necrosis (incidence 2% to 3%) are most likely to require surgical treatment.[164,165] Necrosis of the gastric conduit is generally uncommon but is associated with high mortality and requires immediate intervention with resection of the compromised tissue and diversion.[169] High-volume centers have reported leak rates as low as 5%, though recent reports from the Society of Thoracic Surgeons and an NSQIP analysis showed leak rates even in recent years to be 12.9% and 14%, respectively.[121,141,145]

Anastomotic strictures are somewhat common after esophagectomy. Although generally not life threatening, strictures can cause significant patient discomfort and can put patients at risk for aspiration if they have dysphagia or regurgitation secondary to the stricture. The rate of stricture occurrence has been reported to be as high as almost 50%, though a recent population-based analysis found an incidence of 16.7%, with 6.6% of patients requiring three or more dilations as therapy.[170]

Respiratory Complications

Respiratory complications are the most common cause of death following esophagectomy.[115] Respiratory issues typically are due to poor clearance of secretions or postoperative aspiration. Factors that can increase the risk of aspiration or pulmonary complications include postoperative recurrent laryngeal nerve dysfunction, conduit emptying issues, and swallowing dysfunction. Risk of pneumonia appears to be highest in those approaches that involve a thoracotomy incision. Reducing pulmonary complications with the use of epidural analgesia and aggressive use of bronchoscopy for

clearance of pulmonary secretions appears to reduce perioperative mortality.[171] Other strategies include careful assessment of swallowing abnormalities and risk of aspiration by cineradiography or fiberoptic endoscopy before initiating oral intake.[41,115]

Issues with emptying of the conduit can also predispose patients to both short- and long-term pulmonary complications. Patients are at risk of aspirating contents from a full or dilated intrathoracic stomach, particularly when lying down after meals or when sleeping. A very important step to prevent this situation is to only pull the amount of stomach into the chest necessary to achieve a tension-free anastomosis and avoid having excessive redundant stomach in the chest. Performing a pyloric drainage procedure to enhance gastric drainage is also advocated by many surgeons, to avoid the risk of delayed gastric emptying that could occur from a functional gastric outlet obstruction secondary to resection of the vagus nerves during the esophagectomy.[172] However, a significant number of surgeons prefer very selective use of a pyloroplasty to avoid the risk of biliary reflux and dumping symptoms, as emptying issues can be somewhat easily managed with medications or endoscopic procedures such as balloon dilation, Botox injection, or a gastric per-oral endoscopic myotomy.[173] The evidence supporting either strategy is variable. Early studies showed fewer issues with emptying when a gastric drainage procedure was performed, but more recent studies have not consistently shown a benefit.[174,175]

Recurrent laryngeal nerve injury manifesting as early postoperative hoarseness is a risk of esophagectomy given the course of the recurrent laryngeal nerves in the trachea–esophageal groove. Such injuries occur in 4% to 14% who have a cervical anastomosis, and in 1% to 4.8% of patients who have an intrathoracic anastomosis.[42,121,144,176] Hoarseness is often transient and can resolve in 2 to 12 weeks if the injury was only a nerve palsy. Patients with persistent vocal cord paralysis require cord medialization procedures, as long-term persistent hoarseness is associated with debilitated performance status, as well as swallowing and pulmonary dysfunction.[177] Patients with evidence of aspiration should undergo early cord medialization, as this has been shown to decrease the incidence of pneumonia and need for bronchoscopy.[177]

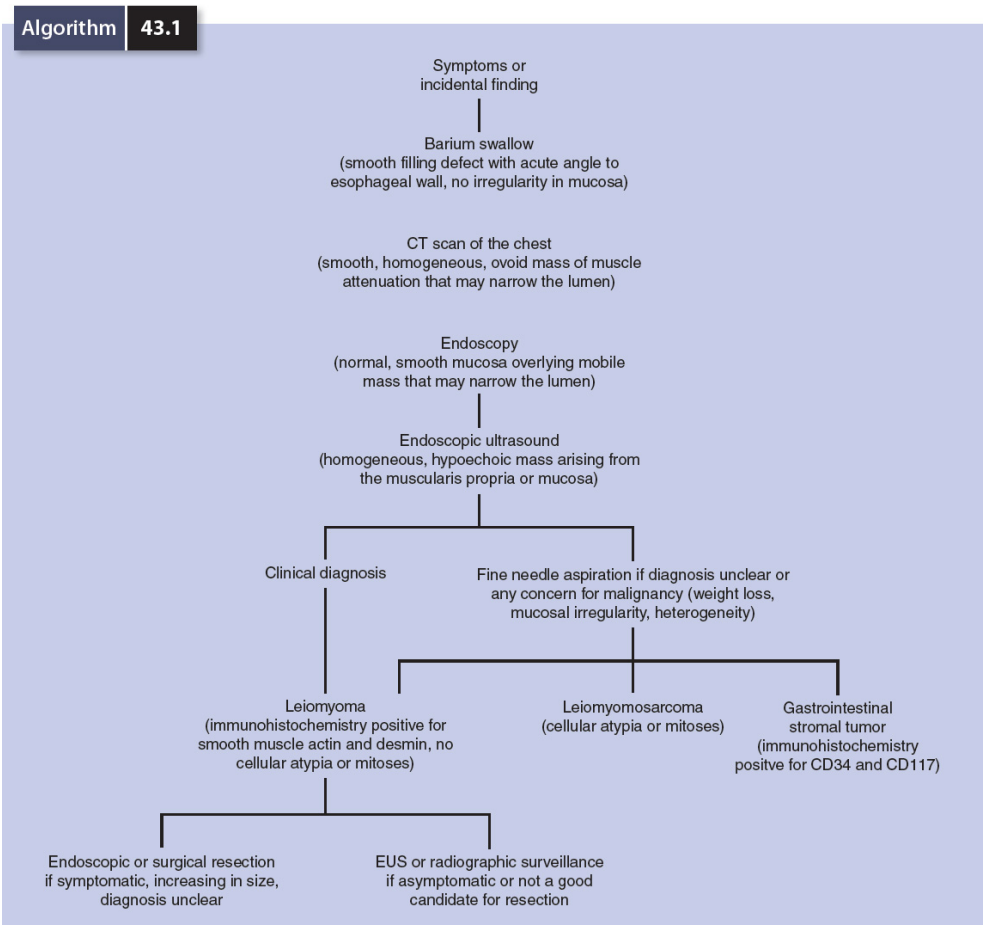
BENIGN ESOPHAGEAL NEOPLASMS

There are several types of benign esophageal neoplasms that are rare and often asymptomatic (**Table 43.9**). They are important to distinguish from esophageal malignancy so they are managed appropriately. Some can be managed conservatively, while others should be removed (endoscopic or surgically) for definitive diagnosis, local symptoms, or rare malignant potential. Generally, if the tumor is subepithelial and resection is indicated, then surgical enucleation or ESD is performed. If the tumor is large or at a difficult location such as the gastroesophageal junction, then a larger resection such as esophagectomy may be required. It is important to coordinate care with an experienced thoracic surgeon and interventional gastroenterologist. The most common benign esophageal neoplasms are discussed here, but all of them should be considered during formulation of a differential diagnosis.

Table 43.9 Classification of Benign Esophageal Neoplasms by Cell Type

Epithelial
Squamous cell papilloma
Fibrovascular polyp
Adenoma
Inflammatory pseudotumor
Inflammatory polyp
Nonepithelial
Leiomyoma
Schwannoma
Lymphangioma
Fibroma
Neurofibroma
Hemangioma
Rhabdomyoma
Lipoma
Hamartoma
Heterotopic
Granular cell tumor
Chondroma
Osteochondroma
Giant cell tumor
Eosinophlic granuloma

Adapted from Choong CK, Meyers BF. Benign esophageal tumors: Introduction, incidence, classification, and clinical features. *Semin Thoracic Cardiovasc Surg* 2003;15(1):3–8.[264]



Algorithm 43.1 Evaluation and management of esophageal leiomyoma.

Leiomyoma

Leiomyomas comprise about two-thirds of the benign neoplasms of the esophagus.[178,179] The incidence of leiomyoma of the esophagus reported in autopsy range from 0.005% to 5.1%. 9 They arise from smooth muscle and thus are usually found in the middle and lower esophagus. Approximately 80% of leiomyoma originate from the muscularis propria and are located intramurally, but they have also been found arising from the muscularis mucosa and protruding into the esophageal lumen.[180] They are usually single lesions, but multiple lesions have been reported.[181] They are generally slow-growing tumors and may not change for many years.

Patients have been diagnosed at all ages, with a peak incidence at 30 to 59 years, and the incidence in men is almost twice that in women.[179] Over 50% of patients are asymptomatic, and slow onset of dysphagia and chest

discomfort are the most common symptoms.[182] Rapid onset of symptoms and weight loss are concerning for malignancy.

Evaluation of a patient suspected of having a leiomyoma should begin with a barium swallow, CT scan of the chest, endoscopy, and EUS (**Algorithm 43.1**). Barium swallow demonstrates a smooth, rounded filling defect with an acute angle at the junction with the esophageal wall, indicating that the mucosa is not involved (**Fig. 43.5**). CT scan of the chest shows a smooth, ovoid mass of muscle attenuation that may narrow the lumen (**Fig. 43.6**). It is not always necessary but can confirm the differential diagnosis and rule out any other chest pathology. Endoscopy shows normal, smooth mucosa overlying a mobile mass that may narrow the lumen without obstruction (**Fig. 43.7**). Endoscopic biopsy is usually unsuccessful because of the subepithelial location. Any mucosal abnormality such as ulceration is concerning for malignancy such as esophageal carcinoma or leiomyosarcoma.

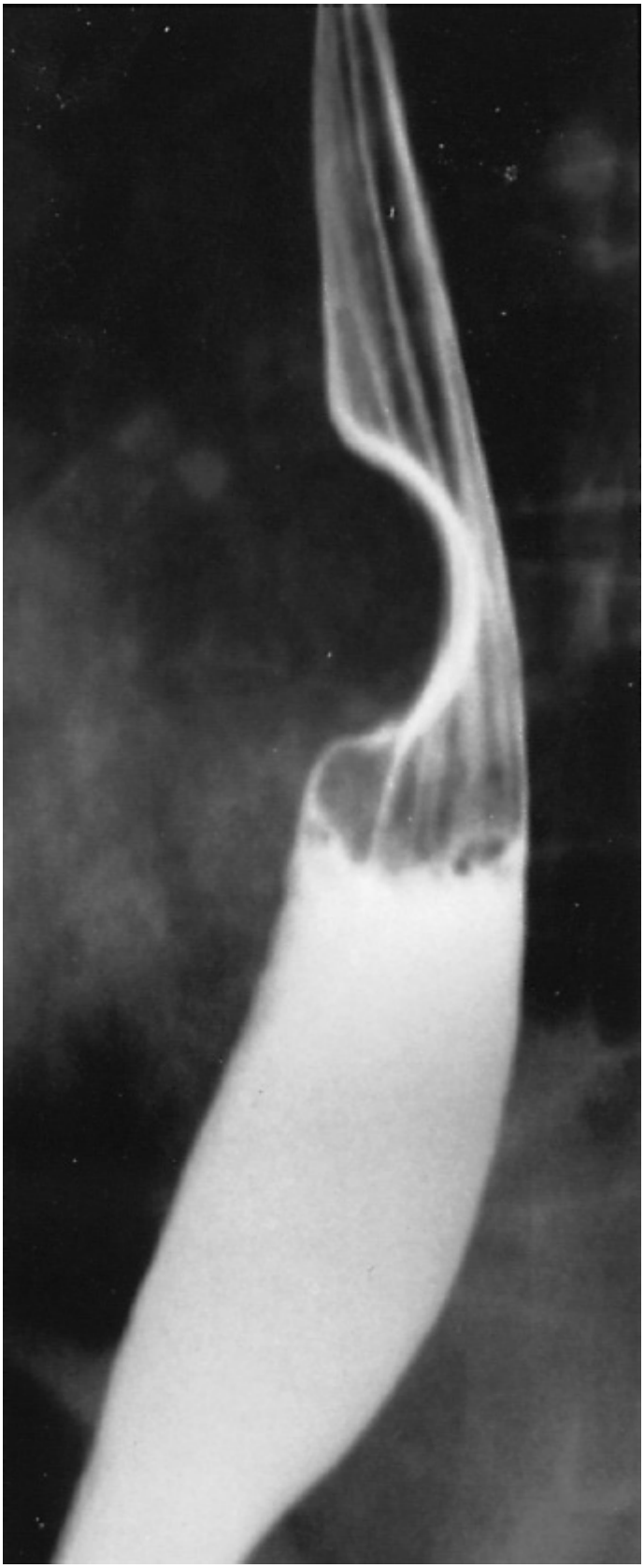


Figure 43.5 Esophagram of a leiomyoma. The acute angle at its junction with the esophageal wall is typical, indicating that the mucosa is not involved. (Reproduced with permission from Orringer MB. Tumors of the esophagus. In: Sabiston DC Jr, ed. *Textbook of Surgery*. 13th ed. Philadelphia, PA: AWB Saunders; 1986:736.)

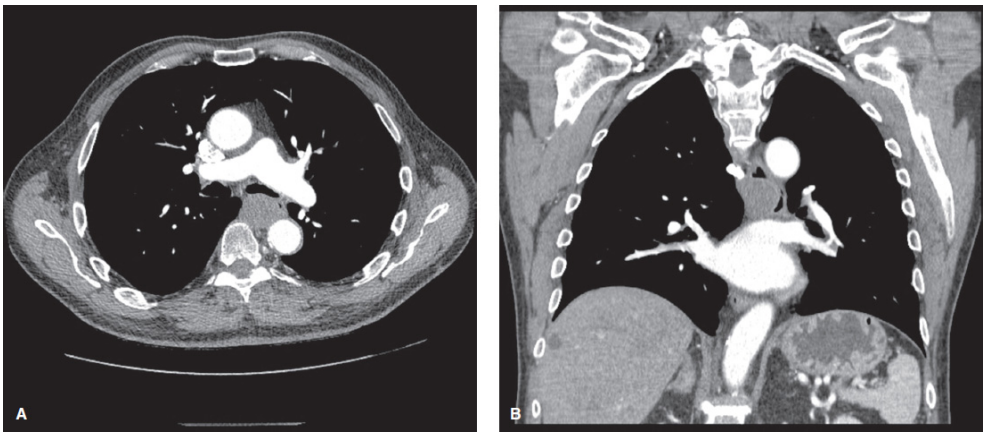


Figure 43.6 Axial (**A**) and coronal (**B**) computed tomography images of a mid-esophageal leiomyoma that was causing dysphagia. The smooth, ovoid mass of muscle attenuation partially occludes the esophagus. (Courtesy of Natalie S. Lui, MD, Division of Thoracic Surgery, Stanford University, Stanford, CA.)

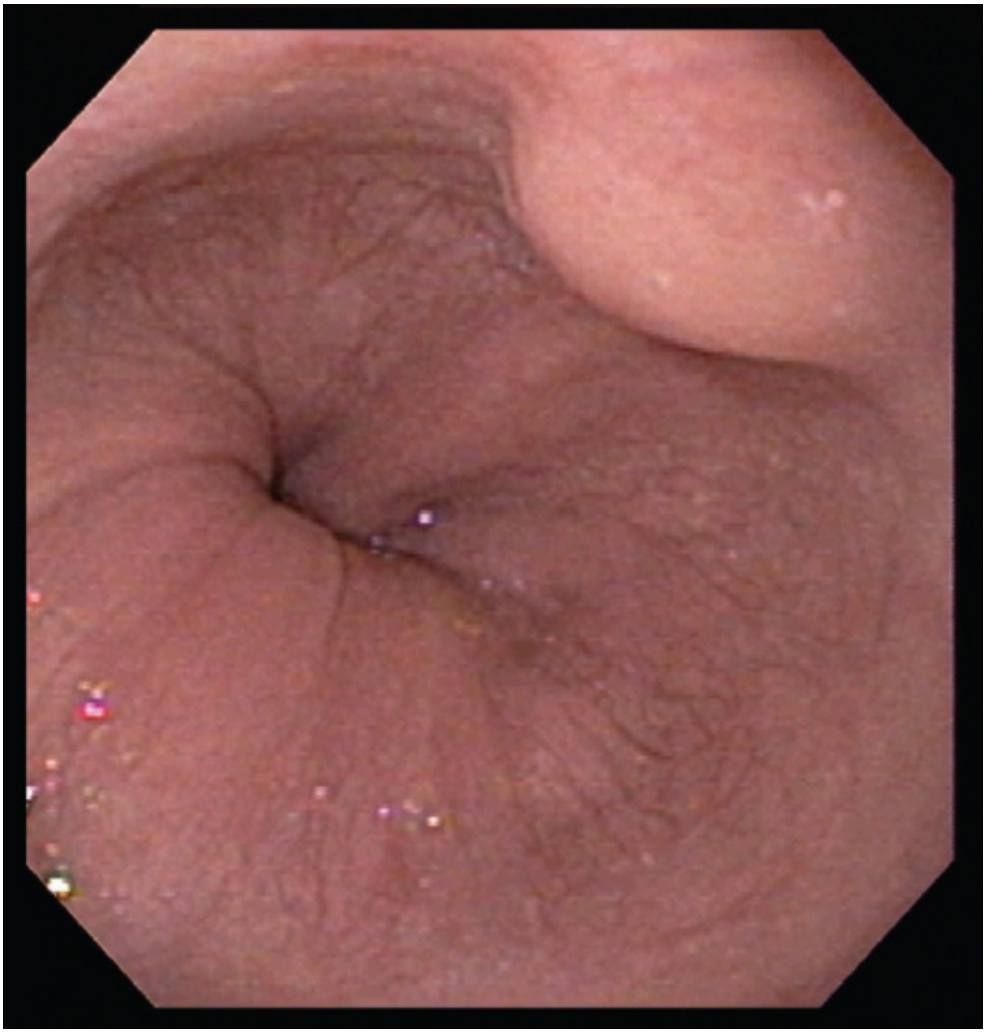


Figure 43.7 Endoscopic appearance of an esophageal leiomyoma in the distal esophagus just proximal to the gastroesophageal junction. The mucosa is smooth and normal overlying the mass, indicating that it is not involved. (Courtesy of Michael L. Kochman, MD, Hospital of the University of Pennsylvania, Philadelphia, PA.)

EUS can confirm the layer of origin, and FNA can be used to obtain tissue for diagnosis and distinguish leiomyomas from the much rarer malignant gastrointestinal stromal tumor (GIST) and leiomyosarcomas. Leiomyomas are positive for smooth muscle actin and desmin, whereas GISTs are positive for CD117 and CD34. Leiomyosarcomas have significant cellular atypia. FNA should not be performed routinely if a clinical diagnosis can be made, since scarring may increase the risk of mucosal perforation during resection. If resection is not necessarily planned or there are any features concerning for malignancy, FNA should be performed.

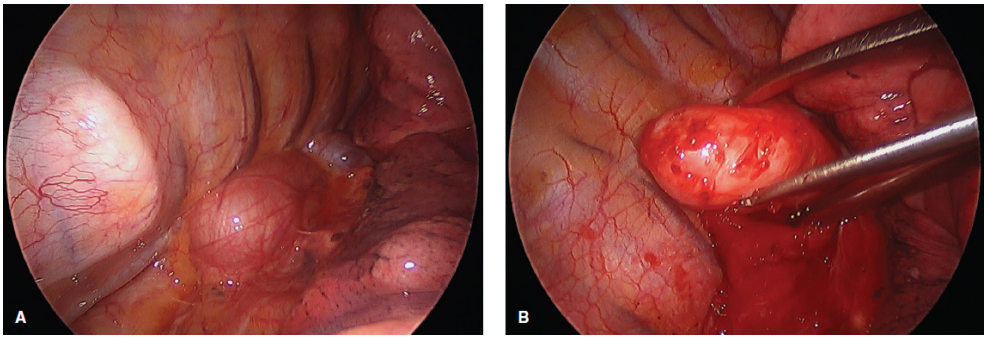


Figure 43.8 Intraoperative photos of a mid-esophageal leiomyoma before (**A**) and after (**B**) the pleura was opened via a right thoracoscopic approach. (Courtesy of Natalie S. Lui, MD, Division of Thoracic Surgery, Stanford University, Stanford, CA.)

Indications for resection are symptoms, increase in size, wish for a definitive diagnosis, and any concern for malignancy such as mucosal ulceration or heterogeneity. Small, asymptomatic leiomyomas may be monitored since they grow slowly and malignant transformation to leiomyosarcoma is rare.[183] Endoscopic submucosal resection can be used for small tumors. Surgical resection is generally performed by enucleation, most commonly through a right thoracotomy or thoracoscopy (**Fig. 43.8**), or through a left thoracotomy for distal esophageal or abdominal for gastroesophageal junction tumors.[184] The tumor is separated from the underlying mucosa, which must be repaired if injured, and the muscle layer is closed over the mucosa. Large tumors greater than about 8 cm and annular tumors may require esophagectomy. Most patients are free of symptoms after surgery and recurrence is rare.[180]

Fibrovascular Polyp

Fibrovascular polyps are rare benign neoplasms of the esophagus. They are extremely rare, described only in case reports and small case series. Recent studies have shown that many of these tumors may actually be liposarcomas, confirmed by review of morphology and MDM2 immunohistochemistry and fluorescence in situ hybridization.[185] They are intraluminal tumors that arise from a stalk near the cricopharyngeus muscle and range from small polyps to large tumors encompassing the entire esophagus (**Fig. 43.9**). They are thought

to grow from excessive mucosal folds in the cervical esophagus that elongate with peristalsis.

Patients are most commonly diagnosed at 50 to 70 years of age, and the incidence is higher in men. They are usually symptomatic and most present with dysphagia. Odynophagia, regurgitation, neck pain, weight loss, and respiratory symptoms have also been reported.[186] Some patients describe coughing or vomiting the tumor out of their mouths, holding the tumor outside the mouth or between the teeth, and swallowing the tumor back into the esophagus.[187,188] Tumors can also cause airway obstruction leading to life-threatening presentations.[189,190] On endoscopy, it may be difficult to identify the stalk, and the polyp may even be missed if it is mistaken for esophageal mucosa. CT scans reveal sausage-shaped tumors of fat or soft tissue density.

Resection is indicated to avoid symptoms including airway obstruction and has been described via endoscopic or surgical approaches, most commonly left cervical esophagotomy. For very large tumors, a combined approach may be required, with stalk division by endoscopy or left cervical esophagotomy and removal of the tumor by right thoracotomy or gastrotomy (**Fig. 43.10**).[188,191] Control of the stalk is important since it contains feeding vessels. Recurrence has been reported, so surveillance endoscopy has been recommended.[188]

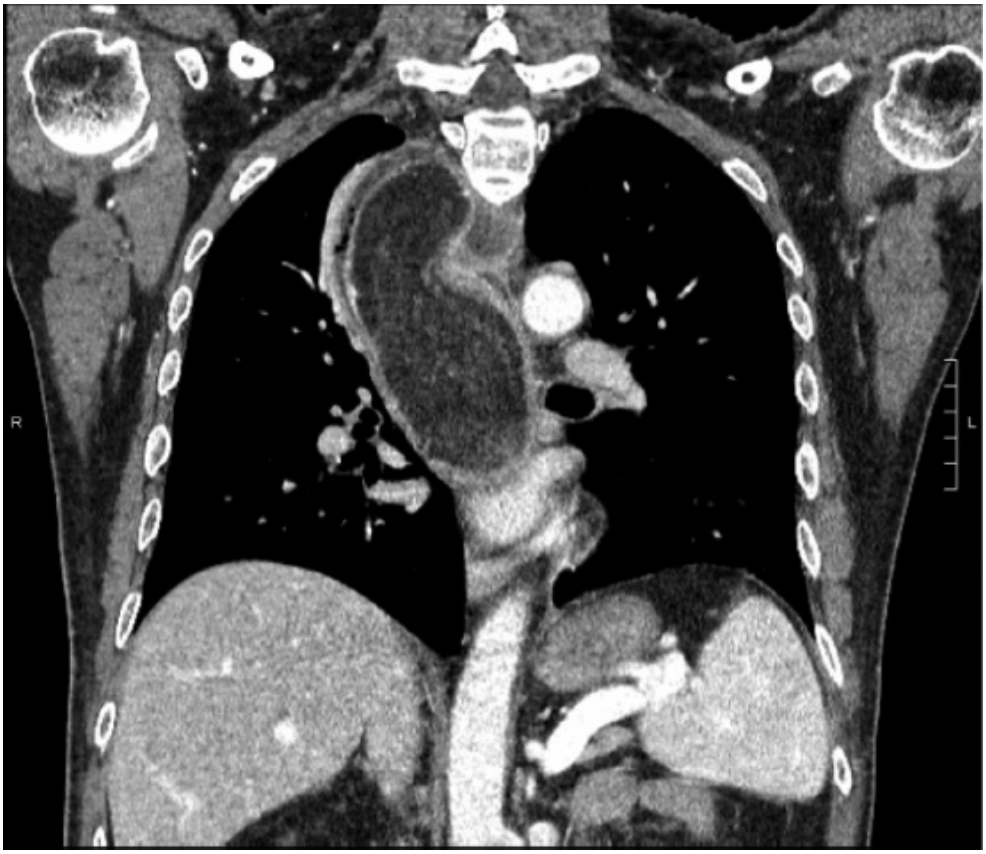


Figure 43.9 Computed tomography scan of the chest showing a large fibrovascular polyp that extended from the cervical to lower thoracic esophagus. (Courtesy of Joseph Shrager, MD and Jeffrey Yang, MD, Division of Thoracic Surgery, Stanford University, Stanford, CA.)

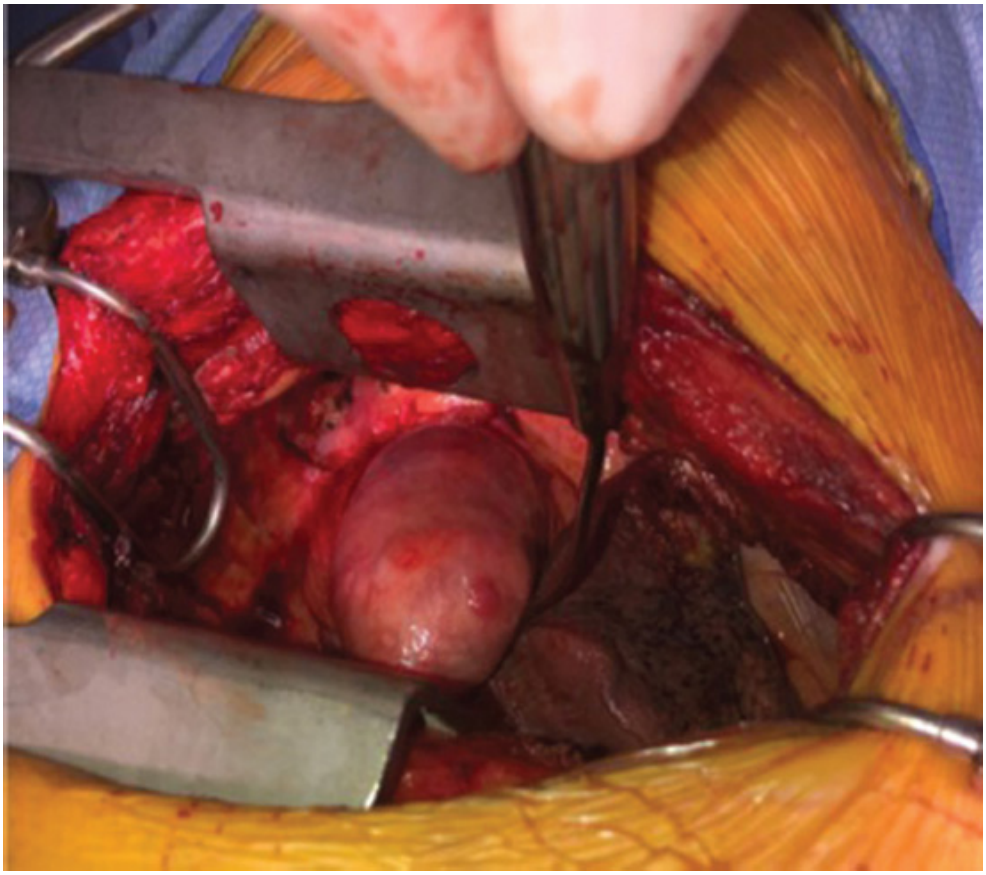


Figure 43.10 Intraoperative photos of a large fibrovascular polyp. The base of the stalk was divided endoscopically, and seen here is the tumor being removed through an esophagostomy via right thoracotomy. (Courtesy of Joseph Shrager, MD and Jeffrey Yang, MD, Division of Thoracic Surgery, Stanford University, Stanford, CA.)

Schwannoma

Schwannomas are neurogenic tumors that comprise less than 2% of benign neoplasms of the esophagus, described by case reports only.[192] They are thought to arise from the neural plexus within the esophageal wall and do not involve a distinct nerve, as compared to schwannomas that arise from the vagus nerve and grow into the esophagus.[193] They can present at all ages and are much more common in women. The most common symptom is dysphagia, but they can also cause compressive symptoms. They are most commonly located in the upper thoracic esophagus.

They can be difficult to distinguish preoperatively from the more common leiomyomas. CT scan of the chest reveals a homogeneous mass with smooth

borders that may compress nearby structures such as the trachea.[194] Endoscopy shows smooth, normal mucosa overlying the mass. Of note, schwannomas have been found to be FDG-avid on PET scan.[195] EUS-FNA may be able to yield a preoperative diagnosis.

Resection is indicated if tumors are symptomatic, greater than about 3 cm, increasing in size, or concerning for malignancy. Endoscopic resection in small tumors [196] and surgical enucleation are most common, while large tumors requiring esophagectomy have been reported.[197] Several case reports describe mucosal injury during enucleation which was repaired. Pathologic examination shows palisading spindle cells that are positive for S-100 protein and neuron-specific enolase, but negative for smooth muscle actin or desmin (leiomyoma), or CD34 or CD117 (GIST). A few cases of malignant schwannoma have been reported, including one with lymph node involvement.[198] Prognosis is good after resection.

Lymphangioma

Lymphangiomas are extremely rare benign neoplasms of the esophagus and described only in case reports. They arise from dilated lymphatic vessels within the esophageal wall, most commonly in the lower esophagus. They most commonly present at 50 to 70 years of age, and they are more common in men. Patients present with dysphagia or chest or epigastric discomfort.[199]

Endoscopy shows a pale, translucent subepithelial tumor. Endoscopic biopsy is often unrevealing and should not be performed if tumor could possibly be an esophageal varix. CT and MRI of the chest show that the tumor has fluid density. Most tumors are smaller than 2 cm, but very large tumors have been reported.[200] Resection is indicated if the tumor is symptomatic, large, increasing in size, or when the diagnosis is unclear. Resection has been described by EMR, submucosal endoscopic resection, surgery, and even laser treatment.[201] Recurrence after complete resection and malignant transformation have not been reported.[202]

ESOPHAGEAL INJURY

Esophageal Perforation

Epidemiology

Esophageal perforations are a major source of morbidity (10% to 60%) and mortality (4% to 50%); Accurate diagnosis and early treatment are essential to the successful management of these complicated and often significantly ill patients.

The causes of esophageal perforation are listed in **Table 43.10**. Generally speaking the incidence of iatrogenic perforation (59%) far exceeds the second most common cause that being spontaneous perforations (15%).[203] Other less common injuries include foreign-body ingestion (12%) and trauma (9%). Ingestion of foreign bodies or caustic materials most commonly causes perforations in the anatomic areas of narrowing: cricopharyngeus, level of aortic arch, and the level of left mainstem bronchus (**Fig. 43.11**). Also included in the area at risk is the lower esophageal sphincter zone. External penetrating trauma can occur at any level but is seen more commonly in the cervical esophagus as the mediastinal portion is posterior and protected by the thorax. The morbidity and mortality of penetrating esophageal trauma is usually related to associated injuries including major vascular and airway structures.[204] Blunt traumatic perforation of the esophagus is exceedingly rare.

Table 43.10 Causes of Esophageal Perforation

Instrumental Endoscopy Dilation Intubation Sclerotherapy Laser therapy
Noninstrumental Barogenic trauma Postemetic (Boerhaave syndrome) Blunt chest or abdominal trauma Other (e.g., labor, convulsions, defecation)
Penetrating neck, chest, or abdominal trauma
Operative trauma Esophageal reconstruction (anastomotic disruption) Vagotomy, pulmonary resection, hiatal hernia repair, esophagomyotomy
Corrosive injuries (acid or alkali ingestion)
Erosion by adjacent infection
Swallowed foreign body

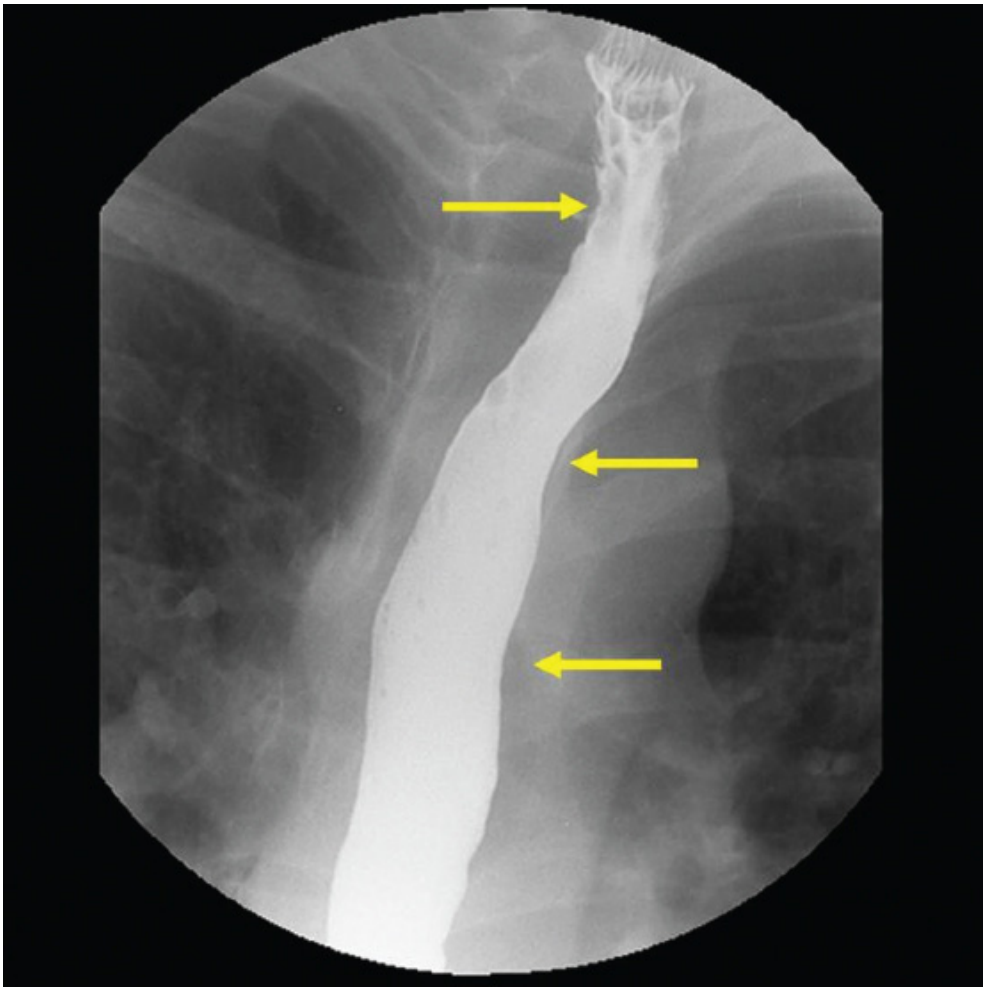


Figure 43.11 Barium esophagram showing the constrictions caused by the cricopharyngeal muscle, aortic arch, and left mainstem bronchus (*arrows*). Indentations of the esophagus made by external structures are important anatomic landmarks and are often sites of perforation due to instrumentation.

The incidence of perforation has risen in the modern era due to the rise in use of advanced endoscopic interventions including EMR, ESD, and per-oral endoscopic myotomy for treatment of achalasia (POEM). A recent report examining the treatment trends for early-stage esophageal cancer identified utilization of endoscopic therapy increased from 42.7% to 50.6% with a reciprocal decrease in esophagectomy from 21.7% to 12.8% from 2010 to 2014.[205] Others have noted similar trends.[206] The incidence of esophageal perforation following EMR and ESD is estimated at 1.9% to 5.8%[207,208] and 2.8% to 6% following POEM.[209]

Spontaneous perforation results from a sudden increase in intraesophageal pressure. The most commonly discussed is Boerhaave syndrome:

spontaneous perforation of the distal esophagus following extensive ingestion of food or alcohol. This leads to violent emesis resulting in a distal esophageal perforation, frequently into the left chest. Perforation can also be associated with hyperemesis, childbirth, seizure, or prolonged coughing.

Clinical Features

The presenting features of esophageal perforation depend on the location of the injury and the time interval from injury to presentation. Underlying comorbidities may also have an influence on the presentation dictated by the patient's physiologic reserve. Patients with cervical perforation present with dysphagia, neck pain, dysphonia, and subcutaneous neck emphysema. Often cervical perforations present earlier than distal perforations given the intolerability of discomfort of neck symptoms. Intrathoracic perforations may present with a spectrum of clinical features ranging from simple persistent substernal chest pain to symptoms of frank mediastinitis and sepsis. Mediastinitis is characterized by chest pain, tachycardia, tachypnea, fever, and leukocytosis. Perforations of the intra-abdominal esophagus may present as an acute abdomen with diffuse abdominal pain in addition to the above. More significant perforations and longer intervals to presentation contribute to the features of systemic sepsis, shock, and rapid deterioration. In a recent systematic review including 2,380 patients, 72.6% presented with perforation of the intrathoracic esophagus of which 46.5% were due to iatrogenic causes. Sepsis on admission was observed in 23.3% of cases. A significant proportion of cases (42%) were diagnosed more than 24 hours post injury which is known to significantly increase the mortality risk.[210]

Diagnosis

The diagnosis of esophageal perforation needs to begin with the clinician and their index of suspicion. Any patient who presents with pain following an endoscopic intervention needs to be carefully evaluated for perforation. The initial workup involves careful history and physical examination, laboratory studies including leukocyte count, and chemistry panel for acidosis. Chest x-ray is a good screening test for other diagnoses in the differential. Contrast esophagography remains the gold standard for diagnosis as the study will diagnose and localize the site of the perforation. This study also gives

important information about coexisting pathology of the esophagus and the degree of extravasation and its trajectory. Water-soluble contrast (e.g., Gastrografin) is the initial agent utilized, followed by thin barium to enhance the sensitivity of the study. Water-soluble agents demonstrate 50% of cervical perforations and 80% of intrathoracic perforations.[211] Thin barium will identify 60% of cervical and 90% of intrathoracic perforations.[212] If there is a chance of aspiration or high concern of tracheoesophageal fistula, thin barium should be used from the outset because the hyperosmolar water-soluble contrast agents may cause rapid pulmonary edema and respiratory compromise. Note that barium would interfere with any subsequent CT scan.

CT scan is very useful in the diagnostic evaluation of the patient with concern for esophageal perforation. Often a CT scan is the first test obtained following a chest x-ray as it affords the clinician the ability to narrow the differential diagnosis. CT may be useful for identifying the site of perforation and any associated mediastinal or pleural fluid collections. It is very common for a CT scan finding to prompt thoracic surgical consultation or facility transfer as it provides additional information routinely utilized in forming the management plan. Although CT scan is very useful, its accuracy in the diagnosis of esophageal perforation is estimated at 38.7% thus it is still limited as a confirmatory test even when performed with the administration of properly timed oral contrast.[210] Thus, it should be emphasized that the barium swallow study is the procedure of choice for optimal diagnostic accuracy unless there is a significant risk of aspiration. The barium esophagram is regarded as a real-time image, whereas the contrast delivery of the CT scan does not provide the same functional and anatomic details of the site and tracking of the leak, thus we prefer both when possible.

Although flexible esophagoscopy raises the concern of worsening the clinical condition of the patient due to contamination of the mediastinum, use of insufflation, and aspiration, it should be utilized liberally in the diagnostic evaluation of the esophagus and in the planning of treatment options. Its diagnostic accuracy is highly variable depending on type of injury and time to presentation, however in a large series it is quoted as 37.4%.[210] Endoscopy also has a distinct advantage in potentially serving as a means of primary treatment intervention in a significant number of cases. The scope is utilized to directly visualize the area of perforation and identify any potential

associated pathology. It has a sensitivity of over 95% and a specificity over 80% depending on the experience of the physician.[213] We routinely perform flexible endoscopy as the initial step in the operating room when considering all options for patient management (**Fig. 43.12**). The vast majority of patients will require an endoscopic evaluation at some point and the timing of this will depend on clinical presentation and findings on radiologic imaging. For very small defects in stable and nontoxic patients, in the absence of free extravasation, we may opt to hold off on an endoscopy in select cases.

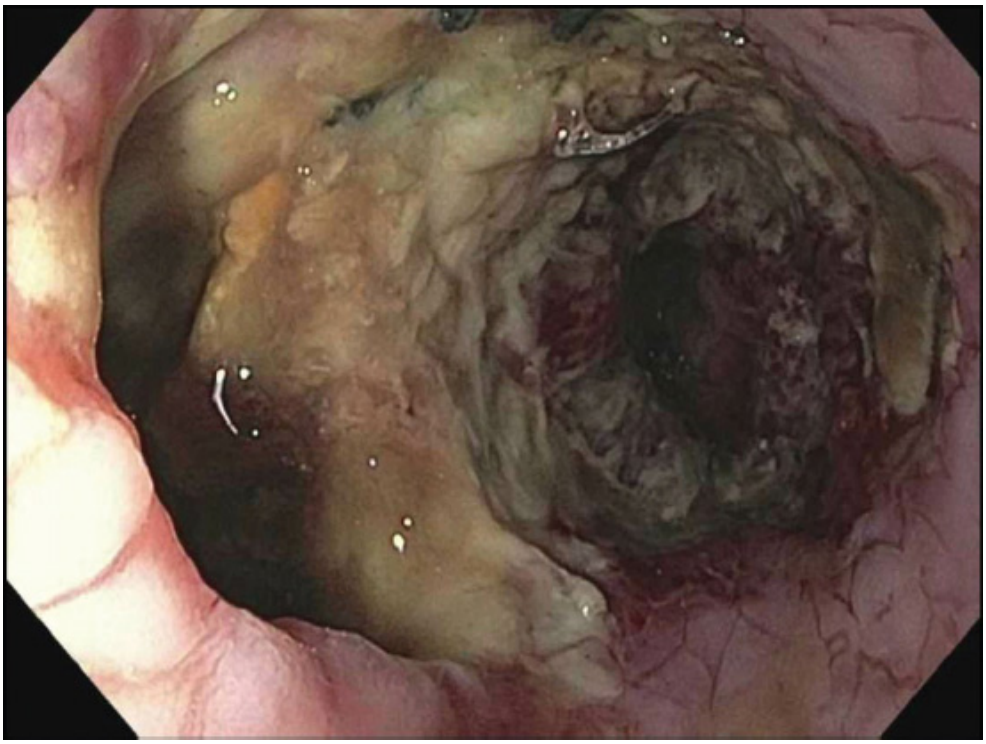
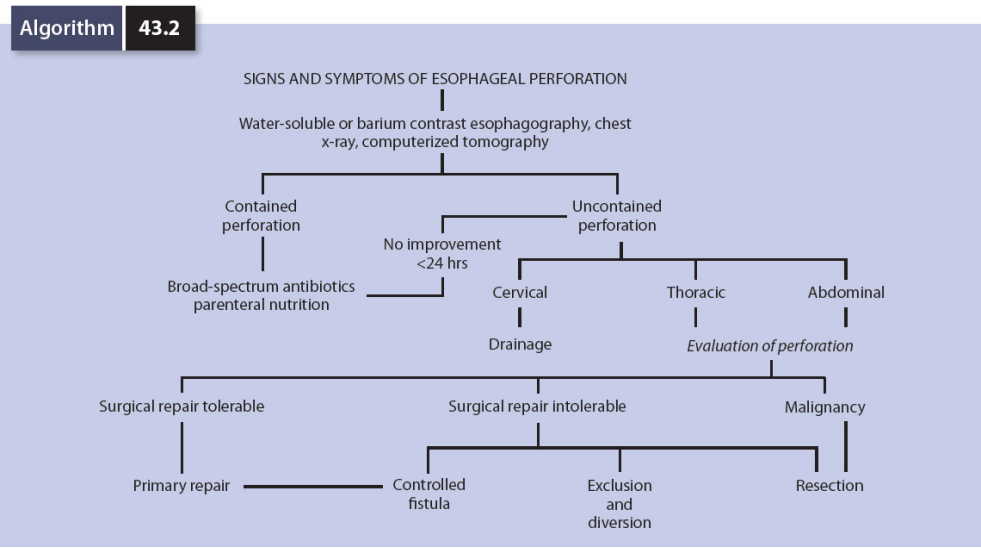


Figure 43.12 Endoscopy showing acute esophageal perforation at time of delayed presentation. (Courtesy of Joo Ha Hwang, MD, Division of Gastroenterology and Hepatology, Stanford University, Stanford, CA.)



Algorithm 43.2 Evaluation and management of esophageal perforation.

Management

Some investigators suggest aggressive operative intervention (e.g., surgical exploration and repair or gastric conduit takedown with diversion) for patients with post-esophagectomy intrathoracic anastomotic leak, while others recommend nonoperative management with stenting, jejunostomy feeds, perianastomotic drainage, and broad-spectrum antibiotics. The decision is influenced by the location and size of the perforation, the timing and mechanism, the degree of periesophageal soiling and extravasation, coexisting pathology of the esophagus, the patient's overall clinical condition, and the experience of the surgeon. The goal of treatment is to stabilize the patient, stop ongoing soilage, control infection, and maintain esophageal continuity if possible. Additional consideration should be given to the need for long-term enteral access predicted by the severity of the injury and condition. **Algorithm 43.2** provides general guidelines to the management of patients with esophageal perforations. Several well-established factors determine treatment strategy and prognosis: (1) time interval between injury and presentation, (2) location of the perforation along the esophagus, (3) severity and size of the perforation, (4) presence of signs of systemic sepsis, (5) presence of underlying esophageal pathology, and (6) experience of the care team.

Two potentially modifiable risk factors for poor outcomes are hospital volume and time to presentation. High hospital volume has been associated

with reduced mortality following esophageal perforation.[214] For patients presenting with spontaneous esophageal rupture (Boerhaave syndrome) diagnosis is often either missed or delayed leading to a mortality rate approaching 60% if time to definitive treatment exceeds 48 hours. This is in stark contrast to the overall mortality in cases managed within 24 hours of presentation which is associated with a 20% mortality.[215] Some have sought to address both delays in care and low-volume centers by developing a regional esophageal emergency referral program emphasizing multidisciplinary care at high-volume institutions with early reports of favorable outcomes.[216] Still others report success in using the Perforation Severity Score (PSS) in an attempt to better triage patients.[217] The PSS is a clinical score based on pre-existing esophageal pathology and clinical findings at the time of presentation (**Table 43.11**). Patients are risk stratified into low-, intermediate-, and high-risk groups according to increasing morbidity and mortality outcomes. The main benefit of such a score is its ability to identify patients at high risk for failure of nonoperative therapy thereby lowering the threshold for operative intervention.

Table 43.11 Perforation Severity Scoring (PSS) Criteria

Clinical Criterion	Weighted Score
Age >75 yrs	1
Tachycardia	1
Leukocytosis	1
Pleural effusion	1
Fever >38.5°C	2
Noncontained leak	2
Respiratory compromise	2
Presentation >24 hrs from injury	2
Hypotension	3
Malignancy	3

Adapted from Schweigert M, Sousa HS, Solymosi N, et al. Spotlight on esophageal perforation: A multinational study using the Pittsburgh esophageal perforation severity scoring system. *J Thorac Cardiovasc Surg* 2016;151(4):1002–1009.

Nonoperative Treatment

For properly selected patients with esophageal perforation, nonoperative management may be appropriate. In fact, in more than 50% of patients presenting with known or suspected esophageal perforation, initial management is nonoperative[210] with a success rate close to 60%.[217] Recently, the rates of nonoperative management have seen a significant increase from 48.6% between 2001–2003 to 54.9% between 2010–2012. Accordingly, there has also been a significant reduction in the utilization of surgery over the same period down to 12.7%.[214] Iatrogenic and traumatic perforations are more likely to be treated nonoperatively (68%) potentially due to the more immediate suspicion and presentation at the time of the procedure that resulted in the injury. By contrast, spontaneous perforations are more likely to be managed operatively most likely due to their relatively delayed presentation.[218] Timing for nonoperative therapy is critical as those

repaired within 24 hours of injury have significantly improved outcomes compared to those with delayed surgical intervention (either primarily or due to failure of initial medical therapy).

Current guidelines for patients who can be managed nonoperatively include those with no transmural perforation and those with a contained transmural perforation. There must also be no associated esophageal pathology such as malignancy and no signs of systemic illness. The nonoperative approach begins with the administration of broad-spectrum antimicrobials, the suspension of oral intake, and vigilant clinical monitoring. Initial broad-spectrum antimicrobial therapy is directed to cover common gram-negative bacteria, anaerobic bacteria, and fungi. We generally use a beta-lactam agent in combination with fluconazole, which is usually sufficient. We adjust therapy to culture findings. Duration of therapy is patient dependent, but it is typically continued for 10 to 14 days after resolution.

The patient is followed clinically and reimaged as needed, generally within 48 to 72 hours with a CT scan and esophagram if clinically indicated. If the patient improves during that time and testing is favorable, the diet may be advanced to clear liquids with the patient eventually being discharged on oral antibiotics and full liquids until reevaluation with imaging in the outpatient setting in 2 weeks. Any signs of sepsis such as fever, tachycardia, or leukocytosis suggest failure of this approach and further intervention should be expeditiously considered.

Esophageal Stents

Endoscopic placement of endoluminal stents for esophageal perforations has been a concept discussed for several decades.[219] In the last 10 years, the technology of stents has improved such that deployment is easier and indications have expanded. Starting with small limited series,[220–226] their use has increased dramatically to the point that they have become one of the main tools in the management of select, contained perforations. Their use in the management of benign esophageal perforation increased over fourfold in just 8 years from 7% in 2007 to 30% in 2014.[227] Highly selected patients with perforations are candidates for stenting in the context of a thoracic surgical consultation according to the principles outlined in this section. Successful stenting facilitates source control, may minimize stricture formation, and

frequently allows for early oral intake. However, success depends on a uniform approach that focuses on appropriate patient selection, proper stent placement technique, thorough drainage procedures (e.g., tube thoracostomy or decortication) which cannot be overemphasized, and meticulous postoperative care.

Patient Selection

For perforations proximal to the cricopharyngeus, stents have little or no role. For perforations 2 cm or more distal to the cricopharyngeus, a stent may work if the proximal extent seats just below the cricopharyngeus muscle. If the stent seats at or above the cricopharyngeus, patients experience intolerable foreign-body sensation during deglutition, and reflux and coughing are generally severe. Also of note, stents placed in the proximal esophagus may cause pressure and compression of the posterior membranous trachea leading to dyspnea and, in severe cases, critical airway compromise. If a stent is considered for placement in the proximal esophagus, the physician should strongly consider performing a simultaneous bronchoscopy to assess airway patency. Distal esophageal injuries may be better candidates for stenting when there is limited perforation, and there is good purchase of esophagus above and below the site of the perforation. This might include perforations associated with malignancy and in benign diseases such as iatrogenic perforation, Boerhaave syndrome, and select cases of achalasia. Patients with perforations from near-obstructing cancers can be ideal candidates for stents as the stent will purchase well against the tumor, leading to sealing of the perforation and relief of any coexisting blockage above or below the level of perforation. In addition, operating on perforated cancers can be a significant clinical challenge as this may represent their initial diagnosis at the time of perforation without the benefit of clinical staging. Perforation may also occur during treatment for esophageal cancer with chemotherapy or radiation. In either event, the patient may have contamination from tumor spillage thus making stenting our procedure of choice in the setting of malignancy.

We emphasize aggressive source control, and operative drainage of any extraluminal material. Stent placement without drainage in the setting of mediastinal soilage is a risky approach and if it is done, one may question whether the perforation was small enough to need intervention. If larger, we

would typically perform a VATS or thoracotomy to debride any soilage. If patients deteriorate clinically following any treatment, consideration of the presence of undrained sepsis should always be considered. At times, a patient might require several interventions to control the local and regional sepsis. Source control measures vary depending on clinical and anatomical findings. In general, the presence of mediastinal air without fluid collection represents the highly select group for which antibiotics only without additional source control measures as an adjunct to stent therapy can be considered. The presence of mediastinal fluid collection or abscess most often requires formal operative drainage. The operative approach to drainage will vary by anatomical location. Cervical esophageal injuries with fluid collections in the neck and superior mediastinum can be approached through lower vertical neck incision with blunt mediastinal dissection, irrigation, open packing, and, if deemed appropriate, drain placement. Often the use of a mediastinoscope can facilitate drainage of fluid collections extending down into the superior mediastinum without the need for formal chest exploration. Collections within the middle mediastinum are best approached via right thoracoscopy or thoracotomy with wide pleural incision, drainage, irrigation, and large-bore chest tube(s) placement. Left thoracoscopy or thoracotomy are best reserved for isolated collections in the lower posterior mediastinum but can also provide the potential for extension down into the abdomen for access to the gastroesophageal junction and upper abdomen.

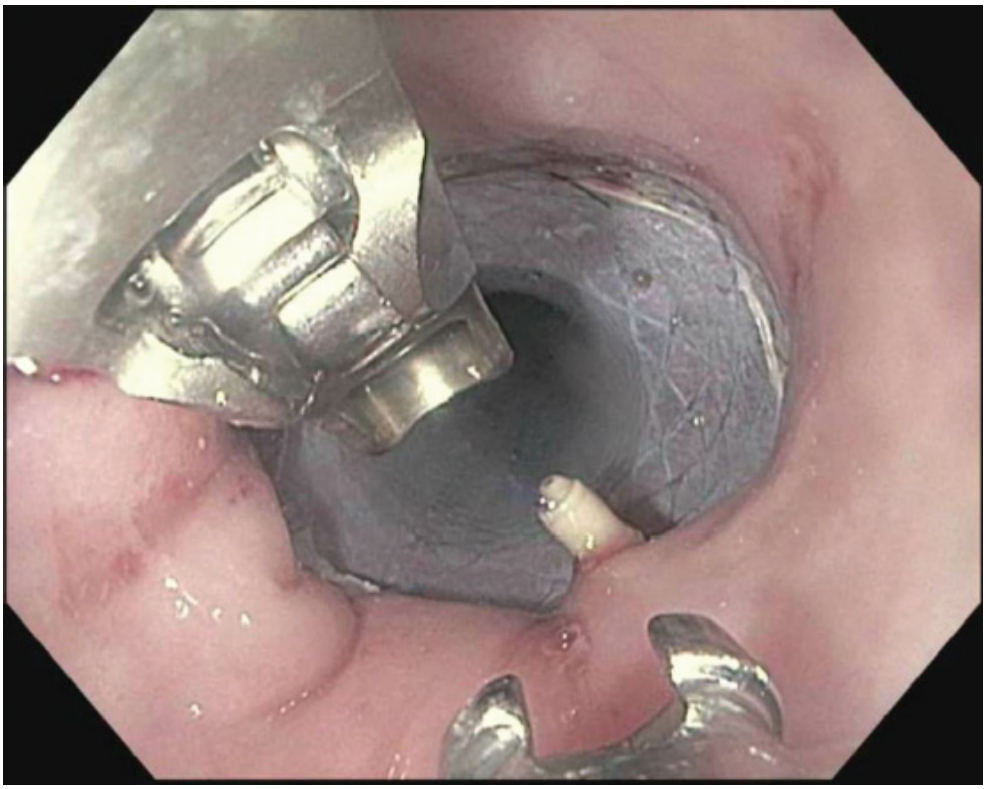


Figure 43.13 Endoscopy showing proximal suture fixation of esophageal stent. (Courtesy of Joo Ha Hwang, MD, Division of Gastroenterology and Hepatology, Stanford University, Stanford, CA.)

Stent Placement

Numerous stents are available for use. Longer stents (15 cm) that are fully covered work better to cover defects than uncovered stents. Newer covered stents which are uncovered at the proximal and distal end offer an advantage over fully covered stents to minimize migration. The procedure can be performed either in the endoscopy suite or the operating room. We prefer the latter with general anesthesia so that the stent can be placed immediately following diagnostic endoscopy followed by surgical exploration for mediastinal and pleural drainage in one setting. Fluoroscopy is useful to aid in optimal stent positioning using radiopaque skin markers. Additionally, fluoroscopy is useful if intraoperative esophagram is required for a small leak that is difficult to localize endoscopically. Ideal stent placement will depend on the location and size of the perforation. The goal is to cover at least 3 to 4 cm above and below the site of leak or perforation with a minimum distance from cricopharyngeus muscle (upper esophageal

sphincter) of 1 to 2 cm. In the case of distal esophageal perforation centering the stent at the site of injury may result in crossing the GE junction which is associated with higher risk of stent migration. In this case, we suggest using a longer stent oriented such that the distal end is lodged against the greater curvature of the stomach which acts as an additional fixation point to minimize migration with peristalsis. Proximal stent fixation using endoscopic sutures or clips is also useful to reduce the risk of stent migration (**Fig. 43.13**). Following placement, intraoperative evaluation of stent position and proper sealing is confirmed with a final endoscopy. It is easier to "pull" a stent back more proximally than to "push" it more distally thus we recommend erring on the side of more distal placement and repositioning, if needed to be done via pulling technique.

Poststent Management

Enteral feeding access should be ensured as soon as possible, preferably at the time of endoscopic and operative interventions. This can be accomplished with laparoscopic or open jejunostomy, percutaneous gastrostomy (PEG), or nasoenteric tube in order of decreasing invasiveness. Anticipation of good stent placement with limited time estimate for enteral access can be managed with nasoenteric tube only which can be placed at the conclusion of the endoscopy. PEG may be ideal for those not requiring laparotomy for other reasons and can also be placed at the time of endoscopy but before stent placement. PEG placement after stent placement has the potential to displace the stent. Daily chest radiograph is performed to monitor stable stent location for several days following placement. We obtain chest radiography immediately after the procedure and daily thereafter to monitor for migration. Ongoing sepsis is generally due to poor source control and/or nonsealing of the perforation. Reintervention is tailored to the situation but might require aggressive surgical intervention and stent removal and/or replacement.

Outcomes

Outcomes for stent therapy for esophageal perforation have a reported success rate of 77% to 84%.[228] Stent migration is the leading complication following stent. It occurs in 30% to 55% of cases of stent placement and proximal fixation with sutures or clips is associated with a reduction in stent

migration and need for replacement.[229] Once stent migration is confirmed radiographically, replacement is required unless the leak has resolved. This is typically not an emergency but should be addressed in a timely fashion. We generally repeat endoscopy at 3-week intervals and remove the stent each time. If a small leak persists, a new stent is placed so that the distal end of the stent is slightly proximal or distal to that of the previous stent to allow the area of inflamed mucosa to heal. Resumption of oral intake depends on the clinical scenario. A speech pathologist evaluates every patient before an esophagram. Only patients who are safe to swallow undergo an esophagram. Oral intake is then resumed and represents a major advantage of stent placement which allows for the possibility of oral nutrition while the perforation is healing.

Esophageal stenting is also a useful tool in the setting of failed primary repair or anastomotic leak. Technical success of esophageal stenting for anastomotic leak is reported as high as 71.4% requiring a median treatment duration of 28 days.[230] Secondary interventions following stent placement for patients with perforation are estimated at 33.7%. Major complications include sepsis (28.1%), pneumonia (17.1%), and multiorgan failure (11.6%). Overall mortality is 15.1%.[231] According to the latest systematic review, the overall technical and clinical success rates of esophageal stenting for esophageal perforation are 91% and 81%, respectively, with mortality of 13% likely reflective of diligent patient selection.[232]

Endoscopic Clipping

Endoscopic interventions in the form of clipping or suturing are gaining in popularity with promising early results (**Fig. 43.14**). Endoscopic clipping can be performed either using a through-the-scope (TTS) method or an over-the-scope (OTSC) system. The OTSC system is a clipping method for mechanical compression of tissues in the GI tract first designed for the management of bleeding, perforation, and fistula. Similar to other interventions for perforation, endoscopic clipping is a viable option only when performed early after the injury. After 24 hours post-injury, tissue integrity becomes a major limitation hindering successful primary repair, and the rate of failure of endoscopic therapy increases significantly.[233] TTS clips are best for defects 10 mm or less in greatest dimension while bigger (<20

mm) lesions can be treated successfully with the OTSC method. Larger defects are best considered for stent placement or surgical repair. In either endoscopic treatment, a significant source of failure is overlooking the need for drainage and treatment for associated mediastinitis as a source of sepsis. Thus, concomitant surgical or nonsurgical drainage of the mediastinum is imperative to accompany the endoscopic intervention as outlined for stenting.

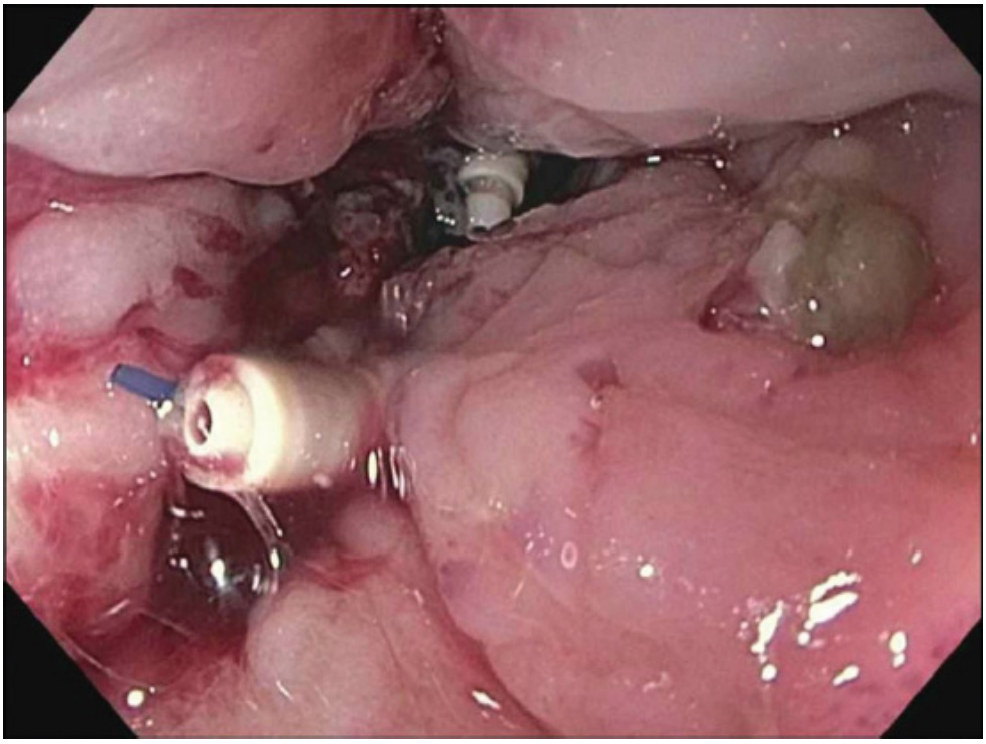


Figure 43.14 Endoscopy showing primary suture repair of esophageal perforation. (Courtesy of Joo Ha Hwang, MD, Division of Gastroenterology and Hepatology, Stanford University, Stanford, CA.)

Vacuum-Assisted Closure Therapy

Endoluminal vacuum-assisted closure (EVAC) therapy is a novel treatment modality for managing esophageal perforations. EVAC therapy facilitates tissue healing by overcoming physiologic negative pressure in the thorax, reducing mediastinal contamination and enabling tension-free approximation of tissue. The procedure can be performed in the endoscopy suite or the operating room under general anesthesia. The endosponge is created using a modified NG tube connected to a tailored wound vac sponge that is trimmed to size per endoscopic examination. The endosponge is then exteriorized for

connection to the wound VAC suction system with continuous negative pressure at 175 mm Hg, on high intensity.[234] There are small series reporting success using EVAC therapy as primary treatment for esophageal perforations and leaks.[228,234–236] Successful closure is reported to range between 91% and 100% closed after a mean duration of 27 days requiring an average of 6 endosponge changes every 4.8 days. An additional advantage of EVAC therapy is the potential to treat patients outside of the 24-hour early presentation window with facilitated drainage of any mediastinal abscess cavity.

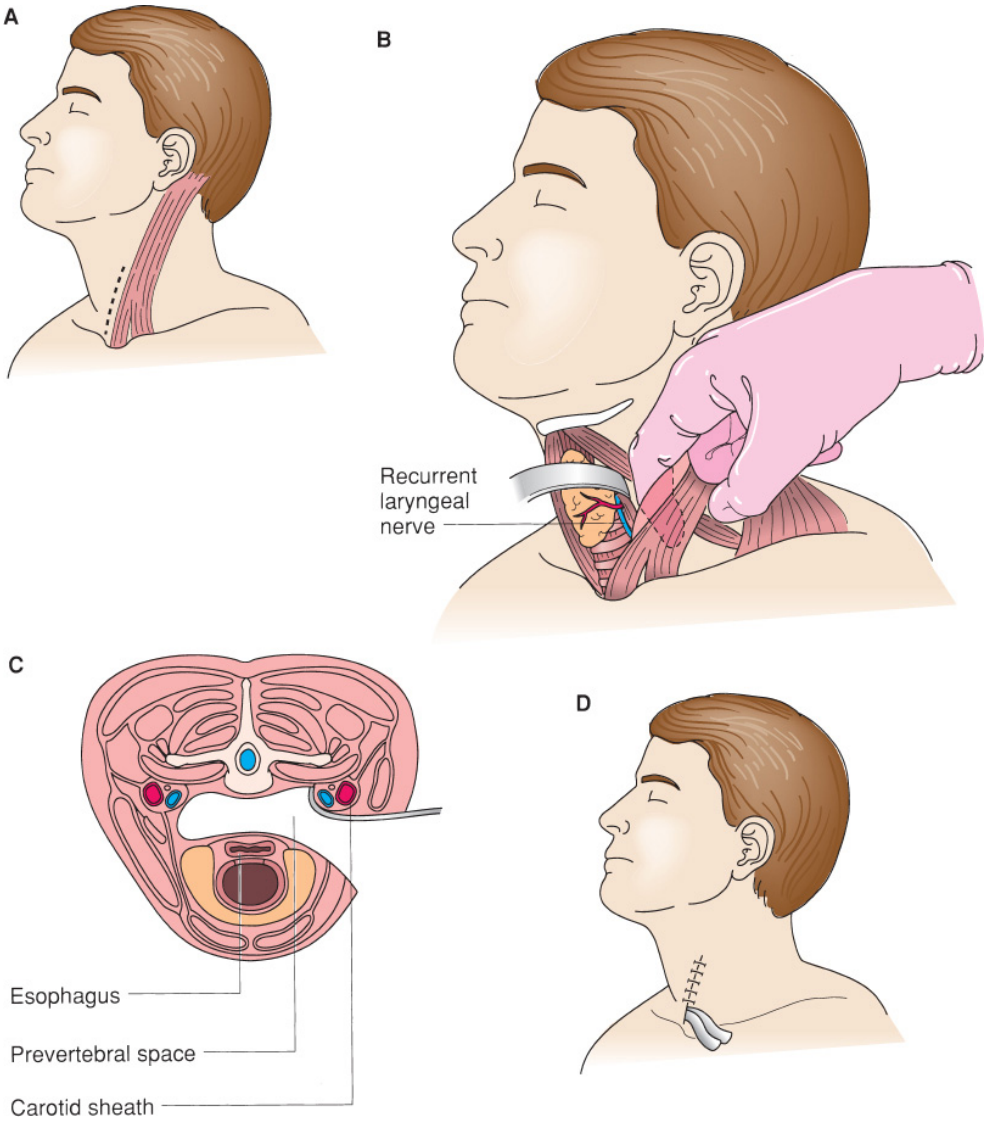


Figure 43.15 Approach for drainage of a cervical esophageal perforation. **A:** Skin incision parallel to the anterior border of the left sternocleidomastoid muscle, extending from the level of the cricoid cartilage to the sternal notch. **B:** With the sternocleidomastoid muscle and carotid sheath retracted laterally and the trachea and thyroid gland retracted medially, blunt dissection is performed along the prevertebral fascia in the superior mediastinum. Injury to the recurrent laryngeal nerve in the tracheoesophageal groove must be avoided. **C:** Schematic drawing of the prevertebral space drained by this cervical approach. **D**: Penrose drains placed into the superior mediastinum are brought out through the neck wound to allow establishment of an esophagocutaneous fistula, which usually heals spontaneously.

Surgical Repair

The operative management of esophageal perforation is dictated by the location of the injury, extent of injury, and underlying pathology. Operative

approaches include drainage alone, primary reinforced repair, esophagectomy with immediate or delayed reconstruction, and esophageal exclusion.

Perforations of the upper third of the esophagus to the level of the carina should be approached via a left neck incision (**Fig. 43.15**). Traditionally it is not necessary to find or close the perforation when approached this way as the injury will seal during the process of healing. In order for this to be successful, however, wide and complete drainage must be accomplished. Preoperative CT scan will aid in ensuring that the important areas of contamination are addressed surgically. In the operating room we liberally use on-table flexible endoscopy to evaluate the defect and the location of the defect. If the defect is identified and it is small, we advocate for an attempt at primary closure. The neck incision is loosely reapproximated with staples over a drain. Typically, a contrast esophagram is obtained 5 to 7 days postoperatively, the patient's diet is advanced, and the drain is removed. If there is continued leak, the patient is left NPO or on clear liquids and restudied in 1 week. There should be no distal obstruction on the contrast study and if there is a stricture that prevents normal contrast flow, we advocate for dilation to aid in eventual closure of the esophageal fistula. As long as there is no underlying pathology or distal obstruction, most cervical injuries will heal spontaneously with adequate drainage.

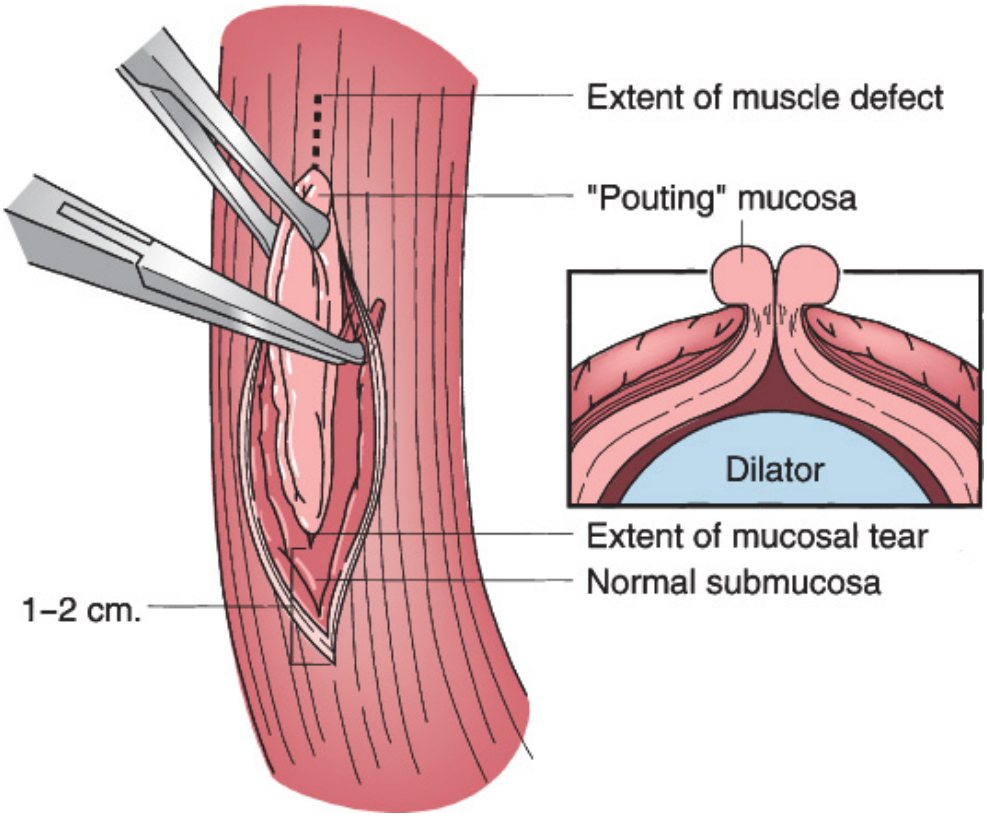


Figure 43.16 Primary repair of esophageal perforation. The edematous mucosa pouting through the muscular defect (*inset*) is grasped with Allis clamps and elevated. A 1-cm vertical esophagomyotomy is made at either end of the muscular defect to expose the entire limits of the mucosal tear. This is facilitated by using a right-angle clamp to direct muscularis away from underlying submucosa around the entire circumference of the tear. The result of this mobilization is exposure of a circumferential rim of normal submucosa that can then be closed.

Perforations of the middle third of the esophagus are best approached via a right fifth interspace posterolateral thoracotomy. We routinely start thoracoscopically, but typically these patients are very ill thus one should have a low threshold for conversion to thoracotomy. At the time of entry into the chest, an intercostal muscle flap is routinely taken. The mediastinal pleura is opened widely and all pleural collections are drained, the lung is decorticated, and the site of perforation identified. Necrotic tissue at the site of the perforation is debrided and the esophagus is mobilized. A vertical myotomy is performed to expose the mucosa and determine the full extent of the tear (**Fig. 43.16**). The mucosa is repaired with simple interrupted or running absorbable suture. The muscular layer is reapproximated with interrupted fine silk suture. On-table endoscopy is performed to ensure the

leak is repaired. The intercostal muscle is then secured as an onlay patch. Large chest tubes are placed and a malleable Blake drain is left in the area of the repair and placed to bulb suction. Nutritional access can be addressed at the index operation if the clinical condition of the patient is favorable. If not, this can be accomplished at a later date. On postoperative day 7, a contrast study is obtained and if there is no leak, the diet is advanced. Persistent leaks are treated with continuation of the surgical drains and potentially placing additional drains via interventional radiology if there are any undrained collections. Esophageal stenting may be used to exclude any persistent leak as outlined above. If there are signs of clinical sepsis despite the above, esophageal exclusion may be required with cervical esophagostomy and establishment of long-term enteral access via jejunostomy or gastrostomy. Esophageal resection can be performed at the time of diversion or delayed depending on the clinical conditions. Patients can be considered for delayed reconstruction 6 to 12 months following perforation most commonly approached as a gastric pull-up, colonic interposition, or jejunal flap placed in the substernal position. Perforations of the distal third of the esophagus can be approached via a left seventh intercostal space thoracotomy using the same principles for repair and drainage.

Operative treatment in the presence of underlying pathology deserves special attention and can be quite challenging. If there is distal obstruction, this must be dealt with. Strictures can be dilated or stented and often support the healing of a proximal perforation. Patients with achalasia who are perforated during pneumatic dilation are especially challenging. Many are candidates for nonoperative intervention as they have small perforations that are asymptomatic and the patients are clinically nontoxic. This is acceptable provided the distal obstruction has been relieved. For those who fail nonoperative management or are not candidates, operative management should be tailored to the individual and their pathology. In patients with preserved motility, the perforation should be repaired primarily and a vertical myotomy should be performed 180 degrees opposite the injury. These patients, and those for whom esophageal motility status is unknown, should have a partial fundoplication performed. For stable patients with advanced achalasia, esophagectomy should be considered. For unstable patients, esophageal exclusion should be performed. Unstable patients with advanced pathology such as cancer should undergo esophageal stenting if

appropriate or exclusion. This includes stapled esophageal diversion with resection of the diseased segment of the esophagus. A linear stapler is deployed on the esophagus proximally and at the gastroesophageal junction. The esophagus is resected. An end cervical esophagostomy is created saving as much esophageal length as possible. Pleural drainage is accomplished. Subsequently the patient undergoes placement of gastrostomy (+/− jejunostomy tube) with repair of the diaphragmatic defect from the abdominal side via laparoscopy or laparotomy. The components of operation may be staged based on the severity of patient illness. If the patient survives and is a candidate for reestablishment of continuity, this can be investigated later once they have recovered. Additionally, consideration should be given to end-of-life discussions depending on the extent of the cancer.

Surgical Resection

Fortunately, esophagectomy is necessary in only a small percentage of patients following perforation. It may be indicated following failed primary repair or as primary treatment with or without immediate reconstruction. The presence of pre-existing benign or malignant stricture or large perforation (>5 cm) is associated with increased risk for need for an urgent esophagectomy.[250] When clinically indicated, emergent esophagectomy represents a safe treatment option with observational studies demonstrating mortality rates comparable between operative and nonoperative management (31% vs. 20%).[237–239]

Caustic Injury

Epidemiology

Caustic burns of the esophagus result from ingestion of substances with pH <2 or pH >12. In children these ingestions are usually accidental, while in adults they are most often associated with suicide attempts. Liquid alkaline agents (e.g., household cleaner) are more likely to be swallowed and subsequently cause more injury. Although mortality from caustic ingestion is low, the morbidity associated with caustic ingestions is significant. Acute

morbidities include perforation and necrosis. Late morbidities are more prevalent and include stricture formation and cancer.

The extent of injury to the esophagus caused by ingested caustic material is dependent on the volume and nature of the ingestion. Injuries resulting from ingestion of liquids are much more severe than those caused by ingestion of solids. The patient usually spits particulate matter out and, thus, it rarely moves beyond the oropharynx. Liquid caustic agents contribute to pathology down the length of the esophagus. Strong acid and alkali ingestions comprise the majority of caustic ingestions. These substances are sold in various liquid and solid/particulate forms. The most commonly ingested strong acids include industrial and swimming pool cleaning solutions, battery fluids, and antirust compounds. Commonly ingested strong alkaline-containing substances include household cleaning products and personal hygiene products. The most commonly ingested weak alkali is ammonia hydroxide, which is found in most bleach solutions.

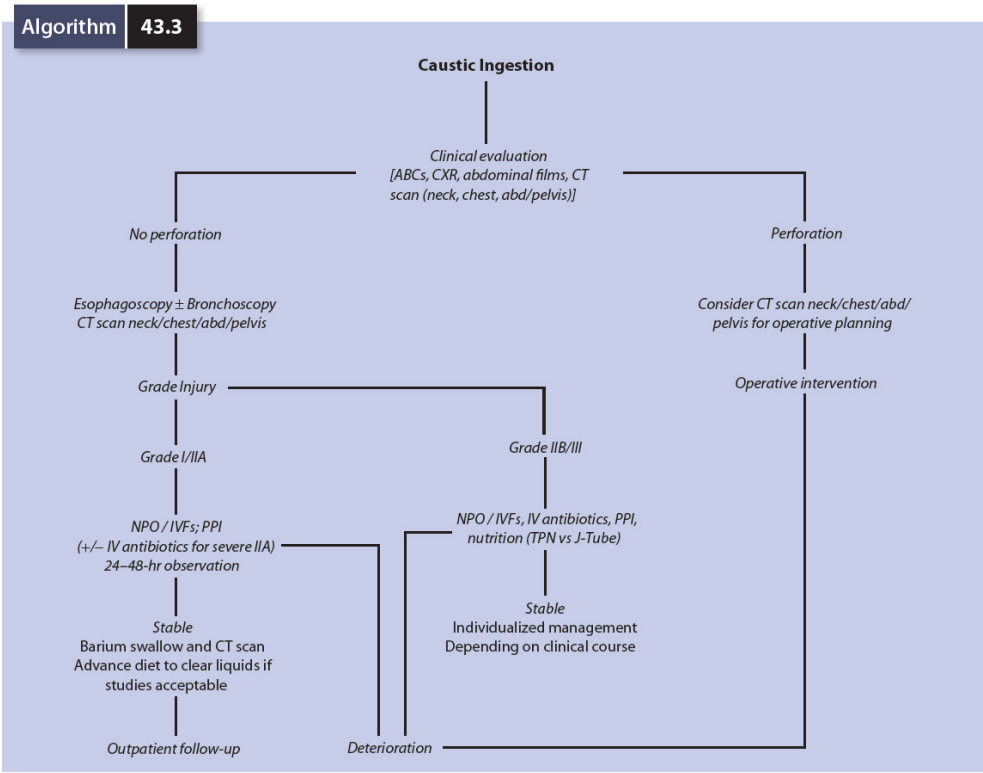
Injury from alkaline ingestion tends to be more severe than acid ingestion, resulting in significantly higher rates of morbidity and mortality and higher incidence of associated stomach injuries (43% vs. 13%).[240] Alkaline burns are characterized by liquefactive necrosis, leading to far greater penetration at the level of the oropharynx and esophagus. Solid alkali has a propensity to adhere to the oropharynx, whereas liquid alkali is rapidly swallowed. Thus, liquid alkali results in more distal esophageal and gastric injury. Frequently there is penetration of all layers of the esophagus causing substantial secondary edema. Commensurate with this, the potential for perforation and circumferential scar formation is greatest with an alkaline ingestion. In contrast to acid ingestion, alkali substances are typically odorless and tasteless, which enhances the potential for deeper injury.

Acids cause more severe damage to the stomach but similar damage to the esophagus when compared to alkalis.[241] The burns from acid ingestion cause coagulative necrosis and a superficial eschar that protects the deeper layers of the esophagus from damage. Fortunately, acids tend to taste bitter and cause immediate pain, thus the patient will usually spit the substance out well before it reaches the esophagus and stomach. When acids are ingested in liquid form, they move quickly, typically spare the oropharynx, and produce skip injuries to the esophagus. Acids in liquid form cause gastric and duodenal injury more frequently than esophageal injury.

Clinical Presentation

The initial clinical presentation comprises oropharyngeal pain; irritability; and, in severe cases, excessive salivation, dysphagia, and airway compromise. Ingestion of particulate caustic substances results in signs of contact readily visible in the oropharynx. Hoarseness and stridor are signs of serious airway injury that mandate intubation. Retrosternal pain, neck crepitus, and sudden onset of epigastric pain imply full-thickness esophageal damage. Many patients present without symptoms and a significant proportion have injuries that will require intervention. Thus, a 24-hour period of observation is reasonable, even for asymptomatic patients, especially if there is any question about the circumstances of the ingestion or extent of injury.

As with any acute situation, management should begin with the standard assessment of the ABCs (airway, breathing, and circulation) (**Algorithm 43.3**). As with most foreign-body ingestions, the most common sites for pathology within the esophagus are its three areas of narrowing: the cricopharyngeus, the level of the aortic arch, and the gastroesophageal junction (**Fig. 43.11**). A stable patient may undergo imaging via posteroanterior and lateral upright chest and abdominal radiographs to evaluate for pleural effusion or free air. CT of the chest and abdomen can provide important anatomical definition of injury. Patients with no visible symptoms or only lip swelling or redness can be observed in the hospital or a short-stay unit for 24 hours to ensure they can tolerate oral feedings. This is typically for pediatric patients. Patients with oral lesions should undergo esophagoscopy and bronchoscopy. The bedside insertion of an NG or orogastric tube is discouraged when the extent and depth of injury have not been fully evaluated.



Algorithm 43.3 Evaluation and management of acute caustic ingestion.

After radiographic imaging, rigid or flexible esophagoscopy to characterize the location and extent of injury should be the next course of investigation. This should be performed within the first 24 hours as the risk of procedural complication increases with time. In a large retrospective study of 21,682 patients following caustic ingestion, patients undergoing endoscopy delayed greater than 48 hours after injury experienced a threefold increased risk for poor clinical outcome.[242] Others advocate for assessment with repeat endoscopy on post-injury day 5 reporting that delayed examination is a better predictor of esophageal and gastric cicatrization than day 1 exam alone, which significantly overestimates the grade of injury.[243] The indications for esophagoscopy include stridor, vomiting, drooling, and intentional ingestion. Caution should be used when moving beyond the first sign of pathology below the cricopharyngeus. If there are respiratory symptoms, laryngoscopy and bronchoscopy should be performed. The latter of which should direct the procedure to be done in the operating room. When injury is identified, the standard grading of the esophageal burn should be reported (**Table 43.12**).

Management

The initial clinical presentation comprises oropharyngeal pain, irritability and, in severe cases, excessive salivation, dysphagia, and airway compromise. Hoarseness and stridor are signs of serious airway injury that mandate intubation. Retrosternal pain, neck crepitus, and sudden onset of epigastric pain imply full-thickness esophageal damage. Many patients present without symptoms but have injuries that will require intervention. Thus, even asymptomatic patients should be observed closely for the first 24 hours.

Patients with grade I injuries have superficial burns causing edema and hyperemia. These patients can be observed, a normal diet can be advanced, and the patient ultimately can be followed in an outpatient clinic. Superficial grade I injuries cause mucosal sloughing and should heal without a stricture. Grade II injuries penetrate into the muscular layer of the esophagus and can result in either patchy (IIA) or circumferential (IIB) injury. Ulcerations (superficial and deep) and pseudomembranes are found during endoscopy (**Fig. 43.17**). Once circumferential injury is identified, the risk of stricture formation increases dramatically. Grade III injuries are full-thickness injuries, and mediastinitis or peritonitis occurs within 48 hours. Grade III findings are characterized by gray mucosal slough, thrombosed submucosal vessels, and black eschar. All grade III burns and >75% of circumferential grade IIB burns cause esophageal stricture and, as expected, are associated with a higher incidence of infection.

Table 43.12 Endoscopic Grading of Acute Caustic Injury to the Esophagus

Injury	Endoscopic	Depth of Grade Appearance Injury
I	Superficial hyperemia	Mucosal
IIA	Sloughing mucosa, superficial ulceration	Patch partial thickness
IIB	Deep ulceration	Circumferential
III	Eschar, necrosis	Full thickness

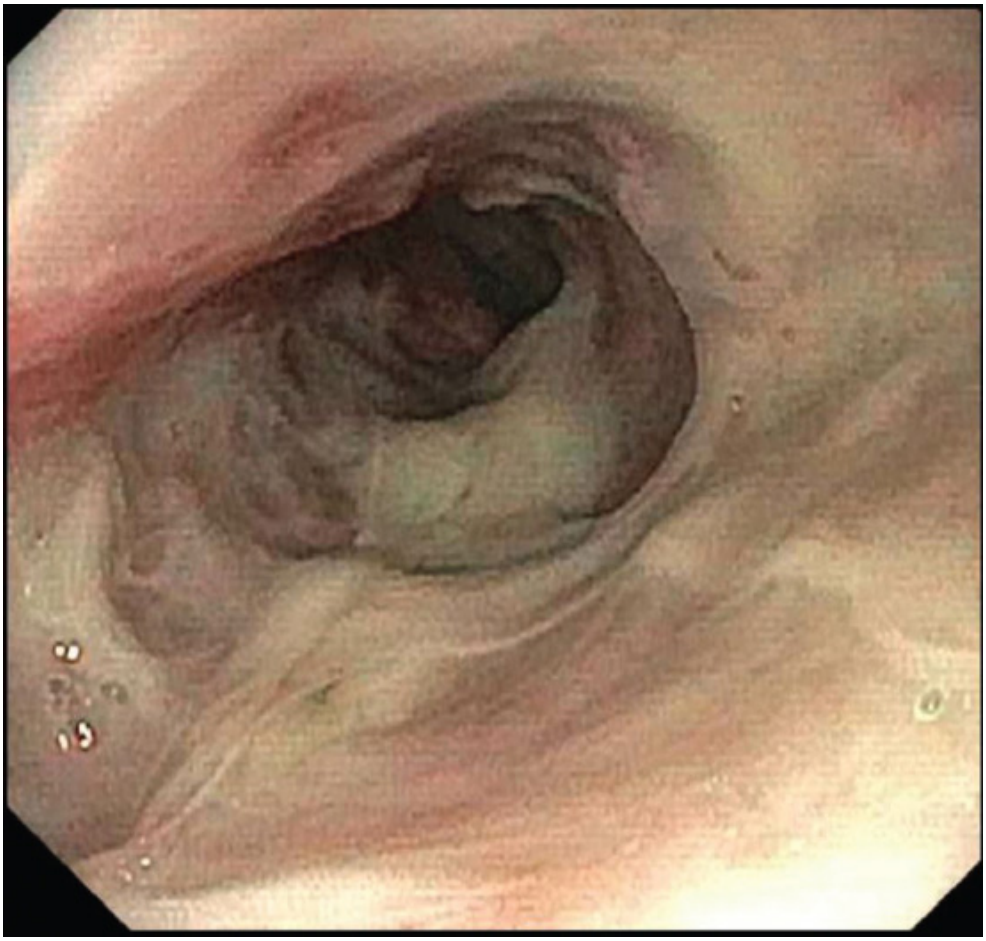


Figure 43.17 Endoscopy showing acute caustic ingestion. (Courtesy of Joo Ha Hwang, MD, Division of Gastroenterology and Hepatology, Stanford University, Stanford, CA.)

Acute management of caustic ingestion should be dictated by the endoscopic grading of the esophagus and the clinical status of the patient (**Algorithm 43.3**). If there is no evidence of perforation, patients with mild exposure (e.g., bleach or detergent ingestion) can be observed for 24 to 72 hours (depending on the clinical presentation). Generally, patients should be kept nil per os (NPO) until pain free. Enteral feedings can likely be introduced within 48 hours for all patients with grade I or IIA burns.

Patients with grade IIB or grade III esophageal burns without evidence of perforation should be placed in a monitored setting, kept NPO, and given IV fluids and IV antibiotics (penicillin derivative or clindamycin). Patients should also be maintained on proton pump inhibitors to reduce acid exposure of the esophagus as this may decrease the stricture incidence. Steroid

administration is controversial, does not prevent stricture formation, and may mask findings in the serial abdominal examination. If corticosteroids (2 to 2.5 mg/kg/d) are used, they should be instituted within the first 24 hours of ingestion and for 3 weeks thereafter. Early introduction of parenteral nutrition is essential for all patients with esophageal perforation and for patients with poor gastric motility. Depending on the extent of injury, the patient may require mechanical ventilation. Esophagram (or CT scan with oral contrast) may be used as an adjunct evaluation. If free contrast extravasation into the mediastinum is visualized, drainage of the mediastinum into the pleural space is indicated. Further, esophageal resection may be required with findings of necrosis. On occasion, a contained mediastinal leak, which returns contrast material back into the esophagus, may be observed without the need for immediate drainage. Pneumoperitoneum is an absolute indication for laparotomy and resection of all dead tissues. Laparoscopic evaluation may be useful to evaluate the abdomen if there is isolated mediastinal pathology.

Surgical Resection

One of the challenges associated with esophagectomy for caustic ingestion is availability of the stomach as a possible replacement conduit. In the case of associated gastric necrosis, the stomach may itself be injured thereby limiting its use as a conduit or it may be completely necrotic requiring concomitant gastrectomy. Initial resection can be performed as outlined above with or without immediate reconstruction. Delayed esophagectomy being done for sepsis or refractory stricture may be best performed in a staged fashion with esophagectomy and esophagostomy followed by substernal interposition graft of either colon or jejunum. Patients with extensive full-thickness esophageal and gastric necrosis should undergo total esophagogastrectomy with cervical esophagotomy and feeding jejunostomy. Of course, any operative intervention should include assessment of other organs involved and complete drainage/resection of necrotic tissue. Options for esophageal replacement have been outlined above.

Complications

Strictures of varying degrees occur in almost all patients following caustic ingestion and, thus, careful follow-up is recommended. The esophagus and stomach should be evaluated via barium swallow 3 weeks, 3 months, and 6 months after the ingestion to rule out stricture formation or gastric outlet obstruction. Esophagogastroduodenoscopy (EGD) is typically performed 3 weeks after the ingestion for full evaluation. Early endoscopy is warranted during the phase of cicatrix formation, and dilation is repeated at varying intervals. Risk factors for development of post-ingestion stricture include initial symptoms such as dysphagia or hematemesis, and grade IIa or higher esophagitis identified on initial endoscopy.[244] The ideal interval for intervention is patient dependent and clinically dictated by the amount of dysphagia or interval to recurrence of dysphagia, the initial severity of burn, and findings on radiographic studies.

In most patients, management of esophageal strictures that develop as a result of caustic burns is the primary operative consideration. Circumferential grade IIB burns can be managed with an open gastrostomy and insertion of a string through the gastrostomy that exits transnasally. Four weeks after the burn, serial dilations using progressive antegrade bougienage from the oropharynx or retrograde stringing bougienage through the gastrostomy is effective. Retrograde string bougienage or antegrade dilations should be performed at 2- to 3-week intervals for consecutive dilations (**Fig. 43.18**). Optimal caliber bougienage is 48 to 50 for adults and 34 to 36 for children. The majority of patients with acid-induced corrosive esophageal stricture are refractory to dilatation with failure rates of 75% of patients. Concomitant cricopharyngeal stricture, long stricture length, requiring frequent dilatation, and stricture refractory to greater than 11-mm dilatation are factors associated with failed dilatation.[245]

Esophageal stenting is another approach for second-degree esophageal burns, which may be more palatable than string bougienage. A removable, fully covered stent is placed endoscopically shortly after injury and left in place for 3 weeks. It can then be removed. Recent reports have suggested that this is an appropriate intervention to prevent stricture formation in some patients. Injection of the stricture with triamcinolone (30 mg/mL) may also be effective, especially in those strictures that are focal. Esophageal replacement is usually considered if a stricture fails to resolve after 1 year of dilations, stricture injections, and antacid therapy. Malignant degeneration is

possible at the area of the stricture, and esophageal cancer occurs at a 1,000-fold greater frequency in individuals with a caustic injury to the esophagus than in the general population.

Esophageal Fistulas

The increasing use of endovascular and advanced interventional cardiology procedures has been associated with uncommon complications of fistulization between the esophagus, pericardium, aorta, or cardiac chambers. Between 1990 and 2005, there were an estimated 133,000 radiofrequency ablations performed in the United States[246] with another 120,000 cases of cryoablation done for atrial fibrillation worldwide since 2011.[247] Fortunately, despite increased use of cardiac ablation procedures, esophagopericardial fistulas are uncommon and are typically related to upper GI malignancy or as complications of esophageal injury, such as caustic ingestion, or prior surgery. Their rarity makes them a diagnostic challenge to clinicians. They are also a known complication of esophageal stents. The radial forces within esophageal stents combined with motion from esophageal peristalsis, respirations, and cardiac pulsatility, can contribute to fistula formation if the stent is left in place for a prolonged period of time.[248]

Most patients will have a delayed presentation of weeks to months after initial insult or index procedure. A systematic review identified a median of 21 days between cardiac ablation and presentation, but patients may present as long as 60 days post procedure. Most common presenting symptoms are fever (73%), neurologic (72%), GI (41%), and cardiac (40%) symptoms.[249] Cardiac tamponade may be present and its severity will depend on the size of the defect and rapidity with which air and/or fluid has accumulated within the pericardial space. Severe clinical symptoms only occur once the pressure in the pericardium exceeds a threshold and most patients do not require pericardial drainage. Plain radiographs may demonstrate pneumopericardium and echocardiography may show tamponade physiology if a large pericardial effusion is present. CT scan can be useful in diagnosing and localizing the site of the fistula. It is important to note that when atrioesophageal fistula is suspected, instrumentation of the esophagus with endoscopy or transesophageal echocardiography is contraindicated, as insufflation of the esophagus can result in the formation of air emboli causing devastating

neurologic injury and death. If either are to be performed, they should be done at the time of surgical repair, and despite limiting the endoscopic examination, insufflation should not be used. Staged repairs may be the most appropriate way to deal with this highly morbid condition. In the case of aortoesophageal fistula, this may consist of a combined endovascular approach as a temporary measure to stabilize the patient followed by a definitive surgical repair or resection.[250] The condition carries a high mortality estimated at 55%. Mortality is significantly less for patients undergoing surgical repair (33%) compared with those undergoing endoscopic treatment (65%) or conservative management (97%).[249]

Esophageal Foreign Body

Foreign-body ingestion and food bolus impaction are common occurrences that physicians can encounter when dealing with the esophagus, commonly seen in children between the ages of 6 months and 3 years, with over 100,000 new cases occurring in the United States annually. Pediatric foreign-body ingestion is typically accidental and most frequently involve coins, followed by toy parts, batteries, bones, and food.[251] Typically, esophageal foreign bodies tend to pass through the GI tract spontaneously. However, roughly 10% to 20% of cases may require nonoperative intervention, with <1% requiring surgery.[252–254] A large percentage of objects that do not pass spontaneously remain in the cervical esophagus. Complete obstruction can lead to inability to tolerate secretions, airway compromise, and death. Pediatric patients are the most common population affected, while in adults, edentulous patients are at greatest risk.

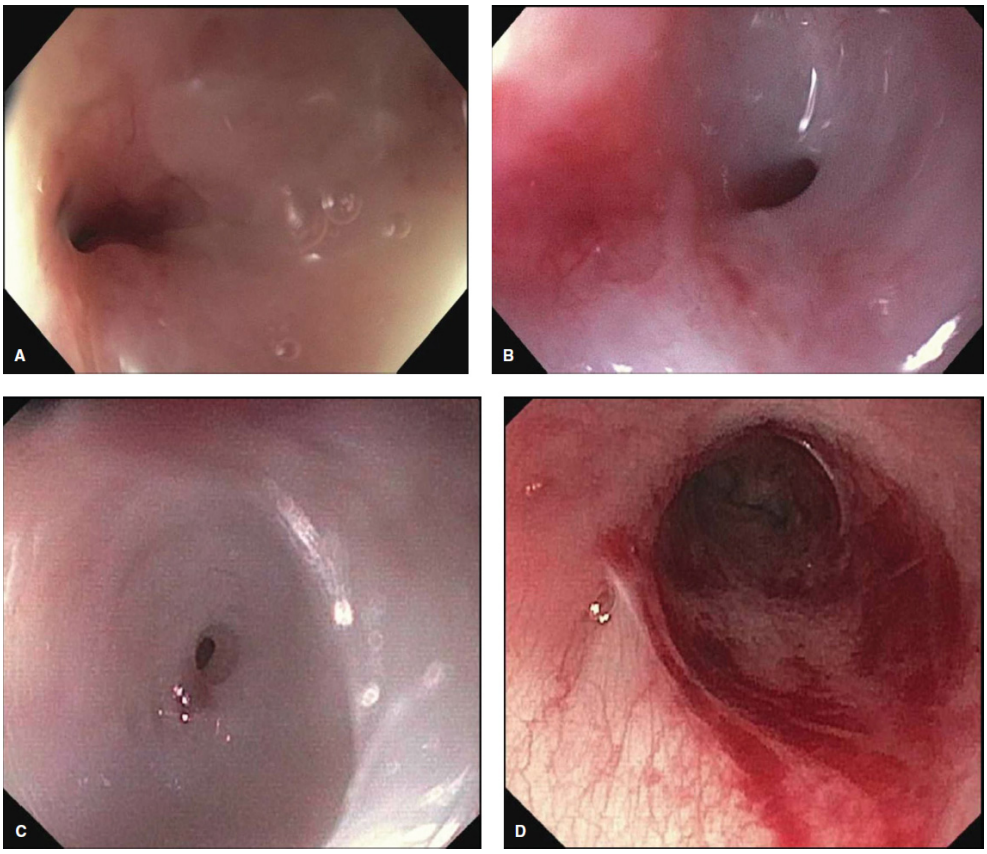


Figure 43.18 Endoscopy showing a stricture at the upper esophageal sphincter after caustic ingestion at baseline (**A**), 3 months after injury (**B**), 6 months after injury (**C**), and after balloon dilation (**D**). (Courtesy of Joo Ha Hwang, MD, Division of Gastroenterology and Hepatology, Stanford University, Stanford, CA.)

Plain radiographs may be a sufficient diagnostic study if the object is known to be radio-opaque in order to determine location and number of foreign bodies. UGI or barium swallow studies are not recommended because of the risk of aspiration and the presence of contrast that may potentially obscure visualization during any subsequent endoscopic examination.[255] Management in the setting of an asymptomatic patient usually consists of simple observation. Others have advocated for the use of glucagon and other effervescent agents as adjuncts to nonoperative treatment. Glucagon is known to decrease lower esophageal sphincter tone by causing smooth muscle relaxation thus making it one of the most widely accepted agents for esophageal foreign-body impaction. This is despite the fact that the literature supporting its use is controversial and of poor quality.[256–258]

Following observation, endoscopy is the gold standard first-line treatment and is much more likely to lead to resolution of symptoms than medical therapy alone (98% vs. 28%).[259] Timing of endoscopy is indicated by the risk of esophageal wall damage or aspiration, as well as the clinical status of the patient. Urgent intervention using endoscopy may be required in patients with severe distress, unable to swallow their own secretions, or with foreign bodies that are batteries or have sharp edges. Patients who do not fit these criteria and have no evidence of severe obstruction can be handled less urgently. Retrieval is the goal when dealing with foreign bodies that are not subjected to spontaneous passing. General anesthesia is recommended during the entirety of this procedure. Flexible endoscopy is the preferred method for most foreign bodies. A rigid endoscope is useful in the retrieval of foreign bodies lodged in the proximal esophagus at the level of the cricopharyngeus muscle. Rigid esophagoscopy is a rarer procedure and one should be familiar with the technique. The object should be reoriented with a grasper and removed safely. When using the flexible esophagoscope, we have found the overtube to be a very useful tool for removal of foreign bodies such that the esophagus is not injured proximally upon extrication of the object. Esophagotomy may be required when the lodged foreign bodies are large, have sharp edges, are embedded in the mucosa, or exceed the diameter of the rigid endoscope in all orientations. Following removal of the foreign body, completion esophagoscopy and contrast esophagoscopy should be performed to rule out injury. If there is a perforation, it should be managed according to the algorithm in **Algorithm 43.2**.

Perforation from esophageal foreign body is also rare with an estimated incidence of 4%.[260] In an analysis of over 1,200 patients presenting with foreign-body impaction, independent risk factors for complications were age ≥60, duration of impaction longer than 1 day, impaction in the esophagus, and sharp foreign body (e.g., chicken or fish bones). Duration of impaction longer than 1 day was associated with 2.5-fold increase in the risk of complications and increased risk of failure of endoscopic retrieval.[261] Sharp foreign-body ingestion is associated with worse outcomes than other object types, however some have advocated for conservative management with good results. The overall mortality rate for esophageal perforation from foreign-body ingestion is 5.3%.[262]

Finally, the prevalence of concomitant motility disorder among patients presenting with esophageal foreign-body impaction cannot be overlooked. Its incidence is estimated at 10%,[260] thus follow-up for these patients should include additional studies to examine for any underlying esophageal pathology including motility testing. Compared with control subjects, patients with foreign-body impaction have marked reduction in amplitude and duration of esophageal contraction in the proximal esophagus.[263]

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Section E: STOMACH AND DUODENUM

44

Gastric Anatomy and Physiology

Michael W. Mulholland

Key Points

1. The stomach is an extremely well-vascularized organ, supplied by a number of major arteries and protected by a large number of extramural and intramural collaterals.
2. Oxyntic glands occupy the fundus and body of the stomach and contain the oxyntic or parietal cells, which are the sites of acid production. Oxyntic glands also contain chief cells, the site of gastric pepsinogen synthesis.
3. The most important stimulant of gastrin release is a meal. Postprandial luminal pH also strongly affects gastrin secretion.
4. The basolateral membrane of the parietal cell contains specific receptors for histamine, gastrin, and acetylcholine, the three major stimulants of acid production.
5. Pepsins are a heterogeneous group of proteolytic enzymes that are secreted by the gastric chief cells.
6. The gastric mucosa is the site of production of intrinsic factor, which is necessary for the absorption of cobalamin from the ileal mucosa. Total gastrectomy is regularly followed by cobalamin malabsorption, as is resection of the proximal stomach or atrophic gastritis that involves the oxyntic mucosa.

GROSS ANATOMY

The stomach and duodenum, along with the esophagus, liver, bile ducts, and pancreas, are derived from the embryonic foregut. During the fifth week of gestation, the future stomach is marked as a dilation in the caudal portion of the foregut. Cranial to this dilation, the trachea forms as a bud from the future esophagus. At this time, the primitive stomach is invested with both ventral and dorsal mesenteries. The embryonic ventral mesentery is represented in postnatal life by the falciform ligament and by the gastrohepatic and hepatoduodenal mesenteries that form the lesser omentum. The celiac artery, the major blood supply to the foregut, passes within the dorsal mesentery.

The primitive dorsal mesentery ultimately forms three structures: the gastrocolic ligament, the gastrosplenic ligament, and the gastrophrenic ligament.

During the sixth and seventh weeks of gestation, the typical morphology of the stomach is established. Accelerated growth of the left gastric wall, relative to the right, establishes the greater and lesser curvatures. This unequal growth also rotates the stomach and causes the left vagal nerve trunk to assume its anterior position, whereas the right vagal trunk is located posteriorly. The growth of structures cephalad to the stomach causes the organ to descend. During the sixth week, the primitive stomach lies between the T10 and T12 vertebral segments. By the eighth week, the stomach is located between the T11 and the L4 segments. In adult life, the stomach is most commonly located between the T10 and the L3 vertebral segments.

The stomach can be divided into anatomic regions based on external landmarks (**Fig. 44.1**). Although this division is commonly referred to in surgical texts and is useful in discussing gastric resective procedures, it does not necessarily reflect the secretory or motor functions of the mucosal and muscular layers of the stomach. The gastric cardia is the region of the stomach just distal to the gastroesophageal junction. The fundus is the portion of the stomach above and to the left of the gastroesophageal junction. The corpus constitutes the region between the fundus and the antrum. The margin between the corpus and antrum is not distinct externally but can be defined arbitrarily by a line from the incisura angularis on the lesser curvature to a point one-fourth the distance from the pylorus to the esophagus along the greater curvature. The gastric antrum is bounded distally by the pylorus, which can be appreciated by palpation as a thickened ring of smooth muscle.

The stomach is mobile in most people and is fixed at only two points, proximally by the gastroesophageal junction and distally by the retroperitoneal duodenum. Therefore, the position of the stomach varies and depends on the habitus of the person, the degree of gastric distention, and the position of the other abdominal organs. Anteriorly, the stomach is in contact with the left hemidiaphragm, the left lobe and the anterior segment of the right lobe of the liver, and the anterior parietal surface of the abdominal wall. The posterior surface of the stomach is related to the left diaphragm; the left kidney and left adrenal gland; the neck, tail, and body of the pancreas; the aorta and celiac trunk; and the periaortic nerve plexuses. The greater

curvature of the stomach is near the transverse colon and the transverse colonic mesentery. The concavity of the spleen contacts the left lateral portion of the stomach.

1 The stomach is an extremely well-vascularized organ, supplied by a number of major arteries and protected by a large number of extramural and intramural collaterals. Gastric viability can be preserved after ligation of all but one primary artery, an advantage that can be exploited during gastric reconstructive procedures. Also, the rich network of anastomosing vessels means that gastric hemorrhage cannot be controlled by the extramural ligation of gastric arteries. Most gastric blood flow is ordinarily derived from the celiac trunk (**Fig. 44.2**). The lesser curvature is supplied by the left gastric artery, which is the first major branch of the celiac trunk, and by the right gastric artery, which is derived from the hepatic artery. Branches of the left gastric artery also supply the lowermost portion of the esophagus. The greater curvature is supplied by the short gastric and left gastroepiploic arteries, which are branches of the splenic artery, and by the right gastroepiploic artery, a branch of the gastroduodenal artery. In instances of celiac trunk occlusion, gastric blood flow is usually maintained from the superior mesenteric artery collaterally by way of the pancreaticoduodenal arcade. In general, venous effluent from the stomach parallels the arterial supply. The venous equivalent of the left gastric artery is the coronary vein.

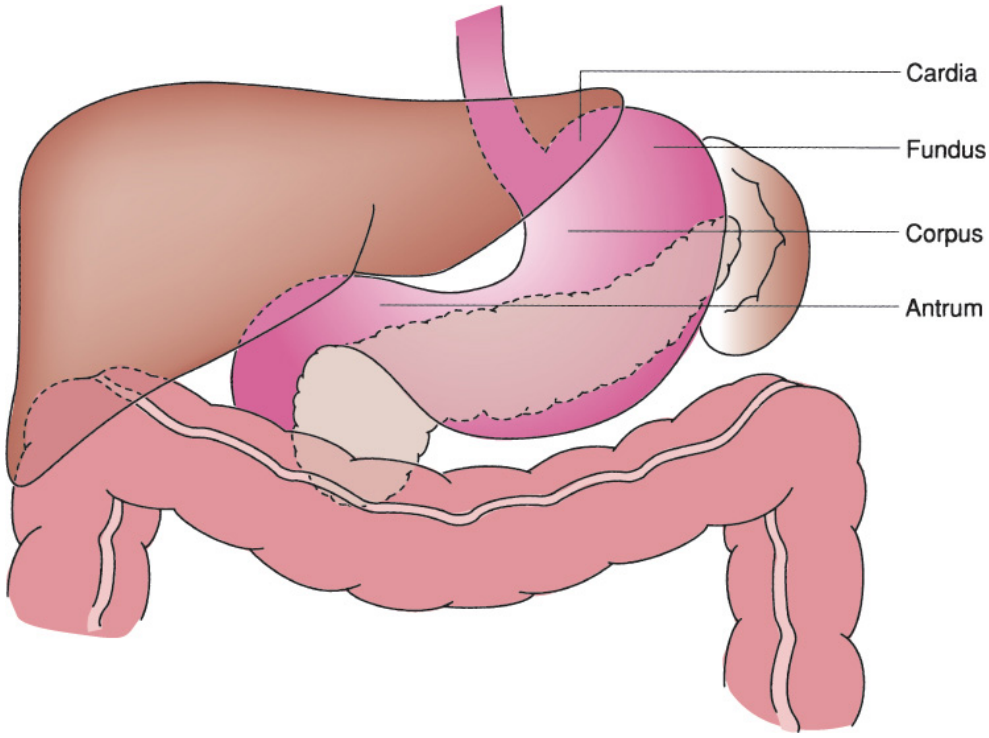

Figure 44.1 Topographic relations of the stomach.

As a first approximation, the lymphatic drainage of the stomach parallels gastric venous return (**Fig. 44.3**). Lymph from the proximal portion of the stomach along the lesser curvature first drains into superior gastric lymph nodes surrounding the left gastric artery. The distal portion of the lesser curvature drains through suprapyloric nodes. The proximal portion of the greater curvature is supplied by lymphatic vessels that traverse pancreaticosplenic nodes, whereas the antral portion of the greater curvature drains into the subpyloric and omental nodal groups. Secondary drainage from each of these systems eventually traverses nodes at the base of the celiac axis. These discrete anatomic groupings are misleading. The lymphatic drainage of the human stomach, like its blood supply, exhibits extensive intramural ramifications and a number of extramural communications. As a consequence, disease processes that involve the gastric lymphatics often spread intramurally beyond the region of origin and to nodal groups at a distance from the primary lymphatic zone.

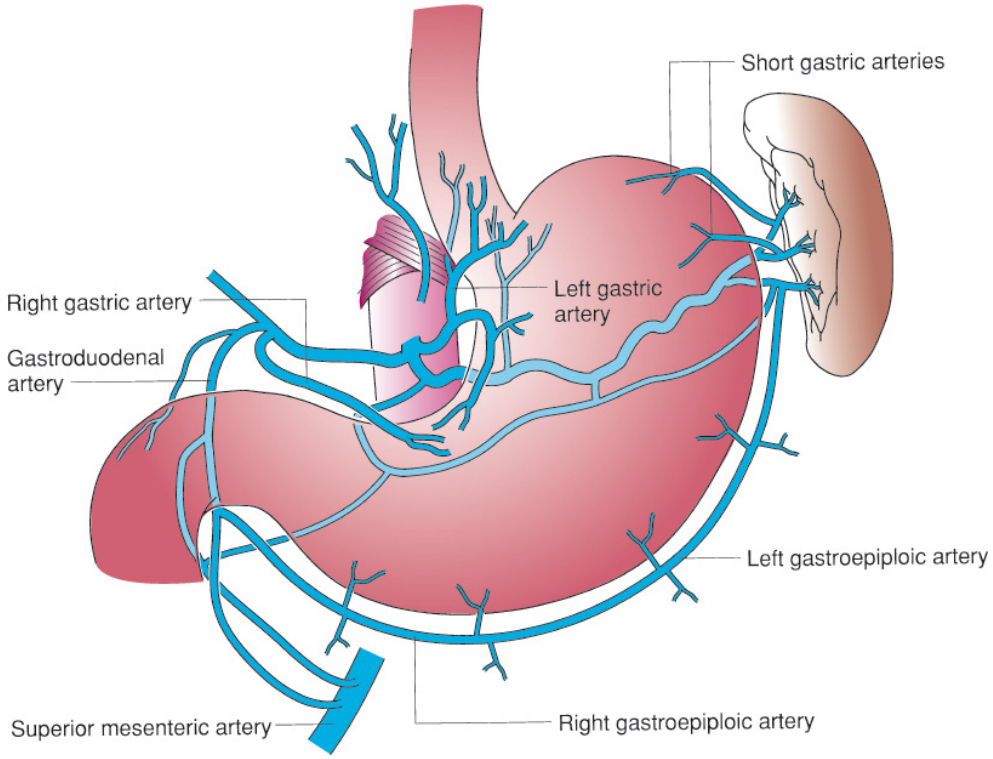

Figure 44.2 Arterial blood supply of the stomach.

The left and right vagal nerves descend parallel to the esophagus within the thorax before forming a periesophageal plexus between the tracheal bifurcation and the diaphragm. From this plexus, two vagal trunks coalesce before passing through the esophageal hiatus of the diaphragm (**Fig. 44.4**). The left vagal trunk is usually closely applied to the anterior surface of the esophagus, whereas the posterior vagal trunk is often midway between the esophagus and the aorta. The anterior vagus supplies a hepatic division, which passes to the right in the lesser omentum before innervating the liver and biliary tract. The remainder of the anterior vagal fibers parallels the lesser curvature of the stomach, branching to the anterior gastric wall. The posterior vagus nerve branches into the celiac division, which passes to the celiac plexus, and a posterior gastric division, which innervates the posterior gastric wall.

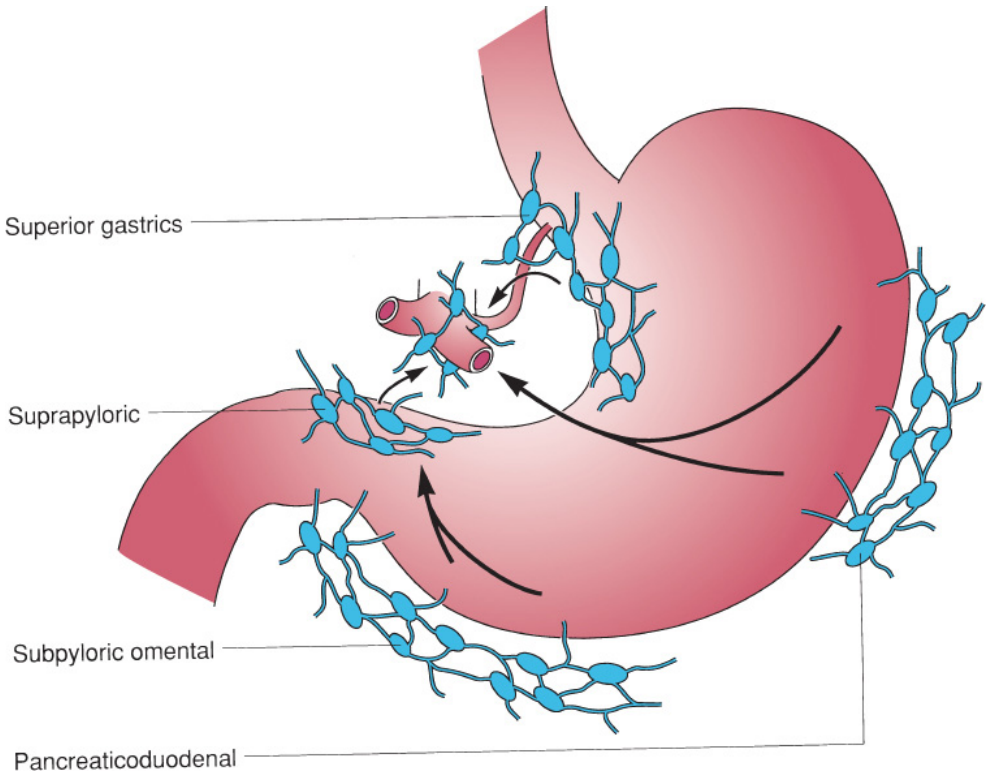

Figure 44.3 Lymphatic drainage of the stomach.

Approximately 90% of the fibers in the vagal trunks are afferent, transmitting information from the gastrointestinal tract to the central nervous system (CNS). Parasympathetic afferent fibers are not responsible for the sensation of gastric pain. Only 10% of vagal nerve fibers are motor or secretory efferents. Parasympathetic efferent fibers contained in the vagus originate in the dorsal nucleus of the medulla. Vagal efferent fibers pass without synapse to contact postsynaptic neurons in the gastric wall in the myenteric and submucous plexuses. Secondary neurons directly innervate gastric smooth muscle or epithelial cells. Acetylcholine is the neurotransmitter of primary vagal efferent neurons.

The gastric sympathetic innervation is derived from spinal segments T5 through T10. Sympathetic fibers leave the corresponding spinal nerve roots by way of gray rami communicantes and enter a series of bilateral prevertebral ganglia (**Fig. 44.5**). From these ganglia, presynaptic fibers pass through the greater splanchnic nerves to the celiac plexus, where they synapse with secondary sympathetic neurons. Postsynaptic sympathetic nerve fibers enter the stomach in association with blood vessels. Afferent

sympathetic fibers pass without synapse from the stomach to dorsal spinal roots. Pain of gastroduodenal origin is sensed through afferent fibers of sympathetic origin.

MICROSCOPIC ANATOMY

The glandular portions of the stomach are lined by a simple columnar epithelium composed of surface mucous cells. The luminal surface, visualized by scanning electron microscopy, appears cobblestoned, interrupted at intervals by gastric pits. Opening into the gastric pits are one or more gastric glands that impart functional significance to the gastric mucosa. The mucosa of the human stomach is composed of three distinct types of gastric glands—cardiac, oxyntic, and antral.

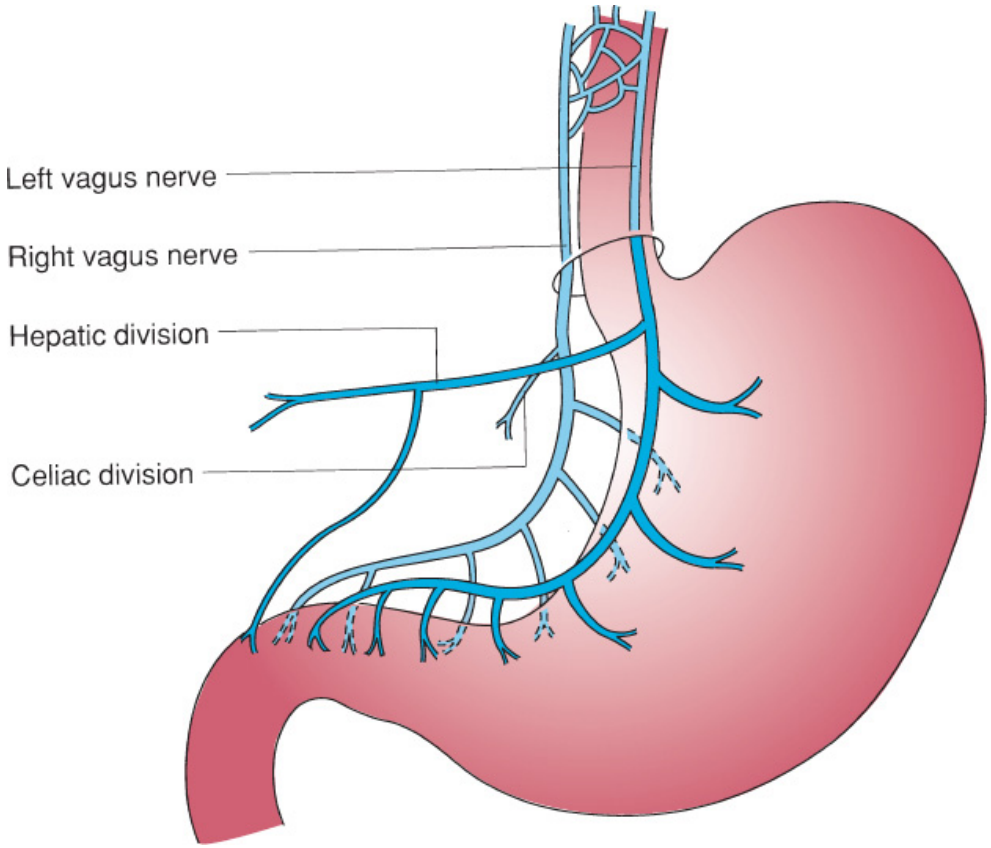

Figure 44.4 Vagal innervation of the stomach.

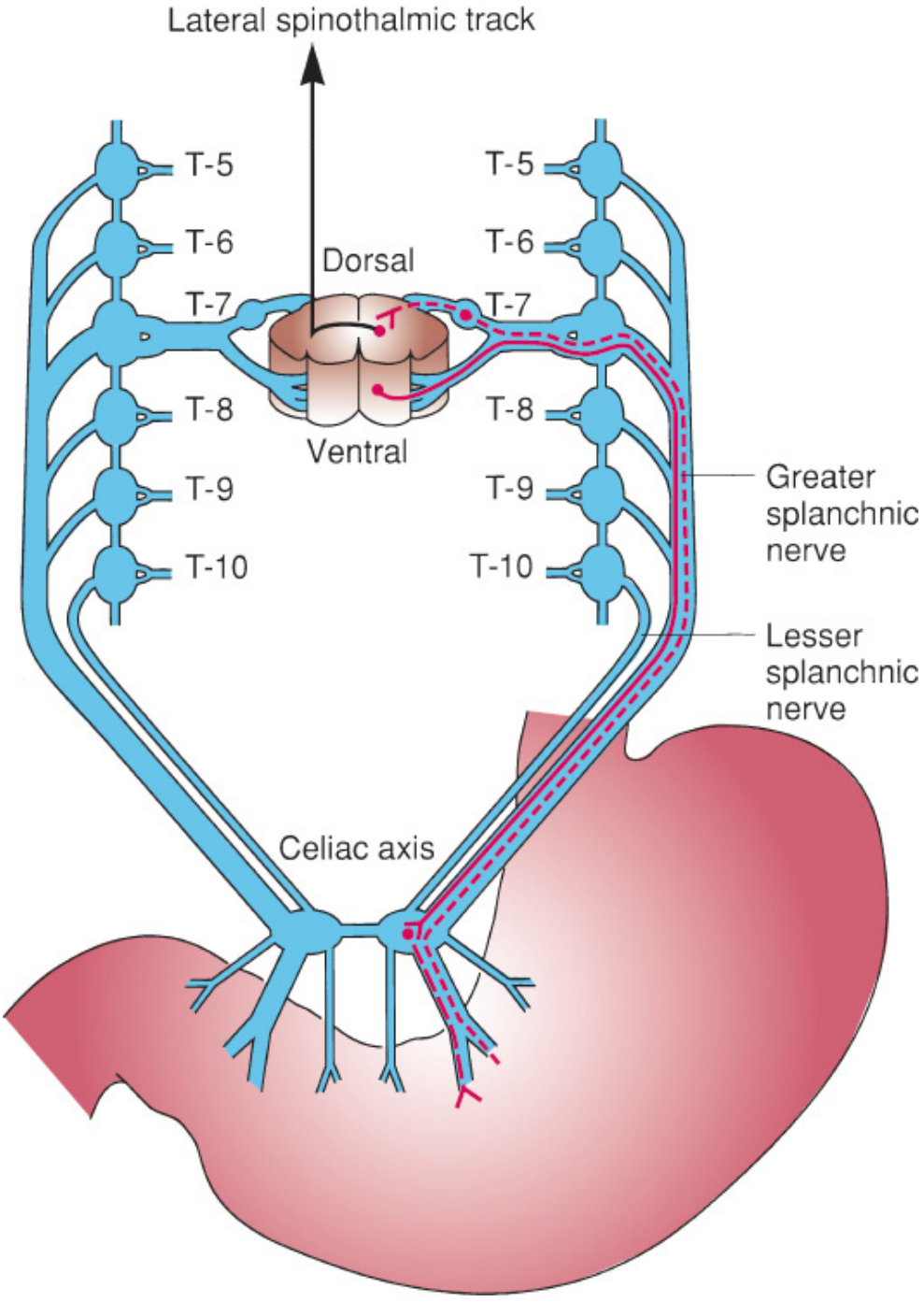

Figure 44.5 Derivation of gastric sympathetic innervation.

In humans, cardiac glands occupy a narrow zone adjacent to the esophagus and mark a transition from the stratified squamous epithelium of the esophagus to the simple columnar epithelium of the stomach. The surface and gastric pit mucous cells of the cardia are not distinguishable from those in other areas of the stomach. Cardiac glands contain mucous and

undifferentiated and endocrine cells but not the parietal or chief cells that are prominent in the adjacent oxyntic mucosa. Cardiac glands are usually branched and connect with relatively short gastric pits. The functional properties of cardiac glands include the secretion of mucus.

2 Oxyntic glands are the most distinctive feature of the human stomach. They occupy the fundus and body of the stomach and contain the oxyntic or parietal cells, which are the sites of acid production. Oxyntic glands also contain chief cells, the site of gastric pepsinogen synthesis. Endocrine cells are scattered throughout all three regions of oxyntic glands.

The most distinctive cell of the gastric mucosa is the acid-secreting parietal cell. Parietal cells have an unusual ultrastructural specialization in the form of intracellular canaliculi, a network of clefts extending to the basal cytoplasm and often encircling the nucleus, which is continuous with the gland lumen (**Fig. 44.6**). The surface area provided by the intracellular secretory canaliculi is large and is further magnified by microvilli lining the canaliculi. In parietal cells that are not stimulated to secrete acid, the secretory canaliculi are collapsed and inconspicuous. On stimulation, a severalfold increase in canalicular surface area occurs, the intracellular clefts become prominent, and the communication with the luminal surface is readily identified. These changes create an intracellular space in communication with the gastric lumen into which hydrogen ions are secreted at high concentration.

In addition to parietal cells, the oxyntic glands contain the gastric chief cells, which synthesize and secrete pepsinogen. Chief cells are most abundant in the basal region of the oxyntic glands. The cells have a morphology typical of protein-secreting exocrine cells and are similar in ultrastructural appearance to pancreatic acinar cells. Zymogen granules containing pepsinogen are most concentrated in the apical cytoplasm. Pepsinogen is released by exocytosis from secretory granules at the apical surface of chief cells.

Antral glands occupy the mucosa of the distal stomach and pyloric channel. Although most cells in the antral glands are mucus secreting, gastrin cells are the distinctive feature of this mucosa. Gastrin cells are pyramid shaped, with a narrow area of luminal contact apically and a broad surface overlying the lamina propria basally (**Fig. 44.7**). Gastrin cells are identified immunocytochemically by the presence of the peptide. Granules ranging from

150 to 400 nm in diameter are the sites of gastrin storage and are most numerous in the basal cytoplasm. Gastrin is released by exocytotic fusion of the secretory granule with the plasma membrane. In contrast to secretion from chief cells, emptying of gastrin-containing granules occurs at the basal membrane rather than at the apical region of the cell. Gastrin thus released diffuses to and enters submucosal capillaries in close apposition to the lamina propria.

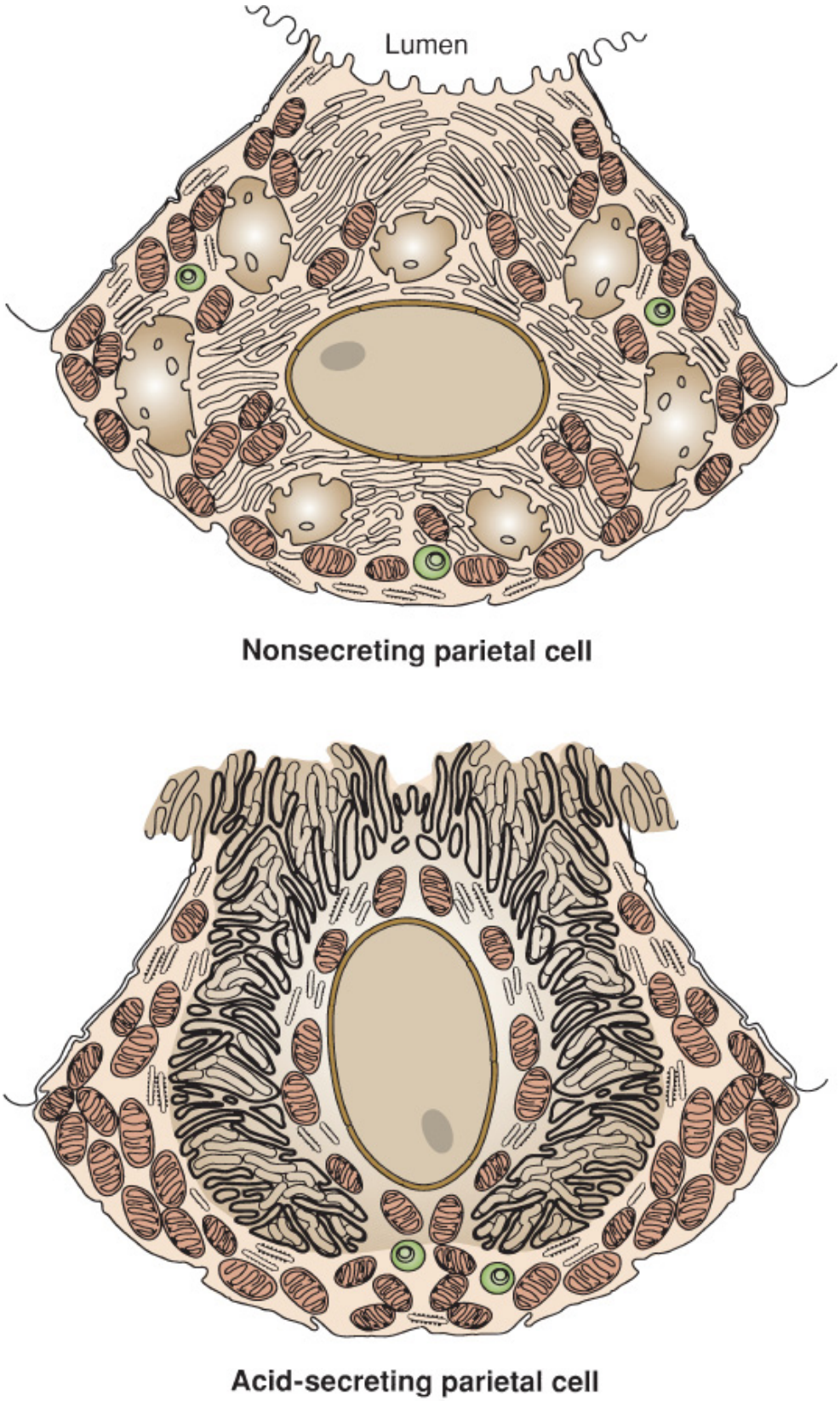

Figure 44.6 Resting and stimulated parietal cell, emphasizing morphologic transformation with increase in secretory canalicular membrane surface area that

occurs with acid secretion.

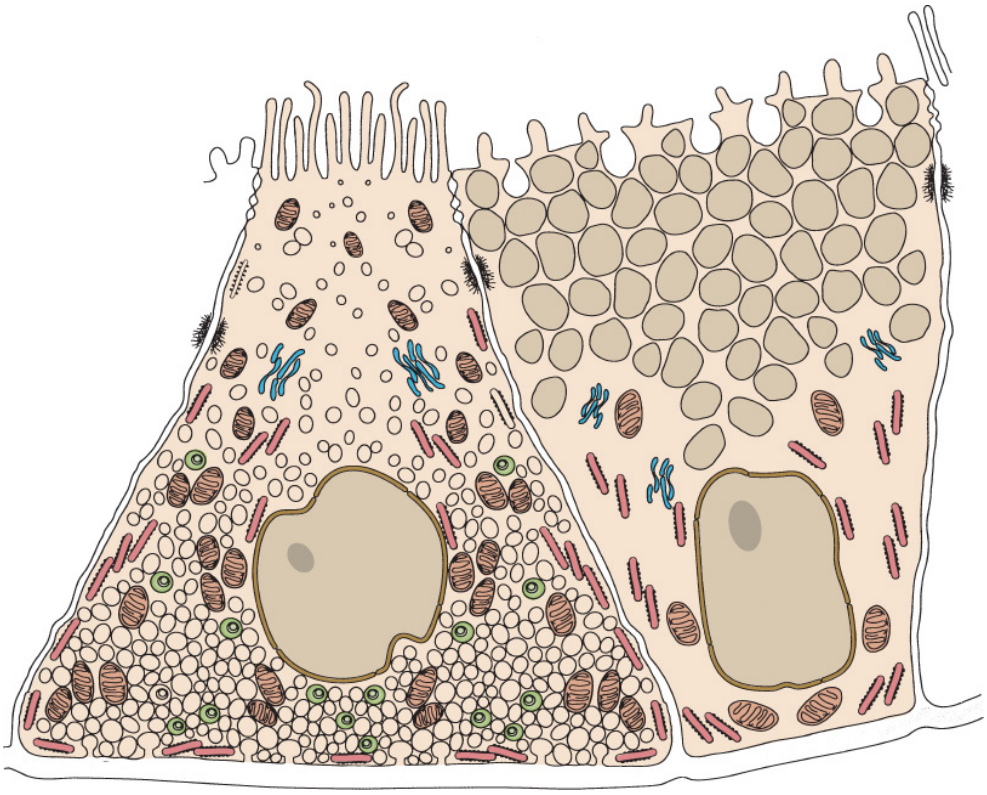

Figure 44.7 Contrasting morphology of antral gastrin cell (*left*) with basally oriented secretory granules, and gastric mucous cell (*right*) with apical mucous granules.

GASTRIC PEPTIDES

The stomach contains a number of biologically active peptides in nerves and mucosal endocrine cells, including gastrin, somatostatin, ghrelin, gastrin-releasing peptide, vasoactive intestinal polypeptide (VIP), substance P, glucagon, and calcitonin gene–related peptide.

Gastrin

The synthesis, secretion, and action of gastrin have been extensively studied, and many aspects of the biology of gastrin appear to be shared by other gastrointestinal peptide hormones.[1] The human gastrin gene contains three exons; two exons consist of coding sequences. The major active product is

encoded by a single exon. In adults, the gastrin gene is expressed primarily in mucosa cells of the gastric antrum, with lower levels of expression in the duodenum, pituitary, and testis.

The human gene encompasses approximately 4,100 base pairs and directs the synthesis of a peptide of 101 amino acids (**Fig. 44.8**). The resulting peptide, preprogastrin, contains the sequence of gastrin within its amino acid sequence. Preprogastrin consists of a signal peptide of 21 amino acids, an intervening peptide of 37 amino acids, the 34-residue region of the gastrin molecule, and a carboxyl-terminal extension of 9 amino acids. Gastrin is derived from its preprohormone by the sequential enzymatic cleavage of the signal peptide, the intervening peptide, and the carboxyl-terminal extension.

The signal peptide region of preprogastrin consists of a series of hydrophobic amino acids that direct the nascent peptide into the endoplasmic reticulum as it is translated from messenger RNA. After directing the preprogastrin molecule into the rough endoplasmic reticulum, the signal peptide is removed. The remaining peptide is termed *progastrin.* Progastrin is further processed as it traverses the endoplasmic reticulum to mature secretory vesicles. Enzymatic cleavage at a pair of basic amino acid residues proximal to the gastrin 34 (G_{34}) sequence removes the intervening peptide. A similar cleavage removes a six-amino-acid fragment at the carboxyl-terminal end. The peptide that remains has a Gly-Arg-Arg sequence at the carboxyl terminus. Carboxypeptidase cleaves the Arg residues, and the peptide that results is termed *glycine-extended gastrin.* G_{34} is formed by cleavage of the Gly-Arg-Arg sequence and amidation of the carboxyl-terminal phenylalanine. Gastrin, like most gastrointestinal peptide hormones, requires terminal amidation for biologic activity. Gastrin 17 (G_{17}), the most abundant form of gastrin in the human antrum, is formed by further processing that removes the first 17 amino acids at the amino terminus of G_{34}. G_{34} is the predominate molecular form of gastrin in the duodenum.

3 The most important stimulant of gastrin release is a meal. Small peptide fragments and amino acids that result from intragastric proteolysis are the most important food components that stimulate gastrin release. The most potent gastrin-releasing activities are demonstrated by the amino acids tryptophan and phenylalanine. Ingested fat and glucose do not cause gastrin release. Gastric distention by a meal activates cholinergic neurons and

stimulates gastrin release. As the meal empties and distention diminishes, VIP-containing neurons are activated, which stimulate somatostatin secretion and thus attenuate gastrin secretion.

Postprandial luminal pH also strongly affects gastrin secretion. Gastrin release is inhibited when acidification of an ingested meal causes the intraluminal pH to fall below 3.0. Conversely, maintaining intragastric pH above 3.0 potentiates gastrin secretion after ingestion of protein or amino acids.[2] Pernicious anemia and atrophic gastritis, which produce chronic achlorhydria, are associated with fasting hypergastrinemia and an exaggerated gastrin meal response. Release of mucosal somatostatin occurs with gastric acidification and this peptide has been implicated in the inhibition of gastrin release that occurs when luminal pH falls.

The vagus nerve appears to both stimulate and inhibit gastrin release.[3] In humans, vagally-mediated stimulation of gastrin release can be demonstrated by sham feeding, insulin-induced hypoglycemia, and administration of the vagal stimulant γ-aminobutyric acid. In contrast to these stimulatory vagal effects, hypergastrinemia, observed after vagotomy, suggests that inhibitory vagal effects on gastrin release may also exist. Cholinergic neurons stimulate gastrin secretion directly by actions on gastrin cells.

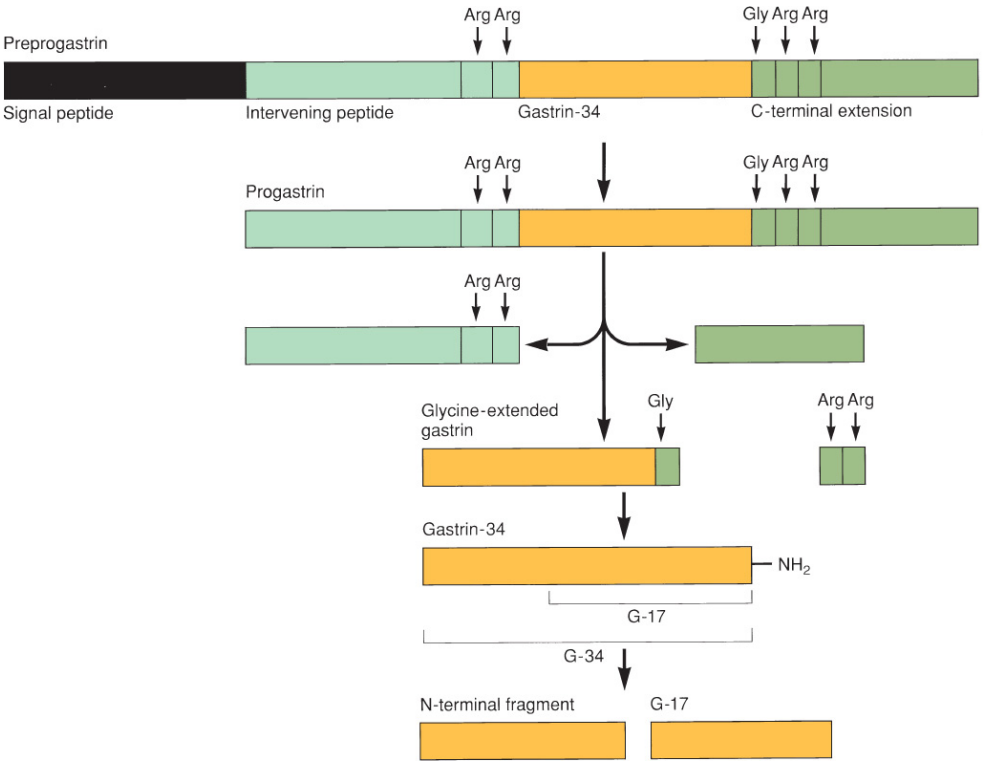

Figure 44.8 Sequential processing of preprogastrin molecule.

Chronic gastric infection with *Helicobacter pylori* causes increased acid secretion by altering gastrin release.[4,5] *H. pylori* has been observed to upregulate proinflammatory cytokines, including interleukin (IL)-6, IL-8, and tumor necrosis factor-α (TNF-α). Several inflammatory mediators have been demonstrated to stimulate gastrin release from isolated gastrin cells. The putative gastrin secretagogues include IL-1, IL-8, TNF-α, interferon-γ, and leukotrienes C4 and D4. The same factors that affect gastrin release also influence gastrin mRNA expression. Food ingestion increases gastrin mRNA abundance, whereas fasting and somatostatin decrease gastrin mRNA production. Chronic achlorhydria, as seen in pernicious anemia, increases gastrin mRNA production.

In addition to stimulating acid secretion from gastric parietal cells (detailed later in this chapter), gastrin has important physiologic actions in the control of gastrointestinal mucosal growth. The acid-secreting oxyntic mucosa is particularly sensitive to the trophic actions of gastrin, but the mucous membranes of the duodenum, colon, and pancreatic parenchyma are also affected. Stimulation of mucosal growth by gastrin is enhanced by the presence of solid food in the diet. The 17- and 34-amino-acid forms of

gastrin are equipotent in stimulating mucosal growth. Prolonged stimulation by high levels of gastrin, as seen in the Zollinger–Ellison syndrome, is associated with hypertrophy of the gastric mucosa. Smaller increases in circulating gastrin, such as those that follow vagotomy, do not cause mucosal hypertrophy.

Somatostatin

Somatostatin, like gastrin, is very significant in gastric physiology. Somatostatin was first isolated from hypothalamic tissues and was named for its ability to inhibit the release of growth hormone. The peptide was subsequently localized in neurons in central and peripheral nervous systems, and in endocrine cells in the pancreas, stomach, and intestine.[6] The wide tissue distribution of somatostatin suggested important regulatory functions, a concept validated by many investigations.

The human somatostatin gene is located on chromosome 3 and encodes for a precursor of 116 amino acids (**Fig. 44.9**). Gastric somatostatin release responds to luminal, hormonal, and neural signals. Luminal acidification is associated with increased somatostatin release, whereas somatostatin release decreases when luminal pH is increased. A number of peptides have been demonstrated experimentally to release somatostatin from the stomach, including gastrin, cholecystokinin, and secretin. β-Adrenergic agonists have also been shown to release somatostatin. In contrast, electrical stimulation of vagal nerves inhibits somatostatin release, as does the cholinergic agonist methacholine.

The most important gastric function of somatostatin appears to be regulation of acid secretion and gastrin release. Circulating somatostatin appears to be important in modulating gastric acid secretion; locally released somatostatin functions to regulate gastrin release. In each instance, somatostatin serves an inhibitory function, decreasing acid secretion and diminishing the release of gastrin. In animals, antral or duodenal acidification has been associated with an increase in circulating somatostatin. Increases in circulating somatostatin are followed, in turn, by decreased gastric acid secretion. Infusion of exogenous somatostatin in doses that produce somatostatin levels similar to those observed postprandially has also been shown to inhibit acid secretion. In humans, concentrations of

somatostatin capable of inhibiting acid secretion can do so without altering serum gastrin levels, indicating a direct action on the acid-secreting fundic mucosa.

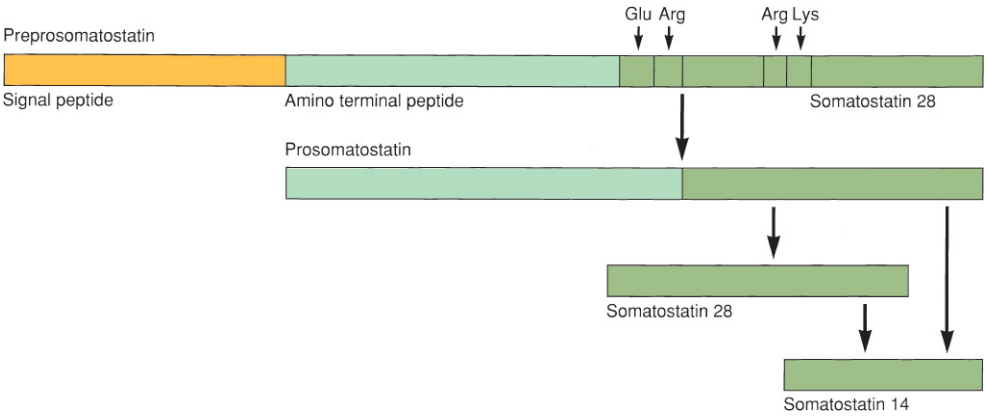

Figure 44.9 Derivation of somatostatin 14 from preprosomatostatin precursor.

Somatostatin is believed to influence gastrin secretion through a locally active intramucosal mechanism. Local actions of somatostatin are supported by ultrastructural studies of antral somatostatin cells, which demonstrate long cytoplasmic processes that make intimate cell-to-cell contact with antral gastrin cells. The presence of somatostatin at these sites of cellular contact implies that somatostatin cells influence the function of gastrin cells through local release of the peptide. Increases in somatostatin release are often associated with decreased gastrin secretion. A family of five somatostatin receptors has been cloned. Inhibition of gastrin-stimulated gastric acid secretion is mediated by somatostatin receptor subtype 2.[7]

GASTRIC ACID SECRETION

Cellular Events

An appreciation of the mechanisms that control gastric acid formation is essential to a discussion of gastric disease. An understanding of the cellular basis of acid secretion by the gastric parietal cell also provides a foundation for discussing the pharmacologic 4 suppression of acid secretion. The basolateral membrane of the parietal cell contains specific receptors for histamine, gastrin, and acetylcholine, the three major stimulants of acid

production.[8] Each stimulant reaches the parietal cell by a different route. Histamine is released from mastlike cells within the lamina propria and diffuses to the mucosa, acetylcholine is released in close proximity to the parietal cells from cholinergic nerve terminals, and gastrin is delivered by the systemic circulation to the fundic mucosa from its source in the antrum and proximal duodenum (**Fig. 44.10**), activating protein kinase A, which in turn catalyzes protein phosphorylation. The target protein molecules for this phosphorylation, in turn, stimulate acid production.

Acetylcholine and related cholinergic agonists activate parietal cells after binding to muscarinic receptors. The stimulatory effects of acetylcholine and its congeners can be abolished by atropine. The action of acetylcholine is mediated by muscarinic receptor subtype 3 (M_3).

Although histamine, acetylcholine, and gastrin occupy separate receptors on the parietal cell, each secretagogue ultimately acts by means of a specialized ion transport system called the *parietal cell proton pump.* This membrane-bound protein is located in the secretory canaliculus of the parietal cell; the peptide has not been identified in other gastric cells or in significant amounts in other organs. The proton pump is an H^+-K^+-adenosine triphosphatase (ATPase) that electroneutrally exchanges cytosolic H^+ for luminal K^+. Hydrogen ions are concentrated 2.5-million-fold within the secretory canaliculus, and the hydrolysis of ATP is the energy source for transport against the steep electrochemical gradient generated. For each H^+ ion transported to the luminal surface of the canalicular membrane, one K^+ ion is transported to the cytosolic surface (**Fig. 44.11**). This cotransport requires that K^+ be continuously supplied to the luminal surface of the secretory membrane.

Activation of the H^+-K^+-ATPase significantly increases intracellular OH^- generation, with potential cellular toxicity. Carbonic anhydrase, which is associated with the canalicular membrane, converts OH^- to HCO_3^-. The HCO_3^- produced is disposed of by exchange for Cl^- at the basolateral membrane. Intracellular Cl^- thus acquired supplies the necessary Cl^- on a one-to-one basis for each H^+ secreted. The transcellular exchange of H^+ for HCO_3^- ensures that the voluminous secretion of hydrochloride at the luminal surface of the gastric mucosa is matched by an equivalent delivery of base to

submucosal capillaries. Parietal cell ionic transport pathways are shown in **Figure 44.12**.

The function of the proton pump is highly regulated. In the unstimulated state, the enzyme is sequestered in cytoplasmic structures termed *tubulovesicles* that are not connected to the gastric lumen. Tubulovesicle membranes in this state have a low permeability to KCl. Stimulation of acid secretion causes tubulovesicles to fuse with apical secretory membranes and increases membrane permeability to KCl. In this way, the fusion of tubulovesicle membrane exposes the H^+-K^+ pump to the gastric lumen and simultaneously provides the K^+ substrate necessary for acid secretion.

Parietal cells also contain membrane receptors that inhibit acid secretion. Specific receptors for somatostatin have been identified using isolated gastric cells. Activation of isolated parietal cells by histamine, pentagastrin, or the cholinergic agonist carbachol can be blocked by somatostatin 28. Gastric parietal cells also contain receptors for prostaglandins, notably prostaglandin E_2 and its derivatives. Prostaglandin E_2 is a potent inhibitor of histamine-stimulated parietal cell activation, probably by a mechanism that inhibits formation of cAMP.

These considerations of the cellular basis of acid production demonstrate how parietal cell function can be altered pharmacologically. Gastric acid production can be blocked by receptor antagonists for each of the three primary stimulants—gastrin, acetylcholine, and histamine. Direct inhibition of acid production can be effected by derivatives of somatostatin or prostaglandin E_2. All forms of stimulated acid production can be blocked by agents that act as inhibitors of the parietal cell proton pump. Agents that act at each of these points have been developed, and their appropriate clinical applications are discussed in subsequent chapters.

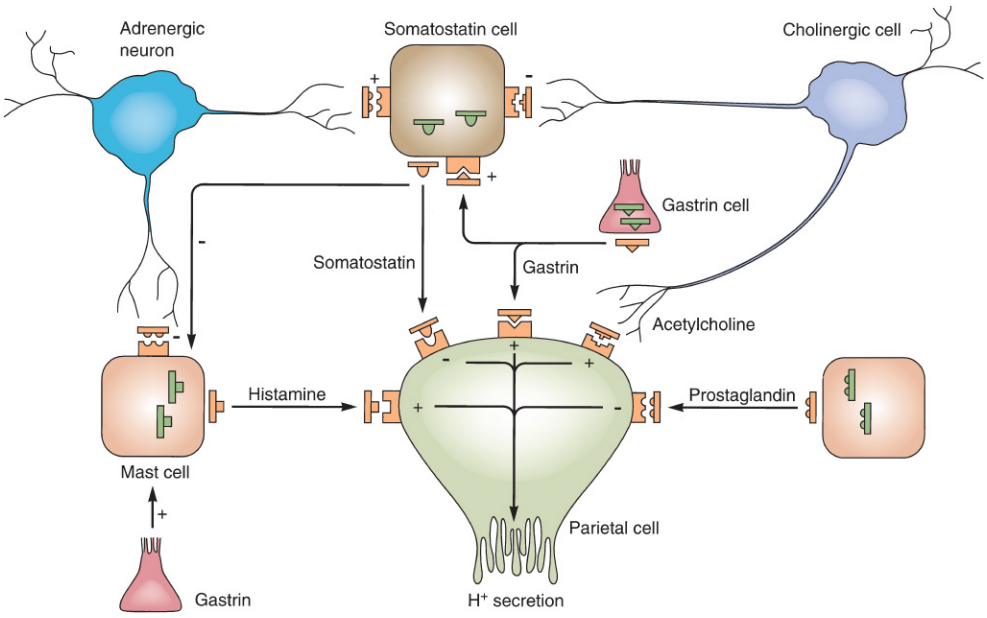

Figure 44.10 Interactions of cell types that affect parietal cell acid secretion.

Regulation of Acid Secretion

Given the multiple receptors on parietal cells, it is not surprising that a great deal of secretagogue interdependence, both stimulatory and inhibitory, exists in humans. Parietal cell activation, and the resultant acid secretion, is greater in response to a combination of agonists than it is in response to the total effect of agents used singly. This increase in responsiveness is defined as *potentiation*. Thus, histamine strongly potentiates the acid-secretory response to pentagastrin or to carbachol in humans. Conversely, blockade of receptors to one stimulant also decreases responsiveness to the other agonists. For example, blocking histamine receptors with agents such as cimetidine decreases responsiveness to pentagastrin, even though gastrin receptors are not directly affected. These inhibitory interactions are exploited therapeutically in the treatment of acid–peptic diseases.

Humans normally secrete 2 to 5 mEq/hr of hydrochloride in the fasting state, constituting basal acid secretion. Both vagal tone and ambient histamine secretion are presumed to be important in determining the rate of basal acid secretion. In humans, truncal vagotomy decreases basal secretion by approximately 85%. Similarly, H_2-receptor antagonists also inhibit basal

acid secretion by approximately 80%. Gastrin does not have an important role in determining basal acid secretion in normal people.

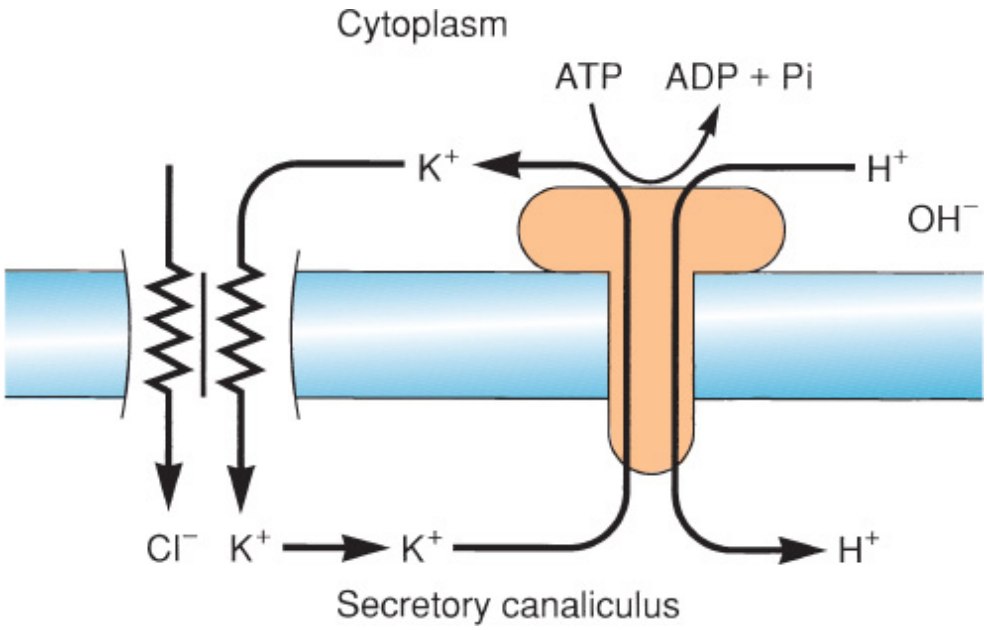

Figure 44.11 Gastric H^+-K^+-adenosine triphosphatase (ATPase). ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, phosphate ion.

Stimulated acid secretion begins with the thought, sight, or smell of food. This cephalic phase of gastric acid secretion is mediated by the vagus nerve. Vagal discharge directs a cholinergic mechanism, and the cephalic phase of acid secretion can be inhibited by administering atropine. The cephalic component of acid secretion can be measured in normal people and is approximately 10 mEq/hr. The cephalic phase approximates 40% of the maximal acid-secretory response to gastrin infusion.

The gastric phase of acid secretion begins when food enters the stomach. The presence of partially hydrolyzed food constituents, gastric distention, and the buffering capacity of food all stimulate acid secretion. In normal humans, acid-secretory rates after a mixed meal average 15 to 25 mEq/hr, approximately 75% of the maximal response achieved with infusion of exogenous gastrin or histamine. The meal response is less than the maximal response to exogenous stimulants because food also causes the release of somatostatin and initiates other inhibitory responses. In humans, 90% of meal-stimulated acid secretion is mediated by gastrin release.[9]

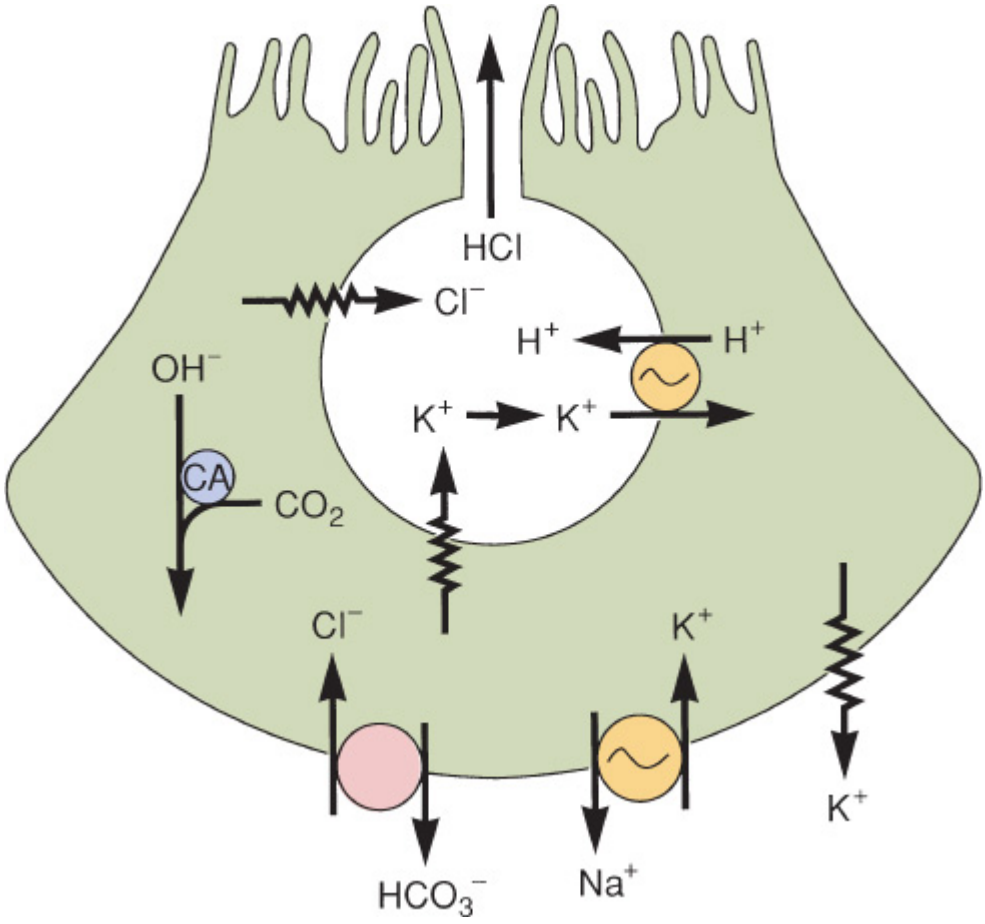

Figure 44.12 Ionic fluxes associated with acid secretion by the parietal cell.

In humans, the most important and clearly established gastric inhibitory influence is the suppression of gastrin release when the antral mucosa is exposed to acid. When luminal pH falls to 2.0, gastrin release stops. Antral acidification also suppresses the gastrin response to an ingested meal. Somatostatin acting locally in the gastric mucosa as a paracrine agent may mediate this important inhibitory response. Release of gastric somatostatin is reciprocally linked to that of gastrin; acidification of the antrum causes increases in somatostatin release and decreases in gastrin secretion. Antral distention also inhibits stimulated acid secretion.

The entry of digestive products into the intestine begins intestinal-phase inhibition of gastric acid secretion. Acidification of the duodenal bulb inhibits acid secretion.

PEPSIN

5 Pepsins are a heterogeneous group of proteolytic enzymes that are secreted by the gastric chief cells. Pepsin is derived under acidic conditions from pepsinogen by the autocatalytic loss of a variable amino-terminal sequence of the parent compound. This conversion occurs slowly at pH values of 5.0 to 6.0 and occurs rapidly when luminal pH approximates 2.0. Pepsin catalyzes the hydrolysis of a wide variety of peptide bonds that contain acidic residues, with a pH optimum for hydrolysis between 1.5 and 2.5. Once activated, pepsin is sensitive to ambient pH values; it is irreversibly denatured at pH 7.0 or greater.

The most important stimulus for pepsinogen secretion is cholinergic stimulation. Acetylcholine and its derivatives stimulate pepsinogen secretion by a mechanism that can be antagonized by atropine, indicating a muscarinic receptor. Endogenous cholinergic stimulation through the vagal nerve results in the formation of a gastric secretion that is rich in pepsin. The oxyntic mucosa contains somatostatin cells near chief cells. Pepsinogen secretion in response to a variety of stimuli has been demonstrated to be inhibited by somatostatin.

The major physiologic function of pepsin is to initiate protein digestion. Pepsin is highly active against collagen and may be important in the digestion of animal protein. Intragastric protein hydrolysis by pepsin is incomplete, and relatively large peptides enter the intestine, although amino acids and small peptide fragments are released. These products of partial hydrolysis are important signals for gastrin and cholecystokinin release, which in turn regulate digestive processes. In this way, pepsin also contributes to the overall coordination of the digestive process.

INTRINSIC FACTOR

The gastric mucosa is the site 6 of production of intrinsic factor, which is necessary for the absorption of cobalamin from the ileal mucosa. Total gastrectomy is regularly followed by cobalamin malabsorption, as is resection of the proximal stomach or atrophic gastritis that involves the oxyntic mucosa.

The parietal cell is the site of intrinsic factor synthesis and storage in humans. Intrinsic factor secretion, like acid secretion, is stimulated by histamine, acetylcholine, and gastrin. Unlike acid production, intrinsic factor secretion peaks rapidly after stimulation and then returns to baseline. The amount of intrinsic factor secreted usually greatly exceeds the amount needed to bind and absorb available dietary cobalamin.

GASTRIC BLOOD FLOW

Because the gastric mucosa is metabolically highly active, control of mucosal blood flow is of great physiologic importance. In addition, studies have implicated perfusion abnormalities in the development of mucosal lesions during periods of stress. Mucosal blood flow is regulated by neural, hormonal, and locally active influences.

Postganglionic sympathetic nerve fibers reach the stomach in association with its blood supply and richly innervate small mucosal arteries. Mucosal capillaries do not receive adrenergic innervation. Electrical stimulation of sympathetic nerves supplying the stomach is followed by decreased total gastric blood flow, decreased flow in celiac and gastroepiploic vessels, and diminished blood flow to the mucosa. Studies in animals demonstrate that vasoconstriction of the gastric vascular bed is mediated by α-adrenergic receptors and that vasodilation is mediated by β-adrenergic receptors.

Stimulation of the vagus nerve is followed by a prompt increase in blood flow, suggesting a dilatory effect of parasympathetic nerves. The effects of vagal stimulation on mucosal blood flow are complicated by accompanying increases in acid secretion. Almost all stimuli that increase acid production also increase blood flow secondarily.

A number of gastrointestinal peptide hormones affect gastric blood flow, most because of their ability to increase or decrease acid secretion. Thus, gastrin, because it is a potent stimulant of acid secretion, also increases mucosal blood flow. Cholecystokinin appears to have direct vasodilatory effects on the gastric vasculature. Vasopressin has been well demonstrated to have direct vasoconstrictor activity.

Nitric oxide modulates basal gastric vascular tone and controls gastric vasodilation and hyperemia. Nitric oxide mediates the hyperemic response

that accompanies increases in acid secretion, although the molecule has no direct stimulatory role in acid production.

Prostaglandins are important mucosally produced compounds that have clear effects on the gastric vasculature. Prostaglandins of the E class have been shown in animals and humans to increase gastric blood flow at doses that decrease acid secretion. Indomethacin, in doses sufficient to inhibit prostaglandin formation, decreases the diameter of submucosal blood vessels and reduces basal blood flow. Complete inhibition of cyclooxygenase activity causes an approximate 50% reduction in resting blood flow. These studies suggest that endogenous, locally produced prostaglandins are crucial to maintaining basal gastric blood flow in humans and probably act in concert with endogenous nitric oxide.

GASTRIC MOTILITY

Gastric Smooth Muscle

Consideration of gastric motility requires that the stomach be viewed in functional terms as two different regions, the proximal one-third and the distal two-thirds. These areas are distinct in terms of smooth muscle anatomy, electrical activity, and contractile function. The regions do not correspond to the traditional anatomic divisions of fundus, corpus, and antrum.

In the proximal stomach, three layers of gastric smooth muscle can be distinguished: an outer longitudinal layer, a middle circular layer, and an inner oblique layer. In the distal two-thirds of the stomach, the longitudinal layer is most clearly defined, and the inner oblique layer is usually not distinct. The gastric smooth muscle ends at the pylorus.

The smooth muscle of the proximal stomach is electrically stable, whereas the smooth muscle of the distal stomach demonstrates spontaneous, repeated electrical discharges. Gastric smooth muscle exhibits myoelectric activity that is based on a highly regular pattern called the *slow wave*.[10] In the stomach, slow waves occur with a frequency of three cycles per minute. Slow waves do not, by themselves, lead to gastric contractions, but they do set the maximum rate of contractions at three per minute. Gastric contractions

occur when action potentials are phase locked with the crest of the slow wave.

Extracellular electrical recording from the serosal surface of the stomach also demonstrates the intrinsic electrical activity of the distal stomach in the form of pacesetter potentials. Pacesetter potentials reflect partial depolarization of the gastric smooth muscle cell and are recorded during relatively long periods (2 or 3 seconds). Pacesetters originate along the greater curvature at a point in the proximal third of the stomach. Pacesetter potentials, discharging at a rate of three times per minute in humans, drive cells located distally. Spread of the pacesetter potentials is faster along the greater curvature, so that a ring of electrical activity reaches the pylorus simultaneously along both curvatures. The pacesetter potentials do not result in smooth muscle contraction unless an additional depolarization is superimposed in the form of an action potential. When action potentials occur, a ring of smooth muscle contraction moves peristaltically along the distal stomach toward the pylorus.

Duodenal slow-wave frequency and maximum rate of phasic contractions are higher than those observed in the stomach. The duodenal rate is approximately 12 cycles per minute; the contraction rate declines progressively to 9 cycles per minute in the distal ileum.

The smooth muscle activity of the proximal stomach is fundamentally different from that of the distal stomach. There are no pacesetters or action potentials in the proximal stomach. As a result, peristalsis does not occur. Proximal gastric contraction is tonic and prolonged, and increases in luminal pressure are often sustained for several minutes.

Coordination of Contraction

Important vagally mediated reflexes influence intragastric pressure, presumably by affecting contractile activity of smooth muscle in the proximal stomach. The most important reflex is termed *receptive relaxation* and occurs with ingestion of a meal. Increasing gastric volumes are accommodated with little increase in intragastric pressure by relaxation of the proximal stomach. This receptive relaxation allows the proximal stomach to act as a storage site for ingested food in the immediate postprandial period. Afferent impulses, presumed to originate from stretch receptors in the

gastric wall, are carried along vagal fibers; efferent vagal discharges are inhibitory. Receptive gastric accommodation is lost after either truncal or proximal gastric vagotomy. After the meal has been ingested, proximal contractile activity increases; alterations in proximal gastric tone cause the compressive movement of gastric content from the fundus to the antrum.

Food that enters the antrum from the proximal stomach is propelled peristaltically toward the pylorus. A number of observations indicate that the pylorus closes 2 or 3 seconds before the arrival of the antral contraction ring. This coordinate closing of the pylorus allows a small bolus of liquid and suspended food particles to pass while retropulsing the main mass of gastric contents back into the proximal antrum. The churning action that results mixes ingested food particles, gastric acid, and pepsin, and contributes to the grinding function of the stomach. Solid food particles do not ordinarily pass the pylorus unless they are no larger than 1 mm.

A consistent finding in humans ingesting a mixed solid–liquid meal is that liquids empty more quickly than solids. Characteristically, solid food empties only after a lag period, whereas liquid emptying begins almost immediately. A traditional interpretation of these human observations has been that the proximal stomach is the dominant force in determining how quickly a liquid meal empties by the gastroduodenal pressure gradient generated by proximal gastric contractions. The distal gastric segment has been postulated to control solid emptying through its grinding and peristaltic actions. This traditional concept of the two-component stomach is useful in considering observations in patients who have undergone gastric operative procedures. Patients who have undergone proximal gastric vagotomy exhibit accelerated emptying of liquids but have normal solid emptying. Because of loss of receptive relaxation, the denervation of the proximal stomach is presumed to increase intragastric pressure and accelerate liquid emptying while leaving the distal gastric segment unaffected. Conversely, vagal denervation of the antrum interrupts gastric emptying of solids to a greater degree than liquids. Although this model of gastric emptying oversimplifies the many mechanisms (gastric, pyloric, and intestinal) that work in concert to control gastric emptying, it provides a useful framework for considering the effects of gastric surgical procedures.

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45

Gastroduodenal Ulceration

Michael W. Mulholland

Key Points

1. Mucosal infection with *Helicobacter pylori* is the factor that contributes to ulcer pathogenesis in most patients.
2. *H. pylori* virulence factors include vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA).
3. As a group, patients with duodenal ulcers have an increased capacity for gastric acid secretion relative to normal people.
4. Current treatment of peptic ulceration involves a combination of an antisecretory drug, usually a proton pump inhibitor, with antibiotics.
5. Hemorrhage is the leading cause of death associated with peptic ulcer. Patients with recurrent hemorrhage and elderly patients are at greatest risk of death.
6. For perforation, current therapy includes omental patch closure with postoperative anti–*H. pylori* therapy. Minimally invasive approaches are becoming standard practice.
7. Major trauma accompanied by shock, sepsis, respiratory failure, hemorrhage, or multiorgan injury is often accompanied by acute stress gastritis.

EPIDEMIOLOGY

Peptic ulceration remains a major public health problem worldwide. Worldwide prevalence of peptic ulcer disease ranges from 0.1% to 4.7% with an overall incidence of 0.2% to 0.3%.[1] With improving public hygiene and effective treatment of *Helicobacter pylori,* most epidemiologic studies are now reporting falling incidence rates. The surgical treatment of peptic ulcer has changed fundamentally. New insights into disease pathogenesis, especially the realization that gastric infection has a role in most cases of peptic ulceration, have been especially exciting. Antibiotics are now front-line antiulcer therapy. A number of powerful antisecretory drugs have been introduced into clinical practice. Medical, endoscopic, and surgical therapies are frequently integrated in the care of individual patients.

PATHOPHYSIOLOGY

The pathogenesis of peptic ulceration is complex and multifactorial but increasingly understood. Approximately 75% of peptic ulcer cases are caused by *H. pylori,* with almost all other cases due to use of nonsteroidal anti-inflammatory drugs (NSAIDs).[2] Both NSAID use and *H. pylori* infection are independent risk factors for development of peptic ulcer disease. The development of peptic ulceration is often depicted as a balance between chronic inflammatory injury, acid–peptic secretion, and mucosal defense, with the equilibrium shifted toward disease. Although acid–peptic secretion is crucial in the development of ulcers, usually a defect in mucosal defense induced by bacterial infection also exists to tip the balance 1 away from health. Mucosal infection with *H. pylori* is the factor that contributes to ulcer pathogenesis in most patients.

Helicobacter pylori

The relation between *H. pylori* infection and ulceration is overwhelmingly strong. Many lines of evidence establish *H. pylori* as a factor in the pathogenesis of duodenal ulceration:

- *H. pylori* is the primary cause of chronic active gastritis, characterized by nonerosive inflammation of the gastric mucosa. Antral gastritis is nearly always present histologically in patients with duodenal ulcer, and *H. pylori* can be isolated from gastric mucosa in almost all cases.
- Gastric metaplasia is extremely common in duodenal epithelium surrounding areas of ulceration. *H. pylori* binds only to gastric-type epithelium, regardless of location; metaplastic gastric epithelium can become colonized by *H. pylori* from gastric sources. Gastric metaplasia of the duodenal bulb is a nonspecific response to damage and is the means by which antral gastritis with *H. pylori* is converted to active chronic duodenitis.
- Eradication of *H. pylori* with antimicrobials that have no effect on acid secretion leads to ulcer healing rates superior to those seen with acid-suppressing agents.
- Relapse of duodenal ulcer after antimicrobial therapy is preceded by reinfection of the gastric mucosa by *H. pylori*.

In addition, half of patients evaluated for dyspepsia, but without ulceration, have histologic evidence of mucosal bacterial infection. Furthermore, 20% of healthy volunteers harbor the bacteria; the incidence of bacterial carriage in the healthy, asymptomatic population increases with age. The occurrence of peptic ulcers in only a small proportion of people who carry the organism suggests that other factors must also act to induce ulceration. The ability of *H. pylori* infection to induce alterations in gastric acid secretion is a prerequisite for ulcer development in most patients.

H. pylori is the most common bacterial infection worldwide. *H. pylori* infection is usually acquired in childhood and lasts lifelong in the absence of specific therapy. Epidemiologic studies suggest that *H. pylori* infection occurs via person-to-person contact, usually among family members. Transmission is believed to occur during a bout of gastroenteritis; the highest risk is associated with vomiting.

H. pylori is the only human bacterium to persistently infect the stomach. The organism is actually somewhat fragile, being killed by exposure to high levels of oxygen and to the low pH found in the acidic lumen of the stomach. To avoid the bactericidal activity of the stomach, the organism has evolved mechanisms to move within the gastric environment, to adhere to gastric

mucosa, and to protect itself from the harmful effects of acid. Over 300 genes of *H. pylori* are regulated by acid.

H. pylori bacteria are spiral shaped with polar flagella. Most bacilli are free swimming within the mucous layer covering the gastric epithelium. The organisms orient according to a pH gradient, moving away from the lower pH of the lumen toward the epithelium. The majority of organisms remain motile within the mucous layer, but contact promotes adherence to epithelial cells, particularly in the region of intercellular junctions. The products of more than 30 genes are expressed on the outer membrane of the bacterium and function as adhesins to promote attachment to the gastric cells' surface. Adhesion triggers the expression of other bacterial genes, including bacterial virulence factors.

All strains of *H. pylori* cause persistent infection and all strains induce gastric inflammation. Yet, only 15% of infected individuals develop peptic ulceration and only 1% develops gastric adenocarcinoma. Differential expression of bacterial virulence factors is presumed to account for these observations.[2] Two virulence factors are best characterized: vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA) (**Table 45.1**).[3]

VacA is a pore-forming cytotoxin. Upon secretion from the bacterium, the protein moves to the host cell membrane, where it forms a ring structure in the shape of a flower.[4] This ring complex inserts into the membrane of the host cell, creating a pore. VacA pores are permeable to anions and small neutral molecules, including urea. Pore formation may be a mechanism by which the organism obtains nutrients from gastric epithelial cells.

The second major virulence factor in *H. pylori* is termed *CagA.*[5,6] The CagA gene is part of a region of DNA that is inserted into the genome of more virulent strains of *H. pylori,* termed a *pathogenicity island.*[5] The genes in this island that are adjacent to the CagA gene encode proteins, which function as microscopic needles for the transfer of bacterial products into host gastric cells. CagA is transferred to host cells through this injection mechanism.

Table 45.1 *Helicobacter pylori* Virulence Factors
Vacuolating Cytotoxin A (VacA)
Forms ring structure in the shape of a flower
Inserts into gastric cell membrane, forming pore
Inserts into endosomal membranes, causing cellular swelling
Damages mitochondrial membranes
Causes leakage of ions and small molecules
Cytotoxin-Associated Gene A (CagA)
Contained within pathogenicity island DNA sequence
Injected into host cells
Phosphorylated by cellular oncogenes
Activates growth factor receptor–like signaling
Disturbs normal proliferation, adhesion, cytoskeletal function
Disturbs intercellular junctions, causing disruption of epithelial permeability
Elicits inflammatory response

After CagA protein is transferred to host cells, it becomes phosphorylated on tyrosine residues by host cell kinases. Phosphorylated CagA activates a number of cellular-signaling pathways involved in cellular polarity, cytoskeletal protein function, and cellular proliferation and differentiation. As a consequence, infected gastric cells change shape and become more elongated. Apical junctions between cells become disrupted, gaps develop between epithelial cells, and epithelial barrier function is lost. CagA protein also stimulates transcription factors involved in regulation of cellular proliferation. Disturbance of cellular function in favor of apoptosis affects epithelia restitution and may inhibit ulcer healing.

Acid-Secretory Status

The formation of duodenal ulcers depends on gastric secretion 3 of acid and pepsin. As a group, patients with duodenal ulcers have an increased capacity for gastric acid secretion relative to normal people (**Table 45.2**). The maximal acid output of normal men is approximately 20 mEq/hr in response

to intravenous histamine stimulation, whereas patients with duodenal ulcer secrete an average of approximately 40 mEq/hr. Considerable overlap exists between these two groups, and the values for most people with duodenal ulcer fall within the normal range.

Groups of patients with duodenal ulcer demonstrate a prolonged and larger acid-secretory response to a mixed meal than do groups of normal subjects. As with histamine-stimulated acid output, overlap exists between patients with duodenal ulcer and normal subjects. Disturbances in gastric motility can exacerbate meal-stimulated acid-secretory abnormalities.

Patients with duodenal ulcer have accelerated emptying of gastric contents, particularly liquids, after a meal, and duodenal acidification fails to slow emptying appropriately. In such patients, the duodenal mucosa can be exposed to low pH for prolonged periods relative to normal subjects.

Groups of patients with duodenal ulcer also demonstrate increased basal secretion of acid. Increased basal secretion can be demonstrated by nocturnal collection of gastric secretions.

Studies indicate that most of these secretory abnormalities are a direct consequence of *H. pylori* infection. Paradoxically, the earliest stages of *H. pylori* infection are accompanied by a marked decrease in gastric acid secretion. Acute antral gastritis is followed by fundal inflammation. Fundal inflammation is associated with mucosal production of a number of cytokines, including interleukin (IL)-1β, IL-6, IL-8, and tumor necrosis factor-α (TNF-α). IL-1β is a potent inhibitor of gastric acid secretion. Investigators have postulated that acute reduction in gastric acid secretion facilitates further gastric colonization with *H. pylori.* Acute hypochlorhydria resolves despite persistence of *H. pylori* and is followed by a state of chronically increased acid secretion.

Table 45.2 Pathogenesis of Peptic Ulcer

Helicobacter pylori infection

Endocrine Consequences

- Increased basal serum gastrin
- Increased gastrin response to a meal
- Increased responsiveness to gastrin-releasing peptide
- Production of N^{α}-methylhistamine
- Decreased density of somatostatin cells
- Decreased mucosal somatostatin content

Gastric Acid Secretion

- Increased acid = secretory capacity
- Increased basal secretion
- Increased pentagastrin-stimulated output
- Increased meal response
- Abnormal gastric emptying

Mucosal Defense

- Decreased duodenal bicarbonate production
- Decreased gastric mucosal prostaglandin production
- Increased apoptosis of epithelial cells
- Disruption of epithelial barrier function
- Inhibited epithelial restitution

Basal and peak acid outputs are increased in patients with duodenal ulcer infected with *H. pylori* relative to uninfected healthy volunteers. With eradication of *H. pylori* infection, basal acid output returns to normal within 4 weeks, and peak acid output declines to the normal range by 6 months.

Abnormalities in acid secretion and parietal cell mass appear to be due to *H. pylori*–induced hypergastrinemia.[7] *H. pylori*–infected patients have increased basal serum gastrin levels, increased gastrin responses to meal stimulation, and an augmented gastrin response to intravenous gastrin-releasing peptide. Eradication of *H. pylori* infection causes serum gastrin levels to return to baseline. Gastric mucosal inflammatory cells and epithelial cells are activated by *H. pylori* infection to release cytokines such

as IL-8, interferon-γ, and TNF-α. These cytokines are stimulants of gastrin release from cultured canine gastrin cells.

Mucosal Defense Against Peptic Injury

Gastric surface epithelial cells secrete mucus and bicarbonate, creating a pH gradient within the mucous layer that is nearly neutral at the mucous cell surface, even when the lumen is highly acidic. Failure of normal bicarbonate secretion locally would, in theory, result in exposure of surface epithelial cells to the peptic activity of gastric secretions at low pH. Patients with duodenal ulcers have been demonstrated to have significantly lower basal bicarbonate secretion in the proximal duodenum than normal subjects. In addition, in response to a physiologically relevant amount of hydrochloric acid instilled into the duodenal bulb, stimulated bicarbonate output was approximately 40% of the normal response. Abnormalities in duodenal bicarbonate secretion normalize after elimination of *H. pylori* in infected patients. These results suggest one mechanism by which ulceration could occur, even in patients secreting normal amounts of acid.

Diminished mucosal prostaglandin production has also been proposed to exist in subsets of patients with duodenal ulcer. Prostaglandins and prostaglandin analogs have been shown to exert cytoprotective effects, to accelerate healing of established duodenal ulcers, and to decrease acid secretion. In patients with active duodenal ulceration, gastric mucosal production of prostaglandin E_2 and other prostanoids has been shown to be diminished. An increase in prostanoid synthesis within the gastric mucosa characterizes ulcer healing.

Inflammatory responses to *H. pylori* infection are central to the pathogenesis of peptic ulceration. While *H. pylori* infection always induces inflammation, the patterns of response are not uniform. Three major patterns have been recognized.[8,9] The most common pattern is a mild to moderate inflammation of all regions of the stomach. This form is not associated with major alterations in gastric acidity and most individuals are asymptomatic and do not develop peptic ulceration. Approximately 15% of infected individuals develop an antral-predominant form of gastritis. These individuals exhibit an intense inflammation limited to the antrum without

involvement of the mucosa of the gastric corpus. Gastrin levels are elevated and acid secretion is high. Inhibitory control of gastric acid production is impaired in this form of gastritis. As a result, duodenal and prepyloric ulcers are common. The third form of inflammatory response, occurring in 1% of infected individuals, is least common but most serious. This form is characterized by corpus-predominant gastritis, hypochlorhydria, and gastric atrophy. This form of inflammatory response is considered a precursor state for gastric cancer.

Environmental Factors

NSAIDs have emerged as a significant risk factor for the development of acute ulceration. Although acute mucosal injury caused by NSAIDs is more common in the stomach than in the duodenum, NSAID-induced ulcer complications occur with equal frequency in these two sites. NSAIDs produce a variety of lesions, ranging from hemorrhage, to superficial mucosal erosions, to deeper ulcerations. In the duodenum, it appears likely that invasive NSAID-associated ulcers result from underlying peptic ulcer diathesis compounded by the direct injurious effects of these drugs.

The ulcerogenic actions of NSAIDs have been attributed to their systemic suppression of prostaglandin production. Ulcers associated with NSAIDs usually heal rapidly when the drug is withdrawn, corresponding to the reversal of antiprostaglandin effects. All available NSAIDs appear to pose the hazard of gastroduodenal ulceration. Clinically important ulceration (of both the stomach and duodenum) is estimated by the U.S. Food and Drug Administration to occur at a rate of 2% to 4% per patient-year. The risks inherent with NSAID use appear to be increased by a history of *H. pylori* infection, by cigarette smoking, and by alcohol use. The incidence of NSAID-caused ulcer complications is highest in older patients, as is the attendant mortality rate. Peptic ulcer disease is rare in individuals who are *H. pylori* negative and who are not receiving NSAID medications.

A role of NSAIDs in upper gastrointestinal (GI) hemorrhage is widely recognized. The risk of bleeding is particularly acute for peptic ulceration. NSAIDs have been linked to 50% to 75% of bleeding peptic ulcers, one-third of deaths due to hemorrhage, and 30% of hospitalizations.[10,11] Use of

NSAIDs increases the risk of bleeding from peptic ulcer threefold for those under 65 years of age, but by eightfold for individuals over 75 years of age.

Because of the risk of gastrointestinal side effects, a selective class of cyclooxygenase-2 (COX-2) inhibitors was developed for long-term pain relief and anti-inflammatory therapy. Selective COX-2 inhibitors have reduced potential to injure the gastrointestinal mucosa relative to standard NSAIDs.[11] Concurrent use of aspirin with COX-2 inhibitors significantly undermines the safety advantages of the COX-2 agents, as does smoking.[12]

DIAGNOSIS

The cardinal feature of duodenal ulceration is epigastric pain. The pain is usually confined to the upper abdomen and is described as burning, stabbing, or gnawing. Unless perforation or penetration into the head of the pancreas has occurred, referred of pain is not common. Many patients report pain on arising in the morning. Ingestion of food or antacids usually provides prompt relief. In uncomplicated cases, abnormal physical findings are minimal. The differential diagnosis is broad and includes a variety of diseases originating in the upper gastrointestinal tract. The most common disorders to be distinguished include nonulcerative dyspepsia, gastric neoplasia, cholelithiasis and related diseases of the biliary system, and both inflammatory and neoplastic disorders of the pancreas. In dyspeptic patients, the principal diagnoses that must be differentiated definitively are peptic ulceration and gastric cancer.

The evaluation of patients with suspected peptic ulceration usually involves endoscopy, the standard against which other diagnostic modalities are measured. Endoscopy is employed because it permits biopsy of the esophagus, stomach, and duodenum.

Duodenal ulcer is characterized by lesions that are erosive to the bowel wall. When viewed endoscopically, the ulcers have a typical appearance. The edges are usually sharply demarcated and the underlying submucosa is exposed. The ulcer base is often clean and smooth, although acute ulcers and those with recent hemorrhage can demonstrate eschar or adherent exudate. Surrounding mucosal inflammation is common. The most frequent site for peptic ulceration is the first portion of the duodenum, with the second portion

less commonly involved. Ulceration of the third or fourth portions of the duodenum is unusual, and occurrence in these sites should arouse suspicion of an underlying gastrinoma. Ulceration in the pyloric channel or the prepyloric area is similar in endoscopic appearance to duodenal ulceration, and ulcers in these areas demonstrate other clinical features similar to duodenal ulcers. Endoscopic demonstration of a duodenal ulcer should prompt mucosal biopsy of the gastric antrum to demonstrate the presence of *H. pylori* and guide subsequent therapy.

The ulcer can extend for a variable distance through the wall of the duodenum, including the full thickness of the bowel in cases of perforation.

DRUG TREATMENT OF ULCER DISEASE

In the absence of active treatment, *H. pylori* infection is lifelong. [4] Spontaneous healing of infected mucosa is very rare, occurring in less than 0.5% per patient-year. Current treatment of peptic ulceration involves a combination of an antisecretory drug, usually a proton pump inhibitor, with antibiotics.[13] This therapy is rational for most patients who are *H. pylori* positive and results in a high rate of sustained ulcer healing.

A large number of drug regimens have been described, but the most widely used treatment protocols combine a proton pump inhibitor, usually omeprazole, with two antibiotics, usually clarithromycin and metronidazole or amoxicillin. A combination of antibiotics is more effective than one antibiotic alone in almost all series. This triple therapy is administered for 7 or 14 days. Triple-drug therapy is cost effective and associated with a low rate of side effects, low rates of antibiotic resistance, and acceptable levels of patient compliance. *H. pylori* eradication rates of greater than 90% have been reported.

After elimination of *H. pylori,* ulcer recurrence rates reflect the rate of reinfection. In developed countries, reinfection rates of less than 10% at 5 years have been reported. Eradication of *H. pylori* improves quality of life, as measured by symptoms, drug prescriptions, physician visits, and days of missed employment. To date, antibiotic resistance has been low, approximately 18% for clarithromycin, 14% for levofloxacin, and 35% for metronidazole. Resistance to amoxicillin has been low.[14]

HISTAMINE-RECEPTOR ANTAGONISTS

Histamine, released into the interstitial fluid by cells in the fundic mucosa, diffuses to the mucosal parietal cell. Histamine stimulates acid production by occupying a membrane-bound receptor and activating parietal cell adenylate cyclase. Histamine is released in response to a number of physiologic stimuli; blockade of histamine receptors inhibits most forms of stimulated acid secretion in humans. All clinically useful gastric histamine receptor antagonists are of the H_2 type.

H_2-receptor antagonists bind competitively to parietal cell H_2 receptors to produce a reversible inhibition of acid secretion. An enormous worldwide experience has accumulated with the use of H_2-receptor antagonists. The agents are effective and safe when used in the treatment of peptic ulcer. The various compounds have similar efficacy in terms of ulcer healing when used in doses that produce similar reductions in acid output. It is clear that H_2-receptor blockers do not affect the underlying ulcer diathesis; if H_2-receptor antagonists are stopped, recurrent ulceration occurs in more than half of patients within 1 year. The current understanding of the role of *H. pylori* in ulcer pathogenesis has changed the role of H_2-receptor antagonists from primary therapy to that of a substitute for proton pump inhibitors in conjunction with antibiotic treatment.

PROTON PUMP BLOCKERS

Acid secretion by the gastric parietal cells is due to the active transport of hydrogen ions from the parietal cell cytoplasm into the secretory canaliculus in exchange for potassium. Because this so-called *proton pump* is tissue specific, being present only in gastric mucosa, its blockade would be expected to have minimal effects on nongastric functions. Omeprazole is representative of a family of compounds that selectively block the parietal cell proton pump.

Omeprazole binds to the membrane-bound H^+-K^+-adenosine triphosphatase (ATPase) of the parietal cell. Because the compound is a weak base, omeprazole accumulates selectively within the acidic

environment of the parietal cell secretory canaliculus; 4 hours after administration, the drug is detectable in appreciable quantities only in the gastric mucosa. If enough drug is administered to occupy all parietal cell–binding sites, anacidity can be produced. Omeprazole, in doses from 20 to 30 mg, causes nearly complete inhibition of stimulated gastric acid secretion within 6 hours. At 24 hours after drug administration, a 60% to 70% reduction in acid secretion persists.

Repeated daily dosing with omeprazole results in increasing inhibitory action on gastric secretion and thus in decreased intragastric degradation of the drug. Acid suppression stabilizes after approximately 3 days. Because of tissue accumulation, the secretory actions of omeprazole do not correlate with plasma levels. Several studies have demonstrated a significant inhibition of peak acid output, marked relief of epigastric pain, and decreased use of supplemental antacids during omeprazole therapy. Direct comparisons with H_2-receptor antagonists have generally favored omeprazole in terms of pain relief and rate of ulcer healing.

OPERATIVE TREATMENT OF ULCER DISEASE

Surgical Goals

Operative intervention is reserved for the treatment of complicated ulcer disease. Three complications are most common and constitute the indications for peptic ulcer surgery—hemorrhage, perforation, and obstruction. The first goal in the surgical treatment of the complications of ulcer disease is treatment of coexisting anatomic complications, such as pyloric stenosis or perforation. The second major goal should be patient safety and freedom from undesirable chronic side effects. To achieve these goals, the gastric surgeon can direct therapy through endoscopic or operative means, the appropriate choice depending on the clinical circumstances.

Operative Procedures

A number of operative procedures have been used to treat peptic ulcer, but with decreasing frequency in the past decade. There is currently no indication for surgical treatment of uncomplicated ulcer disease. Operative treatment of gastric outlet obstruction has decreased by approximately 50%. Most surgical patients are now treated emergently for the complications of bleeding or perforation.

Three procedures—truncal vagotomy and drainage, truncal vagotomy and antrectomy, and proximal gastric vagotomy—were widely used in the past in the operative treatment of peptic ulcer disease. With increasing frequency, surgical therapy of peptic ulcer is directed exclusively at correction of the immediate problem (e.g., closure of duodenal perforation) without gastric denervation. The underlying ulcer diathesis is then addressed after surgery by antibiotic therapy directed at *H. pylori*.

Hemorrhage

5 Hemorrhage is the leading cause of death associated with peptic ulcer, and the incidence of this complication has not changed since the introduction of H_2-receptor antagonists. The lifetime risk of hemorrhage for patients with duodenal ulcer ranges from 19 to 57 per 100,000 indvivduals.[15] Most hemorrhages occur during the initial episode of ulceration or during a relapse, and patients who have hemorrhaged previously have a higher risk of bleeding again. Patients with recurrent hemorrhage and elderly patients are at greatest risk of death, and these two groups should be resuscitated vigorously, investigated promptly, and treated aggressively.[16,17] The 90-day all-cause mortality for patients with bleeding peptic ulcer is surprisingly high at 15%.[15]

Operative risk is increased in patients who have shock at admission, recurrent bleeding, delay in operative intervention, or coexisting medical illnesses. Surgical delay may lead to recurrent hypovolemia and, subsequently, multisystem organ failure.

Upper gastrointestinal endoscopy is the appropriate initial diagnostic test when hemorrhage from duodenal ulceration is suspected. Endoscopy can correctly determine the site and cause of bleeding in more than 90% of patients. An ulcer should be accepted as the bleeding source only if it has

one of the stigmata of active or recent hemorrhage. Active hemorrhage is defined by an arterial jet, active oozing, or oozing beneath an adherent clot. The signs of recent hemorrhage include an adherent clot without oozing, an adherent slough in the ulcer base, or a visible vessel in the ulcer. The ability of these endoscopic findings to accurately predict recurrent hemorrhage has been extensively validated. Approximately 30% of patients who have stigmata of recent hemorrhage experience rebleeding, and most of the patients who experience recurrent hemorrhage require emergency treatment. The occurrence of hypovolemic shock, rebleeding during hospitalization, and a posteroinferior location of the ulcer are additional clinical features that have been associated with increased risks of recurrent bleeding. The role of gastric acidity as a cause for in-hospital rebleeding appears to be inconsequential, and reduction of acid secretion by H_2-receptor antagonists or omeprazole is not sufficient to prevent recurrent hemorrhage.

The ability to visualize bleeding duodenal ulcers endoscopically has led to development of methods to treat hemorrhage endoscopically. There are many different methods of endoscopic therapy, but the most established consist of thermal coagulation or injection of sclerosants. Thermal coagulation can be achieved by bipolar electrocoagulation or direct application of heat through a heater probe. Injection of epinephrine into the base of the bleeding ulcer is also effective in control of ulcer hemorrhage.

Proof of efficacy, in the form of lowered rebleeding rates and avoidance of operation, has been convincingly demonstrated for all of these methods of endoscopic hemostasis. The analysis of reports of endoscopic treatment of hemorrhage is complicated by the 70% rate of spontaneous, although sometimes temporary, cessation of bleeding without intervention. In addition to endoscopic stigmata, hemodynamic instability, need for continuing transfusion, red stool or hematemesis, age older than 60 years, and serious medical comorbidity are clinical features that mandate endoscopic therapy. Rebleeding during hospitalization and the endoscopic findings of visible vessel, oozing, or bleeding associated with an adherent clot are other indications for endoscopic hemostasis. Ulcers with clean bases require no treatment.

Table 45.3 Situations in Which Operative Intervention Is Appropriate

Massive hemorrhage leading to shock or cardiovascular instability
Prolonged blood loss requiring continuing transfusion
Recurrent bleeding during medical therapy or after endoscopic therapy
Recurrent hemorrhage requiring hospitalization

Failure of endoscopic hemostasis is usually due to inaccessibility because of scarring, to rapid active bleeding obscuring the endoscopic view, or to an adherent clot. Patients treated endoscopically should be observed closely for further hemorrhage. Patients who rebleed within 72 hours of initial endoscopic control may be successfully retreated without increasing the risk of mortality. Transcatheter arterial embolization has emerged in recent years as an alternative to surgery for patients that fail endoscopic control measures.[18] This method should be considered as a salvage option for patients in whom endoscopic control is not effective.

Table 45.3 lists situations in which operative intervention is appropriate. The need for emergency surgery significantly increases surgical risks; mortality rates are increased approximately 10-fold. Operative therapy should consist of duodenostomy with direct ligation of the bleeding vessel in the ulcer base.

Postoperatively, patients should receive antibiotics directed against *H. pylori*. This treatment paradigm is based on the observation that peptic ulcer hemorrhage recurs in 20% of patients in whom *H. pylori* is not eradicated, whereas rebleeding is reduced to 3% in patients who receive *H. pylori* eradication therapy (**Algorithm 45.1**, **Fig. 45.1**).[19]

Perforation

The lifetime risk for perforation in patients with duodenal ulceration who do not receive therapy approximates 10%. In contrast, ulcer perforation is unusual if initial ulcer healing has been achieved.

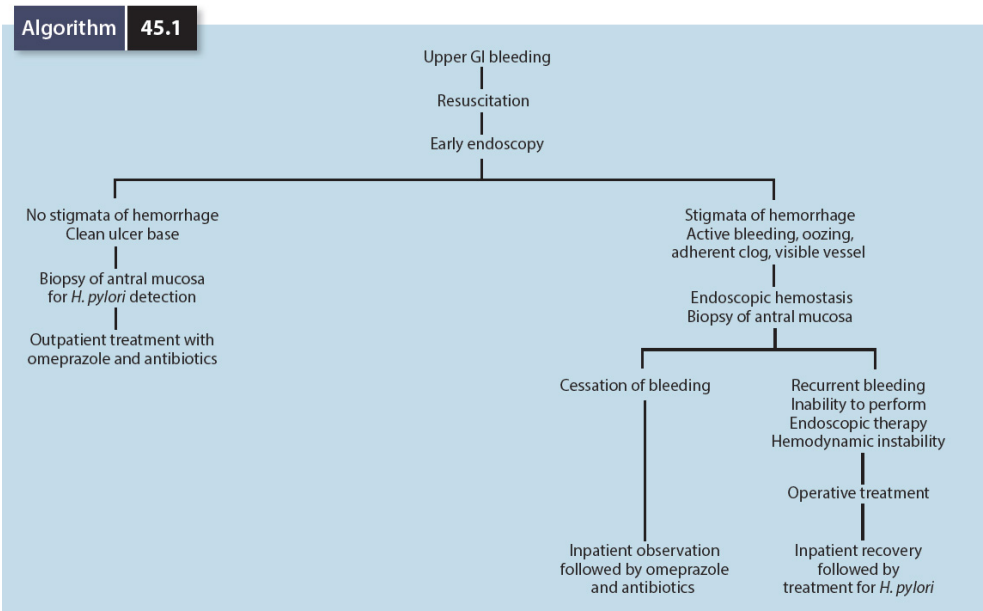
Perforation of a duodenal ulcer is usually accompanied by sudden and severe epigastric pain. The pain, caused by the spillage of highly caustic

gastric secretions into the peritoneum, rapidly reaches peak intensity and remains constant. Radiation to the right scapular region is common because of right subphrenic collection of gastric contents. Occasionally, pain is sensed in the lower abdomen if gastric contents travel caudally through the paracolic gutter. Peritoneal irritation is usually intense and most patients avoid movement to minimize discomfort.

Physical examination reveals low-grade fever, diminished bowel sounds, and rigidity of the abdominal musculature. Usually, upright abdominal radiographs reveal pneumoperitoneum. Computed tomography of the abdomen is very sensitive for demonstrating perforation if pneumoperitoneum is not demonstrated but perforation is still suspected.

Perforation remains a strong indication for surgery in most circumstances. Laparotomy or laparoscopy affords the opportunity to relieve intraperitoneal contamination and to close the perforation (**Fig. 45.2**).

Signs of antecedent duodenal ulceration, in terms of history of prior symptoms and anatomic evidence of duodenal scarring, should be sought. Before the role of *H. pylori* was appreciated, simple omental closure of duodenal perforation resulting from chronic ulceration did not provide satisfactory long-term results; up to 80% of patients so treated had recurrent ulceration, and 10% experienced reperforation if untreated. Approximately four-fifths of all patients with perforation have *H. pylori* infestation and therefore are at risk of recurrent disease.



Algorithm 45.1 Treatment of bleeding duodenal ulceration.

The mortality of emergent ulcer operations is most clearly correlated with the following circumstances: preoperative shock, coexisting medical illness, and presence of perforation for more than 48 hours.[20] Mortality with perforated peptic ulcer disease has also been correlated with the American Society of Anesthesiology (ASA) score and the Peptic Ulcer Perforation (PULP) score.[21]

6 Current reports advocate omental patch closure, often laparoscopically, with postoperative anti–*H. pylori* therapy. This approach presumes that most duodenal ulcers are caused by *H. pylori,* that secure closure of the perforation can be obtained, and that further surgical therapy will be obviated by the effects of medical therapy. Minimally invasive approaches are becoming standard practice.

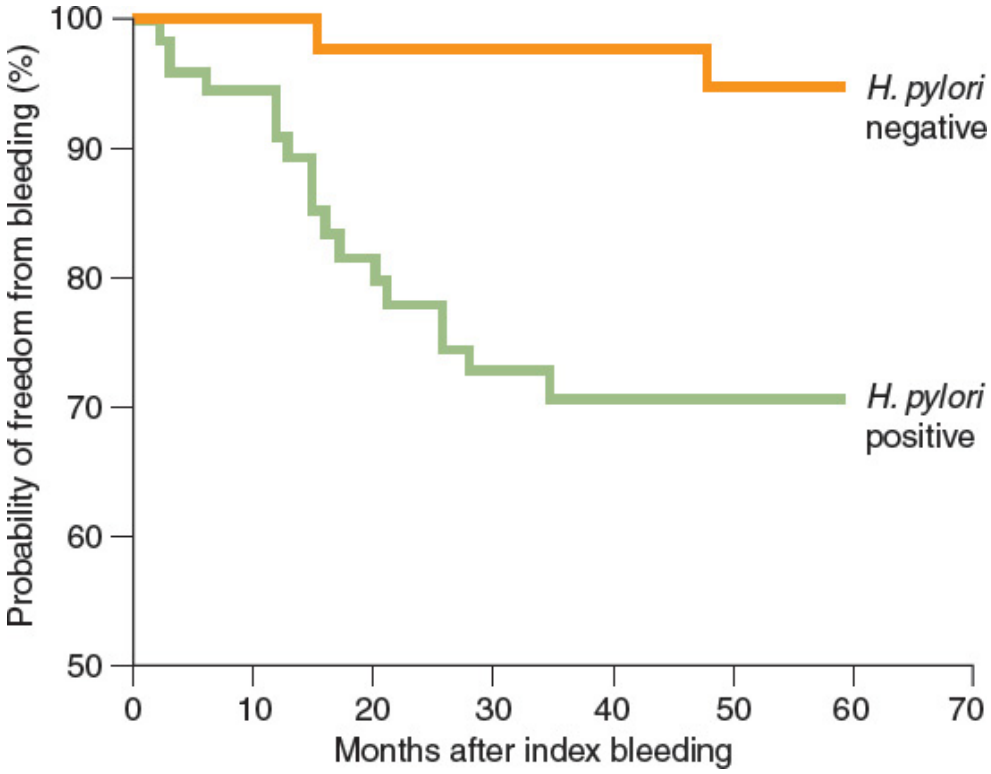


Figure 45.1 Probability of freedom from recurrent hemorrhage according to posttreatment *H. pylori* status.

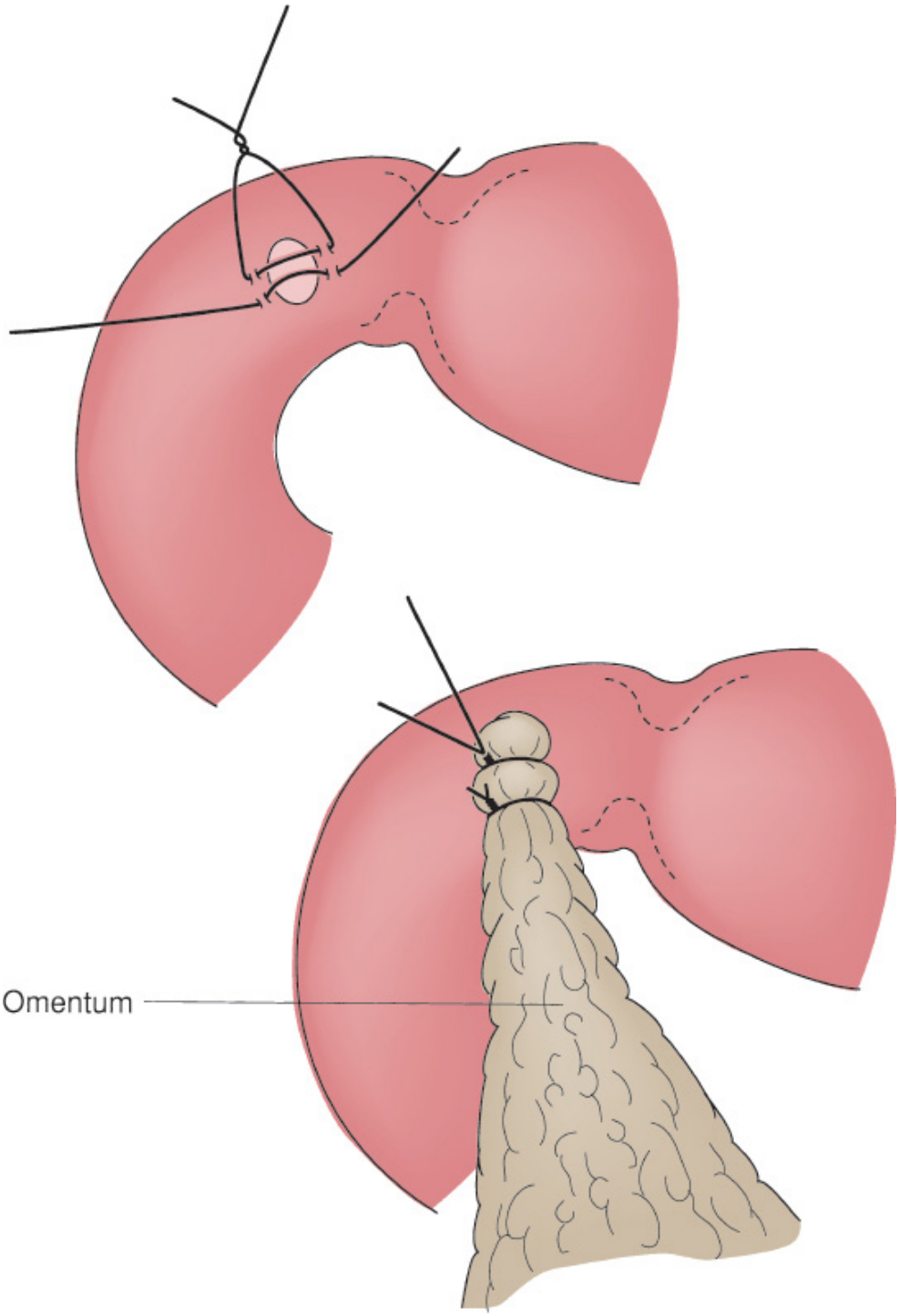


Figure 45.2 Omental patching of perforated duodenal ulcer.

In-hospital analgesic use has been consistently demonstrated to be lower in laparoscopically treated patients, and hospital length of stay shorter for these patients.[22] Overall rates of postoperative complications were not

statistically different between the two approaches, but most studies demonstrate a lower rate of wound infection in the laparoscopic group. Return to normal daily activities and work favor the laparoscopic group. Mortality is similar between patients treated via open or laparoscopic approaches, suggesting that underlying septic complications are more important that the means of access to the abdominal cavity. Peptic ulcer perforation is a serious physiologic challenge to frail patients with increased mortality risk that persists much longer than the acute postoperative period. In population-based studies, 90-day, 1- and 2-year mortality are 19%, 23%, and 25%, respectively.[23]

Obstruction

Gastric outlet obstruction can occur acutely or chronically in patients with duodenal ulcer disease. Acute obstruction is caused by edema and inflammation associated with ulcers in the pyloric channel and the first portion of the duodenum. Pyloric obstruction is suggested by recurrent vomiting, dehydration, and hypochloremic alkalosis due to loss of gastric secretions. Acute gastric outlet obstruction is treated with nasogastric suction, rehydration, and intravenous administration of antisecretory agents. In most instances, acute obstruction resolves with such supportive measures within 72 hours.

Repeated episodes of ulceration and healing can lead to pyloric scarring and a fixed stenosis with chronic gastric outlet obstruction.

Upper endoscopy is indicated to confirm the nature of the obstruction and to exclude neoplasm. Endoscopic hydrostatic balloon dilatation of pyloric stenoses can also be attempted at this time (**Fig. 45.3**). Approximately 85% of pyloric stenoses are amenable to balloon dilatation. Only 40% of patients with gastric stenoses have sustained improvement by 3 months after balloon dilatation. Recurrent stenoses are presumably due to residual scarring in the pyloric channel. Thus, although pyloric dilatation is occasionally durable, in most cases operative correction is required.

Operative management of gastric outlet obstruction should be focused on relief of the anatomic abnormality. Antrectomy has been used with success in this circumstance, with low ulcer recurrence rates and with satisfactory restoration of gastric emptying.

GASTRIC ULCER

Benign gastric ulcers are a form of peptic ulcer disease, occurring with one-third the frequency of benign duodenal ulceration. In the United States, gastric ulcer is somewhat more common in men than in women and occurs in a patient cohort approximately 10 years older than for duodenal ulceration.

Endoscopic Diagnosis

Upper gastrointestinal endoscopy is the preferred method for diagnosing gastric ulceration. The ulcer base in benign disease is commonly smooth and flat and often covered by a gray, fibrous exudate. The margin is usually slightly raised, erythematous, and friable. Differentiation of benign and malignant gastric ulcers is reliably made only by histologic examination. Visual endoscopic differentiation of benign from malignant ulcers is not reliable. All gastric ulcers should have multiple biopsies taken from the perimeter of the lesion. The addition of lesional brushings to biopsy increases diagnostic accuracy to approximately 95%.

Benign gastric ulcers may occur in any location in the stomach, but approximately 60% are located along the lesser curvature proximal to the incisura angularis. Less than 10% of benign gastric ulcers are located on the greater curvature. Virtually all gastric ulcers lie within 2 cm of the histologic transition between fundic and antral mucosa. With increasing age, this mucosal transition zone moves proximally along the lesser curvature. Movement of this transition zone is reflected by the greater prevalence of proximal ulcers in elderly patients.

As with benign duodenal ulceration, *H. pylori* plays a central role in the pathogenesis of benign gastric ulcers.[24] Benign gastric ulcers associated with *H. pylori* respond to antibiotic therapy at a rate equivalent to that of duodenal ulceration. The recurrence rate of ulcerations in these patients after *H. pylori* eradication is equal to the rate of reinfection.

A strong association of benign gastric ulceration with the use of NSAIDs has been recognized. Cigarette smoking is associated with development of gastric ulceration, and continued smoking impedes medical therapy. Gastric and duodenal ulcers have been noted in patients receiving hepatic artery

chemotherapy in whom improper placement of the catheter permits perfusion of gastric and duodenal mucosae.

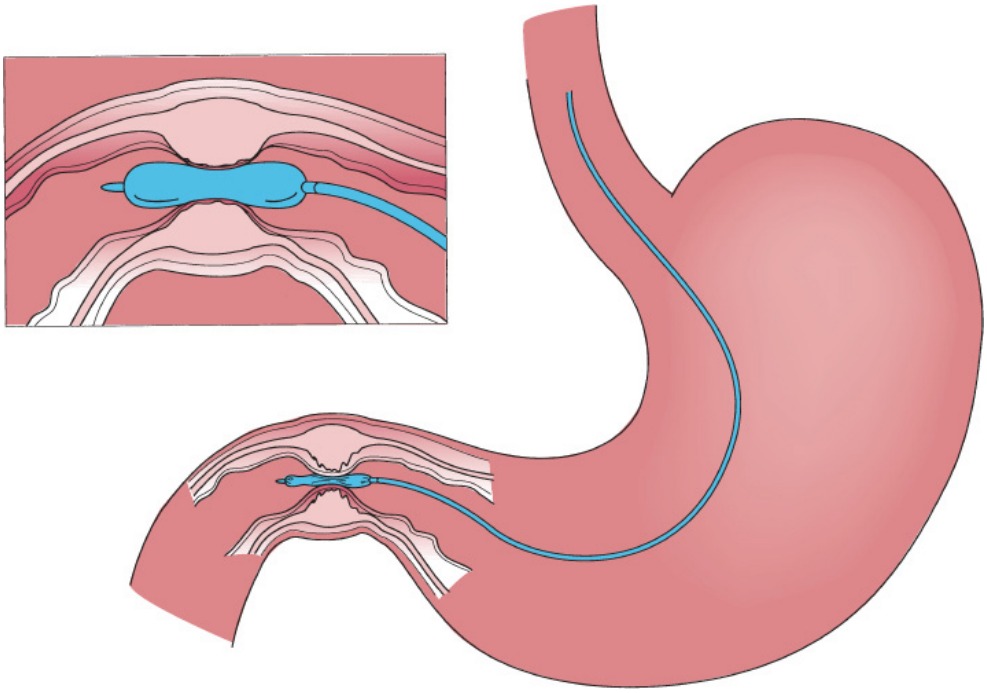


Figure 45.3 Schematic representation of balloon dilatation of pyloric stenosis.

Therapy

The primary therapy for benign gastric ulceration in most patients is antimicrobial treatment of *H. pylori* infection. The treatment protocols are similar to those used for benign duodenal ulceration. For many patients, cessation of NSAID therapy is also required.

Indications for surgical treatment of gastric ulcer include hemorrhage, perforation, failure of a recurrent ulcer to respond to medical therapy, and inability to exclude malignant disease.

For benign gastric ulcers, the elective operation of choice is usually a distal gastrectomy with gastroduodenal (Billroth I) anastomosis. The ulcer should be included in the gastrectomy specimen. With this approach, operative mortality rates of 2% to 3%, with ulcer recurrence rates of less than 5%, have been reported.

The occurrence of a gastric ulcer near the gastroesophageal junction represents a difficult surgical problem. When possible, the ulcer should be

excised. This usually requires a distal gastrectomy with an extension along the lesser curvature near the esophageal wall and reconstruction with gastrojejunostomy.

Emergency operations performed for hemorrhage or perforation require ulcer excision. Distal gastrectomy, performed with gastroduodenal reconstruction, is usually the procedure of choice. Operative mortality rates average 10% to 20% in the presence of hemorrhage or perforation.

STRESS GASTRITIS

7 Major trauma accompanied by shock, sepsis, respiratory failure, hemorrhage, or multiorgan injury is often accompanied by acute stress gastritis. Acute stress gastritis is particularly prevalent after thermal injury with greater than 35% total surface area burned.[25] Multiple superficial ulcerations and erosions are noted in the proximal, acid-secreting portion of the stomach, with fewer lesions in the antrum and only rare ulcerations in the duodenum.

The most sensitive diagnostic test for stress ulceration is endoscopic examination. If patients are examined within 12 hours of the onset of injury, acute mucosal ulcerations may be observed that appear as multiple, shallow areas of erythema and friability, often accompanied by focal hemorrhage. The lesions are progressive during the first 72 hours after injury. When lesions are examined histologically, they are seen to consist of coagulative necrosis of the superficial endothelium with infiltration of leukocytes into the lamina propria. Chronic disease, characterized by fibrosis and scarring, is not observed. With resolution of the underlying injury or sepsis, healing is accompanied by mucosal restitution and regeneration.

Clinical observations and a large number of experimental studies suggest that mucosal ischemia is the central event underlying the development of stress gastritis. In clinical practice, most patients who contract stress gastritis do so after an episode of sepsis, hemorrhage, or cardiac dysfunction accompanied by shock. Experimental studies that cause depletion of high-energy phosphate compounds such as ATP predispose to the development of stress gastritis. Luminal gastric acid secretion, although not the sole cause of stress gastritis, appears to be a necessary concomitant process. A number of

experimental observations suggest that a critical concentration of luminal acid is required to initiate injury in the setting of mucosal ischemia. The fall in mucosal energy supply permits proton back-diffusion into the mucosa; the resultant decrease in mucosal pH exacerbates ischemic damage.

Clinical risk factors that predict development of stress gastritis include adult respiratory distress syndrome, multiple long-bone fractures, a major burn over 35% of the body surface, transfusion requirement above 6 units, hepatic dysfunction, sepsis, hypotension, and oliguric renal failure. Scoring systems of critical illness, exemplified by the Acute Physiology and Chronic Health Evaluation (APACHE) system, accurately predict risk for acute stress gastritis.

The major complication of stress gastritis is hemorrhage. While admission to an intensive care unit is not an independent risk factor for bleeding, development of respiratory failure or coagulopathy (platelet count less than 50,000/mm^3, international normalized ratio [INR] >1.5, or partial thromboplastin time [PTT] greater than two times normal) imparts the greatest risk for hemorrhage.

Diagnosis

Clinical studies that use bloody nasogastric discharge as a sign of stress gastritis probably underestimate its incidence in critically ill patients. Conversely, studies based on endoscopy overestimate the incidence of clinically important stress gastritis. Severely burned patients have endoscopic evidence of gastric erosions in greater than 90% of cases, whereas significant upper gastrointestinal hemorrhage occurs in between 25% and 50% of patients with burn wound infection.

Treatment and Prophylaxis

Critically ill patients are at risk for development of acute stress gastritis. Because hemorrhage associated with stress gastritis significantly increases mortality, these patients should be treated prophylactically.[25–27] Proton pump inhibitors are effective at maintaining gastric pH above 4.0. Stress ulcer prophylaxis with these agents is associated with colonization of the upper GI tract with potentially pathogenic gram-negative organisms.

Early enteral feeding was first introduced as a component of burn care. Enteral feeding was designed to address the hypermetabolic state that develops after burn injury and to prevent visceral protein loss due to catabolic metabolism. Enteral nutrition has also been demonstrated to prevent bacterial translocation across the intestinal wall. In addition, enteral nutrition has been noted to maintain intragastric pH >3.5, suggesting that this modality may be used to prevent gastric hemorrhage from stress ulceration. In burn patients, early enteral feeding decreases upper GI hemorrhage, effects that are not potentiated by the addition of H_2-receptor antagonists.

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Management of Obesity

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Key Points

1. Obesity is chronic disease and is defined and categorized using body mass index (BMI, weight [kg]/height [m]^2) based on World Health Organization (WHO) definitions.
2. BMI directly correlates with the risk of multiple metabolic diseases and long-term mortality.
3. Lifestyle interventions as treatment for obesity, including diet, exercise, and psychological therapy, are of limited efficacy; evolving strategies directed toward environmental manipulation demonstrate potential.
4. Current pharmacotherapy for obesity includes a wide range of agents that act via multiple mechanisms, are prone to side effects, and are of limited efficacy; active research in pharmacotherapy for obesity holds significant promise.
5. Bariatric surgery is safe and highly efficacious in treating obesity and metabolic disease, and includes a wide range of procedures that have evolved over decades.
6. Current dominant bariatric surgery operations include gastric bypass and sleeve gastrectomy.
7. Classic mechanisms of action of bariatric surgery include restriction of caloric intake and malabsorption of ingested calories, but evolving data suggest that other mechanisms predominate, including but not limited to alterations in gut and satiety hormone homeostasis, bile acid metabolism, and enteroenteric and enterocentral nervous systemic communications.

DIAGNOSIS AND EPIDEMIOLOGY

Obesity and Metabolic Disease

Excess adipose tissue is the defining feature of obesity, and metabolic disease arises in adipose tissue. Metabolic disease is diverse, involving every organ system. The correlation between obesity and metabolic disease, while strong, is not perfect—some patients develop metabolic disease at low body weight, while others who are very obese are protected. Visceral adiposity imparts greater risk than subcutaneous adiposity, and heterogeneity of visceral and subcutaneous adiposities partly explains the imperfect correlation between obesity and metabolic disease. Lean patients also develop metabolic disease, albeit less frequently than the obese, demonstrating that non-adipose tissue–based mechanisms contribute to metabolic disease as well. It is beyond the scope of this chapter to discuss the wide spectrum of specific treatment strategies for individual metabolic diseases. Rather, we will discuss the treatment of obesity itself, the goal of which is reduction in adipose tissue mass, because despite the variable relationship between body weight and metabolic dysfunction, in the vast majority of patients, regardless of initial weight, weight loss has beneficial effects on virtually all metabolic diseases. Treatment options for obesity may be broadly divided into medical and surgical approaches.

Diagnosis

1 Body mass index (BMI, weight [kg]/height [m]^2) is the primary metric used to define obesity. Originally devised in the 19th century by the Belgian polymath Adolphe Quetelet as a general measure of human body habitus, BMI was co-opted in the 1940s by the insurance industry and used to stratify humans into high- and low-risk subpopulations based on actuarial data for the purpose of setting life insurance rates. The medical community subsequently used BMI to estimate risk of morbidity and mortality. Much debate exists regarding the appropriate BMI cutoff points for optimal health, with various health and professional organizations setting different values. World Health Organization (WHO) definitions, set in 1995 and agreed upon by the U.S. Centers for Disease Control (CDC), are most commonly utilized and define overweight as BMI >25 and <30 and obesity as BMI ≥30, and categorize obesity into classes 1 (BMI 30 to 34.9), 2 (BMI 35 to 39.9), and 3 (BMI ≥40).[1]

BMI correlates with long-term mortality and metabolic disease in a J-shaped curve, the nadir of which is debated, but may 2 be as low as 20 or as high as 25.[2] BMI in the obese range (≥30) is clearly associated with an increased risk for long-term mortality and multiple metabolic diseases relative to BMI <30. For individuals with BMI 40 to 50, this risk translates into a 10-year decrease in life expectancy. In contrast to obesity, data demonstrating a correlation between overweight BMI and health risk are conflicting. Analyses are complicated by numerous confounding variables including but not limited to sex, age, ethnicity, smoking, cancer, and diabetes. In addition, the choice of control/referent group alters outcomes; for example, the correlations between overweight BMI and clinical outcomes weaken significantly and may be masked when referent groups span a larger BMI range (e.g., 18 to 25) relative to comparison with referent groups spanning a narrow BMI range (e.g., 21 to 23). Despite these conflicting data, the preponderance of evidence suggests that BMI in the overweight range is associated with an increased risk of long-term mortality, albeit lower than the risk associated with BMI in the obese range.[3] Furthermore, mortality aside, compelling data demonstrate that overweight BMI is associated with an increased risk of cardiovascular disease, diabetes, and other metabolic diseases, and is associated with an increased risk of future progression to frank obesity with its attendant risks. Taken together, these observations suggest that overweight should be considered a serious health risk and a predecessor to obesity.

These complex data demonstrate that BMI is not a perfect measure of adiposity. Indeed, muscular athletes may have BMI within the obese range despite low body fat levels and an absence of metabolic disease, while elderly people with a paucity of muscle mass may have low BMI despite increased adiposity and metabolic disease. Ethnic differences further confound the predictive power of BMI, as certain ethnicities, for example, Asians develop metabolic disease at lower BMI, prompting the WHO in 2004 to propose BMI cutoffs of 23 and 27.5 for overweight and obesity, respectively in Asians. In certain subpopulations, including patients with heart failure, renal failure, and other chronic diseases, overweight and obesity are associated with decreased mortality, a phenomenon termed the "obesity paradox."[4]

These observations have led to a search for other measures of adiposity. Waist circumference and waist–hip ratio are easily measured and in many studies correlate more accurately with metabolic disease than BMI, reflecting the disproportionate effect of visceral adiposity on metabolic disease.[5] Water displacement, dual-energy x-ray absorptiometry scanning, double-labeled isotope water measurement, bioelectrical impedance analysis, and quantitative magnetic resonance imaging may provide more accurate measures of adiposity and better predict metabolic disease. More recently a novel CT imaging approach, analytic morphomics, has been used to quantify adipose tissue and risk stratify various patient populations as well as determine adequate drug therapy dosing.[6] However, such methods have not gained widespread acceptance due to cost and complexity. Despite its limitations, BMI remains the most commonly used metric for obesity.

Epidemiology, Disease Burden

Human obesity has existed for millennia as evidenced by prehistoric figurines of obese humans (e.g., Venus of Willendorf) and periodic concerns regarding past obesity "epidemics" over the past two centuries. Nonetheless, the worldwide prevalence of overweight and obesity has increased dramatically over the past 50 years. BMI, like many clinical characteristics, spans a bell curve. Three large U.S. epidemiologic datasets, the National Health and Nutrition Examination Survey (NHANES), the National Health Interview Survey (NHIS), and the Behavioral Risk Factor Surveillance System (BRFSS), demonstrate similar trends, with a rightward shift of the BMI bell curve over the past three decades, mean BMI increasing from 25.5 in the 1970s to 28.5 in 2005, and the prevalence of obesity more than doubling in the same interval.[7] The CDC reports that as of 2017–2018, 42% of U.S. adults were obese and 18.5% of U.S. children between 2 and 19 were obese.[8] To put this in context, the prevalence of obesity in adults increased 30.5% from 1999 to 2000. Sex, ethnic, and regional differences complicate obesity epidemiology. The

rate of increase is higher in women compared to men, and while rates of increase are similar across ethnicities, mean BMI is highest in Blacks, followed by Hispanics, then Caucasians. Data regarding the association between obesity and socioeconomic status are conflicting; evidence suggests an inverse correlation between low socioeconomic status and obesity in low- and middle-income countries but a positive correlation in industrialized countries. Obesity prevalence is increased in rural compared to urban environments in the United States, although this relationship is inverted in developing countries.[8]

The disease burden associated with obesity is substantial. Multiple confounders complicate quantification of risk, not the least of which is variability in the degree of obesity itself, with increasing BMI being associated with increasing risk of mortality and disease in a dose-dependent but nonlinear fashion. Obesity is associated with decreased lifespan. Data from the Framingham Heart Study demonstrate a loss of 3 and 6 years of life for overweight and obese men, respectively,[9] while NHANES data demonstrate a loss of 13 years of life for severely obese men (BMI >45).[10] Overweight and obesity are associated with an increased risk of multiple diseases, among which type II diabetes is particularly important. The association between obesity and diabetes is robust; relative risks for diabetes range from 2 to 15 for BMI in the overweight range and 20 to 90 for BMI in the obese range. The CDC estimates that in the United States in 2018, the prevalence of type II diabetes was 13% among all adults and 27% among those over 65 years of age. Furthermore, 35% of all U.S. adults, and 47% of U.S. adults over 65 years of age have elevated fasting blood glucose or HbA1c consistent with prediabetes. If current trends persist, the prevalence of diabetes in the United States in 2050 will exceed 30%, and worldwide trends parallel these U.S. data.[8]

Obesity is associated with an increased risk of multiple diseases, including atherosclerosis, hypertension, hyperlipidemia, hepatic steatosis and steatohepatitis, sleep apnea, osteoarthritis, gallbladder disease, endocrine disorders, autoimmune disease, allergy and atopy, multiple types of cancer, infertility and depression. Metabolic disease encompasses all of physiology. Risk ratios for overweight and obesity-related diseases vary substantially depending on BMI, ranging from 2 to 5 for class I obesity with dramatic dose-dependent increases in risk with increasing BMI. For example, the prevalence of hepatic steatosis in the general population is generally estimated to be approximately 30%, increases progressively with increasing BMI, and exceeds 90% in obese patients with BMI >40. In the NHANES population, the prevalence of sleep apnea was 3% in nonobese men and 12% in obese men (BMI >30),[11] but in a separate study of patients with severe obesity (BMI >40), prevalence exceeded 70%.[12] This disease burden is associated with significant economic costs. While accurate quantification of obesity-related healthcare costs is challenging and complicated by regional variability in payer systems and patient demographics, the estimated costs directly attributable to overweight and obesity in the United States exceed 100 billion dollars annually and constitute 5% to 10% of total U.S. healthcare spending.[13]

MEDICAL MANAGEMENT

Treatment Strategies

The medical management of obesity falls into two primary categories: lifestyle intervention and pharmacotherapy. Both strategies, with rare exceptions, achieve similar results, with modest weight loss and high recidivism. Nonetheless, both strategies hold significant untapped promise, with advances expected in coming decades, particularly in the areas of environmental engineering and pharmacotherapy.

Lifestyle Interventions

3 Lifestyle interventions for obesity include any or all of three basic components: diet modification, exercise, and psychological therapy. Interventions may be unsupervised or administered under the supervision of clinicians, dieticians, or commercial weight loss plans, and may be individualized or administered in group programs.

Diet modification is the mainstay of lifestyle intervention. Diet strategies vary with respect to macronutrient composition, daily caloric intake, and food and caloric measurement methods, and include low-carbohydrate diets, low-fat diets, meal replacement strategies, Mediterranean diets, very low–calorie diets, and multiple commercial diet plans. No clear evidence demonstrates advantages of any specific diet plan over others. Specifically, macronutrient composition does not impact on weight loss when caloric intake is controlled—total calories, rather than the macronutrient composition of those calories, is the variable that determines weight loss. In contrast to weight loss, conflicting evidence exists regarding the role of macronutrient composition in improvement of metabolic disease, with some evidence suggesting that low-carbohydrate diets (which include low-glycemic index–

high-fiber diets and very low-carbohydrate diets), when compared to low-fat diets, may be associated with greater improvements in insulin resistance and triglyceride levels, and higher resting energy expenditure. These studies must be interpreted with caution as follow-up is relatively short, and low-carbohydrate diets may be associated with adverse changes in low-density lipoprotein levels.[14] Low-carbohydrate diets also appear to provide better compliance than other diet strategies over short-term follow-up of less than 6 months, but compliance differences vanish at follow-up exceeding 1 year.

Physical activity is a central component of lifestyle intervention for obesity. Exercise alone achieves only modest weight loss, but exercise and diet potentiate each other. Importantly, exercise reduces obesity-related mortality and cardiovascular disease risk independent of weight loss. Data regarding the optimal type, duration, frequency, and intensity of exercise are conflicting and specific evidence-based guidelines remain elusive. High intensity exercise may be more effective for weight loss, but many obese patients are unable to engage in even moderate intensity exercise due to comorbid diseases such as osteoarthritis. Increased daily activities such as walking and stair use nonetheless may provide modest weight loss and cardiovascular health benefits.

Of the wide range of psychological techniques used to treat obesity, cognitive-behavioral therapy is most common. Cognitive-behavioral therapy achieves modest weight loss in the obese of approximately 2 to 3 kg at 1-year follow-up, with increased weight loss when combined with diet and/or exercise. Increased frequency of psychological intervention and group therapy compared with individual therapy are associated with greater weight loss.[15]

Intensive lifestyle interventions are supervised multicomponent plans that involve a combination of diet, exercise, and behavioral modification, with periodic monitoring by coaches and dieticians, and individual or group psychological counseling. Two NIH-sponsored randomized controlled trials suggest that intensive lifestyle interventions provide more durable results than standard lifestyle interventions, although long-term outcomes of metabolic disease are conflicting. The Diabetes Prevention Program randomized 3,234 overweight or obese insulin-resistant patients (mean BMI 34) to one of three experimental arms: intensive lifestyle interventions, metformin treatment, or placebo treatment.[16] After a mean follow-up of 2.8 years, average weight loss in the intensive lifestyle interventions group was 5.6 kg compared with 2.1 kg and 0.1 kg for the metformin and placebo groups, respectively; at 10 years an average weight loss of 2 kg was maintained in both intensive lifestyle interventions and metformin arms relative to the placebo arm. The cumulative risk of incident diabetes was 34% lower in the intensive lifestyle interventions arm and 18% lower in the metformin arm relative to the placebo arm. The NIH-sponsored Look AHEAD (Action for Health in Diabetes) study randomized 5,145 overweight or obese diabetic patients to a 4-year intensive lifestyle intervention involving diet and exercise modification with regular on-site visits and counseling, or standard primary care provider-supervised diabetes and weight loss education. After 8 years, mean weight loss was 4.7% and 2.1% in the intensive lifestyle intervention and standard care arms, respectively.[17] Nonetheless, the study was halted after 11 years after no difference in cardiovascular events was observed. These studies demonstrate that while modest, weight loss may be maintained over long periods with intensive lifestyle interventions, although the effects on metabolic disease are equivocal. Of importance, in Look AHEAD, a subset of patients in each arm (27% and 17% in intensive lifestyle intervention and standard care arms, respectively), maintained a loss of >10% of total starting weight, suggesting that subpopulations of patients are more responsive than others to lifestyle interventions, and that identification of predictors of responsiveness would permit better allocation of care.

Assessing the overall efficacy of lifestyle interventions for obesity is challenging, as results vary depending on the subgroup studied, follow-up is variable and often short, and program and outcome reporting methods are widely disparate. The resultant complex body of literature limits our current understanding of the efficacy of such interventions. Nonetheless, a preponderance of data suggests that results of lifestyle interventions for obesity are modest, with mean weight loss between 2% and 10% of total body weight over follow-up periods from 6 to 48 months. Unsupervised individual efforts underperform more intensive, multicomponent, supervised, group interventions. Compliance is a critical issue; individual diet programs are associated with attrition that may exceed 90% over a year or more while attrition for intensive supervised efforts is less. Weight regain after program discontinuation is common and long-term adherence to lifestyle changes is low. Despite these limitations, modest weight loss, or exercise in the absence of weight loss, appears to have measurable if modest beneficial effects on metabolic disease, with a subset of patients being responsive to such interventions. As such, lifestyle interventions should be a component of the treatment of all obese patients, but only rarely achieve dramatic and durable results.

Pharmacotherapy

4 The history of pharmacotherapy for obesity is replete with drugs that have been introduced with much enthusiasm and variable efficacy but subsequently withdrawn due to unacceptable and in many cases life-threatening side effects that became apparent only after widespread use. Sheep thyroid extract was used in the late 19th century, while in the early 20th century, workers in the dye industry exposed to 2,4-dinitrophenol were observed to lose weight, leading to its use as a weight loss drug in the 1930s. Amphetamines were popular weight loss drugs in the 1950–60s. All these agents were abandoned due to prohibitive side effects. The modest efficacy of weight loss drugs is testament to the multiple redundant physiologic systems that act to defend adipose tissue stores in the face of interventions designed to reduce those stores. The frequent adverse effects of weight loss drugs speak to the interface between body weight regulation and multiple fundamental physiologic processes, manipulation of which entails substantial risk.

The largest class of weight loss drugs targets monoamine signaling mediators (norepinephrine, serotonin, dopamine, histamine) involved in CNS/hypothalamic control of satiety and hunger. Many of these agents regulate multiple pathways and demonstrate overlapping activities. Sympathomimetic agents that primarily potentiate norepinephrine release include phentermine, introduced in 1959 and still in use today, and phenylpropanolamine, used as a decongestant and also as a weight loss drug since the 1970s, but withdrawn from the market in 2000 after being associated with an increased risk of stroke. Drugs that primarily potentiate serotonin activity include fenfluramine, introduced in 1973 and withdrawn from the market in 1997, sibutramine (Meridia), a serotonin, norepinephrine, and dopamine reuptake inhibitor with primary effects on serotonin and norepinephrine, introduced in 1997 but withdrawn in 2010 after being linked to increased risks of myocardial infarction and stroke, and lorcaserin (Belviq), a selective serotonin 2C agonist approved by the FDA in 2012, but withdrawn from the market in 2020 after being linked to a possible increased risk of cancer. Drugs that target dopamine signaling are currently being studied in clinical trials (e.g., bupropion, tesofensine). Targeting multiple monoamine signaling pathways provides synergy. The combination drug fenfluramine/phentermine ("Fen-phen"), introduced in 1992, demonstrated increased efficacy over either agent alone, but was withdrawn from the market in 1997 after widespread use revealed serious morbidity attributable to fenfluramine, including pulmonary hypertension and cardiac valvular disease. In 2013, the FDA approved a combination drug of phentermine and topiramate, an antiepileptic with multiple CNS activities (Qsymia). A combination formulation of bupropion and naltrexone, an opioid antagonist which stimulates pro-opiomelanocortin neurons, is currently being studied in research trials.

Gut peptides have diverse metabolic functions including regulating satiety and hunger within the hypothalamic feeding center, and include glucagon-like peptide 1 (GLP-1), cholecystokinin, ghrelin, oxyntomodulin, pancreatic polypeptide, and amylin. Drugs based on these mediators show promise. Many gut peptides have short biologic half-lives and research has focused on long-acting analogs or mediators that target degradation pathways. GLP-1, secreted by ileal L cells in response to a meal, induces satiety and potentiates insulin secretion and peripheral insulin sensitivity. Long-acting GLP-1 analogs, including liraglutide (Victoza) and exenatide (Byetta), are FDA approved for treatment of type 2 diabetes and are under investigation as primary weight loss agents.[18] Ghrelin is an orexigenic hormone secreted by gastric fundus mucosal cells, and ghrelin antagonists, agonists of ghrelin degradation pathways, and antighrelin vaccines are in development. Amylin, released by pancreatic beta cells, induces satiety via CNS-based mechanisms and also potentiates peripheral insulin resistance; pramlintide (Symlin), a human amylin agonist, is approved for treatment of diabetes and induces modest weight loss. Orlistat (Xenical), approved by FDA in 1999, is a pancreatic lipase inhibitor that blocks intestinal absorption of fat, and the only drug to date that functions by reducing absorption of ingested calories. Side effects of orlistat include diarrhea, steatorrhea, and increased risks of kidney stones and pancreatitis. Second-generation lipase inhibitors are in development.

Agents designed to manipulate neuropeptide signaling within the hypothalamus, while not yet approved for use in humans, are important targets, and include drugs directed toward leptin, melanocortin-4 receptor (MC4R), neuropeptide Y, and melanin-concentrating hormone. While leptin resistance has confounded development of leptin as a therapeutic agent, recent data from animal models suggest that concomitant treatment of endoplasmic reticulum stress may abrogate leptin resistance,[19] while separate research demonstrates that amylin agonists also restore leptin sensitivity.[20] These lines of research have reinvigorated interest in leptin therapy. Mutations in the MC4R gene, a central hypothalamic satiety mediator, are implicated in up to 5% of cases of common human obesity, and MC4R agonists are currently in development. Other central-acting agents are directed toward endocannabinoid signaling: rimonabant (Acomplia), a selective endocannabinoid antagonist, was denied FDA approval in 2008 despite promising weight loss results in clinical trials due to an association with depression and suicide, but interest in manipulation of endocannabinoid signaling persists.

Manipulation of thermogenesis and metabolic rate remains an active field of research. Thyroid hormone achieves weight loss by increasing metabolic rate, but is associated with cardiac toxicity and has detrimental effects on glucose homeostasis. Despite these failures, research persists. Many agents discussed above that regulate food intake, most notably the sympathomimetics, also increase metabolic rate, and it is unclear to what extent these effects contribute to weight loss. Agents that regulate steroid metabolism, fatty acid oxidation and other aspects of adipose tissue, and skeletal muscle metabolism are under study. Dietary constituents also regulate thermogenesis, including methylxanthines (e.g., caffeine), polyphenols (e.g., resveratrol, quercetin), capsaicinoids (found in chili peppers and mustards), and medium-chain fatty acids, all of which represent potential therapeutic agents.

Overall efficacy of current obesity pharmacotherapy is modest, achieving weight loss of 3% to 10% of total body weight. Most agents demonstrate synergy with lifestyle interventions. Current drugs approved by the FDA specifically for weight loss include orlistat, the only drug approved for long-term use; phentermine, approved for short-term use (<12 weeks) due to addiction potential and cardiovascular toxicity; phentermine/topiramate, and liraglutide, a GLP-1 agonist. The XENDOS study (XENical in the Prevention of Diabetes in Obese Subjects) randomized 3,305 patients to lifestyle intervention combined with either orlistat or placebo and at 4 years, and demonstrated a 5.8-kg weight loss in the orlistat arm compared with a 3.0-kg weight loss in the placebo arm, as well as a reduced incidence of diabetes with orlistat therapy.[21] Lorcaserin-induced 5% weight loss compared with 3% in placebo-treated patients at 1 year.[22] The phentermine/topiramate combination drug achieved 10.5% weight loss compared with 1.8% in placebo-treated patients at 2-year follow-up.[23]

A complete summary of obesity pharmacotherapy is beyond the scope of this chapter, which has by necessity omitted important areas of research, including drugs that target steroid metabolism, lipid metabolism, adipocyte differentiation and proliferation, and efforts to shift white adipose tissue toward a brown adipose tissue phenotype (the "browning" of adipose tissue). This discussion has focused on agents designed to treat obesity directly with the goal of weight loss, but an important parallel class of drugs target metabolic disease independent of or in conjunction with weight loss. The activities of weight loss drugs are complex and overlapping, with many agents regulating body weight and metabolism via multiple mechanisms. Multiple redundancies in the regulation of energy homeostasis suggest that drug combinations will enhance efficacy. As an understanding of these mechanisms increases, safe and effective pharmacotherapy for obesity and metabolic disease will emerge.

SURGICAL MANAGEMENT

Bariatric Surgery—Beginnings

5 In contrast to lifestyle interventions and pharmacotherapy, surgical management of obesity is highly efficacious. Modern bariatric surgery (Gr. *baros,* heavy, burden) is the result of over a half century of evolution in surgical technique that has its genesis in the 1940–50s with experiments in animals and isolated operations in humans that employed small intestinal resection and jejunocolic and ileocolic bypasses of various anatomic configurations. These operations involved substantial morbidity and did not achieve widespread acceptance, but set the stage for development of the *jejunoileal bypass,* the first bariatric operation to be widely applied in humans. Jejunoileal bypass involved division of the jejunum 14 in distal to the ligament of Treitz and creation of a jejunoileostomy 4 in proximal to the ileocecal valve, and was thus referred to as a "14–4 bypass." In 1969, Payne and DeWind[24] published the first report describing long-term clinical outcomes in a large group of patients who underwent jejunoileal bypass in the 1950–60s, describing dramatic weight loss ("A total of 10,373 pounds have been lost by the [80] patients") along with improvements in insulin resistance, hypercholesterolemia, and hepatic steatosis. Jejunoileal bypass was widely used throughout the 1960s and early 1970s.

Despite its efficacy, as experience accumulated, it became clear that jejunoileal bypass was associated with significant morbidity. Diarrhea, steatorrhea, dehydration, electrolyte imbalances, and micro- and macronutrient deficiencies resulted from the highly malabsorptive nature of the operation. Patients also suffered a host of complications not obviously linked to malabsorption, including liver disease, nephropathy, arthropathy, neuropathy, and myopathy. While the cause of these latter complications was not completely clear, an immune response directed toward bacterial overgrowth in the blind intestinal limb was implicated. Overall morbidity afflicted as many as 70% of patients and led to abandonment of jejunoileal bypass by the late 1970s. Nonetheless, up to 30% of patients achieved good results, and the clinician may still encounter rare remaining patients. Indications for reversal or conversion to modern bariatric operations are not well established and must be considered on an individual basis,

but include progressive liver or kidney disease not attributable to other causes. Some clinicians advocate reversal and conversion to a modern bariatric operation in all patients who are good operative candidates regardless of the presence or absence of complications.

Gastric Bypass

With the decline of jejunoileal bypass, surgeons began searching for alternatives. In the 1960s, Edward Mason at the University of Iowa experimented with operations based on observations that patients who underwent gastric resections for ulcer disease had difficulty maintaining their weight. Mason's efforts led to the development of the *gastric bypass,* for which he earned the title "father of bariatric surgery." Mason's original gastric bypass consisted of a pouch gastroplasty with a loop gastrojejunostomy reconstruction. Gastric bypass subsequently evolved through a number of iterations, all with important clinical implications. Large horizontal fundal-based pouches were replaced with smaller vertical lesser curve–based pouches, which improve gastric emptying. Undivided gastric pouches were associated with high rates of staple-line dehiscence and gastrogastric fistula, and were replaced with divided gastric bypass, expedited by the development of cutting staplers. Roux-en-Y reconstruction, compared to loop reconstruction, reduces tension on the gastrojejunal anastomosis and prevents bile reflux gastritis, but may be associated with higher rates of anastomotic ulcer disease. Retrocolic Roux limbs may improve pouch emptying and generate less tension on the gastrojejunostomy, but at the price of higher rates of mesocolic internal hernias. Banding of the gastrojejunal anastomosis may increase weight loss, but also increases risks of stenosis, obstruction, and erosion. Variations persist, including retrocolic Roux limbs, loop reconstructions ("minigastric bypass"), and prosthetic-banded gastric pouches. The modern gastric bypass practiced by the majority of surgeons today consists of a divided, unbanded, lesser curve-based pouch gastroplasty of 15 to 30 cc with an antecolic Roux-en-Y gastrojejunal reconstruction with a 100- to 150-cm Roux/alimentary limb and a 50- to 100-cm afferent/biliopancreatic limb (**Fig. 46.1**). The modern gastric bypass is a robust operation because within limits, subtle variations in technique, including pouch size and morphology and intestinal limb length and position, do not greatly affect efficacy or morbidity. Gastric bypass remains, as of this writing, the dominant bariatric operation worldwide and the gold standard against which all other operations are measured.

Malabsorption Revisited

Despite the failure of jejunoileal bypass, interest in operations that relied on small intestine bypass persisted. *Biliopancreatic diversion* consists of an antrectomy with a gastrojejunostomy and distal Roux-en-Y jejunoileostomy. The *duodenal switch modification of the biliopancreatic diversion* involves a sleeve gastrectomy, division of the duodenum distal to the pylorus, and a duodenojejunostomy and distal Roux-en-Y jejunoileostomy, thus maintaining the pylorus in the alimentary stream (**Fig. 46.2**). Biliopancreatic diversion/duodenal switch differs from jejunoileal bypass in two important regards. First, maintenance of forward flow of biliopancreatic effluent in the bypassed afferent limb prevents stasis and bacterial overgrowth. Second, common channel length was increased to 100 cm, reducing malabsorptive complications. Biliopancreatic diversion/duodenal switch provides weight loss and metabolic disease remission equivalent to, and in many series, greater than gastric bypass. Morbidity and mortality for biliopancreatic diversion/duodenal switch span a wide range, with centers with significant expertise reporting low rates similar to gastric bypass. Nonetheless, when the literature as a whole is considered, biliopancreatic diversion/duodenal switch is associated with higher morbidity and mortality than gastric bypass. Perioperative mortality reported by meta-analyses is at least twofold higher than gastric bypass, possibly due to a higher risk of anastomotic dehiscence, as laparoscopic creation of the duodenojejunal anastomosis associated with the duodenal switch modification is technically challenging.[25] Late malabsorptive complications which may require surgical revision, while much improved over jejunoileal bypass, range from 2% to 20%. Unlike gastric bypass, in which small changes in pouch size or limb length do not substantially alter clinical outcome, outcomes of biliopancreatic diversion/duodenal switch are relatively sensitive to differences in efferent limb length, small changes in which may make the difference between poor weight loss and malabsorptive complications. Predicting the correct efferent limb length for an individual patient is challenging. Most surgeons advocate a fixed length of 100 cm, while others advocate an ad hoc limb length proportional to total small intestine length. While advocated by select surgeons and associated with good outcomes in centers with significant experience, biliopancreatic diversion/duodenal switch is nonetheless waning in use, currently comprising less than 2% of bariatric operations. This is often reserved as a revisional option for those with insufficient weight loss following sleeve gastrectomy.

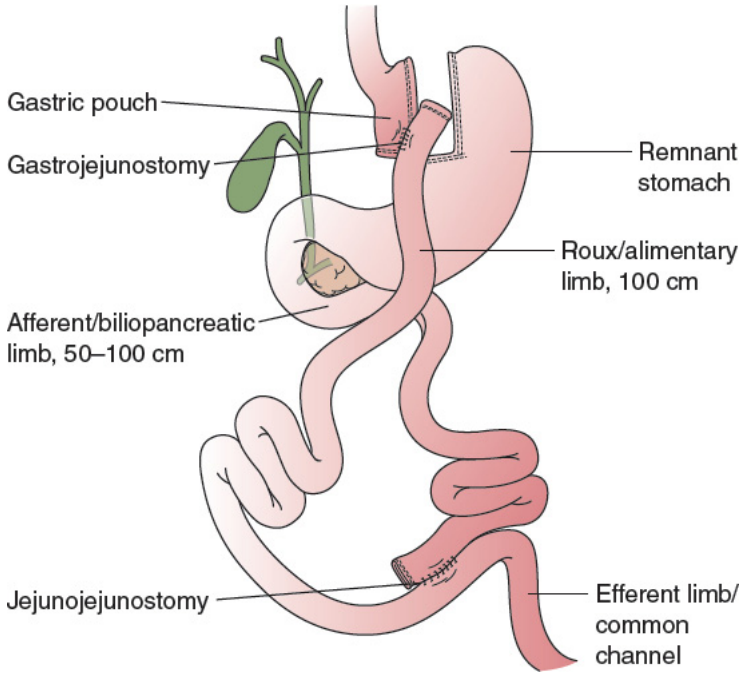


Figure 46.1 Anatomy of modern Roux-en-Y gastric bypass. Modern gastric bypass consists of a divided pouch gastroplasty with Roux-en-Y jejunojejunal reconstruction. The Roux limb is most commonly placed in the antecolic position. Intestinal limbs are termed with either standard Roux (Roux, afferent, efferent) or bariatric (alimentary, biliopancreatic, common channel) nomenclature as shown.

Pure Restriction

In Mason's era, morbidity from gastric bypass was not trivial. In an effort to design a simpler and safer operation, Mason experimented with gastroplasties that precluded the need for small intestinal reconstruction. Like gastric bypass, these operations evolved through a number of iterations, eventually leading to the modern *vertical banded gastroplasty,* which involves creation of a partitioned upper stomach pouch with a prosthetic band restricting pouch outlet diameter. Vertical banded gastroplasty achieved widespread acceptance and peaked in the 1970–80s. Vertical banded gastroplasty weight loss is substantially less and late weight regain substantially greater compared to gastric bypass, however, and vertical banded gastroplasty has therefore been relegated to a minority operation that is rapidly being eliminated from use.

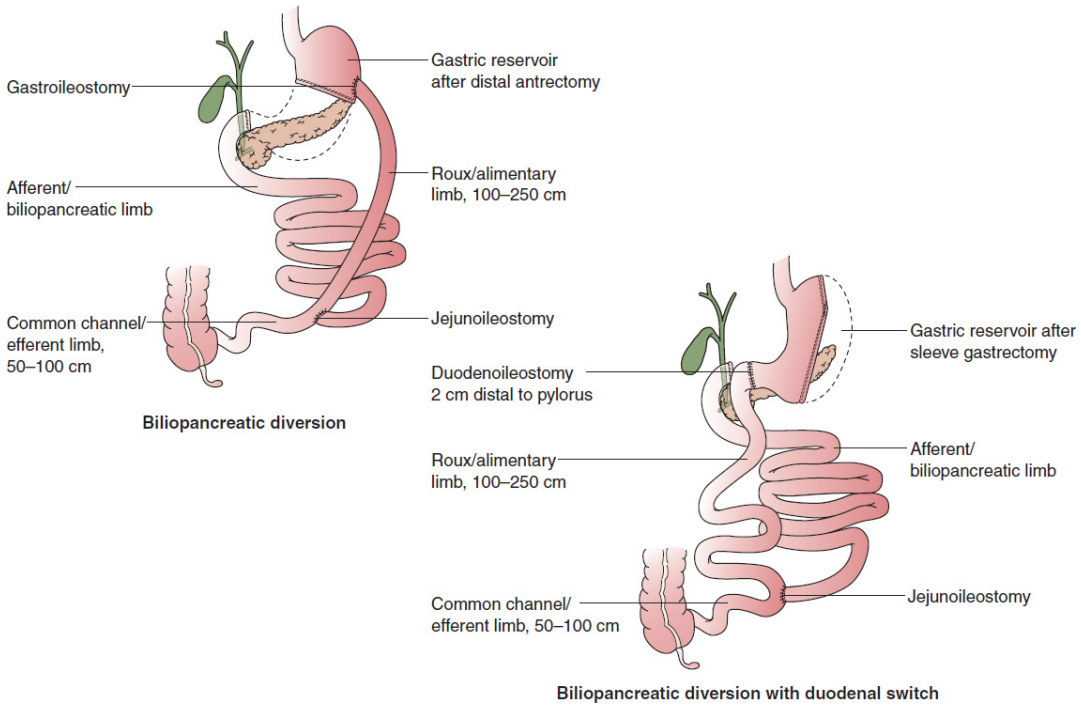


Figure 46.2 Biliopancreatic diversion (BPD). BPD involves a distal antrectomy with a Roux-en-Y jejunoileal reconstruction; BPD+DS involves a sleeve gastrectomy with a Roux-en-Y duodenoileal reconstruction, with the duodenoileostomy created 2 cm distal to the pylorus, thus preserving the pyloric emptying mechanism. Note that, unlike JIBP, the afferent/biliopancreatic jejunoileal limb is in continuity with biliopancreatic effluent, reducing limb stasis.

Study of prosthetic bands applied to the upper stomach to limit food intake began in the late 1970s using devices made from Prolene, Marlex, and other materials. These devices were nonadjustable and plagued with complications related to erosion, migration, stenosis, and obstruction. Efforts persisted, eventually culminating in the modern *adjustable gastric band,* a silicone device that was FDA approved in the United States in 2001 (**Fig. 46.3**). A primary advantage of gastric band is its technical simplicity and low rates of major morbidity and mortality. Unlike gastric bypass, which continues to be associated with low but finite rates of anastomotic dehiscence and mortality, gastric band is associated with 5 to 10 lower rates of life-threatening complications and mortality. Much enthusiasm accompanied the introduction of gastric band in the late 1990s, but over the past decade, enthusiasm has waned for two reasons. First, therapeutic efficacy of gastric band in the majority of patients is substantially less than gastric bypass. Second, as years passed, late complication rates have increased. These complications, including band slippage, erosion, and esophageal dilation and development of gastroesophageal reflux disease (GERD), are usually not life-threatening, but range between 10% and 50% and often lead to band removal.[26] Despite these problems, gastric band efficacy, while not as high as gastric bypass, is acceptable. Gastric band remains the bariatric operation with the lowest major morbidity and mortality rates, an appealing quality for risk-averse patients. Gastric band does not require Roux-en-Y reconstruction, an advantage in patients with complex abdominal surgical histories. However, given the known late term complications and availability of sleeve gastrectomy, gastric bands have fallen out of favor and as of 2018 comprise only 1.1% of bariatric operations.[27]

Sleeve gastrectomy was introduced initially as a component of the duodenal switch modification of biliopancreatic diversion, but did not gain significant attention as a stand-alone bariatric operation until the early 2000s. Sleeve gastrectomy involves a lateral gastrectomy, leaving a narrow "sleeve" of stomach 32 to 40 Fr in diameter (**Fig. 46.4**). Originally proposed as the first step in a staged approach for high BMI patients prior to definitive gastric bypass, early follow-up data demonstrated excellent results, and long-term efficacy appears similar to gastric bypass. Sleeve gastrectomy is associated with perioperative complication rates similar to gastric bypass, but late complications are rare, in part due to elimination of morbidity associated with alterations in small intestinal anatomy. For these reasons, sleeve gastrectomy has engendered significant enthusiasm and is now the most commonly performed primary bariatric procedure.[27]

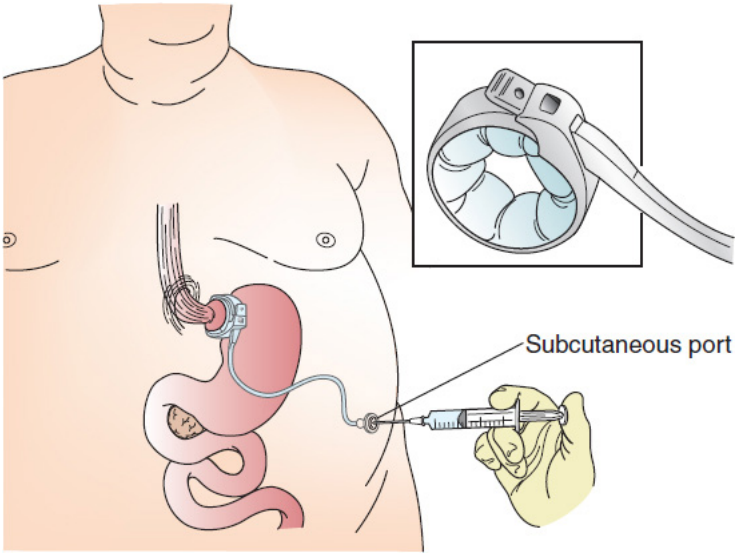


Figure 46.3 Gastric band. A silicone adjustable band is positioned around the upper stomach, creating a gastric pouch. A port attached to the band via silicone tubing is placed in the subcutaneous tissue in the abdominal wall, permitting percutaneous access and adjustment of band diameter.

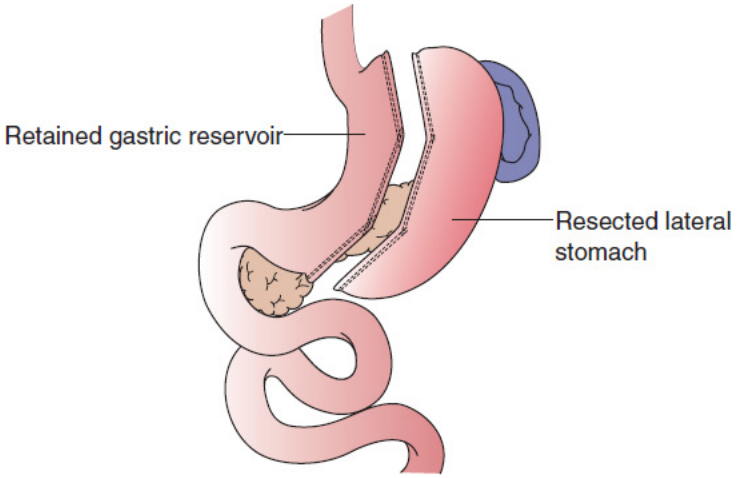


Figure 46.4 Sleeve gastrectomy. A lateral gastrectomy is performed with a linear cutting stapler, creating narrow gastric reservoir 32 to 40 Fr in diameter.

Endoscopic bariatric procedures have recently emerged as attractive interventions for weight management as they are low risk, reversible and potentially applicable to the population who are not candidates for bariatric surgery. In recent years, the Food and Drug Administration has approved several devices with gastric balloon systems the most widely adopted. Gastric balloon systems are intended as restrictive devices that take up space in the stomach. Results vary; however, randomized control trials demonstrate improved excess and total body weight loss (TWL) as compared to sham or diet and exercise alone. This weight loss, however, is much lower than with a bariatric operative procedure. Weight loss at 9 months is reported at up to 26% *excess weight lost* (EWL) and 8.8%TWL.[28] Enthusiasm for these devices has also been dampened due to questions on long-term sustainability of weight loss and emerging safety concerns. The endoscopic sleeve gastrectomy is another novel procedure where an endoscopic suturing device is used to place stitches on the inside of the stomach to reduce its size. Early data demonstrate this procedure as safe and effective, with weight loss outcomes up to 18% EWL. While promising, these procedures should be used in select patients and should not be used in lieu of bariatric surgical procedures where indicated.[29]

Epidemiology of Modern Bariatric Surgery

As of 2017, approximately 228,000 bariatric procedures were performed per year in the United States. Currently, sleeve gastrectomy accounts for the vast majority of primary bariatric procedures at 60%. Gastric bypass accounts for 18% of all procedures and the gastric band and duodenal switch each account for less than 3%. Revisions of bariatric procedures either for complication or weight recidivism have dramatically increased in recent time. In the last 3 years, approximately 14% all bariatric procedures were revisions.[27] The characteristics of the patient population undergoing bariatric surgery have also changed over the past two decades. Nationally representative data show that the mean age increased from 38.9 years in 1993 to 44.4 years in 2016 ($p < 0.001$).[3] Additionally, the proportion of male patients (15.3% to 20.4%), patients who self-identified as Black (11.6% to 17.7%) or Hispanic (1.4% to 13.7%), and those with Medicaid (8.1% to 17.2%) or Medicare insurance (5% to 14.2%) increased significantly. Low socioeconomic status is a documented risk factor for reduced access to bariatric surgery, although recent expansion of Medicaid has attenuated this problem in the United States. Rates of bariatric procedures are also increasing in adolescents, although the total number remains small at approximately 220 cases in 2016.[27,30–32]

While robust data support bariatric and metabolic surgery as the most-effective long-term treatment for severe obesity and associated metabolic conditions, fewer than 1% of eligible persons undergo surgery. Clinician and patient concerns persist about the safety and durability of these operations, and some continue to question whether the short- and long-term risks outweigh the benefits. Many of these concerns stem from a checkered history of poor patient outcomes, unacceptable mortality rates, and poor long-term outcomes when the procedure started gaining traction in the 1990s. With the introduction of laparoscopy, attention to technique and education, options for less morbid procedures such as the adjustable gastric band, and accreditation programs requiring outcome reporting to a national registry and multidisciplinary team review, bariatric surgery is now among the safest operations performed.

Eligibility

In 1991 National Institutes of Health (NIH) guidelines recommended that the surgical treatment for obesity should be reserved for persons with a BMI ≥ 40 kg/m^2 or ≥35 kg/m^2 with serious obesity-related co-morbid condition.[27] These guidelines are still widely used by insurers to determine eligibility for surgery; however, there is growing evidence that bariatric procedures should also be considered for patients with lower BMI (30.0 to 34.9 kg/m^2) and type II diabetes if hyperglycemia is inadequately controlled despite optimal medical treatment.[33] Recent guidelines also recommend the need for separate cut-off limits for Asian populations, and recommend consideration of surgery for BMI ≥35 kg/m^2 regardless of the existence of comorbidities and BMI ≥35 kg/m^2 with the existence of a comorbid condition.[34] All persons who meet the BMI threshold should be further evaluated with a thorough history and physical to mitigate and optimize comorbid conditions, nutritional and psychological evaluation. Patients may be contraindicated for bariatric surgery if they have severe heart failure, unstable coronary artery disease, end-stage lung disease, active or recent history of cancer, cirrhosis with portal hypertension, uncontrolled drug or alcohol dependency, unstable psychiatric disorders, Crohn disease, severely impaired intellectual capacity, or if they are pregnant or planning to become pregnant within the next 1 to 2 years.[35]

Efficacy

Bariatric surgery achieves dramatic results. Weight loss was commonly reported as a percentage of EWL, defined as the difference between presurgical weight and ideal weight, with ideal weight calculated for BMI = 25 for height. Of note, there has been a recent effort to standardize weight loss reporting as percent TWL, total pounds lost divided but initial weight, to align with the medical literature, as TWL is less dependent than EWL on initial BMI.[36] Weight loss typically peaks 1 to 2 years after surgery and may approach 70% to 90% EWL, followed by partial weight regain at 3 to 10 years after surgery, leading to a plateau at 50% to 70% EWL at long-term follow-up.[36–66] The mechanisms underlying this weight loss pattern are unknown but may involve development of adaptive eating patterns that increase caloric intake over time. For gastric band, weight loss is typically slower and more gradual, with a plateau after 2 to 3 years. These varying patterns of weight loss complicate comparison of results of different operations and analysis of published data due to variable length of follow-up among studies. Analysis is further complicated by significant attrition of patients over long-term follow-up in most studies. Despite these challenges, meta-analyses, controlled trials, and uncontrolled case series provide estimates of the efficacy of bariatric operations (**Table 46.1**). Weight loss is highest for biliopancreatic diversion/duodenal switch, ranging from 55% to 75% EWL, followed by gastric bypass and sleeve gastrectomy (50% to 70% EWL) and gastric band (40% to 60% EWL).[36–38]

Table 46.1 Bariatric Surgery Long-Term Weight Loss Responses. Short-Term Comparative Outcomes at 2 Years

	RYGB	SG	BPD/DS
Weight Loss			
% EBWL	61.4–79.8 (21,22,32, 34,115)	60.8–77.8 (32,34,115)	65.1–69.4 (21,25)
% EBMIL	74.7–84.8 (3,19–22,33)	72.1–74.7 (11,33)	76.1–85.0 (16,21,25)
% TBWL	21.0–37.4 (19–22)	23.4–34.1 (23,24)	33.8–36.7 (21,25)
Comorbidities			
Diabetes remission; %	66.7–75.0 (21,69,70)	35.0–41.0 (70,71)	95.0–100 (21,69)
Hypertension remission; %	53.0–65.4 (75)	54.0–72.0 (36,37)	49.3–76.0 (37,76)
Dyslipidemia remission; %	52.0–57.0 (75,77)	60.0–65.2 (36,82)	70.0–92.1 (76,77)
GERD remission; %	61.0 (77)	77.4 (36)	48.0 (77)
OSA remission; %	29.0–100.0 (19,28,33, 35–39)	56.2–100.0 (19,28,33, 35–39)	80.0–100.0 (19,28,33, 35–39)

RYGB indicates Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BPD/DS, biliopancreatic diversion with/without duodenal switch; % EBWL, percent excess body weight loss; % EBMIL, percent excess body mass index loss; % TBWL, percent total body weight loss; GERD, gastroesophageal reflux disease; OSA, obstructive sleep apnea.

Rates of improvement and remission of metabolic diseases parallel weight loss, with gastric bypass, sleeve gastrectomy, and biliopancreatic diversion/duodenal switch associated with higher remission rates than gastric band. Diabetes, steatosis, sleep apnea, hypertension, and hyperlipidemia improvement/remission rates range from 60% to over 90% (**Table 46.1**). Weight loss is durable, lasting decades in most patients, and accompanied by marked reductions in long-term incident diabetes, cardiovascular disease, and cancer, increased quality of life, reduced long-term healthcare costs, and a 25% to 40% reduction in long-term mortality. Currently 12 randomized controlled trials have been published and demonstrate that bariatric surgery is substantially more efficacious than medical therapy for weight loss and diabetes, and multiple medical societies, including the American Diabetes Association, the International Diabetes Federation, and the American Heart Association, endorse bariatric surgery as treatment for metabolic disease.[36–66]

Despite its efficacy, results of bariatric surgery are variable, with a substantial minority of patients achieving significantly better than average weight loss and disease response rates, while a similar minority experience suboptimal results. Anywhere from 10% to 30% of patients achieve <50% EWL, which may be due to insufficient initial weight loss, or weight regain after a period of adequate weight loss. Mechanisms underlying insufficient weight loss are poorly defined, and identification of accurate predictors of response to surgery is an important area of research.[43] While suboptimal results are often attributed to lack of patient compliance with postoperative diet and exercise, these arguments ring false, echoing similar arguments that attribute obesity itself to a lack of "willpower." Instead, compeling evidence implicates genetic and epigenetic mechanisms. Like obesity itself, responses to bariatric surgery are highly hereditable. Ethnicity is a predictor of outcome, with Caucasians and Hispanics experiencing greater weight loss than Blacks and Asians. Multiple single-nucleotide polymorphisms have been

linked to surgical outcome. Future research will identify clinical and genetic predictors of response and permit optimization of allocation of surgical resources (**Table 46.2**).[36–66]

Perioperative Mortality and Morbidity

Morbidity and mortality associated with bariatric surgery have decreased over the past two decades as surgeon experience increased 6 and techniques evolved. Currently, gastric bypass and sleeve gastrectomy are associated with mortality risks similar to hip replacement, Perioperative mortality is high-est for biliopancreatic diversion/duodenal switch, followed by gastric bypass and sleeve gastrectomy, then gastric band (**Table 46.3**).[67–76] Life-threatening perioperative morbidity associated with gastric bypass and sleeve gastrectomy consists primarily of anastomotic dehiscence, staple-line leaks, hemorrhage, thromboembolic events, and cardiac events. Life-threatening perioperative morbidity associated with gastric band is rare and consists primarily of gastric perforation, thromboembolic events, and cardiac events.

The most dire perioperative complication of gastric bypass is anastomotic dehiscence of the gastrojejunostomy which usually occurs within 2 weeks of surgery. Incidences in most series range from 0.1% to 4%, although recent data suggest that anastomotic dehiscence rates are decreasing and high-volume centers report rates in the range of 0.1% to 0.2%. Signs and symptoms are similar to those of anastomotic dehiscence after any intestinal operation, but may be less apparent in the obese. Persistent tachycardia and abdominal pain are important but nonspecific sentinel signs. Upper GI radiographs may be of diagnostic utility but lack sensitivity. Abdominal CT scan, even within a few days of surgery, may be useful, as the lack of a fluid collection near the gastrojejunostomy has a high negative predictive value for leak, while contrast extravasation has a high positive predictive value. Nonetheless, data are conflicting regarding the sensitivity and specificity of radiologic studies for diagnosing anastomotic dehiscence, and laparoscopic reexploration should be employed aggressively in suspected cases. Operative management consists of washout, wide drainage, judicious attempt at repair, and consideration of distal enteral access, usually with a gastrostomy tube in the remnant stomach, although a jejunostomy tube in the distal Roux limb or biliary limb is an option if access to the remnant stomach is difficult. Anastomotic dehiscence can be managed laparoscopically in some cases, reducing the high risk of ventral hernia associated with laparotomy. Most will heal if sepsis is controlled. Endoscopic management of anastomotic dehiscence with suture, over-the-scope clipping systems, and endoscopic esophageal stent placement may also be employed for appropriate patients by advanced endoscopists with the appropriate skill set and training.

Staple-line leaks are an equally dire event after sleeve gastrectomy, occurring anywhere from 1 to 2 weeks to many months after surgery. Leaks may occur at any point along the staple line, but when involving the thicker tissue of the antrum may be less prone to heal, and interval conversion to gastric bypass with resection of the involved portion of gastric sleeve may be necessary. Depending on the acuity and location of the leak and the clinical status of the patient, a wide variety of options may be used to manage sleeve leaks. Options range from nasogastric tube feeding and antibiotics with or without external drainage, to endoscopic interventions such as those mentioned above as well as internal drainage with a pigtail catheter, to operative intervention with wide drainage and potential conversion to RYGB. For chronic leaks that have matured and contain a fibrous septum, endoscopic septotomy has demonstrated reasonable success for definitive treatment. Proper stapler selection and use during primary operation with avoidance of overly narrow sleeves (current consensus recommends 32- to 40-Fr diameter) may reduce the risk of sleeve gastrectomy staple-line leaks, which currently occur with an incidence of approximately 1% to 3%. Gastric band is only rarely associated with perioperative septic complications, most often in the form of gastric perforation, which occurs in 0% to 0.5% of cases. Perforation, if not recognized, may be life-threatening and is a primary cause of rare perioperative mortality and major morbidity after gastric band.

Table 46.2 Bariatric Surgery Long-Term Comorbidity Responses. Mid- and Long-Term Comparative Outcomes at 3 to 10 Years

	RYGB			SG			BPD/DS		
	Mid Term	Long Term		Mid Term	Long Term		Mid Term	Long Term	
	3 yrs	5 yrs	10 yrs	3 yrs	5 yrs	10 yrs	3 yrs	5 yrs	10 yrs
Weight Loss									
% EBWL	61.7–83.0 (13,22,32,34,115)	66.6–74.8 (13,22,32)	57.1–69.0 (13,22)	61.1–68.5 (32,34,115)	60.3–65.1 (32,121)	52.5 (29)	83.0 (15)	63.8–79.3 (25,122,123)	67.9–73.4 (25,31)
% EBMIL	64.1–78.2 (19,3,4,33,13,22)	46.1–79.8 (4,13,17,19,22,26)	52.5–71.3 (13,19,22)	70.9–82.4 (27,33)	59.0–74.8 (28,121)	62.5[a] (27)	—	71.1–74.9 (17,25,26)	66.2–78.9 (25,30,31)
% TBWL	29.4–35.3 (13,19,22)	25.6–34.4 (13,17,19,22,26)	27.7–29.6 (13,19,22)	28.2–34.6 (24,27)	23.6–25.1 (24,28)	21.0[a]–26.3 (27,29)	45.2 (15)	31.1–40.7 (17,25,26)	33.4–39.0 (25,30,31)
Comorbidities									
Diabetes remission; %	77.0–90.0 (33,34,69)	37.0–66.7 (69,70)	42.6–54.7 (19,73)	60.0–91.2 (33,34,72)	26.0–80.0 (28,70–72)	—	90.0–93.1 (37,69)	63.0–91.7 (69)	91.3 (74)
Hypertension remission; %	52.0–71.2 (33,34,68)	42.0–57.0 (75,79)	20.4 (19)	65.2–80.0 (33,34,36,72)	52.9–54.5 (28,72)	—	68.0–85.8 (77,78)	70.6–88.4 (78,80)	80.9–91.4 (78,81)
Dyslipidemia remission; %	26.3–90.0 (34,77)	51.4–53.0 (39,75)	—	57.4–75.0 (34,36,72)	25.0–52.2 (28,72)	—	72.0–79.1 (77,80)	61.9 (83)	50.9–95.0 (74,81)
GERD remission; %	64.7–100 (33,34,77,86)	—	25.5 (19)	61.0–100 (33,34,36)	30.8–95.7 (38)	—	48.6 (77)	—	—
OSA remission%	74.0–85.0 (19,28,33,35–39)	50.0–93.5 (19,28,33,35–39)	54.7 (19,28,33,35–39)	23.0–100.0 (19,28,33,35–39)	33.0–88.9 (19,28,33,35–39)	—	74.0 (19,28,33,35–39)	—	—

RYGB indicates Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BPD/DS, biliopancreatic diversion with/without duodenal switch; % EBWL, percent excess body weight loss; % EBMIL, percent excess body mass index loss; % TBWL, percent total body weight loss; GERD, gastroesophageal reflux disease; OSA, obstructive sleep apnea.
[a]Outcomes at 11+ years.

Table 46.3 Bariatric Surgery Perioperative Mortality and Morbidity. Early and Late Comparative Complications[77–83]

	RYGB	SG	BPD/DS
Early <30 d			
VTE; %	0.1–1.1 (10,11,79,117,118)7)	0.0–1.7 (10,11,37,117,118)7)	0.2–3.4 (10,15,15,37,117,12
Leak; %	0.2–6.5 6)(10,11,16,19,79,114–117,125,126)	0.1–2.8 (10,11,24,37,114,117,121,127,128)7)	0.0–8.4 (10,15,16,37,116,117,12
Bleeding; %	0.8–2.0 (10,11,19,114,115,117)6)	0.5–5.7 (10,11,24,37,114,115,117,121,128)7)	0.4–3.4 (10,15,37,117,123,12
SBO/Sleeve Stenosis; %	0.1–5.3 (21,79,114,116,117)5)	0.1–3.5 (24,114,128,130)9)	0.5–7.7 (15,116,117,124,131
Death; %	0.0–0.8 2)(16,114–116,132)	0.0–0.02 (24,114,115,121)0)	0.6–4.1 (16,74,116,129,133
PNA; %	0.4 (11,16)6)	0.4–0.6 (11,121)0)	0.4–0.9 (15,16,123)2)
SSI; %	0.0–5.2 (11,16,19,79,114,115,117)6)	0.0–2.0 (11,114,115,117,121)0)	0.6–5.1 (15,16,117,123,124
Readmission; %	0.4–1.9 (11,114)6)	1.6–4.5 (11,114,128)7)	2.8–6.7 (74,124)3)
Reoperation; %	1.0–3.9 (11,16,114,117)6)	1.2–5.6 (11,24,114,117)6)	0.6–3.5 (15,16,74,117,124)
Late >30 d; %			
Readmission; %	3.3–29.0 (114,120,126)5)	1.0–32.0 (114,120)9)	8.0–17.2 (74,126)5)
Reoperation; %	1.3–4.8 (11,16,19,114)6)	0.5–10.2 (11,114)6)	1.1–13.0 (16,74)1)

RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; BPD/DS, biliopancreatic diversion with/without duodenal switch; VTE, venous thromboembolism; SBO, small bowel obstruction; PNA, pneumonia; SSI, surgical site infection.

Perioperative hemorrhage after gastric bypass occurs with an incidence of 1% to 4%, often originating from staple lines, and may be intraperitoneal or intraluminal. Intraluminal bleeding presents with melena and is often self-limited, requiring only transfusion and observation. Infrequently, endoscopic or operative intervention may be necessary. Hemorrhage after sleeve gastrectomy ranges from 1% to 4%, is usually intraperitoneal from the gastric staple line, and may require operative intervention, although observation in the hemodynamically stable patient is a reasonable initial course. Early small bowel obstruction, and thromboembolic, pulmonary, and cardiac events comprise the majority of the remainder of acute postoperative complications after bariatric surgery. Pathophysiology is not substantially different than after nonbariatric GI operations, although the obese may be at higher risk, reinforcing the importance of preoperative evaluation and preparation.

Late Morbidity

Late morbidity after bariatric surgery is similar to that associated with complex nonbariatric GI operations, may occur months or years later, and often presents with abdominal pain. Gallbladder disease and small bowel obstruction from adhesions and ventral/trocar hernias may occur after all bariatric operations. Other complications are operation specific. While definitions vary, overall late morbidity rates for gastric bypass range from 5% to 10%.

Many late complications of gastric bypass result from Roux-en-Y anatomy. Internal hernias occur in 0.5% to 9% of patients, and are categorized as mesenteric (common to all Roux-en-Y reconstructions, in which bowel passes through the mesenteric split in the Roux limb), mesocolic (specific to retrocolic reconstructions, in which bowel passes through the mesocolic defect created for the Roux limb), and Petersen (more often associated with antecolic than retrocolic reconstructions, in which bowel passes under the Roux limb and its mesentery) (**Fig. 46.5**).[67] Closure of internal hernia defects at primary operation is straightforward and recommended, and recent meta-analyses suggest that this practice likely reduces internal hernia rates, but does not obviate the future risk of hernia.[67] Patients often present years after surgery with a history of severe episodic abdominal pain. Diagnosis may be challenging, as obstipation may be absent and imaging normal even in the face of incarceration, especially if the biliopancreatic limb, which is out of continuity with the alimentary stream, is involved. A low threshold for operative exploration must be maintained in any patient with unrelenting abdominal pain after gastric bypass. Operative reduction and closure of internal hernia defects can usually be performed via a laparoscopic approach.

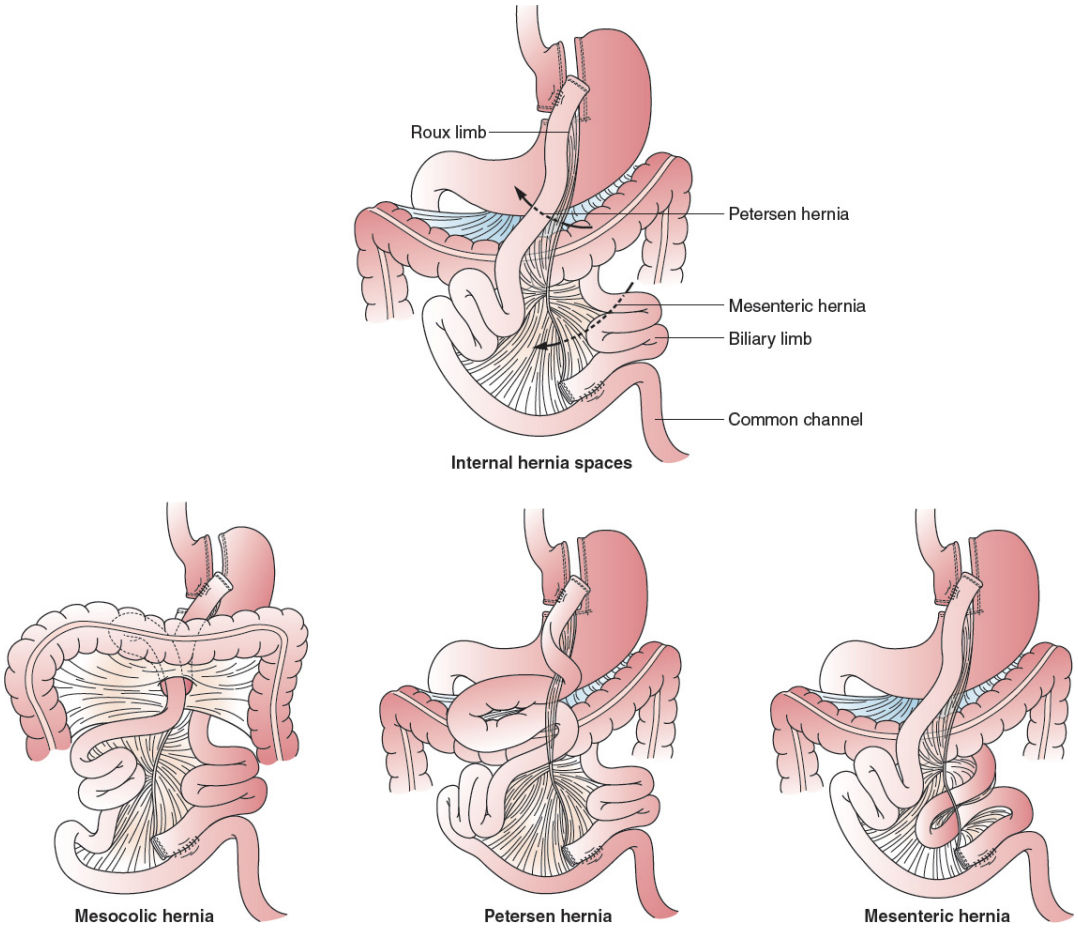
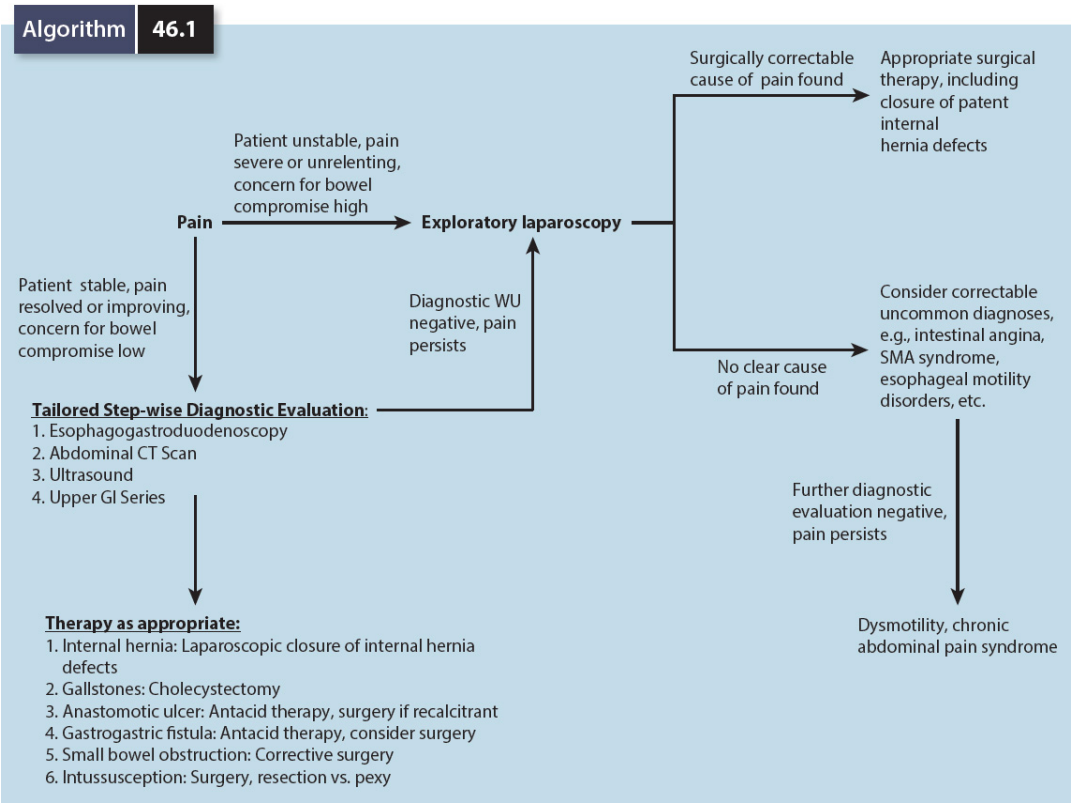


Figure 46.5 Internal hernias. Internal hernias may occur after any Roux-en-Y reconstruction, and include mesenteric, Petersen, and mesocolic hernias. Weight loss after gastric bypass and loss of adipose tissue in the intestinal mesentery may predispose to internal herniation.

Gastrojejunal anastomotic ulcer occurs in 0.5% to 25% of patients after gastric bypass, with the majority of series reporting incidences between 2% and 8%. Tobacco or NSAID use increases risk, but ulcers may occur in the absence of these risk factors. Diagnosis by upper endoscopy is usually straightforward. Upper GI radiography is advisable to rule out an associated gastrogastric fistula, especially if an ulcer is recalcitrant to medical treatment or is associated with weight regain. Most ulcers heal with high-dose antacid therapy, and once healed, most surgeons recommend maintenance antacid therapy for life, although data supporting this practice are sparse. Rarely, ulcers recalcitrant to medical therapy require resection with anastomotic revision or reversal of the gastric bypass. Large pouches are a risk factor for ulcers due to retention of parietal cells in the distal gastric pouch that do not participate

in negative inhibition of gastrin secretion, thus rationalizing pouch resection and anastomosis revision as a treatment strategy. Gastrogastric fistula occurs with an incidence of 0% to 2% and may be associated with ulcers. Gastrogastric fistula incidence has decreased substantially since the advent of divided gastric bypass. Gastrogastric fistula often results from incomplete division of the gastric pouch from the gastric remnant at primary operation. Stenosis of the gastrojejunostomy typically presents with intolerance of solid foods and vomiting within 1 to 3 months of surgery with a wide range of reported incidences from <1% to >20%, but most commonly 3% to 7%. Stenosis is usually easily treated with endoscopic dilation, although rare cases may require anastomotic revision. Retrograde intussusception at the jejunojejunostomy is a rare cause of abdominal pain after gastric bypass with a reported incidence of 0.1%. Pathogenesis is likely related to motility disorders resulting from disruption of enteroenteric nerves and divorce of the small intestine from duodenal pacemaker plexi with subsequent development of aberrant ectopic pacemakers in the involved intestinal limbs. Diagnosis may be challenging and imaging unreliable. Treatment consists of either plication/pexy of involved limbs or resection and revision of the jejunojejunostomy, with the latter approach associated with lower rates of recurrence.



Algorithm 46.1 Algorithm for management of abdominal pain months or years after Roux-en-Y reconstruction.

The clinical presentation and differential diagnosis of abdominal pain after gastric bypass is diverse and diagnostic imaging may be unreliable. The clinician is not infrequently faced with a gastric bypass patient who presents with persistent pain in the absence of a clear cause after thorough diagnostic evaluation. Exploratory laparoscopy in such patients provides a diagnosis in up to 90% of cases. Even in the absence of intraoperative findings other than patent internal hernia defects without incarceration, closure of defects provides relief in the majority of patients. Less commonly, in the absence of a clear cause, pain is presumed to result from atypical motility disorders associated with Roux-en-Y anatomy and may be difficult to treat **(Treatment Algorithm 46.1)**.

Rates of reoperation following bariatric surgery range from 5% to 22.1%, with higher rates of reoperation for the gastric bypass as compared to sleeve gastrectomy. However, two small randomized control trials reported no significant difference in 5-year rates of reoperations between the two operations. Specifically, the SLEEVEPASS trial reported an 8.3% reoperation rate following sleeve gastrectomy and a 15.1% rate of reoperation for gastric bypass.[76] Data from the SM-BOSS trial mirrored these finding with rates of reoperation at 15.8% for sleeve gastrectomy versus 22.1% for gastric bypass.[84] Later complications of sleeve gastrectomy include stricture, stenosis,

or GERD. GERD is a more frequent complication for patients who undergo sleeve gastrectomy. While many patients respond to therapy with antacid medication, conversion to a gastric bypass may be required for those with refractory symptoms. As such, gastric bypass is often the procedure choice for patients with both severe obesity and GERD due to the reduction of acid in a small gastric pouch and a long Roux limb. There is increasing clinical concern that sleeve gastrectomy may worsen GERD or increase risk for development of Barrett esophagus. Studies are mixed in their findings of symptoms or complications of GERD after a sleeve gastrectomy.

Late complications after gastric band are common, afflicting 10% to 50% of patients, may occur years after primary operation, and include band slippage, band erosion, and development of GERD and esophageal motility disorders. Treatment often requires band explant, with late explant rates of 30% to 50% in some series.

Bariatric operations alter absorption of macro- and micronutrients. Protein and lipid malabsorption, steatorrhea, and protein wasting are rare after modern gastric bypass and virtually absent with gastric band and sleeve gastrectomy, but afflict anywhere from 2% to 20% of patients after biliopancreatic diversion/duodenal switch.[85,86] The elimination of the pyloric emptying mechanism in gastric bypass is associated with dumping and hypoglycemic syndromes, the underlying mechanisms of which are not well understood. Early dumping occurs within 10 to 30 minutes of a meal, and is thought to result from intraluminal fluid shifts and acute intravascular volume depletion secondary to rapid emptying of hyperosmolar gastric contents into the small intestine. Early dumping is associated with tachycardia and diaphoresis. Aberrations in gut hormone secretion, including elevated secretion of vasoactive intestinal polypeptide, enteroglucagon, pancreatic polypeptide, and GLP-1, have been associated with a predisposition to early dumping. Late dumping occurs hours after a meal and is thought to be due to hypersecretion of insulin with subsequent reactive hypoglycemia; excess secretion of GLP-1 and vasoactive intestinal peptide (VIP) have also been implicated. Dumping and hypoglycemia typically respond to a low-carbohydrate diet and preprandial therapy with acarbose, an intestinal alpha glucosidase inhibitor that decreases glucose release from ingested carbohydrates. In cases recalcitrant to these measures, pharmacotherapy with agents that reduce insulin secretion, including octreotide, diazoxide, and calcium channel blockers, may be of benefit. Surgical banding of the gastric pouch to delay emptying has been employed with variable efficacy.

Micronutrient deficiencies are underreported after bariatric surgery. The reported prevalence of deficiencies of virtually all micronutrients after surgery span a broad range from 10% to >80% for biliopancreatic diversion/duodenal switch and gastric bypass. Deficiencies are less common after sleeve gastrectomy and gastric band. An understanding of the anatomic sites and mechanisms of micronutrient absorption affected by gastric bypass foregut diversion guides diagnosis and management. Anemia, neurologic, dermatologic, and GI symptoms are common clinical manifestations of many micronutrient deficiencies (**Table 46.4**). Acute deficiencies may involve dramatic presentations (e.g., thiamine deficiency and Wernicke encephalopathy). Chronic occult micronutrient deficiencies are associated with increased risk of chronic disease. Chronic magnesium deficiency, for example, is associated with an increased risk of type II diabetes. Chronic selenium deficiency has been associated with an increased risk of cancer and cardiovascular disease. The most common deficiencies associated with gastric bypass involve calcium, vitamin D, folate, iron, and B12. Vomiting due to stenosis or gastroenteritis increases the risks of severe micronutrient deficiencies, and nutritional status should be monitored carefully in any bariatric surgery patient with significant vomiting. It is important to note that obesity is associated with multiple micronutrient deficiencies independent of bariatric surgery, which should be identified and corrected in the preoperative period, and which may resurface in the postoperative period.

Operative Considerations

A thorough discussion of the technical aspects of bariatric surgery is beyond the scope of this chapter, but a few important issues warrant mention. Obesity is a risk factor for DVT, and aggressive DVT prophylaxis should be employed. Optimal prophylaxis agents and regimens have not been determined, but unfractionated or low–molecular-weight heparin during operation and continued through the hospitalization period is typical. Subtherapeutic dosing of these agents is common in the obese, and the American College of Chest Physicians recommends weight-based dosing.

Hand-sewn, linear stapler, and circular stapler techniques are used to create the gastrojejunostomy in gastric bypass. No single technique demonstrates a clear advantage, although stenosis rates may be higher with the circular stapler technique. Absorbable suture should be used for all anastomoses, as nonabsorbable suture is a nidus for ulcer formation. Routine intraoperative testing of the gastrojejunal anastomosis with EGD-air insufflation or methylene blue instillation may be associated with reduced anastomotic dehiscence rates and is advisable. The use of drains at

the gastrojejunal anastomosis is practiced selectively, and no clear data demonstrate that routine drain placement aids in early detection or reduced morbidity of anastomotic dehiscence. Routine closure of internal hernia defects during gastric bypass is controversial, as data do not clearly demonstrate that this practice reduces late hernia incidence. Nonetheless, closure is straightforward, entails low morbidity, and is therefore recommended. Risk–benefit analyses do not support prophylactic cholecystectomy during laparoscopic bariatric surgery in the absence of cholelithiasis, or in the presence of asymptomatic cholelithiasis. It is therefore reasonable to manage cholelithiasis in bariatric surgery patients as in all patients, that is, perform cholecystectomy only if symptoms are present.

Perioperative and Postoperative Management

Perioperative care of the bariatric surgery patient is similar to that of any patient undergoing complex GI surgery but must be tailored to the obese. Inpatient, outpatient, and operating room facilities should be equipped with beds, chairs, lifting and transfer apparatuses, and other equipment capable of bearing the weight of obese patients. Anesthesia, nursing, dietician, physical therapy, and other subspecialty staff with experience in the management of obese patients are necessary. Hospital stays after laparoscopic gastric bypass and sleeve gastrectomy are typically 1 to 3 days, while gastric band is generally performed on an outpatient basis.

The dietary regimen in the first few weeks after surgery is designed to prevent food impaction at an edematous surgical site and maintain adequate hydration, and includes clear liquids progressing to soft foods. Caloric intake in the early postoperative period may be less than 500 cal/d, which is acceptable as long as hydration is maintained. Within 2 to 3 weeks of surgery, solid foods may be introduced and caloric intake will slowly rise, with a long-term maintenance target of 1,200 to 1,500 calories and 50 to 70 g of protein per day. Within a few months of surgery, most patients are able to eat any foods in small quantities with few exceptions. Deviation from this pattern should raise concerns for anastomotic stenosis, ulcer, or other complications. Persistent vomiting, unless clearly associated with a specific food that when eliminated ameliorates symptoms, is abnormal and should prompt a diagnostic workup, usually with UGI and/or EGD.

The incidence of cholelithiasis after bariatric surgery ranges from 15% to over 70%, but only approximately 7% of patients will require cholecystectomy. Prophylactic treatment with ursodeoxycholic acid reduces the risk of postoperative cholelithiasis, from 28% to 9% in one recent meta-analysis. Such therapy entails little morbidity and a 6-month postoperative treatment regimen is common practice. Data are equivocal, however, regarding whether this practice reduces cholecystectomy rates or is cost-effective.[87]

The variability in surveillance practices makes accurate estimation of the incidence of postoperative nutritional deficiencies challenging, and a wide range of supplementation practices exist. Interpretation of the data is made more difficult because obese patients are at high risk for pre-existing micronutrient deficiencies independent of surgery. Vitamin D and zinc deficiencies, for example, afflict over 50% and 30% of obese patients, respectively. Abnormal serum levels of micronutrients after surgery are common, ranging from 10% to >80% depending on the micronutrient, operation, and patient population studied; clinically symptomatic deficiencies are less common. Consensus guidelines from the American Association of Clinical Endocrinologists, the Obesity Society, and the ASMBS recommend that gastric bypass patients undergo annual surveillance of 25-hydroxyvitamin D, calcium, iron, and B12 levels, along with a complete blood count, electrolyte and lipid panels, and liver function tests and periodic bone scans, and receive lifelong daily multivitamin (including folate), calcium citrate, vitamin D, and vitamin B12 supplementation, with iron supplementation in menstruating women.[88] Sleeve gastrectomy patients likely have a lower risk of nutritional deficiencies, but similar regimens are recommended. Gastric band patients receive a daily multivitamin, calcium, and vitamin D supplementation.

Table 46.4 Select Micronutrient Deficiencies Associated with Bariatric Surgery

Micronutrient	Signs, Symptoms of Deficiency	Site of Absorption	Mechanism of Absorption, Other Issues
B9 (folate)	Macrocytic megaloblastic anemia, leukopenia, thrombocytopenia, glossitis, elevated homocysteine levels, neural tube defects in pregnancy	Duodenum, jejunum, ileum	Water soluble, conserved via enterohepatic circulation; B12 required for folate activation, B12 deficiency can cause folate deficiency; multivitamin generally sufficient for supplementation after surgery
B1 (thiamine)	Wernicke encephalopathy (ophthalmoplegia, nystagmus, ataxia, dementia), Korsakoff psychosis, beri-beri, peripheral neuropathy	Jejunum, ileum	Water soluble, depletion may occur with 2 to 3 weeks; rapid weight loss, vomiting increase risk of deficiency; symptoms of acute deficiency may mimic stroke
B6 (pyridoxine)	Seborrheic dermatitis, atrophic glossitis, conjunctivitis, neuropathy	Jejunum, ileum	Water soluble, passive absorption
B12 (cobalamin)	Macrocytic anemia, leukopenia, thrombocytopenia, glossitis, irreversible neuropathies	Ileum	Binds salivary R-proteins which prevent acid hydrolysis, then binds intrinsic factor secreted by parietal cells in gastric antrum; intrinsic factor-B12 complex absorbed in ileum; found in foods of animal origin—be alert for deficiency in vegetarians
C	Scurvy: malaise, myalgias, petechiae, mucosal bleeding, edema; iron deficiency	Jejunum	Symptomatic deficiency rare after bariatric surgery; potentiates iron absorption, should be used in iron deficient patients
D	Fatigue, myalgia, arthralgia, osteopenia	Jejunum, ileum	Fat soluble; deficiency common in obesity independent of surgery in up to 50% of patients
A	Xerophthalmia, night blindness, keratitis	Duodenum, jejunum, ileum	Fat soluble; deficiency associated with

			malabsorptive procedures
E	Ataxia, paresthesias, myopathy, arthropathy, anemia, retinopathy, immune dysfunction	Jejunum, ileum	Fat soluble; deficiency associated with malabsorptive procedures
K	Coagulopathy	Jejunum, ileum	Fat soluble; deficiency associated with malabsorptive procedures
Calcium	Tetany (Trousseau, Chvostek signs), paresthesias, QT prolongation, cardiac arrhythmias, petechiae, purpura, osteopenia	Duodenum, jejunum	Symptoms of acute deficiency rare; chronic deficiency common, manifests as osteopenia, related to vitamin D deficiency
Copper	Ataxia, anemia, demyelinating neuropathy, paresthesias; chronic deficiency associated with osteoporosis, cardiovascular disease, cancer	Stomach, duodenum	Involved in antioxidant metabolism
Iron	Microcytic anemia, fatigue, cold intolerance, atrophic glossitis, angular stomatitis	Duodenum	Conversion from ferric to ferrous form requires acid hydrolysis; supplements interfere with calcium absorption, should be taken at different times
Magnesium	Alopecia, muscle cramps, hypocalcemia, hypokalemia, hypoparathyroidism, chronic deficiency linked to increased risk of diabetes, cardiovascular disease	Duodenum	Deficiency common in obesity independent of surgery in up to 35% of patients
Selenium	Acute deficiency rare; chronic deficiency linked to increased risk of cancer, diabetes, long-term mortality	Duodenum	Involved in antioxidant metabolism; excess selenium is toxic
Zinc	Alopecia, dermatitis	Duodenum	Deficiency common in obesity independent of surgery in up to 50% of obese patients

Dominant anatomic sites of absorption are listed, but many micronutrients are absorbed throughout the GI tract. In cases of micronutrients absorbed via active transport mechanisms, passive absorption also occurs in lesser amounts, and supplementation with suprapharmacologic doses overcomes bypassed

active uptake mechanisms via passive absorption (e.g., B12).

Clinical follow-up after bariatric surgery should be lifelong. Primary care providers play a critical role in preoperative and postoperative care. Endocrinology expertise may be required, especially in the early postoperative period when diabetes may resolve rapidly. A medical bariatrician subspecialty is evolving to care for this expanding patient population.

Physiologic Mechanisms Underlying Bariatric Surgery Efficacy

7 Restriction of caloric intake and nutrient malabsorption are the classic presumed mechanisms of bariatric operations. These mechanisms are important, but their relationship to outcome is complex and nonlinear. For example, data are conflicting regarding the correlation between gastric bypass pouch size and weight loss. In general, pouch volumes <50 cc are associated with good results with little evidence that smaller pouches achieve greater weight loss, while efficacy may decrease substantially as pouch sizes increase beyond 50 cc. Similar observations apply to sleeve gastrectomy: a recent MBSAQIP study of 189,477 sleeve gastrectomies demonstrated that bougie size ≥40 Fr was associated with greater weight loss relative to smaller bougies.[89] Similarly, common channel length teeters on a less well-defined threshold, above which weight loss is poor and below which malnutrition results. Other features of restriction are counterintuitive: more rapid gastric pouch emptying on oral contrast studies is associated with greater weight loss after gastric bypass while sleeve gastrectomy is associated with increased gastric emptying rates compared to native anatomy. These observations suggest a complex relationship between weight regulation, metabolism, and gut anatomy and motility.

Complex mechanisms in addition to restriction and malabsorption contribute to weight loss and improved metabolism after surgery, with qualitatively different responses than those associated with diet-induced weight loss. Satiety is increased, hunger decreased, and metabolic rate increased after bariatric surgery, the opposite of responses observed with diet-induced weight loss. Bariatric surgery somehow "sidesteps" the normal compensatory responses that act to defend body weight with nonsurgical weight loss. The mechanisms underlying these counterintuitive responses are not well established. Among putative mechanisms are changes in gut hormone secretion secondary to altered intestinal anatomy. Decades ago, it was observed that an oral glucose load elicits a greater insulin response than an intravenous glucose load, leading to postulation of the existence of *incretins,* gut hormones secreted in response to a meal that regulate systemic glucose metabolism. Subsequent research led to the discovery of GIP and GLP-1, incretins secreted by duodenal K cells and ileal L cells, respectively, in response to nutrient delivery to the small intestine. Incretins have diverse effects on glucose homeostasis, potentiating central insulin secretion and peripheral insulin sensitivity. Alterations in incretin hormone secretion secondary to gut anatomic derangements were invoked to explain the observation that diabetes often improved within days of gastric bypass, well before substantial weight loss.

The *foregut and hindgut hypotheses* have been proposed to explain this phenomenon: bypass of the alimentary stream from the stomach, duodenum, and proximal jejunum (the foregut hypothesis), and increased caloric delivery to the distal jejunum and ileum (the hindgut hypothesis) alter secretion of gut hormones with improvement in glucose homeostasis. While data are less compelling for GIP and other putative foregut hormones, evidence supports the hindgut hypothesis, including data demonstrating increased serum GLP-1 levels after gastric bypass. While debate persists regarding the magnitude of these effects on diabetes remission after gastric bypass, an understanding of incretin physiology has led to the development of GLP-1 agonists as pharmacologic therapy for diabetes independent of bariatric surgery.

Gut anatomic derangements mediate additional metabolic changes. Gastric bypass and sleeve gastrectomy are associated with alterations in serum levels of the orexigenic hormone ghrelin, which is secreted by gastric fundus enteroendocrine cells, and peptide YY and oxyntomodulin, gut hormones secreted by L cells in parallel with GLP-1 in response to a meal that induce satiety and inhibit gut motility and are central mediators of the "ileal brake" mechanism. These changes may contribute to satiety and altered food responses after bariatric surgery. Gastric bypass and sleeve gastrectomy alter bile acid metabolism, increasing serum levels of conjugated bile acids with beneficial effects on glucose and lipid metabolism. Bariatric surgery disrupts vagal and enteroenteric innervations of the gut with downstream effects on CNS satiety responses. Finally, bariatric surgery is associated with alterations in gut microbiota that contribute to weight loss and resolution of metabolic disease, with data demonstrating that fecal transplant from mice that have undergone bariatric surgery transfers a lean, insulin sensitive phenotype to obese, nonoperated mice. The precise mechanisms by which these diverse effects contribute to weight loss and metabolic disease remission remain unclear but are areas of active research.

Mechanisms other than restriction and malabsorption underlie the systemic effects of bariatric surgery. An emerging field of *metabolic surgery* is exploring operations designed to mimic the metabolic effects of gastric bypass (e.g., ileal transposition, foregut exclusion, biliary diversion) in animals and lean diabetic humans with promising results. Also in development are endoscopic and laparoscopic gastric plications, intragastric balloon placement, vagal nerve blockade, gastric simulators, and impermeable intraluminal duodenal and jejunal stents designed to prevent caloric absorption. Bariatric surgery in the 21st century will evolve to include a broad array of procedures applied to a diverse patient population as these efforts mature.

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47

Gastric Neoplasms

Andrew P. Loehrer and Sandra L. Wong

Key Points

1. While the incidence and mortality of gastric cancer have decreased substantially over the past several decades, it is still a leading cause of cancer-related mortality in many parts of the world.
2. *Helicobacter pylori* infection is the predominant risk factor for gastric carcinogenesis and *H. pylori* eradication is responsible for a marked decline in intestinal type gastric cancers.
3. The symptoms produced by gastric cancer are nonspecific and can mimic those associated with a number of nonneoplastic gastroduodenal diseases, especially benign gastric ulcer.
4. The extent of gastric resection is determined by the need to obtain a resection margin free of microscopic disease, and examination of a minimum of 16 nodes is suggested for adequate staging.
5. Multimodality treatment should be the standard of care for treating locally advanced resectable gastric cancer.

Gastric cancer remains a relatively common and frequently lethal malignancy, noting that it is the fifth most commonly diagnosed cancer in the

world.[1] The disease is often not recognized until it is at an advanced stage. Gastric cancer usually cannot be treated with resection alone, and surgical cure rates have remained disappointingly low. Multidisciplinary approaches must be considered the standard of care for these difficult neoplasms, noting some modest improvements in outcomes finally being observed. Technical innovations and basic/translational scientific investigations must continue to be applied to this disease.

ADENOCARCINOMA

Epidemiology

1 The incidence of gastric cancer has declined dramatically in the United States over the past century, noting that it still constitutes a major global health problem in low- and middle-income countries. There is truly wide geographic variation in incidence, with 15- to 20-fold difference between the high- and low-incidence regions. The rates are particularly high in Japan, Korea, and China, where gastric cancer is commonly diagnosed and a leading cause of cancer-related mortality. Globally, there will be an estimated 1,030,000 cases and over 782,000 deaths in 2018.[1] In comparison, gastric cancer is an uncommonly diagnosed cancer in the United States, with an estimated 27,600 cases and an estimated 11,010 deaths in 2020.[2] Of note, Asian Americans appear to have a much higher incidence (15 cases per 100,000) compared to non-Hispanic Whites (6 per 100,000), and Korean Americans and Japanese Americans (40 per 100,000 and 30 per 100,000, respectively) face a particularly high risk of disease.[3]

Worldwide geographic variability in the incidence of gastric cancer is shown in **Figure 47.1**. The highest incidence occurs in Eastern Asia, but Central and Eastern Europe and South America also have high incidence of gastric cancer. The lowest incidence of gastric cancer is seen in Africa and North America. It has long been thought that environmental exposures play a role in gastric carcinogenesis, a notion that is supported by the finding that groups who migrate from regions with high prevalence of gastric cancer to those with low prevalence experience a decreasing incidence of gastric cancer with time.[4,5] Factors including diet and associated issues of hygiene

and food conservation have been linked to incidence, and variation in the gut microbiome, which is closely linked with both diet and environment, is being increasingly explored as a causal determinant.

Specifically, the intestinal histologic subtype of gastric adenocarcinoma appears to account for most of the geographical variation seen with this disease and is strongly related to environmental exposures. The strongest known risk factor for intestinal type gastric cancer (with well-differentiated tumor cells) is infection with *Helicobacter pylori*. Approximately 75% of gastric cancer cases are, in fact, attributable to *H. pylori* infection, making this organism the dominant infectious cause of cancer in the world.[6] It is associated with a six-fold increased risk of (noncardia) gastric cancer[7,8] and eradication of *H. pylori* is a major factor in the marked declines of intestinal type cancers of the distal stomach in the United States and much of the developed world.[9]

The anatomic distribution of gastric cancers also varies widely. Unfortunately, the incidence of diffuse type gastric cancer, characterized by undifferentiated tumor cells arranged in scattered formation in fibrous stoma, of the proximal stomach is rising. While distal tumors still predominate in developing countries, proximal cancers appear to occur more commonly in relatively younger, white, and male patients.[10,11]

Premalignant Lesions

The risk for development of gastric cancer is greater in stomachs that harbor polyps. This risk is related most closely to polyp histologic type, size, and number. Variations in these three factors account for the wide range in reported risk associated with gastric polyps. In terms of malignant potential, gastric polyps can be divided into two broad categories— hyperplastic polyps and adenomatous polyps. Although not premalignant, hyperplastic polyps are discussed here because they are common, occurring in up to 1% of the general population and accounting for 75% of all gastric polyps. The hyperplastic polyp contains an overgrowth of histologically normal-appearing gastric epithelium. Atypia is rare, and hyperplastic gastric polyps have little to no neoplastic potential.

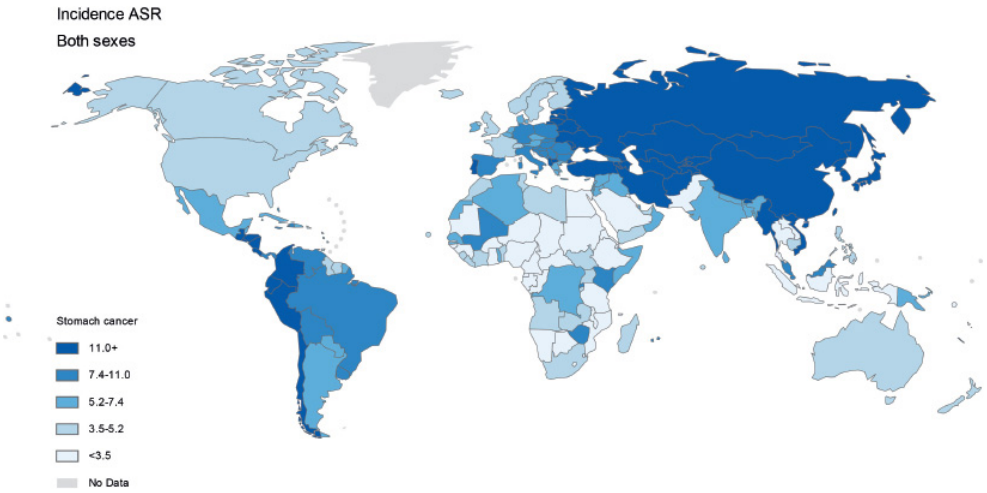


Figure 47.1 Worldwide geographic variability in gastric cancer incidence. (Reprinted from Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012 v1.0 Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. France: International Agency for Research on Cancer, 2013.)

Hyperplastic polyps are generally asymptomatic. When hyperplastic polyps are discovered, endoscopic removal for histologic examination is indicated and such removal results in sufficient treatment. Subsequent surveillance is not necessary, given the lack of neoplastic potential in these polyps. Adenomatous polyps also tend to be asymptomatic, but in contrast to hyperplastic polyps, adenomatous polyps carry a distinct risk for the development of malignancy.[12] Mucosal atypia is frequent, and mitotic figures are more commonly seen than in hyperplastic polyps. Dysplasia and carcinoma in situ have developed in adenomatous polyps observed over time. In fact, the risk for the development of carcinoma has been estimated at 10% to 20% and is greatest for polyps more than 2 cm in diameter. The presence of multiple adenomatous polyps increases the risk of cancer.

Endoscopic removal is indicated for pedunculated lesions and is sufficient if the polyp is completely removed and shows no evidence of invasive cancer on histologic examination. Operative excision is recommended for sessile lesions larger than 2 cm, for polyps with biopsy-proved invasive carcinoma, and for polyps complicated by pain or bleeding. Because the presence of gastric adenomatous polyp is a marker of increased risk for the development of cancer in the remaining gastric mucosa, repeat endoscopic surveillance is indicated. Enrollment in a surveillance program is indicated in order to rule out recurrence at the site of previous excision, evaluate for

new or missed polyps or an early carcinoma, and confirm eradication of *H. pylori,* if applicable.

Gastritis

The incidence of atrophic gastritis and gastric cancer increases with age. Chronic gastritis is frequently associated with intestinal metaplasia and mucosal dysplasia, and these histologic features are often observed in mucosa adjacent to gastric cancer. Gastritis is frequently progressive and quite severe in the gastric mucosa of patients with cancer. Gastric malignancy seems to be increased in patients with chronic gastritis associated with pernicious anemia, although the risk appears to have been overstated in the past. Nevertheless, this disease, which is characterized by fundic mucosal atrophy, loss of parietal and chief cells, hypochlorhydria, and hypergastrinemia, is present in 3% of people older than 60 years. For people in whom pernicious anemia has been active for more than 5 years, the risk of gastric cancer is twice that of age-matched control subjects and there is increased risk for gastric carcinoid tumors as well.

Helicobacter Pylori

2 As outlined above, infection with *H. pylori* has been unequivocally associated with chronic inflammatory conditions in the stomach, and this association has stimulated interest in the role of chronic infection by this organism in gastric carcinogenesis. Childhood acquisition of *H. pylori* infection is frequent in areas of high gastric cancer incidence, and high rates of infection have been identified in patients with premalignant lesions and invasive cancer. Infection with *H. pylori* is associated with an increased risk of adenocarcinoma of both the body and the antrum of the stomach.[13] In contrast, *H. pylori* infection is not a risk factor for proximal cancers of the cardia or gastroesophageal junction, which are associated with mucosal abnormalities of Barrett esophagus and which seem to follow the metaplasia to dysplasia to carcinoma pattern of development.

The mechanism of carcinogenesis related to *H. pylori* infection is incompletely understood but is thought to be related to the chronic inflammation caused by the organism.[14] Only ~1% of patients chronically

infected with *H. pylori* will develop the gastric cancer phenotype, which consists of corpus-predominant gastritis, multifocal atrophic gastritis, high gastrin levels, hypo/achlorhydria, and low pepsinogen I/II ratio. The majority of subjects infected with *H. pylori* will develop the simple gastritis phenotype which is not associated with any significant clinical outcome, or the duodenal ulcer phenotype (10% to 15% of infected subjects) which consists of antral-predominant gastritis and high gastrin and acid secretion and actually provides protection from developing gastric cancer.[15] Of note, there is variable distribution of these three phenotypes geographically, with particular prevalence of the gastric cancer phenotype in certain parts of Asia where gastric cancer is common.[16] While eradication of *H. pylori* is globally associated with decreased incidence of gastric cancer, it may not prevent the development of gastric cancer once premalignant lesions have already developed.[17]

Previous Gastric Surgery

A number of historical reports[18,19] have suggested that gastric cancer is more likely to develop in people who have undergone previous partial gastrectomy, with patients who have undergone a gastrojejunal (Billroth II) anastomosis at apparently higher risk for carcinogenesis than those reconstructed with a gastroduodenal anastomosis (Billroth I). The so-called *gastric remnant cancer* is a true clinical entity, although the risk for development of this gastric neoplasm appears to have been overestimated. Several large, prospective studies with long-term follow-up indicate that the relative risk is not increased for up to 15 years after gastric resection, likely due to surgical removal of mucosa at risk for development of gastric cancer, followed by modest increases in cancer risk (three times the control value) observed only after 25 years.[20–23] The cellular mechanisms that contribute to the development of neoplasia in the remnant stomach are unknown. Decreased luminal pH, bacterial overgrowth with increased production of *N*-nitroso carcinogens, and reflux of bile acids into the stomach have been postulated to promote cancer development but remains unproved. Vagotomy, when performed in conjunction with (legacy) gastric surgery for benign disease, does not appear to promote cancer development. A population-based study from Sweden of 7,198 patients who had previously undergone

vagotomy and then followed for up to 18 years did not seem to have increased risk of gastric cancer.[21]

A recent study explored genetic alterations in gastric remnant cancer and found that the microsatellite instability-high (MSI-H) phenotype was much more common (43%) in gastric remnant cancers than in sporadic gastric cancers (6%), and that this incidence was much higher in patients who had undergone a Billroth II anastomosis (67%) as compared to those who had undergone a Billroth I anastomosis (11%). The MSI-H phenotype in these tumors was associated with inactivation of the DNA mismatch repair genes hMLH1 and hMSH2 though the significance of this relationship is not yet clear.[24] Reported 5-year survival ranges from only 7% to 33% for gastric remnant cancers, but this poor prognosis is most likely due to the fact that these cancers are usually diagnosed at an advanced stage when treatment options are limited.

Hereditary Syndromes

Approximately 5% to 10% of gastric cancer may have a familial component, and 3% to 5% are associated with known inherited cancer syndromes. Hereditary diffuse gastric cancer (HDGC) is an autosomal dominant syndrome that confers a lifetime risk for the development of gastric cancer by age 80 years of 67% for men and 83% for women.[25] The average age at diagnosis is 37 years, and these cancers tend to be of the diffuse histologic type. Germline mutations in CDH1, a tumor suppressor gene that encodes the cell-to-cell adhesion protein E-cadherin, are found in at least 25% of patients with HDGC.[26] CDH1 carriers, with and without close family histories of diffuse gastric cancer, appear to have similar incidence of gastric cancer on endoscopic surveillance and gastrectomy.[27] Therefore, those patients with documented CDH1 mutations may be offered prophylactic total gastrectomy, with or without lymph node dissection at a young age (between 18 and 40 years of age).

Other familial cancer syndromes associated with an increased risk of gastric cancer include Lynch syndrome (hereditary nonpolyposis colorectal cancer), juvenile polyposis syndrome, familial adenomatous polyposis (FAP), and Peutz–Jeghers syndrome. Given the autosomal dominant nature of these syndromes, screening upper endoscopy may be considered in these

patients, often starting at a young age. Findings of polyps could lead to recommendations for surveillance upper endoscopy in patients with these syndromes though no formal guidelines exist. In FAP, with germline mutations in the adenomatous polyposis coli (APC) gene on chromosome 5q21, the majority of polyps are benign (nonadenomatous). In individuals with FAP, 10% of gastric polyps are adenomatous in nature and could lead to gastric cancer, noting a 1% to 2% lifetime risk.[28]

Clinical Features

3 The symptoms produced by gastric cancer are nonspecific and can closely mimic those associated with a number of nonneoplastic gastroduodenal diseases, especially dyspepsia or benign gastric ulceration (**Fig. 47.2**). In early gastric cancers, epigastric pain is present in over 70% of patients.[29] Pain may be relieved, at least temporarily, by antacids or gastric antisecretory drugs. Anorexia, nausea, and weight loss are present in less than 50% of patients with early gastric cancers but become increasingly common with disease progression. Dysphagia is present in 20% of patients with proximal gastric lesions. Overt gastrointestinal hemorrhage (5%) and perforation (1%) are uncommon.

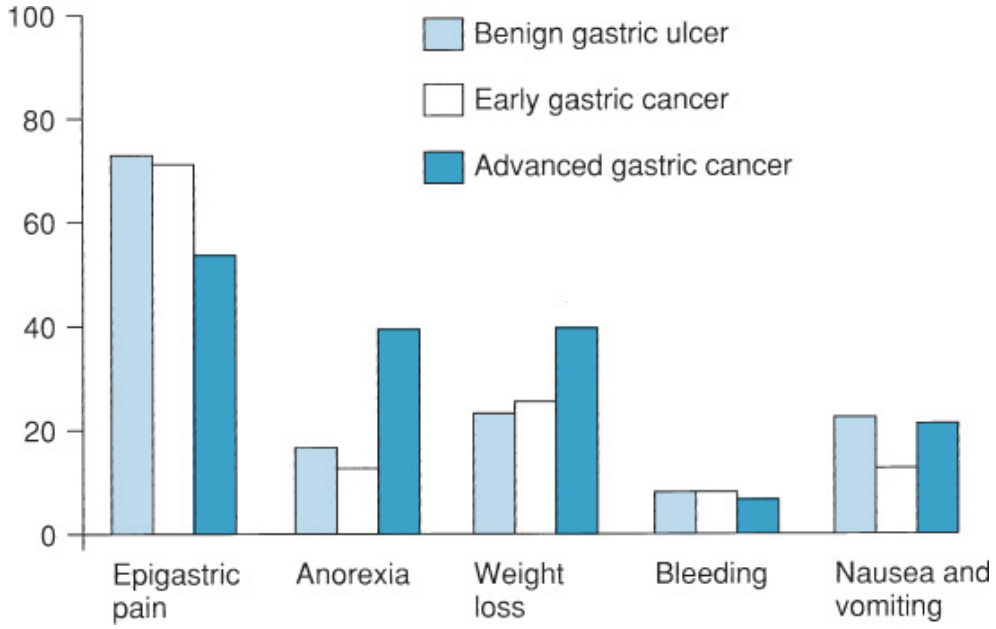


Figure 47.2 Clinical symptom frequency in benign gastric ulcer, early gastric cancer, and advanced gastric cancer. (From: Meyer WC, Damiano RJ Jr, Postlethwait RW, et al. Adenocarcinoma of the stomach. Changing patterns over the past four decades. *Ann Surg* 1987;205[1]:1–8.)

In most patients with early gastric cancers, physical examination is typically unremarkable. Stool tests positive for occult blood in one-third. There are no laboratory tests specific for gastric neoplasms. Abnormal physical findings usually reflect advanced disease (**Table 47.1**). Cachexia, abdominal mass, hepatomegaly, and supraclavicular adenopathy usually indicate advanced or metastatic disease.[30]

Diagnosis and Staging

Fiberoptic endoscopy is the most definitive diagnostic method when gastric neoplasm is suspected. In the initial stages, gastric cancers can appear polypoid, as flat, plaque-like lesions, or as shallow ulcers. Advanced lesions are typically ulcerated. The ulcer border can have an irregular, beaded appearance because of infiltrating cancer cells, and the base is frequently necrotic and shaggy. The ulcer can appear to arise from an underlying mass. Although each of these features suggests a malignant ulcer, differentiation of benign from malignant gastric ulcers can be made definitively only with gastric biopsy. Multiple biopsies of any gastric ulcer

should be performed, increasing sensitivity to 98% as compared to 70% for single biopsy.[31] False-negative results occur in approximately 10% of patients, usually as the result of inadequate sampling, sampling error, or due to the absence of a mucosal abnormality as can occur with linitis plastica; false-positive results in this setting are rare.

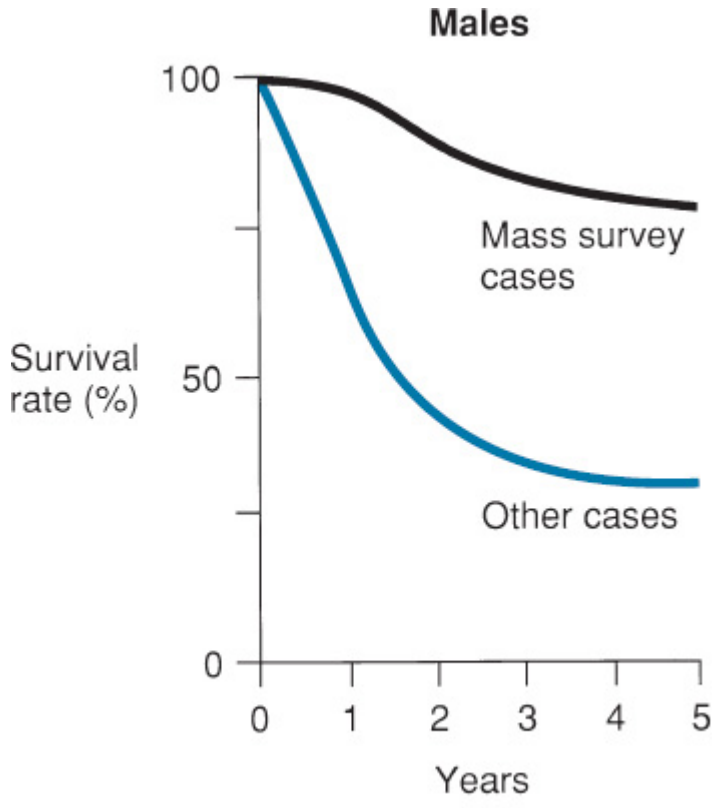
Table 47.1 Common Symptoms and Physical Findings in Gastric Cancer

Symptoms	Physical Findings
Weight loss	Guaiac-positive stool
Pain	Cachexia
Nausea and vomiting	Abdominal mass or fullness
Anorexia	Abdominal tenderness
Dysphagia	Hepatomegaly
Melena	

Diagnostic accuracy can be further enhanced by the addition of endoscopic ultrasound (EUS) with fine-needle aspiration biopsy for infiltrative tumors involving the wall of the stomach without obvious mucosal abnormalities. EUS has added benefit of being able to provide staging information on the depth of tumor invasion when done by experienced endoscopists.

Annual mass screening programs have been instituted in some countries (e.g., Japan, Venezuela, Chile) where there is a high incidence of gastric cancer. However, whether such programs significantly reduce gastric cancer mortality is unclear. In Japan, compliance with screening has been associated with a 50% decrease in gastric cancer mortality, but most of this benefit may actually be attributable to confounding factors such as good general health at baseline.[32] Cancers detected in screened patients do tend to be earlier cancers with fewer nodal metastases,[33] and patients with resected gastric cancer diagnosed by screening in Japan have better survival than those diagnosed after development of symptoms (**Fig. 47.3**). However, a survival difference between screened and unscreened gastric cancer patients persists

even after accounting for stage,[33] suggesting that patient selection confounds the effect of screening on mortality. The Japanese findings that early detection and identification of early gastric cancer can improve survival has been confirmed by European investigations, in which patients with early gastric cancers have been shown to have survival rates equivalent to those of patients with benign gastric ulcer (**Fig. 47.4**).[29] Mass screening programs have been found to be cost-effective in high-incidence countries such as Japan and China,[34] but they are unlikely to be cost-effective in lower-incidence countries such as the United States.


Males
100
50
0
Survival rate (%)
Mass survey cases
Other cases
0
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2
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Years

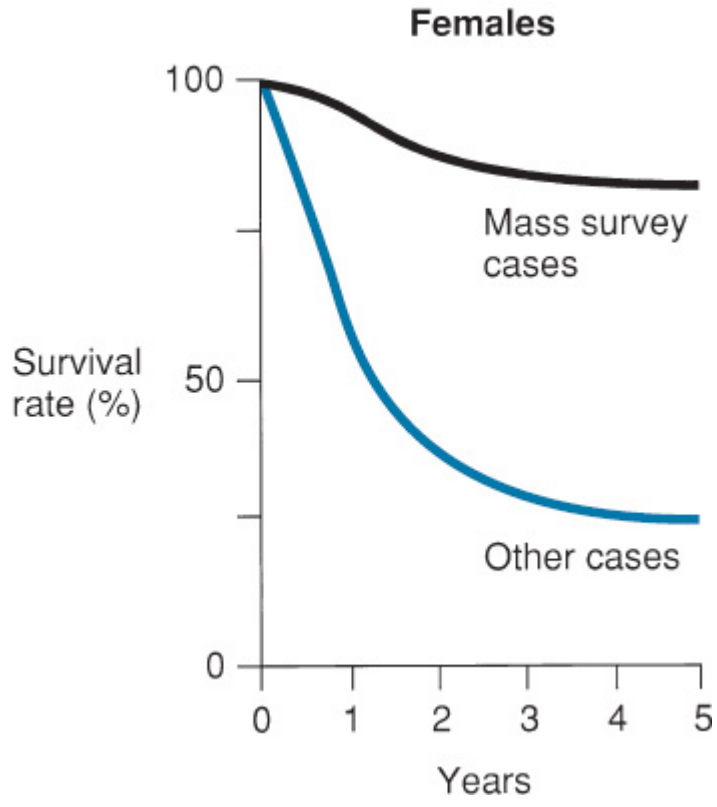

Females
100
50
0
Survival rate (%)
Mass survey cases
Other cases
0
1
2
3
4
5
Years

Figure 47.3 Early cancer survival rate in Japan. (From Kunisaki C, Ishino J, Nakajima S, et al. Outcomes of mass screening for gastric carcinoma. *Ann Surg Oncol* 2006;13(2):221–228.)

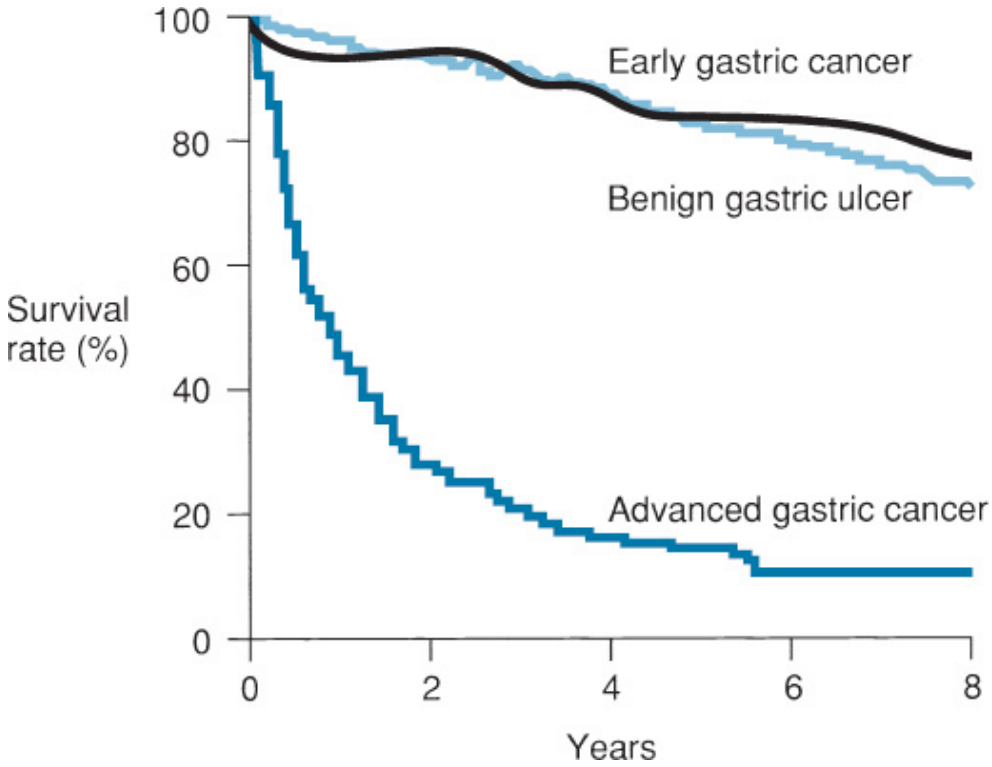


Figure 47.4 Early cancer survival rate in Europe. (From Moreaux J, Bougaran J. Early gastric cancer. A 25-year surgical experience. *Ann Surg* 1993;217(4):347–355.)

Barium-contrast radiographs have, in the past, been the standard method for diagnosing gastric neoplasm. Single-contrast examinations have a diagnostic accuracy of 80%. This diagnostic yield increases to approximately 90% when double-contrast (air and barium) techniques are used. Typical findings include ulceration, the presence of a gastric mass, loss of mucosal detail, and distortion of the gastric silhouette (**Fig. 47.5**). However, contrast radiography has been largely supplanted by endoscopy (with or without EUS) in contemporary practice because of the ability to obtain biopsy material concurrently by the latter technique.

Computed tomography (CT) can provide information both about the primary tumor and visceral metastatic disease. Because it is noninvasive and widely available, it is often the first staging modality that is employed in a patient diagnosed with gastric cancer. Patients who are found to have

metastatic disease can be spared further, potentially invasive staging studies. When performed with intraluminal and intravenous contrast, CT can demonstrate infiltration of the gastric wall by tumor, gastric ulceration, and the presence of hepatic metastases (**Figs. 47.6 and 47.7**). While depth of invasion and serosal involvement can be assessed, CT is generally not as accurate as EUS for assessment of depth of tumor (T category).

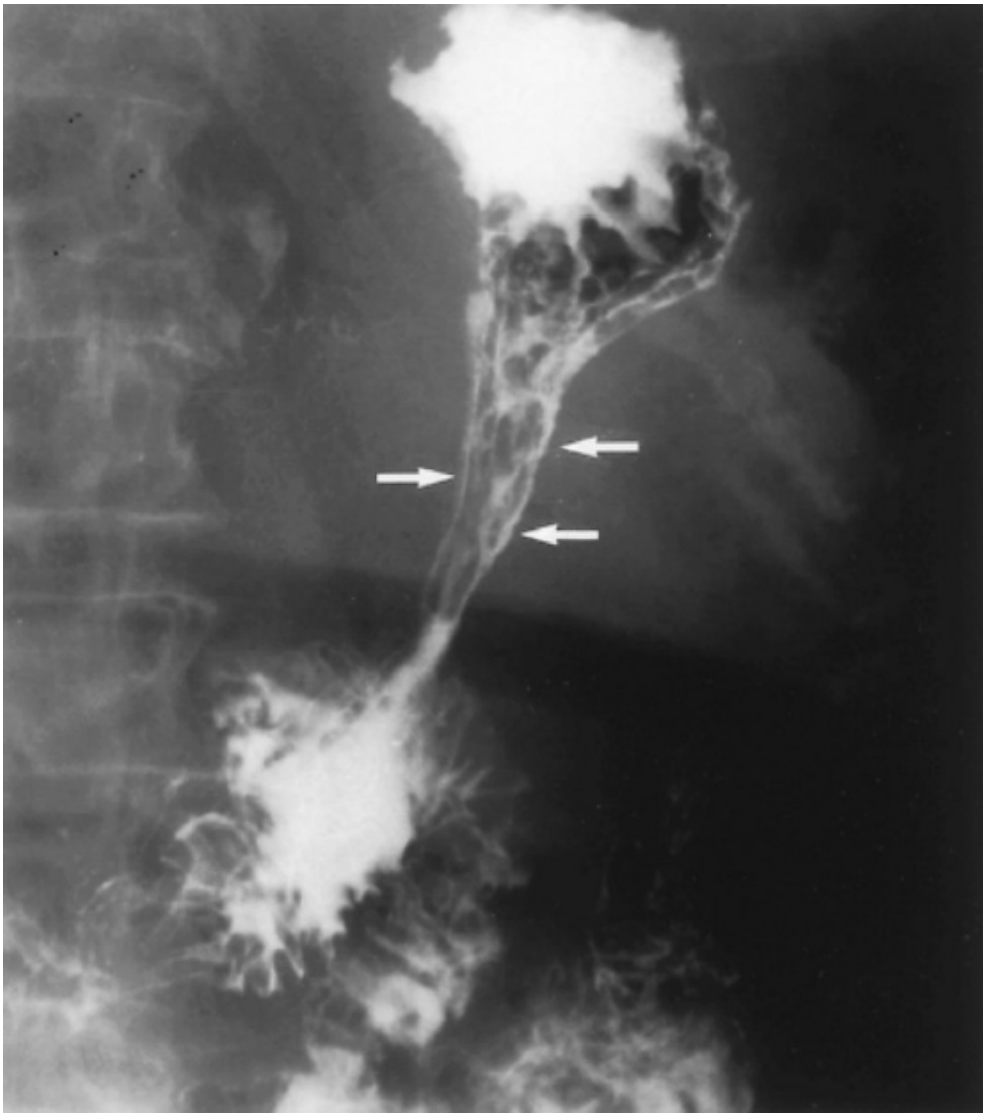


Figure 47.5 Barium-contrast radiograph demonstrating extensive involvement of the gastric body by infiltrating adenocarcinoma (linitis plastica). The gastric silhouette is narrowed (*arrows*), and the stomach is nondistensible.

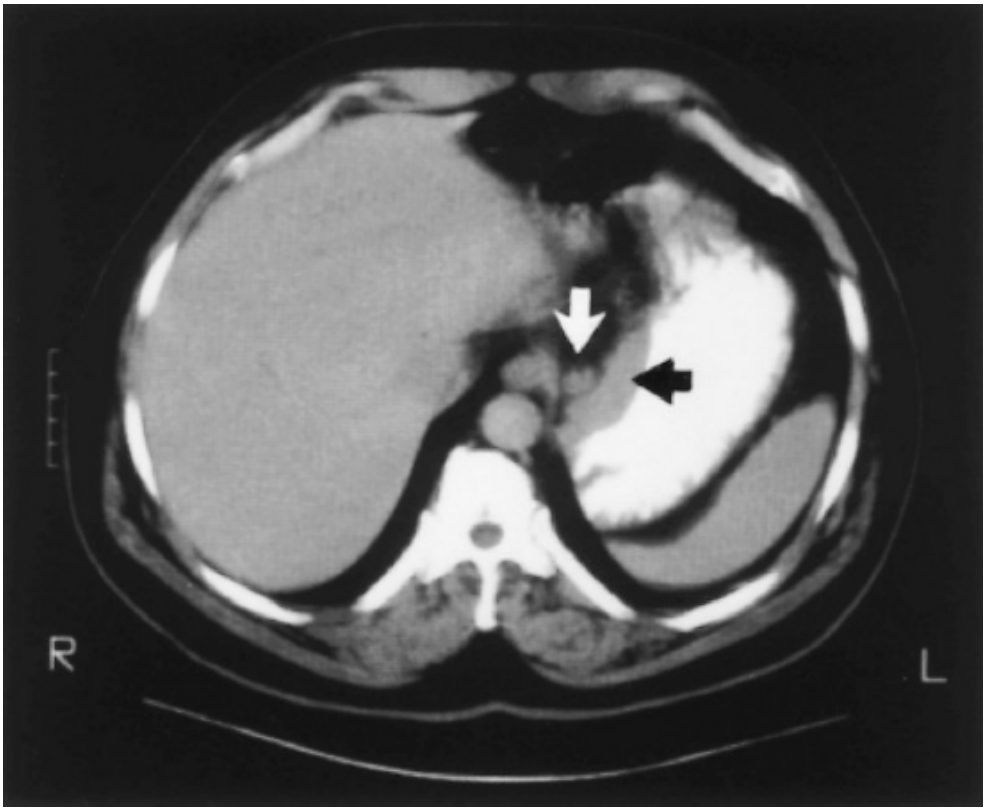
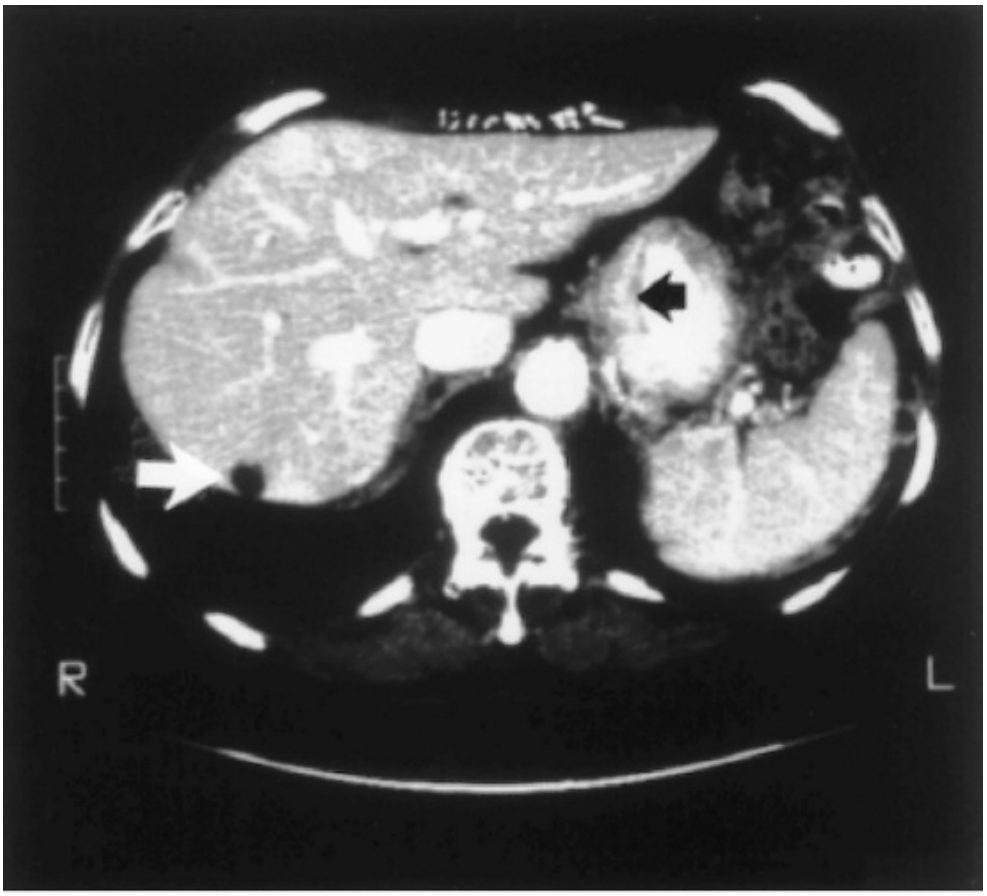


Figure 47.6 Computed tomography scan demonstrating mass along lesser curvature of the stomach (*black arrow*) and associated lymph node enlargement (*white arrow*).

EUS is a useful method of preoperative evaluation for local staging and diagnosis. As noted above, EUS can assess subepithelial lesions that may be confused with gastric cancer and guide biopsy of submucosal tumors within the wall of the stomach. Investigation of submucosal masses, infiltrative gastric disorders, and enlarged gastric epithelial folds, as well as differentiation of gastric lymphoma from gastric adenocarcinoma are all aided by EUS. This technique has the ability to assess the depth and pattern of gastric wall penetration by the tumor as well as relationship to adjacent structures and has good correlation with intraoperative assessment and histologic findings. Perigastric lymph nodes involved with tumor are also reliably identified by EUS, though limitations with the transducer makes visualization of more distant lymph nodes difficult. Nevertheless, EUS provides an accurate assessment of local stage of disease (TN status), with an accuracy of 46% to 88% for staging depth of tumor invasion and 30% to 90% for nodal involvement.[35,36]

EUS serves as a useful adjunct to cross-sectional imaging and can help guide selection of patients for further staging studies or multimodality therapy. Evaluation of nodal disease by CT is very limited and CT is not reliable for detection of small peritoneal metastases, which may be missed in 30% of cases.[37] Interestingly, the addition of 18-fluorodeoxyglucose (FDG) positive emission tomography (PET) has been found to be less accurate than cross-sectional imaging and EUS for assessing locoregional involvement, but more sensitive for detecting distant metastases in patients with gastric cancer.[38] A meta-analysis comparing PET, ultrasound, CT, and magnetic resonance imaging (MRI) found that PET scan was the most sensitive imaging modality for detecting hepatic metastases.[39] A separate study found that tumors which demonstrated metabolic response to neoadjuvant chemotherapy on PET correlated highly with histopathologic response and improved patient survival.[40] Therefore, current recommendations regarding the use of PET for staging gastric cancer are for selective use for patients with locally advanced tumors where the metastatic potential is high and for cases in which neoadjuvant therapy is being considered.[39]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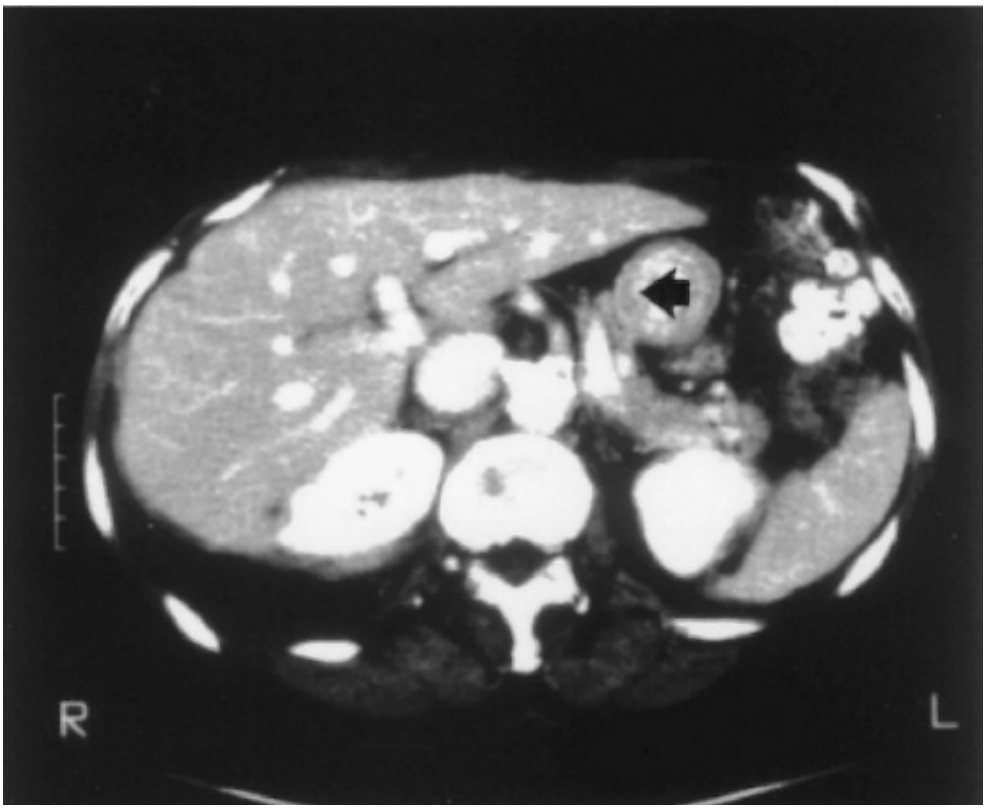
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Figure 47.7 Computed tomography scans of the upper abdomen showing extensive thickening of the gastric wall (*black arrows*) caused by infiltrating adenocarcinoma and associated hepatic metastasis (*white arrow*).

EUS is generally not useful for detecting metastatic disease, but it may help identify patients at risk for radiographically occult metastatic disease (e.g., peritoneal metastases) for staging laparoscopy.[37] However, even with adequate endoscopic evaluation and cross-sectional imaging, occult metastases may be missed in 16% to 37% of patients.[41] As such, staging laparoscopy is recommended for patients with potentially resectable gastric cancer.[42]

Staging Laparoscopy

The peritoneal lining, omentum, and liver capsule are common sites for gastric cancer metastasis that are difficult to evaluate preoperatively by CT scanning. In prospective studies, diagnostic laparoscopy has been superior to preoperative CT or percutaneous ultrasound in detection of peritoneal, hepatic, or lymphatic metastasis.[43] Accurate identification of patients with metastatic disease is important in order to spare them futile, ultimately noncurative surgical procedures. Laparoscopy, that includes peritoneal lavage and acquisition of fluid for cytologic examination, will detect metastatic disease that precludes curative resection in up to 37% of patients.[41,42] The highest yield for detection of occult metastatic disease is in those with T3 or T4 disease, and nodal involvement, noting low yield in cases that are T1 or T2, and N0.

Even in cases with planned upfront resection, staging laparoscopy should be performed prior to gastrectomy. Most patients with systemic metastasis detected at time of laparoscopy can be treated without the need for palliative surgical resection. Laparoscopy affords excellent visualization of the peritoneum, especially if care is taken to examine parietal and visceral surfaces, including the diaphragm, liver, spleen, bowel, and omentum. In addition to detection of grossly evident intra-abdominal metastatic disease, patients with findings of microscopic metastatic disease are at high risk for early recurrence and death after attempted curative resection.[44–46] Based on

such a finding, patients with positive cytology in peritoneal washings are considered to have M1 disease. Approximately one-fourth of patients subjected to staging laparoscopy prior to planned curative resection of gastric cancer will have positive peritoneal cytology; one-third of these patients will not have had grossly apparent metastatic disease. The peritoneum also remains the most common organ of recurrence after R0 resection.[46] Patients who clear their initially positive peritoneal cytology after systemic chemotherapy have an improved prognosis.[45] These considerations have led to recent work examining the role of heated intraperitoneal chemotherapy (HIPEC) with or without cytoreductive surgery for patients with evidence of carcinomatosis.[47–49] Early results suggest that survival can be improved to comparable patients without peritoneal disease. However, long-term survival or cure remains highly unlikely in presence of peritoneal disease.

Patients with locally advanced (T3–T4 or node-positive) tumors who are being considered for neoadjuvant therapy should undergo diagnostic laparoscopy with peritoneal washings prior to initiation of chemotherapy. In this situation, the finding of positive peritoneal cytology should prompt adoption of a noncurative paradigm of treatment in most cases. If carcinomatosis is limited or cytology positive only, patients may be eligible for ongoing trials neoadjuvant HIPEC (with or without cytoreduction) with chance to treat the carcinomatosis and proceed with curative-intent gastrectomy.

Relative to laparotomy, the shorter hospitalization and reduced operative trauma following laparoscopy may both hasten recovery and facilitate earlier initiation of systemic chemotherapy. Despite strong evidence supporting benefits of accurate staging, laparoscopy is underused in the management of gastric cancer, noting that less than 10% of potentially eligible patients[50,51] undergo staging laparoscopy prior to planned gastrectomy or neoadjuvant treatment.

Pathology

Gastric adenocarcinoma occurs in two distinct histologic subtypes—intestinal and diffuse. These subtypes are characterized by differing

pathologic and clinical features and by differing patterns of metastatic spread.

In the intestinal form of gastric cancer, the malignant cells tend to form glands. The intestinal form of malignancy is more frequently associated with gastric mucosal atrophy, chronic atrophic gastritis, intestinal metaplasia, and dysplasia. Gastric cancer with the intestinal histologic subtype is more common in populations at high risk (e.g., Japan), and it occurs with increased frequency in men and older patients. Clinical studies suggest that this subtype more frequently demonstrates blood-borne metastases.

The diffuse form of gastric adenocarcinoma does not demonstrate gland formation and tends to infiltrate tissues as a sheet of loosely adherent cells. Lymphatic invasion is common. Intraperitoneal metastases are frequent. The diffuse form of gastric adenocarcinoma tends to occur in younger patients, in women, and in populations with a relatively low incidence of gastric cancer (e.g., the United States). The prognosis is poorer for patients with the diffuse histologic subtype.

Additionally, signet ring cell carcinoma (SRC) is being investigated as a unique form of adenocarcinoma. SRC tumors contain scattered malignant cells containing intracytoplasmic mucin and this prognostic importance in both Western and Eastern studies remains less than clear. A recent analysis that compared over 1,600 patients with SRC with well-to-moderately differentiated adenocarcinoma found that SRC has mixed prognosis, having better survival for early gastric cancer (i.e., T1) but worse prognosis in advanced disease compared to well-to-moderately differentiated adenocarcinoma.[52]

Sporadic gastric adenocarcinomas demonstrate a number of chromosomal and genetic abnormalities. Cytometric analysis reveals that gastric tumors with a large fraction of aneuploid cells (with a greater-than-normal amount of nuclear DNA) tend to be more highly infiltrative and have a poorer prognosis. Amplifications of both the HER-2/*neu* and K-*ras* proto-oncogenes have been consistently detected in gastric adenocarcinomas, and in a small percentage of tumors a lack of expression of the tumor suppressor gene *MKK4* is robustly associated with poor survival.[53]

In the United States, the incidence of proximal gastric cancers has been increasing markedly over past few decades while tumors of body and distal stomach are relatively stable.[54] Proximal cancers are more likely to occur in

young White men and distal cancers are more likely to occur in Asian, African American, and Hispanic patients within the United States. In 10% of cases, the stomach is diffusely involved at the time of diagnosis based on historical data.[30] Prognosis is poorer for tumors arising from the proximal stomach and for those with diffuse involvement of the organ relative to distal tumors. As such, these patients are much more likely to need neoadjuvant and adjuvant therapy.[10,55]

The 8th edition American Joint Committee on Cancer (AJCC) staging system[56] for gastric cancer is presented in **Table 47.2.** The staging system accurately discriminates prognosis based on pathologic factors for tumors located 5 cm distal to the esophagogastric junction (EGJ) and below or arising within 5 cm of, but not crossing, the EGJ (**Fig. 47.8**). The AJCC recommends that cancers arising within 5 cm of the EGJ that cross into the EGJ or esophagus be staged and treated as esophageal cancers. A consideration of staging data illustrates the high frequency with which lymph node metastases are present at the time of diagnosis in the United States, and the severe impact lymphatic involvement has on survival. Even early gastric cancers (tumors restricted to the mucosa and submucosa) have a 15% prevalence of nodal metastasis.

Curative-Intent Treatment

Surgical resection is the only potentially curative therapy for gastric cancer, but an advanced stage of disease at the time of diagnosis precludes curative resection for most patients. Since the mid-1990s, the surgical treatment of gastric cancer has continued to evolve, with minimally invasive approaches increasingly pursued for early cancers and increasingly radical operations advocated by some for advanced tumors. The Japanese Gastric Cancer Association defines early gastric cancer as tumor in which invasion is restricted to the mucosa or submucosa, noting that the presence or absence of lymph node metastasis is not considered in this classification.[57] While the presence of lymphatic metastasis cannot be correctly judged by endoscopic findings, it is critically important in prognosis. For tumors confined to the mucosa, lymphatic metastasis is present in 1% to 3% of cases; with submucosal involvement, the rate of nodal positivity increases to 14% to 20%.[58,59]

Endoscopic Resection

Endoscopic approaches to the treatment of gastric cancer continue to evolve and advance. Endoscopic mucosal resection (EMR) and endoscopic mucosal dissection (EMD) may be considered as alternatives to surgical resection for very early-stage gastric cancer, especially by those with extensive experience with the techniques. For intestinal-type mucosal tumors less than 2 cm in size without ulceration or evidence of lymphovascular invasion, EMR may be performed with achievement of an R0 resection. With this approach, postoperative bleeding or perforation has been reported in up to 5%, and in up to 17% histologic examination revealed submucosal invasion that required further operative treatment.[60] A Japanese series of 131 patients reported disease-free survival of 99% at 10 years[61] and others have demonstrated long term results comparable to gastrectomy in terms of recurrence and mortality.[62] ESD is an emerging technique that may allow larger tumors (>3 cm) to be endoscopically resected. Even in experienced hands at high volume centers, there are higher associated rates of bleeding and perforation and there may not be any benefit over EMR for lesions less than 5 cm in size.[63,64] Attention to surveillance endoscopy following EMR or ESD is mandatory.

Table 47.2 8th Edition AJCC Staging System for Carcinoma of the Stomach

Primary Tumor	
T0	No evidence of primary tumor
Tis	Carcinoma in situ; intraepithelial tumor without invasion of the lamina propria, high-grade dysplasia
T1a	Tumor invades lamina propria or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures
T4a	Tumor invades serosa (visceral peritoneum)
T4b	Tumor invades adjacent structures
Regional Lymph Node Involvement	
N0	No regional nodal metastasis
N1	Metastasis to 1–2 regional lymph nodes
N2	Metastasis to 3–6 regional lymph nodes
N3a	Metastasis in 7–15 regional lymph nodes
N3b	Metastasis in 16 or more regional lymph nodes
Distant Metastasis	

M0	No distant metastasis
M1	Distant metastasis
Stage Grouping—Pathological Staging (pTNM)[a]	
Stage 0	Tis N0 M0
Stage IA	T1 N0 M0
Stage IB	T1 N1 M0 T2 N0 M0
Stage IIA	T1 N2 M0 T2 N1 M0 T3 N0 M0
Stage IIB	T1 N3a M0 T2 N2 M0 T3 N1 M0 T4a N0 M0
Stage IIIA	T2 N3a M0 T3 N2 M0 T4a N1 M0 T4a N2 M0 T4b N0 M0
Stage IIIB	T1 N3b M0 T2 N3b M0 T3 N3a M0 T4a N3a M0 T4b N1 M0 T4b N2 M0
Stage IIIC	T3 N3b M0 T4a N3b M0 T4b N3a M0 T4b N3b M0
Stage IV	Any T Any N M1

[a]Refer to AJCC staging classifications for clinical staging (cTNM) and post-neoadjuvant staging (ypTNM).

Adapted from the American Joint Committee on Cancer (AJCC) Staging Manual, 8th Edition (2017).

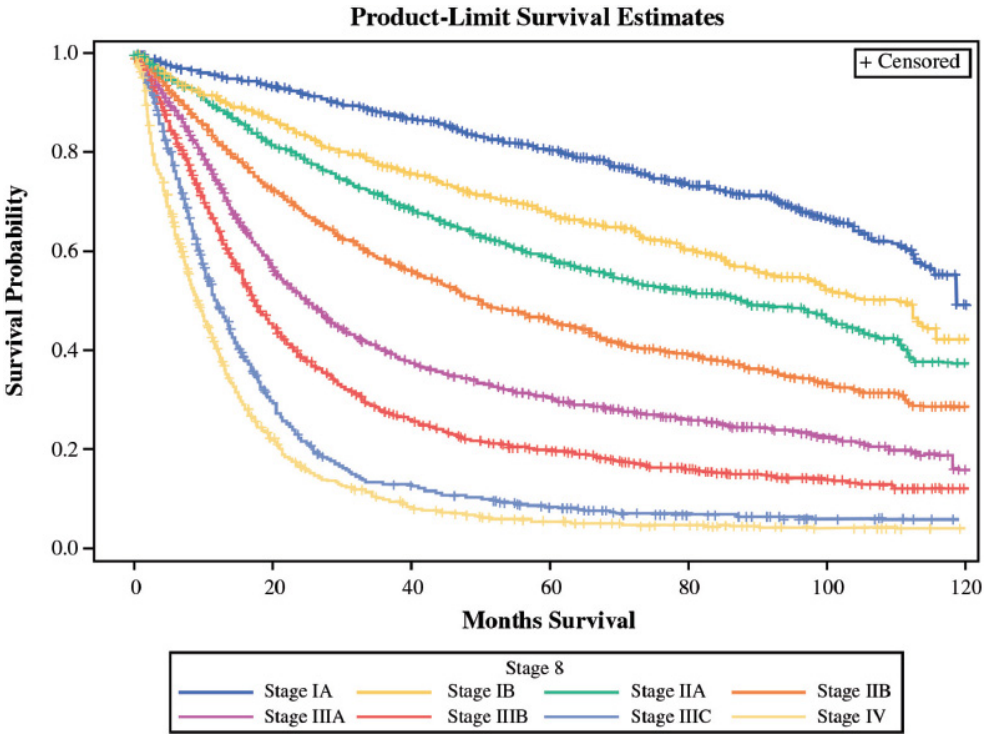


Figure 47.8 Gastric cancer 5-year survival by AJCC 8th edition pTNM stage groupings, based on data from the National Cancer Database. (From In H, Solsky I, Palis B, et al. Validation of the 8th edition of the AJCC TNM staging system for gastric cancer using the National Cancer Database. *Ann Surg Oncol* 2017;24:3683–3691.)

Surgical Resection

4 The fundamental principle of surgical resection of gastric cancer is complete extirpation of the primary tumor. The extent of gastric resection is determined primarily by the need to obtain a resection margin free of microscopic disease (R0 resection) and requires formal, anatomic gastrectomy. Microscopic involvement of the resection margin by tumor cells (R1 resection) is associated with poor prognosis. Patients with positive surgical margins are at high risk for development of recurrent disease, and histologically positive margins are strongly correlated with the development of anastomotic recurrence. In the setting of ≥5 positive nodes, however, margin positivity itself does not impact survival,[65] because these patients are

at higher risk for systemic recurrence. In contrast to other gastrointestinal malignancies such as colon cancer, gastric cancer frequently demonstrates extensive intramural spread, especially the diffuse type. The propensity for intramural spread is related, in part, to the extensive anastomosing capillary and lymphatic network in the wall of the stomach. As such, wedge or segmental resections are inadequate and should not be performed. Based on retrospective studies as well as prospective data from the Italian Gastrointestinal Tumor Study Group, when performing a subtotal gastrectomy, a 3- to 6-cm (commonly cited as 5-cm) margin of resection is adequate and necessary to minimize anastomotic recurrence.[66,67]

For lesions in the distal two-thirds (middle or distal third) of the stomach, subtotal gastrectomy is usually sufficient for complete removal of the primary tumor.[42] In contrast, lesions in the upper third of the stomach generally require total gastrectomy (or esophagogastrectomy) to assure adequate resection (**Fig. 47.9**).[42] For tumors involving the cardia without involvement of the gastroesophageal junction, some have advocated proximal gastrectomy as an alternative to total gastrectomy with esophagojejunostomy with the goal of preserving a gastric reservoir. This procedure does not compromise oncologic outcomes,[68] but there is a significantly higher incidence of severe reflux esophagitis with proximal gastrectomy and is generally not recommended even with jejunal interposition or fundoplication. The distal stomach is typically divided at the level of the duodenal bulb, beyond the pylorus. Local invasion into the duodenum on the distal margin can occur though pancreaticoduodenectomy is rarely needed to assure clearance of disease. Frozen section evaluation of resection margins may be obtained prior to proceeding with reconstruction in order to improve the probability that radical (R0) resection is achieved, especially if gross margins are deemed closer than 3 cm. However, the decision to reresect in the setting of a positive frozen section margin is controversial and must take operative risk as well as tumor biology into account. Reexcision has only been associated with improved survival in early-stage gastric cancer.[69,70] It is plausible that positive frozen section margins may be a surrogate for aggressive disease.

During the course of a radical resection, ligation of the right gastric and right gastroepiploic artery is standard. Ligation of the left gastric artery is a required part of a total gastrectomy, and is done selectively for partial gastrectomy. While the omentum is commonly removed en bloc as part of a

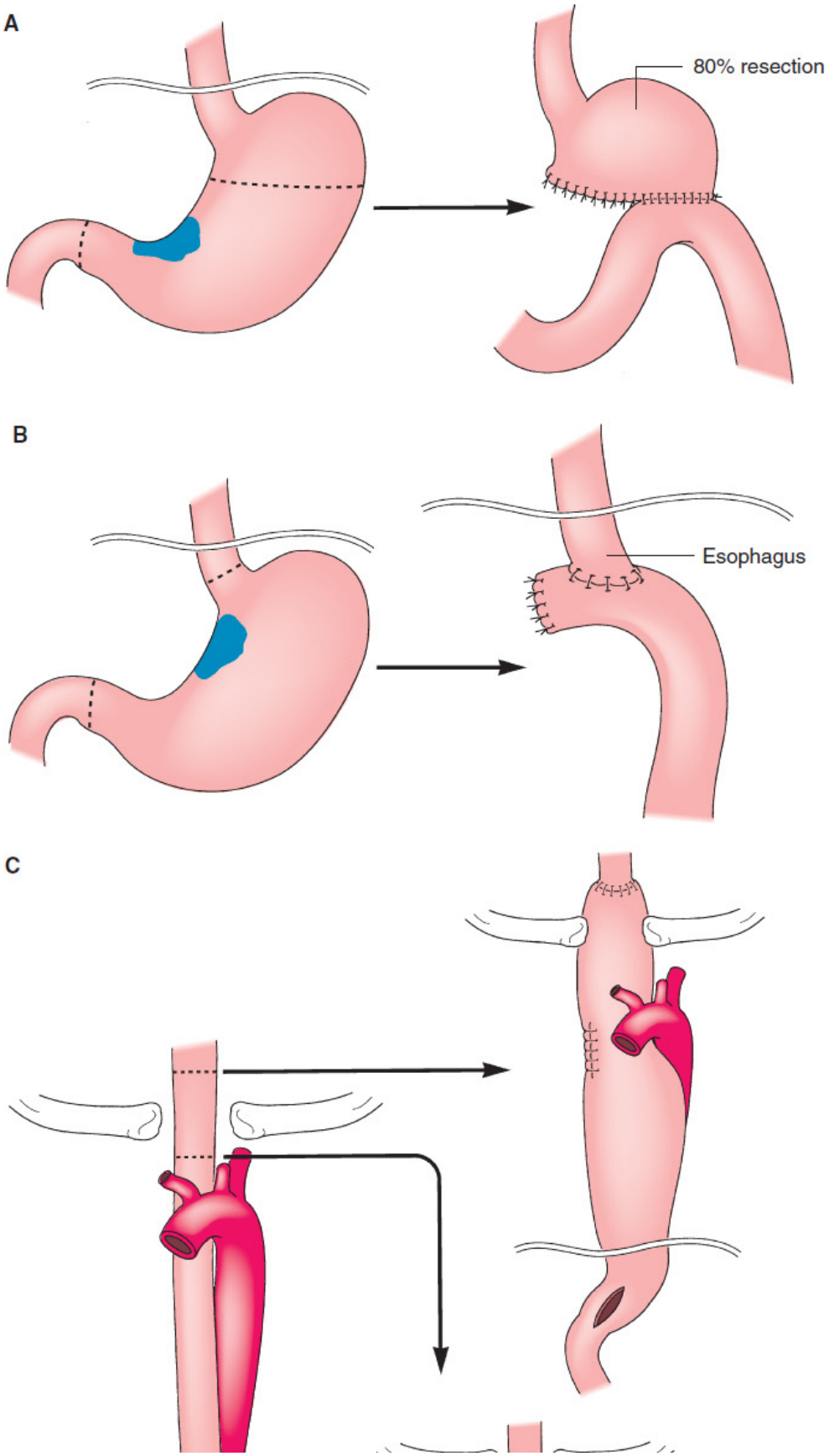
radical gastrectomy, complete removal of the omental bursa (the peritoneum overlying the pancreas and anterior transverse mesocolon) is not indicated.[42] For some T4 tumors, a multivisceral resection is indicated if required to achieve complete removal of the tumor in the course of a curative intent resection. Data evaluating the additional morbidity and mortality associated with multivisceral resection is variable and may be dependent on the organs removed, with higher risks associated with pancreatectomy than with splenectomy or colectomy.

Radical gastric operations can be performed with acceptable morbidity and low mortality rates in the older age groups at greatest risk for gastric cancer. In modern series, mortality rates for total gastrectomy range from 3% to 6%.[71] There is some evidence that outcomes are superior at higher-volume centers.[72,73] In the postacute setting, nutritional support in the immediate postoperative period is an important adjunctive measure as patients resume oral intake, and many surgeons place a jejunal feeding tube at the time of total gastrectomy to ensure that optimal enteral nutrition can be delivered in the postoperative period. Surgical reconstructions that interpose a small intestinal reservoir between the esophagus and the jejunum have been advocated after total gastrectomy, but a clear nutritional benefit has not been demonstrated.[74–76] Postoperative complications, including malnutrition, adversely impacts long-term survival in patients with gastric cancer due to a generalized failure to thrive or perhaps due, at least in part, to lower rates of adjuvant therapy.

Because gastric cancer metastasizes so frequently to lymph nodes, radical extirpation of draining lymph nodes has both diagnostic/staging and therapeutic implications.[77] The value of routine-extended lymphadenectomy beyond the perigastric lymph nodes in the treatment of gastric adenocarcinoma, however, is controversial. The first favorable experience was reported from Japan[78,79] and extent of resection in the original Japanese system is shown in **Table 47.3**; the current nomenclature used to define extent of lymphadenectomy is shown in **Table 47.4** and **Figure 47.10**. Only retrospective studies of extended perigastric lymphadenectomy have been reported from Japan and those reports suggested an improvement of approximately 10%, stage for stage, for patients with advanced disease treated with D2 or D3 operations.[78–80] The benefits of extended lymphadenectomy have not been confirmed in non-Japanese centers, and

several randomized trials in Western centers have failed to show a survival benefit for extended lymphadenectomy when the entire patient population was analyzed.[81–84] Long-term follow-up results from the Dutch trial of D1 versus D2 lymphadenectomy have shown a lower gastric cancer–related death rate in the D2 group (37% vs. 48%) and lower rates of local and regional recurrence.[85] However, the significance of this finding and implications for extended lymphadenopathy is unclear given the absence of an overall survival benefit as well as intervening improvements in adjuvant therapy over the 15-year follow-up period.

Data from a national Japanese registry indicate a contemporary mortality of less than 1% associated with extended lymphadenectomy[86] and low mortality risks have been reported from multi-institutional trials conducted in Italy and Germany.[84,86,87] Investigations from the United States, Britain, and the Netherlands have been less optimistic, indicating increased short-term morbidity and in-hospital mortality.[81,82] Histologically positive lymph nodes are frequently present in the splenic hilum and along the splenic artery, and routine splenectomy has been practiced in some centers. Splenectomy in this setting has not been demonstrated to improve outcome for similarly staged patients.[88,89] Associated splenectomy or pancreatosplenectomy is only beneficial when there is direct extension or bulky adenopathy at the splenic hilum.


A
80% resection
B
Esophagus
C

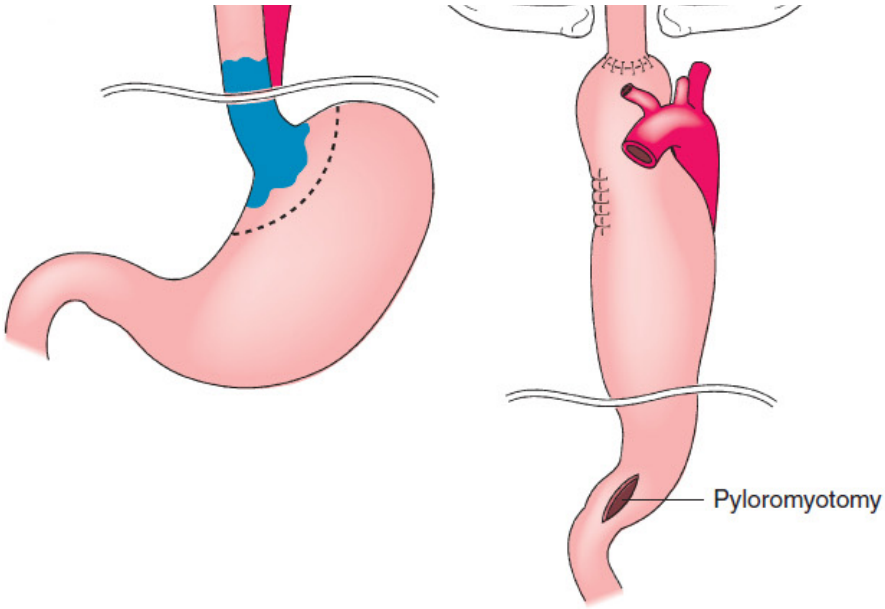


Figure 47.9 Surgical options for resection of gastric neoplasms. **A:** Subtotal gastrectomy with gastrojejunal reconstruction. **B:** Total gastrectomy with esophagojejunostomy. **C:** Esophagogastrectomy with anastomosis in cervical or thoracic position.

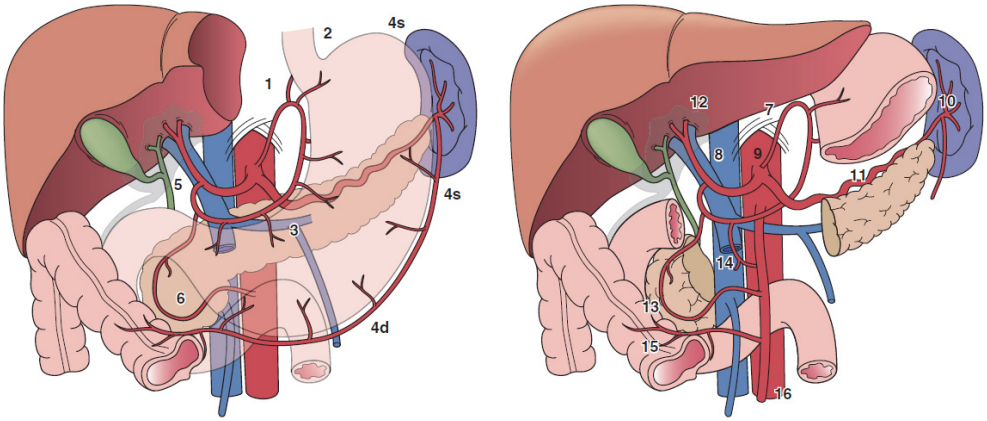
Table 47.3 Lymphadenectomy in the Original System of the Japanese Research Society for Gastric Cancer

Level	Description
R1	Resection of stomach, omentum, and perigastric lymph nodes
R2	Resection of stomach, omentum, and en bloc removal of the superior leaf of the transverse mesocolon, the pancreatic capsule and lymph nodes along the branches of the celiac artery and in the infraduodenal and supraduodenal areas
R3	Resection of the above structures plus lymph nodes along the aorta and esophagus, along with the spleen and the tail of the pancreas, and skeletonization of vessels in the porta hepatis

Recommendations for a minimum number of regional lymph nodes retrieved and examined with lymphadenectomy serve as a proxy for adequacy of resection. Emphasis on the total number of nodes removed rather than the location of the nodes (e.g., D1 lymphadenectomy) continues to be debated. While the AJCC staging system does not strictly specify a minimum number of nodes, N3b disease is defined by metastases in 16 nodes. As such, current recommendations for gastric cancer staging suggest that a minimum of 16 nodes need to be evaluated.[42,56,90]

Table 47.4 Current Nomenclature Used to Describe the Extent of Lymphadenectomy Performed in Conjunction with Gastrectomy

Level	Description
D0	Any lymph node removal that is less than D1
D1	Resection of greater and lesser omenta, including the perigastric nodes along the right and left cardia, nodes along the lesser and greater curvatures, suprapyloric nodes along the right gastric artery, and infrapyloric nodes
D2	D1 dissection plus nodes along the left gastric artery, common hepatic artery, celiac trunk, splenic hilum, and splenic artery
D3	D2 dissection plus nodes in the hepatoduodenal ligament, retropancreatic nodes, and nodes at the root of the mesentery the para-aortic lymph nodes
D4	D3 dissection plus paracolic and para-aortic nodes



N1 Lymph nodes (perigastric)
1 Right cardiac nodes
2 Left cardiac nodes
3 Nodes along the lesser curvature
4d Lymph nodes along the short gastric and the left gastroepiploic vessels
4s Lymph nodes along the right gastroepiploic vessels
5 Suprapyloric nodes
6 Infrapyloric nodes

N2 Lymph nodes (celiac axis branches)
7 Nodes along root left gastric artery
8 Nodes along common hepatic artery
9 Nodes around celiac axis
10 Nodes at splenic hilum
11 Nodes along splenic artery

N3 Lymph nodes
12 Nodes at the hepatoduodenal ligament
13 Retropancreatic (periduodenal) nodes
14 Nodes at the root of the mesentery

N4 Lymph nodes
15 Nodes along the middle colic vein
16 Para-aortic nodes

Figure 47.10 Lymph node locations and groupings. D1 dissection: removal of N1 nodes. D2 dissection: removal of N1 and N2 nodes. D3 dissection: removal of N1, N2, and N3 nodes. D4 dissection: removal of N1–N4 nodes.

A minimally invasive approach to gastrectomy, defined as laparoscopic or robotic, appears to be increasingly acceptable as an alternative to open surgery. The main use of minimally invasive gastrectomy includes, but is not necessarily limited to, early and distal tumors. Resection of more advanced cancers or total gastrectomy have been reported for treatment of known gastric malignancy, but must take surgeon experience into account. Multiple studies from Japan, Korea, and Italy have demonstrated that distal, subtotal, or total gastrectomy with lymphadenectomy is feasible with acceptable morbidity and mortality. A meta-analysis of four small single-institution randomized trials from Asia demonstrated lower nodal harvests with a laparoscopic approach for early gastric cancer. Complication rates were lower in the laparoscopic group but did not translate into differences in time to oral intake or length of stay.[91] However, a single-institution Western randomized trial of laparoscopic versus open subtotal gastrectomy for distal gastric cancer (both early and locally advanced) did report equivalent lymph node retrieval (33.4 ± 7.4 in the open group vs. 30 ± 14.9 in the laparoscopic group), as well as similar rates of perioperative morbidity and mortality. Their 5-year overall and disease-free survival were also similar for both groups: 55.7% and 54.8% for the laparoscopic group versus 58.9% and

57.3% for the open group, respectively.[92] More recently, results of the Korean Laparoendoscopy Gastrointestinal Surgery Study (KLASS), a multicenter randomized trial focused on distal gastrectomy for early gastric cancer demonstrated improved perioperative morbidity and no differences in oncologic outcomes have been shown with short follow-up.[93] Early results from the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) Group randomized clinical trial comparing the safety of laparoscopic versus open total gastrectomy with lymphadenectomy for patients with clinical stage I gastric cancer showed that overall morbidity and mortality rates were not significantly different between the groups.[94]

Neoadjuvant and Adjuvant Therapies

5 Given the largely disappointing outcomes of locoregional or locally advanced gastric cancer in Western countries, significant interest has focused on the use of multimodality therapy. Several neoadjuvant and adjuvant approaches have been explored. Although there is no consensus on the optimal approach, it is clear that all patients with locally advanced disease should be considered for multimodality therapy. Several landmark trials highlight a primary role for both adjuvant and neoadjuvant chemotherapy. Despite the limitations of these studies, which are beyond the scope of the present discussion, improved survival observed across trials makes it clear that a multimodality approach is superior to surgery alone for those patients with locally advanced gastric cancer. The addition of radiation to surgery has also been associated with improved local control and survival.[95] A randomized phase III trial (CRITICS) comparing perioperative chemotherapy with preoperative chemotherapy followed by postoperative chemoradiation found no improvement in overall survival with the addition of postoperative radiation.[96] However, numerous ongoing studies are investigating the relative benefits of various chemotherapeutic regimens as well as the incremental benefit of chemoradiotherapy (with radiation in both the preoperative and postoperative settings) versus chemotherapy alone. This includes CRITICS II which compares three preoperative strategies: chemotherapy, chemoradiation (concurrent), and sequential chemotherapy and chemoradiation treatments.[97]

A neoadjuvant, or perioperative, approach is preferred for resectable disease. A randomized controlled phase II/III trial led to standard

recommendations for fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with T2 or greater disease and/or node-positive disease if performance status is good.[98] Other regimens may be considered if performance status is more concerning since a regimen of fluorouracil and oxaliplatin (FOLFOX) is better tolerated and has a lower chemotherapy-related toxicity profile. There are newer considerations for a total neoadjuvant therapy approach, meaning that all systemic therapy is administered in advance of the operation. In these cases, additional chemotherapy in the postoperative setting is only administered if microscopic disease or unexpectedly advanced nodal disease is found at time of gastrectomy. Some have advocated for the total neoadjuvant approach in order to mitigate against the adverse impact postoperative complications, and subsequent delays in adjuvant treatment, may have on long-term survival[99] as it appears that rates of completion of multimodality treatment are much higher when given in the preoperative setting.

Targeted therapies, which are currently approved for use for recurrent, advanced, or metastatic disease, are also being actively investigated for use in the neoadjuvant setting. Treatment with trastuzumab is based on HER-2 status, with phase III trial evidence supporting first-line use in metastatic gastric cancer.[100] Testing for HER-2 expression, microsatellite instability/DNA mismatch repair deficiency, and PD-L1 status are recommended in the setting of metastatic disease.

As preoperative strategies continue to evolve, patients with locally advanced resectable gastric cancer are optimally treated in a center where a collaborative multidisciplinary treatment approach can be devised and executed (**Algorithm 47.1**). Not only is discussion at a team meeting, or tumor board, important for decision making and treatment planning, but it also helps with careful coordination across the continuum of cancer care.

Palliative Surgical Treatment

When preoperative evaluation demonstrates disseminated disease, palliation of symptoms becomes a primary consideration. Palliation does not usually require surgical intervention. Obstruction and bleeding can be managed nonoperatively with endoscopic techniques, including intraluminal stents, or radiotherapy in selected patients. Dysphagia and bleeding caused by

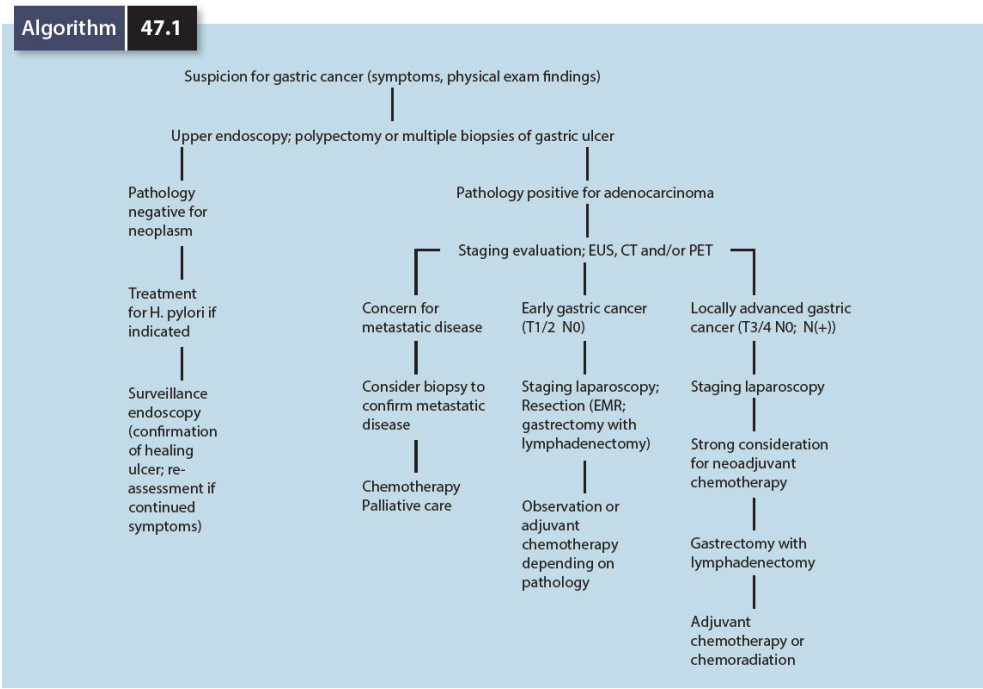
proximal lesions can also be alleviated endoscopically (laser therapy or stenting) in the majority of patients. Surgical palliation of obstructive symptoms (via formal resection or gastrojejunostomy) should generally be reserved for cases in which less invasive methods are contraindicated, technically infeasible, or unsuccessful. In addition to radiotherapy and endoscopic ablation or stenting, placement of a feeding jejunostomy tube with or without venting gastrostomy may be used to palliate gastric outlet obstruction, especially in patients with limited life expectancy. Many of these interventions area associated with high morbidity and are often ineffective at relieving symptoms; for example, gastrojejunostomy intended as a bypass procedure often does not afford gastric drainage and could delay onset of systemic treatments. Nonetheless, for a minority of patients, surgical palliation may be indicated; for example, noncurative resection may be necessary in the setting of intractable bleeding from the primary tumor. In the setting of metastatic gastric cancer, palliative resection does not improve survival, and systemic therapy is considered first-line treatment.

OTHER GASTRIC NEOPLASMS

Gastric Lymphoma

Clinical Features

The stomach is the site of more than half of gastrointestinal lymphomas and is the most common organ involved in extranodal lymphomas. Non-Hodgkin lymphomas account for approximately 5% of malignant gastric tumors. Patients are considered to have primary gastric lymphoma if initial symptoms are gastric in origin and the stomach is exclusively or predominantly involved with the tumor. Patients who do not fulfill these criteria are considered to have secondary gastric involvement from systemic lymphoma.



Algorithm 47.1 Diagnosis and management of gastric cancer.

Gastric lymphoma has peak incidence in the sixth and seventh decades. Symptoms are usually indistinguishable from those of peptic ulcer disease and gastric adenocarcinoma. Epigastric pain, weight loss, anorexia, nausea, and vomiting are common.[101] Systemic B symptoms such as fever and night sweats occur in a minority of patients but may be suggestive of the diagnosis. Although gross bleeding is uncommon, occult hemorrhage and anemia are observed in more than half of patients. Patients rarely have spontaneous perforation.

Diagnosis

Radiologic findings are similar to those for adenocarcinoma (gastric thickening and lymphadenopathy). Endoscopic examination is the diagnostic method of choice. The endoscopic appearance of lesions may be ulcerated, polypoid, or infiltrative, and this morphology may be further characterized by EUS. Gastric lymphoma is most commonly localized to the middle or distal stomach and unusually involves the proximal stomach, in contrast to gastric adenocarcinoma. Endoscopic biopsy, combined with endoscopic brush cytology and EUS, provides positive diagnosis in 90% of cases. Submucosal growth without ulceration of the overlying mucosa can occasionally render

endoscopic biopsy nondiagnostic. EUS-guided biopsy is useful in this circumstance.

Appropriate staging should search for evidence of systemic disease. CT of the chest and abdomen (to detect lymphadenopathy), bone marrow biopsy, and biopsy of enlarged peripheral lymph nodes are all appropriate.

Mucosa-Associated Lymphoid Tissue

The concept that low-grade gastric lymphomas have features resembling mucosa-associated lymphoid tissue (MALT) is a major advance in the understanding of gastric lymphomas. A number of observations support a causal relationship between chronic *H. pylori* infection and gastric lymphoma development. *H. pylori* is present in the stomachs of more than half of patients with gastric lymphoma[102] and 90% of those with gastric MALT lymphoma.[103] As with gastric adenocarcinoma, geographic regions with a high prevalence of *H. pylori* also have a high incidence of gastric lymphoma. Infection with *H. pylori* has been noted to precede development of gastric lymphoma.[104]

Gastric MALT lymphoma is postulated to begin with chronic inflammation due to infection with *H. pylori*. Chronic gastritis leads to the accumulation of CD4+ lymphocytes and B cells in the gastric lamina propria. *H. pylori*–derived antigens drive T-cell activation, interleukin-2 (IL-2) release, and B-cell proliferation.[105] Progressive genetic rearrangements lead to IL-2–independent B-cell proliferation. With cumulative genetic defects, low-grade MALT lymphoma progresses to high-grade disease.

Low-grade MALT lymphomas resemble Peyer patches. Lymphoma cells invade between follicles and into gastric epithelium; invasion of gastric glands forms characteristic lymphoepithelial lesions. Low-grade lesions are often multifocal. Low-grade MALT lesions are less likely than high-grade tumors to invade transmurally, involve perigastric lymph nodes, or invade adjacent organs.[104] Approximately 40% of gastric lymphomas are low-grade MALT lymphomas.

The concept that low-grade lymphoma depends on continued *H. pylori* antigenic stimulation supports eradication of *H. pylori* with antibiotics as first-line antineoplastic therapy. Complete regression of low-grade gastric MALT lymphomas with antibiotic treatment has been reported in 70% to

100% of cases. The median time to complete response is 5 months.[106–108] Most patients with partial responses were subsequently determined also to have foci of high-grade lymphoma. Radiation and chemotherapy have been proposed as salvage for antibiotic treatment failures or for the minority of patients with *H. pylori*–negative gastric MALT lymphoma.

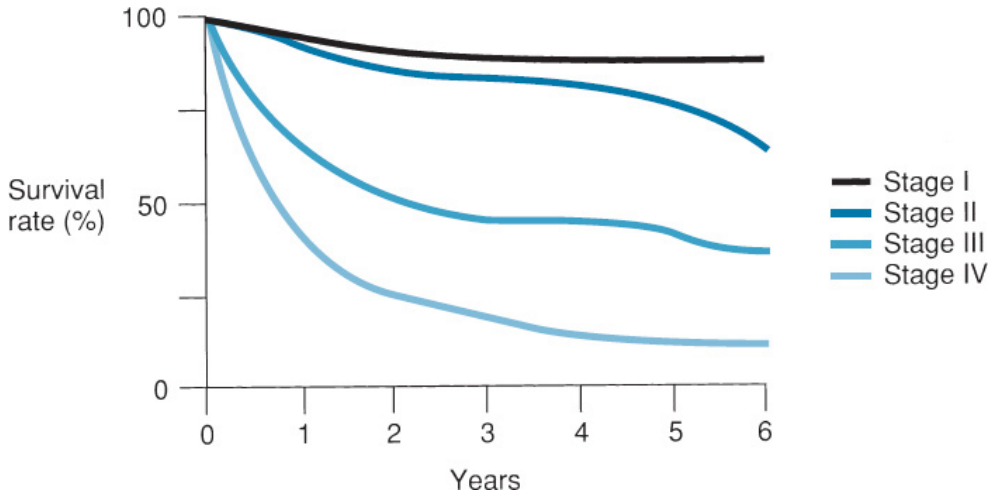


Figure 47.11 Survival with gastric lymphoma, by stage.

Non-MALT Lymphomas

Most non-MALT gastric lymphomas are diffuse large B-cell lymphomas (DLBCLs), including those that were previously called "high-grade MALT lymphomas." DLBCLs typically exhibit more aggressive behavior and worse prognosis than MALT lymphomas. Other histologies, such as mantle cell, follicular, and peripheral T-cell lymphomas can also be seen. Survival for gastric lymphoma is closely linked to stage at diagnosis (**Fig. 47.11**).

In the past, a multimodality treatment program was used in most centers for primary gastric lymphomas, with gastrectomy as the first step in the therapeutic strategy.[109] Even without prospective data to support gastrectomy, several advantages of this approach had been cited: (a) more accurate histologic evaluation was possible; (b) in cases with localized tumor, the procedure could be curative; and (c) gastrectomy eliminated the risk of life-threatening hemorrhage or perforation which may occur with the treatment of tumors involving the full thickness of the gastric wall.[110] However, the role of gastrectomy for both staging and treatment of gastric lymphoma has diminished significantly, based in part on results of a randomized trial

demonstrating superior outcomes with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy compared with surgery, surgery plus radiotherapy, or surgery with CHOP (**Fig. 47.12**).[111] It has also been recognized that the incidence of perforation during chemotherapy is only 5%. Most patients are currently treated with chemotherapy (commonly CHOP with rituximab) with or without radiotherapy. Surgical intervention is generally reserved for complications such as obstruction, bleeding, or perforation.

Gastric Carcinoids

Neuroendocrine, or carcinoid, tumors of the stomach were previously considered to be very rare tumors, but more recent studies report that as many as 10% to 30% of all carcinoids occur in the stomach, and they account for at least 1% of all gastric neoplasms.[112] Most patients with small gastric carcinoids are asymptomatic, and these tumors are most commonly diagnosed incidentally. Occasionally, however, larger tumors can present with abdominal pain, bleeding, or symptoms related to the secretion of bioactive substances (serotonin, histamine, or tachykinins) which can be produced by the tumor. When viewed endoscopically at an early stage, carcinoids are reddish-pink to yellow submucosal nodules in the proximal stomach. Endoscopic biopsy is usually diagnostic if sampling can be directed deep enough to sample submucosal tumor cells.

Classically, three types of gastric carcinoids have been described. Type 1 is the most common (70% to 80%) and is associated with chronic atrophic gastritis and pernicious anemia. These tumors tend to be small (<1 cm) and multiple, and exhibit indolent behavior. When they are less than 2 cm in size, they metastasize less than 10% of the time.[113] They can typically be followed and removed endoscopically, but surgery may be necessary for larger or very numerous tumors. Type 2 tumors comprise approximately 5% of gastric carcinoids and occur in patients with Zollinger–Ellison syndrome (gastrinomas), often in the setting of multiple endocrine neoplasia type 1 (MEN-1). Like type 1 tumors, they are often small, multiple, and indolent, and they can be treated endoscopically for the most part. Both type 1 and type 2 gastric carcinoid tumors are associated with hypergastrinemia. Type 1 and 2 gastric carcinoids arise from enterochromaffin-like (ECL) cells, which

mediate the secretion of histamine and in turn stimulate parietal cells to secrete acid. Hypergastrinemia (due to chronic atrophic gastritis in type 1 and gastrinoma in type 2) is thought to cause ECL cell hyperplasia and lead to the development of gastric carcinoids over time.

Type 3 lesions account for 20% of gastric carcinoids. Type 3 gastric carcinoids tend to be larger, solitary lesions. They are associated with normal gastrin levels and behave much more aggressively than other gastric carcinoid tumors.[114] Metastases are common, and these tumors can cause an atypical carcinoid syndrome. Type 3 carcinoids are best dealt with by resection and lymphadenectomy, the extent of which depends on the size of the tumor.

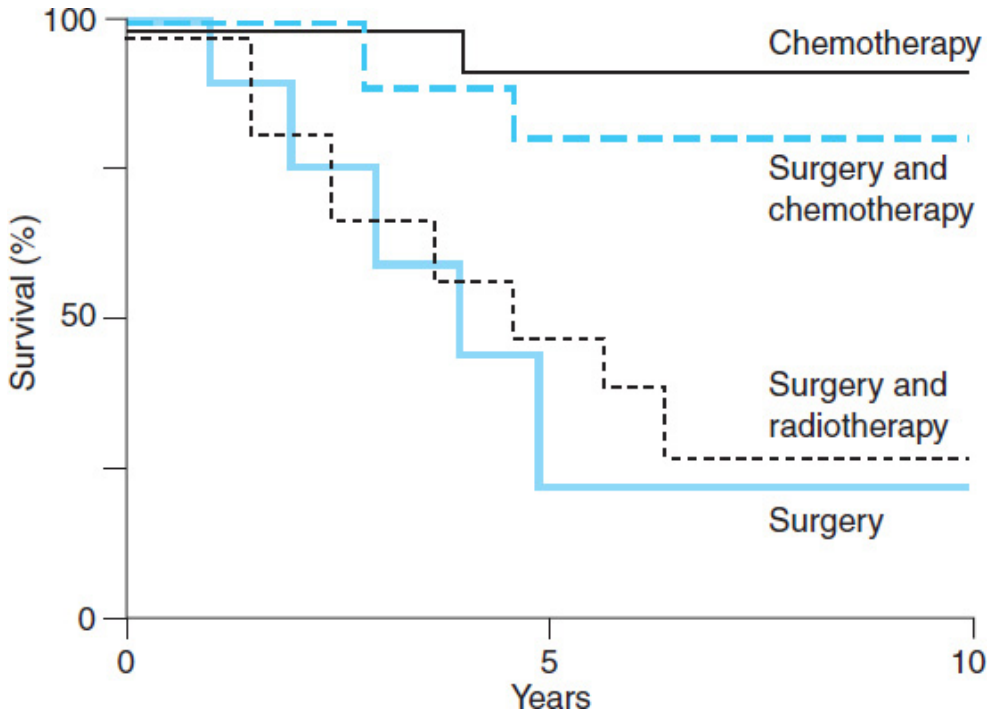


Figure 47.12 Relapse-free survival by treatment assignment for primary gastric diffuse large B-cell lymphoma.

Gastrointestinal Stromal Tumors of the Stomach

Gastrointestinal stromal tumors (GISTs) were historically misclassified as leiomyomas, leiomyosarcomas, and leiomyoblastomas due to a mistaken belief that they arose from the smooth muscle in the bowel wall. However, it

is now recognized that GISTs represent a distinct mesenchymal tumor type, and actually arise from the interstitial cells of Cajal, intestinal pacemaker cells located in and around the myenteric plexus in the bowel wall. While GISTs can arise anywhere within the gastrointestinal tract, approximately 50% of these tumors are found in the stomach. With a slight male predominance, GISTs are typically present in middle-aged and elderly individuals, with a median age at presentation of approximately 60 years. They are typically asymptomatic and are most commonly identified incidentally during endoscopy performed for other reasons. Their endoscopic appearance is that of a submucosal mass with normal overlying mucosa. If these tumors become large, however, they may present with symptoms of abdominal pain and bleeding. GISTs frequently have prominent extraluminal growth patterns, and central necrosis occurs as these tumors become very large and outgrow their blood supply (**Fig. 47.13**). If the majority of the growth is extraluminal, endoscopic examination may be unrevealing or only demonstrate umbilication of the mucosa suggestive of an underlying mass. EUS or CT imaging may be helpful for diagnosis in these cases. With large tumors, symptoms related to mass effect may occur. Ulceration of the overlying gastric mucosa may occur with tumor necrosis, and these patients may present with significant and intermittent gastrointestinal hemorrhage even at relatively small sizes.

The molecular hallmark of GISTs is overexpression of the CD117 antigen, which is part of the KIT transmembrane receptor tyrosine kinase. Mutations in *c-kit,* the proto-oncogene that encodes KIT, can lead to constitutive activation of the receptor and abnormal cell proliferation. Approximately 95% of GISTs overexpress KIT. Of those that do not, many have activating mutations in platelet-derived growth factor receptor alpha (PDGFRA), another receptor tyrosine kinase. However, some GISTs lack mutations in either of these genes, and many of these are characterized by inactivating mutations in the succinate dehydrogenase (SDH) complex. The molecular pathogenesis of GIST is important because of the availability of tyrosine kinase inhibitors (TKIs), such as imatinib and sunitinib. However, for GISTs that lack KIT or PDGFRA mutations, as well as those with certain types of KIT or PDGFRA mutations, there is resistance to TKI therapy.

Figure 47.13 CT scan of GIST of stomach arising from lesser curvature. The *arrow* indicates central tumor necrosis. The lesion caused mucosal erosion with gastrointestinal hemorrhage.

Table 47.5 Risk of Aggressive Behavior in Gastrointestinal Stromal Tumors

Risk	Size (cm)	Mitotic Count (per 50 HPF)	Primary Tumor Site
Very low	<2.0	≤5	Any
Low	2.1–5.0	≤5	Any
Intermediate	2.1–5.0	>5	Gastric
	<5.0	6–10	Any
	5.1–10	≤5	Gastric
High	>10	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1–5.0	>5	Nongastric
	5.1–10	≤5	Nongastric
	Any	Any	Tumor rupture

HPF, high-powered fields.

All GISTs should be considered potentially malignant, especially those >1 cm in size.[115] Tumor size and mitotic index are the most important prognostic variables (**Table 47.5**).[116] Site of origin is also prognostic, with gastric GISTs behaving generally less aggressively than intestinal GISTs.[117] For localized GISTs, surgical resection is the treatment of choice. When GISTs do metastasize, they do so by a hematogenous route (most commonly to peritoneal surfaces and the liver). Therefore, associated lymphadenectomy is typically not recommended or performed at the time of gastric resection for GIST. Additionally, unlike adenocarcinoma, GISTs do not present with an intramural growth pattern and thus gross margins of 1 to 2 cm are deemed adequate for resection of a GIST. Ultimately the goal of resection is a negative microscopic margin. If the tumor involves adjacent structures, then en bloc resection of nonvital structures should be performed whenever possible. Due to the less radical nature of surgery required for appropriate oncologic resection of these tumors as compared to adenocarcinoma of the stomach, minimally invasive surgical techniques have become widely

accepted as an appropriate and acceptable operative approach for these tumors.

For patients with metastatic or locally advanced, unresectable GISTs, imatinib is first-line therapy. Although most patients will respond to imatinib therapy, development of resistance is common, likely due to selection of clones with secondary KIT mutations.[118,119] These patients may be managed either with imatinib dose escalation or by using another TKI (e.g., sunitinib). Imatinib is also indicated in the adjuvant setting for tumors at high risk for recurrence. The ACOSOG Z9001 trial evaluated the efficacy of 1 year of adjuvant imatinib versus placebo in patients with resected GIST ≥3 cm in size and KIT positive.[120] Recurrence-free survival at 1 year was significantly higher in the imatinib arm (98% vs. 83%). No overall survival difference was shown, likely because patients were allowed to cross over to the imatinib arm after the study was unblinded. The Scandinavian Sarcoma Group evaluated the effect of 3 years versus 1 year of adjuvant imatinib after resection of high-risk GIST and found differences in 5-year recurrence-free survival (66% vs. 49%) and overall survival (92% vs. 82%), respectively.[121] Based on these data, 3 years of imatinib therapy are recommended after resection of high-risk GIST. Rates of recurrence after discontinuation of imatinib therapy are similar to those in untreated patients, suggesting that TKI therapy may simply be delaying recurrences rather than actually preventing them. Though no prospective randomized trial has determined a role for neoadjuvant imatinib, there are compelling data that in select populations (namely large and locally advanced tumors), neoadjuvant imatinib may help decrease size of tumor and morbidity of resection. If using neoadjuvant imatinib to help downsize borderline resectable GIST, early evaluation with PET CT can determine whether tumor is responding to therapy with decreasing FDG avidity within 1 to 2 weeks of onset of treatment, noting that changes in size are lagged and can take 6 to 9 months.

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Section F: SMALL INTESTINE

48

Anatomy and Physiology of the Small Intestine

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Key Points

1 The normal adult anatomy of the small intestine is the result of a complex cascade of embryologic events which result in 270 degrees of counterclockwise rotation of the bowel around its axis. A failure of these precise steps produces a spectrum of congenital abnormalities.

2 There is no clear anatomic boundary between the jejunum and ileum. The proximal two-fifths of the small intestine distal to the ligament of Treitz have been defined as *jejunum* and the distal three-fifths as *ileum.*

3 The small intestine is the largest endocrine organ in the human body. The secretion of numerous hormones and neurotransmitters are specific to distinct anatomic zones within the small intestine.

4 The coordinated movement of the gastrointestinal (GI) tract is necessary for the proper digestion of food. Well-timed contraction and relaxation patterns are initiated in GI nervous system causing coordinated electrical activity and muscular movements.

5 The lumen of the GI tract is connected to the outside environment and comes in direct contact with many potentially pathogenic microorganisms. Consequently, the small intestine needs a complex defense mechanism to battle against these exposures in different ways.

6 While the exact mechanisms of many of the interactions between the gut microflora and the small intestinal microenvironment are still speculative, it has become evident that a symbiotic environment is present which, at least in part, is responsible for proper homeostasis of the small intestine.

7 The small intestine reabsorbs nearly 80% of the fluid that passes through it. This dynamic process is accomplished by a rapid bidirectional movement of fluid in the intestinal lumen.

8 The small intestine's intrinsic design provides a maximum amount of surface area to absorb nutrients, water, and electrolytes. Specialized areas provide neurohormonal stimulation to the digestive tract. Its

structure also provides an important physical barrier to potential pathogens and certain areas are critical in immune surveillance.

GROSS ANATOMY AND EMBRYOLOGY

The small intestine spans from the pylorus to the ileocecal valve, and includes three distinct regions: the duodenum, the jejunum, and the ileum. These areas combined measure approximately 200 to 300 cm in a newborn and 5 to 7 m (16 to 23 ft) in an adult, comprising greater than 60% of the total length of the alimentary tract. The gastrointestinal (GI) tract is formed from the endodermal layer of the developing embryo. The small intestine is derived from the distal foregut, midgut, and the adjacent splanchnic mesenchyme. Epithelium and glands develop from the embryonic endoderm, while connective tissue, muscle, and serosa develop from the mesoderm. During the fifth and sixth weeks of development, the duodenal lumen is temporarily obliterated due to proliferation of its mucosal lining. In subsequent weeks, luminal vacuolization and apoptosis result in recanalization of the duodenal lumen. From the 7th to 10th week of development, a large portion of the midgut is herniated through the umbilicus. At about 8 weeks of gestation, the midgut rotates counterclockwise 90 degrees around the axis of the mesenteric vasculature. The extra-abdominal portion of the gut returns to the abdominal cavity approximately 2 weeks later, rotating an additional 180 degrees. These two rotations provide 270 degrees of total rotation and result in the typical anatomy found in humans. Failure 1 of these precise steps produces a spectrum of anatomical variants which are grouped together as malrotation of the intestinal tract (**Table 48.1**).[1]

DUODENUM

The duodenum comprises the first portion of the small intestine and plays an important role in connecting the foregut organs to the midgut. It begins immediately distal to the pylorus and terminates at the ligament of Treitz,

where it joins the jejunum. The duodenum is divided into four distinct areas totaling approximately 20 to 30 cm in length.

The first portion (the bulb or cap) is approximately 5 cm in length. This area is directly attached to the pylorus and extends laterally and cephalad. It serves as an attachment for the hepatoduodenal ligament and traverses the common bile duct, portal vein, and pancreatic head. The mucosal surface of the duodenal bulb is smooth until its junction with the second portion of the duodenum. This area of the duodenum is prone to ulceration, accounting for approximately 90% of duodenal ulcers. These ulcers may erode into the gastroduodenal artery which lies directly posterior, causing potentially life-threatening bleeding (**Fig. 48.1**).

The second portion of the duodenum (descending duodenum) extends from the origin of the Kerckring folds to the beginning of the transverse duodenum and travels over the right renal vasculature and the inferior vena cava to the right of the L1 and L2 vertebrae. It is approximately 10 cm in length and 3 to 5 cm in diameter. The Kerckring folds (plicae circulares) are 1 to 2 mm thick and 2- to 4-mm high concentric mucosal folds separated by 2 to 4 mm of smooth, flat mucosa. The midportion of the descending duodenum serves as the entry point for pancreatic and biliary secretions into the GI tract, typically through the major papilla (ampulla of Vater), 7 to 10 cm from the pylorus. Through this point, the confluence of the common bile duct and the main pancreatic duct (duct of Wirsung) joins the duodenum. The valvular function of the papilla is regulated through the muscular sphincter of Oddi. The minor pancreatic duct (duct of Santorini) enters through the minor papilla proximal to the ampulla of Vater and endoscopically appears as a 1 to 3 mm polypoid structure.

Table 48.1 Small Intestine Development and Associated Pathology

Wk of Development	Key Steps in Small Bowel Formation	Associated Pathophysiology
3	Gut tube forms from endoderm lining the yolk sac	Duplication cysts
3–4	Regions of the gut become more defined as embryo grows and folds	
5–6	Obliteration of intestinal lumen due to endodermal proliferation	
7–8	Physiologic herniation of midgut into umbilical cord accompanies rapid increase in length	
7–9	Apoptosis of endoderm and growth of mesoderm recanalizes gut tube. Midgut rotates 90 degrees counterclockwise. Omphalomesenteric/vitelline duct closes	Duodenal atresia; malrotation; Meckel diverticulum, patent vitelline duct, umbilical hernia
8–12	Midgut rotates an additional 180 degrees counterclockwise (total rotation: 270 degrees) as it returns to the abdomen	Malrotation; omphalocele

The descending duodenum is important surgically as it represents the entry of the duodenum into the retroperitoneum. Surgical evaluation of the retroperitoneal duodenum, as well as the pancreatic head and bile duct,

requires mobilization from its posterior and lateral attachments (Kocher maneuver).

The third (transverse) and fourth (ascending) portions of the duodenum complete the duodenal sweep. The third portion is about 10 cm in length and courses from right to left; crossing the midline anterior to the spine, aorta, and inferior vena cava; and is closely attached to the uncinate process of the pancreas. The superior mesenteric artery (SMA) and vein (SMV) course anterior to the transverse duodenum to provide blood supply to the gut. The SMA forms an acute angle as it originates from the aorta and crosses over the duodenum, marking the transition to the fourth portion. An abnormally narrow angle can result in obstruction of the duodenum. The ascending duodenum is approximately 5 cm long and courses upward and obliquely to the ligament of Treitz, marking the end of the duodenum and the return of the small bowel to the peritoneal cavity.

VASCULAR AND LYMPHATIC SUPPLY

The vascular supply to the duodenum follows its embryologic origins, with branches of the celiac trunk supplying the foregut portion and branches of the SMA feeding the distal (midgut origin) duodenum. Venous drainage includes a series of pancreaticoduodenal veins which drain into the SMV–portal vein system. Lymphatic drainage follows the vascular supply with drainage to the pancreaticoduodenal nodes. From here, lymph drains superiorly to the hepatic nodes or inferiorly to the superior mesenteric nodes.

JEJUNUM AND ILEUM

2 Distal to the ligament of Treitz, the jejunum and ileum form the intraperitoneal small intestine. The boundary between them is determined such that 40% of the intraperitoneal small intestine comprises jejunum and 60% comprises ileum. This portion of the bowel is suspended within the peritoneal cavity by a thin, broad-based mesentery attached to the posterior abdominal wall. The jejunum and ileum move freely within the peritoneal cavity. The jejunum is the widest portion of the small intestine, whose

caliber progressively decreases until it terminates in the right lower quadrant at the ileocecal valve. The mucosa of the jejunum has a thick lining characterized by prominent plicae circulares that become shorter and less frequent in the ileum. The ileocecal valve exhibits motor characteristics separate from the terminal ileum and colon, postulated to prevent reflux of fecal material from the colon into the small intestine.[2] However, contrast studies have shown between 70% and 90% of patients have an incompetent ileocecal valve.[3,4]

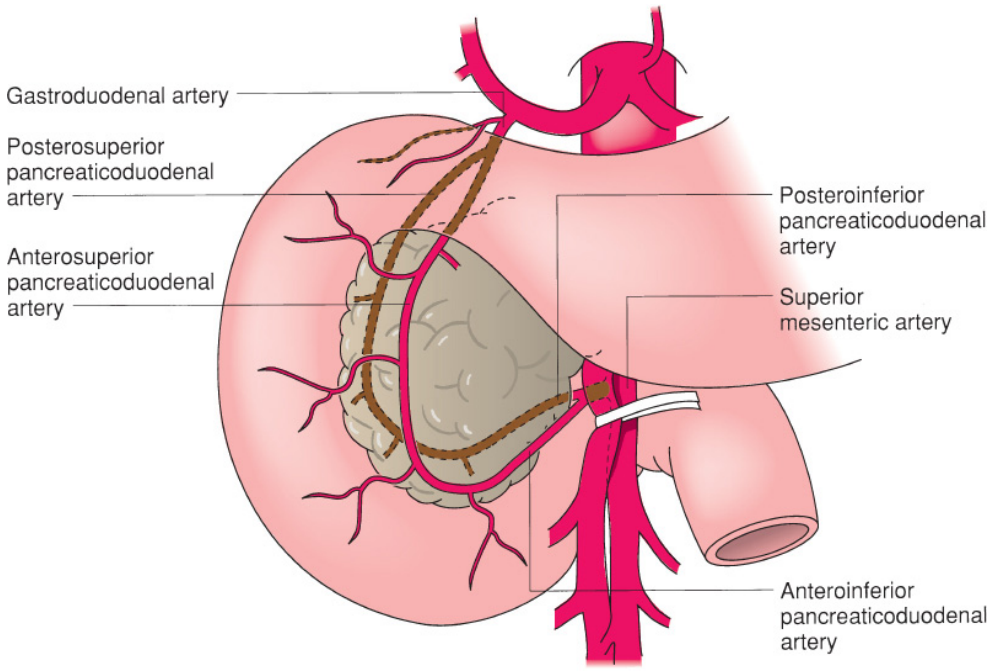

Figure 48.1 Arterial blood supply to the duodenum.

VASCULAR AND LYMPHATIC SUPPLY

The arterial blood supply of the jejunum and ileum arises from the SMA. The main vascular branches form arcades within the mesentery. The vasa recta, intestinal arterial branches, enter into the intestinal wall without anastomosing. The vasa recta of the jejunum are straight and long, in contrast to those of the ileum, which are shorter with greater arborization (**Fig. 48.2**). The venous and lymphatic drainage follow the arterial supply. The main venous outflow is through the SMV.

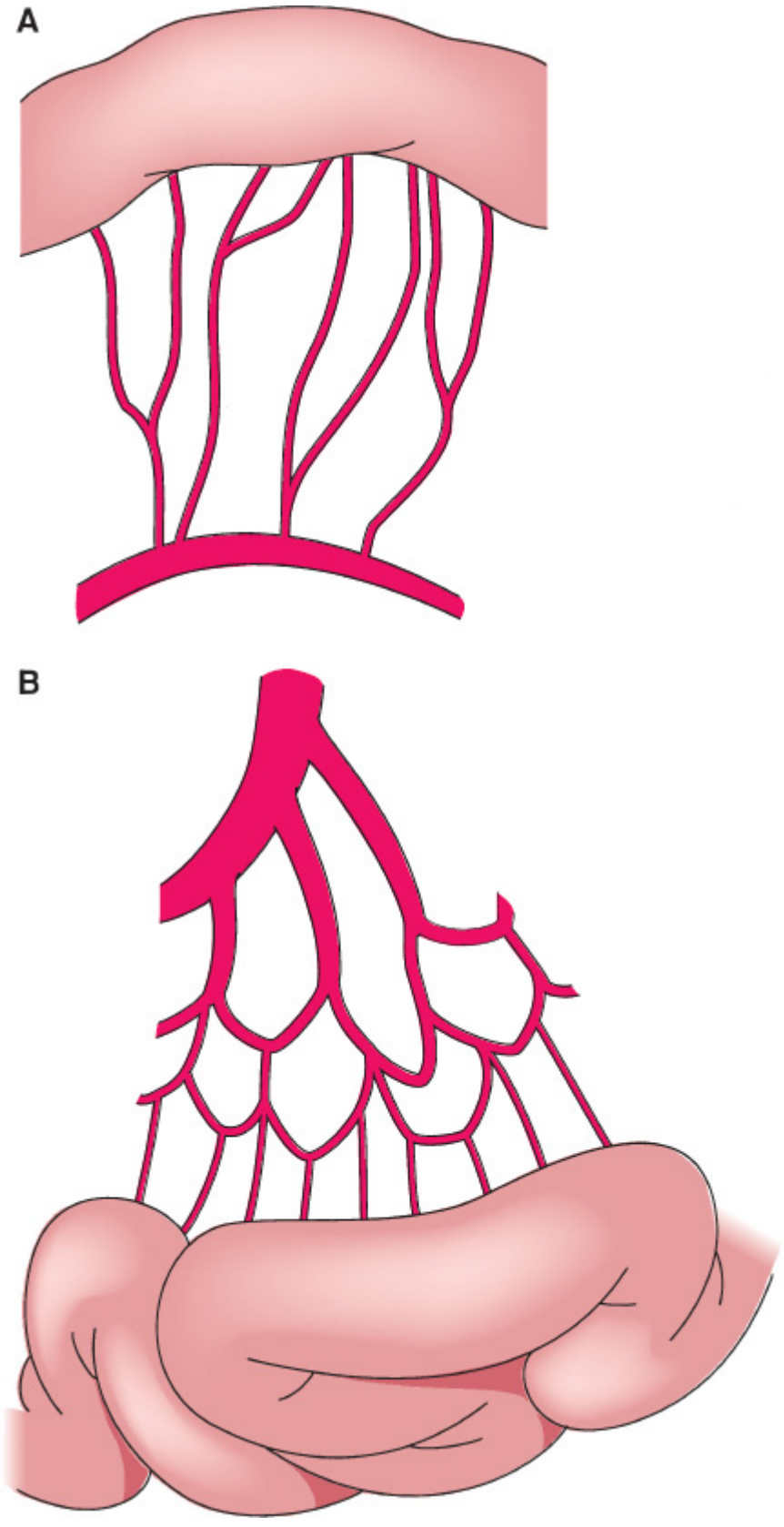
A
B

Figure 48.2 The superior mesenteric artery supplies blood flow into the small intestinal arteries (vasa recta) which branch within the mesentery. In the jejunum (**A**), the vasa recta are straight and long; this is in contrast to the vasa recta within the ileum (**B**), which are shorter with greater arborization.

MICROSCOPIC ANATOMY

General Considerations

The wall of the small intestine is composed of four distinct layers—mucosa, submucosa, muscle, and serosa. The role of the mucosa is absorption and secretion. The luminal mucosal surface forms circular folds known as plicae circulares or valvulae conniventes in all segments of the small intestine distal to the first portion of the duodenum. The submucosa contains an elaborate network of blood vessels, lymphatics, and nerves. The muscular portion of the wall includes outer longitudinal and inner circular muscle layers. Between the muscle layers lies the myenteric (Auerbach) plexus. The muscular layers are responsible for coordinating peristaltic movements. The outermost layer, the serosa, is composed of a thin layer of mesothelial cells overlying loose connective tissue. The serosa covers only the anterior surface of the retroperitoneal segments of small bowel, but it completely covers the portions of small bowel that are invested with mesentery.

Mucosa

The mucosa lines the luminal surface of the small intestine. It consists of three layers: epithelial cells, lamina propria, and a narrow layer of smooth muscle, the muscularis mucosae. Most of the intestinal lining is renewed over a period of approximately 5 days. The basic structural unit of the mucosa is the crypt and villus. Villi are finger-like projections of extending into the intestinal lumen that have a columnar epithelial surface and a cellular connective tissue core of lamina propria. Each villus contains a central lacteal (lymphatic), and a vascular network consisting of a small artery, vein, and capillaries. Ninety percent of the cells of the villi are columnar epithelial cells responsible for absorption and secretion. The apices of these cells have microvilli, produced by numerous folds in the apical membrane,

which account for the brush border appearance. Their surface is coated by glycoproteins rooted in the cell membrane. These glycoprotein filaments are referred to as the glycocalyx and are essential for digestion and absorption. The lateral membranes of neighboring enterocytes are connected by tight junctions, an apparent fusion of adjoining plasma membranes just below the level of the brush border. Movement of ions and water can occur by either a transmembrane or a paracellular route through tight junctions, which behave as selective pores.

Between the villi lie the crypts of Lieberkühn. Stem cells within the crypts of Lieberkühn are the source of the four major types of differentiated cells: the absorptive enterocyte, goblet cells, enteroendocrine cells, and Paneth cells. At the base of the crypt are Paneth cells that not only secrete antimicrobial peptides and play a key role in host microbiome interactions, but also help provide much of the environment for maintaining a stem cell niche.[5] As the stem cells divide, they move upward and out of the crypt, moving along signaling gradients triggering differentiation to the mature cell types populating the intestine. Mature cells include the enterocytes that make up the bulk of the cell type of the villus epithelium and are responsible for nutrient absorption. In addition, many epithelial cell genes are selectively expressed in the proximal small intestine, whereas other genes are specifically expressed only in the ileum.[6,7] Goblet cells secrete mucus into the intestinal lumen to help protect the epithelial lining of the intestine, and aid in the movement of luminal contents through the intestine. Enteroendocrine cells remarkably constitute the largest endocrine system in the body and secrete multiple regulatory hormones to regulate metabolism and postprandial secretion and motility.[8] As new cells arise in the crypt, all cells continue to migrate toward the tip of the villus, then undergo apoptosis and are shed into the intestinal lumen (**Fig. 48.3**).[7]

Enteroendocrine (also referred to as amine precursor uptake and decarboxylation, or APUD) cells may reside in either the crypts or the villi, depending on the particular neuroendocrine substance they produce. Specific areas of the small intestine have higher concentrations of specific neuroendocrine substances than other areas. These cells do not contact the intestinal lumen, unlike exocrine cells, and their secretory granules are located below the nucleus near the basement membrane. This suggests that

these cells secrete their contents into the circulation rather than into the intestinal lumen.

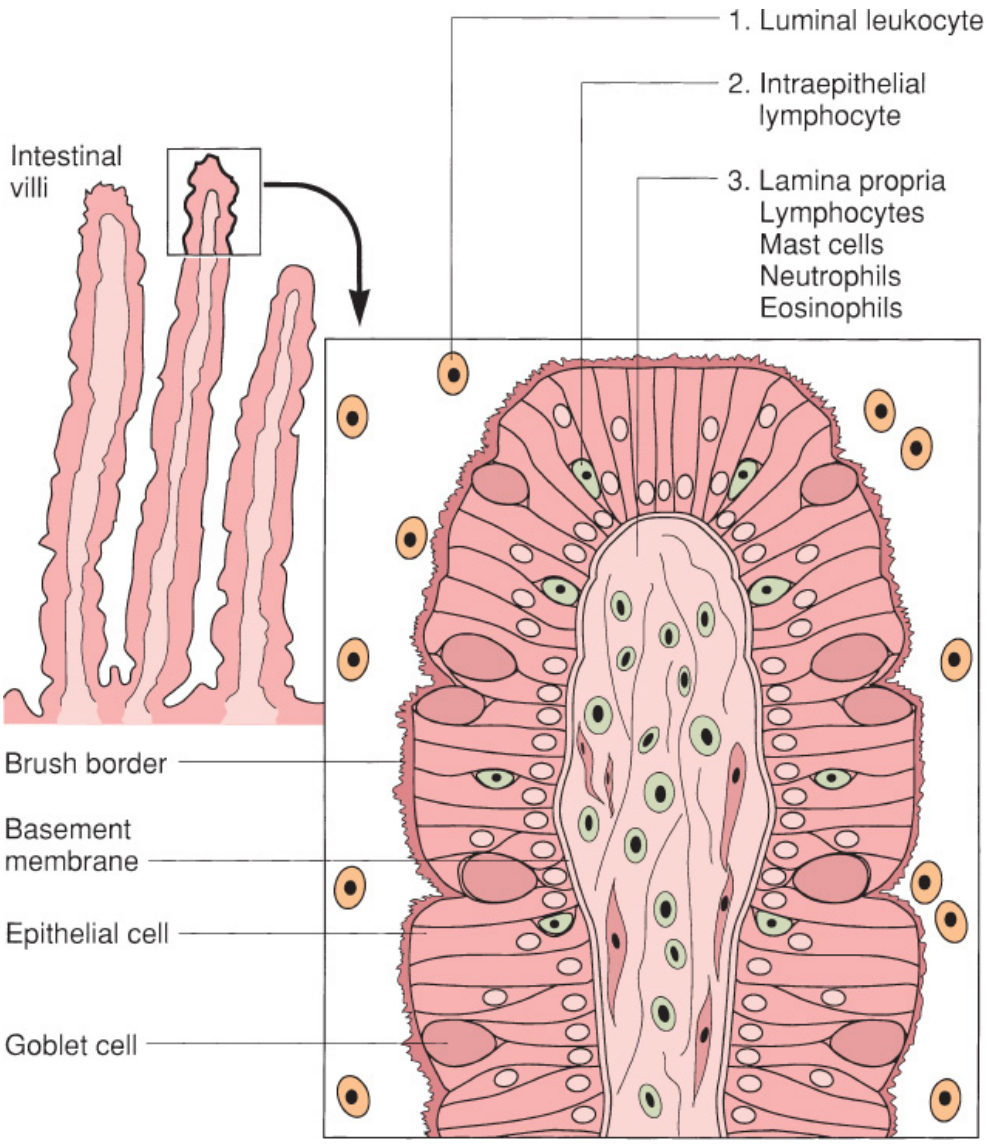

Figure 48.3 Small intestinal villus with associated immunologic cells.

Submucosa

The submucosa is a dense connective tissue layer with a rich network of blood vessels, nerves, and lymphatics. The submucosa contains Meissner plexus and is the strongest layer of the intestinal wall. Brunner glands are found in the submucosa of the duodenum and secrete mucus and bicarbonate into the intestinal lumen. These secretions aid in the neutralization of the

gastric acid load which enters the duodenum. Peyer patches are localized collections of lymphoid follicles that are most prominent in the submucosa of the ileum. These are most abundant early in life, gradually disappearing with age.

Physiology

The small intestine plays important physiologic roles in motility, blood flow, growth, digestion, absorption, immune function, and endocrine secretion. In fact, the small intestine is the largest 3 endocrine organ in the human body.[9] The secretion of numerous hormones and neurotransmitters are specific to distinct anatomic zones within the small intestine (**Table 48.2**). There is no specific cell mass which produces these hormones, but rather individual cells scattered along the GI tract.

Gastrin is a peptide produced in the gastric antrum and in the duodenum by the G cells and secreted into the circulation in response to gastric distension, vagal stimulation, amino acids, and hypercalcemia. Its release is inhibited by low intraluminal pH, somatostatin, secretin, gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP), glucagon, and calcitonin. Gastrin binds to cholecystokinin 2 (CCK2)/gastrin receptors on enterochromaffin-like (ECL) cells causing a release of histamine which in turn stimulates the parietal cells in a paracrine fashion. Gastrin also causes an increase in gastric blood flow and the release of pepsinogen by the chief cells and pancreatic enzymes from the pancreatic centroacinar cells.

CCK is produced in the proximal two-thirds of the small intestine by the I cell and is released into the gut lumen. It shares the final five amino acids adjacent to the C-terminus with gastrin, and this accounts for its hormonal activity. Stimulation of I cells by amino or fatty acids causes release of CCK; this in turn stimulates contraction and emptying of the gallbladder, increases bile flow, causes relaxation of the sphincter of Oddi, and stimulates pancreatic enzyme secretion. CCK also has trophic effects on the small intestinal mucosa and pancreas.

Secretin is produced by the S cells of the duodenum and jejunum. Secretin is released into the circulation and intestinal lumen in response to low intraluminal pH, fatty acids, and bile salts. Water and bicarbonate are secreted by the pancreas in response to secretin. Bicarbonate is also released

from the biliary ductal epithelium and Brunner glands in response to secretin. In turn, pancreatic enzymes are released from the pancreas. The increased pH and the presence of pancreatic enzymes aid in the digestion of lipids. The increased pH also provides a negative feedback loop to inhibit further production of secretin. Secretin produces a paradoxical release of gastrin in patients with gastrinomas but does not produce this effect on normal individuals.

Somatostatin is a peptide hormone is produced by the D cells in the pancreatic islets, gastric antrum, and duodenum. Its primary role is inhibition of other GI hormones and inhibition of pancreatic, biliary, and gastric secretion. In addition, somatostatin decreases splanchnic and portal blood flow. Somatostatin is stimulated by the presence of fat, proteins, acid, glucose, amino acids, and CCK. Octreotide, a long-acting synthetic somatostatin analog, is used in the treatment of variceal bleeding, hormone secreting neuroendocrine tumors, carcinoid syndrome, and enterocutaneous and pancreatic fistulas.[10]

Table 48.2 Intestinal Hormones

Hormone	Location	Cell	Stimulated by	Function
Gastrin	Stomach, duodenum	G cells	Vagal stimulation, gastric distension, amino acids, and hypercalcemia	Stimulates secretion of gastric H^+ and intrinsic factor from parietal cells and pepsinogen from chief cells, promotes gastric and intestinal motility, mucosal growth
Cholecystokinin (CCK)	Duodenum, jejunum	I cells	Vagal stimulation, fatty acids	Gallbladder contraction, release of pancreatic enzymes, relaxes sphincter of Oddi to release bile, induces satiety
Secretin	Duodenum, jejunum	S cells	Low intraluminal pH, fatty acids, and bile salts	Secretion of HCO_3 from pancreas inhibits gastrin and gastric acid secretion
Somatostatin	Throughout small intestine	D cells	Fatty acids, proteins, low intraluminal pH, glucose, amino acids, and CCK	Inhibits secretion and function of gut hormones
Vasointestinal Peptide (VIP)	Enteric nerves	Fat	Vagal stimulation	Increases water and electrolyte secretion from gut and pancreas
Gastrin-Releasing Peptide	Duodenum, jejunum	K cells	Vagal stimulation	Reduces gastric acid secretion and motility
Motilin	Throughout small intestine	Mo and ECL cells	Released during interdigestive periods, high pH	Increases small bowel motility (MMC) and gastric emptying
Neurotensin	Ileum, proximal small intestine	N cells	Fatty acids	HCO_3, motility
Pancreatic glucagon	Proximal small intestine	L cells	Low serum glucose	Induces glycogenolysis, lipolysis, gluconeogenesis, and ketogenesis

Gastrin-releasing peptide, the mammalian homolog of bombesin, is a peptide which is produced by the small intestine and is released in response to vagal stimulation. It is a prostimulatory molecule which causes the release of most GI hormones, except for secretin. It also has a promotility effect and stimulates endothelial proliferation. GIP or glucose-dependent insulinotropic peptide (GIP) is a 42 amino acid peptide produced by the K cells of the duodenum and jejunum. It is released in response to glucose, fat, protein, and adrenergic stimulation. It stimulates secretion of insulin and inhibits gastric acid and pepsin production.

Motilin is a peptide produced by the enteroendocrine cells in the duodenum and jejunum. Release of motilin occurs during the interdigestive and fasting periods. Release may also be related to alkalinization of the duodenum. Motilin's main function is to stimulate the migrating myoelectric

complex. Motilin agonists such as erythromycin, are used clinically as stimulants of GI motility.

VIP is an amino acid peptide which is produced by GI tract neurons. It serves as a neurotransmitter stimulating pancreatic exocrine and intestinal secretion. Conversely, it has an inhibitory effect on gastric acid secretion. VIP is a potent vasodilator and relaxant of enteric smooth muscle and stimulates secretion of water into pancreatic juice and bile, and cause inhibition of gastric acid secretion and absorption from the intestinal lumen. These effects work together to increase motility.[11]

Neurotensin is a peptide that is produced by the N cells primarily in the ileum, but also in the proximal small intestine and colon in response to the presence of intraluminal fat. It stimulates pancreatic bicarbonate secretion and intestinal motility. Neurotensin also serves as a trophic factor on the small intestinal mucosa and inhibits gastric secretion.

Pancreatic glucagon and enteroglucagon are peptides produced by the α-islet cells of the pancreas and the L cells of the small intestine, respectively. Pancreatic glucagon is released in response to low serum glucose and subsequently induces glycogenolysis, lipolysis, gluconeogenesis, and ketogenesis. Enteroglucagon is released in response to the presence of a mixed meal and inhibits gastric emptying and small bowel motility.

Motility

The coordination of movements of the GI tract is necessary for 4 the proper digestion of food. Well-timed contraction and relaxation patterns are initiated in GI nervous system causing coordinated electrical activity and muscular movements. This may be influenced by both internal and external factors. During and immediately following times of feeding, the intestinal movements are not rhythmic, with complexes of peristaltic and antiperistaltic contractions. This is thought to be a disruption of the migrating motor complex (MMC) from bolus feeding. This seemingly random pattern of movements allows for effective mixing of chyme. Hormonal changes are thought to play a role in this process. Physiologic doses of neurotensin, insulin, gastrin, and CCK cause an alteration in the MMC similar to bolus feeding. The MMC is more significantly inhibited by fatty meals as opposed to protein or carbohydrate meals of similar caloric value. The intrinsic

nervous plexus or Meissner plexus innervating the submucosa helps to regulate mucosal absorption and secretion but has no control on motility.

The small intestine has motor functions which are distinct from the other parts of the GI tract. The intrinsic nerves (myenteric or Auerbach plexus) provide the basis for coordinating the circular and longitudinal smooth muscles of the small intestine. Extrinsic sympathetic (epinephrine) stimulation slows motility while parasympathetic (acetylcholine) stimulation increases motility. The intrinsic electrical activity of the small intestine is based on the intestinal smooth muscle normal resting potential. This normally is maintained by Na^+–K^+-ATPase activity.[12] The resting potential varies and results in a phasic depolarization which is referred to as slow waves, basic electrical rhythm, or pacemaker potential. These depolarizations occur at regular intervals of approximately 11 to 13 times per minute in the duodenum and decrease to 8 to 10 times in the ileum, but do not directly lead to muscular contractions. The electrical activity is coupled to muscular contraction at the level of gap junctions, which are low resistance cell-to-cell connections. These gap junctions become less regular in the midjejunum and in the distal small intestine. This causes slowing of the frequency of contractions distally, allowing for absorption of more slowly digested intestinal contents, including fats and bile salts.

Spike potentials represent a second mode of electrical stimulation of the small intestine. Spike potentials result in rapid depolarization of the membrane potential. Repeated bursts of spike potentials cause a short area of contraction. In contrast to the always present slow waves, spike potentials occur at discrete time intervals. The coordination of a slow wave and a spike potential leads to the initiation, duration, and frequency of rhythmic migratory small intestinal contractions.

During the interdigestive period between feeding, the small intestine follows a well-defined rhythmic pattern. This pattern consists of muscular contractions that migrate from the stomach or duodenum, continue to the terminal ileum, and are regulated by the MMC. This pattern can be broken down into four distinct phases. Phase I is a period of relative quiescence; phase II is a period of accelerated irregular electrical spiking and muscular activity; phase III is a series of high-amplitude rapid electrical spikes corresponding to rhythmic gut contractions; and phase IV is a period of subsiding activity. This process occurs over a period of 90 to120 minutes

and progresses from the proximal small bowel and terminates in the ileum. Once the MMC reaches the terminal ileum, the process starts over again in the proximal small bowel. The circular muscles provide segmental contraction over a 1-cm length of small intestine. These contractions occur approximately 11 to 13 times per minute in the duodenum and decrease to 8 to 10 times in the ileum. This creates functional compartments where prolonged exposure to the mucosa and mixing of the intestinal chyme occurs, aiding the process of digestion and absorption. The circular muscles are also responsible for the peristaltic waves which propagate regularly at a rate of 1 to 2 cm/sec. These regular waves may be interspersed with rushes of contractions followed by periods of no motor activity. This rate becomes progressively slower in the distal small intestine. These peristaltic movements serve as a method of propelling chyme through the length of the small intestine. The total transit time from the duodenum to the terminal ileum is approximately 220 minutes (+/−53 minutes).[13] Serum motilin levels have been found to mirror the activity of the MMC. Exogenous motilin administration has been found to increase MMC activity.

IMMUNOLOGY

Principles of Gut Immunology

The lumen of the GI tract is connected to the outside environment and comes in direct contact with many potentially pathogenic microorganisms. Lymphocytes, macrophages, polymorphic granulocytes, and other cells that take part in immune response are distributed throughout the whole gut. The commensal microflora has many benefits to the host by supporting digestion and keeping the appropriate balance among different microbial species.[14] The immune system is highly effective at responding selectively to invading pathogens, yet on the other hand tolerating a much larger number of harmless food antigens and commensal organisms. Many bacteria, viruses, and parasites are digested and enter the small intestine 5 every day.[15] Consequently, the small intestine needs a complex defense mechanism to battle against these exposures in different ways.[16]

While the immune system in the small intestine is important for host defense, other mechanisms within the small intestine also participate in host defense. Proteolytic and lipolytic enzymes are produced in high concentrations by extraintestinal cells in the pancreas and degrade different pathogenic agents at an early phase of digestion. In addition, mucin is produced by the enterocytes which is cytoprotective and inhibits bacterial growth. The small intestine can actively increase peristalsis functions to mechanically get rid of pathogenic agents, which may be potentially dangerous to the gut. In addition, tight junctions between epithelial cells prevent penetration of bacteria in between cells. Potential pathogens vary greatly in size, from very small viruses that are nanometer in size, to parasites such as helminths that are macroscopically visible and quite large. To put this into the broader picture of evolution, a large range of defense mechanisms is essential for survival of each individual.

The primary cellular barrier in the gut that prevents antigens from encountering the immune system is the single layer of gut epithelium. The total surface area of the small intestine is 400 m^2, due not only to intestinal length but also due to the formation of millions of villi in the small bowel which contribute significantly to the overall surface area.[17] In the upper small intestine, the bulk of antigen exposure comes from the diet, whereas in the ileum and colon, the additional antigenic load of an abundant and highly complex commensal microflora is prevalent. The epithelial cells of the gut mucosa have developed features that make the intestinal epithelium an active immunologic as well as anatomic barrier. For example, these nonclassical immune cells express major histocompatibility complex (MHC) class I and II molecules, consistent with their ability to participate in adaptive immune recognition of pathogenic bacteria. Small intestinal epithelial cells also express toll-like receptors on their apical surface that enables them to detect bacterial products and to initiate an innate immune response. Antigen-presenting dendritic cells (DCs) also send processes between gut epithelial cells without disturbing tight junction integrity and sample commensal and pathogenic gut bacteria.[18,19] The gut epithelial barrier therefore represents a highly flexible structure that limits antigens from entering the systemic body. The gut-associated immune system represents one of the largest immunologic compartments in the body. Lymphoid tissue in the GI tract is a major part of the whole-body immune system and consists of both aggregated (lymphoid

follicles, Peyer patches) and nonaggregated (luminal, intraepithelial and in lamina propria) immune cells. Under physiologic circumstances, oral administration of protein antigens induces systemic unresponsiveness when the same antigen is given parenterally (a phenomenon known as oral tolerance). In animal models, oral tolerance appears to be a specific consequence of the immune environment in the gut, which favors the generation of regulatory T cells.

Nonaggregated and Aggregated Lymphoid Tissue

The gut epithelium and its mucous layer form a major barrier to trap pathogens which are then eliminated when the gut epithelium is shed and replaced by new cells deriving from stem cells in the crypts. Several different cell types face antigenic exposure present in the intestinal lumen and include the epithelium, neutrophils, lymphocytes, and macrophages. These luminal cells represent an initial effector mechanism in the first front directed toward an antigenic exposure. In addition, there are also immigrated intraepithelial lymphocytes, which are found in between epithelial cells beneath the tight junctions. Local defense depends in part on these T lymphocytes that are nestled among gut epithelial cells. These T cells modulate homeostasis of the gut epithelium through local production of cytokines and have cytolytic effects. In fact, the number of intraepithelial lymphocytes can increase dramatically in response to inflammation or infection. After exposure to antigens, these cells reenter the circulation to initiate a systemic immune response. The lamina propria contains nonaggregated, diffusely distributed lymphoid tissue, including different types of immune cells. B cells in the lamina propria undergo cytokine-induced differentiation to become active producers of immunoglobulin A (IgA) that is secreted into the gut lumen. Mast cells and eosinophils are also present in the lamina propria in small numbers. They exhibit an important role in allergic and hypersensitivity reactions as well as defense against parasites. Parasites including worms are recognized and tagged using the monovalent immunoglobulin E (IgE) which is mostly bound to host cell

surfaces. Actual parasite killing is depending on toxic proteins secreted by eosinophils.

There are also large aggregates of lymphoid tissue found in the small intestine. These so-called Peyer patches are localized collections of lymphoid follicles that are most prominent and macroscopically visible in the submucosa of the ileum. Peyer patches are most prominent in children and gradually disappear with age. Along with the nonaggregated immune system, the enormous quantity and diversity of antigens present within the gut are also processed via Peyer patches in the lamina propria and the mucosa-associated lymphoid tissue (MALT), which in total contains about 70% of the body's lymphoid cells. Another often used term to describe the immune system within the small intestine is gut-associated lymphoid tissue (GALT). Peyer patches do not have any villi, and so-called microfold (M) cells concentrated within the epithelium allow the selective uptake of food antigens and microorganisms. M cells are specific cells in the intestinal epithelium over lymphoid follicles that endocytose antigens. M cells transport them into the underlying tissue, where they are taken up by local DCs and macrophages.[20] DCs and macrophages that receive antigens from M cells present them to T cells in the GALT, leading ultimately to appearance of IgA-secreting plasma cells in the mucosa. B-lymphocyte precursors proliferate in germinal centers within the Peyer patches. DCs below the epithelium can also take up luminal antigens by pushing pseudopods up between epithelial cells.

Immunoglobulin Secretion

At an early level of exposure at the gut epithelium, M cells take up antigen and transport it transcellularly using an endocytic mechanism into the underlying lymphoid tissues of Peyer patches. Lymphocyte activation ensues, and these activated lymphocytes migrate into afferent lymphatics, pass through mesenteric lymph nodes, and enter the circulation through the thoracic duct. During this process, the lymphocytes mature into B and T lymphoblasts with an enriched population of IgA-producing B cells.[21] Passage of viable bacteria from the intact GI tract to the mesenteric lymph node and beyond has been termed bacterial translocation, possibly explaining septic complications and multiple organ failure in peritonitis, burn, and trauma patients. The immunogenic integrity of the mucosa is

significantly damaged by systemic injury of different kinds. A major protective mechanism of the intestinal immune system is synthesis and secretion of IgA. In the intestine, IgA exists as a dimer that is linked with two additional molecules—the J chain—linking two IgA molecules, and the polymeric immunoglobulin receptor, which transports the IgA complex across the cell and allows release of the complex, termed secretory component, into the intestinal lumen. The transmembranous immunoglobulin receptor is produced by the intestinal epithelial cell. It is thought that the secretory component may prevent proteolytic degradation of the IgA molecule and may stabilize the structure of the polymeric IgA complex in an environment containing numerous proteolytic enzymes and bacteria that would otherwise rapidly degrade it. Unlike IgG and IgM, IgA does not activate complement and does not promote cell-mediated opsonization. The major function of secretory IgA in host defense is protection against bacteria, viruses, and luminal antigens. Secretory IgA inhibits the adherence of bacteria to epithelial cells. It is well known that a breast-feeding mother transfers secretory IgA to her nursing infant, protecting the infant from bacteria and viruses that were originally present in the mother's GI tract.

Small Intestine Microbiota

The importance of the microbiota of the small intestine on metabolism and its impact on health and disease processes are increasingly being realized. The communities of microorganisms in the human digestive tract are a complex ecosystem that is both essential for human life and a potential driver of a variety of human diseases. The small intestine is not highly populated by bacteria due to its relatively short transit time, intermittent substrate availability, and its inhospitable environment, which is comprised of a variety of antimicrobial proteins, immunoglobulins, bile and a low pH. A challenging feature of the small intestine when compared with the colon is its relative inaccessibility, which makes sampling for microbiome studies.[22] Bacterial populations of the small intestine have been estimated at 103/g in the duodenum to 108/g in the distal ileum, but despite these relatively low populations there is evidence that there is interplay between the microbes and the intestinal lining that may directly affect intestinal health (**Fig. 48.4**).[22,23] One of the key determinants of small intestine microbiota is

host diet. The proportion of gram-positive to gram-negative, as well as facultative anaerobic and strict anaerobic species increases from proximal to distal segments of the small intestine and colon based on oxygen use.[24,25]

Carbohydrate metabolism is a key function of the small intestine microbes by comparison to colonic microbes. The role of microbes and bile acid metabolism is relatively well understood, but new findings about the regulation of bile acid conjugation are cited as possible factors in irritable bowel disease and inflammatory bowel disease.[26] Metabolism of fatty acids, dietary fiber, and amino acids alter the production of microbial anti-inflammatory and proinflammatory factors and is thought to play an important role in mucosal integrity and translocation, as well as, hepatic function and may have a role in the pathogenesis of nonalcoholic 6 fatty liver disease.[27,28] While the exact mechanisms of many of the interactions between the gut microflora and the small intestinal microenvironment are still speculative, it has become evident that a symbiotic environment is present which, at least in part, is responsible for proper homeostasis of the small intestine.

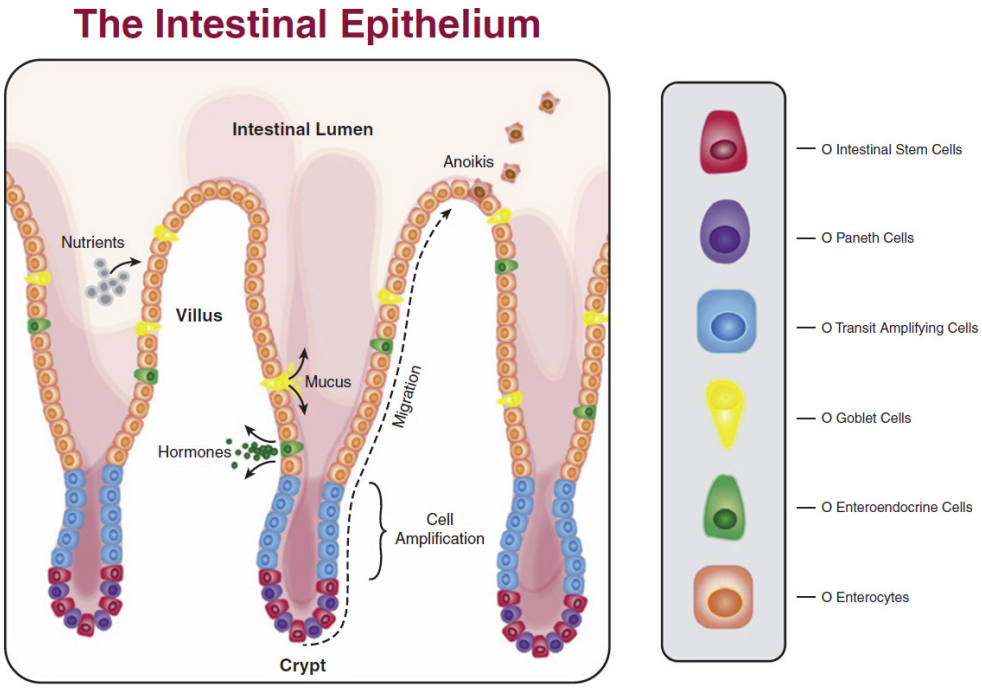

Figure 48.4 Intestinal epithelium. (Reprinted from Dey I and Bradbury NA. Physiology of the Gut: Experimental Models for Investigating Intestinal Fluid and Electrolyte Transport. Chapter 10.)

DIGESTION AND ABSORPTION

Absorption of Water

Recommended daily intake of water from all sources (water, other beverages, and food) is 3.7 L for men and 2.7 L for women. This varies depending on personal and environmental factors. Approximately 2 L (64 oz) per day is recommended from water alone. The GI tract adds notable fluid volume along its course (**Table 48.3**). The small intestine reabsorbs nearly 80% 7 of the fluid that passes through it. This dynamic process is accomplished by a rapid bidirectional movement of fluid in the intestinal lumen. This ebb and flow of fluid in the intestinal lumen is critical in maintaining normal homeostasis. Minor changes in intestinal permeability or rate of flow of the intestinal contents can result in net secretion and diarrheal states.

Table 48.3 Average Daily Intestinal Secretions

Anatomic Source	Intraluminal Secretion (mL)	Fluid Reabsorption (mL)
Oral Intake	**2,000**	—
Oropharyngeal	**1,500**	—
Stomach	**5,000**	—
Liver	**1,000**	—
Pancreas	**1,000**	—
Small Intestine	**2,000**	**8,000**
Large Intestine	**200**	**1,250**

The tonicity of the intraluminal contents determines the overall net movement of water. In general, after a meal is consumed, the addition of large amounts of saliva, gastric juice, and hypotonic chime enters the proximal small intestine. Acid gastric contents are neutralized by the secretion of bicarbonate, creating NaCl and water, and decreasing the

osmotic pressure. The jejunum is effective at passively reabsorbing water in a paracellular fashion due to its relatively large intercellular pores. As the chyme travels through the length of the small intestine, the intercellular channels become more tightly arranged and the movement of water becomes dependent on the active transport of solutes into the paracellular spaces. A total of 6 to 11 L of water enters the duodenum every day, of this, less than 1 L enters the colon.

Absorption of Electrolytes

The small intestine is responsible for the bulk of electrolyte transport via transport protein mechanisms located along the brush border driven primarily by active transport of sodium, chloride, and bicarbonate (**Table 48.4**). This results in a net fluid movement across the GI epithelium.

Sodium

Approximately 800 mmol of sodium passes through the intestinal lumen daily. Apical transport in the small intestine are reliant on the Na^+–K^+-ATPase pump on the basolateral membrane of the cell. This pump utilizes the hydrolysis of ATP providing energy to move three Na^+ ions out of the cell while transporting 2 K^+ ions into the cell; movement against an electrical gradient. This process maintains a negatively charged low Na^+ intracellular environment, allowing for several mechanisms of absorption:

Table 48.4 Small Intestine Absorption of Electrolytes

Major Mineral	Recommended Daily Intake	Route of Absorption	Function	Dietary Source
Sodium	less than 2.3 g	Small intestine, colon	Fluid balance, nerve	Foods, small amounts in milk, breads, unprocessed meat
Chloride	2.3 g	Ileum, colon	Gastric acid, fluid balance	Table salt, soy sauce, processed foods, small amounts in milk, breads, unprocessed meat
Potassium	5–6 g	Jejunum, ileum (passive)		Meats, milk, fresh fruits and vegetables, whole grains, legumes
Calcium	1 g	Duodenum (Ca-ATPase, vit D dependent), ileum	Bone and teeth health; muscle contractility	Milk and milk products, canned fish with bones, leafy green vegetables, fortified tofu and other soy products, baked goods made with fortified flour
Phosphorus	0.5–1 g	Jejunum	Bone and teeth health; acid–base balance	Meats, fish, poultry, eggs, milk, nuts, seeds, legumes, grains, processed foods (incl. sodas)
Magnesium	350–450 mg	Jejunum, ileum (both passive and active)	Bone composition; protein; muscle	Nuts and seeds, legumes, leafy green vegetables, seafood, whole grains, and some fortified cereals and other foods
Sulfur	2–3 g total in conjunction with sulfur amino acids	Jejunum	Protein molecules, complex biosynthesis	Meats, poultry, fish, eggs, milk, legumes, leafy green vegetables, nuts, beer, wine, coffee

Simple electrogenic absorption is the process of an influx of Na ions from the sodium-rich intestinal lumen into the negatively charged, low-sodium intracellular environment. This process is indirectly energy dependent, as it relies on the function of the Na^+–K^+-ATPase pump and resultant negative intracellular charge. The process can be inhibited by ouabain, a Na^+–K^+-ATPase inhibitor.[29]

Nonelectrolyte-stimulated sodium absorption occurs when sodium is coupled with an organic solute, such as glucose, amino acids, dipeptides, tripeptides, and bile acids. Sodium is preferentially transported down its electrochemical gradient which is created by the Na^+–K^+-ATPase pump.

Electroneutral absorption of sodium chloride is a process which couples two neutral ion counter transport mechanisms. Na^+ is exchanged for H^+ and Cl^- is exchanged for HCO_3^-, resulting in no net change in intracellular charge. This process provides an influx of NaCl in exchange for H^+ HCO_3^- efflux. This 8 electroneutral transfer of ions allows for intracellular pH regulation and for sodium and chloride transport.

Chloride

Efficient chloride absorption passing through the gut lumen daily allows for normal stool concentration of 10 to 15 mmoles/L. In states of malabsorption and diarrhea, the concentration can exceed 90 mmoles/L. Chloride is a major determinant of the regulation of fluid secretion into the small intestine and in intestinal hydration.[30] Three distinct mechanisms of physiologic absorption occur:

Electroneutral transfer is the main route of chloride absorption in the ileum and colon mediated by apical Na/H and Cl/HCO_3 exchangers.[31]

Paracellular passive diffusion is predominant in the small intestinal epithelium and depends on the positively charged interstitium compared to the gut lumen. This allows negatively charged chloride ions to be absorbed via transmural potential and the downhill Cl^- gradient.

HCO_3-dependent Cl absorption is the alkalinization of HCl in the duodenum and proximal small bowel and recycling of chloride back into cells in exchange for HCO_3.

Bicarbonate

Absorption of bicarbonate primarily takes place in the jejunum and requires the formation of carbon dioxide and water in the intestinal lumen from HCO_3^- and H^+, thereby increasing the intraluminal pressure of CO_2. Carbon dioxide diffuses back into the enterocyte and is enzymatically cleaved into H^+ and HCO_3^- by the action of carbonic anhydrase. HCO_3^- diffuses into the interstitium and H^+ is resecreted in exchange for other cations, predominantly Na^+. In the duodenum and ileum, HCO_3^- is secreted in exchange for Cl^-. This efflux of HCO_3^- provides a mechanism to neutralize gastric acid entering into the duodenum. HCO_3^- secretion in the ileum most likely helps maintain acid–base equilibrium, although this process is not well understood.[32]

Potassium

Approximately 90 mEq/d of potassium is ingested in a normal diet of which 90% is absorbed. An equal amount of potassium is excreted in the urine as is absorbed in the intestine, allowing maintenance of potassium homeostasis.

Most of the absorption occurs in the small intestine mainly through passive mechanisms.[33] This process is thought to occur through intercellular pores or through an H^+–K^+ exchange pathway facilitated by the intracellular electrochemical gradient which is created predominantly by the basolateral ATPase pump. Intracellular K^+ then diffuses across the basolateral membrane by a K^+ channel or carrier.

Carbohydrates

Comprised of sugars and starches, carbohydrates provide a major source of daily caloric intake in Western diets with each absorbed gram producing 4 kcal of energy. Carbohydrates are present in three main digestible forms with the enzymatic breakdown into simple sugars being required for transport across the apical cell membrane.

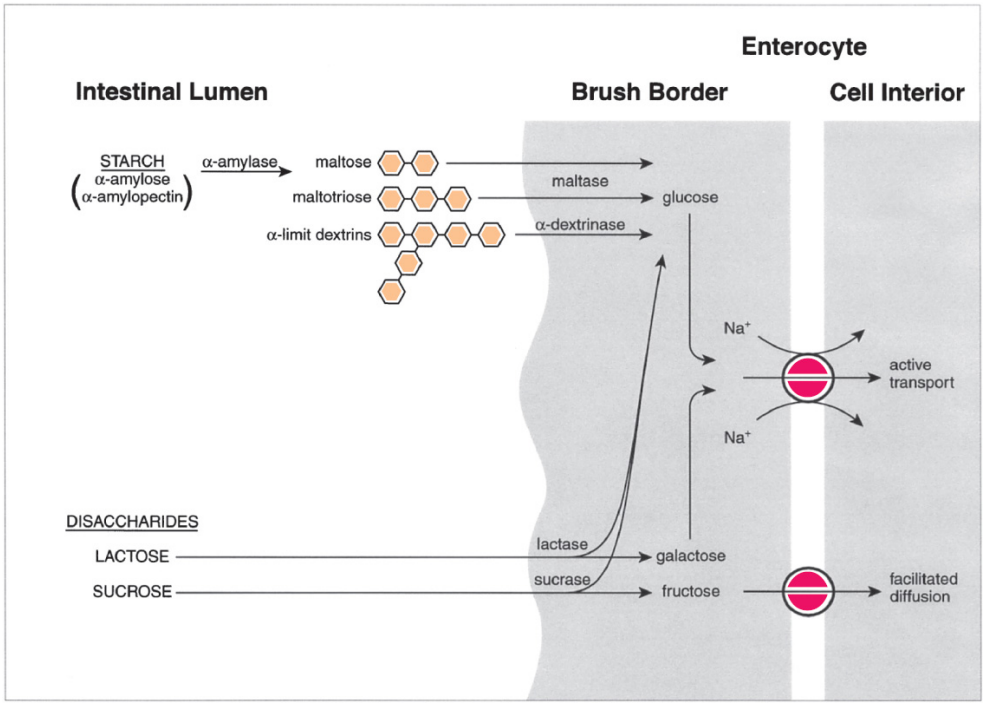

Figure 48.5 Digestion and absorption of carbohydrates.

Complex Starches: The storage carbohydrate of plants consisting mainly of sugars linked together, these account for approximately 60% of daily carbohydrate intake. The most common form is amylopectin. Amylose is a long linear grouping of glucose molecules connected with α(1,4)-glycosidic

bonds without branch points. Amylopectin and amylose are digested with the aid of salivary but mainly pancreatic amylase. This process yields maltose, which are glucose dimers with α(1,4)-glycosidic bonds, and maltotriose, which are glucose trimers with α(1,4)-glycosidic bonds. This digestive process is usually completed before the carbohydrate bolus leaves the duodenum. These small oligosaccharides along with ingested disaccharides, typically sucrose and lactose, are then further digested by the brush border saccharidases in the jejunum.

Disaccharides: Comprising mainly of sucrose (glucose–fructose dimers) and lactose (glucose–galactose dimers), but also maltose and trehalose, these are the next most common source of dietary carbohydrate representing nearly a third of daily intake. The brush border of the small bowel contains specific enzymes which, through catalytic reactions involving amylase, sucrase, and isomaltase, hydrolyze both oligo- and disaccharides into their component monosaccharide moieties such as glucose, galactose, and fructose.

Monosaccharides: These simple sugars of glucose, galactose, and fructose can be transported across the apical cell membrane of the small intestine. A sodium-dependent hexose transporter (SLGT1) actively transports glucose and galactose from the intestinal lumen utilizing energy from the Na^+–K^+-ATPase pump on the basolateral membrane to maintain a sodium gradient allowing for this influx. Fructose is transported in a carrier-mediated diffusion-dependent manner by GLUT5 and does not require sodium as a cotransporter.

The movement of monosaccharides into the cellular cytoplasm provides an additional gradient by which water is absorbed by the enterocytes from the intestinal lumen. The monosaccharides are then transported across the basolateral membrane by GLUT2. This hexose transporter allows for the diffusion of all three monosaccharides into the extracellular space and ultimately into the portal blood flow. A small portion of these monosaccharides may be used by the enterocyte (**Fig. 48.5**).

Nondigestible Carbohydrates (Dietary Fiber)

Dietary fiber, such as cellulose are thought to be an important part of a normal diet even though they do not provide dietary calories. Dietary fiber is present in grains, vegetables, and pulpy fruits. Dietary fiber helps decrease

bowel transit time by absorbing water in the intestinal lumen. In addition, fiber can absorb organic materials such as lipids and bile salts and inorganic minerals such as zinc, calcium, and magnesium. These actions of fiber are thought to play a role in preventing carcinogenesis and in helping to maintain normal serum lipid profiles. Unfortunately, fiber is underrepresented in most Western diets. Guidelines suggest a daily intake of 14 g of dietary fiber per 1,000 kcal.[34]

Protein

Protein consumption is essential to the daily diet. An average adult requires 0.75 g/kg of protein per day, although this requirement may be significantly increased during childhood, pregnancy, and times of significant illness. Protein provides an important caloric energy source as well as the essential building blocks for production of new proteins. A nearly equal amount of protein is ingested daily from dietary sources (70 to 100 g) as is provided by endogenous proteins (50 to 60 g of protein per day) in the small intestine from secreted enzymes, desquamated cells, and plasma protein leakage. Nearly 90% of this protein load is metabolized in a similar fashion to dietary proteins.

The initial digestion of protein begins with the activation of pepsinogen to pepsin in the acid environment of the stomach. Pepsin hydrolyzes protein into its component amino acids; however, this action only represents a small part of overall protein digestion. The majority of protein digestion occurs in the small intestine by pancreatic peptidases and proteases. Pancreatic enzymes flow into the duodenum, initiating this phase of protein digestion. These pancreatic proteases are initially released as proenzymes (zymogens). These zymogens are inactive and require a further catalytic process to occur for their activation. This is initiated by the brush border enzyme enteropeptidase (enterokinase) in the duodenum. Endopeptidase cleaves trypsinogen into the active enzyme trypsin. Trypsin in turn activates the other zymogens into their active endopeptidases (trypsin, chymotrypsin, and elastase) which hydrolyze internal peptide bonds. Additional protein digestion is performed by exopeptidases (caroxypeptidase A and B) which are able to cleave amino acids from the C-terminal ends of proteins.

Short oligopeptides are further digested by enzymes in the brush border of the small intestine or within the cell cytoplasm. Single amino acids, dipeptides, and tripeptides can diffuse through the apical membrane into the cytoplasm. Single amino acids are co-transported into the cytoplasm with sodium along an electrochemical gradient. This electrochemical gradient is maintained by the Na^+–K^+-ATPase pump on the basolateral cell membrane. Peptides greater than three amino acids in length are broken down into smaller peptides by enzymes in the brush border. The resultant dipeptides and tripeptides are then moved into the cytoplasm along with H^+ by a cotransporter PepT1, where they are hydrolyzed by specific peptidase into their component amino acids. Transport of amino acids into the cytosol provides an osmotic gradient by which water is further absorbed from the intestinal lumen. A small portion of the processed amino acids are utilized by the enterocyte, and the vast majority is shuttled into the portal blood flow via amino acid transporters on the basolateral membrane.

Fat

Forty percent of the average daily caloric intake (60 to 90 g) in a Western diet is in the form of fat. Ninety percent of these ingested fats are triglycerides, while the remainder is comprised of cholesterol, phospholipids, and fat-soluble vitamins. The initiation of lipid digestion occurs when CCK is stimulated by the presence of fatty acids on the duodenal mucosa. CCK in turn stimulates pancreatic secretion of lipase and its cofactor colipase. Lipase hydrolyzes triglycerides, yielding two fatty acids and a monoglyceride (a fatty acid esterified to glycerol). Cholesterol and fat-soluble vitamins are hydrolyzed by pancreatic cholesterol esterase and phospholipids by phopholipase A2. The products of lipolysis interact with bile salts to form water-soluble micelles. Mixed micelles are a combination of fatty acids, bile salts, and monoglycerides. The structure of a micelle is composed of an inward-facing hydrophobic region and a hydrophilic region facing outward toward the aqueous environment of the intestinal lumen. Due to the hydrophobic core, cholesterol, phospholipids, and fat-soluble vitamins can reside within the micelle structure. Micelles are able to interact with the mucosal cells and empty their contents into the cytoplasm. This occurs by the process of dissolution of the micelles into the

lipid bilayer of the mucosal cell. Once this is completed, the components of the micelle are ready to reform with new lipid components to repeat this process. There is no energy consumed directly in the transfer of lipids into the cell cytoplasm.

Once in the cytoplasm, long-chain fatty acids and β-monoglycerides are carried by cytosolic fatty acid–binding proteins to the smooth endoplasmic reticulum (SER). In the SER, resynthesis of triglycerides occurs. These triglycerides are further processed in the Golgi apparatus where a phospholipid and an apoprotein coat are added to form a chylomicron. Chylomicrons are 90% triglyceride; the remaining 10% is composed of phospholipid, cholesterol, and protein. Before exiting the Golgi apparatus, the chylomicrons are packaged into secretory vesicles. They exit the cell membrane by exocytosis and enter the central lacteal of the villus and the intestinal lymphatic system. In addition, enterocytes also produce smaller lipoprotein particles, very low–density lipoproteins, which contain a higher cholesterol/triglyceride ratio and provide the major route of entry for dietary cholesterol into the lymphatic system.

Short-chain fatty acids contain less than eight carbon atoms and are water soluble. This allows these molecules to enter and exit the enterocyte by simple diffusion independent of bile micelles or chylomicrons. Medium-chain triglycerides consist of 6 to 12 carbon atoms and can be absorbed by simple diffusion or through the previously mentioned process of transport of long-chained fatty acids via the formation of bile micelles and chylomicrons. Both short- and medium-chain fatty acids may enter the portal circulation without entering the lymphatics. Most of the dietary fat is processed and absorbed in the duodenum and upper jejunum.

Bile Salts

Approximately 95% of the bile salts secreted into the intestine are reabsorbed and returned to the liver through the portal circulation. Once in the liver, these bile salts are reprocessed and secreted and stored in the gallbladder in preparation for the next meal. This process of recycling of bile salts is referred to as the enterohepatic circulation. This reabsorption occurs by both passive and active means. A small amount of bile salts is passively reabsorbed along the entire length of the small intestine. The majority of bile

salts, however, are reabsorbed though an active Na^+-dependent transport mechanism in the terminal ileum. Bile, which is not reabsorbed, passes into the colon where it is deconjugated by bacteria. This process increases the solubility of the bile and promotes further passive absorption. High concentrations of bile salts within the colon inhibit sodium and water reabsorption, resulting in diarrhea. Patients who have undergone resection of their ileum may suffer from diarrhea due to this process. These patients may be treated with the bile-binding resin, cholestyramine, to help alleviate their symptoms.

Mineral

Mineral absorption is necessary for the proper form and function of the human body. These inorganic elements are responsible for approximately 4% to 6% of a person's mass. Many of these minerals are best absorbed in their ionized forms, which is aided by the presence of hydrochloric acid in the gastric lumen. Calcium accounts for approximately 50% of this mass, phosphate provides an additional 25%, and a variety of other minerals constitute the remaining 25%.

Macrominerals (major) have a daily requirement exceeding 100 mg/d while microminerals (trace) have a daily requirement of less than 15 mg/d. These two groups are equally important, and the amount needed in the body is not indicative of importance. A balanced diet usually provides all the essential minerals. However, certain pathologies, postsurgical states, or inadequate dietary consumption may necessitate supplementation to avoid pathologies secondary to deficiency. The following tables highlight the function and source of such elements (**Table 48.5**). Approximately 1 g of calcium is consumed per day, mainly from dairy products. Once in its ionized form, calcium is primarily absorbed in the duodenum, although this process occurs throughout the length of the small intestine. When calcium is present intraluminally at low levels, it is transported across the apical membrane of the enterocyte by carrier-mediated facilitated diffusion. Once calcium is in the cytoplasm, it is bound to calcium-binding proteins and delivered to the basal membrane. Calcium is then transferred into the interstitium by a Ca^{2+}-ATPase pump. This process is indirectly regulated by parathyroid hormone (PTH). PTH in low-calcium states promotes conversion of vitamin D to its

active form 1,25-$(OH)_2$ vitamin D. This activated form of Vitamin D causes an increase in the expression of both calcium-binding proteins and Ca^{2+} ATPase, causing an increase in the absorption of calcium by the small intestine.[35,36] When intraluminal calcium is in excess of its capacity to be actively transferred by the apical membrane's carrier-mediated mechanism, passive paracellular calcium absorption occurs in the distal small intestine. Absorbable dietary sources of iron are typically either contained within a protein, such as heme, or as a ferrous (Fe^{2+}) ion. Iron-containing proteins are usually from ingested meats, whereas ferrous forms are typically present in vegetables, grains, and fruits. Vitamin C (ascorbic acid) increases iron absorption by reducing the ferric (Fe^{3+}) ion into the more soluble ferrous state. Absorption of iron is facilitated by carrier-mediated translocation across the apical membrane of the enterocyte in the duodenum and proximal jejunum. Once in the cytoplasm, the ferrous ion is released by enzymatic cleavage. Ferrous ions may be stored intracellularly by ferritin or transported into the circulation by transferrin. The process of iron absorption is regulated in the enterocyte by hypoxia-inducible factor signaling and iron-regulatory proteins.

Table 48.5 Small Intestine Absorption of Minerals

Trace Element	Recommended Intake	Dietary Source	Route of Absorption	Function
Zinc	8–11 mg/d	Meat, chicken, nuts, lentils	Duodenum and jejunum	Part of many enzymes; genetic material and protein synthesis. Wound healing
Copper	900 mcg/d	Vegetables, grains, legumes, meat, fish, poultry	Stomach and proximal small intestine	Part of many enzymes; iron metabolism
Manganese	1.8–2.2 mg/d	Grains, dried fruits, vegetables	Small intestine	Part of many enzymes
Selenium	5 mcg/d	Seafood, kidney, liver	Small intestine	Antioxidant
Chromium	25–35 mcg/d	Processed meats, grains, cereals, vegetables, fruits	Small intestine	Works with insulin in regulating glucose levels
Iodine	150 mcg/d	Seafood, vegetables, drinking water	Proximal small intestine	Thyroid hormone
Fluoride	4 mg/d	Water, seafood, toothpaste	Stomach and small intestine	Bone and teeth metabolism
Molybdenum	45 mcg/d	Legumes, cereal grains, leafy vegetables, beef liver	Small intestine	Part of some enzymes
Cobalt	5–8 mcg/d	Milk, dairy, fish, shellfish	Small intestine	Red blood cell production
Iron	8–18 mg/d	Red meat, fish, poultry, shellfish, egg yolk, legumes	Duodenum and proximal jejunum	Hemoglobin molecule, energy metabolism

Table 48.6A and 6B Small Intestine Absorption of (A) Water-Soluble and (B) Fat-Soluble Vitamins

Water-Soluble Vitamin	Dietary Source	Route of Absorption	Resultant Deficiency
Vitamin C	Citrus; tomato; cantaloupe, strawberry	Carrier-mediated Na dependent	Scurvy
Vitamin B7 (Biotin)	Liver, egg yolks, soybeans, milk, meat	Carrier-mediated Na dependent	Seborrheic dermatitis, alopecia, myalgia, paresthesia
Vitamin B12 (Cobalamin)	Meats, fish, poultry, and eggs		Megaloblastic anemia (also due to lack of gastric intrinsic factor (IF) deficiency in atrophic gastritis)
Vitamin B9 (Folic Acid)	Vegetables, liver, oranges, cantaloupes, fortified breads	Specific folate carriers once unconjugated	
Vitamin B3 (Niacin)	Milk, eggs, meat, fish, whole grains	Specific carrier	Pellagra
Vitamin B6 (Pyridoxamine)	Meats, fish, potatoes, fruits, gut bacteria	Unknown	Irritability, depression, dermatitis, glossitis, cheilosis, peripheral neuritis, microcytic
Vitamin B2 (Riboflavin)	Dairy, eggs, meats, green leafy vegetables	Riboflavin transporters	Glossitis, corneal vascularization, and poor growth
Vitamin B1 (Thiamine)	Whole grains, nuts, dried legumes	Thiamine transporters	Megaloblastic anemia, encephalopathy

Fat-Soluble Vitamins	Route of Absorption	Daily Intake	Dietary Source	Result of Deficiency
Vitamin A	Small intestine micelles	3,000 IU	Meat, cheese, milk, fruit, vegetable	Night blindness (early), blindness (late), keratinization, infection, impaired wound healing
Vitamin D	Small intestine micelles	600–800 IU	UVB	Fatigue, depression, rickets (childhood), osteomalacia (adults)
Vitamin E	Ileum	15 mg	Sunflower oil, nuts	Peripheral neuropathy, immuno-deficiency, weakness, impaired vision
Vitamin K	Small intestine micelles	100–120 µg	Coagulation, bone formation	Bleeding

Vitamin Absorption

Fat-soluble vitamins (A, D, E, and K) are incorporated into micelles along with fats in order to pass into the enterocyte. These vitamins are then processed and packaged into chylomicrons so that they can exit into the lymphatic system. Water-soluble vitamins are absorbed in the jejunum and ileum through a variety of mechanisms. Vitamin C (ascorbic acid), biotin, and niacin are transported by Na^+-dependent mechanisms. Folate, vitamin B1 (thiamine), and vitamin B2 (riboflavin) are absorbed by Na^+ independent mechanisms and vitamin B6 is absorbed by passive diffusion.[37] Vitamin B12 (cobalamin) absorption is dependent on the presence of intrinsic factor, a glycoprotein produced by the gastric parietal cells. One molecule of intrinsic factor binds two molecules of cobalamin to form a complex which attaches

to a specific membrane receptor in the terminal ileum. Unbound cobalamin cannot be absorbed. Cobalamin becomes unbound from its complex in the enterocyte and exits from the cell into the portal circulation with the aid of B12-binding proteins called transcobalamins. Cobalamin is essential for DNA synthesis and a deficiency usually presents with megaloblastic anemia. Inability to absorb sufficient amounts of cobalamin may be due to lack of intrinsic factor after proximal or total gastrectomy, autoimmunity to gastric parietal cells or intrinsic factor, or atrophic gastritis. In addition, cobalamin-intrinsic factor complexes may fail to be absorbed due to distal ileal disease or resection, and cobalamin deficiency may occur from bacterial overgrowth due to bacterial overconsumption of cobalamin (**Table 48.6**).

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49

Ileus and Bowel Obstruction

David I. Soybel and Amanda B. Cooper

Key Points

1. In simple obstruction the intestinal lumen is partially or completely occluded without compromise of intestinal blood flow. Simple obstructions may be complete, meaning that the lumen is totally occluded, or incomplete, meaning that the lumen is narrowed but permitting distal passage of some fluid and air. In strangulation obstruction, blood flow to the obstructed segment is compromised and tissue necrosis and gangrene are imminent.
2. Peritoneal adhesions are the most common cause of obstruction of the small intestine.
3. Four key symptoms variably associated with acute mechanical bowel obstruction include abdominal pain, vomiting, distention, and obstipation; abdominal pain out of proportion to physical findings should raise concern about rapidly evolving closed-loop obstruction and the need for urgent resuscitation and operation.
4. CT (computerized tomography) is the “go-to” imaging modality to detect and identify the likely site and source of obstruction.
5. Conservative management consisting of intravenous hydration, nasogastric decompression, and restoration of electrolyte balance is a cornerstone of initial management of any patient suspected of having intestinal obstruction.
6. Use of water-soluble contrast for patients with small bowel obstruction (SBO) may be both diagnostic and therapeutic.
7. Open exploratory laparotomy is the gold standard in the treating of unresolved SBO. Laparoscopic management may be considered in select group of patients. Types of intestinal obstruction that are more likely to lead to strangulation and the need for urgent/emergent operation include closed-loop obstructions, obstruction due to hernia, obstruction without a prior history of operation, and obstructions that occur after some laparoscopic procedures.
8. Ileus denotes underlying alterations in motility of the gastrointestinal tract, leading to functional obstruction.

9 Postoperative ileus (POI) can be differentiated from SBO with the use of contrast CT and enteroclysis imaging techniques. POI is often self-limiting; less frequent interventions are required for prolonged POI, if proper precautions have been taken during surgery.

10 Pseudoobstruction of the colon, also known as Ogilvie syndrome, can be complicated by perforation; it is treated with attention to underlying neurologic or metabolic disturbances and, as a first line of treatment, with decompressive colonoscopy.

INTRODUCTION

The purpose of this chapter is to provide an overview of the pathophysiology, natural history, diagnosis, and management of acute obstruction and ileus of the small and large intestines. Of note, the principles of early diagnosis, rapid intravenous fluid resuscitation, gastrointestinal decompression, and early operation to avoid intestinal gangrene and peritonitis, were established well before the advent of antibiotic therapy, invasive hemodynamic monitoring, and parenteral nutrition.[1] These early developments were critical in reducing morbidity and mortality of mechanical intestinal obstruction and ileus.[2,3]

MECHANICAL OBSTRUCTION OF THE INTESTINE

Terminology and Classification

The term *mechanical obstruction* means that luminal contents cannot pass through the intestine because the lumen is blocked. Mechanical causes of obstruction are contrasted with *neurogenic* or *functional* causes, in which luminal contents are prevented from passing because of disturbances in gut motility that prevent coordinated peristalsis from one region of the gut to the next. This latter form of obstruction is commonly referred to as *ileus* in the

small intestine and *pseudoobstruction* in the large intestine. In *simple* obstruction, 1 the intestinal lumen is partially or completely occluded without compromise of intestinal blood flow. Simple obstructions may be *complete*, meaning that the lumen is totally occluded (**Fig. 49.1**), or *incomplete*, meaning that the lumen is narrowed but permitting distal passage of some fluid and air. In *strangulation* obstruction, blood flow to the obstructed segment is compromised and tissue necrosis and gangrene are imminent. Strangulation usually implies that the obstruction is complete, but some forms of partial obstruction can also be complicated by strangulation such as a Richter hernia.

As summarized in **Table 49.1**, causes of obstruction can include intraluminal objects such as foreign bodies or gallstones, intramural lesions such as tumors or intussusceptions, and extrinsic or extramural lesions such as adhesions. Adhesions are the most common cause of intestinal obstruction, accounting for more than half of all cases 2 .[4,5] It is equally instructive to classify obstruction according to the location of the obstructing lesion. Proximal or "high" obstructions involve the pylorus, duodenum, and proximal jejunum. Intermediate levels of obstruction involve the intestine from the mid jejunum to the mid ileum. Obstructions arising in the distal ileum, ileocecal valve, and proximal colon are considered "distal" whereas those termed as "low" arise in segments beyond the transverse colon. Obstructions in the colon will be discussed elsewhere in this volume. As outlined in **Table 49.2**, symptoms and signs of obstruction (pain, vomiting, abdominal distention, gas pattern on abdominal radiographs) vary with the level of obstruction.

It is also important, however, to distinguish between *open-* and *closed-loop* obstructions. An open-loop obstruction occurs when intestinal flow is blocked but proximal decompression is possible through vomiting. A closed-loop obstruction occurs when inflow to the loop of bowel and outflow from the loop are both blocked. This obstruction permits gas and secretions to accumulate in the loop without a means of decompression, proximally or distally. Examples of closed-loop obstructions are torsion of a loop of small intestine around an adhesive band (**Fig. 49.2**), incarceration of the bowel in a hernia, volvulus of the cecum or colon, or development of an obstructing carcinoma of the colon with a competent ileocecal valve. The primary symptoms of a closed-loop obstruction of the small intestine are sudden,

severe mid-abdominal pain and vomiting whereas symptoms of the large intestine are pain and sudden abdominal distention. Such pain often occurs before associated findings of localized abdominal tenderness or involuntary guarding. When signs of peritoneal irritation or frank peritonitis develop, there is a high level of suspicion that the viability of the bowel is compromised.

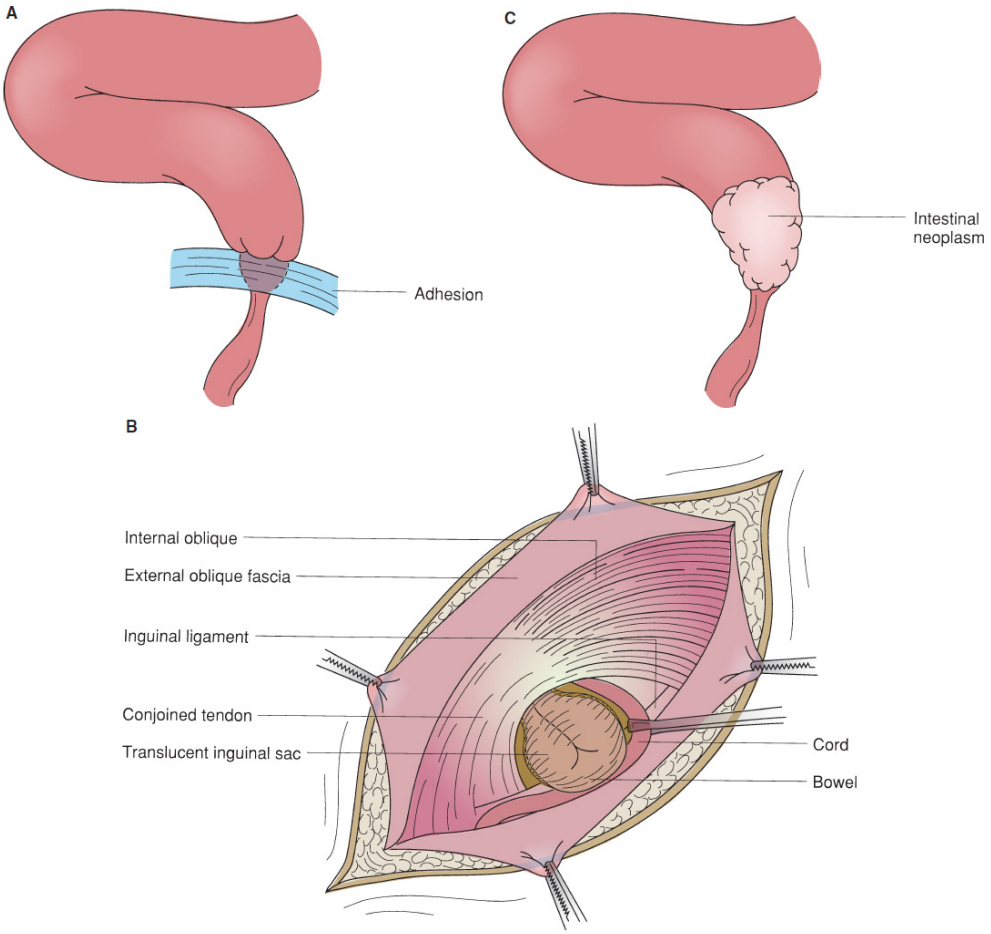


Figure 49.1 Schematic illustration of different forms of simple mechanical obstruction. Simple obstruction is most often due to adhesion, (**A**), groin hernia, (**B**), or neoplasm, (**C**). The hernia can act as a tourniquet, causing a closed-loop obstruction and strangulation.

Pathophysiology of Intestinal Obstruction

When a segment of intestine becomes obstructed, subsequent pathophysiologic events include (1) the accumulation of gas and fluid; (2) luminal stasis in association with release of microbe-generated toxins that

impair mucosal secretion and absorption, as well as translocation of bacteria to the gut wall, lymphatics, and systemic circulation; (3) a series of adaptive changes in intestinal motor function—at first relaxation to keep luminal pressures low, then hyperperistalsis in the effort to clear the blockage, and finally loss of organized motility patterns; and (4) alterations in blood flow to the mucosa and the gut wall, resulting not in ischemia, loss of mucosal integrity, inflammation, edema, and ultimately gangrene.[6,7] Ultimately it is the confluence of these disturbances that determines how quickly a simple obstruction evolves to cause symptoms and complications or a closed-loop obstruction to gangrene and perforation.

Table 49.1 Classification of Adult Mechanical Intestinal Obstructions

Intraluminal	Intramural	Extrinsic
Foreign Bodies Barium inspissation (colon) Bezoar	Congenital (rare in adult) Atresia, stricture, or stenosis Web Intestinal duplication Meckel diverticulum	Adhesions Congenital: Ladd or Meckel bands Postoperative Postinflammatory (after pelvic inflammatory disease)
Inspissated feces Gallstone ileus Meconium (cystic fibrosis)	Inflammatory Process Crohn disease Diverticulitis Stricture from ischemia Radiation enteritis or stricture Medication induced (NSAIDs, KCl tablets)	Hernias Abdominal wall Internal Groin Volvulus External mass effect Abscess
Parasites (ascaris, diphyllobothrium) Enterolith Intussusception	Neoplasms Primary intestinal or colon (malignant or benign) Secondary (metastasis or carcinomatosis)	Annular pancreas Pancreatic pseudocyst Carcinomatosis Endometriosis
Polypoid and exophytic lesions	Trauma (e.g., intramural hematoma)	Pregnancy

Complications and Systemic Effects of Bowel Obstruction

Closed-Loop Obstructions

The onset of obstruction is often caused by twisting of the bowel around the axis of its mesentery induced by an adhesive band or due to incarceration in a hernia (internal or external). Reflex hyperperistalsis and twisting of the mesentery occur early and are associated with intense pain and reflex nausea and vomiting. In a relatively short segment of intestine, and depending on region involved, continued secretion of mucus to high intraluminal pressures, stasis, bacterial overgrowth, mucosal disruption, and elevation of luminal pressures convert intermittent cramps to constant and worsening pain. When luminal pressure exceeds mural venous pressure and then capillary perfusion pressures, inflammatory cells are recruited from surrounding peritoneal structures. This sequence of events leads to intense inflammation, release of exudate and the first localization of pain from the umbilicus to the area of peritoneum lying nearest the involved segment of intestine. Peritoneal findings (localized tenderness, involuntary guarding, rebound or referred tenderness) and fevers appear. Subsequently, 20 to 24 hours into the illness, the blood supply of the appendix is compromised. Gangrene and perforation follow and, if not contained by surrounding structures, free perforation leads to release of intestinal fluid containing toxic microbes as well as the influx of fluid from the circulation due to intense peritoneal inflammation. Toxins from necrotic intestinal tissue and bacterial overgrowth are released resulting in circulatory collapse and shock.

Open-Loop Obstructions

Complications in open-loop obstructions do not necessarily evolve as rapidly as in closed-loop obstructions. Not uncommonly, an open-loop obstruction located in the proximal jejunum can be decompressed by the patient's ability to vomit. Proximal obstruction is characterized by vomiting and loss of gastric, pancreatic, and biliary secretions, with resulting electrolyte disturbances. These disturbances include dehydration, metabolic alkalosis, hypochloremia, hypokalemia, and usually hyponatremia. In contrast, obstructions of the distal ileum may lead only to a slowly progressing distention of the small intestine, with accommodation by

intestinal myoelectrical function and minor alterations in fluid and electrolyte balances. Open-loop obstructions located in the midgut are often complicated by events similar to those seen in closed-loop obstructions or by combinations of events seen in proximal and distal obstructions (**Table 49.2**). Patients with distal jejunal obstruction tend to present with a combination of complications resulting from loss of intestinal contents from vomiting, as well as distention and compromise of intestinal wall perfusion.

Table 49.2 Symptoms and Signs of Bowel Obstruction

Symptom/ Sign	Prox. Small Bowel (Open Loop)	Dist. Small Bowel (Open Loop)	Small Bowel (Closed Loop)	Colon/Rectum
Pain	Intermittent, intense, colicky, often relieved by vomiting	Intermittent to constant	Progressive, intermittent to constant; rapidly worsens	Continuous
Vomiting	Large volumes, bilious, and frequent	Low volume and frequency, progressively feculent with time	May be prominent (reflex)	Intermittent, not prominent; when present, feculent
Tenderness	Epigastric or periumbilical; quite mild, unless strangulation is present	Diffuse and progressive	Diffuse, progressive	Diffuse
Distention	Absent	Moderate to marked	Often absent	Marked
Obstipation	May not be present	Present	May not be present	Present

Adapted from Schuffler MD, Sinanan MN. Intestinal obstruction and pseudo-obstruction. In: Sleisenger MH, Fordtran JS, eds. *Gastrointestinal Disease, Fifth Edition*. Philadelphia, PA: W. B. Saunders Co.; 1993:898–916.

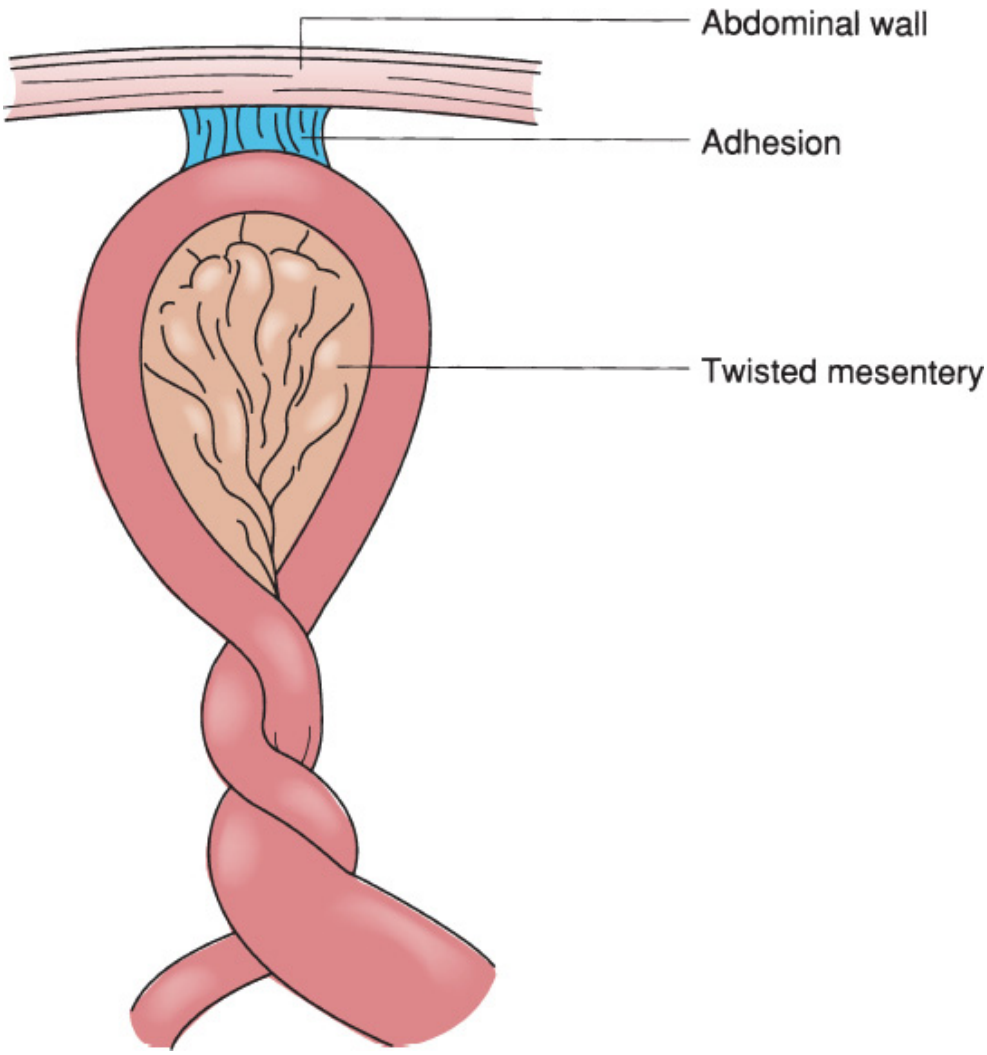


Figure 49.2 Schematic illustration of a closed-loop obstruction. The small intestine twists around its mesentery, compromising inflow and outflow of luminal contents from the loop. Also, the vascular supply to the loop may be compromised due to the twisting of the mesentery. The risk of strangulation is high.

Clinical Presentation and Diagnosis of Small Bowel Obstruction

Acute Obstructions: Symptoms and Signs

Four key symptoms associated with acute mechanical obstruction of the small intestine include *abdominal pain, vomiting, distention, and obstipation.* When a patient presents with abdominal pain that is evolving but not associated with other signs—that is, "pain out of proportion to physical findings," the differential diagnosis includes closed-loop obstruction, along with entities such as mesenteric ischemia, pancreatitis, ureteral colic, a

leaking or ruptured aortic aneurysm, as well as metabolic disturbances. The diagnosis of closed-loop obstruction must be excluded by expeditious testing and imaging or acted on as a surgical emergency 3 . Other consequential factors in the history and clinical examination[8,9] include previous abdominal surgery, quality of pain (colic/intermittent vs. steady), abdominal distention, and hyperactivity of bowel sounds (**Tables 49.2** and **49.3**). In addition, it is important to focus on symptoms that may reflect underlying malignancy as the cause, including fatigue, deconditioning, anorexia, and weight loss; and useful to consider a history of prior malignancies. In simple obstruction, laboratory studies do not play a direct role in diagnosis, but aid in understanding the likelihood of complications such as dehydration, strangulation, and sepsis. Plain abdominal radiographs and other imaging studies with enhancements are useful in confirming the clinical diagnosis of simple obstruction and in differentiating obstruction that is partial in contrast to obstruction associated with intestinal ischemia or gangrene.

Strangulation: Symptoms and Signs

The presentation usually involves an evolving picture of abdominal pain as well as physical signs and laboratory tests that suggest peritonitis, large fluid shifts, and ultimately systemic toxicity (**Table 49.3**). Such signs include abdominal tenderness or involuntary guarding localizing to the area of the strangulated loop of small bowel, decreasing urine output, fever, and tachycardia. The likelihood of strangulation is low if such signs are not present.[10] It should be stressed, however, that when complete obstruction is present, no satisfactory clinical criteria are available to reliably exclude the possibility of strangulation.[6,11,12]

Strangulation: Laboratory Testing

Different laboratory tests have been advocated for early detection of strangulated intestine. Metabolic (i.e., lactic) acidosis and increases in serum amylase, inorganic phosphate, hexosaminidase, intestinal fatty acid–binding protein, serum D-lactate levels and procalcitonin have all been associated with intestinal ischemia.[13–16] Such laboratory abnormalities may be helpful in diagnosing established strangulation in a small group of patients where the diagnosis of necrotic bowel is not clear. However, a noninvasive and rapid

assay has not yet been developed that can provide information to suggest that tissue necrosis is imminent but not yet established.[12]

Obstruction and Strangulation: Differential Diagnosis

Other abdominal conditions, such as appendicitis, diverticulitis, perforated peptic ulcer, cholecystitis or choledocholithiasis can usually be distinguished from small bowel obstruction (SBO), by clinical history, examination, and basic laboratory data. Obstruction of the colon is usually accompanied by varying levels of pain with massive abdominal distention and obstipation. It should also be emphasized that the presence of another abdominal process does not exclude the complication of SBO.

Obstruction and Strangulation: Radiographs and other Imaging Modalities

The role of imaging is to confirm the diagnosis of bowel obstruction while excluding other diagnoses, locate the site of obstruction, and gain insight into the lesion responsible for the obstruction.

Plain Radiographs

A plain, supine abdominal radiograph provides evidence of dilated loops of small bowel (>3 cm) proximal and clearance of fluid and air distal to the point of obstruction (**Fig. 49.3**), while upright or lateral decubitus films classically reveal multiple air–fluid levels located at different levels on the upright film or lateral decubitus film (**Fig. 49.4**). When the clinical symptoms and signs make a simple obstruction likely, plain abdominal radiography can be diagnostic in 67% to 80% of patients.[17,18] It should be emphasized, however, that plain radiographs can miss SBO in patients without air–fluid levels because of fluid-filled distended loops.[19] If there is air in the colon, the obstruction may be complete, but early in the clinical course, or it may be incomplete. Free air in the peritoneal cavity, reflecting perforation of a viscus, is best diagnosed on upright or lateral views, and is easily missed on the supine view. These considerations underscore the importance of obtaining all three views but also should serve as a warning that plain films are not consistently accurate in localizing the specific site of obstruction or predicting clinical progression.

Table 49.3 Diagnosis and Decisions in Bowel Obstruction in Three Hypothetical Patients

	PATIENT I Early Closed-Loop Obstruction	PATIENT II Intestinal Obstruction with Strangulation	PATIENT III Open-Loop Obstruction of the Distal Small Intestine or Cecum
History/Symptoms	Crampy periumbilical pain rapidly evolving from colic to constant pain, with 2–3 episodes of emesis (sometimes dry emesis)	Diffuse, crampy abdominal pain over 24–48 hrs with many episodes of vomiting. Evolves to constant pain. Bowel movements or flatus not uncommon early in the illness, but not late.	Progressive abdominal distention over previous 2 wks. Mild discomfort. No vomiting. Few bowel movements and little flatus
Physical Findings/Signs	No distention, minimal flatus. Minimal disturbance in vital signs. Often with minimal or no tenderness. Peritoneal	Temperature >100 deg F, Heart Rate >100/min, dehydrated. Mild distention; local tenderness often present with focal	Distention prominent, mild tenderness, often with minimal localizing tenderness and no peritoneal findings

	findings absent	peritoneal signs. Strangulated segment may be palpable in thin individuals	
Lab	No leukocytosis, pH, or electrolyte disturbances	WBC 16K. Serum Na^+ low, K^+ low, Cl^- low, pH alkalotic	WBC normal, serum electrolytes mildly decreased
X-Ray	Nonspecific gas pattern on plain film	Multiple dilated loops and air–fluid levels. No gas in colon	Multiple dilated small bowel loops and air–fluid levels. Some gas and stool in proximal colon
Differential Dx	Broad: includes appendicitis, closed-loop SBO, pancreatitis, nonsurgical conditions	Narrow: Complete SBO likely, strangulation cannot be excluded	Narrow: distal small bowel or proximal colon obstruction likely, possibly incomplete
Initial Rx	Admit with q3–4 hr reevaluation by clinical examination, WBC. Repeat	Admit for rapid resuscitation with IVFs, IV antibiotics. Urinary catheter and	Admit for IVFs, NG intubation. Hypaque enema followed by

	films q8–12 hr. NG tube if vomiting persists. IVFs	NG intubation indicated	barium to evaluate colon. CT if malignancy suspected
Indications for Surgery	If pain worsens, local tenderness or peritoneal signs evolve, WBC rises, urine output falls	Already present. Patient should be scheduled and brought to O.R. after adequate resuscitation (dramatic improvement with resuscitation may permit observation for 4 hrs)	Surgery performed when evaluation is complete or if clinical course deteriorates during evaluation

Figure 49.3 Plain supine abdominal film of a patient with small intestinal obstruction. Note the multiple dilated loops of small intestine (*black arrow*) in the left upper quadrant characterized by complete markings of the plicae. Also note absence of air in colon and rectum.

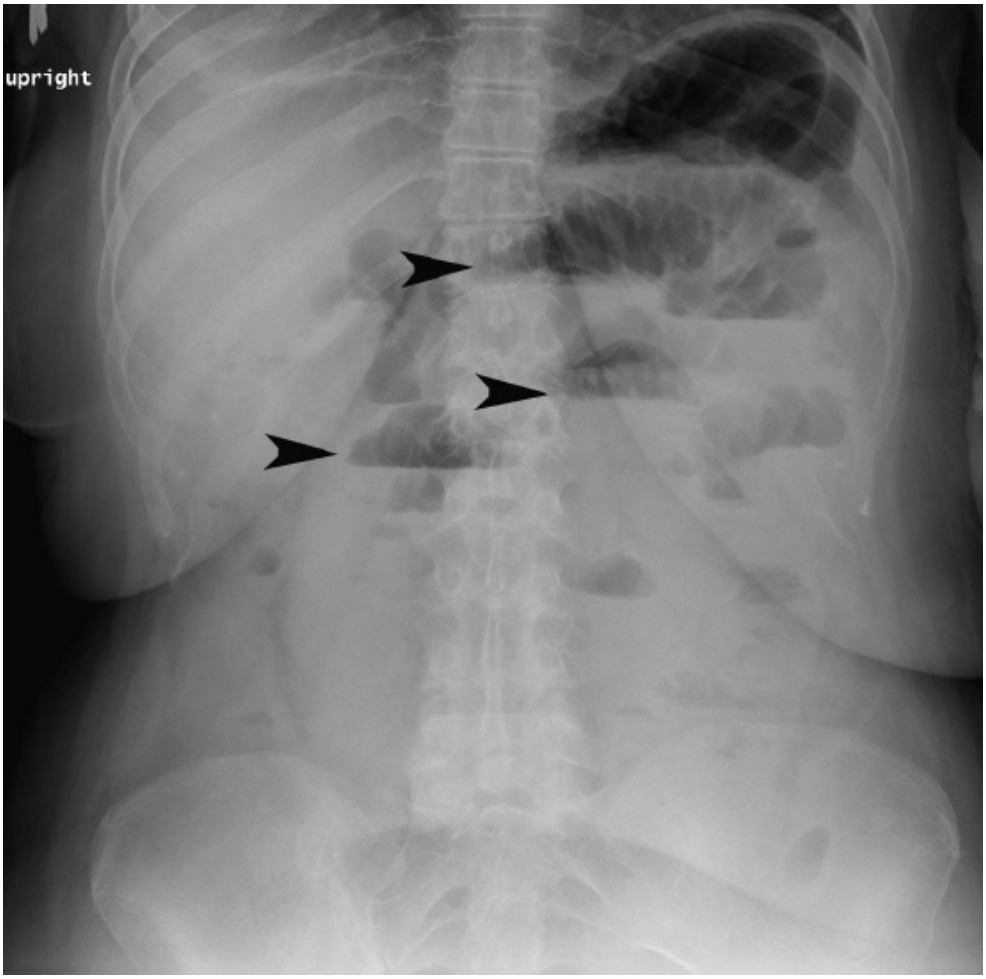


Figure 49.4 Plain upright abdominal film of a patient with small intestinal obstruction. Note the air–fluid levels in the stomach and multiple dilated loops of small intestine (*arrowheads*), and absence of air in the colon or rectum.

Contrast-Enhanced Radiography

Use of water-soluble contrast is diagnostic and can be therapeutic 6. Contrast studies (i.e., small bowel follow-through, enteroclysis, contrast enema) may provide specific localization of the point of obstruction and the nature of the underlying lesion. When obstruction of the small intestine is not progressing or resolving, a small bowel follow-through may be performed to confirm the presence and location of the obstruction. The choice of contrast materials includes water-insoluble suspensions of barium and water-soluble agents such as Gastrografin® or Hypaque™. Barium studies provide the clearest images, in both small bowel studies where the contrast is given from above and colon/rectum studies in which the contrast is given by enema. If

barium leaks into the peritoneum, however, it elicits intense peritonitis. If there is any possibility of bowel perforation or gangrene, barium should not be used. Water-soluble agents such as sodium amidotrizoate/meglumine amidotrizoate oral solution (Gastrografin) or diatrizoate sodium/diatrizoate meglumine (Hypaque) are hyperosmotic and can elicit fluid translocation into the gut.

When the obstruction of the small intestine is simple or incomplete, the use of these agents may also facilitate resolution. Gastrografin is hyperosmolar (1,900 mOsm/L). Its administration permits mobilization of fluid into the bowel lumen which decreases edema of the intestinal wall and increases the pressure gradient across obstructive site. It is thought that these fluid and pressure shifts can contribute to resolution in cases of incomplete obstruction. Thus, the appearance of contrast within 24 hours after administration clearly predicts resolution of the episode (>95%). It remains controversial whether the use of contrast alters the need for surgical intervention or reduces resource utilization when used routinely.[20–22] With respect to the protocol, the 2013 Bologna guidelines for diagnosis and management of adhesive SBO recommended a dosage of 50 to 150 mL of Gastrografin administered either orally or via NGT immediately on admission or after an attempt of conservative treatment for 48 hours.[23]

Computerized Tomography

The resolution and anatomic clarity afforded by computerized tomography (CT) provides several benefits, including improved localization of the obstructed segment and the points of transition, characterization of the completeness of obstruction, detection of ischemia and strangulation, and identification of the etiology of obstruction and exclusion or confirmation of other diagnoses. If the offending lesion is malignant, secondary information about local characteristics and stage can also be obtained.[24,25] The anatomic information obtained, particularly if other diagnoses such as hernia are present, is equally valuable. Attributes of impending ischemia include mesenteric edema, vascular engorgement, high-density fluid in the peritoneal cavity,[26] and moderate to severe intestinal wall thickening (greater than 2 mm) (**Fig. 49.5A,B**). High attenuation of bowel wall on unenhanced CT scans, low or reduced attenuation of bowel wall on intravenous contrast CT scans, and presence of intramural air (pneumatosis) or portal venous gas are

CT findings suggestive of strangulation. Using such criteria, CT scan has a >90% sensitivity and >90% specificity with a negative predictive value of 99% in diagnosing intestinal strangulation. Increasingly, CT scan is considered the "go-to" study for confirmation of the diagnosis, relevant anatomy, and complications.[22]4

Ultrasound and Magnetic Resonance Imaging

Ultrasound can be useful in excluding other diagnoses in the differential, especially lesions in the pelvis, and in detecting signs of mesenteric infarction, such as loss of bowel motility and presence of free peritoneal fluid.[22] MRI has comparable sensitivity to CT scan in diagnosing obstruction but limitations include limited availability after hours, poor definition of mass lesion, and poor visualization of colonic obstructions.[22] The use of MRI should be limited to patients who have contraindications to CT or are allergic to contrast material.[23] It is difficult to recommend the use of ultrasound, except in cases where CT is contraindicated and the sonographer very experienced.

Caveats to the Use of Imaging When Strangulation or Closed-Loop Obstruction Are Suspected

It should be emphasized that when the clinical picture provides strong suspicion for closed-loop obstruction complicated by strangulation, the decision for obtaining imaging studies should not lead to delay in resuscitation and timely operation. The information sought from imaging studies should be weighed against the risk of such delays. The message of the literature on imaging is that the clinical picture is usually correct, especially when multiple clinical signs (tenderness, peritoneal signs, leukocytosis, profound dehydration) of strangulation are present. An imaging study that provides the most rapid confirmation of diagnosis (plain film or CT) is usually sufficient, unless the surgical or medical histories are so extensive as to warrant concern for a complex cause of obstruction or signs that otherwise would be attributed to strangulation.

General Considerations in Management of the Patient with Bowel Obstruction

The Diagnosis Is Suspected

Patients with obstruction of the large bowel present with abdominal pain, distention, and obstipation. Vomiting and electrolyte imbalances are sometimes prominent, though usually delayed. Elderly patients are prone to dehydration. The presentation of SBO depends on level of obstruction, open- or closed-loop nature, and interval since onset of symptoms. Symptoms and signs of intermittent crampy abdominal pain, vomiting, obstipation, and distention are present in variable degrees. The overall picture, however, is usually one of a patient with abdominal symptoms that are evolving and getting worse. In the settings described previously, the following questions must be addressed as expeditiously as possible.

1. *Is the abdominal pain disproportionate to the physical findings and laboratory studies?*
2. *How rapidly are the symptoms and signs evolving: over minutes, hours, or less acutely?*
3. *Does the patient suffer from dehydration, electrolyte imbalance, and acid–base disturbance?*
4. *Is the obstruction complete or incomplete?*
5. *Is there a possibility of strangulation?*

Clinical data and basic laboratory studies will provide reliable information to answer the first three questions. Answering questions 4 and 5 will often depend on close clinical observation and reexamination in the first hours or days after presentation. Abdominal radiographs and imaging studies are frequently used to provide additional information to help answer these latter questions, as well as to provide information to identify the obstructing lesion.

Summarized in **Table 49.3** are thumbnail sketches of different, but typical, kinds of patients presenting with symptoms and signs consistent with obstruction of the small intestine. The principles of diagnosis and management of each of these patients begin with clinical information that indicates the likelihood of a bowel obstruction. Laboratory studies and plain abdominal films are used to confirm the diagnosis of obstruction and determine the extent of physiologic impairment. The patient's history and clinical course in the first few hours of observation are used to determine the likelihood of strangulation. Indications for surgery include rapid evolution of symptoms and signs and high suspicion/confirmation of closed-loop

obstruction. Contrast or imaging studies are used when symptoms are not evolving rapidly and when identification of the underlying lesion might alter the operative strategy.

Resuscitation

The initial management of all patients with suspected bowel obstruction includes designating the patient "NPO" and starting intravenous fluids comprised of isotonic Ringer or normal saline solutions. Restoration of fluid and electrolyte balance is a priority, often requiring frequent evaluation of serum electrolytes and pH[5] . In acute cases when significant dehydration is detected, an indwelling urinary catheter should be placed to monitor urine output. Hemodynamic monitoring may be necessary to monitor the response to fluid resuscitation in patients with severe cardiac, pulmonary, or renal insufficiency.

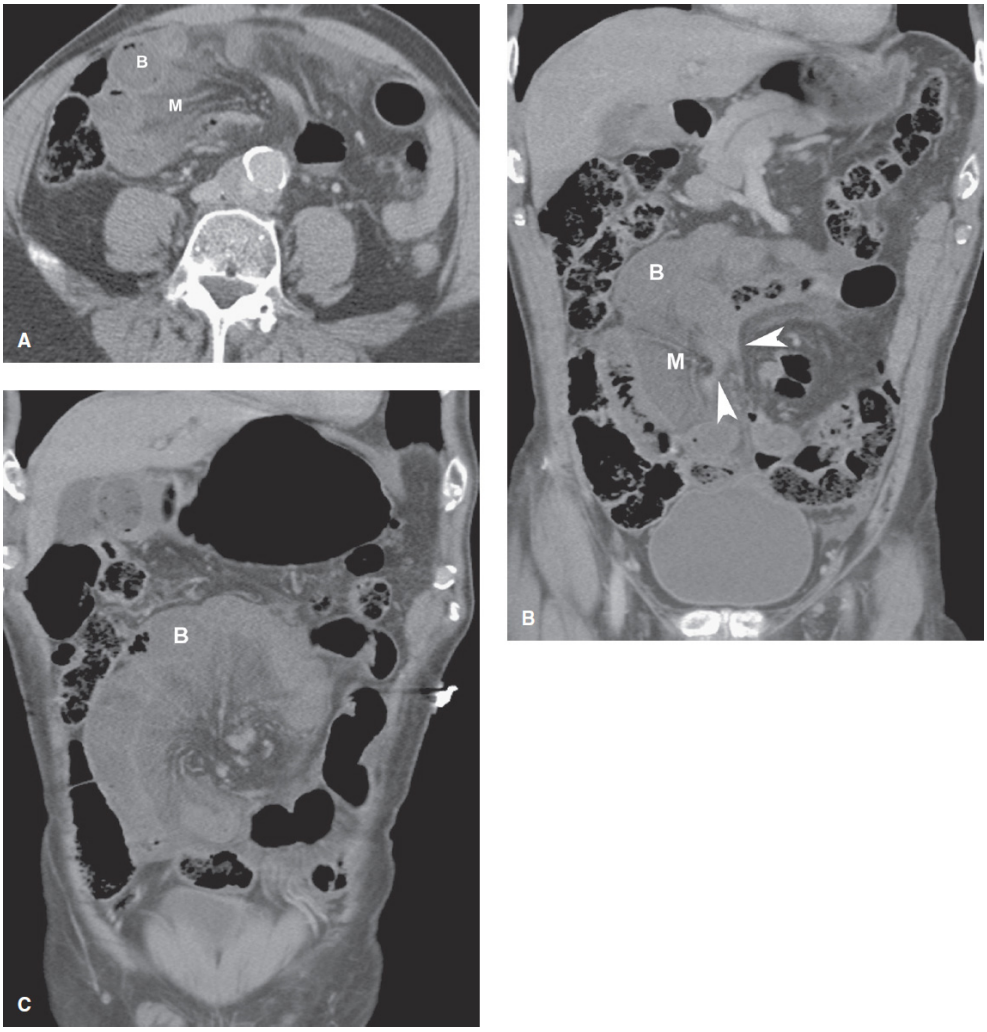


Figure 49.5 Axial, (**Panel A**), and coronal, (**Panel B**), images of a closed-loop obstruction with strangulated small bowel secondary to a volvulus from an adhesive band. Distended fluid-filled loops of small bowel (B) in a radial distribution converging toward the point of torsion (*white arrowheads*). There is edema within the mesentery (M). Shown in **Panel C** is a coronal view of vascular engorgement and mesenteric edema in a closed-loop obstruction.

Nasogastric Decompression

The nasogastric tube, typically a 16- or 18-French sump tube, serves to prevent distal passage of swallowed air and minimizes the discomfort of refluxing intestinal content. The use of longer tubes has been advocated in certain settings, especially for patients with chronic but intermittent obstruction arising from Crohn disease, peritoneal carcinomatosis, radiation enteritis, or many previous laparotomies for obstruction. The underlying rationale is that advancement of the tip of the long tube to the obstructed loop

would permit more effective decompression, perhaps resulting in relaxation of the loop and relief of the obstruction. While the use of long tubes has been reported to be of benefit in some settings[27] and has had its advocates over the year, there remains no clear consensus on indications for its use and its overall utility[22,28] for adhesive obstruction. An important caveat in the use of any form of nasogastric or nasoenteric tube decompression is the risk of aspiration pneumonia and other discomforts. Placement of decompressive tubes is indicated in the early phase of resuscitation and observation, with ongoing nausea, vomiting, distention; but can be avoided when symptoms are mild and quickly resolved.[29]

Antibiotics

It is well recognized, clinically, that bacterial overgrowth is a consequence of obstruction and, experimentally, that the presence of luminal bacteria accelerates the evolution of symptoms and signs of strangulation in closed-loop obstruction. In experimental studies, bacterial translocation to the lymph nodes, mesentery, and circulation has been demonstrated with obstruction; and release of bacterial toxins appears to play a role in mediating the mucosal epithelial and immune response to obstruction.[30–33] These considerations do not provide a rationale for using antibiotics to avoid operation, but they do provide a scientific basis for using antibiotics once the decision for operation has been made and if operation is unavoidably delayed. Nevertheless, the use of antibiotics in patients who have not yet been committed to operation has not been evaluated systematically. Giving antibiotics to patients who are being observed can obscure the underlying process and, in the end, delay optimal therapy. Once the decision has been made to proceed with surgery, broad-spectrum antibiotics, covering gram-negative aerobes and anaerobes should be given. A second-generation cephalosporin or a combination of a first-generation cephalosporin and metronidazole is a rational practice for perioperative coverage in both simple and strangulation obstruction.

Adjuncts to Resuscitation and Decompression

In addition to the use of oral water-soluble contrast, diverse adjunctive strategies have been reported in the effort to optimize resolution of simple adhesive obstruction and avoid surgical intervention. One such adjunct

included oral therapy with the laxative magnesium oxide (500 mg), a defoaming agent simethicone (40 mg) that dissipates large air bubbles, and the probiotic *Lactobacillus acidophilus* (0.3-g tablet) given three times daily via NGT. This appeared to be effective in hastening the resolution of the conservatively treated partial adhesive SBO and shortening the hospital stay with no difference in complication rate and recurrence.[27] Another strategy employed with a reported benefit was hyperbaric oxygen, testing the hypothesis that a high partial pressure of oxygen in blood would hasten evacuation of inert gases from the bowel lumen and reduce edema in the bowel wall.[34] A follow-up randomized controlled trial, however, failed to demonstrate any improvement in the need for operative intervention for SBO when hyperbaric oxygen was used.[35]

Indications and Timing of Operation

The decision to perform abdominal exploration to relieve intestinal obstruction should be made expeditiously, but not in the absence of critical information or before adequate resuscitation (**Algorithm 49.1**). Indications for surgery are outlined in **Table 49.3**, for each of the thumbnail vignettes. It should be emphasized that once a diagnosis of closed-loop obstruction or strangulation with obstruction, the safest course is to proceed to operation without undue delay. Conversely, when the diagnosis is uncertain (i.e., there is a possibility of a nonsurgical diagnosis or that the obstruction is not complete), a period of close observation is appropriate that includes resuscitation, restoration of electrolyte balance, serial examinations, and nasogastric suction when nausea, vomiting, and pain are prominent.

Current practice is in transition, with respect to the need for surgery when the obstruction is complete but not yet complicated by evidence of strangulation, peritonitis, or sepsis. Recent studies have provided evidence to challenge the well-established principle of early operation in this situation. Thus, with management enhanced by administration of water-soluble contrast,[36] there are circumstances in which uncomplicated obstruction may safely be observed unless and until clinical follow-up indicates failure of resolution. Similarly, in patients with obstruction but without a history of prior operation, the so-called “virgin abdomen” may safely be observed to resolution.[37–40] Under circumstances such as these, it is important to recognize the circumstances under which scheduling for surgery

may not be urgent but should not be unduly delayed. Such circumstances would include obstruction due to nonreducible hernia (internal or external) or malignancy amenable to curative resection. A decision to observe, rather than early operation, may also be influenced by resources, expertise, and ancillary services that are available.[41]

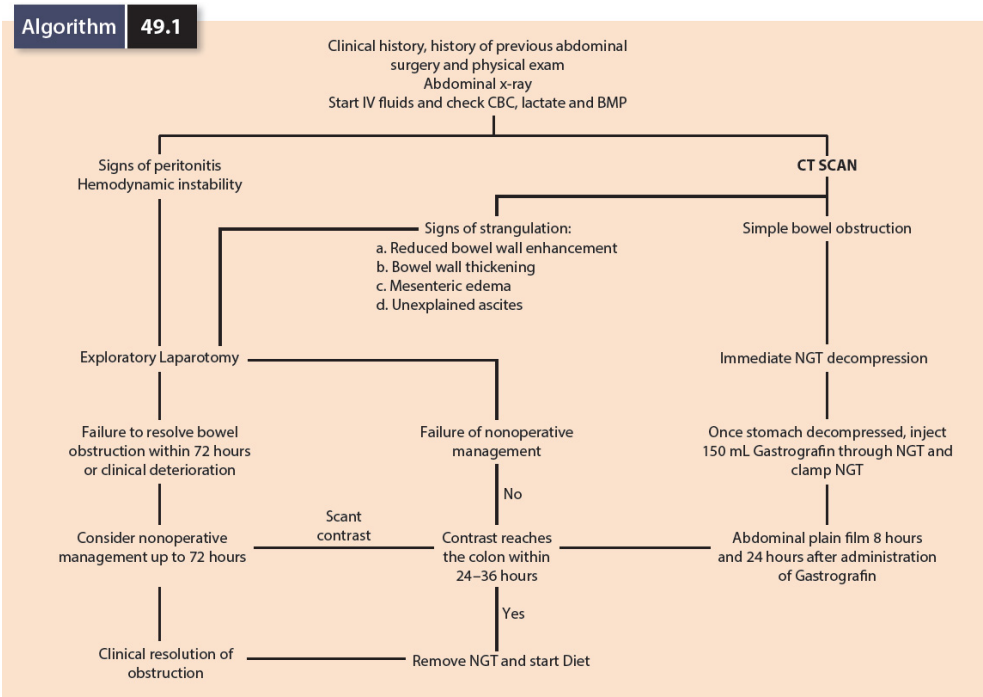
Specific Types of Bowel Obstruction

Chronic Adhesions

Peritoneal adhesions account for more than half of SBO cases. Lower abdominal procedures such as appendectomy, hysterectomy, colectomy, and abdominoperineal resection are common precursor operations to adhesive obstruction. Adhesions may form after any abdominal procedure, however, including cholecystectomy, gastrectomy, and abdominal vascular procedures. In long-term follow-up, about 5% of patients undergoing laparotomy will develop adhesive obstruction[42]; of these, 10% to 30% will suffer from additional episodes. Over 80% episodes of SBO due to adhesions may resolve nonoperatively.[6,22,28] An index episode and three recurrences indicate a likelihood of over 80% that there will be more recurrences.[43] The critical question, then, is whether outcomes, complications, and costs, on balance, favor operative intervention or observation and follow-up in cases where either strategy for management could be chosen. In a series of recent reports, utilizing retrospective administrative data from all acute care hospitals in Ontario, Canada, it would appear that early surgical intervention with an index case of obstruction is associated with less frequent recurrence[44] and comparatively long-term survival.[45] A clear message from this set of reports is that boundaries should be set on the interval for expectant management (**Algorithm 49.1**), so as to avoid the higher morbidity and mortality caused by undue delays.[46]

The pathobiology of adhesion formation has been the subject of considerable investigation.[6] Histologic examination of chronic adhesions reveals foreign-body reaction, usually to talc, starch, lint, intestinal content, or suture. Talc and starch are found less commonly now than previously, because of improvements in techniques of manufacture and sterilization of surgical gloves, and the increasing applications of laparoscopy for intra-

abdominal operations. Mesothelial cells are the presumed origin of tissue plasminogen activator (TPA). TPA binds fibrin and plasminogen, thereby preventing adhesion formation. In early studies, inflammatory cells, including mast cells, were implicated in the process that produces adhesions, along with macrophages which secrete cytokines and chemokines that drive inflammation, resolution, and formation of scar. Ischemia, injury, and rough handling of tissues also play a role to incite local inflammatory response, and recent studies[47] have highlighted the role of various proinflammation cytokines in exacerbating or inhibiting adhesion formation in different animal models. It also seems likely that genetic variants, perhaps among the various cytokines and their receptors,[48] will be found to modify the risk of developing adhesions that lead to obstruction.



Algorithm 49.1 Approach to recognition and management of early postlaparotomy obstruction of the small intestine.

Current strategies to prevent adhesions at a first, or subsequent laparotomy, include first and foremost, minimizing tissue manipulation and injury to the peritoneal surfaces, meticulous attention to hemostasis and surgical technique, use of laparoscopic approaches where safe and feasible, and removal of any foreign material whenever possible. Adjuncts to prevent

adhesions after a first laparotomy include targeting of the fibrinolytic system in order to enhance rapid healing and minimize formation of peritoneal adhesions.[49] Popular strategies have also included the effort to develop temporary barriers that can be placed intraperitoneally at the time of laparotomy in order to prevent adherence of loops of bowel to each other and to other peritoneal surfaces.[50] Such barrier compounds include hyaluronic acid–carboxymethylcellulose membrane (Seprafilm, Genzyme, Cambridge, MA), icodextrin solution, hydrogen adhesion spray, and lyophilized human peritoneal membranes. Such barrier compounds may be useful in preventing adhesions at an initial laparotomy,[51] but only one (icodextrin) has been tested in a trial setting of preventing recurrence following an index episode of adhesive SBO.[52]

Early Postoperative Obstruction and Adhesions

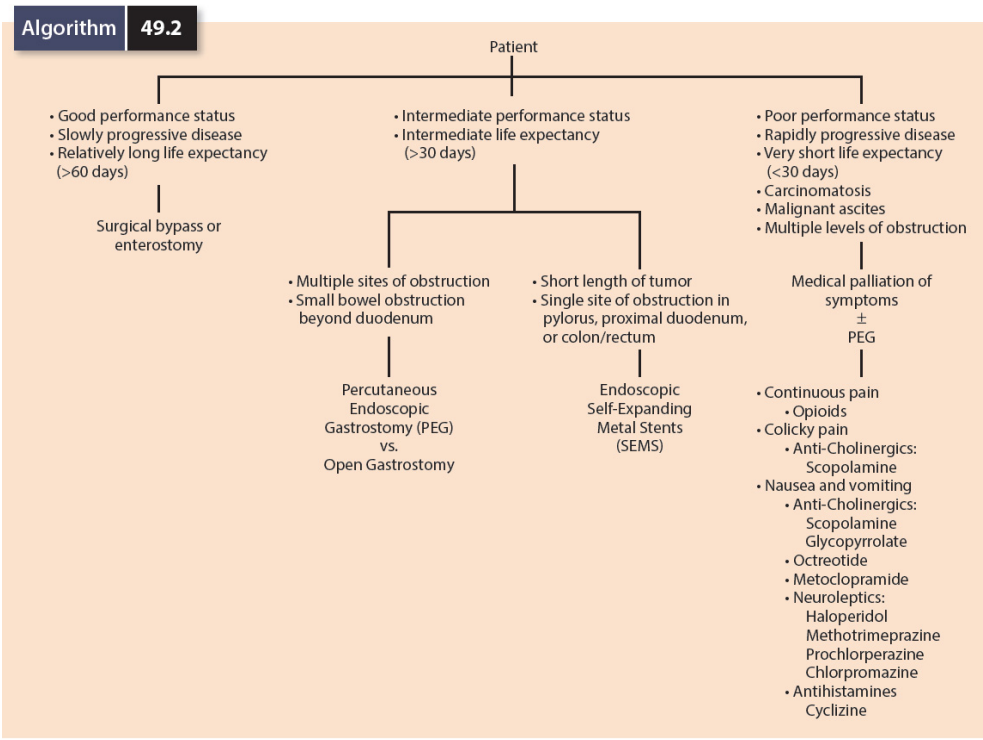
Early Obstruction after Open Operations

Obstruction in the immediate period following open abdominal surgery is uncommon but may occur in up to 1% of patients in the 4 weeks following laparotomy. Adhesions are responsible for approximately 90% of such cases and hernias for approximately 7%.[53] Intussusception, internal herniation, inflammation, abscess, intramural intestinal hematoma, or technical errors may be responsible for the remainder of cases.[54–56] Most cases occur after surgery of the colon, especially abdominoperineal resections, or operations in the lower abdomen. It is rare for upper abdominal surgery to cause such obstructions. A common scenario is that a patient will undergo colectomy uneventfully, pass flatus, and have bowel sounds by postoperative day 3. On the fourth postoperative day the patient will suddenly become distended and uncomfortable, and with cessation of flatus and stool. Patients with acutely evolving symptoms and signs should be suspected of having a complete obstruction and should be managed as such. In this latter setting, the mortality may be as high as 15% due to delays in recognition and operative intervention.[54,57] The loss of bowel sounds after a short period of normal or hyperactive activity is worrisome for ischemia of the obstructed segment. The great majority of such cases may be treated as partial intestinal obstruction; nasogastric suction and intravenous fluids will help resolve symptoms within a few days (**Algorithm 49.2**). When the clinical course

does not demand earlier intervention, a nonoperative approach may be tried for 10 to 14 days and will resolve the obstruction in over 75% of such cases.[57] Patients who experience early postoperative obstruction from adhesions have a higher risk of subsequent adhesive SBO (26.5% vs. 7.5% at 5 years, $P < 0.001$).[56]

Early Obstruction After Laparoscopic Procedures

Requires a different kind of vigilance, in order to determine whether early operative intervention is warranted. In general, laparoscopic procedures are associated with lower short- and long-term risks for intestinal obstruction.[5,58–61] Individual laparoscopic procedures do, however, have individual complication profiles,[57,62,63] reflecting differences in etiology. A port-site hernia is common to all laparoscopic procedures, but the risk likely varies with the site and diameter of port placement. Thick adhesions are a risk where there is localized inflammation, and more likely to occur when procedures involve viscera of the lower abdomen (appendicitis, diverticulitis); but also in cases where there are extensively dissected surfaces, surgically stapled surfaces or intraperitoneally placed prosthetics such as occurs during hernia repair. Internal hernias are a risk when windows are opened in mesentery, such as in bariatric procedures or intestinal/colon resections. Based on these considerations, it is recommended that imaging be obtained when the etiology of obstruction is unclear and that patients with early postlaparoscopy obstruction be followed closely when a decision is made for expectant management rather than expeditious operation.



Algorithm 49.2 Algorithm for management of malignant obstruction.

Bowel Obstruction after a Bariatric Procedure

The obesity epidemic has seen the growth in the number of bariatric procedures which includes gastric banding, sleeve gastrectomy, gastric plication, Roux-en-Y gastric bypass, and biliopancreatic diversion with or without duodenal switch. Band slippage can occur in 15% to 20% of patients and typically presents with a history of upper abdominal symptoms of reflux, regurgitation, and dysphagia. Upper GI study is the preferred method of diagnosing band slippage, showing evidence of malposition of the band and proximal pouch dilatation with obstruction. The initial management is urgent band deflation using a Huber needle and if this is unsuccessful or patient is acutely unwell, necrosis, abscess, or erosion must be considered, which may require surgery. Intestinal obstruction occurs in 4.4% of patients after Roux-en-Y gastric bypass. The etiology of obstruction includes internal hernia (53%), roux limb compression due to scarring (20%), adhesion (14%), stricture at gastrojejunal anastomosis, kinking of the alimentary limb, incisional hernia, and intestinal intussusception. The most common site of internal herniation is the mesojejunal mesenteric window, followed by Petersen window (the defect between the small bowel limb, the transverse

mesocolon, and the retroperitoneum), and the mesocolic window.[64] Obstruction in the postbariatric surgery patient is thus different in its likely etiologies and presentations than in other patients. Thus, while early postoperative intestinal obstruction in the latter patients generally resolves without operation, surgery is required more than 50% of the time in the former and the acute presentation leads to reoperation more quickly, usually within 24 hours after the onset of obstructive symptoms.[65]

Hernia

Indications and Timing of Surgery

Hernias of all types are second only to adhesions as the most frequent causes of obstruction in western countries. External hernias such as inguinal (**Fig. 49.6A,B**) or femoral hernias may present with the symptoms of obstruction and will not be diagnosed unless sought.[66] Femoral hernias are particularly prone to incarceration and bowel necrosis due to the small size of the hernia inlet.[66] Other hernias such as umbilical, incisional, parastomal, or lumbar hernias are obvious. Still others, such as internal hernias are usually diagnosed at laparotomy for obstruction. These include obturator hernias, paraduodenal hernias, and hernias through the foramen of Winslow (posterior to the porta hepatis) or mesenteries. When hernia has been identified as the cause of the obstruction, the patient is quickly resuscitated, given antibiotics, and taken to the operating room. The hernia is reduced and the viability of the bowel assessed. If viable, the bowel is left alone; if not, it is resected. The hernia defect is then repaired. One important consideration is the Richter hernia (**Fig. 49.7**).[67] In this variant, only a portion of the wall of the bowel is incarcerated and thus incarceration and strangulation may not be associated with complete obstruction. These most frequently occur in association with femoral or inguinal hernias. Complete obstruction can occur if more than half of the bowel circumference is incarcerated.

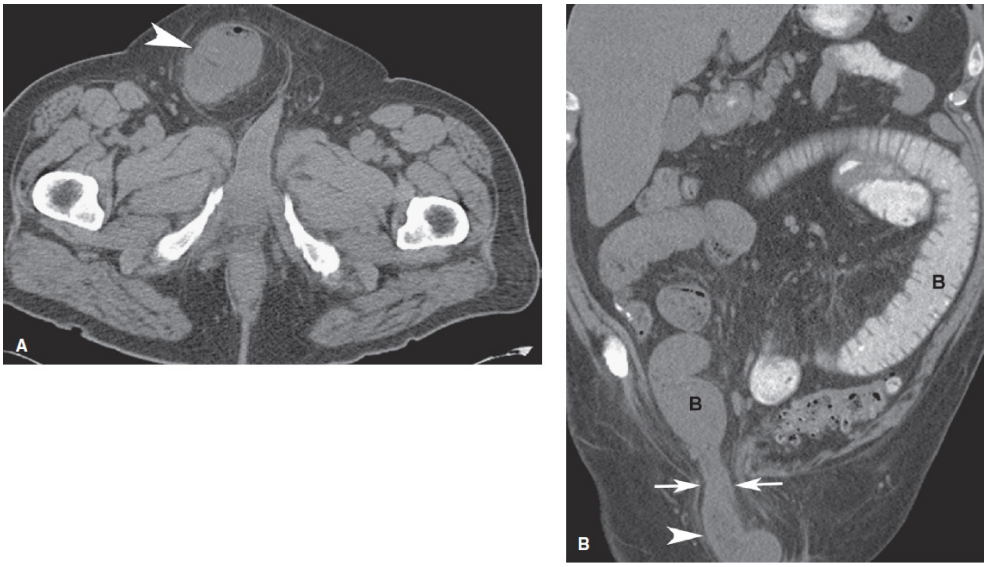


Figure 49.6 CT images of groin hernia. **Panel A:** Axial view. **Panel B:** Coronal view. *White arrowheads* identify the herniating segment. White *arrows* indicate the location of the hernia orifice.

Use of Mesh in Repair in Obstruction-Associated Hernia

Inguinal Hernia

With respect to inguinal hernia, current recommendations do not treat the use of mesh as contraindicated or as a preferred method for repair.[68] A recent large institutional experience confirms the higher likelihood of short-term complications and recurrence in emergency open hernia repairs and found no benefit in using mesh.[69] Based on these considerations, it seems most prudent to perform open tissue repair, saving mesh for recurrences should they occur. Laparoscopy, or laparotomy if necessary, is useful to assist in reduction and assess viability of bowel as needed. The laparoscopic approach to a nonreducible hernia, with reduction and placement of mesh, has been reported with acceptable results; in cases where there was significant contamination or when bowel required resection, a two-stage approach was utilized, with repair delayed until healing after reduction, washout, and resection.[70]

Ventral Hernia

It remains uncertain whether repair of a ventral hernia can safely include use of permanent prosthetic mesh. Recent studies suggest that obstruction without

ischemia or gangrene poses no special risk for postoperative wound occurrence or mesh infection.[71] Complication rates increase if contamination occurs during hernia repair, due to perforation advertent enterotomy, or intestinal resection, risks of postoperative wound infection, fistula, reoperation, and mortality.[72] At the same time, recent studies have shown that, in expert hands, such contamination need not lead to complication rates that are higher even when permanent synthetic meshes are used.[73] These considerations suggest that the approach to hernia complicated by intestinal obstruction should be tailored to the experience of the surgeon and the specific details of the case.

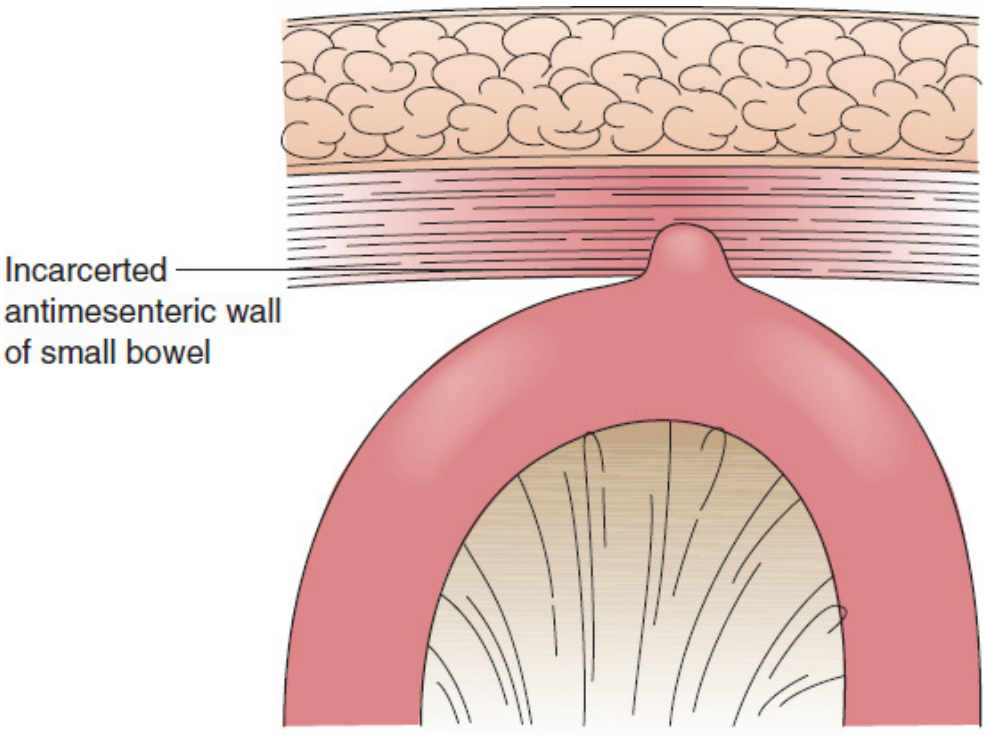


Figure 49.7 Schematic diagram showing Richter hernia, in which the antimesenteric border (but not the whole wall) of the intestine is incarcerated.

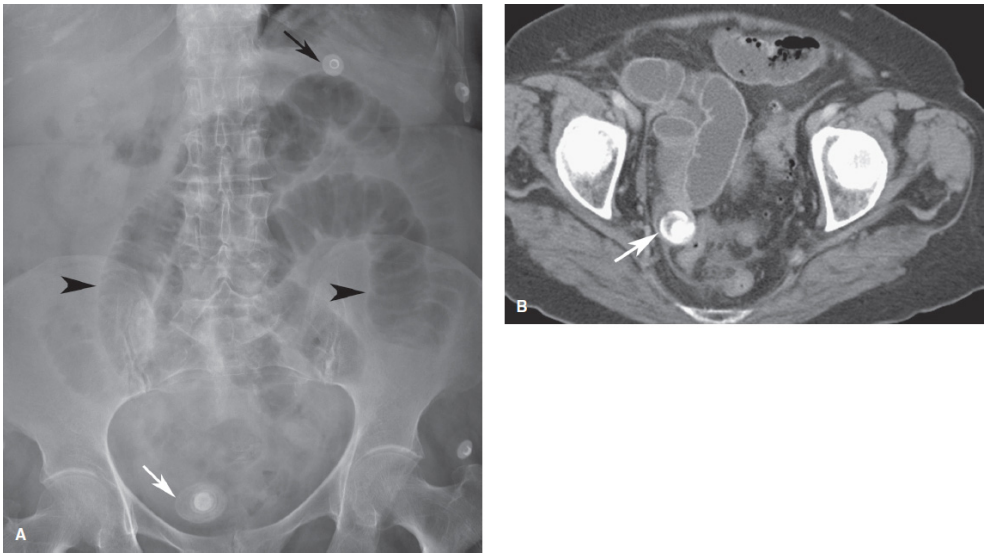


Figure 49.8 Gallstone ileus: **Panel A:** Plain film showing dilated loops of small intestine (*black arrowheads*), with air visible in biliary tree characteristic of biliary enteric fistula. **Panel B:** CT scan showing gallstone (*white arrow*) in the distal ileum and fecalization of luminal content adjacent to the stone.

Preoperative Reduction of Hernia to Relieve Obstruction (Taxis)

Reduction of the hernia is often successful but can occasionally result in reduction of the contents of the hernia still within its peritoneal sac, also known as reduction en masse. This can lead to persistence of a pre-existing obstruction or development of a new obstruction due to twisting of the loop of bowel in the sac. This is one reason for using circumspection in relying on taxis as a mode of treatment for incarcerated inguinal, femoral, and incisional hernias. In general, taxis should be followed by an expeditious operative repair.[74–76]

Gallstone Ileus

As a result of intense inflammation surrounding a gallstone, a fistula may develop between the biliary tree and the small or large intestine. Most fistulae develop between the gallbladder fundus and duodenum. If the stone is greater than 2.5 cm in diameter, it can lodge in the narrowest portion of the terminal ileum, which is just proximal to the ileocecal valve. This condition is rare, accounting for no more than 3% of cases of intestinal obstruction. Typically, the patient is elderly and female and presents with intermittent symptoms over several days, as the stone tumbles distally toward the ileum.

The classic findings on plain radiographs include those of intestinal obstruction, a stone lying outside the right upper quadrant, and air in the biliary tree (**Fig. 49.8A,B**). Treatment includes removal of the stone (via a proximal enterotomy) and resection of the obstructed segment only if there is evidence of tissue necrosis. The risk of a recurrent gallstone ileus is about 5% to 10%.[77,78] Such recurrences usually occur within 30 days of the initial episode and are usually due to stones in the small intestine that were missed at the original operation. Concurrent disconnection of the fistula and cholecystectomy is associated with higher morbidity[79] but can be performed selectively in good-risk patients. The current consensus is that cholecystectomy should not be performed at the initial operation for gallstone ileus, except in highly selected patients. A careful search of the entire intestine should be performed to exclude the possibility of additional large stones which can occur in up to 25% of patients.[80,81] For patients with Bouveret syndrome (duodenal obstruction due to an intraluminal gallstone), particularly those with high operative risk, an endoscopic approach may be considered as lithotripsy can often successfully relieve the obstruction. It should be noted, however, that up to 15% of these patients may go on to require laparotomy due to the development of a more distal obstruction due to migration of a stone fragment.[81,82]

Intussusception

About 5% of intussusceptions occur in adults. An intussusception occurs when one segment of bowel telescopes into an adjacent segment, resulting in obstruction and ischemic injury to the intussuscepting segment (**Fig. 49.9A**) and the obstruction may become complete, particularly if tissue inflammation and necrosis occur. Of adult cases, 90% are associated with pathologic processes.[83,84] Tumors, benign or malignant, act as the lead point of intussusception in more than 65% of adult cases. A significant proportion of cases have been reported to occur after abdominal surgery for lesions other than neoplasm. In cases not associated with neoplasm, Sarr et al.[85] reported that approximately 20% were related to the suture line, approximately 30% to adhesions, and approximately 60% to intestinal tubes. Intussusception related to long tubes can occur when the tube is withdrawn, but most frequently occurs with the tube in place. Perioperative intussusception

frequently subsides without intervention. It should also be noted, that as CT scans have become more widely used, transient intussusceptions without evidence of bowel obstruction are not infrequently identified and do not typically require intervention.[84,86]

Four types of intussusception are recognized: enteric, ileocolic (**Fig. 49.9B,C**), ileocecal, and colonic. In the ileocolic form, the ileum telescopes into the colon past a fixed ileocecal valve. In the ileocecal form, the valve itself may be the lead point of the intussusception. Radiographic features of intussusception are not specific. Plain films reveal evidence of partial or complete obstruction. Occasionally, a sausage-shaped soft tissue density will be seen, outlined by two strips of air. In both pediatric and adult cases ultrasonography may be useful in diagnosis. Nevertheless, in adult patients the mainstays of diagnosis are contrast studies or CT scan. Because of the high incidence of tumors, surgery has generally been recommended. Reduction by hydrostatic pressure, which is the standard of care in pediatric cases, is not usually attempted in adults.

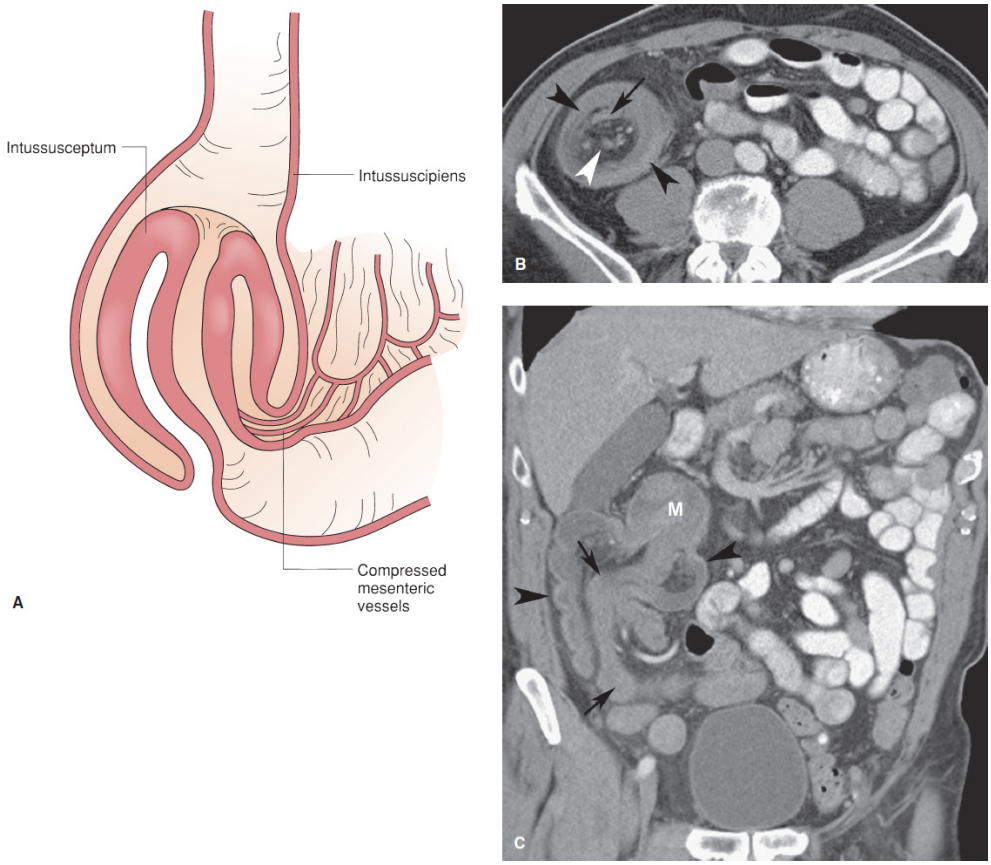


Figure 49.9 Anatomy and CT views of intussusception. **Panel A:** The intussusceptum is the segment of bowel that invaginates into the intussuscipiens. Axial view, (**Panel B**), *white arrowhead* shows the lumen, *thin arrow* shows the intussuceptum, and *thick black arrowheads* show the intussuscipiens. Coronal view, **(Panel C)**, M indicates the mesentery of the intussusceptum, while *black arrows* indicate the intussuscipiens. The *black arrowhead* indicates the edematous wall of the intussuscipiens.

In adults, preoperative reduction with barium or endoscopic insufflation might be successful in about one-third of patients, while intraoperative reduction is successful in another one-third.[83,84,87] Preoperative reduction has several benefits, including avoidance of emergency surgery, allowing radical surgery for cancer, reducing the extent of intestinal resection, and allowing time for preoperative preparation of the patient.[87] Clear indications for operation include long length and wide diameter of the intussusception, presence of a lead point, or evidence of bowel obstruction.[83,86] When malignancy is detected, preoperative reduction is inadvisable.[83] In the absence of malignancy, recent studies have called into question the need to operate in all cases detected on sensitive imaging studies such as CT scan,

arguing that a number of these patients can be safely managed without operation.[86] Given the possibility occult and potential malignant lesions such as gastrointestinal stromal tumor or carcinoid, expectant management should probably not be initiated without additional studies such as enteroscopy or capsule endoscopy.

Crohn Disease

Indications for surgery in Crohn disease are discussed elsewhere in this book. In this disease, obstruction occurs under two different sets of circumstances.[88] When the disease has flared acutely, the lumen may be narrowed by a reversible inflammatory process. The result is an open-loop obstruction that may respond, first to intravenous hydration and nasogastric decompression, and ultimately to therapy with corticosteroids or other anti-inflammatory regimens.[89] Alternatively, obstruction may occur in the setting of a chronic stricture. Such strictures may respond temporarily to conservative measures but, once diagnosed, operative therapy should not be delayed. One important clinical point is that perhaps 7% of Crohn strictures in the colon and an uncertain but smaller number in small bowel may harbor malignancy.[88] Extent of resection of a Crohn stricture is thus based on intraoperative findings, that is, to margins beyond visibly diseased bowel. If there is suspicion for malignancy, a lymphadenectomy is performed but not otherwise.

Malignant Obstruction

Obstruction can complicate malignancies of the small and large bowel in a number of settings. Studies have documented that 10% to 28% of patients with colorectal cancer and 20% to 50% of patients with ovarian cancer will present with a malignant bowel obstruction at some point during the course of their disease.[90] Most commonly, a primary lesion such as an adenocarcinoma or lymphoma will enlarge until the lumen of the intestine is blocked. The lesion then presents with symptoms and signs associated with the level of obstruction and is managed accordingly.

A second setting involves a patient who previously has undergone surgery for malignancy and now returns with evidence of bowel obstruction. The

likelihood that that the obstruction is due to recurrent disease is based on several factors, including the origin of the primary malignancy, the stage of the primary malignancy, and the designation of the original surgery as curative or palliative. Gastric and pancreatic carcinomas often present with or are subsequently complicated by peritoneal carcinomatosis and thus the subsequent obstruction is most likely due to malignancy. With respect to colon and rectal carcinomas, as many as 50% of cases presenting with obstruction after resection of the primary may be due to adhesions and not recurrent malignancy.[90,91] In addition, even if the obstruction is due to now unresectable disease, significant palliation can be obtained through bypass or enterostomy in up to 75% of patients (**Fig. 49.10**). However, the underlying diagnosis of cancer in this patient population mandates careful attention be paid to patient selection prior to any surgical intervention and risk factors for poor outcome (**Table 49.4**).

Management of incurable malignant obstruction may require an approach that moves away from classical surgical teaching of nothing by mouth (NPO), nasogastric tube, intravenous fluids, and serial radiographs.[92] Patients with advanced malignant obstruction in the absence of a solitary or correctable obstructing lesion are generally managed without surgery. Patients are managed without a nasogastric tube if possible. They are encouraged to eat as soon as obstructive symptoms resolve using a low-fiber diet. Antiemetics and opioids via continuous subcutaneous infusions are used to manage nausea, vomiting, and colic, respectively. In addition, octreotide, a somatostatin analog, is used in palliation of refractory malignant intestinal obstruction by improving intestinal mucosal absorption, improving motility, reducing gastrointestinal hormone levels and intestinal secretions, and having a direct antineoplastic effect on the obstructing tumor.[93] This may allow true palliative care outside a hospital setting saving patients the pain, discomfort, and complications of hospitalization and unproductive surgery.[92] In patients presenting with gastroduodenal and colorectal obstructing lesions who are not candidates for surgical bypass or enterostomy, endoscopic management options including percutaneous endoscopic gastrostomy tube (PEG) placement and self-expanding metallic stent (SEMS) placement, are available (**Algorithm 49.2**). These options have been associated with symptomatic relief in greater than 75% of patients.[90]

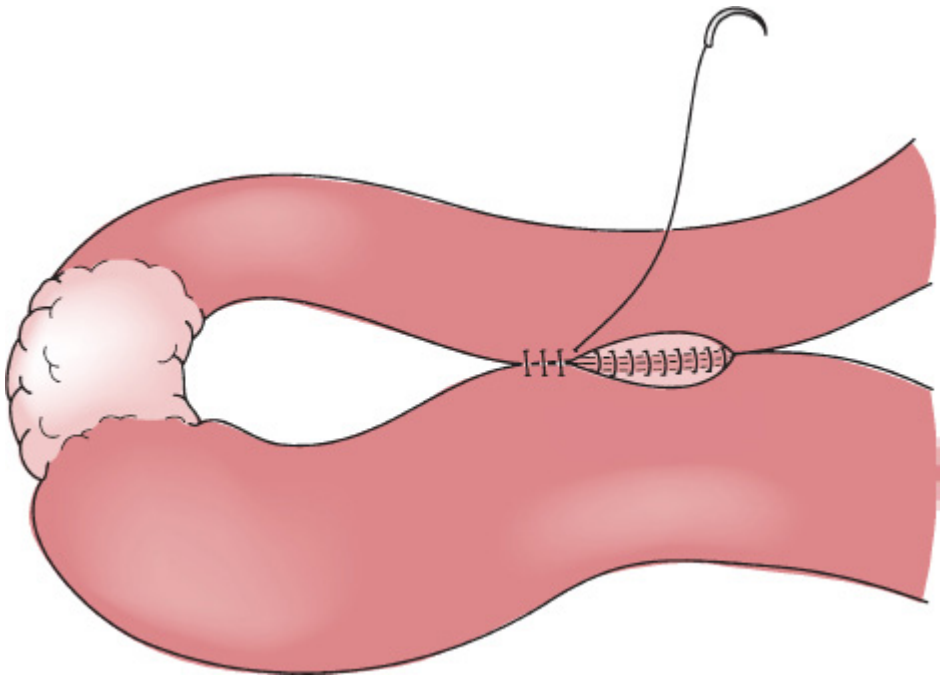


Figure 49.10 Significant palliation can be achieved in a patient with obstructing, but unresectable malignancy. Enteroenterostomy is performed to bypass the obstructing segment.

Table 49.4 Management of Malignant Obstructions: Risk Factors for Unfavorable Outcome

Advanced age (biologic/physiologic)
Poor performance status
Advanced stage of primary malignancy (previous treatments, availability of anticancer options, life expectancy)
Malnutrition/cachexia
Comorbidities
Absence of psychosocial support
Ascites (>100 cc associated with poor outcome)
Single vs. multiple sites of obstruction
Carcinomatosis (believed to respond poorly to surgical intervention)

Volvulus

The term *volvulus* indicates that a loop of bowel is twisted more than 180 degrees about the axis of its mesentery. Volvulus has been reported for the cecum, transverse colon, splenic flexure, and sigmoid colon. A special variant of volvulus, complicating a condition known as *Chilaiditi syndrome*, can occur when redundant loops of the transverse colon slip between the liver and diaphragm and then torse.[94] Generally, the condition is asymptomatic, but when associated with volvulus must be relieved surgically.

The most common site for volvulus is the sigmoid colon, accounting for 65% of cases. Volvulus occurs less often when an unusually mobile cecum, or rarely the transverse colon twists around their mesenteries.[95,96] A volvulus is a form of closed-loop obstruction of the colon. Air is always present in the colon and rectum, and thus volvulus of any segment of the colon is associated with abdominal distention and, usually, severe abdominal pain. As shown in **Figure 49.11**, the most common radiographic feature is the "bent inner tube" appearance of the sigmoid, which is usually visualized in the upper abdomen. The preferred method of management involves endoscopic decompression. A rigid or flexible proctosigmoidoscope is advanced gently into the rectum until a rush of air and feces indicates that the loop has been untorsed. A rectal tube is then advanced well into the loop as a stent to prevent retorsion. Gangrene of the colon does not usually complicate the picture if the patient is seen and treated promptly. This conservative approach resolves the volvulus in 85% to 90% cases and elective resection or fixation of the redundant segment can then be planned. Following endoscopic decompression alone, recurrence of the volvulus is higher than 60%.[97] Thus, an operation to remove the sigmoid should be performed if the patient is fit for surgery.[98] However, a majority of these patients are elderly and infirm and approximately 15% have a history of psychiatric disorder. As a result, the patient may present with peritoneal findings, sepsis, and shock. In this setting, rapid resuscitation followed by urgent resection and colostomy is warranted. Other forms of volvulus generally cannot be detorsed without operation. Fixation of the torsed segment (e.g., via cecostomy or cecopexy) is not as effective as resection of the involved segment and is not generally recommended.[95,96]

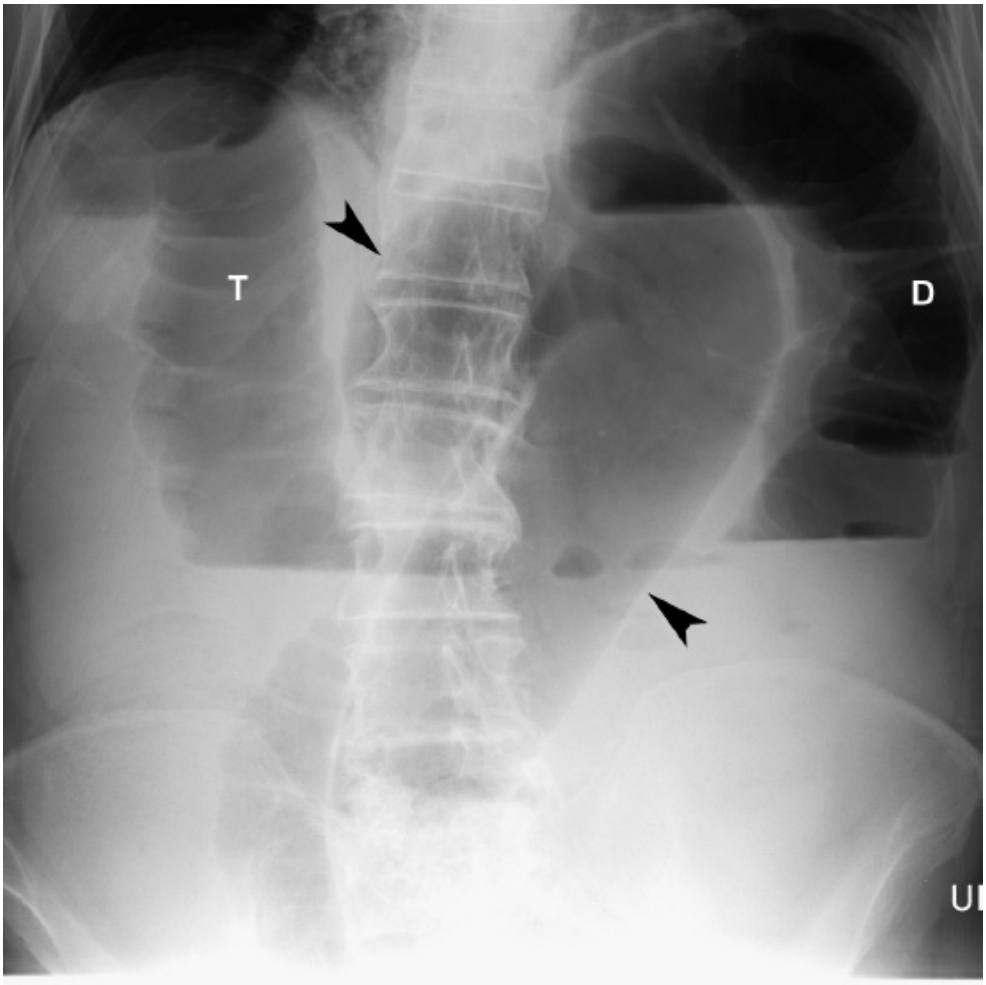


Figure 49.11 Plain supine abdominal film of a patient with sigmoid volvulus (*black arrowheads*). The centrally located sigmoid loop is outlined by trapped air. The proximal small intestine is dilated as well suggesting that the volvulus has been present for sufficient time to cause accumulation of air and fluid proximally.

Radiation Enteritis

After asymptomatic periods lasting at least 10 years, chronic intestinal obstruction can result. Radiation injury elicits an underlying vasculitis and fibrosis that lead to chronic, recurring low-grade partial obstruction of the small intestine or stricturing and bleeding in the colon and rectum. Operation is indicated for incapacitating symptoms and obstruction not resolved by conservative management.[99,100] Recurrence of the original tumor as a cause of obstruction should be considered and excluded. However, the diffuse nature of the injury and pathologic responses can lead to massive resections that leave the patient with short-bowel syndrome. Attempts to suture scarred

loops can also result in chronic inflammation and formation of interloop abscesses and fistulae. The incidence of suture line leak is high.[101] A critical feature is preoperative malnutrition and diarrhea that is often associated with radiation enteritis, due to both malabsorption and maldigestion,[100] leading to deficiencies in fat-soluble vitamins (especially Vitamin B_{12}) and interruption of the enterohepatic circulation. Surgical approaches include resection, when structuring disease is localized to distal segments and the intestinal loops not too densely adherent to each other or other structures such as major blood vessels. When resection is not feasible, it may be possible to perform a bypass of the obstructing segment (**Fig. 49.10**).

Open and Laparoscopic Operation in the Management of Small Bowel Obstruction

General Principles of Open Laparotomy and Lysis of Adhesions

Currently, open laparotomy is the preferred method for managing SBO complicated by strangulation or perforation, or in the setting of complex abdominal conditions such as malignancy, inflammatory bowel disease, or hernia. It is also generally the safest approach for operative management when multiple operations have been performed previously. An incision is made, usually in the midline and starting, if possible, cephalad to any prior incisions. The technique of adhesion lysis requires patience and gentle traction on structures to reveal opportune planes of dissection. Sharp dissection, in some cases using a scalpel blade, is used on very dense adhesions in order to avoid unnecessary crush or tear injuries. When areas of dense adherence are visualized, it is wise to tease the less densely adherent structures on all sides—cephalad, caudad, and lateral to the most difficult areas. Moist sponges are used to as much as possible when handling the bowel in order to prevent desiccation. Areas of serosal abrasion or tear are imbricated and covered with uninjured serosa, while full-thickness enterotomies are closed, resected with enteroenteral anastomosis, or converted to enteroenterostomy. In general, the longer a lysis of adhesions takes, the more physiologic disturbance and the slower the recovery. Exploration of the peritoneal cavity for obstruction requires unhurried but steady progress, conscious of the clock but not driven by it.

General Principles of Laparoscopically Assisted Lysis of Adhesions

Over the past two decades, technical advances have permitted laparoscopy to enter the mainstream of surgical management for intestinal obstruction.[102] Such approaches have been used, with varying degrees of success, to manage obstruction from a number of different etiologies.[103–105] The benefits of laparoscopic management include faster recovery of bowel function, shorter hospital stay, less postoperative pain, reduced recovery time and earlier return to full activity, and fewer postoperative complications including a decreased incidence of wound infection and pneumonia. Additionally, laparoscopy is associated with decreased incidence, extent, and severity of intra-abdominal adhesions compared with open surgery. Thus laparoscopic management of bowel obstruction may result in a decreased lifetime risk for recurrent bowel obstruction. According to a systematic review and meta-analysis, laparoscopic adhesiolysis was associated with reduced overall complication rate with no significant difference in the occurrence of intraoperative injury to bowel and overall mortality.[106] The predictive factors for a successful laparoscopic adhesiolysis are fewer than two previous laparotomies, nonmedian previous laparotomy, appendectomy as prior surgery, unique band adhesion as the mechanism of SBO, early laparoscopic management (within 24 hours of the onset of symptoms), no signs of peritonitis on physical examination, and experience of surgeon.[107] Reasons for conversion from laparoscopic to open operation include the overall burden of dense adhesions, inadvertent enterotomy, and inability to determine the underlying cause of obstruction.[102]

In adults, the most common indication for laparoscopic management of bowel obstruction is adhesive bowel obstruction.[7,22,102] Studies of laparoscopic lysis of adhesions for SBO indicate that it is feasible, with acceptable operative times, length of hospital stay, as well as conversion and complication rates. Studies directly comparing laparoscopic to open surgical management of adhesive SBO highlight the benefits of the laparoscopic approach as indicated by statistically significant decreases in complication rates, time to return of bowel function, length of hospital stay, and even overall cost.[102,108,109]

Laparoscopic management of bowel obstruction should be approached with caution and individualized to specific clinical situations.[110]

Laparoscopy is discouraged when the surgeon is uncomfortable with the technique or in patients presenting with peritonitis, hemodynamic instability, severe comorbid conditions, complete and distal obstruction, or when contraindications to pneumoperitoneum exist. Recently, consensus guidelines have been published emphasizing its role in selected group of patients.[111] Laparoscopically assisted lysis of adhesions may be attempted in case of first episode of SBO or anticipated single band lesion. In addition, it is safe to approach the patient with intestinal obstruction in the setting of a prior history of uncomplicated laparoscopically assisted procedures such as appendectomy or cholecystectomy. Under these circumstances, success in using laparoscopy to confirm the diagnosis of obstruction is between 60% and 100%; its success in therapeutic resolution of the obstruction is lower, perhaps 40% to 80%.

Operative technique plays a paramount role in the success of laparoscopic approach. In obtaining laparoscopic access, an open access (Hasson) technique, entry into the left upper quadrant, and ultrasound-guided site entry are recommended.[23,111] It is also important to point out the need for adhesion quantification in future research. Coccolini et al. proposed a Peritoneal Adhesion Index ranging from 0 to 30, providing a more precise and standardized system for describing findings at operation.[112] Such standardization would enable integration of the results of different studies, permitting a better understanding of circumstances where treatments may be standardized and those where individualization is important.[5]

7 Open exploratory laparotomy is the gold standard in treating unresolved SBO but laparoscopic management should be considered in select groups of patients. Types of intestinal obstruction that are more likely to lead to strangulation and the need for urgent/emergent operation include closed-loop obstructions, and obstructions that occur after laparoscopic procedures.

ILEUS AND PSEUDOOBSTRUCTION

Ileus

Etiologic Factors

An *ileus* or *"eileos"* (Greek for "twisting") reflects a loss of forward peristalsis and coordination of the motility of the different regions of the gastrointestinal tract causing a functional obstruction 8 .[113] Clinically, bowel sounds, passage of flatus, and bowel movements have been used to signal the return of bowel function and coordination of peristalsis. Liquid contrast and radiolabeled marker studies suggest that duration of motor dysfunction varies in different regions of the alimentary tract.[114,115] Ileus is a known consequence of systemic metabolic disturbances such as sepsis or ketoacidosis, activation of reflexes after injury to the central nervous system, direct contact of bowel with inflammation and infection (peritonitis), or inflammation or bleeding in the retroperitoneum caused by conditions such as pancreatitis, aneurysm rupture, or pelvic fracture.

A postoperative ileus (POI) may last for 0 to 24 hours in the small intestine, 24 to 48 hours in the stomach, and 48 to 72 hours in the large bowel.[116,117] The overall duration of ileus, however, is determined by the coordination of motor function along the length of the gastrointestinal tract. Ileus is most commonly associated with operations of the abdomen; it is also observed in the setting of major orthopedic operations such as hip reconstruction or spine surgery.[118,119] Duration of ileus is primarily dependent on the return of colonic motility and its coordination with other regions of the gastrointestinal tract. A typical period of ileus is self-limited and easily tolerated.[120,121]

Neurohumoral Factors

Implicated in the pathogenesis of ileus (**Table 49.5**) is a diverse array of circulating peptides and neurotransmitters, some that enhance gastrointestinal motility and others that inhibit myoelectric function. Among them are acetylcholine, calcitonin gene related peptide (CGRP), Substance P released through vagal pathways (activate motor function) and catecholamines released by sympathetic neurons and the adrenal medulla (dampen motor function).[122] Among the most clinically consequential are the opioids, both synthetic and endogenous, which delay gastric emptying and promote nonperistaltic contractions that increase intraluminal pressure along the length of the gastrointestinal tract.[123,124]

Inflammation

A relatively recent series of experimental and clinical investigations have focused attention on the role of inflammatory cells and mediators of inflammation in the development of prolonged ileus. Surgical intervention results in activation of mast cells and macrophages within the gut wall, leading to release of proinflammation cytokines and activation of their receptors, including interleukins 1, 6, and 10; activation of cyclooxygenase isoform-2 (COX-2) and inducible nitric oxide (iNOS).[125–127] Thus, the hypothesis has evolved that focal manipulation of the bowel results in a pan-enteric inflammation and modulation of the enteric nervous system that leads to ileus.[126,128–130]

Diagnosis

Clinically, it is important to distinguish between normal POI, pathologic, or the so-called paralytic ileus and early postoperative mechanical obstruction. POI is self-limited, usually lasting 2 to 4 days, predominantly a reflection of colon dysmotility. Paralytic ileus lasts longer, and reflects dysmotility of the small intestine. Symptoms and signs of normal POI include mild nausea and perhaps vomiting with mild distention and sparse but not absent bowel sounds. A prolonged postoperative ileus (PPOI) is manifest in protracted signs or symptoms of abdominal distention, bloating, diffuse and persistent and constant abdominal discomfort, nausea, vomiting, and inability to pass flatus or tolerate an oral diet. In contrast, mechanical obstruction is characterized by intense colicky pain, feculent emesis, or rapidly progressing pain or distention is more suggestive of SBO than PPOI. Classically, localized tenderness, fever, tachycardia, and peritoneal signs suggest bowel ischemia or perforation.[10,131–133] Differentiation of ileus from obstruction is often difficult without objective confirmation through imaging and systematic, serial clinical observations.

Table 49.5 Etiologies of Prolonged Ileus after Abdominal Operations

Neurogenic	Metabolic	Pharmacologic	Infectious
Spinal cord lesions or injury	Hypokalemia Uremia	Anticholinergics Opiates	Systemic sepsis Pneumonia
Retroperitoneal process hematoma, tumor	Ca^{++}, Mg^{++} imbalance	Autonomic blockers	Peritonitis
Ureteral colic	Hypothyroidism Diabetic coma or ketoacidosis	Antihistamines Psychotropics Phenothiazines Haloperidol Tricyclic antidepressants Clonidine Vincristine	Herpes Zoster Tetanus Bacterial overgrowth (blind-loop)

A variety of clinical circumstances and laboratory tests may also increase suspicion for prolonged ileus and lessen concern for mechanical obstruction and associated complications. In addition to opiates, diverse medications have been associated with slow recovery of intestinal motor function (**Table 49.5**). Isolated metabolic disturbances such as ketoacidosis, hypomagnesemia, hypercalcemia, hypokalemia can prolong ileus.[134,135] Ileus can be caused and perpetuated by systemic inflammatory responses to sepsis, abscess, pneumonia, pancreatitis, and major burns. In addition, there is some clinical and experimental evidence to suggest that when there are pre-existing micronutrient abnormalities that lead to systemic inflammation, recovery of intestinal motor function may be delayed.[136,137]

When the patient's POI has extended beyond the expected period, plain films of the abdomen reveal gas in segments of both small and large bowel (**Fig. 49.12**). At this point, the patient may begin to experience some

discomfort and distention, as swallowed air fills loops that do not have effective peristalsis. Bowel sounds may be present, if hypoactive. The differential diagnosis now includes the possibility of mechanical obstruction from early postoperative adhesions (see earlier).9 To differentiate early postoperative obstruction from ileus, contrast studies or CT scans are helpful. The latter may be useful if other abdominal pathology such as an abscess could be contributing to the clinical picture. *CT with oral contrast has a sensitivity and specificity of 90% to 100% in distinguishing ileus from a complete postoperative SBO.*[138] However, it is less reliable in distinguishing ileus from a partial SBO.[138] If the diagnosis is uncertain after CT, upper GI contrast studies (enteroclysis) with water-soluble radio-opaque contrast material (e.g., Gastrografin) are especially helpful in distinguishing ileus from partial SBO (which more closely mimics ileus than complete SBO) and in identifying the severity of partial obstruction.[138] POI is usually self-limited.

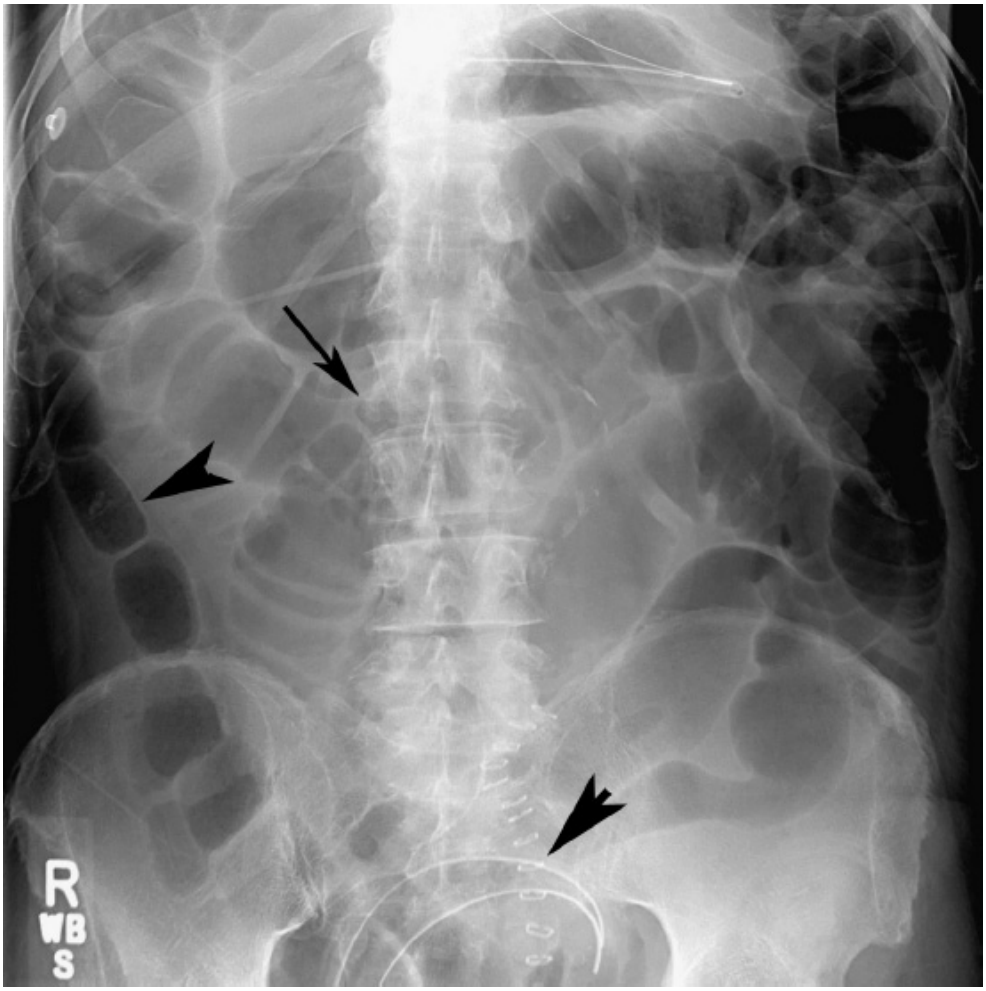


Figure 49.12 Plain upright abdominal radiograph of a patient with ileus. Air–fluid levels are present in the small intestine (*thin black arrow*). Air is also seen in the ascending colon (*black arrowhead*) and the distal colon (*arrowhead with short stem*). These findings are characteristic of, but not specific for, ileus.

Management

The principal goal in managing a normal POI is to prevent uncomfortable distention, vomiting, and aspiration. A secondary goal is to limit its duration. Passage of flatus is used, in reliable patients, as the index indicating coordination of all segments of the gastrointestinal tract and resolution of ileus. For many years, the mainstay of therapy was the use of nasogastric suction to prevent accumulation of swallowed air and secreted fluids in an alimentary tract not yet coordinating flow distally. Subsequent studies have demonstrated that the putative benefit does not compensate for risks of aspiration and discomfort of the tube.[139,140] Thus, following moderately

complex abdominal operations such as colectomy or complex abdominal wall reconstruction, nasogastric suction is not used; resolution of ileus is encouraged with preoperative preparation that includes resolution of any preoperative electrolyte and metabolic disturbances, carbohydrate loading, and protocols for avoidance of fluid overload. Nasogastric suction is used selectively, mainly to relieve the discomforts associated with nausea and distention. In individual cases, use of nasogastric suction may be extended, when in the surgeon's judgment the ileus is likely to be prolonged because of intraoperative findings such as peritonitis or because of extensive manipulation of the bowel due to widespread adhesions. Serial and standardized examinations will usually reveal that ileus is resolving as evidenced by normalization of bowel sounds and passage of flatus. Until the patient's bowel functions are clearly restored, close attention to fluid and electrolyte balance is important.

In recent years, considerable attention has been given to identifying and systematically addressing the multiple and potentially interacting risk factors for prolongation of POI (**Table 49.6**).[113,134,141,142] Such risk factors include perioperative fluid overload, electrolyte disturbance, and transient acute kidney injury; and taking measures to standardize fluid management in the perioperative period. Early mobilization and walking is encouraged directly with physical therapy and indirectly by removing barriers to mobility such as nasogastric tubes and urinary catheters; mobilization stimulates bowel function, reducing the risk of pulmonary complications and possibly improving cognition. Adjuncts such as gum chewing or use of hard candy theoretically stimulate vagal function and have been studied extensively, without strong evidence for or against their routine use. Use of epidural catheters and regional nerve blocks, when appropriate, have been shown to accelerate return of bowel function after laparotomy, not only by decreasing pain and use of opioid medications but also potentially by interfering with motility-inhibiting influences of the sympathetic nervous system. Early feeding also stimulates secretions, coordinated propulsive activity and likely improves immune function, thereby reducing the risk of postoperative infection and metabolic disturbance.[143–146]

Based on experimental studies, pharmacologic interventions have been proposed to shorten recovery of gastrointestinal motility and coordination between different regions of the gastrointestinal tract. Thus, opioid

antagonists, somatostatin analogs, sympatholytics, injection of local anesthetics into mesenteric nerve roots, or nonsteroidal anti-inflammatory agents, such as ketorolac, all appear to promote faster recovery to normal myoelectric activity and intestinal transit times. Over the years, prokinetic agents that target vagal or other components of the enteric neuroendocrine system and including metoclopramide, erythromycin, and cisapride (currently not permitted for use in the United States) have also been studied but without clear, demonstrable benefit in accelerating resolution of POI and shortening hospital lengths of stay.[147] Laxatives have no proven benefit for earlier resolution[113] of POI, although anorectal stimulation with suppositories can facilitate passage of flatus.

Table 49.6 Management Treatment for Postoperative Ileus

Treatment	Benefit	Drawback
Nasogastric tube	Possible relief of vomiting and bloating	Does not shorten duration of ileus May contribute to fever, atelectasis, and aspiration Discomfort
Early postoperative feeding	Stimulates reflex for propulsive bowel motility and enzyme secretion Stimulates immune system Reduces postoperative and posttraumatic infectious complications Reduces risk of anastomotic dehiscence, wound infection, pneumonia	Patients may not tolerate feeding
Opioid antagonists (alvimopan)	Peripheral acting FDA approved to hasten postoperative ileus following partial large or small bowel resection with primary anastomosis	Possible cardiovascular or neoplastic risk Currently restricted to in-patient use only

Laparoscopic procedures	Earlier return of bowel function and discharge from hospital Minimal skin incision, minimal mechanical bowel manipulation	Not all patients and procedures are amenable to the laparoscopic approach
Epidural anesthetics/analgesics	Reduced duration of ileus vs. systemic opioid Increases splanchnic blood flow Anti-inflammatory	Risks associated with epidural catheter placement
Gum chewing	May shorten duration of ileus Simple and inexpensive	Limited data
Laxatives	May shorten duration of ileus Inexpensive	Limited data on efficacy
Nonsteroidal anti-inflammatory drugs (COX-2 inhibitors)	Decreases opioid needed for pain control May increase motility by acting as an anti-inflammatory	Possible increased risk of postoperative bleeding Other adverse effects

Adapted from **Table 49.2** Luckey A, Livingston E, Taché Y. Mechanisms and treatment of postoperative ileus. *Arch Surg* 2003;138(2):206–214. Prepared by Zain Khalpey.

Of special interest, however, are strategies that target the μ-opioid receptor or serotonin-receptor 5-HT_4. Thus the opioid μ-receptor antagonist alvimopan (Entereg™) has been reported to reduce GI recovery time and to

facilitate hospital discharge following major abdominal operations,[148,149] as well as operations outside the abdomen.[108] More recently, benefit in resolving POI has been observed with selective 5-HT_4 blockers, mosapride and prucalopride[150,151] and herbal supplements such as Escin, a natural mixture of triterpene saponins extracted from dried seeds of horse chestnut (*Aesculus hippocastanum* or *A. chinensis*).[152] Short-term use, such as that utilized in trials for patients with POI, has not been associated with clinically irreversible side-effects such as cardiotoxicity, but it is important to be mindful of the toxicities of longer-term, or off-label use.

Along with pharmacologic measures, it should be emphasized that, in otherwise routine laparotomy or laparoscopy, gentle handling of tissues, meticulous attention to hemostasis, and applications of sound principles of wound management are likely to have the greatest impact on optimizing recovery from ileus and minimizing the incidence of prolonged ileus. Efforts to reduce incision size and time spent handling the intestines through the use of laparoscopic approaches clearly improve recovery from ileus in some if not all patients undergoing standardized intra-abdominal procedures such as appendectomy,[153] and colectomy.[154] Even in open procedures,[155] standardization of management and effective communication help expedite clinical fast-track pathways and facilitate earlier recovery of bowel function and discharge from hospital.[113,156,157] Currently proposed measures to minimize the prolongation of ileus are summarized in **Table 49.7**.

Colonic Pseudoobstruction (Ogilvie Syndrome)

Etiologic Factors

Acute pseudoobstruction of the colon, also known as *Ogilvie syndrome*,[158] is a paralytic ileus of the large bowel, characterized by rapidly progressive abdominal distention, often painless.[159] Although the distention of the colon is not due to mechanical obstruction, the wall of the bowel, particularly that of the cecum, can become sufficiently distended so that its blood supply is compromised. Gangrene, perforation, peritonitis, and shock can follow. In

95% of the cases, there are underlying diseases.[159,160] Less than 5% of the cases occur in the absence of other conditions.

Table 49.7 Management Measures to Prevent Prolongation of Ileus
Minimization of trauma to tissues; using proper technique in the operating room with gentle handling of bowel during surgery.
Minimal use of narcotics for analgesia, for any route of administration (intravenous, intramuscular, epidural)
Use of opioid antagonists (alvimopan)
Generous use of mid-thoracic epidural anesthesia with local anesthetic use
Use of nonsteroidal anti-inflammatory (COX-2 inhibitors) agents for analgesia
Early feeding
Correction of any electrolyte or metabolic imbalances
Early recognition of septic complications (e.g., abdominal abscess, pneumonia, central line sepsis) that may contribute to prolongation beyond the expected period for ileus

Major risk factors for development of Ogilvie syndrome include traumatic injury (11%), infections such as pneumonia, sepsis (10%); obstetric/gynecologic conditions (10%); myocardial infarction and congestive heart failure (10%); abdominal and pelvic surgery (9%); neurologic conditions such as Parkinson disease, spinal cord injury, multiple sclerosis, and Alzheimer disease (9%); orthopedic procedures (7%); other medical conditions including metabolic imbalances, for example, hypokalemia, hypocalcemia, hypomagnesemia (32%); other surgical conditions (12%).[158,160] Evidence suggests that Ogilvie syndrome is thought to be related, at least in part to sympathetic nervous overactivity or interference with sacral parasympathetic efferents.[159,161] It is postulated that the distal colon becomes atonic due to interruption of the S2 to S4 parasympathetic nerve fibers. Other theories about the pathophysiologic

causes include autonomic dysfunction, reduced colonic ganglion cells, and loss of intrinsic nitric oxide activity but the cause remains unknown.[159]

Diagnosis

This syndrome is commonly encountered in patients hospitalized over 3 to 7 days, often in men greater than 60 years of age. Primary manifestations variably include gastrointestinal symptoms such as nausea, vomiting, abdominal pain, constipation, and diarrhea.[159,160] Labored breathing, caused by abdominal distention, may be observed as part of the clinical picture. Other than distention, there are no characteristic physical or laboratory findings for this syndrome. On percussion, the abdomen is resonant due to the presence of air in dilated segments of small intestine and colon. Sounds from the small intestine are present and may not be high pitched, as they are in intestinal obstruction.

Laboratory findings associated with this syndrome may include hypokalemia, hypocalcemia, hypomagnesemia, and hypophosphatemia, which are implicated as etiologic factors. Leukocytosis, elevation of sedimentation rate, or C-reactive protein is also present if low-grade systemic inflammation is present or perforation is impending.

The diagnosis is usually apparent from plain films. Radiographs of the abdomen may reveal air in the small bowel and distention of discrete segments of the colon (i.e., cecum or transverse colon often up to splenic flexure) or the entire abdominal colon. Haustral markings disappear with increasing distention. In doubtful cases and when bowel necrosis is not a significant worry, a Hypaque contrast enema can establish the nonmechanical nature of the dilatation. Alternatively, colonoscopy can be diagnostic as well as therapeutic. Features suggesting the complication of bowel ischemia may include localized tenderness, worsening leukocytosis, metabolic acidosis, evidence of sepsis, or a rapidly deteriorating clinical course.

It is important to differentiate this syndrome from toxic megacolon and mechanical obstruction before establishing a final diagnosis. Mechanical obstruction of the colon, occurring in volvulus or obturator obstructions from cancer or diverticular disease, presents with acute pain along with distention. In contrast, pseudoobstruction is less often associated with acute pain and more likely to present with discomfort due to distention. However,

lack of pain in postoperative patients on opiates or elderly patients cannot exclude mechanical obstruction. On plain x-rays, the pathognomonic signs of mechanical obstruction such as lack of gas in the distal colon or rectum, or air fluid levels in small intestine on x-ray can also be seen in Ogilvie syndrome. CT scan is currently the standard method for identifying colon pseudoobstruction and excluding other forms of obstruction.[159] Patients with toxic megacolon may manifest typically with symptoms such as fever, tachycardia, abdominal tenderness, bloody diarrhea or other manifestations of chronic inflammatory bowel disease along with "thumb printing" on the appearance of the abdomen on plain x-ray film in upright posture. Flexible sigmoidoscopy is contraindicated if toxic megacolon is thought likely. If toxicity is not likely, flexible sigmoidoscopy and/or contrast enema can be useful diagnostically and therapeutically.

Management

Initial management includes resuscitation and correction of any underlying metabolic or electrolyte imbalances (**Table 49.8**). Patients should have physical examination and plain abdominal radiographs serially to follow colonic diameters in order to determine which cases need colonoscopic decompression or surgery. If the patient is not very uncomfortable and the colonic distention is no greater than 12 cm, conservative treatment can be continued for 1 to 2 days. It may be helpful to place the patient in a prone position or in the knee to chest position with hips held high, alternating right and left lateral decubitus position each hour. A nasogastric tube is helpful if the patient is vomiting and will prevent swallowed air from passing distally. When bowel ischemia is suspected, surgery is indicated. If bowel necrosis is found, the affected segment is resected and an ileostomy or colostomy should be performed. If the bowel is viable, a cecostomy is placed to vent the colon and prevent distention.

Table 49.8 Management Treatment for Pseudoobstruction

Treatment	Benefit
Nasogastric tube	Prevention of swallowed air from passing distally
Neostigmine	Increase motility through its parasympathomimetic action Premedication with colonoscopic decompression adding benefits
Erythromycin	Increases intestinal motility through motilin receptors in intestinal wall
Colonoscopic decompression	Prevention of complications such as perforation
Surgical interventions: total colectomy, Hartmann procedure, percutaneous endoscopic cecostomy	Required in case of refractory medical therapy

If, initially, the distention is painless and the patient shows no signs of toxicity or bowel ischemia, expectant management is successful in 50% of cases.[159,162] The risk of spontaneous perforation is approximately 3%, with an attendant mortality of 50%. In most patients, acute colonic pseudoobstruction usually resolves within 3 days.[159,163] If the clinical picture is worsening and the cecal diameter increases beyond 10 to 12 cm or if it persists for more than 48 hours, intervention is recommended. The duration of distention may be more important than the absolute size of the cecum with respect to spontaneous perforation. Colonoscopy should only be performed by experienced endoscopists. Endoscopic decompression is successful in 60% to 90% of cases, but the condition can recur in up to 40% of patients. This rate of recurrence may be decreased by placement of a decompressive tube. Recurrence requires repeat colonoscopic decompression in approximately 40% of cases after initial successful decompression. The

placement of a decompression tube with the aid of a guidewire at the time of colonoscopy may reduce the need for repeated colonoscopic decompression. Rectal tubes are ineffective as primary modalities in managing distention of the proximal colon. Such tubes may be useful in promoting passage of air and feces after colonoscopy but should not be used as a substitute for colonoscopic decompression. Percutaneous endoscopic left-sided colostomy (PEC), a minimally invasive technique, can be used to treat pseudoobstruction provided these cases are carefully selected in the hands of a skilled endoscopist because of a high failure rate caused by infection.[164]

In anecdotal reports, prokinetic agents such as cisapride and erythromycin have been used to treat Ogilvie syndrome with some success. Erythromycin acts by binding to motilin receptors in the small intestine, causing intestinal smooth muscle contraction and perhaps better coordination with colonic motor function. Anecdotal reports have suggested the success of erythromycin treatment by either intravenous route for 3 days or oral route for 10 days.[165,166] However, the relative paucity of motilin receptors in colon smooth muscle may explain why erythromycin is only anecdotally effective in relieving colonic pseudoobstruction. Successful resolution of pseudoobstruction has been reported with sympatholytic agents or spinal sympathetic block. The efficacies of these modalities have not been systematically evaluated.[159,167]

Neostigmine, a parasympathomimetic, is used in the treatment of acute colonic pseudoobstruction. Decompression with this drug has been achieved in 80% to 100% of patients with a recurrence rate of 5%.[159,168] Neostigmine may be a viable alternative to colonoscopy in pregnant women, provided mechanical obstruction is excluded. The administration of a polyethylene glycol electrolyte balanced solution after initial resolution of colonic dilatation may reduce the recurrence rate with use of neostigmine.[169]

Neostigmine has expected cardiovascular side effects such as bradycardia, hypotension, and dizziness; and is excreted via the kidneys. The few relative contraindications to its use in treatment of acute colonic pseudoobstruction are a baseline heart rate of less than 60 beats/min or systolic blood pressure of less than 90 mm Hg; active bronchospasm requiring medication; a history of colon cancer or partial colonic resection; active gastrointestinal bleeding; pregnancy; or a serum creatinine concentration of more than 3 mg/dL (265 μmol/L). Other side effects include mild to moderate crampy abdominal

pain, excessive salivation, and vomiting. Side effects, such as increasing airway secretions and bronchospasm, can be reduced by concomitant use of glycopyrrolate without reduction of colonic response.[170,171] Ponec et al.[172] recommend use of neostigmine prior to colonoscopy, based on its easy administration, lower expense, and superior results in comparison to colonoscopy. Reported rates of response to treatment with neostigmine are 91% (single administration) and 100% (second administration).[159,161,172,173] While earlier recommendations suggested that colonoscopy would prove superior to neostigmine as first-line treatment,[168] more recent studies have suggested that neostigmine therapy should be used initially and this is now the recommended sequence of therapeutic intervention.[161,173]

In the absence of signs of clinical deterioration, a nonoperative or "conservative course" of therapy can be continued safely for several days, with resolution of acute colonic pseudo-obstruction in 70% to 90% of patients.[161,173] It should be emphasized, however, that patients should undergo immediate exploration if they exhibit signs of clinical deterioration or bowel perforation (peritoneal signs on physical examination or free air on radiographs). Surgery is reserved for patients not responding to medical and endoscopic management and for patients who develop signs of peritonitis or perforation. Percutaneous endoscopic cecostomy can also be performed if conservative measures fail.[174] Cecostomy tubes are often poorly tolerated because of issues related to skin breakdown; in the authors' opinion, this approach is advisable only when more extensive surgical procedures are considered too risky. Procedures such as total colectomy, ileostomy, and Hartmann procedure are taken into consideration in cases of perforation.[159,168] Pseudoobstruction 10 of the colon, also known as Ogilvie syndrome, is usually benign but it can be complicated by bowel gangrene or perforation. Initially it is treated with attention to underlying neurologic or metabolic disturbances, followed in sequence by use of neostigmine and then decompressive colonoscopy. Surgery is reserved for patients with evidence of ischemic bowel, perforation, peritonitis, or clinical deterioration.

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50

Crohn Disease

Anuradha R. Bhama and Scott R. Steele

Key Points

1. Crohn disease can affect the entire gastrointestinal (GI) tract from mouth to anus and is likely from a multifactorial etiology.
2. Crohn disease may manifest in the GI tract in one or more disease patterns—fistulizing, inflammatory, and fibrostenotic—resulting in fistulas, abscess/phlegmons, and/or obstruction, respectively.
3. Crohn disease is associated with an increased long-term risk of developing colorectal cancer compared to the general population. Patients should be screened accordingly, and surgical treatment is typically more aggressive in the setting of underlying microscopic colorectal dysplasia or dysplastic lesions.
4. Several classes of medications are available for Crohn disease, depending on the spectrum of disease, ranging from topicals and aminosalicylates to steroids, immunosuppressants, and/or biologic agents.
5. The indications for operating on a patient with Crohn disease involve managing complications of the disease, not achieving cure.
6. Preservation of functional bowel length is paramount in this patient population, given the high need for future resections and potential for diseased/nonfunctioning bowel.
7. The decision making for embarking on surgical intervention must account for the patient's clinical presentation, concomitant medical therapy, underlying continence, anatomy, and overall nutritional status.
8. Anorectal conditions in Crohn patients must be managed with special considerations given the potential for poor wound healing, incontinence, and worsened quality of life with aggressive surgical intervention.

INTRODUCTION

Crohn disease is a chronic, inflammatory condition of the alimentary tract. To date, the underlying mechanism of disease is not known, and it can manifest with a wide spectrum of presentations and severity. A number of Crohn patients may respond well to medications, while others are recalcitrant to multiple high-dose biologics or steroids. Therefore, treatment options must be individualized for each patient with Crohn disease. Basic tenets of Crohn disease include that it may occur anywhere along the alimentary tract, has no "curative" operation, and is hallmarked by periods

of flares and quiescent disease. Despite improvements in medical therapy, upward of 75% of patients will still require at least one operation during their lifetime to treat complications associated with the disease or nonresponsiveness to medical therapy.[1] As such, careful consideration must be given to each individual patient's future function when weighing therapeutic options in order to resolve the current problem at hand. Surgeons must be exceedingly aware of the indications, surgical options, and expected outcomes for patients with Crohn disease. In order to maximize the latter, it is crucial to also have a thorough understanding of not only the principles guiding surgical treatment, but also the medical therapies that may either allow avoidance of surgery altogether. This chapter will cover the clinical presentation, diagnostic evaluation, medical therapies, and surgical treatment for Crohn disease.

EPIDEMIOLOGY

The a 1 ge of onset of Crohn disease follows a bimodal distribution, either in the second to fourth decades of life or in the sixth decade.[2] Systematic reviews have found an annual incidence of Crohn disease ranging from 20.2 per 100,000 person-years in North America and 12.7 per 100,000 person-years in Europe to 5.0 person-years in Asia and the Middle East.[2] Males and females tend to be affected equally, though whites and certain ethnic groups such as Ashkenazi Jewish descent have higher overall rates.[3] Given the geographic and temporal variation in the epidemiology of Crohn disease, recent research has focused on environmental and genetic factors that may be driving these shifts.[4–6]

ETIOLOGY

Despite tremendous progress in the overall understanding of the disease and advancements in comprehension of various phenotypical manifestations, the exact etiology of Crohn disease remains unknown. The development of the disease is thought to be a result of environmental triggers acting upon a combination of genetic and intestinal factors that drive the development of compromised intestinal immune response followed by mucosal inflammation.

Approximately 2% to 14% of patients report a family history of Crohn disease and is higher in those of Jewish ancestry.[7,8] The concordance rate for monozygotic twins ranges from 20% to 50%, suggesting that genetics plays a role and the disease is not entirely dependent on environmental and/or acquired factors.[9] Over 200 alleles have been associated with inflammatory bowel disease (IBD), though only 37

are specific for Crohn disease.[10,11] Several of the genes involved and linked to Crohn disease are related to the host's ability to sense bacterial, or control innate immunity, Th17-cell function, and can result in an altered mucus layer of the GI tract.[10,12] Attention has revolved around the NOD2 (formerly CARD15) gene on chromosome 16, a region felt to be involved host interactions with bacterial lipopolysaccharide to activate NF-κB, which correlates to Crohn disease phenotype.[13,14] Genome-wide association studies have provided insight that polymorphisms in genes such as ATG16L1 and IRGM play a role in autophagy in Crohn patients. This process involves the regulation of cell development and differentiation, senescence, and ultimately the inflammatory system response to what the body deems is normal and abnormal.[15] Impaired recognition and processing in this aspect results in a deregulation and ultimately disease pathogenesis. In addition, other genes such as TLR4, HLA, and IRF5 that are involved in the innate and adaptive immune system response are seen to be altered in Crohn patients.

Theories regarding a host–microbiome connection have been evolving over the past few decades. The gut microbiome is the largest reservoir of microbes in the entire body and functions in digestion, immunity, and suppression of harmful organisms.[16] The state of an individual's microbiome is influenced by a variety of elements including genetics, age, geography, hygiene, diet, drugs, smoking, and potentially many others.[17] An interplay between the immune system and the microbiome has been identified in IBD, and various microbes may be either protective against or increase susceptibility to the development of the disease. *Escherichia coli*, in particular the adherent-invasive strains, have been found in higher concentrations in patients with ileal Crohn disease and can induce granuloma formation—a pathognomonic feature of Crohn disease.[18–20] Conversely, there is evidence to suggest that certain microbes are protective in IBD. *Bacteroides* and *Clostridium* have been shown to reduce intestinal inflammation through upregulation of regulatory T cells as well as regulate NF-kB activation to decrease mucosal inflammation.[21,22] *Bifidobacterium, Lactobacillus,* and *Faecalibacterium* have been shown to be protective against mucosal inflammation through a downregulation of inflammatory cytokines and an upregulation of IL-10.[23,24] Although the beneficial effects of antibiotics in the treatment of Crohn disease provide indirect evidence for a bacterial etiology, no distinct organism has been identified to date. Similarly, several viruses, such as EBV, CMV, and measles, have been postulated to have an association with the development of Crohn disease; however, multiple reports have found little evidence to support this notion.[25] Other causative immune factors have included overexpression and dysregulation of tumor necrosis factor, an imbalance between proinflammatory and anti-inflammatory cytokines, and an impaired mucosal

susceptibility in sampling gut antigens.[26] Combined, these all contribute to regulatory mechanisms that may be altered and play a role in the pathogenesis of Crohn disease.

Environmental factors may also play a role, highlighted by the well-established link between smoking and an increased susceptibility to Crohn disease as well as a worsened clinical course with higher recurrence rates. While patients with Crohn disease frequently have concomitant food intolerances, the role of dietary habits remains debatable.[27] Taken together, rather than a causative effect, it is felt that the microbiome in the human gastrointestinal (GI) tract is heavily influenced by dietary intake, leading to a local environment ripe to foster susceptibility to Crohn disease. This remains an area of increasing discovery and rapid change that is certain to evolve as the etiology and underlying reasons for such wide variability in phenotypical manifestations and clinical course in this disease are explored.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for Crohn disease is wide and includes both benign and malignant processes (**Table 50.1**). Crohn disease has certain traits that are highly suggestive of its presence (e.g., noncontiguous multisite disease, fistulas, creeping fat) versus other disorders. Yet, a variety of abdominal processes may mimic Crohn disease. For example, ileocolic Crohn disease can be misdiagnosed as acute appendicitis, right-sided diverticulitis, an infectious process, or a perforated malignancy. Radiologic studies may demonstrate patterns of bowel inflammation consistent with Crohn disease, and laboratory examination may reveal elevated CRP and/or white blood cell count. Careful consideration of the differential diagnosis must be taken both preoperatively and intraoperatively.

Table 50.1 Differential Diagnosis of Crohn Disease

Ulcerative colitis
Irritable bowel syndrome
Acute appendicitis
Diverticulitis
Malignancy
Infectious colitides (CMV, *Yersinia*, *Escherichia coli*, *Salmonella*, etc.)
***Clostridium difficile* colitis**
Ischemic colitis
Pancreatitis
Meckel diverticulum
Tuberculosis
Radiation enteritis
Behçet disease

When disease is isolated to the colon, the major differentiation involves distinguishing Crohn colitis from ulcerative colitis, though other infectious and inflammatory colitides remain in the differential. Both diseases share common histopathologic traits, which contributes to the diagnostic dilemma. Perianal Crohn disease differential diagnosis includes traditional cryptoglandular abscess and fistulas, skin tags may mimic routine hemorrhoids and/or tags, and infectious causes such as HIV, syphilis, and tuberculosis may share phenotypical manifestations with Crohn. Ultimately, it is the entire evaluation of the individual disease presentation including information taken from history, laboratory, pathologic, endoscopic, radiologic, and clinical examinations that will help clarify the picture and aid in diagnosis.

DIAGNOSTIC EVALUATION

Crohn disease and ulcerative colitis both fall under the umbrella of inflammatory bowel disease and no specific tests at present permit a definitive diagnosis of either condition. The diagnosis is established using a combination of history and physical examination, laboratory values, radiographic findings, and endoscopic findings. Even so, 5% to 15% of patients with ulcerative colitis are eventually diagnosed with Crohn disease or indeterminate colitis when new concerning symptoms arise.[28,29] There are several available classification schemes available for Crohn disease. Classification based on phenotypic manifestations includes fibrostenotic disease

(stricturing), fistulizing disease (penetrating), and inflammatory disease (phlegmonous). Patients may have one, two, or all three, as evidenced by the high rate of strictures with proximal fistulas. Location is also frequently used to classify disease, with the distal ileum having the highest rate of disease incidence (**Fig. 50.1**). Localized inflammation in the ileocecal region occurs in approximately 45% of patients, colonic in 25% to 33%, proximal small-bowel disease in 25%, <10% will have isolated upper GI or isolated perianal disease, with many patients having disease in more than one location. In general, patients with concomitant perianal disease tend to have a more severe clinical course, and perianal disease in the setting of Crohn may precede abdominal manifestations in up to 45% (**Fig. 50.2**).[30,31] Identification of suspicious perianal disease should prompt an investigation into more proximal disease.

Figure 50.1 Terminal ileitis.

Due to the chronic and heterogeneous nature of the disease, different classification manifestations may occur independently, concomitantly, or may even vary along the longitudinal course of the disease. Fibrostenotic pattern may occur in any location, though most commonly occurs in the terminal ileal region, where patients present with obstructive-type symptoms such as nausea, vomiting, and decreased oral intake. More proximal disease (e.g., gastroduodenal) can often present with obstructive-type symptoms such as nausea, vomiting, and early satiety. Inflammatory disease may

present with a wide range of symptoms such as abdominal pain, fever, an abdominal mass, change in bowel habits, and/or weight loss. Finally, penetrating or fistulizing disease may be completely asymptomatic (e.g., enteroentero fistula of adjacent bowel), present with anorectal abscesses and/or fistulas, or more commonly complain of symptoms depending on the involvement of the secondarily involved organ; for example, recurrent urinary tract infections, pneumaturia, vaginal discharge, or diarrhea.

Figure 50.2 Perianal fistulas.

CLINICAL EVALUATION

Upper Gastrointestinal

Gastroduodenal Crohn disease is rare, occurring in only 0.5% to 4% of all Crohn patients and typically asymptomatic.[32] Yet up to 40% of these patients will demonstrate early subclinical evidence of Crohn disease on radiologic or endoscopic evaluation.[33] When present, symptoms typically represent a gastric outlet obstruction and include epigastric abdominal pain, nausea, vomiting, early satiety, bloating, weight loss, and anorexia. Crohn disease of the esophagus is exceedingly rare, involving <0.5% of patients and extraesophageal disease is nearly always present.[34] A high index of suspicion should lead to diagnostic testing such as contrast imaging (e.g., fluoroscopic upper GI, small-bowel follow-through) and endoscopy that will confirm the diagnosis (**Fig. 50.3**).

Small Bowel

2 The distribution of disease and phenotypic classification dictates the clinical presentation, with ileocecal disease the most commonly affected site. Patients with disease in this location will classically present with slow onset of right lower quadrant abdominal pain, fatigue, nausea, vomiting, abdominal mass, and pain with hip extension from psoas muscle involvement. Obstructive symptoms may also occur in patients with either fibrostenotic or acute inflammation (**Fig. 50.4**). Diarrhea tends to be nonbloody, though heme-positive stools may occur, and rarely gross blood is a manifestation from a small-bowel source.

Colonic

Colonic involvement may occur in isolation in approximately 25% of patients, though it is most often seen concomitantly with perianal (associated with left-sided colonic inflammation) or terminal ileal (associated with cecal and ascending colon inflammation) disease.[35] Within the colon, the distribution is somewhat variable, with approximately one-third of patients having total colonic involvement, 40% showing segmental disease, and left-sided only in up to 30%.[36] Regardless of the exact location within the large intestine, patients with colonic involvement may experience abdominal pain, mucus drainage, and malnutrition. Unlike ulcerative colitis, rectal bleeding is not routine, and bowel movements are often nonbloody, except in those with moderate to severe colitis. Diarrhea is often of smaller volume and may be from several sources—malabsorptive (e.g., salt/water and bile acid malabsorption), infectious (e.g., CMV superinfection), or as a result from an enterocolonic fistula.[37,38] In addition, similar to disease in the small bowel, patients can experience hip or back pain from fistulas, cramping, and obstructive symptoms. Patients with penetrating disease may also experience symptoms with associated involvement of the secondary organ (e.g., feculent vaginal drainage from a

colovaginal fistula, pneumaturia or fecaluria from bladder involvement, or skin drainage from an enterocutaneous fistula).

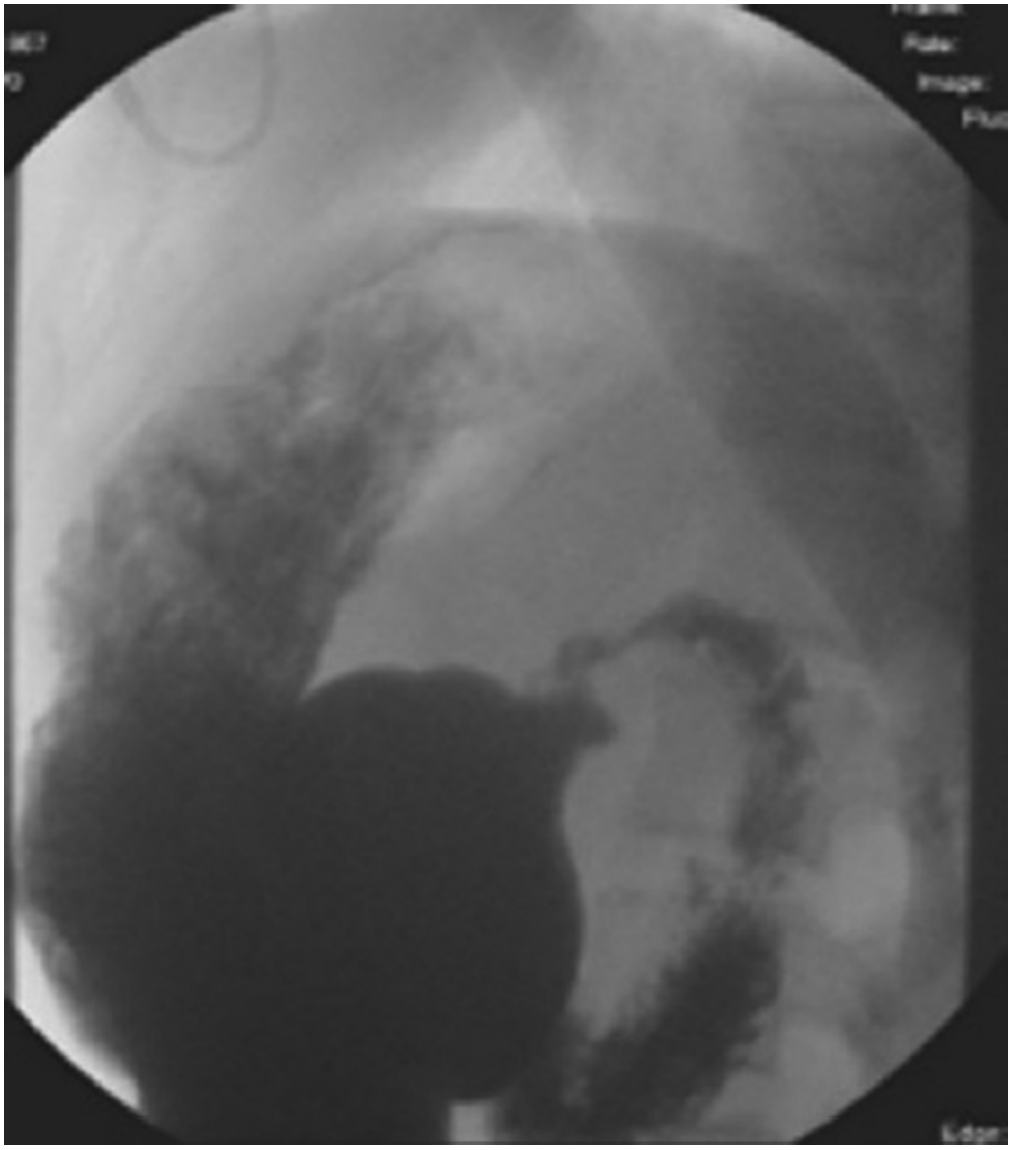


Figure 50.3 Upper GI contrast study demonstrating a stricture in the duodenum.

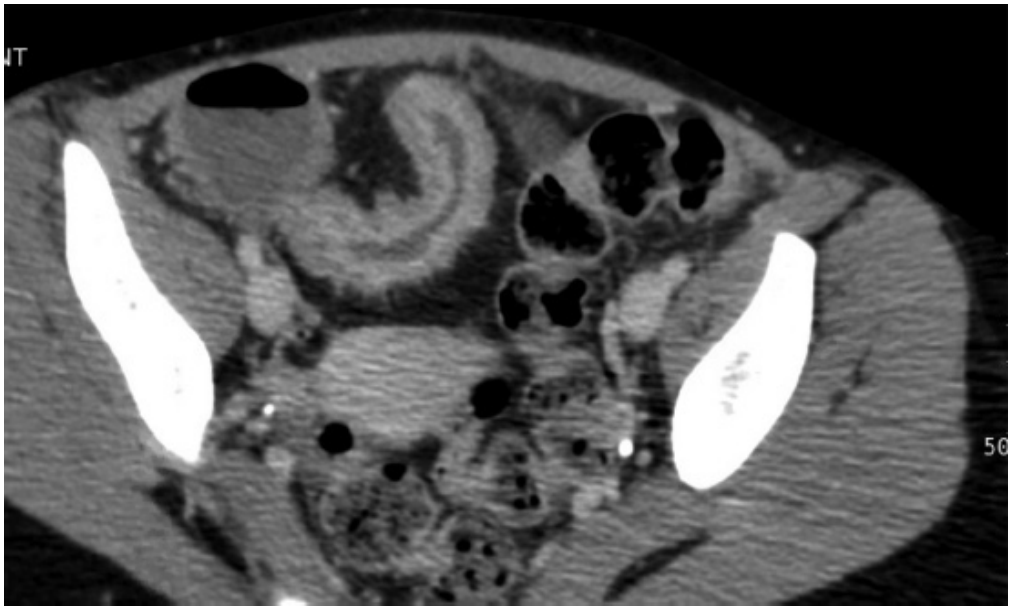


Figure 50.4 CT enterography demonstrating terminal ileal disease resulting in obstructive symptoms.

Anorectal

Despite advances in the understanding of many features of Crohn disease, perianal complaints have been recognized as one of its most challenging aspects. Isolated perianal disease is the presenting symptom in 5% to 15% of Crohn patients; though upward of 25% to 80% may experience symptoms at some point. Perianal involvement is more common in those with concomitant rectal or colonic disease.[39,40] In addition, active disease in the perineum is felt to act as a harbinger of an overall more virulent course.[41] Patients with Crohn disease may also have "traditional" anorectal complaints, the most common being perianal skin tags. These tend to be large, flat, with a bluish hue and classically described as an "elephant ear" appearance. Perianal abscesses, fistulae, and fissures that do not follow the typical pattern of cryptoglandular disease should raise suspicion for a diagnosis of Crohn disease. Fissures tend to be deeper, off the midline, and much more painful than routine hypertonic-associated fissures (**Fig. 50.5**). Patients presenting with perianal findings consistent with or concerning for Crohn disease should undergo a thorough physical examination and full endoscopic and radiologic evaluation. Finally, patients with long-standing Crohn may develop anal stenosis or an anal stricture at the verge secondary to repeated bouts of chronic inflammation.

Extraintestinal Disease

Similar to ulcerative colitis, patients with Crohn disease may have manifestations from the disease process that extend outside of the GI tract (**Table 50.2**).

Extraintestinal disease (EID) has been reported in 6% to 47% of patients with inflammatory bowel disease, and has an increased concordance among siblings and first-degree relatives—suggesting a genetic component that has been linked to the major histocompatibility complex (MHC) on chromosome 6.[42,43] EID occurs secondary to the systemic inflammatory process associated with the underlying disease and affects a wide range of organ systems. While the GI tract may be the primary source, the dysfunction in immune regulation incites a pathologic response that may occur in nearly every location in the body simultaneous with, preceding, or following GI manifestations.[44] Overall, rheumatologic/joint problems (e.g., peripheral or sacroiliac arthritis, arthralgias) are the most common, occurring in up to one-third of patients. Other more frequent sites of involvement include the skin, eyes, and hepatobiliary system; while the renal, pulmonary, nervous, and coagulation systems are involved to a lesser extent. It is important to distinguish between manifestations that parallel bowel disease activity (episcleritis, peripheral arthritis, erythema nodosum) from those that do not (ankylosing spondylitis, pyoderma gangrenosum, primary sclerosing cholangitis) (**Fig. 50.6**). In these cases, EID may flare prior to the bowel (or in the setting of asymptomatic active bowel disease) and necessitate adjustments in medical management. Conversely, surgical intervention directed at the bowel may occasionally be required for recalcitrant extraintestinal disease that may go into remission following bowel resection.[45]

Figure 50.5 Anal fissure in Crohn disease.

Table 50.2 Classification of Extraintestinal Manifestations of Crohn Disease

Organ System	Extraintestinal Manifestation
Musculoskeletal	Arthralgias, peripheral arthritis, ankylosing spondylitis, sacroiliitis, myopathy, metabolic bone disorders
Ocular	Uveitis, iritis, episcleritis, conjunctivitis, optic neuritis
Renal	Glomerulonephritis, amyloidosis, urolithiasis
Skin/Mucocutaneous	Erythema nodosum, pyoderma gangrenosum, aphthous ulcers
Hematologic	Thromboembolic disease, anemia
Pulmonary	Bronchitis, pleuritis, tracheal stenosis
Hepatobiliary	Hepatitis, primary sclerosing cholangitis, primary biliary cirrhosis, pancreatitis, cirrhosis, cholangiocarcinoma, portal vein thrombosis
Cardiac	Pericarditis, myocarditis
Neurologic	Demyelinating disease, neuritis

Figure 50.6 Pyoderma gangrenosum surrounding an ileostomy.

DIAGNOSTIC METHODS

Radiology

Over recent years, the radiographic assessment of Crohn disease has developed dramatically. Previously, fluoroscopic imaging, including small-bowel follow-through or retrograde contrast studies, with the use of barium or gastrografin contrast was essential. These studies were used to identify ulcerations that create cobblestone and nodular patterns, mucosal granularity, loss of villous morphology, skip lesions, strictures, and fistulas (**Fig. 50.7**).[46] Contrast studies can still provide a wealth of information regarding anatomy and aid in operative planning. Over the

years, the utilization of computed tomography enterography (CTE) and magnetic resonance imaging enterography (MRE) has become the most effective method for the evaluation of Crohn disease and these imaging modalities have been shown to alter treatment course and evaluate response to treatment (**Figs. 50.8** and **50.9**).[47–49] Both modalities have high sensitivity (>90%) and specificity (>90%) for diagnosing active small-bowel disease.[47,50] In regard to identifying and quantifying small-bowel disease activity, CTE and MRE are equally sensitive and specific, although CTE has the advantage of better-quality images[51–57] while MRE has been shown to be superior to CTE in the identification of fistulas and strictures.[53,57,58] The radiographic findings of transmural healing on CTE and MRE have been shown to correspond to mucosal healing on endoscopic examination in the majority of settings.[59–61] Although CTE and MRE will include imaging of the pelvis and sphincter complex, if imaging is deemed necessary for perianal fistula or abscess, a standard pelvic MRI should be obtained.[62–64] Positron emission tomography (PET) and PET-MRI are other modalities that have shown some promise for the evaluation of Crohn disease, though not currently used routinely.[65]

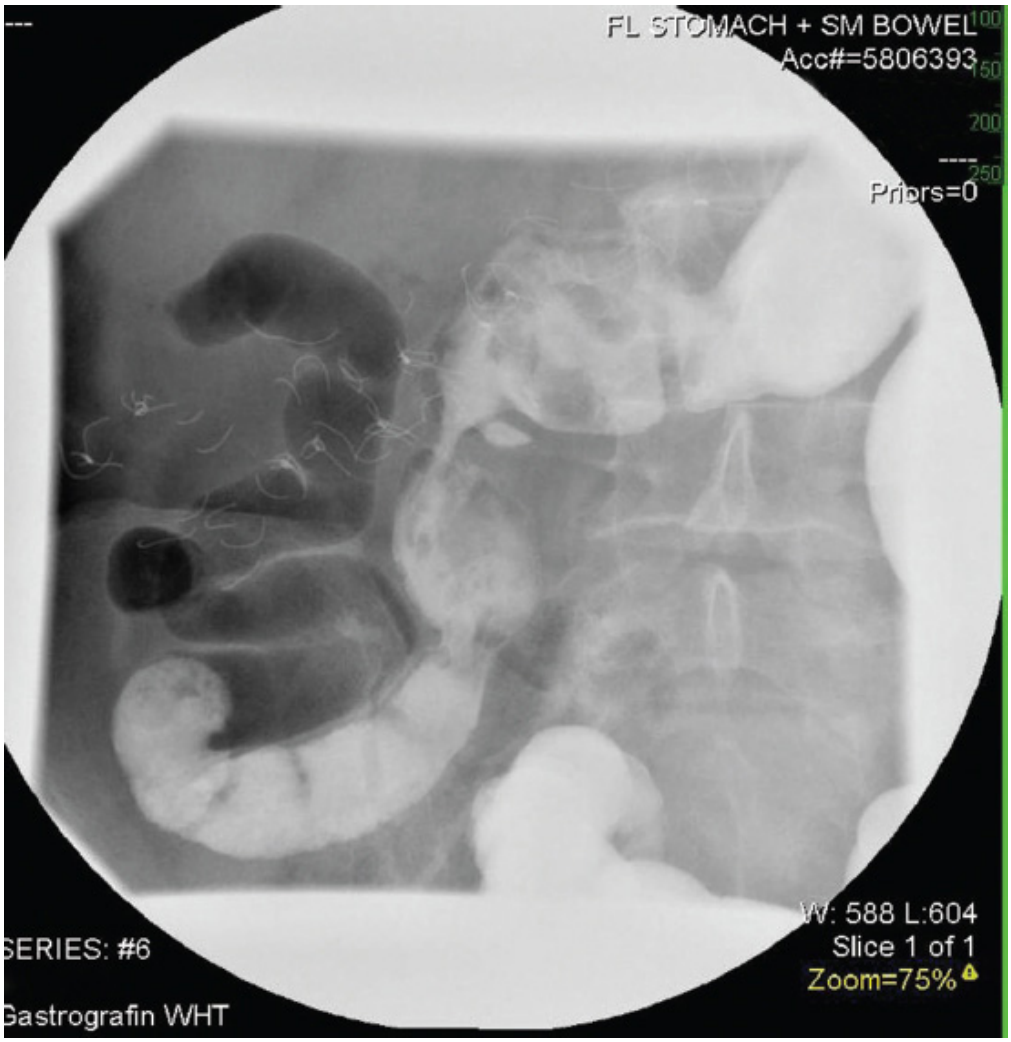


Figure 50.7 Contrast study demonstrating Crohn stricture.

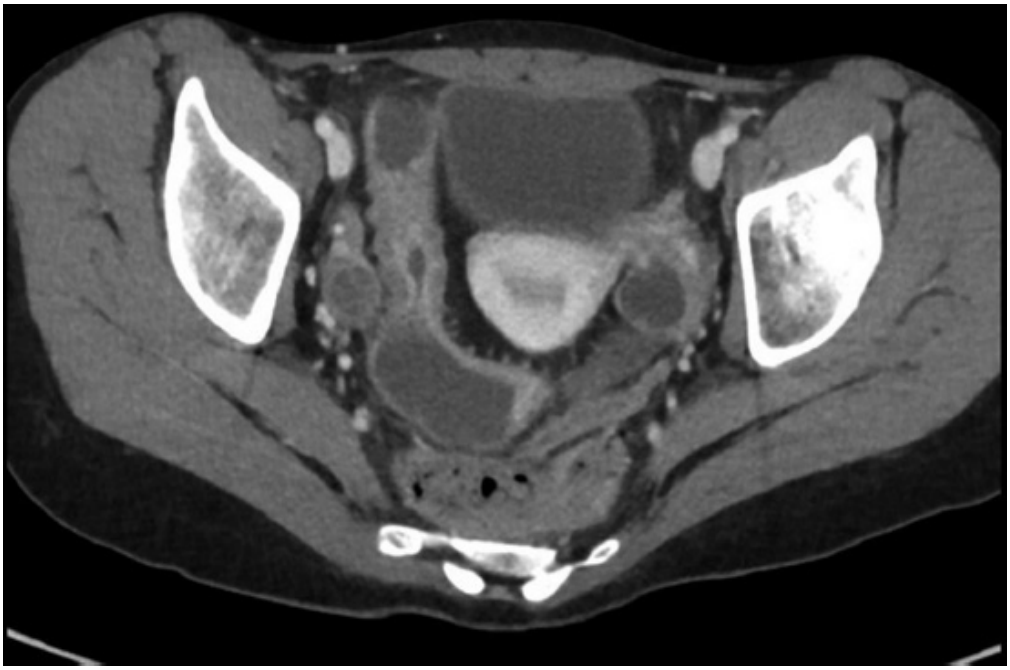


Figure 50.8 CT enterography demonstrating small-bowel stricture.

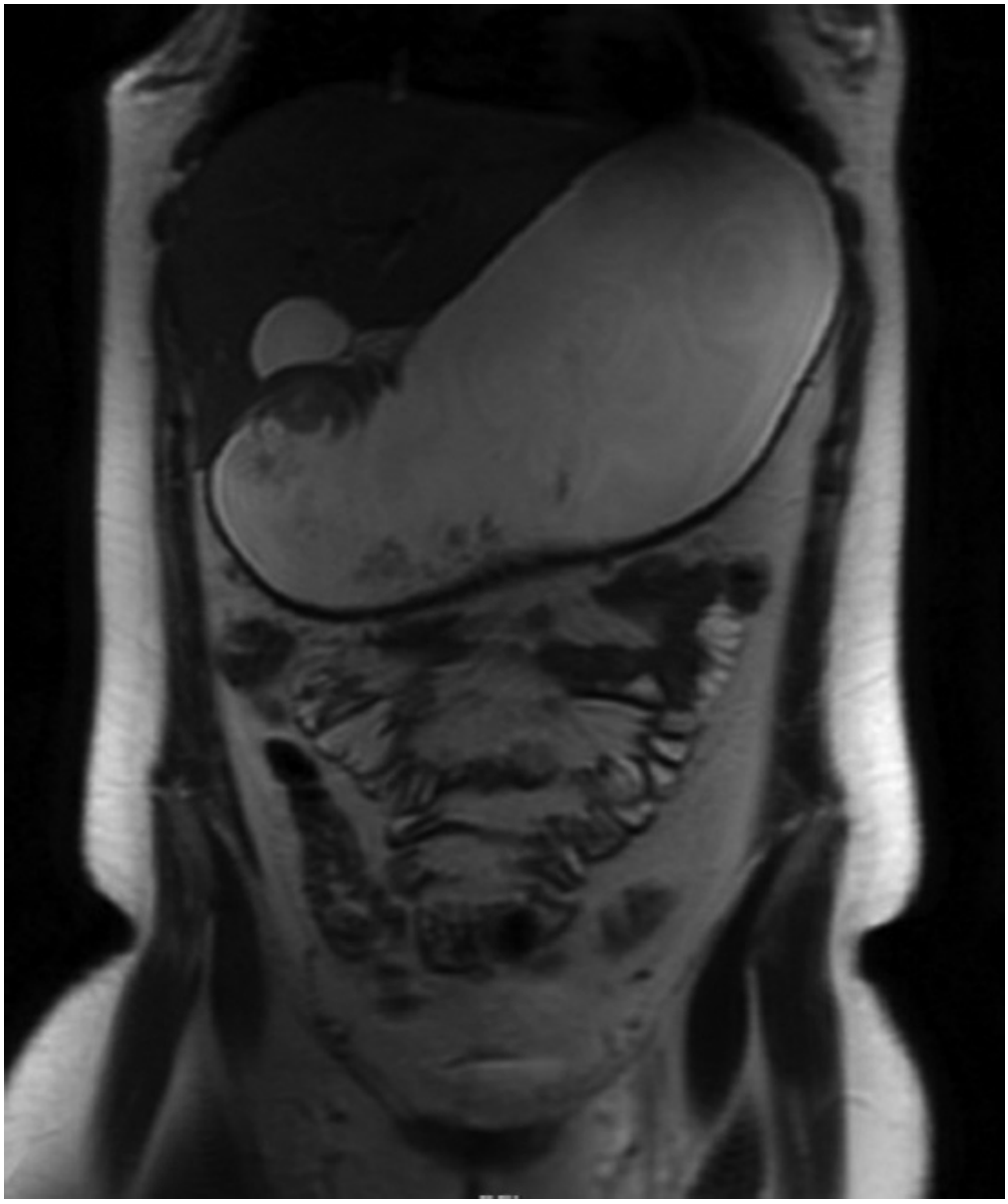


Figure 50.9 MR enterography demonstrating terminal ileal disease in the setting of multifocal disease. This patient also has a duodenal stricture resulting in marked gastric dilation.

Endoscopy

Endoscopy is an indispensable tool used to identify the extent and severity of the disease and perform biopsies to aid in diagnosis.[66] Endoscopic evaluation of the entire colon, including the terminal ileum along with appropriate biopsies, is required in patients suspected of Crohn disease. Early changes seen in the mucosa include aphthous ulcerations, erosions, and serpiginous ulcers that occur in a skip-type pattern. As the full-thickness inflammatory cycle continues, these ulcerated

areas progressively enlarge and coalesce forming the cobblestone-type pattern. The presence of rectal sparing and active terminal ileal disease may help differentiate Crohn disease from ulcerative colitis, although the latter may demonstrate similar characteristics due to medical therapy and backwash ileitis, respectively.[67] Finally, the presence of strictures or associated masses may indicate the need for surgical or therapeutic intervention (**Fig. 50.10**).

3 Patients with Crohn disease should undergo more aggressive malignancy surveillance compared to the general population. Screening colonoscopy should start 8 to 10 years after the onset of colitis and have repeat examinations every 1 to 2 years.[68–70] Previous recommendations supported routine biopsies in four quadrants every 10 cm throughout the colon. While high-definition white light endoscopy remains the current recommendation for neoplasia screening in IBD, recently there has been a shift toward the use of chromoendoscopy.[71–74] When compared to white light endoscopy, chromoendoscopy using methylene blue or indigo carmine demonstrate higher rates of both adenoma detection and dysplasia detection.[74–77] Narrow-band imaging (NBI) can be helpful for adenoma detection in a healthy colon; however, due to the presence of background inflammation in the setting of Crohn disease, NBI is not recommended as an adjunct for endoscopic surveillance in these patients.[71,78–80] Patients with chronic disease may demonstrate pseudopolyps on endoscopic examination (**Fig. 50.11**). Pseudopolyps are masses of scar tissue that represent the formation of granulation tissue that result from alternating cycles of ulceration and regeneration.[70] In general, they are benign, and do not warrant intervention, but will make for increasing difficulty with screening for colorectal cancer with more severe incidence.

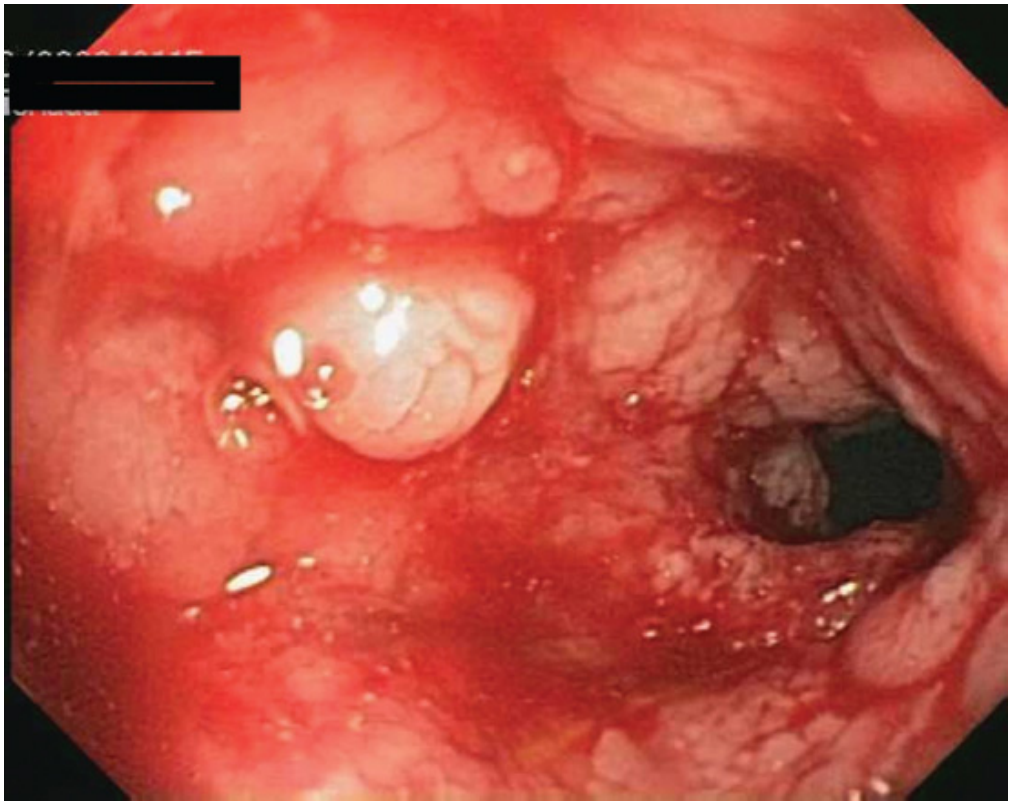


Figure 50.10 Endoscopic view of terminal ileal stricture.

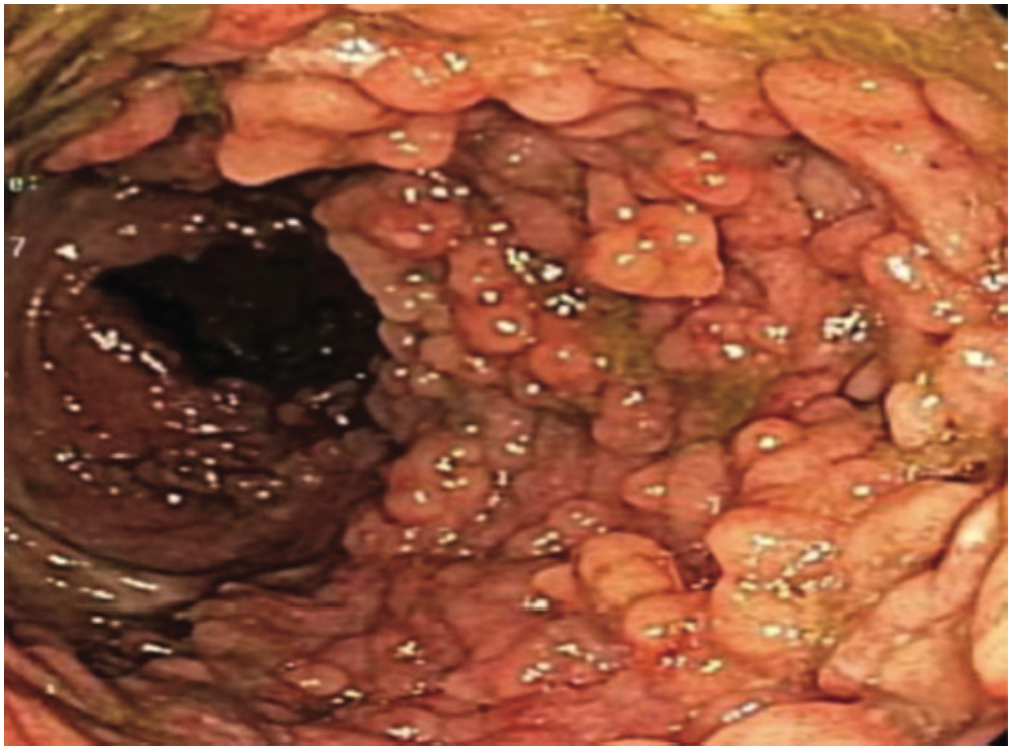


Figure 50.11 Colonic pseudopolyps.

Esophagogastroduodenoscopy (EGD) also plays a role for patients with suspected or known proximal disease and can identify ulcers, fistulas, and strictures that may be responsible for various upper GI symptoms. In addition, through the scope, therapeutic interventions (e.g., dilation, needle-knife) can be performed. Overall, both upper and lower endoscopy are relatively safe procedures with complications in IBD patients occurring in <5%, and generally consist of bleeding—though perforation remains a very small risk of every endoscopic procedure.[81] Additionally, endoscopic evaluation provides an ability to track and quantify disease activity by use of the scoring systems such as the Crohn Disease Endoscopic Index of Severity (CDEIS) or Simple Endoscopic Score for Crohn Disease (SES-CD) (**Table 50.3**).[82]

Video capsule endoscopy uses wireless technology to capture continuous images of the upper GI tract mucosa to help determine disease presence and activity that are beyond the reach of endoscopy and the limitations of traditional small-bowel imaging. While the diagnostic yield may not be as high, it has been shown to be comparable to ileocolonoscopy and better than small-bowel follow-through for the detection of small-bowel inflammation.[83] Furthermore, negative predictive values range from 96% to 100%, essentially ruling out the diagnosis of Crohn disease when the results are normal.[84] Of note, it is imperative to exclude the presence of moderate–severe strictures prior to its use, as their presence can result in bowel obstruction from the capsule becoming lodged at the point of stenosis (**Fig. 50.12**).

Pathology

The presence of noncaseating granulomas on pathologic examination is pathognomonic of Crohn disease. However, they are only found in 25% to 42% of patients, and may simply be a marker of more virulent disease.[85] In addition, a small subset of long-standing ulcerative colitis patients may have granulomas on biopsy.[86] Routine depth endoscopic biopsies may miss granulomas and often they are only visible on resected full-thickness specimens. Other histologic evidence of Crohn disease includes architectural distortion of the crypts (size, shape, symmetry), ulcerations, pseudopolyps, and skip areas—some of which may also be found in ulcerative colitis (**Fig. 50.13**). Other discriminating features of Crohn disease on gross examination include the potential for full-thickness involvement of the bowel wall, and the presence of "creeping fat," where the mesenteric fat extends over the serosal surface of the bowel wall—"creeping" over the normally distinct mesenteric/bowel wall interface (**Fig. 50.14**). Furthermore, gross pathologic examination of Crohn disease specimens may range from acutely inflamed, edematous, hyperemic bowel to thickened, fibrotic, and "woody." Finally, the mesentery is classically thickened, with increased edema, friability, and vascularity.

Table 50.3 Clinical Endoscopic Scoring Systems for Crohn Disease

Simple Endoscopic Score for Crohn Disease (SES-CD)

Severity	0	1	2	3
Size of ulcers	None	<0.5 cm	0.5–2 cm	>2 cm
Ulcerated surface	None	<10%	10–30%	>30%
Inflamed surface	None	<50%	50–75%	>75%
Stenosis	None	Single, passable	Multiple, passable	Not passable

Each segment of bowel is assigned values for all four severity variables.

Crohn Disease Endoscopic Index of Severity

	Rectum	Sigmoid and Left Colon	Transverse Colon	Right Colon	Ileum	Total	
Deep ulceration (0 = absent; 12 = present)						1	
Superficial ulceration (0 = absent; 6 = present)						2	
Surface involved by the disease (cm)						3	
Ulcerated surface measured (cm)						4	
						Total 1 + total 2 + total 3 + total 4 =	A
						Number (n) of segments explored =	n
						Total A divided by n	B
						Ulcerated stenosis anywhere: 0 = absent, 3 = present	C
						Nonulcerated stenosis anywhere: 0 = absent; 3 = present	D
						Total score = B + C + D	CDEIS

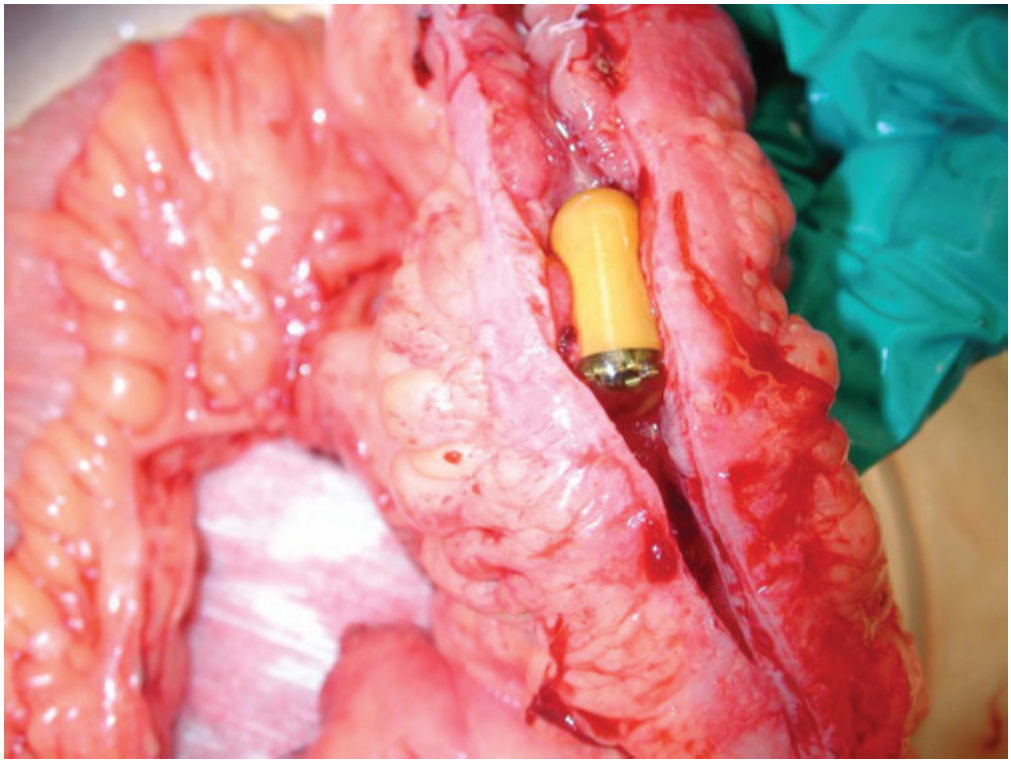


Figure 50.12 Capsule endoscopy pill lodged in small-bowel stricture.

Laboratory Analysis

No single laboratory examination will provide a definitive diagnosis of Crohn disease; yet, there are tests available to help discriminate between Crohn and other processes. Though not recommended for routine use, serum measurements of perinuclear antineutrophil cytoplasmic antibodies (p-ANCAs) and anti-Saccharomyces cerevisiae antibodies (ASCAs) can been used to help differentiate Crohn disease from ulcerative colitis.[71,87,88] The former is a known marker associated with ulcerative colitis, whereas elevated levels of ASCA are associated with Crohn disease. Unfortunately, only 30% to 50% of Crohn patients will test positive for ASCA, and up to 10% of healthy individuals will also have elevated serum levels.[89]

C-reactive protein is a nonspecific marker for inflammation that has been useful in tracking disease activity and response to treatment. More recently, fecal biomarkers such as fecal calprotectin,[71,90] lactoferrin, and neopterin[91] are used to monitor intestinal inflammation and have been shown to reliably correlate with endoscopic disease activity and response to anti-TNF therapy.[92–94] While nonspecific, elevations in fecal biomarkers have been shown also to correlate with higher levels of recurrence following surgical resection.[95,96]

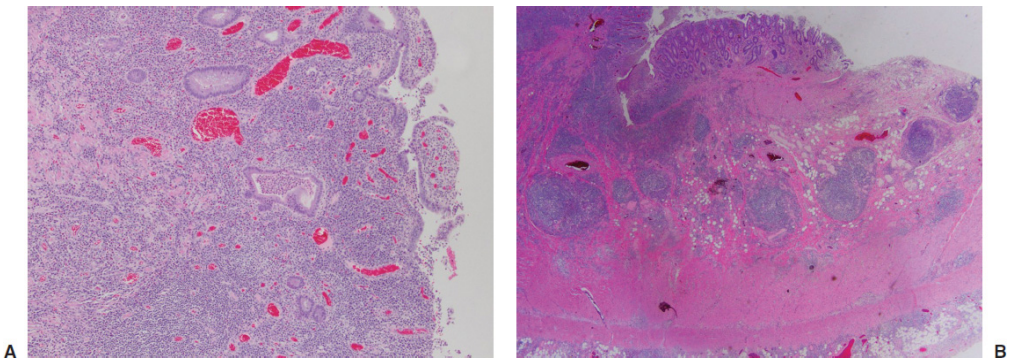


Figure 50.13 **A**: Active colitis with crypt abscess formation and atypical regenerative features consistent with chronic crypt-destructive colitis. (Courtesy of George Leonard, MD.) **B**: Full-thickness involvement of chronic inflammatory infiltrate from mucosa to serosa and pseudopolyp formation. (Courtesy of George Leonard, MD.)

TREATMENT

Medical Management

4 While an in-depth discussion of medical management of Crohn disease is beyond the scope of this chapter, a few points are worth noting. First, despite the spectrum of disease presentations, Crohn remains one hallmarked by inflammation (i.e., abdominal pain) and diarrhea. As such, supportive care to include antidiarrheal and antimotility agents, along with a bland diet, are good first-line approaches to provide symptomatic control. It is important to exclude the concomitant presence of "superinfections" such as cytomegalovirus or *C. difficile* infection, as antimotility medications may result in the onset of toxic megacolon and a rapidly progressive clinical deterioration. These can be ruled out by endoscopic biopsies in addition to stool studies. Simple over-the-counter, readily available medications such as loperamide and bismuth, along with prescription medications such as diphenoxylate, codeine, and tincture of opium often provide tremendous relief to abdominal pain, cramping, and loose stools.

Figure 50.14 Creeping fat along terminal ileum.

Nutritional support in all patients with Crohn disease is paramount. Ideally, preservation of oral feeding in any form is crucial for maintenance of the absorptive and protective mechanisms provided by the GI mucosal lumen villi and microvilli. Exclusive enteral nutrition involves a completely liquid diet using formula per nasal tube or orally for 6 to 8 weeks followed by slow reintroduction of other foods. This is the first-line therapy for treatment of Crohn disease in the pediatric patient as it avoids growth suppression associated with steroids and has been shown to result in complete mucosal healing in adults as well.[97–99] When enteral intake is not possible, parenteral nutrition is invaluable in preserving nutritional stores, maintaining positive nitrogen balance, preventing weight loss, and improving perioperative

outcomes.[100] This must be weighed against the potential complications involved with intravenous routes to include infectious complications and thromboembolic events.

When considering the treatment strategy for patients with Crohn disease, it is important to keep in mind the goals of treatment, which include resolution of current inflammation and resultant symptoms and to prevent the risk of long-term complications. With these goals at the forefront, it is necessary to take into account several patient-specific factors such as age, extent of inflammation, severity of symptoms, nutritional status, and long-term function. Treatments are aimed at the induction and maintenance of remission, with surgery reserved for patients with complications from, or refractory to, the disease.

There are several classes of medications used to treat Crohn disease including probiotics, antibiotics, 5-aminosalicylate (5-ASA) compounds, glucocorticoids, immunomodulators, and biologic agents with differing mechanisms of action and purpose of use (**Table 50.4**).

Probiotics, which are typically not harmful, may have the effect of altering the gut microbiome; however, no randomized control trials or meta-analyses have demonstrated this consistently. The influence of antibiotics on maintenance of remission of Crohn disease remains unclear.[101] Though there currently are no antibiotics approved by the Federal Drug Administration specifically for the treatment of inflammation in Crohn disease, they may aid in remission and decrease relapse. Metronidazole can be used for the treatment of symptoms of perianal Crohn disease and there are some data to suggest that rifaximin may be beneficial in maintaining remission.[102–106]

Table 50.4 Available Medications for Crohn Disease

Class of Medication	Examples	Role in Therapy
Antibiotics	Metronidazole	Induction of remission Treatment of infection
5-ASA	Mesalamine Olsalazine Sulfasalazine	Maintenance of remission in mild cases
Steroids	Budesonide[a] Methylprednisolone Prednisone Prednisolone	Induction of remission
Immunomodulators	6-Mercaptopurine Azathioprine Cyclosporine[b] Methotrexate Tacrolimus	Induction and maintenance of remission
Biologics	Adalimumab Certolizumab Infliximab Natalizumab Ustekinumab Vedolizumab	Induction and maintenance of remission

[a]Budesonide is taken enterally and has only topical effect, no systemic effect.

[b]Cyclosporine can be used as rescue therapy/induction in refractory cases, but has not been supported by evidence in the treatment of Crohn disease.

5-ASA compounds are released at various locations along the digestive tract and control apoptosis, cell proliferation, inflammation, and metabolite function. These drugs must be taken with folic acid supplementation. Previously these drugs were the standard therapy for treatment of Crohn disease; however, several trials have not shown benefit over placebo.[107–109] There is no role of 5-ASA drugs in the induction of remission in Crohn disease, though these drugs can be used in the setting of mild to moderate active colonic Crohn disease.[71] Side effects of 5-ASA compounds include GI upset, headache, bone marrow suppression, hemolytic anemia, hepatitis, fever, hypersensitivity reactions, pancreatitis, pneumonia, and rash. For patients with mild disease, they may still be useful as a frontline agent.

Glucocorticoids are frequently used for the induction of remission, but not a preferred treatment for the maintenance of remission. They function by modulating the immune response inhibiting expression of adhesion molecules, and decreasing inflammatory cells infiltrating the intestine. The side effect profile of these drugs limits their use to acute episodes. Budesonide is an oral glucocorticoid with minimal systemic absorption that works topically in the terminal ileum and proximal colon. Induction of remission is achieved at a dose of 9 mg daily for 8 weeks and then tapered to a maintenance dose of 6 mg/day. Prednisone is a systemically absorbed glucocorticoid that can be used for induction of remission at a dose of 40 to 60 mg/day and tapered down after 2 to 6 weeks until discontinuation of the medication. Side effects include acne, hyperglycemia, hypertension, mood disruption, moon facies, weight gain, glaucoma, cataract, insomnia, osteonecrosis, osteoporosis, and adrenal suppression. Patients should be closely monitored for symptom response as they may develop "steroid-resistant" or "steroid-dependent" disease and should be considered for additional therapies, including surgery.

Immunomodulators, such as thiopurines and methotrexate, are another class of medications used for induction and maintenance of remission. The addition of these medications can also allow for tapering of glucocorticoids. Thiopurines, 6-MP and its precursor azathioprine, interfere with nucleic acid metabolism and a clinical improvement can typically be seen 6 to 12 weeks following initiation of therapy. Prior to starting therapy, thiopurine methyltransferase (TMPT) levels should be measured, and the drug should not be given if levels are deficient. Side effects include nausea, vomiting, increase in liver enzymes, pancreatitis, leukopenia, and lymphoma. A complete blood count should be monitored routinely. Methotrexate is a folic acid analogue used for both induction and maintenance of remission that has inhibitory activity against enzymes in the metabolic pathway of folic acid. This leads to decreased production of inflammatory mediators via accumulation of adenosine by way of thymidylate, purine, and methionine inhibition. Patients must take folic acid supplementation along with the medication. Side effects include GI upset, stomatitis, leukopenia, hepatic fibrosis, hypersensitivity reactions, and pneumonitis.

The introduction of biologic agents dramatically changed the landscape of medical management of Crohn disease. These medications include anti-TNFα agents, integrin receptor agonists, and interleukin agonists**.** The anti-TNF agents infliximab, adalimumab, and certolizumab are the most widely used and are now considered first-line agents in the treatment of Crohn disease. Infliximab is given by intravenous infusion with a loading dose followed by maintenance doses either biweekly or monthly. Adalimumab and certolizumab are given as subcutaneous injections. All three drugs have similar response rates.[110] Drugs should be monitored closely as side effects and the development of antibodies can occur. Side effects of these

medications include a risk of infection, tuberculosis autoimmune reactions, liver dysfunction, heart failure, lymphoma, and multiple sclerosis. Prior to starting these medications, patients should be tested for tuberculosis and hepatitis.

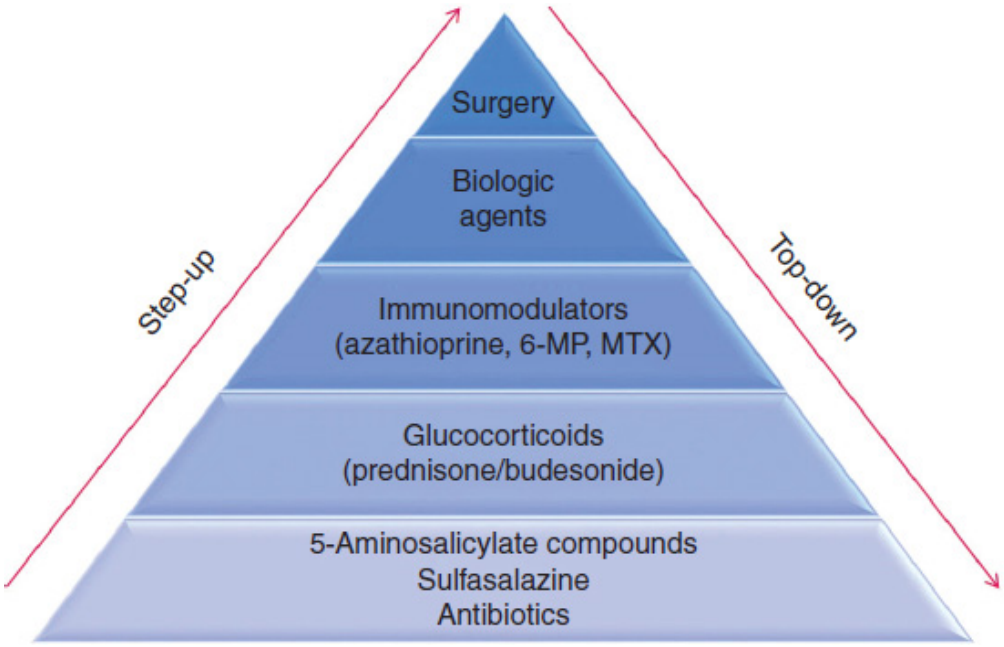


Figure 50.15 Step-up and top-down treatment strategies for Crohn disease.

Integrin receptor agonists are a newer class of medications that include natalizumab and vedolizumab. Both drugs are useful for the induction and maintenance of remission. These drugs must also be monitored closely. Natalizumab is FDA approved for the treatment of Crohn disease after the failure of anti-TNF agents. This medication has been shown to have the potential for progressive multifocal leukoencephalopathy and should be monitored closely. Vedolizumab is an anti-inflammatory drug that works through inhibition of cell adhesion molecules. This medication is well tolerated and has been shown to not have an increased risk of infectious complications or lymphoma.

Ustekinumab, an inhibitor of IL-12 and IL-23, has been shown to have efficacy in induction and in maintenance of disease with a limited side effect profile. The infection profile of this medication is similar to that of placebo and the risk of malignancy mirrors that of the general population.[111,112]

There are two general approaches to treatment of Crohn disease (**Fig. 50.15**). Traditionally, a "step-up" approach was taken where less effective medications are started first with an incremental increase to more effective medications, which are potentially riskier (**Table 50.5**). The other approach is a "top-down" approach, in which the more aggressive medications are initiated despite the potential for greater

risk. There are advantages and disadvantages to both approaches and must be individually weighed for each patient with close monitoring for safety. This may include monitoring of serum drug levels of biologic agents, which recently has become clinically useful for guiding therapy. Drug levels of adalimumab >8.5 μg/mL have been shown to be associated with decreased levels of serum CRP, fecal calprotectin levels, and endoscopic mucosal healing.[113–115] Multidisciplinary management and close discussion with medical colleagues, primarily gastroenterology, are extremely useful in this aspect—especially when patients may require surgical therapy while on certain medications that could affect decision making and outcomes.

OPERATIVE MANAGEMENT

Indications for Surgery

The basic tenet in the management of Crohn disease is that surgery is typically reserved either for disease refractory to medical 5 therapy or complications from the disease. Refractory disease is still the most common reason for surgery in patients with Crohn disease. Complications resulting in a potential need for operative intervention include fistula, abscess, obstruction (stricture), growth retardation, perforation, extraintestinal disease, bleeding, and malignancy. Of note, hemorrhage in Crohn disease is a rare event and is more commonly seen in ulcerative colitis or diverticular disease. Despite improvements in medical therapy, over 70% of all Crohn patients will require surgery at some point in their lives, with almost half of those requiring additional procedures. Therefore, having a firm understanding of the general principles and technical specifics is important for surgeons who care for these patients.

General Principles

6 Certain overarching principles guide the planning and operative management. First, Crohn disease is a process marked by lifelong potential for recurrence; therefore, preservation of intestinal length is paramount during the planning phase.[116] This translates to not only maximizing bowel length, but also ensuring functional bowel. Next, the extent of resection versus intestinal sparing procedures is dependent on multiple factors, including location and duration of disease, indication for surgery, ability to exclude malignancy, and prior resections that may have resulted in shortened small bowel. In addition,7 as the stools tend to be loose, consideration must be given to rectal compliance and sphincter function during

surgical planning to avoid a "perineal colostomy," whereby continuity is preserved but the patient has no sphincter control—significantly affecting quality of life. Furthermore, unlike ulcerative colitis where removal of the entire colon and rectum is a curative operation, in Crohn disease, a segmental resection for both small and large bowel is often sufficient with ileocolonic, colocolonic, and rectal anastomoses, all playing a role in avoiding a permanent stoma while maximizing functional bowel.[117] Crohn patients with pancolitis may undergo a total abdominal colectomy with ileorectal anastomosis (for those with rectal sparing) or total proctocolectomy with end ileostomy.[118] While there are select patients with Crohn disease whose manifestations are more on the spectrum of ulcerative colitis and may do well with a total proctocolectomy with ileal pouch–anal anastomosis, this is typically discouraged, and is normally the result of an initial misdiagnosis of ulcerative colitis.

Table 50.5 Medications for the Induction of Remission of Crohn Disease

	Ileum	Colon	Upper GI
Mild	Budesonide	Sulfasalazine Systemic steroids	Systemic steroids Immunomodulators
Moderate	Budesonide or systemic steroids Antibiotics if sepsis Consider anti TNF	Systemic steroids If relapse: anti TNF +/− immunomodulators Discuss surgery	Systemic steroids If relapse: anti TNF +/− immunomodulators Discuss surgery
Severe	Systemic steroids If relapse: anti TNF +/− immunomodulators Discuss surgery Infrequent relapse: steroid + immunomodulator	Systemic steroids If relapse: anti TNF +/− immunomodulators Discuss surgery	Systemic steroids + immunomodulators If relapse: anti TNF +/− immunomodulators

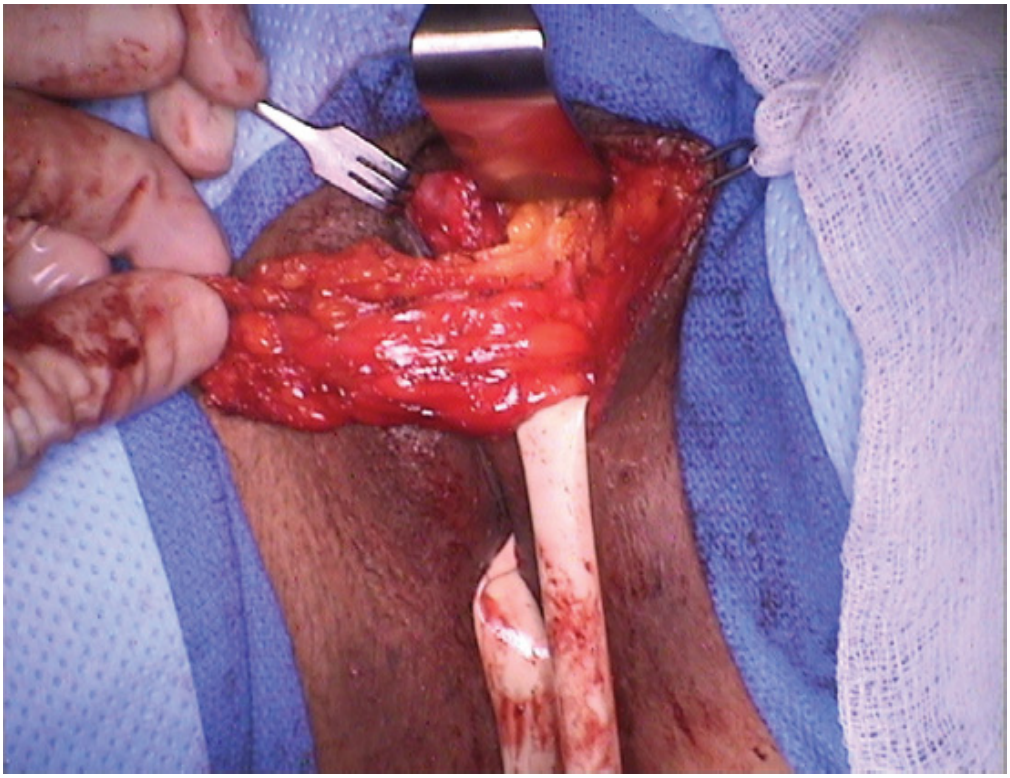


Figure 50.16 Bulbocavernosus flap for rectovaginal fistula (Martius flap).

Technical tips also come into play when planning for Crohn resections. For example, when performing a proctectomy, it is important to consider the potential for a delayed or nonhealed perineal wound. An intersphincteric dissection, which maximizes the amount of healthy muscle/tissue remaining, helps avoid this complication. Some patients will require more extensive procedures such as flaps (i.e., gracilis, myocutaneous thigh), and may require plastic surgeon involvement (**Fig. 50.16**).[119] As with small-bowel resection, length of resection margin does not influence the risk of risk of relapse and resection to grossly normal bowel is all that is required.[120] Finally, diversion is more commonly used due to both the presence of active disease as well as the potential negative healing effects of the Crohn medications.

Given the advances in imaging, unexpected inflammatory bowel disease is less frequently encountered in the operating room. In the case of suspected acute appendicitis in a patient with unknown Crohn disease, careful consideration should be paid to the extent of resection–ileocectomy versus appendectomy alone. Traditional teaching recommends performing an appendectomy alone if the cecum is normal, or to withhold on resection and undergo medical treatment only. Performing an appendectomy in the setting of cecal inflammation leaves the patient at risk of developing a perforation and/or fistula at that site. However, ileocolonic resection

for isolated disease may be in the patient's long-term best interests, with one series reporting almost half of patients required no further surgery, compared to 92% of those undergoing appendectomy only.[121] A complete evaluation of the GI tract should be performed at the time of surgery.

Strictures in Crohn disease most commonly occur in the terminal ileum, but may arise anywhere along the GI tract (**Fig. 50.17**). Due to the transmural inflammation, it is not uncommon to have luminal narrowing within the bowel especially with repeated flares. However, the underlying cause of obstruction may be from external compression from a phlegmonous/inflammatory process or secondary to the fibrostenotic pattern of disease. In the former, medical management may be successful by decreasing the inflammation and resolving the compression on the bowel wall, though surgery may still be required if symptoms are refractory to medical therapy. Patients with fibrotic strictures typically have little to no response to medical management and most often require surgery.[122–124] Emerging evidence suggests that early treatment of strictures with aggressive biologic therapy may aid in preventing the onset of fibrosis, especially in patients under 40.[125]

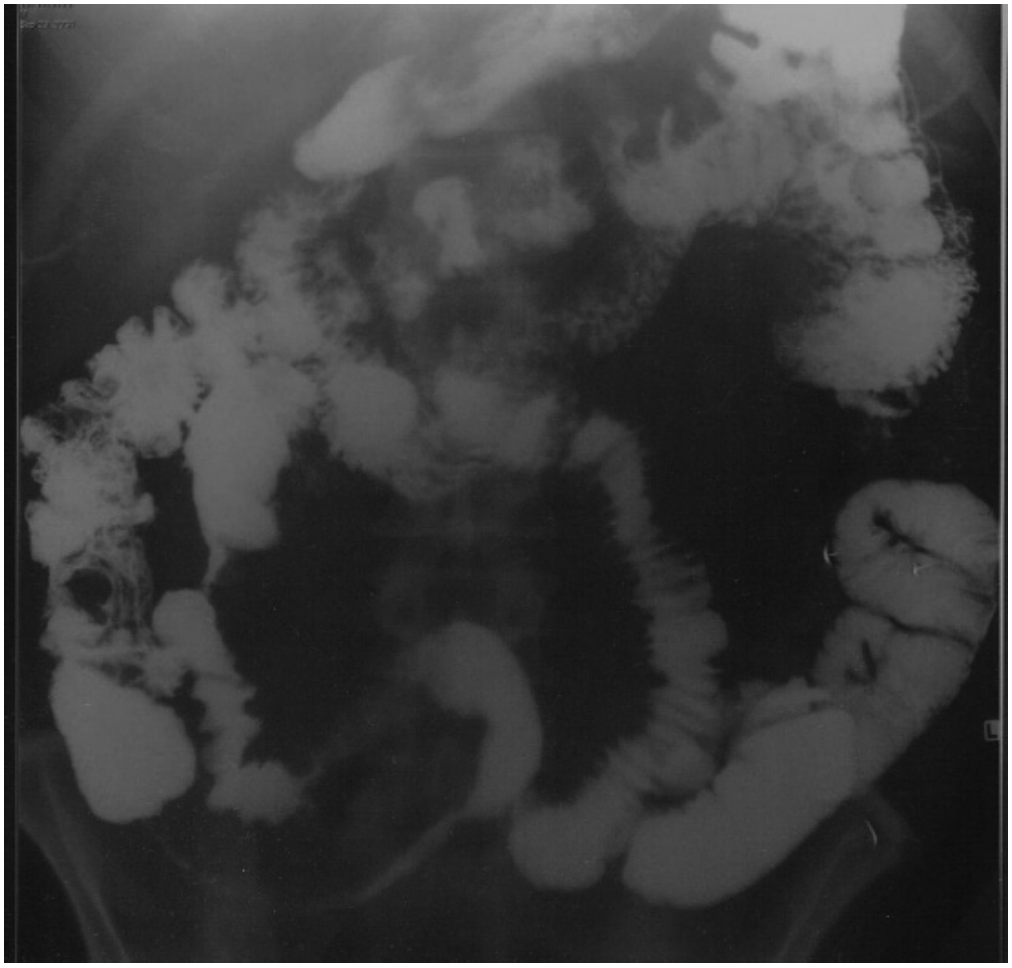


Figure 50.17 Multiple strictures demonstrated on small-bowel follow-through.

Strictures also differ based on their location. The rate of colonic strictures has been reported to be as high as 7% to 17%.[126] In general, these benign strictures are responsive to medical management as well as endoscopic dilation for moderate- to high-grade stenosis. EGD allows for therapeutic intervention such as dilation for those with gastric outlet obstruction.[127] Malignancy has been shown to be present in approximately 7% of all colonic strictures, and Crohn disease carries an increased risk of colorectal cancer above the general population.[128] It is very difficult to differentiate malignant from benign strictures clinically, therefore all colonic strictures should typically undergo endoscopic evaluation and biopsy. If malignancy is suspected, a standard oncologic resection should be performed (**Fig. 50.18**). For those that are clearly benign and nonresponsive to medical management, endoscopic dilation has been shown to provide symptomatic relief in over 80% of patients, with most patients with colonic strictures requiring repeated dilations.[129]

Strictures of the small bowel have been reported in 20% to 40% of Crohn patients.[130] Treatment typically consists of medical management; though depending

on the severity of obstructive symptoms, many patients will require intervention. Small-bowel strictures are often amenable to dilation if accessible via double-balloon enteroscopy.[131,132] Symptomatic relief occurs in 75% to 90% following the first dilation, while approximately 30% to 40% will require repeated intervention. For those with initial success, the cumulative dilation-free rate at 3 years is 40% to 50%.[133] Overall complications occur in 10% to 15% (<5% major complications), and include pain, fistula, fevers, bleeding, and perforation.[134] Despite this success, many will require operative intervention when symptoms fail to resolve, repeated bouts occur, or when a stricture is associated with a nonresolving inflammatory process, malnutrition, immunosuppression, or fistula. Surgical options then include stricturoplasty or resection.

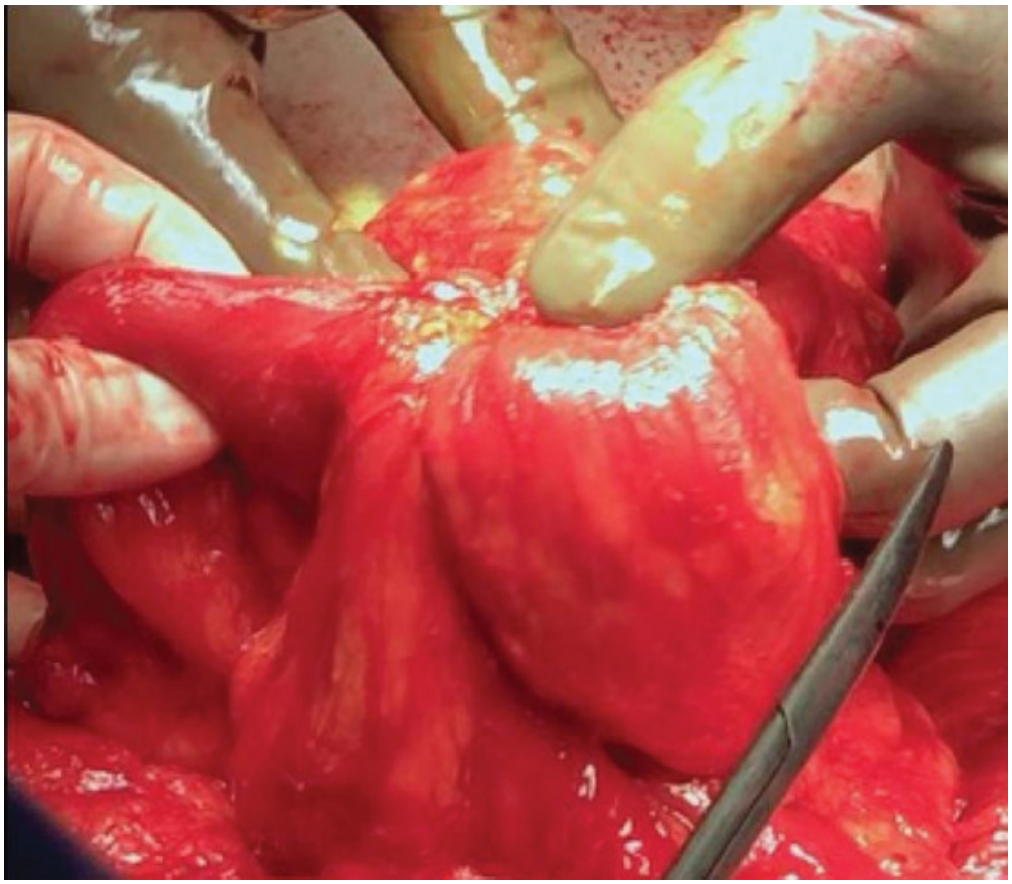


Figure 50.18 Colonic stricture.

Stricturoplasty can be performed to address fibrostenotic disease in the absence of inflammation and acts to preserve bowel length by avoiding resection altogether (**Fig. 50.19**). There are several surgical techniques based on the length of the stricture. The Heineke–Mikulicz method involves a longitudinal incision along the antimesenteric border of the bowel with a transverse closure and is useful for

shorter segments of bowel. The Finney stricturoplasty, classically used for longer strictures of 7 to 15 cm in length, involves a longitudinal enterotomy along the length of the diseased segment of intestine. The bowel is then folded upon itself and a full-thickness anastomosis is created. Finally, for longer strictures, the Michelassi stricturoplasty involves dividing the stricture and its associated mesentery in the middle of the length of the stricture. The intestine is overlapped in an isoperistaltic fashion and longitudinal enterotomies are created along the length of the strictured bowel and anastomosed together. Complications have been reported in 4% to 15% in large series, and include obstruction, bleeding, sepsis, perforation, and death.[135,136] Contraindications to stricturoplasty include malnutrition, presence of a phlegmon/perforation/fistula at the site, multiple strictures within a small segment, and suspicion of a malignancy.[137]

Figure 50.19 Small-bowel stricturoplasty.

Strictures at prior anastomotic sites may occur from recurrent disease or secondary to technical problems. They are often amenable to dilation,[138] yet failure is high, thus requiring resection for symptomatic strictures. There are some data to suggest that side-to-side stapled ileocolic anastomoses have a decreased rate of postoperative complications including leak, recurrence, and reoperation when compared to handsewn end-to-end anastomoses.[139,140]

Intra-abdominal fistulas may arise from either the small or large bowel and affect any adjacent structure. It is important to determine the site of origin of the fistula, as

this section of bowel will typically require a formal resection. On the other hand, the adjacent organ may simply be involved in the process secondarily without primary disease involvement. Therefore, it is important to evaluate the adjacent organ when possible (such the colon in an ileosigmoid fistula) to ensure there is no active disease that will need to be addressed (**Fig. 50.20**). The preferred treatment is to take the fistula down, resect the diseased segment of bowel, and primarily repair the adjacent site. If there is concern for active disease in the adjacent site, such as in the above example with the ileosigmoid fistula, the preferred strategy would be to perform a concomitant colonic resection.[141] Transmural bowel inflammation and communication can also occur with the skin, bladder, or vagina. Once again, the bowel is the offending organ and should be resected, while ligation of the fistula and closure of the secondarily involved organ is adequate treatment. These organs do not have potential for active Crohn disease and they can often be simply repaired. If the inflammatory process is severe or there is a concern for concomitant malignancy, the entire process should be resected en bloc with appropriate reconstruction. When an abscess is present, it is often preferable to percutaneously drain the abscess first and ensure adequate medical therapy prior to embarking on abdominal exploration.[142] Finally, asymptomatic enteroenteric or enterocolonic fistulas do not require surgery and medical treatment, especially with biologic agents that have relatively good success.[143]

Treatment for malignancy in the Crohn patient is similar to that of the general population, with resection following standard oncologic principles. As synchronous and metachronous lesions have been reported in up to 10%, consideration should be given to a subtotal colectomy with ileorectal anastomosis in the absence of rectal lesions, though segmental colectomy has been well described in Crohn disease.

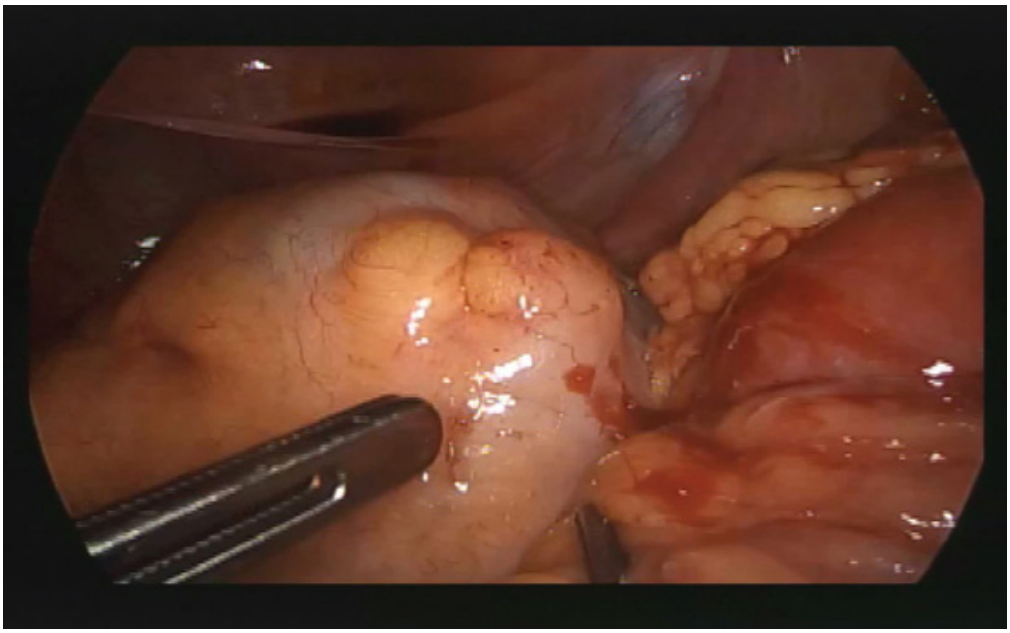
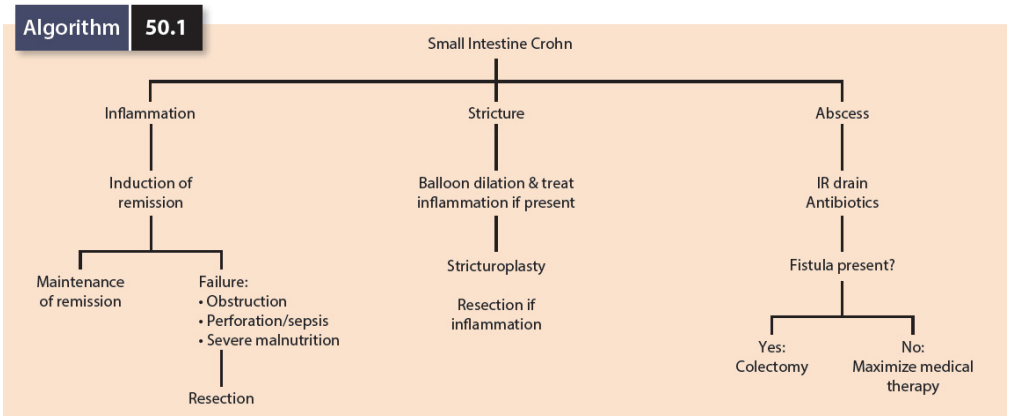


Figure 50.20 Ileosigmoid fistula.



Algorithm 50.1 Management of small-bowel disease in Crohn disease.

SPECIFIC CONSIDERATIONS

Small-Bowel Disease (Algorithm 50.1)

Following resection, consideration should be given to the nutritional status of the patient, medications, and overall physiologic state, as diverting stoma may be required to minimize the incidence and consequences of an anastomotic leak. As the rate of perioperative complications tends to be higher in this population, a minimally invasive approach has been associated with improved short-term outcomes in Crohn

disease patients, including decreased morbidity and shorter length of stay for both primary and recurrent disease (**Table 50.6**).[144]

The mesentery in active Crohn disease always presents a particular challenge for surgeons. Due to its thick, edematous nature with increased neovascularization, adequate hemostasis is a particular concern. Safe division involves techniques such as overlapping clamps with both mass and individual vessel suture ligation where appropriate. Minimally invasive approaches typically rely on advanced vessel-sealing devices for hemostasis, though they may be inadequate in the Crohn disease patient and conversion to an open procedure may be necessary to control hemorrhage. Avoidance of mesenteric hematomas is crucial, as these may result in continued bleeding and may as well compromise the blood supply to the healthy remaining bowel. Recently, wide resection of the mesentery in Crohn disease, similar to that of an oncologic resection, has been shown to have decreased need for reoperation and decreased future recurrence of Crohn disease.[145,146]

Table 50.6 Perioperative Complications of Bowel Resection in Crohn Patients[a]

Complication[a]	Incidence (%)
Bleeding	1–5
Anastomotic leak	1.3–17[b]
Anastomotic stricture	6–13
Anastomotic recurrence of disease	15–39
Bowel obstruction/ileus	5–23
Abscess/intra-abdominal sepsis (excluding leak)	2.1–15
Surgical site infection	10–33
Venous thromboembolic event	1.4–3.3

[a]Risk factors: malnutrition, obesity, emergent surgery, immunosuppressant use, smoking, older age, open approach, stoma surgery.

[b]Depending on location and definition (clinical vs. radiologic).

The recommended type of anastomosis used to restore continuity following resection is variable. Options include stapled or handsewn, antiperistaltic, isoperistaltic, end to end, and end to side. The Kono-S–type anastomosis is a novel

antimesenteric end-to-end handsewn anastomosis thought to prevent recurrence of Crohn disease (**Fig. 50.21**).[147]

Colorectal Conditions

Toxic colitis may occur in Crohn disease patients similar to those with ulcerative colitis (**Algorithm 50.2**).[148] Following resuscitation and intravenous steroids or immunosuppressants, emergent surgical intervention is required for those with recalcitrant disease, perforation, or a deteriorating clinical state. The operative procedure of choice is a subtotal colectomy with end ileostomy. Debate exists as to the handling of the rectal stump, though options include a distal mucus fistula with remnant sigmoid, implantation into the subcutaneous space, or local reinforcement of the stump. Proctocolectomy should be avoided in this situation due to the prolonged operative time and increased risk of morbidity and mortality.

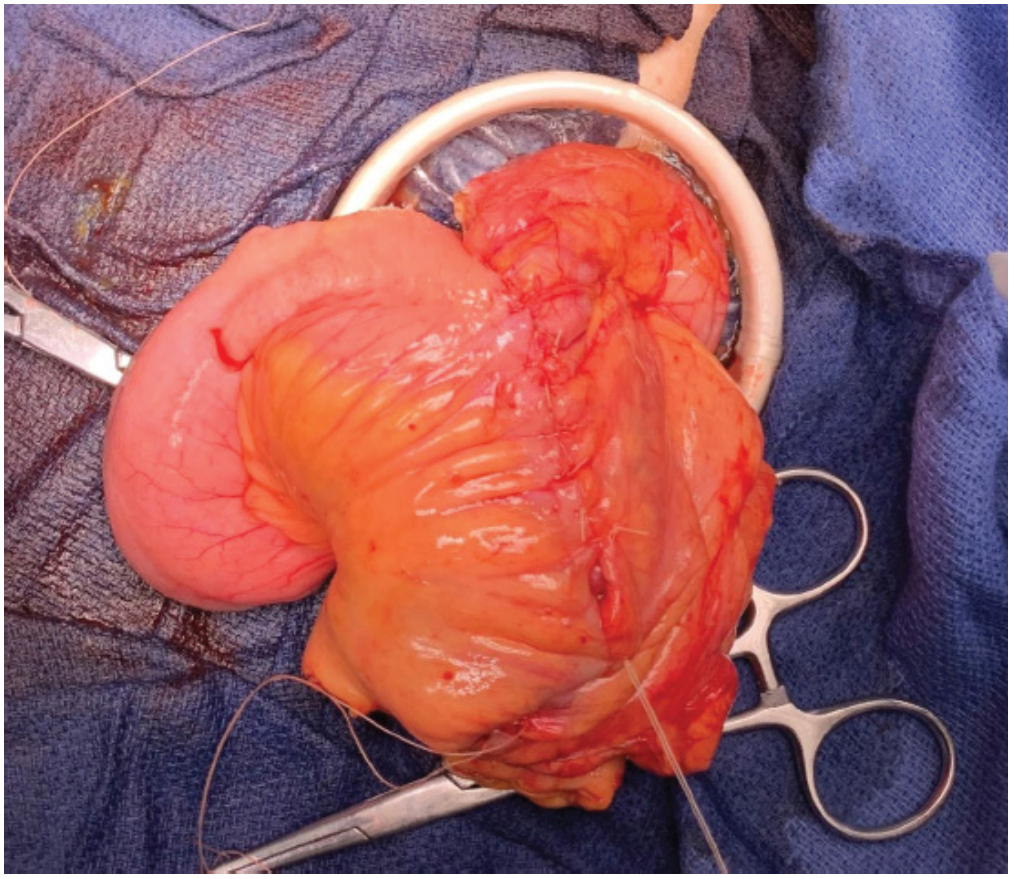
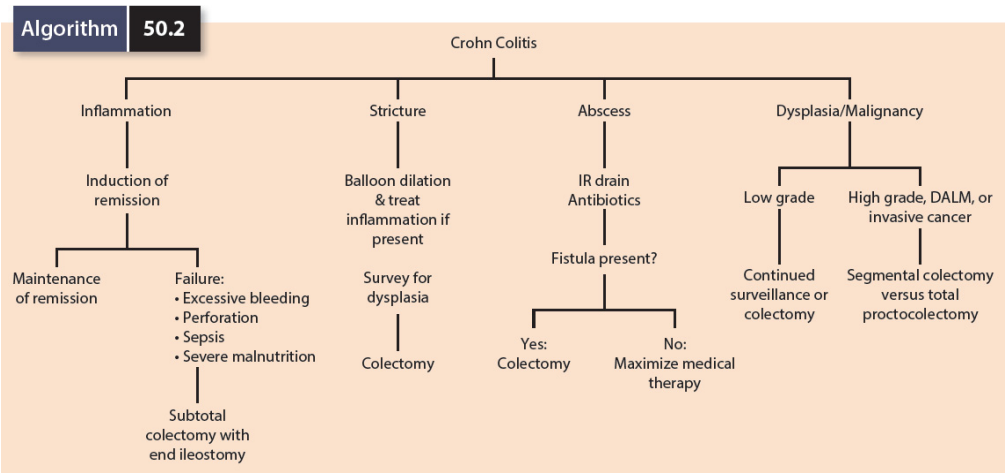


Figure 50.21 Kono-S–type anastomosis.



Algorithm 50.2 Management of colitis in Crohn disease.

An ileoanal pouch in the patient with Crohn disease is mostly commonly encountered in the setting of an initial diagnosis of ulcerative colitis with manifestations of Crohn disease at a later stage. While certain expert centers may advocate total proctocolectomy and ileal pouch construction for highly select patients with Crohn disease, in general, this is to be discouraged. Retrospective studies have reported 35% to 93% of patients will have Crohn-related complications such as pouchitis, abscesses, and pouch–anal fistulas, with another 10% requiring pouch excision or permanent diversion.[149] Furthermore, roughly half of patients will experience urgency or continence issues. Of those patients with a functioning pouch, over half will continue to require medication to treat active Crohn disease.[126,150,151]

Colorectal Malignancy

The risk of developing malignancy is elevated in the setting of Crohn disease and the management of dysplasia and invasive cancer remains controversial.[152] In the setting of inflammatory bowel disease, the type of lesion must be taken into consideration and a sporadic adenoma is managed differently than a nonadenomatous dysplasia–associated lesion or mass (DALM). Traditional sporadic adenomas can be managed with polypectomy and surveillance.[153–155] A DALM is a raised dysplastic lesion that does not have the appearance of a traditional sporadic adenoma. In general, the presence of a DALM raises consideration for total proctocolectomy given the high incidence of synchronous dysplastic lesions and metachronous colorectal cancers.[156] Absolute indications for surgery include high-grade dysplasia, multifocal dysplasia, and invasive cancer. Low-grade dysplasia and high-grade dysplasia are both risk factors for invasive cancer as they are associated with the identification of synchronous cancer in 19% and 42%, cases respectively.[157] In the setting of invasive

cancer, the extent of resection is controversial—segmental colectomy can be considered for select patients with Crohn disease, although total proctocolectomy remains the traditional recommendation.[156,158] Ileoanal pouch anastomosis can be considered in only highly selected patients.

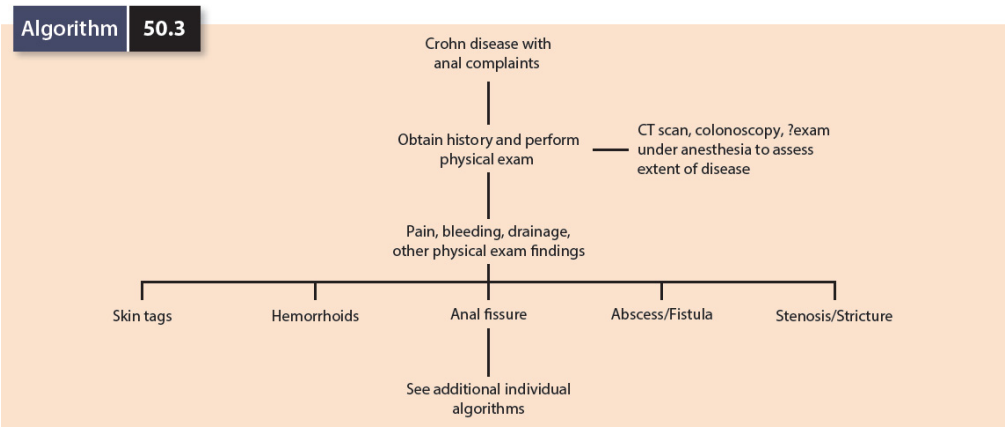
Influence of Immunosuppressive Medications on Surgical Outcomes

A strong consideration when operating on patients with Crohn disease is the potential for adverse postoperative outcomes in patients on immunosuppressive medications such as steroids and biologic agents. Patients undergoing colectomy for inflammatory bowel disease have been shown to have higher rates of infections when compared to those undergoing colectomy for cancer.[159] The main postoperative complications of concern are anastomotic leak, superficial surgical infection, and deep-organ space infection. Currently, no strict guidelines exist regarding the preoperative management of steroids and biologic agents. Several studies have demonstrated that anti-TNF agents are associated with higher rates of surgical site infection but not higher rates of anastomotic leak, and newer biologic agents are still under investigation.[160–166] However, the administration of immunosuppressive medications must be taken into consideration regarding surgical intervention. Decision making must balance the risk of holding these medications (such as disease flares and antibody development) with the benefit of decreasing postoperative morbidity. Furthermore, a combination of biologic medications, steroids, and malnutrition must be considered intraoperatively, potentially leading to higher rates of diversion.

Steroids are typically unable to be stopped due to steroid-dependent disease control. In general, anti-TNF agents are held for 4 weeks preoperatively, vedolizumab for 4 to 8 weeks preoperatively, and ustekinumab for 4 weeks preoperatively.[167] It is generally recommended to schedule surgery as far from the last dose of medication, around the time of what would be the next scheduled dose.

Venous Thromboembolism Prophylaxis

Patients undergoing surgery for inflammatory bowel disease experience higher rates of postoperative venous thromboembolism (VTE). The rate of postoperative VTE in patients with Crohn disease ranges from 0% to 4.9%.[168] Seventy-four percent of patients who experience VTE present during the initial postoperative hospitalization and 61% within the first 2 weeks postoperatively.[169] Standard perioperative VTE prophylaxis should be administered while patients are hospitalized and patients should be considered for extended prophylaxis upon discharge.[170]



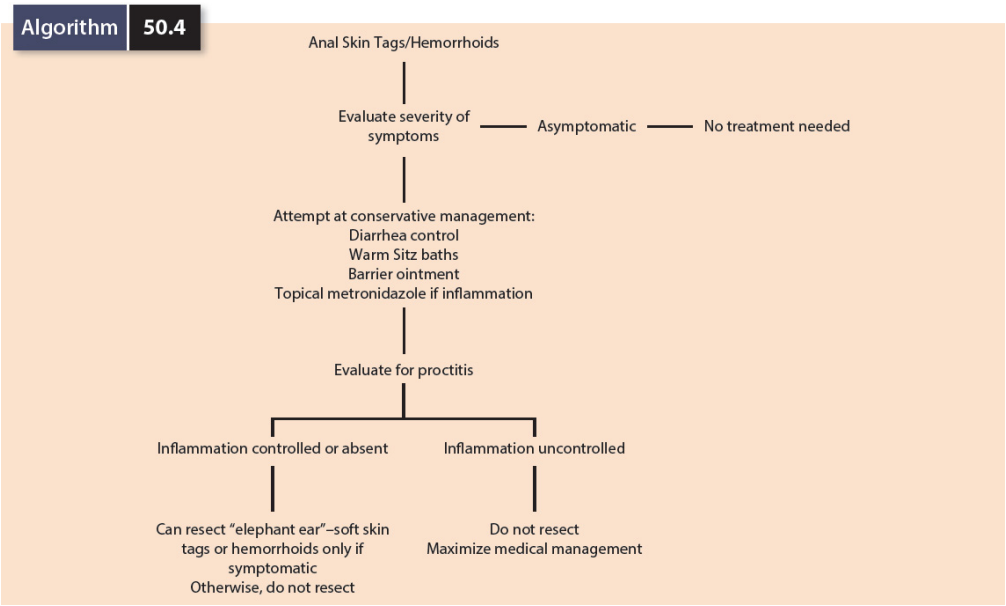
Algorithm 50.3 Crohn disease with anal complaints.

Treatment of Anorectal Conditions (Algorithm 50.3)

8 A distinguishing characteristic of the surgical treatment for anorectal Crohn disease is to first consider whether or not they are symptomatic. As a follow-on principle, aggressive intervention in the asymptomatic patient is unwarranted and potentially dangerous.

Anal Skin Tags and Hemorrhoids (Algorithm 50.4)

There are two types of skin tags associated with Crohn disease. The first type is a result of lymphedema due to concomitant intestinal disease and is hard, blue-colored, edematous, and tender (**Fig. 50.22A**). The other type is often referred to as "elephant ear" skin tags and are broad based, soft, and painless (**Fig. 50.22B**). When considering surgical intervention for these tags, it is important to keep in mind that Crohn disease patients have the propensity for poor healing, especially in the face of diarrhea. Patients should be counseled as to the risk of nonhealing wounds, continence problems, and mucus drainage.[171] An initial attempt at conservative treatment with warm Sitz baths and control of diarrhea is warranted. During this time, medical therapy toward Crohn disease should also be optimized, as active inflammation/proctitis will lead to increased morbidity. In the absence of proctitis, the "elephant ear"–type skin tags may be excised if personal hygiene is particularly bothersome, and wound healing can ensue normally.



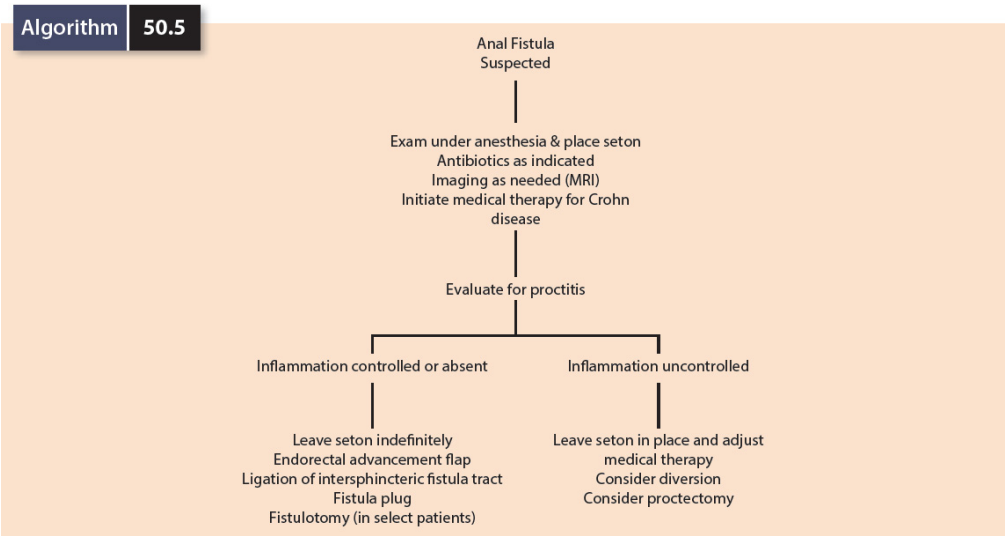
Algorithm 50.4 Management of anal skin tags and hemorrhoids in Crohn disease.

Figure 50.22 **A:** Crohn skin tags: elephant ear–type skin tags. **B:** Type of Crohn skin tags that should not be excised.

Internal hemorrhoids are not common in the setting of Crohn disease and patients that present with rectal bleeding should initially be evaluated for a flare of the underlying disease. However, if present, in the absence of proctitis and/or active perianal disease, they may be treated in a similar manner as a patient without Crohn disease, with conservative management of proper bowel hygiene, fiber supplementation, and band ligation, reserving surgical management as a last resort after failure of nonsurgical treatment.

Anorectal Abscess/Fistula (Algorithm 50.5)

Upward of 30% of patients with Crohn disease will develop perianal abscess or fistula and the treatment remains controversial. Perianal abscesses and fistulas in the setting of active perianal Crohn disease do not typically follow the traditional patterns of routine cryptoglandular-based disease (**Fig. 50.23**). The primary goal of treatment is the same, however, to control sepsis and maintain continence. The best treatment course depends on individual patient and fistula characteristics.



Algorithm 50.5 Management of anal fistula in Crohn disease.

Figure 50.23 Perianal fistulas in Crohn disease with "watering-can perineum." Hydrogen peroxide is injected through an external opening, with bubbles coming from multiple other openings.

When presenting initially as an abscess, incision and drainage is indicated and it is important to place the incision as close to the anal verge as possible while still achieving adequate drainage, considering the possibility of fistula development.[172] Alternatively, a small mushroom-tipped catheter may be placed in the cavity close to the anal verge, thus evacuating the abscess and allowing the cavity to close around the catheter, while allowing continued drainage.

If there is suspicion for a fistula, determining the anatomy of the tract is required, and attention must be paid to the presence of proctitis, status of the sphincter, prior anal operations, and potential for chronic diarrhea. In the setting of a fistula, a seton should be placed initially until further workup can be completed (**Fig. 50.24**). The goal of the seton is to allow for continuous drainage and prevent abscess formation. In addition, it has the potential of turning a chronic inflammatory tract into a more chronic fibrotic one. After the acute situation is handled, patients should then be evaluated thoroughly for the presence of intestinal disease and considered for medical treatment.

In the absence of proctitis, treatment is determined based on the characteristic of the fistula. A low-lying fistula in the absence of overt proctitis can often be treated

safely with fistulotomy.[173] Care must be given, even in these situations, as decreased continence may still ensue. When the fistula is higher or more complex, the initiation of anti-TNF agents has been reported to heal fistulas in up to 60% of patients.[174] Other treatment options include fibrin glue (not recommended), fistula plugs (success rates <20%), endorectal advancement flaps, or the LIFT procedure (ligation of the intersphincteric fistula tract). Meta-analysis of endorectal advancement flap versus LIFT procedure for Crohn disease demonstrates no difference in healing rates, with both procedures achieving success in approximately 50% to 60% of cases.[175]

Figure 50.24 Seton drains made of Penrose drains placed through fistula.

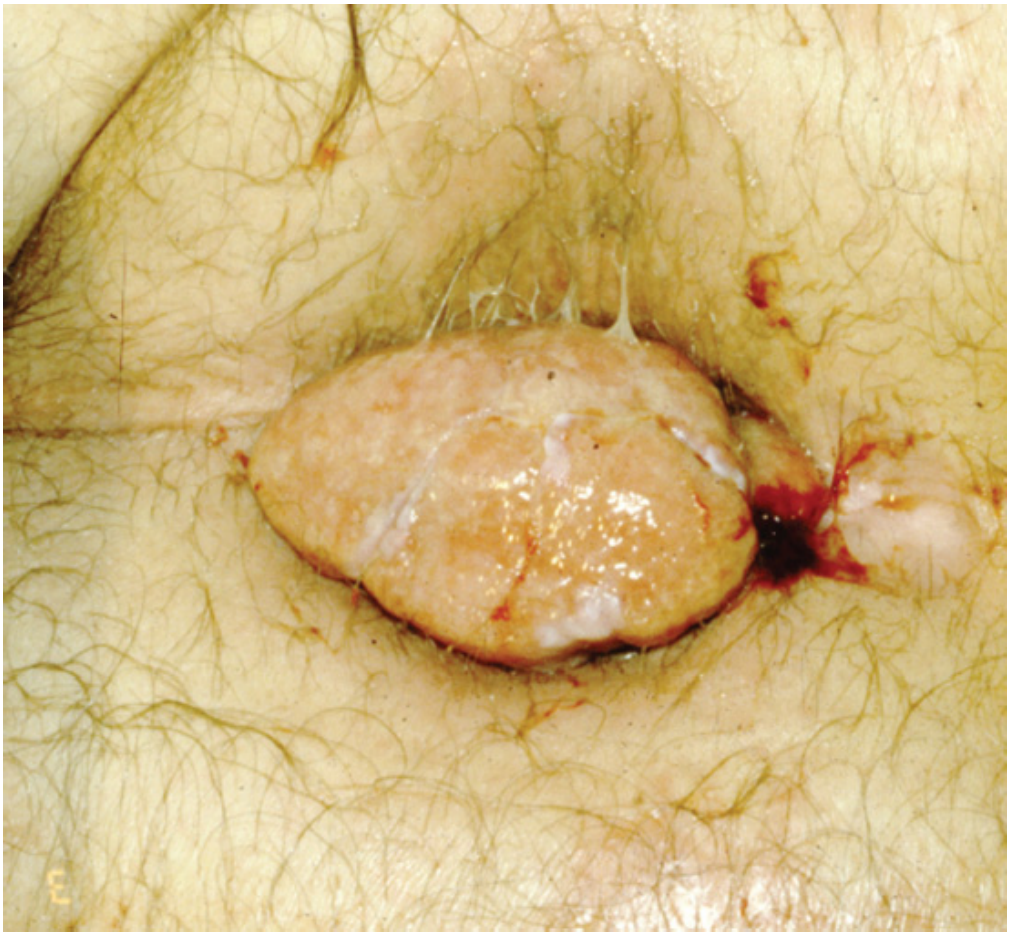


Figure 50.25 Anal cancer arising in perianal Crohn disease.

In the presence of active proctitis, typically the best way to proceed is to place a seton and initiate medical therapy. Setons can remain indefinitely, but patients should be periodically reexamined both to ensure that there is adequate drainage and to screen for the development of squamous cell carcinoma and adenocarcinoma arising in a fistulous tract (**Fig. 50.25**). Unfortunately, fistulas and fistula procedures all vary in their outcomes, with healing rates ranging from 15% to 97% and morbidity rates 3% to 78%, making it difficult to accurately compare results. As such, consideration should be given for a diverting stoma for recurrent or complex fistulas and upward of 68% of patients may require permanent diversion or even proctectomy.[176–179]

Rectovaginal/Anovaginal Fistula

Rectovaginal fistulas are particularly problematic in the Crohn disease patient. Passage of air and/or stool from the vagina can be extremely disturbing to the patient, but rarely constitutes a surgical emergency (**Fig. 50.26**). Clearance of active sepsis should take first priority with drainage of any abscess and initiation of antibiotics. After sepsis is controlled, the anatomy should be defined and medical

therapy with immunologic and/or biologic therapy should be initiated. The mainstay of management of these patients is medical therapy, with surgical therapy taken into consideration with caution. Recurrence rates are high and even with optimal treatment, upward of 20% of patients will eventually require proctectomy with permanent stoma.[180] Surgical options include fistula plug, endorectal advancement flap, LIFT procedure, episioproctotomy, sphincteroplasty, tissue interposition, and proctectomy.[181] Diversion is used liberally to improve healing. In certain situations, a lifelong seton may be necessary.

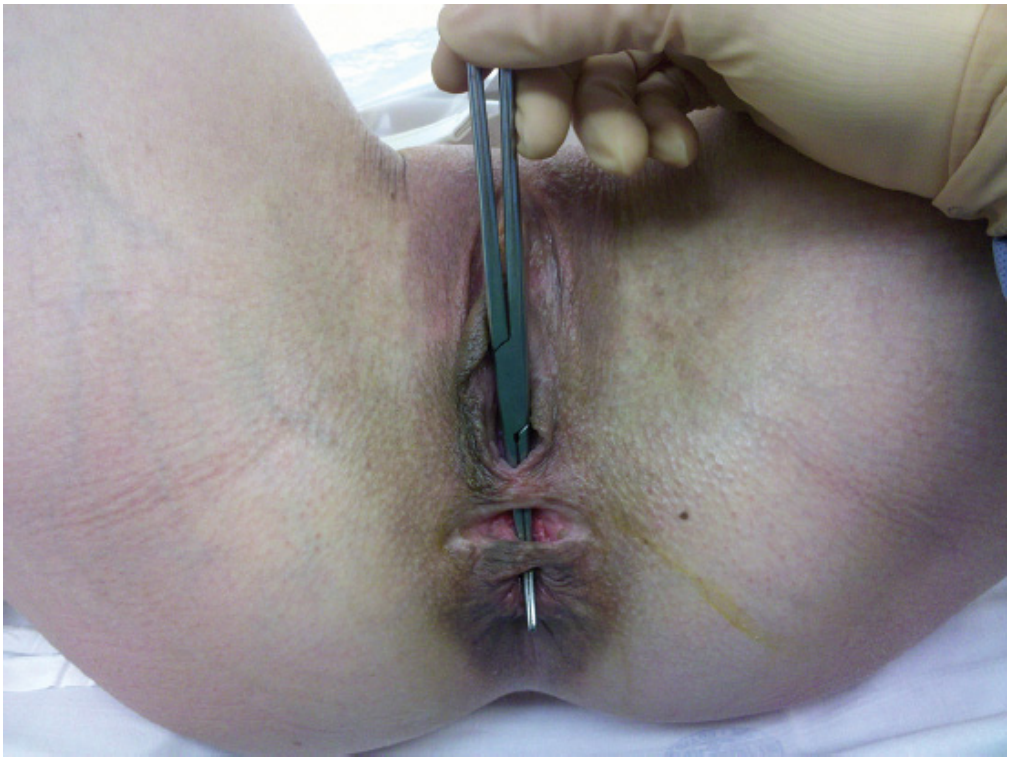


Figure 50.26 Rectovaginal fistula.

Anal Fissure (Algorithm 50.6)

Patients with Crohn disease can present with routine typical fissures associated with anal sphincter hypertonicity versus atypical fissures that are the result of the Crohn disease itself. All patients should be evaluated for the extent and severity of active intestinal Crohn disease. Excessive pain should raise the suspicion for an underlying abscess and prompt an examination under anesthesia.

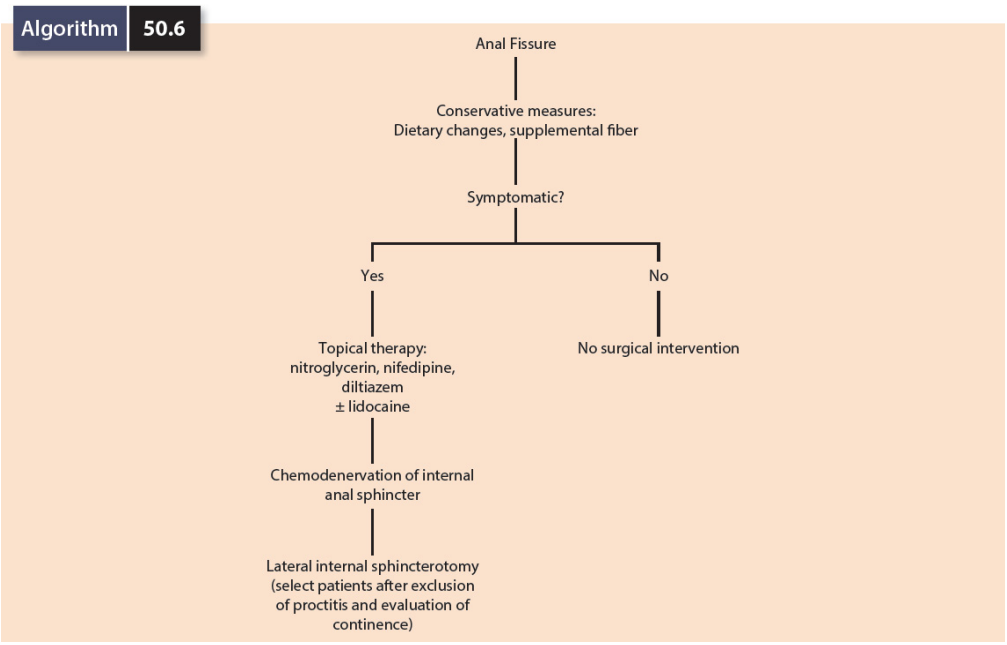
Routine typical fissures in the absence of active perianal disease can be treated in the standard fashion. Bowel habit management with high-fiber diet, stool softeners, fiber supplementation, and topical calcium channel blocker ointment are first-line treatments. Botulinum toxin injection and sphincterotomy can also be considered if

medical therapy fails, though sphincterotomy should minimize the wound as much as possible.

Crohn disease–associated fissures are hallmarked by deep, burrowing, off the midline, and sometimes multiple wounds. Many anal fissures are fortunately painless and require no intervention. Initial attempts at conservative therapy with topical metronidazole, smooth muscle relaxants, and local anesthetics may be attempted to palliate symptoms and help with healing.[182] For particularly symptomatic fissures, botulinum toxin has also been used. In contrast, other authors have advocated a more aggressive surgical approach in Crohn disease patients, with one report citing 67% of patients who were treated surgically with either lateral internal sphincterotomy or fissurectomy ultimately healed.[183] Given the continence risks associated with surgery, medical management directed toward Crohn disease is the preferred initial therapy in patients with Crohn-related fissures. Surgical intervention with a tailored lateral internal sphincterotomy should be reserved for those patients with minimal active anorectal inflammation who fail all reasonable conservative therapy, and still sphincter muscle division should be kept to a minimum.

Anorectal Malignancy

Risk factors in patients with Crohn disease include the presence of chronic inflammation, long-standing open wounds, and use of immunosuppressant medication. Both squamous cell carcinoma (Marjolin ulcer) and adenocarcinoma, and their variants may occur.[184] Patients, especially those with long-term indwelling setons, should be periodically examined at least annually to exclude the presence of malignancy or other pathology. All suspicious lesions should undergo biopsy and any malignancy identified should undergo proper staging and treatment.



Algorithm 50.6 Management of anal fissure in Crohn disease.

SUMMARY

Crohn disease remains a complex disease process with many different manifestations in the GI tract as well as extraintestinal locations. Although advances in medical therapy continue to evolve and significantly alter the way patients are managed, surgeons still play a large role in the medical and surgical therapy of the disease, though multidisciplinary care with gastroenterologists is crucial to achieve optimal therapy. Due to its recurring nature, providers must adhere to the principles of preventing and managing disease complications versus aiming for cure. By focusing on the maximization of functional outcomes, surgeons can optimize outcomes through a multimodal approach and minimize additional complications.

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51

Small Intestinal Neoplasms

James W. Fleshman Jr and Steven G. Leeds

Key Points

1. The main types of primary small bowel tumors include adenoma, adenocarcinoma, neuroendocrine (carcinoid), lymphoma, and sarcoma (GIST). Surgical resection remains the treatment of choice for all except lymphoma (only needed for symptomatic lesions causing obstruction or bleeding).
2. There is a rising incidence of small bowel tumors, directly caused by a relative increase in the incidence of neuroendocrine tumors (NETs) over adenocarcinoma of the small bowel. This trend is occurring globally.
3. Research is now focused on the molecular cause of the discrepancy between the number of small bowel and colorectal adenocarcinomas.
4. Size and location influence the symptoms caused by tumors within the small bowel. The majority of tumors found incidentally are asymptomatic.
5. Capsule endoscopy (CE) is helpful for diagnosis but lack of spatial orientation, inability to biopsy, and capsule retention causing obstruction limits its usefulness. Small bowel enteroscopy, device-assisted enteroscopy (DAE), or deep enteroscopy (DE), are excellent alternative modalities.
6. Even though small NETs can metastasize, the risk of metastasis correlates with the size of the primary tumor.
7. There are three common radiographic modalities used to diagnose small bowel tumors which include CT scan, MRI and CT, or MR enterography. NETs also benefit from octreotide scanning as a functional scan to detect metastasis.
8. Chromogranin A tends to be the most sensitive indicator of recurrence during surveillance of NET, and sensitivity and specificity depends on the functionality of the tumor.
9. Gastrointestinal stromal tumors (GISTs) arise from pacemaker cells (interstitial cells of Cajal) of the small intestine and, based on mutations in the c-kit protooncogene region of the tyrosine kinase

gene, respond to imitinib (tyrosine kinase inhibitor) monoclonal antibody. Surgical resection remains the only curative method of treatment.

10 Melanoma is the most common extraintestinal malignancy with predilection to metastasize to the small bowel.

INTRODUCTION

The small bowel comprises about 75% of the entire length of the gastrointestinal tract and provides about 90% of its mucosal surface area. Small intestinal neoplasms represent less than 5% of the cancer affecting the entire gastrointestinal tract (**Table 51.1**).[1] The main types of malignancy include adenocarcinoma (40%), neuroendocrine (carcinoid), lymphoma (17%), and sarcoma (gastrointestinal stromal tumor [GIST]) (32%). [1] Several benign neoplasms such as lipomas, hamartomas, leiomyomas, and desmoid tumors are found in the small intestine. Recent large database queries have demonstrated that the most common malignancy is now neuroendocrine tumors (NETs) (6.98 per 100,000). Metastatic tumors to the small bowel are rare, but direct invasion and carcinomatosis tend to be the common presentation for nonprimary tumors. Operative treatment with extended resection is not possible with the small bowel. Treatment modalities and multidisciplinary approaches which do not rely on wide resection may offer improved survival.

EPIDEMIOLOGY

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program estimates that 10,590 new cases of small bowel cancer will be seen in 2019 with an estimated 1,590 deaths.[2] The incidence increased from 2007 to 2016 for small intestine cancer by 1.6% and mortality increased by 1.3%. At the same time cancer from all sites has decreased by 1.3 annual percent change and mortality dropped 1.5% (all races, both genders, age stratified). This may be due to an increased incidence of

neuroendocrine small intestine tumors to 1.05 per 100,000 in 2012. 2 This trend is occurring not only in the United States, but across the world. The same rising incidence is demonstrated in the United States in patients 65 years or older with proximal distribution of the neuorendocrine tumors (3.56 per 100,000 in gastropancreatic sites and 1.05 per 100,000 in small intestine).[3]

In the population below the age of 40, the incidence of small bowel neoplasms is low. The incidence for males and females is essentially the same. Sporadic, nonfamilial cancer occurs rarely in young patients.

PATHOGENESIS

The small intestine is the portion of the GI tract with the largest surface area, but has the lowest rate of cancer. Several factors have been identified as potential explanations: (1) The small bowel has liquid contents with an alkaline pH exposing the mucosa to a decrease in mechanical and chemical inflammation; (2) transit through the small bowel is rapid, thus shortening the time carcinogens are in contact with the mucosal surface; (3) there is a rapid turnover in epithelial cells in the mucosa outpacing the potential growth and development of neoplastic cells; (4) there is lower luminal bacterial load, particularly of anaerobes, which results in less total production of potential carcinogens; (5) the small bowel mucosa has an apparent enhanced ability to metabolize and/or detoxify certain dietary components or breakdown products that may be carcinogenic; and (6) the elaborate lymphoid tissue network surrounding the small bowel, and in particular, its ability to secrete immunoglobulin A, which might confer an increased immunologic-related tumor control (**Table 51.2**).[1]

Table 51.1 Small Intestinal Neoplasms

	Duodenum (%)	Jejunum (%)	Ileum (%)
Small bowel adenocarcinoma[1]	55–82	11–25	7–17
NETS[43]	11.4	6.3	49.9
Lymphoma[69]	6.5	25	65
Small intestine	4–5%	15%	15%

Small bowel adenocarcinoma is a molecularly unique intestinal cancer with a relatively high incidence of genomic alterations 3 predictive of response to targeted and immunotherapies. It has demonstrated distinct genomic differences compared with colorectal adenocarcinoma and gastric adenocarcinoma, including variations in the frequency and types of alterations of P53, KRAS, *APC, SMAD4, BRAF, ERBB2/HER2, EGFR, PIK3CA, ATM*, and a number of other genes (**Table 51.3**).[4] Small bowel adenocarcinoma has a higher percentage of microsatellite instability-high (MSI-H)/mismatch repair–deficient (dMMR) tumors compared with colorectal cancer.[5] Universal MMR or MSI testing is recommended in all patients with a personal history of small bowel adenocarcinoma to identify individuals with hereditary nonpolyposis colorectal cancer (HNPCC).

PREDISPOSITION TO SMALL BOWEL CANCER

There are several predisposing risk factors for development of small bowel cancers. These include genetic and environmental factors. The pathway to small bowel adenocarcinoma is the polyp–cancer pathway common to large intestinal cancer and as such the risk of small bowel adenocarcinoma is increased in all of the inherited polyposis syndromes (**Table 51.4**).

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) patients have hundreds, and even thousands, of adenomas in their gastrointestinal tract, and have a 100% transformation rate to colorectal cancer if untreated. Interestingly, the leading cause of death for patients with FAP is not the progression of colorectal cancer, due to the fact that most of the patients undergo a total colectomy. It is actually the malignant transformation of the periampullary adenoma to adenocarcinoma.[1]

Table 51.2 Protective Features of Small Intestine[1]

1. Liquid alkaline contents limit mechanical and chemical inflammation
2. Rapid transit to cecum (<1½ hrs)
3. Rapid turnover of epithelium
4. Lower bacterial load and less potential carcinogens
5. Epithelium detoxifies dietary components
6. Secreted IgA to give immunologic-related tumor control

Table 51.3 Mutational Complexity of Small Bowel Adenocarcinoma	
p53	58.4%
KRAS	53.6%
APC	26.8%
SMAD4	17.4%
PIK3CA	16.1%[a]
CDKN2A	14.5%
ERBB2	9.5%[a]
HER2	
BRAF	9.1%[a]
ATM	7.6%[a]
FBW7	6.9%[a]
ERBB3	6.3%[a]
NFI	6.0%[a]
MDM2	5.7%[a]
PTEN	5.7%[a]
CTNNB1	5.7%[a]

[a]Targetable genetic alterations.

Crohn Disease

Crohn disease is a significant risk factor for small bowel adenocarcinoma. The duration of disease, distal jejunal or ileal disease, early age of diagnosis, fistulizing-type disease, and male gender all contribute to a higher risk for development of small bowel adenocarcinoma.[7] The relative risk was reported as 33 (95% CI: 15.9–60.9).[8] The areas of the small intestine that are particularly susceptible are where long-standing inflammation has caused

stricture formation. In these areas, the tumor tends to occur after at least 10 years of inflammation (0.2% cumulative risk) and commonly contains signet-ring cell features similar to those found in colon cancer due to ulcerative colitis.[9]

Table 51.4 Genetic Syndromes Predisposing for Small Bowel Adenocarcinoma

Familial adenomatous polyposis (FAP)
Crohn disease
Celiac disease
Peutz–Jeghers syndrome
Lynch syndrome
Multiple endocrine neoplasia type I (MEN-1)
Von Hippel–Lindau syndrome
Neurofibromatosis—type I

Celiac Disease

There is an increased risk for small bowel lymphomas as well as small bowel adenocarcinoma in patients affected by celiac disease. Lymphomas tend to be both T-cell and non-Hodgkin lymphomas.[10] The relative risk for small bowel adenocarcinoma in patients with celiac disease has been estimated 10 to 13.[11,12]

Peutz–Jeghers Syndrome

This is an autosomal dominant syndrome characterized by hamartomatous polyps in the gastrointestinal tract and mucocutaneous melanin pigmentation. The increased risk of cancer is for breast, ovarian, testicular, pancreas, stomach, esophagus, and others. The mutation has been identified on the serine/threonine kinase 11 (STK 11) gene. Meta-analysis of Peutz–Jeghers

syndrome indicated a relative risk for small bowel cancer of 520 when compared to the general population.[13]

Lynch Syndrome

Lynch syndrome or HNPCC is an autosomal dominant gene that is associated with the mutation of mismatch repair genes. There is an increased risk to develop small bowel cancer with a relative risk of greater than 100 in carriers for the gene mutation.[14] Other affected organs include uterus, ovaries, and urothelium.

Other Familial Syndromes

Multiple endocrine neoplasia type 1 (MEN-1), von Hippel–Lindau syndrome, and neurofibromatosis type 1 all carry increased risk for developing NETs.[10]

Dietary and Lifestyle Predisposition

There are several indicators to the increased risk of developing small bowel cancer including cigarette smoking, increased BMI/obesity, red meat (saturated fats), low-fiber diet, and alcohol consumption (**Table 51.5**).[12,13]

CLINICAL PRESENTATION

4 The majority of small bowel tumors, whether benign or malignant, are typically asymptomatic and are encountered incidentally. The biggest factor relating to the way small bowel tumors present is the size and location within the small bowel. Generally, tumors less than 4 cm are asymptomatic. This is even truer with benign lesions. The most common presenting symptoms are weight loss (30% to 50%), nausea, vomiting, anemia, and abdominal pain.[12] Late detection of asymptomatic malignant tumors results in metastases in about 50% of patients at the time of diagnosis.[15] Ulceration, perforation (in cases of lymphoma), obstruction, and bleeding are other common presenting symptoms.[16] Intussusception or volvulus can occur rarely. NETs can present

as functional syndromes, such as "carcinoid syndrome" with flushing, diarrhea, and tachycardia with late valvular dysfunction due to fibrotic scarring induced by serotonin (**Table 51.6**).

Table 51.5 Modifiable Risk Factors for Small Bowel Adenocarcinoma

Diet (high fat, low fiber)
Alcohol
Smoking
Obesity
Biliary tract disease
Occupational exposure (organic solvents, nuclear waste)
Vitamin D deficiency
Sedentary lifestyle

From Barsouk A, Rawla P, Barsouk A, et al. Epidemiology of cancers of the small intestine: trends, risk factors, and prevention. *Med Sci (Basel)* 2019;7(3):46.

Table 51.6 Complications Resulting from Small Bowel Tumors

Complication	Details
Weight loss	30–50% of patients History and physical examination of the patient
Nausea/vomiting	Nonspecific finding
Obstruction	Include in differential for patients never undergoing an abdominal surgery Diagnosis made with radiographs or CT scan
Ulceration/bleeding	Commonly with lymphoma Mass can be seen on CT scan, but ulceration and bleeding found with capsule endoscopy or deep endoscopy
Perforation	Emergent surgical management May see free air on radiographs or CT scan
Metastasis	50% metastasis with incidence of malignant small bowel tumors at time of diagnosis

DIAGNOSIS

Examining the small bowel with accuracy is a difficult process. Upper and lower gastrointestinal endoscopy provides little information because of the limited access to the vast amount of mucosal surface. Colonoscopic intubation of the ileocecal valve is ideal but is not possible in about 5% to 10% of the patients.[17] Even with this intubation, only the most distal 25 cm of the terminal ileum can be surveyed. During upper endoscopy (EGD), the

duodenum is visualized in the proximal portion typically leaving the distal duodenum and the rest of the small bowel unevaluated. In certain cases, and with maximal effort, the endoscope can be advanced beyond the ligament of Treitz. However, the risk of duodenal injury increases due to pressure in the curve of the duodenum. Nevertheless, both of these procedures are indicated to begin the workup. The entire small bowel needs to be evaluated for a source of the symptoms. Endoscopic gastroduodenoscopy (EGD) with endoscopic ultrasound is recommended during initial workup and staging for detection and pathologic sampling when a duodenal malignancy is suspected. If obstruction is detected during imaging, palliative diversion or stenting may be considered.[6,18]

CAPSULE ENDOSCOPY

5 Capsule endoscopy (CE) uses a miniature camera introduced orally that is capable of producing images throughout the small bowel to depict its entire mucosal lining as the first-line method to evaluate the small bowel for a source of occult gastrointestinal bleeding (OGIB).

Generally, CE is safe and widely used as a diagnostic test.[19] The only contraindications to its use are patients having swallowing disorders or bowel obstruction, with the possibility of capsule retention. There is a 2% capsule retention rate in most series.[20] Other limitations to CE are that it is time consuming; there is no biopsy potential, and no therapeutic capability. The European Society of Gastrointestinal Endoscopy (ESGE) endorses CE for small bowel investigation in overt obscure gastrointestinal bleeding.[18]

A large meta-analysis completed by Triester et al.[21] demonstrated the incremental yield of CE over enteroscopy and small bowel barium radiography to be 35% and 59%, respectively. CE's ability to evaluate more mucosal surface area than other modalities yields a higher rate of lesion detection.[22] The 50,000 images must be manually reviewed.[23]

SMALL BOWEL ENTEROSCOPY

Device-assisted enteroscopy (DAE) (double-balloon enteroscopy [DBE], single-balloon enteroscopy [SBE], spiral enteroscopy [SE], and balloon-guided enteroscopy) utilizes a fixation point provided by the scope and the small bowel is brought to the viewing tip of the scope. Traditional endoscopy utilizes pushing the endoscope through the gastrointestinal tract which is impossible without external intraoperative manipulation of the bowel over the scope. The disadvantages of CE are difficulty with orientation, inability to biopsy, possible obstruction, and capsule retention.

DAE allows the operator to obtain biopsies and to perform therapeutic interventions. There are four methods for DAE available today.

Double-Balloon Enteroscopy

The double-balloon endoscope consists of a balloon at the tip of an endoscope that has a length of 140 cm. An overtube, also containing a balloon at the tip, fits over the scope to employ a push-and-pull technique.[24] This allows for examination of 240 to 360 cm. Scope diameters are 8.5 mm to 9.3 mm with working channels of 2.2 mm and 2.8 mm. The working channels allow for the therapeutic and diagnostic options provided by these systems.

Double-balloon enteroscopy has a diagnostic yield of 60% to 80% in patients with OGIB and other small bowel pathologies.[25] Success rates vary from 16% to 86%.[26] The complication rate overall is reported as 0.8% but can be higher while performing therapeutic procedures such as electrocautery for a GI bleed, polypectomy, or dilation. The main complications are pancreatitis, ileus, and perforation.[27–29]

Single-Balloon Enteroscopy

SBE uses a balloon on the overtube placed over the scope. The scope tip is hooked to hold the scope fixed to aid in the advancement of the overtube. The overtube is referred to as the splinting tube which has a hydrophilic coating that is activated with application of 30 mL of water. Radiopaque material is present at the tip to aid in the advancement with fluoroscopy.

Spiral Enteroscopy

SE provides potential benefits with regard to shorter procedure time. A raised spiral on the exterior of the scope pulls the small bowel over the scope as it advances. This scope is 118 cm in length and has a diameter of 9.8 mm. The raised spiral grooves are 16 mm high. Clockwise rotation of the scope will advance the scope and counterclockwise rotation will withdraw the scope. Studies for SE demonstrate shorter insertion depths with faster procedure times. There is variation in the insertion depth varying from 176 cm to 262 cm.[30,31] The complication rate is noted to be 0.3% with a perforation rate of 0.27%.[25] Overall, the device is simple to use with a learning curve of five cases.[25,32] The ESGE endorses DAE to confirm findings of CE and possible biopsy or treatment of identified lesions.[18]

Exploratory Laparoscopy for Small Bowel Neoplasms

The role of laparoscopy has improved the management of small bowel lesions over the last decades.[33,34] There are distinct advantages to laparoscopy. Direct visualization of the small bowel on the extraluminal side adds significant value to the management of small bowel tumors. Complete evaluation of the small bowel can be obtained laparoscopically by examining the entire small bowel in a systematic approach in order to visualize all aspects of the small bowel including the mesentery. In conjunction with endoluminal approaches, like small bowel enteroscopy, lesions can be located, biopsied, and if needed, resected.

Small bowel enteroscopy can tattoo the lesion to provide evidence of the lesion on the extraluminal side. This would also facilitate a sound oncologic resection of the tumor. Hand-assisted laparoscopy is also helpful if palpation is essential and a small incision is desired.

A laparoscopic case should be converted to an open technique if conditions prevent oncologically sound technique in order to provide the patient with the best outcome.

Imaging

A prospective study comparing computed tomography enterography (CTE) to magnetic resonance enterography (MRE) in 150 patients with suspected small bowel disease, but negative findings on endoscopy, reported that MR enterography was more accurate than CT enterography, particularly for neoplastic diseases.[35]

CTE and MRE have clinical value in small bowel examination and tumor detection. They can be used with video CE, sequentially or complementarily. DAE might be better employed for endoscopic treatment or biopsy after CE or MRE/CTE detection of a small bowel tumor.[36]

MANAGEMENT

Benign

Adenomas are benign lesions that have malignant potential and are most commonly seen in the periampullary region due to the exposure to bile.[37] The most common location is immediately distal to the papilla in the second portion of the duodenum.[38]

Hamartomas are benign vascular tumors with a low malignant potential and usually associated with Peutz–Jeghers syndrome.[16] Lipomas are encountered incidentally as a single mass. Hemangiomas are rare benign tumors in the small bowel that present as GI bleeding.

Operative management may be required to control symptoms of a benign small bowel lesion. Mass effect causing intussusception or obstruction, hemorrhage, or a questioned presence of malignancy generates the need for segmental resection of the lesion. The "diagnostic dilemma" is a common reason for resection of an incidentally found mass on contrast study or endoscopy. Hemangiomatous lesions can usually be managed with angiographic embolization. The use of angiographic isolation with intraoperative angiographic methylene blue injection can be very helpful to guide resection in a field of bleeding small bowel hemangiomas which cannot be embolized.

Malignant

Cancers of the small intestine account for 5% of all gastrointestinal cancer. Within the group of malignant tumors found in the small bowel, there are four main types. The most recent data from a single-institution tumor registry show that neuorendocrine tumors of the small bowel have surpassed the incidence for adenocarcinomas of the small bowel.[1] Small intestinal tumors include NETs (40%), adenocarcinomas (40%), lymphoma, GIST, and sarcoma account for the remaining 20%.

Neuroendocrine Tumors

Diagnostic techniques such as device-assisted and capsule enterography, CT and MRI enterography have increased the NET diagnosis rates and accuracy of staging.[39] The most dramatic rise in incidence of GI tumors was in patients 65 or older (3.56/100,000 gastropancreatic, 1.02/100,000 in small intestine) in a recent SEER program review.[3]

NETs arise from secretory cells, called enterochromaffin cells, which produce vasoactive substances. NETs, formerly known as carcinoid tumors, can be almost benign or very aggressive. The increased production of serotonin causes systemic effects such as diarrhea, flushing, bronchospasm, cutaneous vasomotor symptoms, and right heart valvular dysfunction (Carcinoid syndrome). Serotonin is derived from its precursor tryptophan, and when in circulation, it elicits particular symptoms. The liver inactivates serotonin, to make 5-hydroxyindoleacetic acid (5-HIAA) which is excreted by the kidney, and only tumors outside the portal vein drainage system will produce the carcinoid syndrome.[40]

Tumor size can elicit effects such as obstructive symptoms or abdominal pain especially if mesenteric implants and a desmoplastic, fibrotic scar causes retraction and eventual constriction of the vascular supply to the small intestine. Small intestinal NETs have increased in incidence over the last 40 years, likely due to improved imaging and endoscopic techniques (1.05 per 100,000). Most commonly these tumors metastasize to the liver, mesentery, and peritoneum.[41]

Metastasis of small bowel NETs is related to primary tumor size; tumors >2 cm versus tumors less than 1 cm, there was 12% 6 nodal metastasis and 5% distant metastasis.[42] The risk of metastases correlates with size, grade, site, and differentiation of the primary tumor. This is influenced by the early

invasion of bowel wall lymphatics and blockage of the lymphatics in the mesentery, forcing cells to flow retrograde into lymphatics along the bowel to produce nodal and distant metastases (**Table 51.7**).

Table 51.7 Prognostic Factors Influencing Overall Survival (OS) in NETs

Good Prognosis (OS)	Poor Prognosis (OS)
Localized to bowel	Distant Spread
30+ yrs	1 yr
Grade 1	Grade 4
16.2 yrs	0–1 yr
Rectum	Pancreas
25 yrs	3.6 yrs
Appendix	Small intestine
30 yrs	14 yrs
Well differentiated	Poorly differentiated
Size <1 cm	Size >2 cm

Table 51.8 Pathologic Classification of Neuroendocrine Tumors[40]

Pathologic Classification of Neuroendocrine Tumors		
Differentiation	**Grade**	**Criteria**
Well differentiated	Low (typical)	<2 mitoses/10 HPF and ≤2% Ki67 index
Intermediate (atypical)	2–20 mitoses/10 HPF or 3–20% Ki67 index	
Poorly differentiated	High	>20 mitoses/10 HPF or >20% Ki67 index

The mitotic rate and Ki-67 index are measured in order to provide the histologic grade of these tumors, which correlates closely with clinical behavior (**Table 51.8**). These measurements categorize the tumors into one of four categories by grade; low (1) to high (4). Grades 1 and 2 typically fall into the well-moderately differentiated category and grades 3 and 4 are considered poorly differentiated or anaplastic. Resection to maximally debulk the tumor, or maximize cytoreduction, is the only chance for cure in NETs, but peptide receptor radionuclide therapy which attaches indium, yttrium, or lutetium to octreotide to seek out somatostatin-binding tumor receptors may have a role in the future.[43]

A formal Tumor Nodes Metastasis (TNM) staging classification stratifies tumors into localized, locally advanced, and metastatic categories with associated 5-year survivals of 95%, 84%, and 51%, respectively (**Table 51.9**). The American Joint Committee on Cancer TNM staging system utilizes tumor size, depth of bowel wall invasion, regional nodes, and distant metastasis.[44]

Table 51.9 AJCC TNM Classification for Neuroendocrine Tumors of Lower Jejunum and Ileum

T-Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor invades mucosa or submucosa and size <1 cm
T2	Tumor invades muscularis propria or size >1 cm
T3	Tumor invades subserosa
T4	Tumor invades peritoneum/other organs
For any T, add (m) for multiple tumors	
N Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
M	Distant metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastases
M1	Distant metastasis

Table 51.10 5-Year Survival Rates by Neuroendocrine Tumor Location (1973–1997)[a]

Site	All Stages (%)	Local Stage (%)	Regional Stage (%)	Distant Stage (%)
Stomach	75.1/55.3	90.2/69.6	40.4/27.2	18.0/9.0
Small bowel	76.1/54.6	94.5/70.4	84.4/64.1	51.2/32.4
Appendix	76.3/65.0	95.6/87.8	80.0/67.6	37.5/26.8
Colon	69.5/41.8	94.1/77.1	72.5/35.3	27.8/4.1
Rectum	87.5/77.8	94.9/86.2	53.7/42.1	14.6/13.1

Survival rates are all age-adjusted to standard 2000 population.
[a]Cancer-specific survival/relative overall survival.
From Maggard MA, O'Connell JB. Updated population-based review of carcinoid tumors. *Ann Surg* 2004;240(1):117–122, with permission.

Several factors influence survival of NETs from small intestine, which has the best survival behind rectal NET and is similar to lung NET. Localized NETs in the small intestine have a median overall survival of 14 years. Distant spread from small intestine NETs reduced median overall survival to 5.83 years. Higher-grade NETs from the small intestine (grade 3 or 4 histology—poor or anaplastic differentiation) have median overall survival of 30 months. Survival has been improving over recent years (**Table 51.10**).[3]

Diagnosis of NETs

Generally, diagnosis is made based on radiographic findings in conjunction with tumor markers. There are three common radiographic modalities used to diagnose these tumors, which include CT scan and MRI enterography and octreotide scanning.

7 Three-phase CT should be used for optimal evaluation of vascular liver metastasis in patients with active serotonin-based symptoms.[45]

NETs often express somatostatin receptors rendering them detectable by imaging with radiolabeled octreotide or SRS (somatostatin receptor scintigraphy). Five subtypes of somatostatin receptors have been identified and the somatostatin analogs from the octreotide scan bind with subtypes 2 and 5 which are present in 70% to 90% of NETs.[46] Single-photon emission computed tomography (SPECT) can enhance the detection of pathologic and

physiologic uptake in the abdomen. This is a full-body scan that enables visualization of somatostatin uptake throughout the entire body.

Positron emission tomography with use of functional radiotracers provides higher spatial resolution than the octreotide scanning and detects smaller lesions than other scanning methods. Octreotide, metaiodobenzylguanidine (MIBG), and positron emission tomography (PET) scanning are used for follow-up of patients and staging of patients for distant disease when planning aggressive, multiorgan resections. Serum levels of chromogranin A is a sensitive indicator of NET 8 persistence when the NET was found to produce chromogranin A. Because of false positives in non-NET settings, it is not appropriate for screening.[40,47,48]

Surgical excision of the primary tumor and local node metastasis is still the only curative therapy for these patients.[49] Several management options are available once any functional disorder is controlled. These include close surveillance of indolent tumors, radiofrequency ablation (RFA) therapy for liver metastases, systemic therapy with somatostatin analogs, interferon, or cytotoxic or molecular targeted therapies. These have never been compared in a controlled trial, making these therapies highly individualized based on underlying symptomatology.

Surgical management with complete resection and the use of RFA for liver disease still provide the best survival benefit for patients with advanced NET.[50,51] Debulking procedures have been shown to be effective in improving symptoms with greater than 90% resection.[50] A two-step approach for radical resection to achieve complete resection has been shown to be effective.[52] Recurrence rates can be as high as 81%.[53] Transarterial chemoembolization (TACE) has been shown to be highly effective against nonresectable diffuse liver lesions to reduce symptoms.[51]

Medical management of NET includes a wide variety of agents including somatostatin analogs (octreotide) and peptide receptor radionucleotide therapy (PRRT), chemotherapeutic agents (doxorubicin–streptozotocin, dacarbazine, temozolomide, oxaliplatin, or interferon), monoclonal antibody therapy (bevacizumab), mTOR inhibitors (temsirolimus and everolimus), and multikinase inhibitors (sunitinib, sorafenib, and pazopanib).[3]

A combination of both medical and surgical management is outlined in **Algorithm 51.1**.

Since NETs can develop in all areas of the intestine, surveillance with endoscopy is important. Scanning with CT/MRI of the liver can guide reexploration and resection. Octreotide scanning, MIBG, or PET scanning can be helpful in controversial cases of possible metastases.

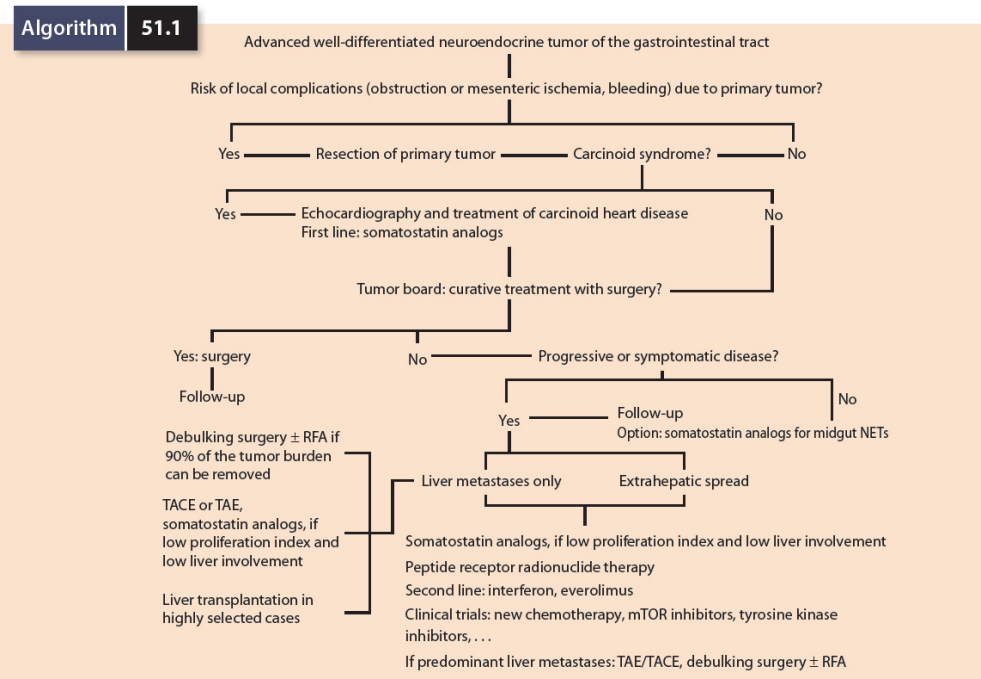
Small Bowel Adenocarcinoma

Small bowel adenocarcinomas represent the second-most common cancer of the small bowel with an incidence of 7.3 cases per million worldwide.[54,55] Small bowel adenocarcinoma, along with colorectal cancer, is more common in developed countries, and has higher incidence rates in North America and Western Europe.[56] Black populations have an age-adjusted incidence rate of about twice the rate of white individuals, and the Hispanic population follows. The lowest incidence is in the Asian/Pacific Islander population.[57]

Small bowel adenocarcinomas, which comprise an estimated 30 to 40% of small bowel cancer diagnoses, have until recently lacked many established guidelines for management. A French intergroup recently published 2018 clinical practice guidelines.[58]

Presentation for small bowel adenocarcinoma is very nonspecific with the most common symptom on presentation being abdominal pain (45% to 76%).[55] Other common symptoms include nausea and vomiting, weight loss, fatigue and anemia, and GI bleeding.[59,60] Interestingly, with the indolent presentation of these cancers, patients can recall symptoms for long periods of time prior to diagnosis. Talamonti et al. were able to identify a mean duration of symptoms at presentation for 10 months, reflecting the need for a high index of suspicion.[60]

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) are elevated in only about 30% to 40% of patients.[61] Radiologic and endoscopic modalities provide the best method for detecting small bowel adenocarcinoma but often fail to make a diagnosis given the nonspecific nature of the presenting symptoms.



Algorithm 51.1 Management algorithm for patients with advanced neuroendocrine tumors (NETs) of the gastrointestinal tract. mTOR, mammalian target of rapamycin; PPI, proton pump inhibitor; RFA, radiofrequency ablation; TAE, transarterial embolization. (Walter T, Brixi-Benmansour H, Lombard-Bohas C, et al. New treatment strategies in advanced neuroendocrine tumours. *Dig Liver Dis* 2012;44(2):95–105.)

Upper GI swallow study with small bowel follow-through or enteroclysis are unable to assess extraluminal spread. CT enterography has 84.7% sensitivity rate for detecting small bowel tumors and a specificity of 96.9%.[62] MRE has a sensitivity of 91% and a specificity of 95%.[63]

Endoscopic evaluation with DAE plays an important role in detecting small bowel adenocarcinomas when the symptom is anemia.

Prognosis after treatment is directly related to the tumor staging.[59] Poor differentiation, positive margins after resection, duodenal location, male gender, elderly age, and black ethnicity all drive poor prognosis.[55] Lymph node harvest at the time of surgery should yield 8 or 10 or more nodes for accurate assessment.[64,65] Patients can be staged (**Table 51.11**) and their disease-specific survival rates can be assessed based on the tumor site (**Fig. 51.1**) and change based on the number of lymph nodes examined (**Fig. 51.2**) and the number of positive lymph nodes (**Fig. 51.3**).

Longer survival after resection is strongly associated with a lower ratio of positive-to-negative lymph nodes as well as with a higher number of regional

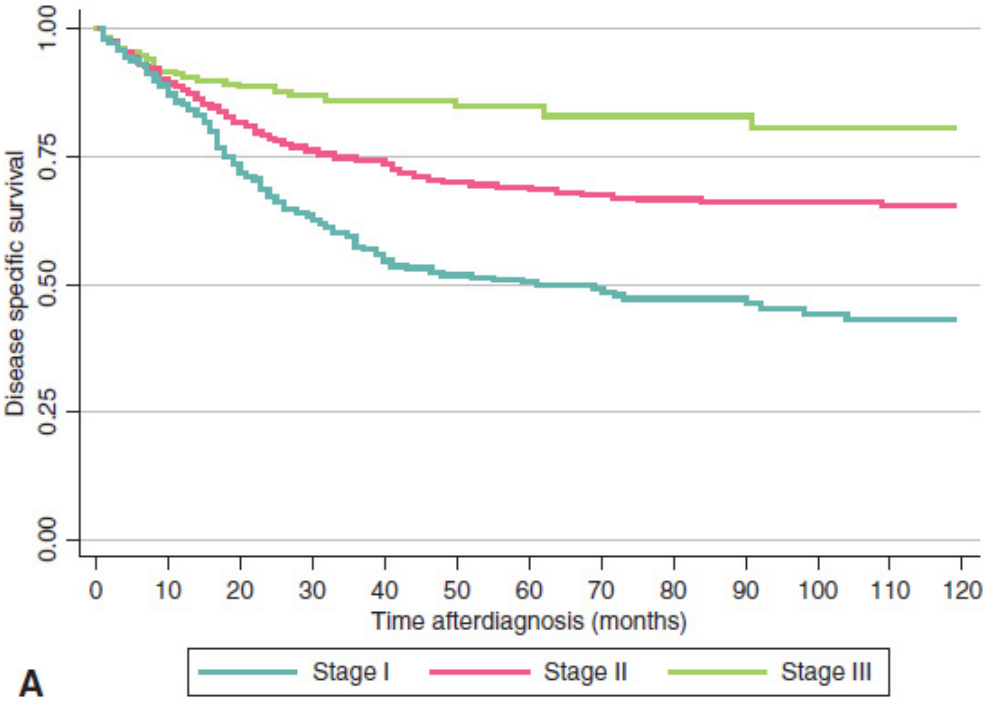
lymph nodes assessed during surgery.[65–68] Two of these analyses, which considered duodenal and jejunoileal adenocarcinomas separately, concluded that, for adequate staging, a minimum of five lymph nodes should be retrieved for duodenal tumors and a minimum of nine lymph nodes for jejunal or ileal tumors.[67,68] Based on these studies, a goal for all small bowel adenocarcinoma resections should be the removal of at least eight regional lymph nodes for evaluation.

Table 51.11 Disease-Specific Survival for Small Bowel Adenocarcinoma According to Disease Stage, Total Number of Lymph Nodes Assessed, and Total Number of Positive Lymph Nodes[65]

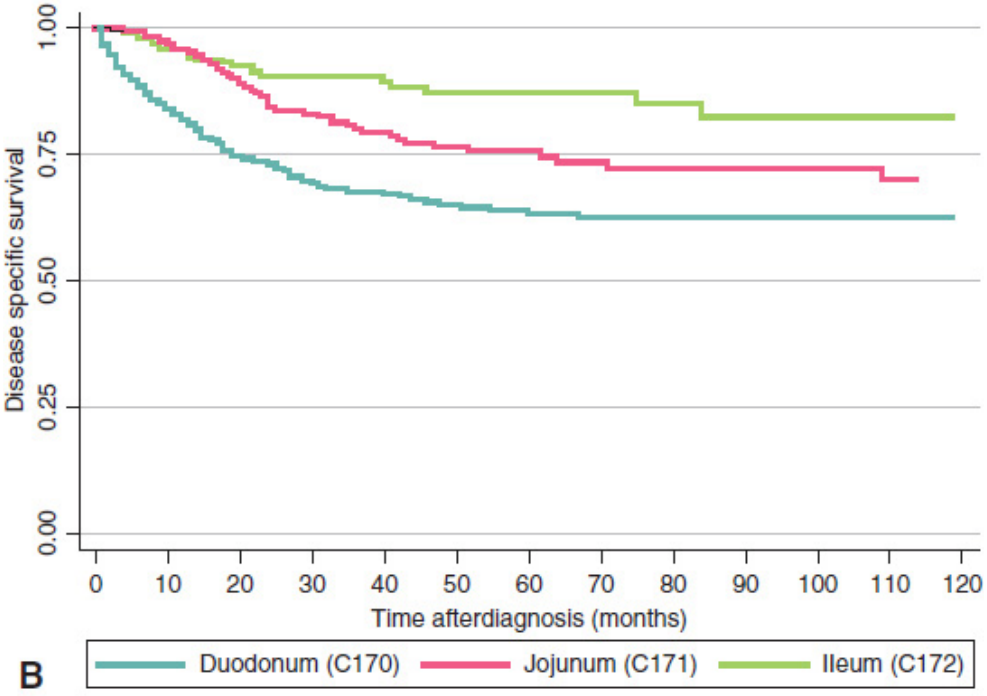
	%Cumulative 5 year DSS		
No. of Lymph Nodes	**Stage I**	**Stage II**	**Stage III**
TLN			
0	70	44	
1–7	93	69	43
>7	95	83	56
PLN			
<3			58
>3			37
LNR[a]			
T1 (0.02–0.2)			63
T2 (0.21–0.5)			53
T3 (0.52–1)			30

[a]Stratified by tertiles.

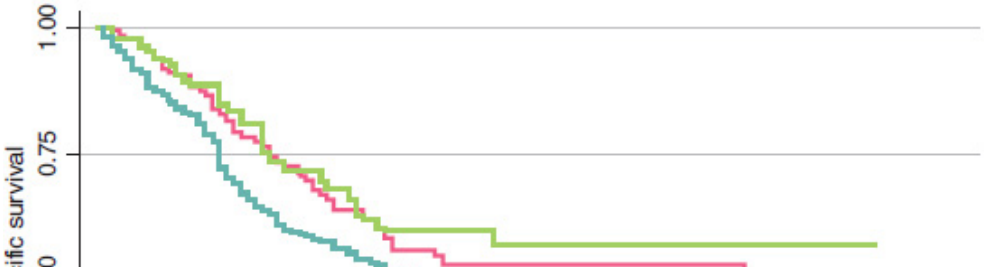
DSS, disease-specific survival; TLN, total number of lymph nodes assessed; PLN, total number of positive lymph nodes; LNR, lymph node ratio.


Disease specific survival
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
70
80
90
100
110
120
Time afterdiagnosis (months)
Stage I
Stage II
Stage III

A


Disease specific survival
1.00
0.75
0.50
0.25
0.00
0
10
20
30
40
50
60
70
80
90
100
110
120
Time afterdiagnosis (months)
Duodonum (C170)
Jojunum (C171)
Ileum (C172)

B


1.00
0.75

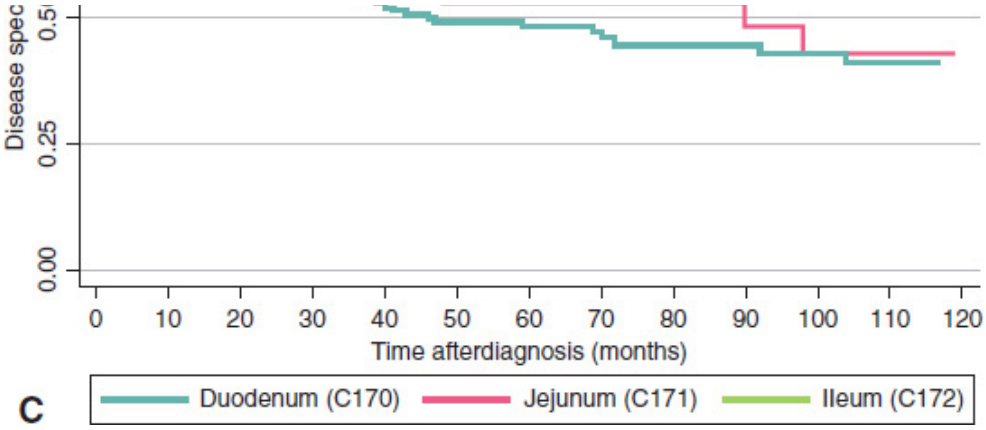
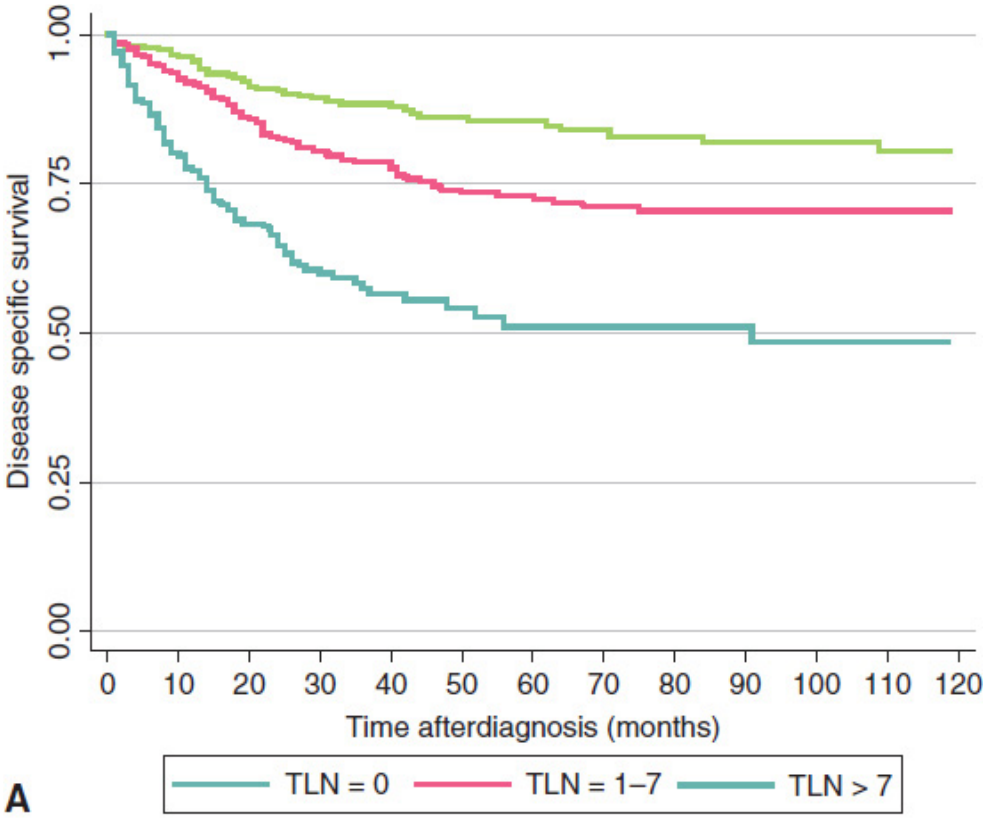
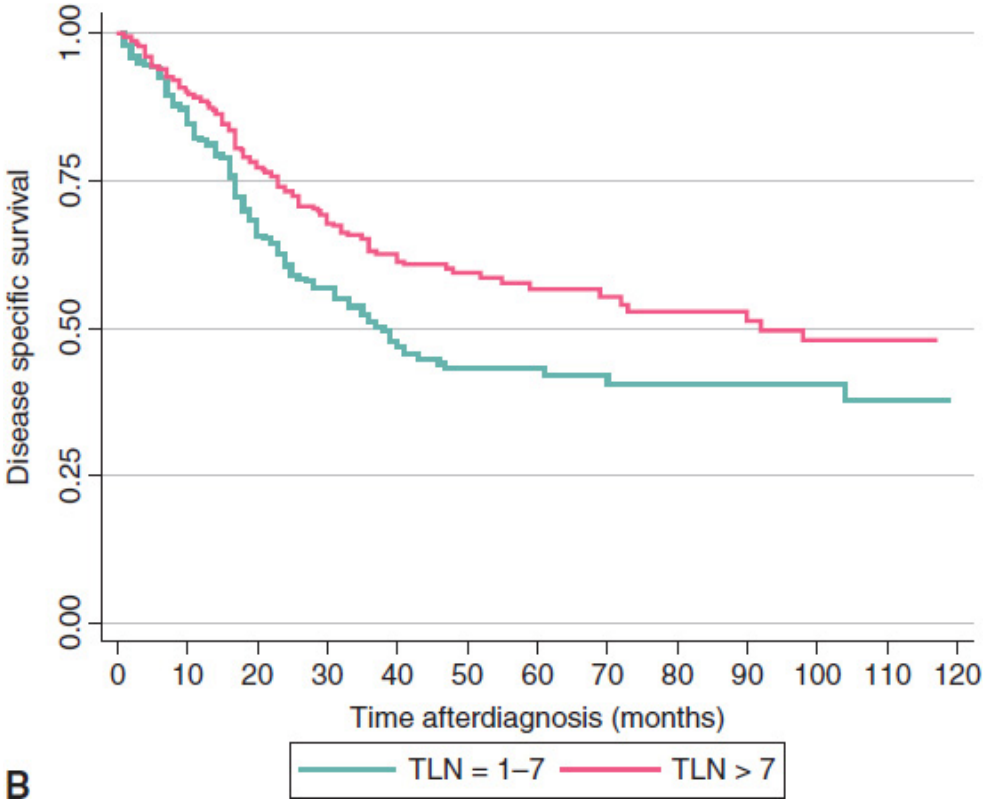


Figure 51.1 These Kaplan–Meier curves illustrate disease-specific survival for small bowel adenocarcinoma stratified by (**A**) disease stage, (**B**) subsite in the small bowel for stage I and II diseases, and (**C**) subsite in the small bowel for stage III disease. Codes for the duodenum (C17.0), jejunum, (C17.1), and ileum (C17.2) are from the International Classification of Diseases for Oncology and Related Health Problems, 10th Revision. (Overman MJ, Hu CY, Wolff RA, et al. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the surveillance, epidemiology, and end results database. *Cancer* 2010;116(23):5374–5382.)

Surgical management is the mainstay of therapy for small bowel adenocarcinoma with locoregional disease.[55] It has been known for almost two decades that resection of duodenal adenocarcinomas yields a 56% survival at 5 years with complete surgical resection and 0% survival at 5 years without resection.[69] Duodenal adenocarcinomas can be managed with pancreaticoduodenectomy or with segmental resection for the distal third and fourth portions for resectable tumors. Nodal involvement should prompt adjuvant therapy, but otherwise observation is sufficient (**Algorithm 51.2**). Jejunal and ileal adenocarcinomas should be managed with similar principles of segmental resection and regional lymph node dissection, with a right hemicolectomy for tumors involving the distal ileum.[55]


Disease specific survival
0.00
0.25
0.50
0.75
1.00
0
10
20
30
40
50
60
70
80
90
100
110
120
Time afterdiagnosis (months)
TLN = 0
TLN = 1–7
TLN > 7

A


Disease specific survival
0.00
0.25
0.50
0.75
1.00
0
10
20
30
40
50
60
70
80
90
100
110
120
Time afterdiagnosis (months)
TLN = 1–7
TLN > 7

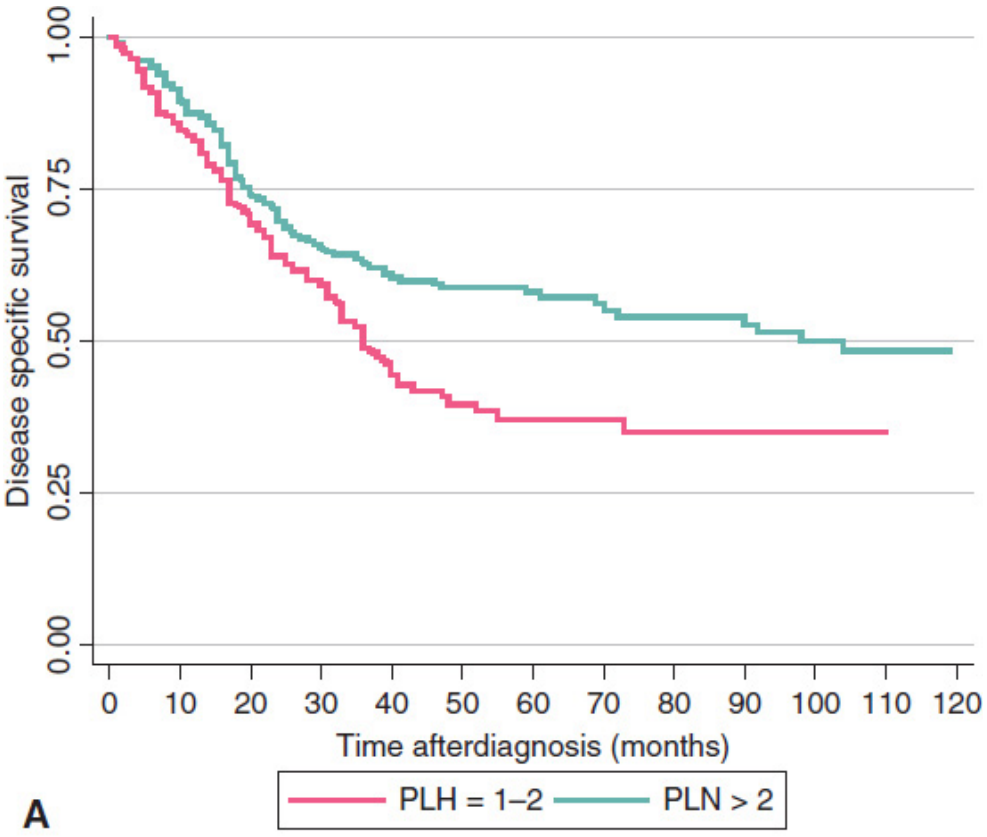
B

Figure 51.2 These Kaplan–Meier curves illustrate disease-specific survival for small bowel adenocarcinoma stratified by (**A**) the total number of lymph nodes assessed (TLN) in patients with stage I and II diseases and (**B**) the TLNs assessed in patients with stage III disease. (Overman MJ, Hu CY, Wolff RA, et al. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the surveillance, epidemiology, and end results database. *Cancer* 2010;116(23):5374–5382.)

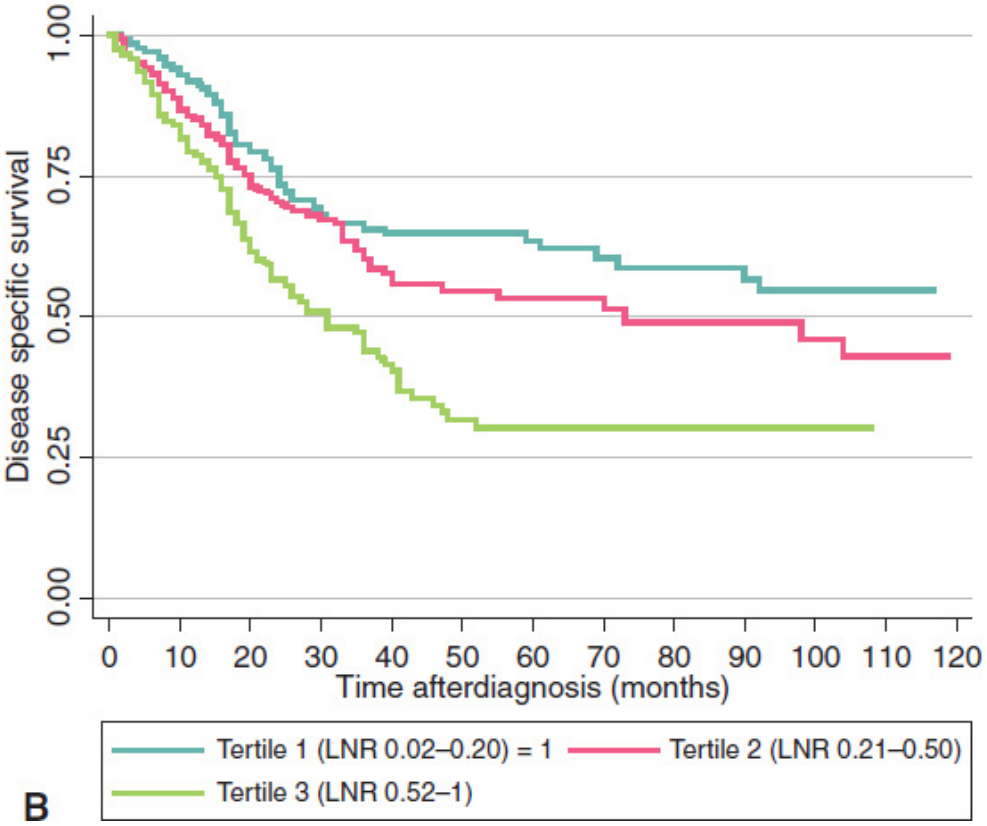
Adjuvant and Neoadjuvant Therapy

Adjuvant therapy is aimed toward controlling recurrence of adenocarcinoma at distant sites. Distant recurrence predominates over locoregional recurrence for duodenal adenocarcinomas.[55] After pancreaticoduodenectomy for duodenal adenocarcinoma, the first site of recurrence was predominantly distant (59%) followed locoregional (19%) or both (22%).[70] Adjuvant therapies involve 5-fluorouracil/capecitabine, FOLFOX/CAPOX, FOLFIRI, or gemcitabine.

The ongoing international phase III BALL Trial (or 5-FU/LV plus oxaliplatin (FOLFOX) compared with observation alone) for patients with stage I–III small bowel adenocarcinoma will determine the usefulness of adjuvant chemotherapy for local regional disease.[6,71,72]


Disease specific survival
0.00
0.25
0.50
0.75
1.00
0
10
20
30
40
50
60
70
80
90
100
110
120
Time afterdiagnosis (months)
PLH = 1–2
PLN > 2

A


Disease specific survival
0.00
0.25
0.50
0.75
1.00
0
10
20
30
40
50
60
70
80
90
100
110
120
Time afterdiagnosis (months)
Tertile 1 (LNR 0.02–0.20) = 1
Tertile 2 (LNR 0.21–0.50)
Tertile 3 (LNR 0.52–1)

B

Figure 51.3 These Kaplan–Meier curves illustrate disease-specific survival for small bowel adenocarcinoma stratified by (**A**) the number of positive lymph nodes (PLN) and (**B**) the lymph node ratio (LNR) in tertiles. (Overman MJ, Hu CY, Wolff RA, et al. Prognostic value of lymph node evaluation in small bowel adenocarcinoma: analysis of the surveillance, epidemiology, and end results database. *Cancer* 2010;116(23):5374–5382.)

Microsatellite instability/mismatch repair (MSI/MMR) is an important piece of information to consider when deciding whether to use adjuvant chemotherapy in patients with stage II small bowel adenocarcinoma.[6,73] Tumors related to Lynch syndrome with high MSI do not respond to 5-fluorouracil–based chemotherapy.

For some patients with locally unresectable or medically inoperable small bowel adenocarcinomas, conversion to resectable disease may be a goal.[6] A retrospective study of patients with unresectable or recurrent duodenal adenocarcinoma who were treated with neoadjuvant chemotherapy or chemoradiation found that 9 of 10 patients showed conversion to resectable disease after neoadjuvant therapy.[74] Based on these data, patients with locally unresectable or medically inoperable small bowel adenocarcinoma may undergo neoadjuvant therapy, during which they should be routinely monitored for conversion to resectable disease.

Lymphoma

Lymphomas account for about 15% to 20% of small intestine neoplasms.[15] SEER database analysis from 1975 to 2003 shows a distribution of 60% to 65% in the ileum, followed by 20% to 25% in the jejunum, and 6% to 8% in the duodenum (**Table 51.1**).[75] Secondary lymphoma is much more common than primary lymphoma because the gastrointestinal tract is the most common site for extranodal disease.[16]

The typical clinical presentation of small bowel lymphoma is nausea, vomiting, abdominal pain, anemia, and weight loss. Severe symptoms such as obstruction, intussusceptions, or perforation are rare.[15]

The most common intestinal lymphoma is diffuse large B-cell lymphoma. Despite the incidence of lymphoma in the small intestine, surgery is typically not the method for management. These patients should undergo resection in situations of obstruction or bleeding, and should still receive chemotherapy.[15] Immunoproliferative small intestinal disease (IPSID) occurs

in patients who are chronically immunosuppressed, as a result of infection by *Helicobacter pylori* and *Campylobacter jejuni*. Antibiotic therapy for these bacteria usually results in regression of immunoproliferative small intestinal disease. Most of these patients relapse and will need radiation and chemotherapy with nutritional support.[76,77]

Gastrointestinal Stromal Tumor

GISTs are the most common mesenchymal tumors of the small bowel. GISTs are found in the stomach (60% to 70%), small intestine (20% to 30%), and in the duodenum (4% to 5%).[78] GISTs are known to arise from the interstitial cells of Cajal, which are described as the gastrointestinal pacemakers.[79] Hirota et al. recognized the c-kit protooncogene which codes for a tyrosine kinase inhibitor, as the genetic mutation leading to GISTs.[80]

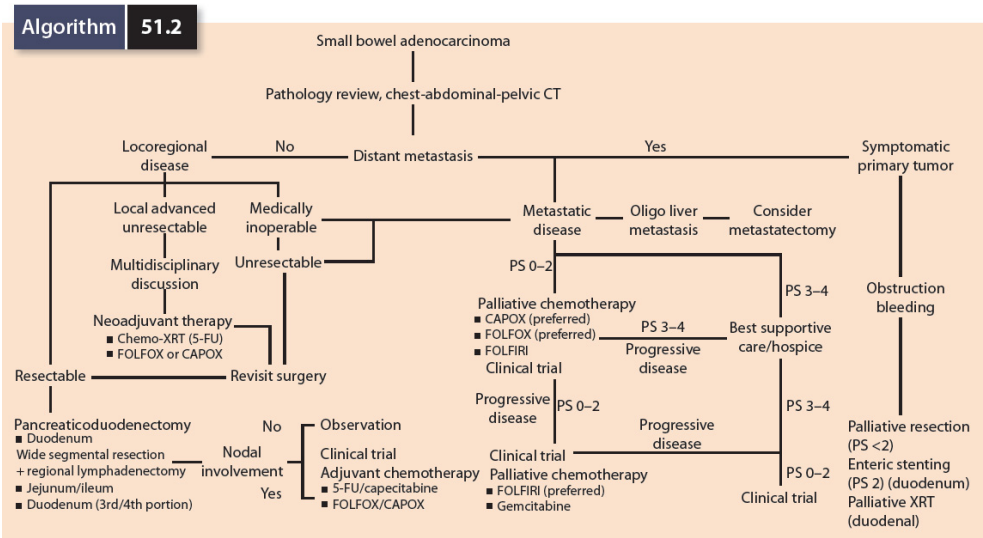
GIST is unique with regard to the submucosal origin and its likelihood to grow in size away from the lumen of the small bowel. This makes it difficult to make a diagnosis with intraluminal biopsy. Bümming demonstrated that only one-third of diagnoses are made with biopsies, and that the most common method of detection was endoscopy and CT scan.[81] Patients with GISTs present with vague abdominal symptoms, pain, GI bleeding from a mucosal erosion, or an abdominal mass.[82]

9 GISTs do not have the malignant pattern predicted in other types of cancers based on histopathology alone. Several factors influence malignant behavior including tumor size, mitotic rate, tumor location, kinase mutational status, and occurrence of tumor rupture. Mitotic rate and tumor size are the most commonly acceptable indices for prognosis.[78]

Complete surgical resection remains the only method for curative treatment, and simple negative margins are needed, as wide margins have not shown significant benefit. Small segmental resection of the small bowel is adequate because GISTs rarely metastasize to lymph nodes. Lymph node dissection is not warranted. En bloc resection should be done for locally advanced GISTs. Overall 5-year survival rate for patients with complete resection of GISTs is 50% to 65%.[78–84]

Patients have a defined risk for recurrence and may benefit from adjuvant therapy. The Modified NIH–Fletcher GIST Risk Assessment Criteria is presented in **Table 51.12**. Other risk assessment tools are available such as

Armed Forces Institute of Pathology Classification and the Memorial Sloan-Kettering Cancer Center Prognostic Nomogram. Adjuvant therapy utilizes imatinib (Gleevec). This drug is used in the treatment algorithms for patients with advanced or metastatic GIST (**Algorithm 51.3A**) or with resectable GIST (**Algorithm 51.3B**). Imatinib is a competitive inhibitor for multiple tyrosine kinase inhibitors and was originally recommended for chronic myelogenous leukemia treatment. It became first-line adjuvant treatment for GIST once it was recognized to disrupt the KIT oncogene in GISTs.[85] Shortly after that, imatinib was approved for use in unresectable or metastatic disease shown in **Algorithm 51.3A**.[86,87] Imatinib adjuvant therapy yields 98% 5-year recurrence-free survival.[88] The management of GISTs benefits from a standard algorithm.[89]



Algorithm 51.2 Algorithm showing the management of patients with small bowel adenocarcinomas. The treatment strategy depends on disease stage and involves en bloc resection for locoregional disease and systemic chemotherapy for metastatic disease. All current recommendations are based on case series, retrospective reviews, or nonrandomized prospective trials because of an absence of any randomized data. 5-FU, 5-fluorouracil; CAPOX, capecitabine and oxaliplatin; FOLFIRI, 5-FU, leucovorin and irinotecan; FOLFOX, 5-FU, leucovorin and oxaliplatin; KRAS-WT, *KRAS* wild-type; PS, performance status; XRT, radiation therapy. (Elias D, Lefevre JH, Duvillard P, et al. Hepatic metastases from neuroendocrine tumors with a "thin slice" pathological examination: they are many more than you think. *Ann Surg* 2010;251(2):307–310.)

METASTATIC TUMORS TO THE SMALL BOWEL

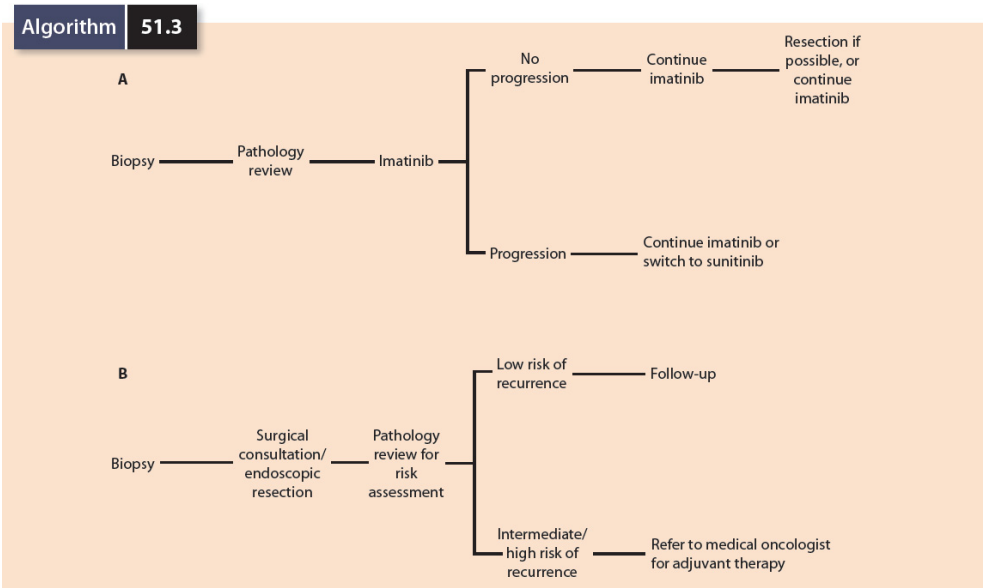
Metastasis to the small bowel occurs in two different ways, either from distant spread or direct invasion from a nearby organ malignancy. The most common extra-abdominal metastases are from breast cancer and melanoma. Melanoma is the most common extraintestinal malignancy with predilection to metastasize to the small bowel (**Fig. 51.4**).[90] 10 Patients with metastatic melanoma to the small bowel often present with other extraintestinal metastasis.[91] Primary tumors of intraperitoneal organs such as colon, ovary, uterus, and stomach metastasize to the small bowel.[84]

Patients with small bowel metastasis are usually offered palliative systemic chemotherapy. Other palliative measures can be considered on a case-by-case basis including surgical resection, internal bypass, or usage of an endoscopically placed stent.[9]

Table 51.12 Modified NIH–Fletcher GIST Risk Assessment Criteria

Risk Category	Tumor Size (cm)	Mitotic Index (/50 HPF)	Primary Tumor Site
Very low risk	<2.0	≤5	Any
Low risk	2.1–5.0	≤5	Any
Intermediate risk	2.1–5.0	>5	Gastric
	<5.0	6–10	Any
	5.1–10.0	≤5	Gastric
High risk	Any	Any	Tumor rupture
	>10	Any	Any
	Any	>1G	Any
	>5.0	>5	Any
	2.1–5.0	>5	Nongastric
	5.1–10.0	≤5	Nongastric

GIST, gastrointestinal stromal tumor; HPF, high-power field.



Algorithm 51.3 Treatment algorithms for patients with (**A**) advanced/metastatic GIST and (**B**) resectable GIST. GIST indicates gastrointestinal stromal tumor. (Mullady DK, Tan BR. A multidisciplinary approach to the diagnosis and treatment of gastrointestinal stromal tumor. *J Clin Gastroenterol* 2013;47(7):578–585.)

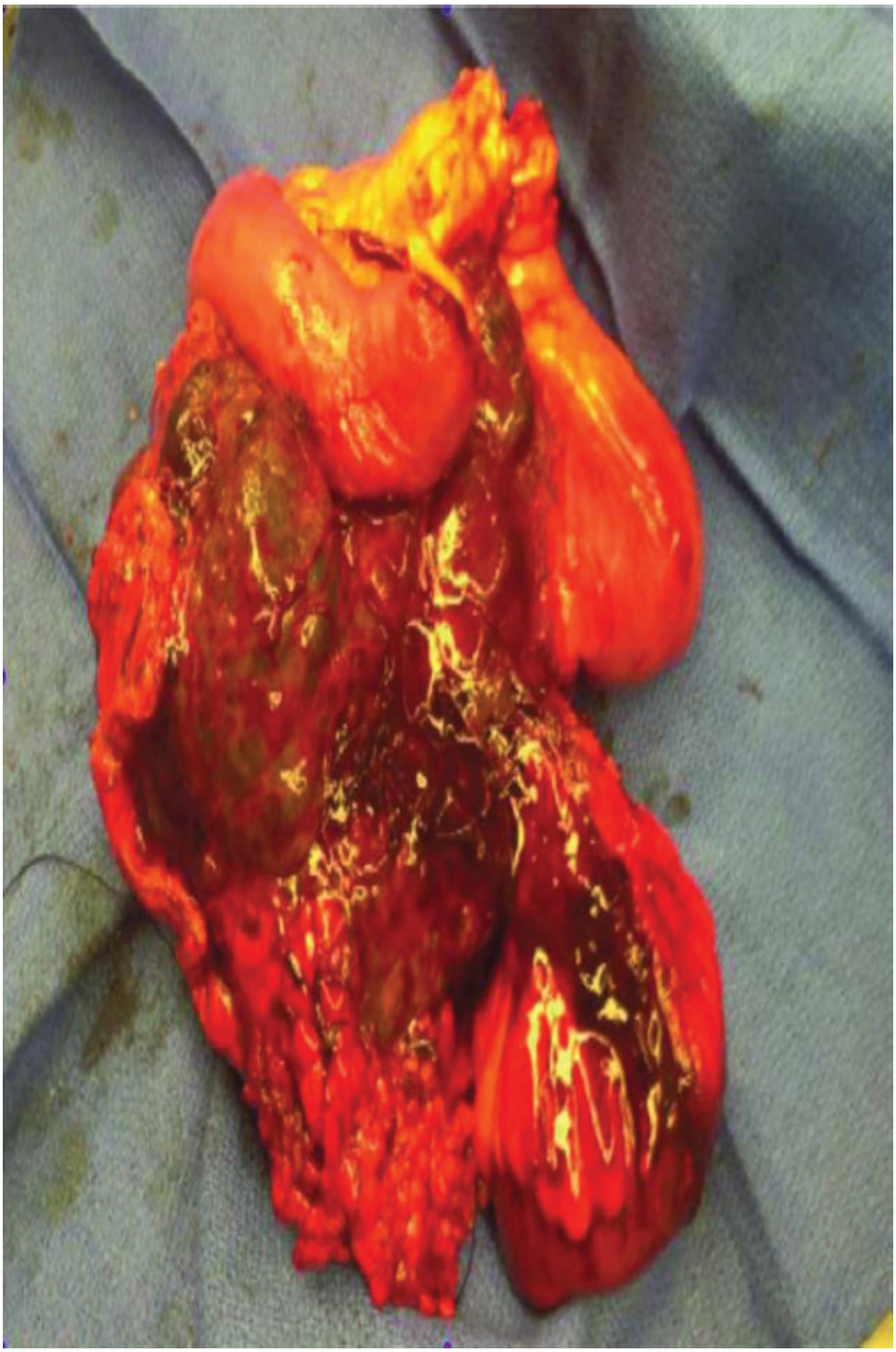


Figure 51.4 Metastatic melanoma to small bowel resecting en bloc.

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Section G: PANCREAS

52

Pancreas Anatomy and Physiology

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Key Points

1. The pancreas is an endocrine and exocrine organ which lies in the retroperitoneum whose primary functions are to regulate carbohydrate metabolism and secrete enzymes to aid in digestion.
2. Its head lies in the second and third portions of the duodenum, its body lies behind the stomach and its tail terminates in the hilum of the spleen. It abuts several highly critical organs and blood vessels along its course.
3. Embryologically, the pancreas is derived from a ventral and dorsal bud which rotate with the duodenum and fuse together to create a single gland. Abnormal rotation or fusion can lead to variant pancreatic anatomy including pancreatic divisum and annular pancreas.
4. The exocrine pancreas makes up 90% of the mass of the gland, and can primarily be divided into the central acinus, which secrete fluid and enzymes for digestion, and the ductal network through which the enzymes are flushed into the duodenum.
5. The central acinus is made up of acinar cells which produce and secrete enzymes, and the centroacinar and terminal duct cells which secrete sodium bicarbonate solution.
6. The endocrine pancreas makes up 1% to 2% of the pancreatic mass but accounts for 15% of its blood flow. Its main functional unit is the islets of Langerhans which are composed of a multitude of cells including α (alpha) cells which secrete glucagon, β (beta) cells which secrete insulin, and δ (delta) cells which secrete somatostatin.
7. Insulin and glucagon act opposite one another to maintain glucose homeostasis, with insulin-increasing glucose uptake by cells and glucagon-stimulating gluconeogenesis and glycogenolysis from the liver. Somatostatin acts on both α and β cells and slows intestinal transit.
8. The superior mesenteric artery runs behind the neck of the pancreas, as does the superior mesenteric vein, which joins the splenic vein behind the pancreatic neck to form the portal vein. Understanding this anatomy, as well as the multiple variants that exist, is crucial for all who operate in the abdomen and retroperitoneum.

INTRODUCTION

- The 1 pancreas is a soft, tan-colored organ which is found in the retroperitoneum, and has two main functions: the regulation of serum glucose and the production of pancreatic enzymes 2 critical for digestion. It lies in close proximity to a multitude of upper abdominal organs and major vasculature, making the understanding of its anatomy of utmost importance to the surgeon.
- The pancreas is considered an upper gastrointestinal organ that acts in an exocrine, paracrine, and endocrine capacity.[1,2] The exocrine portion of the gland is comprised of acinar and ductal cells and accounts for up to 95% of the mass of the pancreas. The function of these cells is to produce and secrete an array of enzymes which are essential for absorption of nutrients in the small intestine. The endocrine function of the pancreas is carried out by the islets of Langerhans, which are distinct groupings of endocrine cells found throughout the pancreas. As opposed to the exocrine portion of the gland, these cells make up less than 1% of pancreatic tissue. However, despite their diminutive volume they receive nearly 15% of pancreatic blood flow, which substantiates their importance.[3] These cells secrete a variety of hormones, most notably insulin, glucagon, and somatostatin, in order to regulate carbohydrate metabolism.[1,4] These endocrine hormones act not only systemically, but upon the islets themselves in a paracrine fashion as well, in order to maintain a relatively consistent serum glucose.[2] The sequelae of insult to the pancreas, whether it be surgical, traumatic, acute or chronic disease, can be devastating to the patient, and therefore a thorough understanding of pancreas physiology is paramount.

EMBRYOLOGY OF THE PANCREAS

- The pancreas develops from two distinct primordia: the dorsal 3 and ventral pancreatic buds. These are derived from the endoderm and form at the junction of the foregut and midgut at the septum transversum. The majority of the pancreas arises from the dorsal bud, to eventually include the superior aspect of the head, the neck, the body, and the tail of the pancreas. The remainder of the head of the pancreas and the uncinate process derive from the ventral bud, which arises laterally beside the growing biliary tract. As the duodenum matures and rotates, the ventral bud follows, rotating clockwise to fuse with the dorsal bud. At the junction of the ventral and dorsal buds of the pancreas, the ducts of each bud fuse, and the duct which lies in the distal and main body of the dorsal bud empties via the ventral duct through the ampulla of Vater (major papilla) and into the duodenum. The remaining proximal duct of the dorsal bud empties directly into the duodenum more proximally, via the minor papilla (**Fig. 52.1**). The main pancreatic duct is known as the duct of Wirsung, while the minor pancreatic duct is known as the duct of Santorini.

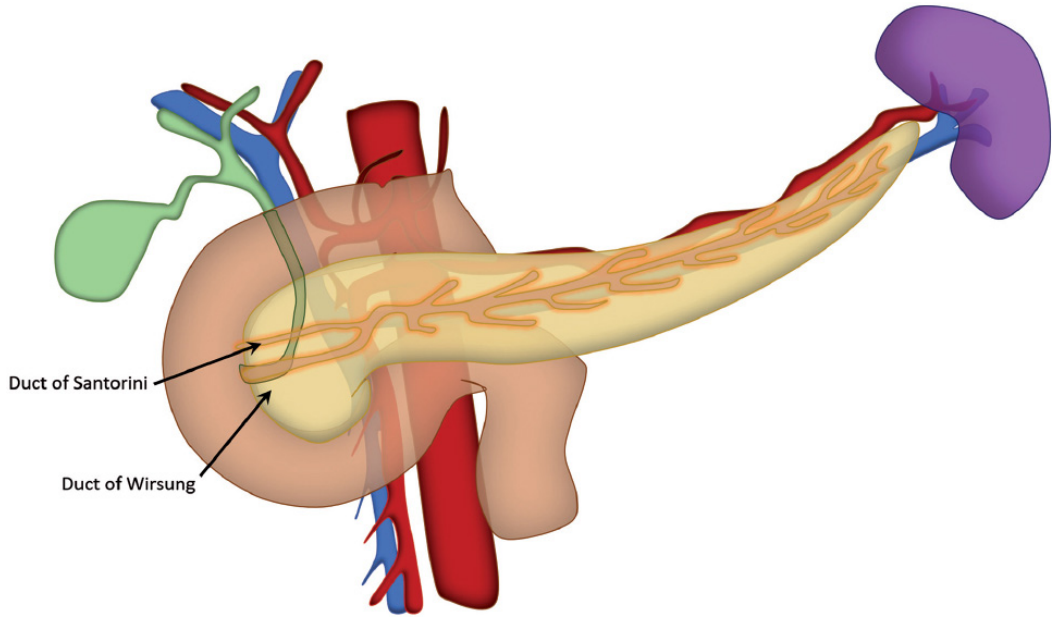

Figure 52.1 Pictorial demonstration of normal pancreatic ductal anatomy.

- While it is not clearly understood what roles the endocrine cells have in early development, endocrine function can be measured as early as 10 weeks of gestation. Glucagon-producing α cells differentiate first, followed by δ cells (somatostatin) and β cells (insulin).

VARIANT EMBRYOLOGIC ANATOMY

- The variants in anatomy that come with improper embryologic development may occur in up to 30% of patients, however, most are inconsequential.

Pancreas Divisum

- When there is incomplete fusion of the ventral and dorsal pancreatic buds, the intrapancreatic ducts also fail to fuse, leading to drainage of the main pancreatic (dorsal) duct through the minor papilla. Pancreatic divisum, as it is called, occurs in less than 5% of patients,[5] and only about 5% of those affected will develop symptoms. There are three types of pancreatic divisum. The first type (type 1) is the most common and occurs when there is complete separation between the dorsal and ventral pancreatic ducts. Type 2 (absent ventral pancreatic duct) and type 3 (small communication between dorsal and ventral pancreatic ducts) are far more rare, and of little clinical significance.[6] The most common associated symptom of pancreatic divisum is acute and/or chronic pancreatitis, and is most often seen in young women. Whether pancreas divisum itself is the cause of the pancreatitis, or merely a cofactor with other genetic predisposition, remains to be clearly understood.[7]

Annular Pancreas

- Annular Pancreas may occur when a bifid or dual ventral bud forms (**Fig. 52.2A**). These two ventral buds may rotate in opposite directions (**Fig. 52.2B**) around the septum, leading to a circumferential ring of pancreatic tissue around the second portion of the duodenum (**Fig. 52.2C**). It

is rare, although more common than previously thought, with an incidence of approximately 1 per 1,000.[8] It is thought to occur slightly more commonly in females and is usually an incidental finding in adults. When symptomatic, it can cause a range of symptoms from chronic abdominal pain to acute pancreatitis.[9] In neonates and children, symptoms can be more severe and will often present with duodenal obstruction. In these cases, operative intervention is usually necessary to bypass the obstructed segment of intestine.

- When annular pancreas is encountered incidentally in the operating room, care should be taken to avoid transection, as the pancreatic duct may lie within this tissue and transection can lead to leak or even a chronic pancreatic fistula.
- In some cases, the distal common bile duct traverses the pancreas at the region of the annular pancreas in such a way that it can lead to biliary obstruction and jaundice. These cases commonly require intervention either endoscopically or operatively to relieve the obstruction.

Ectopic or Heterotopic Pancreas

- In ectopic or heterotopic pancreas, pancreatic tissue forms elsewhere in the gastrointestinal tract. These pancreatic rests are devoid of vascular or anatomic communication to the actual pancreas.[10] There are four types of pancreatic heterotopia, depending on the type of tissue identified histologically (**Table 52.1**).[11] Heterotopic pancreatic tissue can occur anywhere within the GI tract but is most commonly found in the stomach followed by the duodenum, jejunum, and gallbladder. These lesions may cause symptoms including abdominal pain and fullness, or—when large enough—obstruction. In rare cases there can be malignant degeneration, and endoscopic ultrasound with biopsy can be helpful in establishing a diagnosis when these lesions are encountered.

Table 52.1 Types of Heterotopic Pancreatic Tissue as Defined by the Type of Tissue Identified on Histologic Examination

Type of Heterotopia	Distinction	Tissue Identified
I	Normal pancreas	Acini, ducts, and islet cells
II	Canalicular	Pancreatic ducts
III	Exocrine	Acini
IV	Endocrine	Islet cells

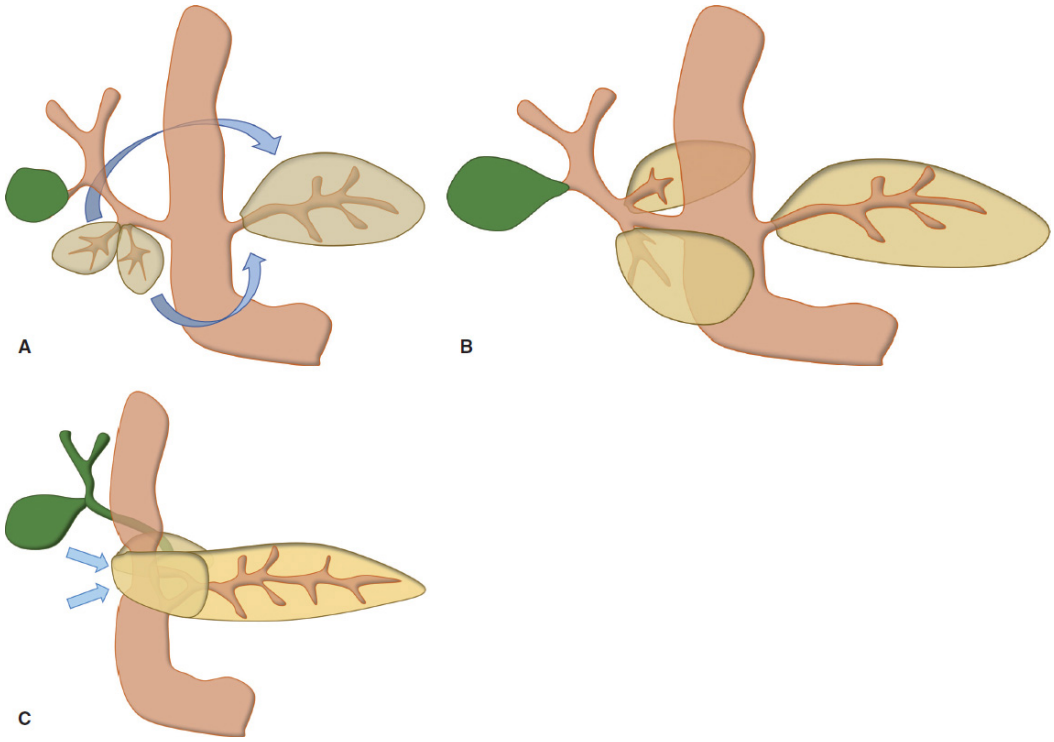

Figure 52.2 Annular pancreas can occur when two ventral buds form instead of one (**A**). These ventral buds then rotate in opposite directions around the growing duodenum (**B**). As they fuse with the dorsal duct, they can cause narrowing or stricturing of the duodenum (**C**), (*blue arrows*).

CELLULAR ORGANIZATION OF THE PANCREAS

- 4 The pancreas can be thought of as one gland with exocrine and endocrine functions. The cellular arrangement of the pancreas facilitates these functions. Up to 90% of the pancreatic tissue is exocrine in nature while only 1% to 2% of the pancreas is considered endocrine. The remaining tissue consists of pancreatic stroma and vasculature.

Exocrine Pancreas

- 5 The exocrine pancreas has two main functions: to produce enzymes for digestion and to deliver them into the intestine. The first function is carried out by the acini which produce all the enzymes and zymogens necessary to break down proteins, carbohydrates, and lipids for absorption by the small intestine. The acinus is the functional unit of the exocrine pancreas and consists of clusters of between 30 and 40 pyramidal cells that are arranged circumferentially around a central lumen, with their apices pointing toward the duct. These cells create the proenzymes (enzymes in their inactive form) and package them into zymogen granules for eventual secretion into the ductal network. Also important are the centroacinar cells, which secrete the fluid in which the proenzymes are delivered through the duct, and which keeps these proenzymes in their inactive form, at an alkaline pH around 8.0. The acinar cells and centroacinar cells deliver their secretions into the intercalated ducts, which then coalesce to form interlobular ducts. These interlobular ducts, in turn, empty through a network of secondary ducts and eventually into the main pancreatic duct for secretion into the duodenum.

Endocrine Pancreas

- The islets of Langerhans are the functional unit of the endocrine 6 pancreas. These islets can contain anywhere from a few hundred to several thousand cells. The dominant cells in the islets are the β cells, which primarily produce insulin.[2] The β cells account for up to 70% of the mass of the islet and are clustered toward its center. Further out from the β cells are the α and δ cells, which are arranged more circumferentially around the β cells. These cells make up as much as 20% of the pancreas.[12] The α cells produce glucagon which has a counter-regulatory effect to insulin. The δ cells produce somatostatin and vasoactive intestinal peptide (VIP). F cells (also known as PP cells) which produce pancreatic polypeptide (PP) and can account for up to 10% of the volume of the islet itself.[13] The remaining cells include epsilon (ε) cells which produce ghrelin, and C cells which produce substance P and serotonin.[12]
- The islets are well vascularized compared to their size, and account for 15% of the pancreatic blood flow.[3] The islets have an afferent arteriole and efferent venule, between which a rich capillary bed allows for transmission of the islet hormones into circulation.
- The cellular distribution of the islets is disproportionate throughout the gland. The islets in the tail of the pancreas are dominated by β and δ cells, whereas the proximal portion of the gland has more F cells. The glucagon-producing α cells are more evenly spread throughout the gland (**Table 52.2**).

Table 52.2 Pancreatic Endocrine Cell Types

Cell Type	% Islet Cell Mass	Major Hormone Secreted	Location within Islet	Location within Pancreas	Associated Tumor Syndrome
A (α)	10%	Glucagon	Peripheral	Evenly distributed	Glucagonoma: necrolytic migratory erythema, diabetes, hypoaminoacidemia
B (β)	70%	Insulin	Central	Body/Tail	Insulinoma: hypoglycemia and associated symptoms
D	5%[a]	Somatostatin	Evenly distributed	Body/Tail	Somatostatinoma: diabetes, gallstones, steatorrhea
D_2	5%[a]	Vasoactive intestinal peptide (VIP)	Evenly distributed	Body/Tail	VIPoma: high-volume secretory diarrhea, hypokalemia, metabolic acidosis, hypochlorhydria
F	15%	Pancreatic polypeptide	Peripheral	Head and uncinate process	Treatment directed at presenting symptoms
E C	<1%	Substance P, serotonin	Evenly distributed	Evenly distributed	None
G	Not present in normal physiologic state	Gastrin, ACTH-related peptides	Not applicable	Head, uncinate process, duodenum	Gastrinoma: acid hypersecretion, gastric/duodenal ulcers, diarrhea

[a]Combined D and D_2 mass.

- 7 The main function of the exocrine pancreas is to regulate serum glucose, through the secretion of glucagon and insulin. These hormones act in a paracrine fashion on the exocrine pancreas. As serum insulin rises, exocrine functions are stimulated, leading to increased enzyme and protein synthesis, and amino acid transport.[14] Glucagon acts in the opposing fashion, to downregulate pancreatic exocrine function. Somatostatin may act on β cells and the acinar cells in order to

downregulate pancreatic insulin secretion as well as pancreatic exocrine secretions, while VIP acts to increase water secretion in the pancreatic duct, decrease gastric secretion, and increase small intestine motility.[15]

PHYSIOLOGY OF THE PANCREAS

Exocrine Physiology

- The pancreas produces between 1.5 and 3 L of alkaline (pH 7.1 to 8.2) fluid per day, in which the secretory enzymes of the pancreas are delivered to the duodenum.[16] Maintaining a consistent alkaline pH is necessary for proper enzymatic function and provides a means to neutralize the acidic effluent of the stomach as it enters the duodenum.

Enzymatic Secretions

- Vagal innervation of the pancreas through cholinergic fibers acts as the primary stimulus for the acinar cells to increase the production and secretion of enzymes. Unlike classical synapses, neurotransmitters are released next to the islet cells, and norepinephrine and acetylcholine act on the islet cells themselves to stimulate or inhibit secretion of hormones.[17]
- Enzymes produced in the acinar cells can be grouped into those which act on carbohydrates (amylolytic), lipids (lipolytic), and proteins (proteolytic) (**Table 52.3**). Amylolytic enzymes, like amylase, break down carbohydrates into more easily digestible sugars such as maltose. Lipolytic enzymes such as lipase break down triglycerides into their main components: fatty acids and glycerols. Phospholipases break down cell membranes into arachidonic acids and phospholipids. The proteolytic enzymes (endopeptidases, exopeptidases, elastases, and nucleases) break down proteins into amino acids and nucleotides.
- Endopeptidases, like trypsinogen and chymotrypsinogen, are proenzymes, or zymogens, which are inactive forms of the enzymes. They are secreted by the acinar cells via the zymogen granules and into the apical duct lumen. They are not activated until they enter the duodenum, where enterokinase is secreted by the duodenal mucosa. The enterokinase then cleaves the endopeptidase, trypsinogen, initiating the proteolytic enzyme cascade where the remaining inactive precursor endopeptidases are converted into their active forms.
- The proportion of each of these groups of enzymes will fluctuate based on a variety of stimuli from neuropeptides, gastric acid secretion, and hormonal influences. Exocrine pancreatic secretion can be divided into three phases: cephalic, gastric, and intestinal (**Table 52.4**). The cephalic phase occurs with sensory stimulation, where the sight or smell of food triggers parasympathetic pathways via the vagal innervation to the acinar cells of the pancreas. The acinar cells, in response to acetylcholine and other neurotransmitters increase production of enzymes and zymogens which are brought toward the center of the acinus. The gastric phase occurs when food enters the stomach, stimulating additional cholinergic activation and further production of pancreatic enzymes and zymogens. Upon food entering the duodenum, the intestinal phase begins, primarily mediated by cholecystokinin (CCK), VIP, and secretin, which flood the ductal network with sodium bicarbonate solution and flush the products of the acinar cells into the main pancreatic duct for secretion through the ampulla of Vater and into the duodenum.

Table 52.3 Most Common Enzymes Secreted by the Exocrine Pancreas

Enzyme	Category	Target of Action	End Product
Amylases	Amylolytic	Carbohydrates	Oligosaccharides/Maltose
Lipases	Lipolytic	Lipids	Fatty acids/Glycerols
Phospholipases/Phospholipase B	Lipolytic	Phospholipids/Cell membranes	Arachidonic acids
Cholesterol esterases	Lipolytic	Cholesterol esters	Unesterified cholesterols/Fatty acids
Trypsin/Chymotrypsin	Proteolytic	Peptides	Amino acids
Carboxypolypeptidase	Proteolytic	Peptides	Amino acids
Nucleases	Proteolytic	DNA/RNA	Nucleotides

Bicarbonate Secretion

- Sodium bicarbonate solution is made up of water and sodium bicarbonate and is secreted by the centroacinar and terminal duct cells. The content of bicarbonate in pancreatic secretions can be as high as 145 mEq/L, as compared to bile (45 mEq/L) and serum (27 mEq/L).[18]
- When gastric acid enters the proximal duodenum, the cells of the duodenal mucosa release secretin. In addition, the presence of long-chain fatty acids and essential amino acids in the proximal small intestine leads to the release of CCK. Secretin, and to a lesser extent VIP and CCK, accelerate the uptake of bicarbonate from plasma and into the centroacinar and terminal duct cells of the acini.[19] Secretin increases cyclic AMP (cAMP) in these cells and activates the cystic fibrosis transmembrane conductance regulator (CFTR). The CFTR is primarily responsible for the exchange of bicarbonate for chloride, which is excreted back into the plasma in order to maintain anion balance.[18]
- Just as bicarbonate production by the centroacinar and terminal duct cells is activated via vagal stimulation it also inhibited by the vagus via the release of atropine, and further dampened in a paracrine fashion by the hormonal effects of glucagon, PP, and somatostatin.[3,4]
- Surgical transection of vagal innervation to the upper gastrointestinal tract via truncal vagotomy can decrease the production of sodium bicarbonate solution by as much as half.[20]

Exocrine Insufficiency

- Exocrine function can be impaired by a variety of means, including loss of functional pancreatic parenchyma (surgical resection, chronic pancreatitis) or secondary loss of exocrine pancreatic function or enzyme activity. Exocrine pancreatic insufficiency occurs when enzymatic production falls below 10% of normal.[21] Pancreatic exocrine insufficiency commonly presents with steatorrhea from insufficient lipase production.[22]
- Differentiating intestinal malabsorption from pancreatic exocrine insufficiency is the first step and can be done with a variety of tests with varying efficacy (**Table 52.5**). The most accurate tests are also the most invasive, often requiring duodenal intubation via Dreiling tube or endoscopy. Less invasive testing such as fecal fat and breath testing are easier, but less specific.
- Serum tests for amylase, lipase, and other enzymes are not useful in the diagnosis of pancreatic insufficiency as these enzymes are not elevated at baseline. Amylase, lipase, and trypsinogen are

all useful, however, in the diagnosis of acute pancreatitis, discussed elsewhere in this book.

- The etiology of exocrine pancreatic insufficiency must be determined in order to treat the patient properly.

Testing for Pancreatic Exocrine Insufficiency

Pancreatic Effluent Testing

- The secretin stimulation test is the gold standard test for pancreatic exocrine insufficiency. Historically this was done via a Dreiling tube. After fasting overnight, patients would undergo fluoroscopic placement of the tube and basal aspirate of duodenal contents were taken. Additional aspirates were taken every 20 minutes after secretin bolus (2 units/kg) for four successive measurements. Analysis of pancreatic secretions including total volume, amylase, and bicarbonate concentrations are used for diagnosis. More recently, endoscopic techniques have been employed to assess pancreatic output.[23] In endoscopic pancreatic function testing (ePFT), patients are given an intravenous bolus of secretin (0.2 µg/kg). Via endoscopic intubation, pancreatic secretions are aspirated and quantified at 30 and 45 minutes post injection. Peak bicarbonate concentrations less than 80 mmol are considered abnormal.[24] While easier for the patient, the endoscopic technique requires sedation and does not yield as much information as total volumes are not obtained, nor are basal rates for comparison. The results of secretin stimulation testing can differentiate between various causes of pancreatic exocrine insufficiency (**Table 52.5**).

Table 52.4 Three Phases of Pancreatic Exocrine Secretion

Phase	Initiated by	Mediated by	Action on	Result
Cephalic	Sensory stimuli (sight, smell, taste, etc.)	Vagus nerve	Acinar cells to produce digestive enzymes	Enzymes and zymogen granules are produced in the acini
Gastric	Food within the stomach	Vagus nerve	Acinar cells to produce and secrete digestive enzymes	Enzymes and zymogens accumulate in the ductal network
Intestinal	Emptying into duodenum	Secretin and cholecystokinin	Ductal cells secrete aqueous bicarbonate solution	Enzymes and zymogen granules are washed through the ductal network and into the duodenum for activation

Table 52.5 Differential Diagnosis of Intestinal and Pancreatic Steatorrhea

Parameter	Intestinal Steatorrhea	Pancreatic Insufficiency
24-hr fecal fat	<20 g; soapy consistency	>20 g; only seepage
D-xylose	Abnormal (low)	Normal
Secretin test	Normal	Abnormal
Small bowel series	Abnormal	Normal
Small bowel biopsy	Abnormal	Normal
PABA test	Normal	Abnormal
PP response to meal	Normal	Abnormal
Vitamin B_{12} and folate	Abnormal (low)	Normal
Treatment with pancreatic enzymes	No change	Improvement

- The Lundh test is a direct measurement of enzyme secretion. Similar to the secretin stimulation, patients fast overnight and the duodenum is then fluoroscopically intubated. A protein-, fat-, and carbohydrate-rich meal enters the stomach and duodenal aspirates are taken at 30-minute intervals for 2 hours.[25] Often, a promotility agent such as metoclopramide is given intravenously to stimulate gastric motility and emptying. The activity of trypsin, amylase, and lipase are analyzed. In patients with abnormal secretion of CCK or secretin, this test may yield a false-positive result.
- The most invasive of enteral access testing, the dimethadione (DMO) test is done over a period of 3 days and measures the pancreatic metabolism of trimethadione to dimethadione in the setting of secretin stimulation.[26] While highly sensitive and specific for pancreatic exocrine insufficiency, it is rarely employed.

Serum Testing

- While serum testing of amylase and lipase are not useful in diagnosing pancreatic exocrine insufficiency, serum testing of PP can be useful. This test is performed after a period of overnight fasting. A meal rich in carbohydrate, fat, and protein is given enterally. Basal and postingestion serum values of PP are obtained. If both basal levels and response levels are low (less than 100 pg/mL and less than 250 pg/mL, respectively) then a diagnosis of exocrine pancreatic insufficiency is appropriate. However, because PP release is dependent upon vagal innervation, prior gastric resection, truncal vagotomy, or chronic enteroneuropathic disease states such as diabetic gastropathy can lead to a false positive.

Urine Testing

- The BT-PABA test is much less invasive than those above. A 1-g bolus of N-benzoyl-1-tyrosyl paraaminobenzoic acid (BT-PABA) is given to the patient enterally. BT-PABA is cleaved by chymotrypsin in the intestine and the resultant PABA is excreted in the urine. Urine is collected over a 6-hour period and the total volume is analyzed. Concentrations less than 60% of the initial dose of BT-PABA given are consistent with exocrine pancreatic insufficiency.

Fecal Testing

- Quantitative analysis of fecal fat calls for patients to maintain a strict diet of 100 g of fat per day for 5 consecutive days and collect the full volume of feces for a period of 3 consecutive days. The coefficient of fat absorption is then quantified.[22] While accurate at diagnosis, it is cumbersome, unpleasant, and rarely utilized in clinical practice. A 24-hour fecal fat testing measures total volume of fat. In pancreatic insufficiency, this volume will be greater than 20 g. More often, a qualitative analysis or “spot” sample is procured and the acid stain of fat within the sample is analyzed. Fecal elastase has shown to be useful in the diagnosis of pancreatic exocrine insufficiency in chronic pancreatitis, but not in postpancreatic resection.[27] While useful in cases of severe pancreatic insufficiency, all fecal testing is less sensitive in mild and moderate cases.

Breath Testing

- This is a noninvasive test which is often used in conjunction with urinary or fecal elastase testing in the initial workup of steatorrhea. The mixed triglyceride (MTG) breath test involves giving the patient a small oral bolus of the radioactive isotope C^{14} bound to corn oil. Normal enzymatic digestion and absorption should produce carbon dioxide, which retains the radiolabeled carbon, and this can be quantified at the 4-hour mark in the patient’s breath. A more recent advent is the use of C^{13} which is not radioactive and therefore safer for patients, especially children.[27] It provides similar results to the C^{14} MTG test, with high sensitivity and specificity for steatorrhea,[28] but it cannot differentiate between intestinal malabsorption and true pancreatic exocrine insufficiency. However, in the latter case, patients should show improved excretion with oral pancreatic enzyme replacement.

All of these tests can aid in the diagnosis of exocrine pancreatic insufficiency. In practice, however, when there is a high suspicion, improvement with the addition of oral pancreatic enzyme replacement can be both diagnostic and therapeutic.

Endocrine Physiology

- The islet cells produce hormones that act in an endocrine and paracrine fashion to regulate serum glucose and affect carbohydrate metabolism. The two most important hormones are insulin (β cells) and glucagon (α cells), which act in opposition to one another. Insulin activates transport of glucose into cells and inhibits the breakdown of glycogen into glucose in the liver and muscle cells. It similarly inhibits the metabolism of fatty acids from the adipose tissues. Glucagon acts to increase serum glucose and simulate glycogen and fatty acid metabolism in the tissues. Somatostatin (δ cells) causes secondary hormone activation in the intestine, and likely plays a paracrine role on the other islet cells in response to hormone.[12] There is some evidence that endogenous somatostatin stimulates growth of pancreatic tissue.[29]

Endocrine Insufficiency

- Endocrine insufficiency is generally related to insulin. A loss of β cells, as occurs in type I diabetes, is most often due to autoimmune destruction. In these patients, the sensitivity to insulin is unaffected, and serum glucose homeostasis can be compensated with exogenous insulin. A loss of greater than 80% of β cells in the pancreas will generally lead to type I diabetes.[30] In type II diabetes, the islet cells produce insulin normally, but there is a loss of function or affinity for insulin on the cell surface, leading to elevated plasma glucose levels. Increased endogenous insulin stimulation, such as occurs with sulfonylureas, can be effective in type II diabetes, in addition to exogenous insulin.

Insulin

- Produced in the β cells, insulin is comprised of two small polypeptide chains, A and B, which are 21 amino acids and 30 amino acids long, respectively. These two chains are bound covalently via two disulfide bridges creating a 51 amino acid structure. The structure of bovine and porcine insulins is very similar to that of humans, making them the mainstay of treatment for diabetes up until synthetic insulin was created.
- Preproinsulin is synthesized in the endoplasmic reticulum, where it is cleaved to form proinsulin, the precursor to insulin. Proinsulin is cleaved by a protease in the secretory vesicles, forming active insulin and C-peptide, both of which are secreted into blood.
- Serum levels of exogenous insulin can be differentiated from endogenous insulin by the presence of C-peptide in the bloodstream.
- The exocytosis of cytoplasmic insulin occurs in a biphasic manner.[14] The first phase occurs with the release of prepackaged insulin at the plasma membrane. This occurs quickly, within the first 10 minutes of stimulation. The second phase is characterized by the synthesis of new hormone, and is slow, lasting as long as serum glucose remains elevated.
- Insulin has a half-life of 8 to 10 minutes and is metabolized quickly by nearly all cells in the body, the exceptions being red blood cells and cells of the brain, both of which depend on glucose constantly and cannot be dependent on insulin activation for its metabolism. In the liver, uptake and storage of glucose by hepatocytes can also be completed independent of insulin.
- Insulin receptors on the cell surface are activated with elevated serum insulin, leading to activation of glucose transporters in the plasma membrane facilitating the uptake of glucose into the cell.

- Insulin resistance is the hallmark of type II diabetes and can be due to a decrease in the number of insulin receptors or a loss of affinity for insulin. Similarly, reduced numbers and impaired activity of glucose transporters contribute to cellular insulin resistance and the further development of diabetes mellitus.[31]
- The enteroinsular axis, as described by Unger, demonstrates in increased activity of a variety of enteric hormones to glucose.[32] Gastric inhibitory peptide, CCK, glucagon, and glucagon-like peptide-1 (GLP-1) all stimulate insulin production and secretion, while somatostatin and pancreastatin are inhibitory.

Glucagon

- The preproglucagon gene encodes the precursors of glucagon as well as both GLP-1 and GLP-2. These latter two products are secreted in their inactive forms, while glucagon is secreted as a 29 amino acid polypeptide in its active form. Interestingly, in the small intestine, the reverse occurs, with GLP-1 and GLP-2 being secreted as active peptides and stimulating insulin secretion, while proglucagon remains inactive.[17]
- Glucagon is stimulated in direct response to hypoglycemia via three mechanisms: direct effects of hypoglycemia on the α cells, a release of suppression by the β cells, and autonomic stimulation of the α cells. The first two mechanisms are likely small, and it is the autonomic stimulation that is thought to be the major driver of glucagon secretion.
- Autonomic stimulation can occur via direct parasympathetic fibers that innervate the islet cells, or via direct or indirect sympathetic stimulation. Indirect sympathetic stimulation occurs from circulating epinephrine in response to stress.[33]
- Whereas insulin is an anabolic hormone, glucagon is highly catabolic. Its main effects are on the liver, as one might expect. Glucagon is secreted into the pancreatic venules and from there enters the portal circulation, acting on hepatocytes and causing an increase in glycogenolysis and gluconeogenesis in the liver.
- Glucagon oversecretion, as can happen with functional pancreatic neuroendocrine tumors, can lead to profound hyperglycemia. The opposite is true in patients who have undergone total pancreatectomy, where the absence of glucagon can cause hypoglycemia that can be difficult to control.

Somatostatin

- Secreted by δ cells, somatostatin is primarily secreted in response to rising serum glucose, as well as amino acids leucine and arginine.[34] Only 5% of somatostatin that is found in circulation, however, is from the islet cells, with the remainder coming from the gastrointestinal tract and hypothalamus.[12] This difference in distribution is why the majority of effects of somatostatin are seen either centrally or in the proximal GI tract, where somatostatin inhibits gastric, pancreatic, and biliary secretion.
- Somatostatin analogs, such as octreotide, are commonly used to slow intestinal transit and limit the effects of neuroendocrine tumors. It has also been variably shown to reduce fistula output in patients after pancreatic resection.[35]
- Less well understood are the paracrine effects of somatostatin. Somatostatin inhibits both insulin and glucagon from β and α cells, respectively. How this is accomplished is multifactorial but involves direct mediation via gap junctions as well as somatostatin receptors on the cells themselves.[12] It also has been shown to regulate islet cell growth. The dysregulation of somatostatin may affect hyperglycemia seen in diabetics.

Ghrelin and Pancreatic Polypeptide

- ε Cells produce ghrelin, known as the "hunger hormone" which acts in a paracrine fashion to stimulate somatostatin thereby inhibiting insulin and glucagon.[36] Its effects systemically are less well understood.
- PP has been shown to have numerous functions, the best known of which are its effects to decrease glucagon and hepatic gluconeogenesis and glycogenolysis. It has also been shown to decrease pancreatic and biliary secretions.

PANCREATIC ANATOMY

- Understanding 8 of the anatomic relationships of the pancreas with other organs is paramount for the surgeon.
  - Location: The pancreas is a retroperitoneal organ running somewhat obliquely from where its head, surrounded by the second and third portions of the duodenum, to its tail in the hilum of the spleen. Physiologically, the pancreas empties its exocrine contents from the tail, along the body and neck and through the head into the duodenum. However, anatomically we distinguish the head and uncinate process of the gland as proximal and the body and tail as distal.

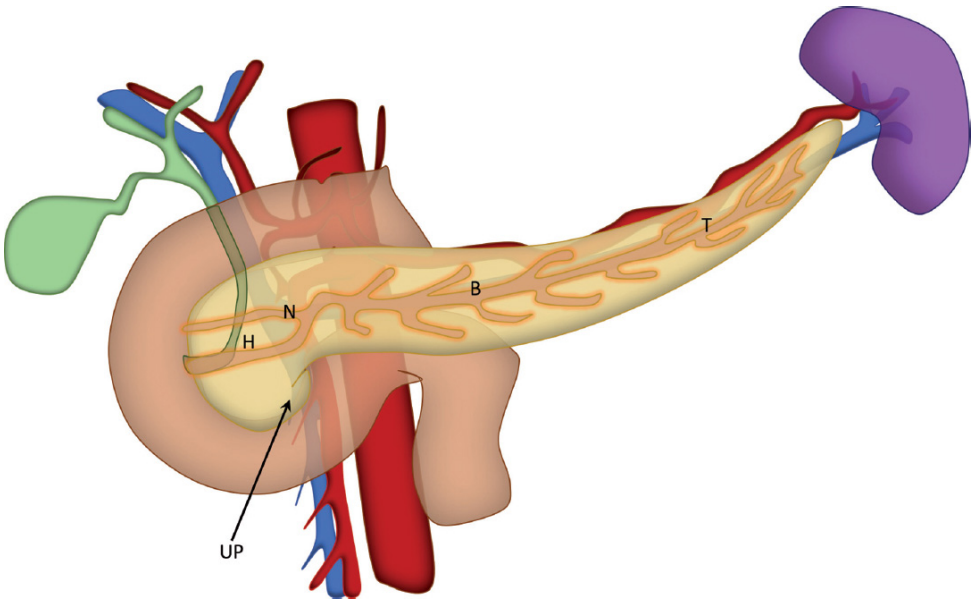

Figure 52.3 Pictorial demonstration of zones of the pancreas. H, head; UP, uncinate process; N, neck; B, body; T, tail.

  - Zones: The pancreas is often thought of as having four zones of significance: the head/uncinate process, the neck, the body, and the tail. However, there is little anatomic distinction between these areas, other than their relationship to adjacent organs and vasculature.
    - Head/Uncinate Process: The head of the pancreas is nestled within the second and third portions of the duodenum. It anatomically begins just to the right of the superior mesenteric vein. It is fused with the uncinate process which wraps inferiorly and posteriorly around the superior mesenteric vein and superior mesenteric artery (**Fig. 52.3**). Posteriorly the head and uncinate process lie atop the medial half of the inferior vena cava and the distal left renal vein, as well as the right renal artery. The common bile duct runs through the head of the pancreas and joins the pancreatic duct as they empty through the ampulla of Vater and into the duodenum.

- Neck: The neck of the pancreas is the region under which the superior mesenteric vein joins the splenic vein and empties into the portal vein. The superior mesenteric vein exits the aorta behind the neck and proximal body of the pancreas, running medially and slightly posterior to the superior mesenteric vein. During proximal pancreatic resection, the neck of the pancreas is divided.
- The body and tail of the pancreas lie posterior to the body of the stomach. Their anterior surface has a peritoneal layer, acting as the posterior reflection of the lesser sac. The posterior body and tail have no such layer, and lie in direct contact with the aorta, left adrenal gland, superior portion of the left kidney and the left renal vein and artery. The tail of the pancreas is variably intimate with the splenic hilum. The splenic vein and artery run posteriorly along its course prior to entering and exiting the spleen, respectively (**Fig. 52.4**). The distal transverse colon and splenic flexure lie along its anterio-inferior border.

- Vasculature: The arterial blood supply to the pancreas comes from the celiac axis.
  - The head/uncinate process and the neck of the gland are supplied by the gastroduodenal artery (GDA) which arises from the common hepatic artery as it leads into the proper hepatic artery. The GDA then produces the superior pancreaticoduodenal artery which has anterior and posterior branches. The inferior pancreaticoduodenal artery arises from the proximal superior mesenteric artery, and similarly divides into anterior and posterior branches. Together, these arteries form an intricate and well-collateralized supply to the proximal pancreas as well as the distal common bile duct and the duodenum. The ampulla of Vater receives its blood supply from the superior and inferior pancreaticoduodenal arteries, which produce three small branches at the 11, 1, and 6 o'clock positions (**Fig. 52.5**).
  - The body and tail of the pancreas receive blood from the splenic artery as it courses first posterior and then slightly superior to the gland. Along its course are several branches to the pancreas, the three most important of which being the dorsal pancreatic artery (proximal body), the great pancreatic artery (midbody), and the caudal pancreatic artery (pancreatic tail).
  - The venous drainage of the pancreas follows a similar distribution as the arterial supply. The superior aspect of the head of the pancreas drains via the superior venous arcade and into the portal vein. The inferior head and uncinate process drain into the superior mesenteric vein via the anterior and inferior venous arcades. The body and tail of the pancreas drain directly into the splenic vein via several branches, the most important of which are the caudal pancreatic vein, the great pancreatic vein, and the inferior pancreatic vein.
  - The inferior mesenteric vein does not receive blood from the pancreas, but lies behind the body of the pancreas, where it most commonly drains into the splenic vein, although it may also drain into the superior mesenteric vein or at the inferior confluence of the superior mesenteric vein and splenic vein.
  - Aberrant arterial anatomy exists in approximately 20% to 30% of patients (**Fig. 52.6**). The most common anomaly is a replaced or aberrant right hepatic artery arising from the superior mesenteric artery, which can occur over 20% of the time.[37] In these cases, the right hepatic artery courses posterior to the head of the pancreas and along the posterolateral aspect of the bile duct. Palpation of this border of the bile duct is paramount prior to any dissection to avoid unnecessary injury or transection. The second most common anomaly is the replaced left hepatic artery, which most commonly is supplied by the left gastric artery. In these cases, which occur in 5% to 10% of patients, the vessel can be found along the anterior border of the caudate lobe, entering the liver between segments 3 and 4, alongside the round ligament. It should be noted that either of these anomalies can present as an accessory artery, whereby there is some degree of duplication of the arterial inflow. In some cases the accessory artery

is more or less diminutive than the true artery. Care should be taken to avoid injuring these accessory vessels, even so, as they may provide important inflow to segments of the liver. Less commonly than the other two variants is the replaced common hepatic artery, whereby all the inflow to the liver is supplied by a common trunk arising from the superior mesenteric artery. This can occur up to 5% of the time. Unlike the replaced right hepatic artery, these course more medially, between the neck and head of the pancreas, and along the posteromedial border of the common bile duct.

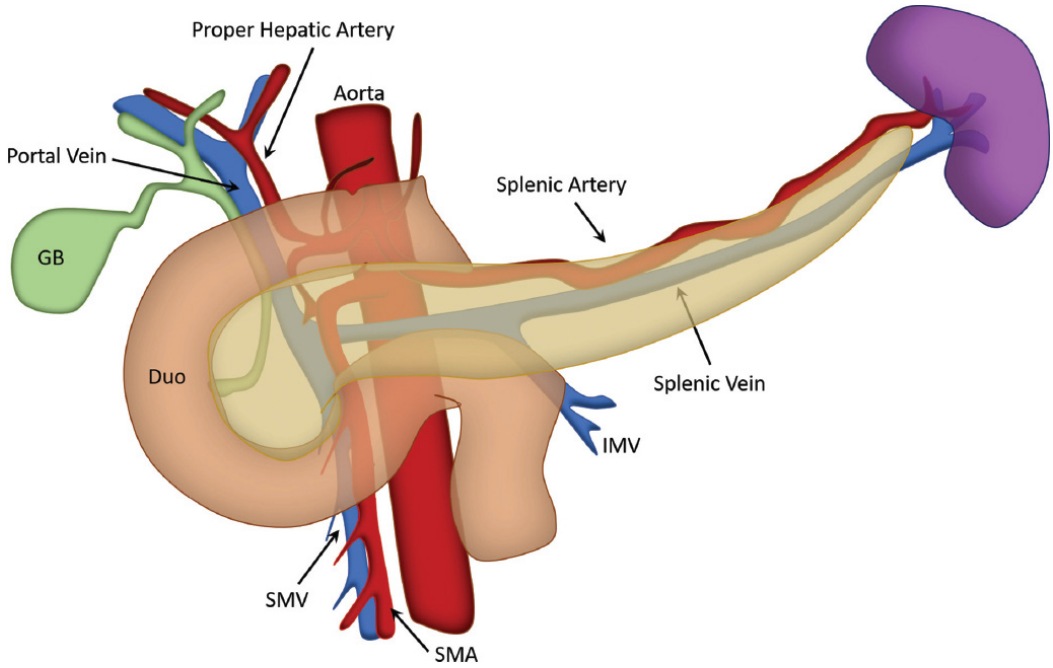

Figure 52.4 Pictorial demonstration of vasculature of the pancreas. SMV, superior mesenteric vein; SMA, superior mesenteric artery; IMV, inferior mesenteric vein; GB, gallbladder; Duo, Duodenum.

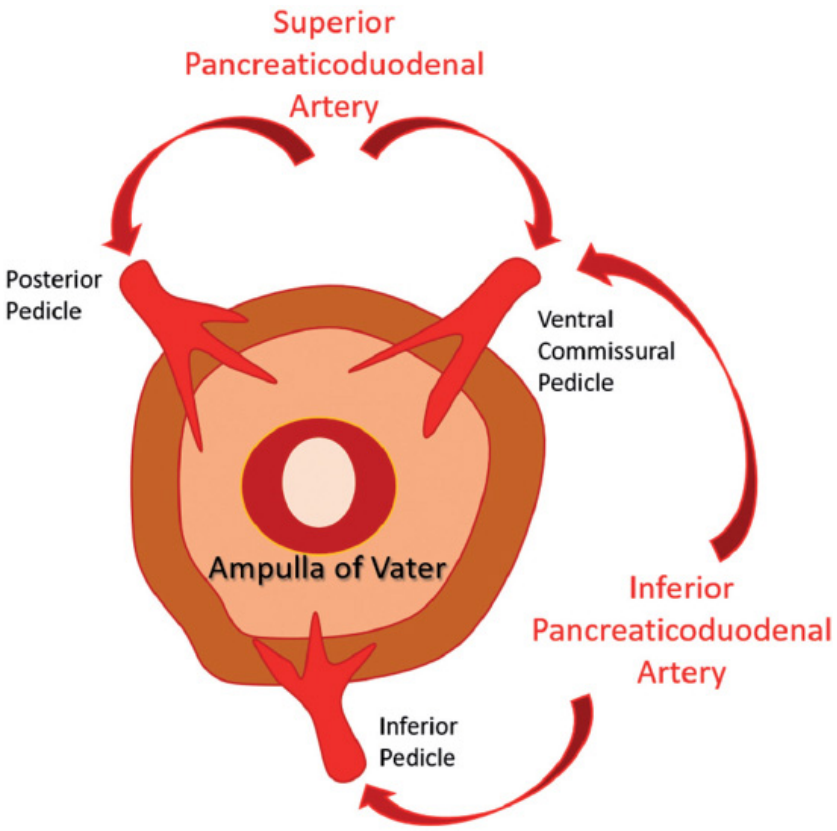

Figure 52.5 Pictorial demonstration of blood supply to the ampulla of Vater.

Lymphatics

- Due to its rich vascular supply and drainage, the pancreas has a similarly prominent lymphatic drainage. There are five major drainage patterns of the pancreas:
  - Superior: drain superior portion of pancreas head and neck
  - Inferior: drain inferior portion of pancreas head and uncinate
  - Anterior: drain prepyloric and infrapyloric regions
  - Posterior: portions of the head, distal common bile duct and, ampulla
  - Splenic: drain the pancreatic body and tail
- The 18 nodal stages as described by the Japanese Pancreas Society are presented in **Table 52.6**.

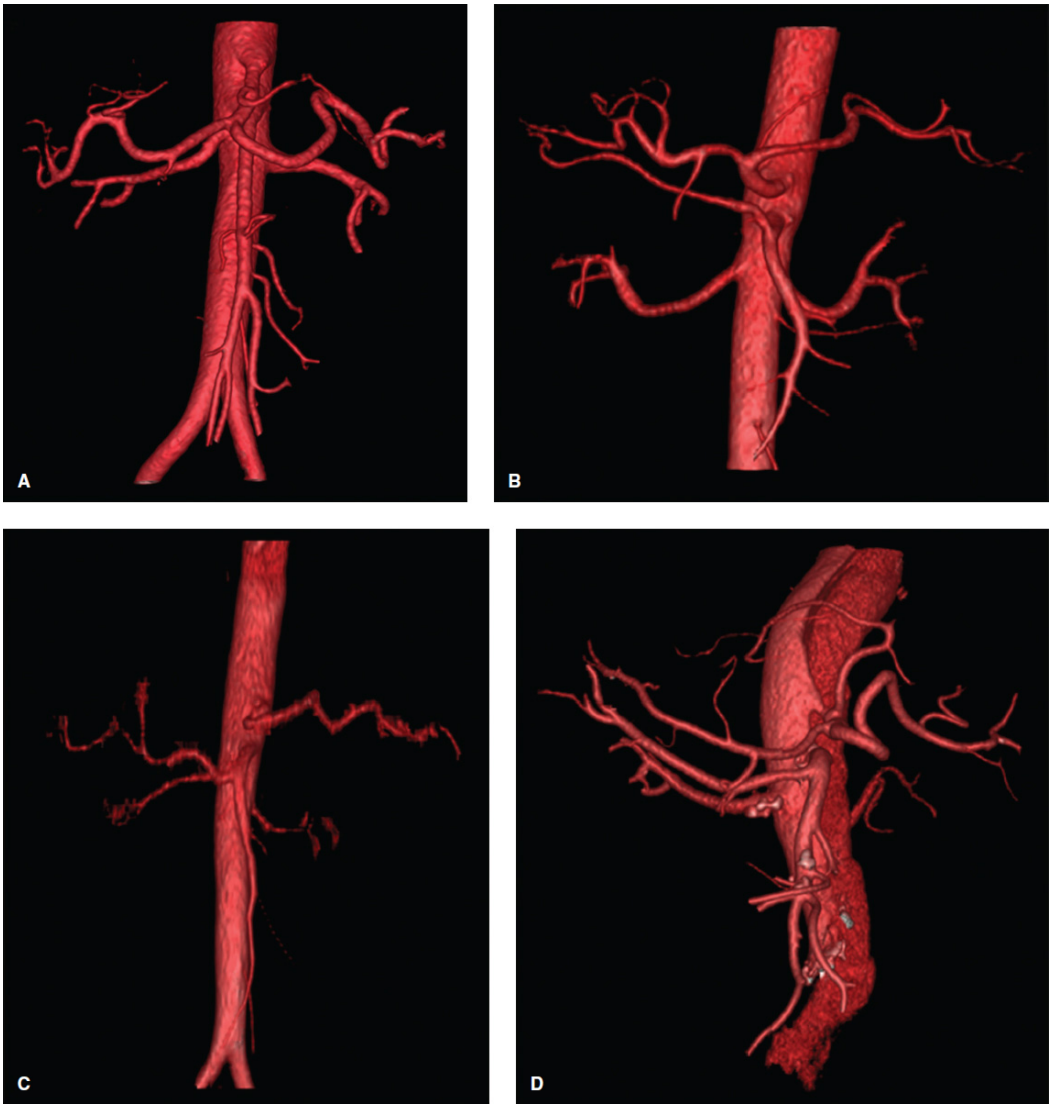

Figure 52.6 3D CT reconstructions of (**A**) Normal arterial supply to the pancreas, (**B**) Replaced right hepatic artery arising from the superior mesenteric artery, (**C**) Replaced common hepatic artery arising from the superior mesenteric artery, and (**D**) Replaced left hepatic artery arising from the splenic artery.

Innervation

- As previously noted, the pancreas is innervated via the vagus nerve as well as the thoracic splanchnic nerves. The sympathetic and parasympathetic nerves travel from the ganglia of the celiac axis and the proximal superior mesenteric artery. The sympathetic nerves inhibit exocrine and endocrine function while the parasympathetic nerves stimulate these functions. In addition to direct stimuli, the vagal branches also have secretory neurons which secrete both stimulatory and inhibitory hormones to the islets and acini. Sensory fibers from the pancreas track toward the celiac and superior mesenteric artery ganglia, which can be an important focus for pain control in patients with pain from pancreatic disease.

Table 52.6 Japanese Lymph Node Stations

Station Number	Name	Standard	Radical
3	Gastric lesser curve	No[a]	Yes[b]
4	Gastric greater curve	No[a]	Yes[b]
5	Superior pyloric	No[a]	Yes
6	Inferior pyloric	No[a]	Yes
8	Common hepatic artery	No	No
9	Celiac origin	No	Yes[c]
12	Hepatoduodenal ligament		
12a2	Proper hepatic artery near GDA	No[d]	No[d]
12b2	Bile duct below cystic duct	Yes[e]	Yes[e]
12c	Around cystic duct	Yes	Yes
12p2	Retro portal vein below cystic duct	No[d]	No[d]
13	Posterior pancreaticoduodenal	Yes	Yes
14	SMA and SMV nodes		
14a	Origin of SMA	No	No
14b	Right side of SMA	Yes[e]	Yes[e]
14c	Anterior SMA at middle colic	No	No
14d	Left side of SMA at first jejunal branch	No	No
14v	SMV nodes	Yes[e]	Yes[e]
16	Aortocaval nodes		
16a2	Celiac to left renal vein	No	Yes[f]
16b1	Left renal vein to IMA	No	Yes
17	Anterior pancreaticoduodenal	Yes	Yes

[a]Unless a distal gastrectomy is performed as part of standard resection.

[b]Some of these nodes may accompany the distal gastrectomy specimen.

[c]Sampled only.

[d]Not formally resected.

[e]Some of these nodes may accompany the pancreaticoduodenectomy specimen.

[f]Some of these nodes, cephalad to the left renal vein, but not required to dissect the celiac axis origin.

With permission from Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality? *Ann Surg* 2002;236(3):355–366; discussion 366–368.

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53

Acute Pancreatitis

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Key Points

1. The annual incidence of acute pancreatitis (AP) varies from 13 to 45 per 100,000 persons.
2. In most Western countries, gallstones and/or bile sludge are the most frequent cause (up to 80%) of AP.
3. Diagnosis of AP according to the 2012 Revised Atlanta Classification (RAC) requires at least two of the following three criteria: (1) abdominal pain compatible with pancreatitis, (2) serum amylase and/or lipase of at least three times greater than the upper limit of the normal serum value, or (3) imaging findings consistent with AP.
4. Among the many methods to predict the severity of AP, the SIRS criteria are preferred.
5. The two most accepted classifications for the severity of AP are the three-tiered RAC and the four-tiered Determinant-Based Classification (DBC).
6. The use of crystalloid solutions such as Ringer lactate, or balanced saline solutions (Plasmalyte) are currently recommended in the early phase of AP, since they have advantages over the use of colloid solutions.
7. As current evidence is limited, pain can be managed according to general pain protocols.
8. The use of antibiotics in AP is justified as treatment of suspected or documented infection of necrosis, whereas prophylactic use in sterile necrosis is not recommended.
9. No benefits for the use of enteral probiotics were found; a higher mortality potentially related to nonocclusive mesenteric ischemia was observed.
10. Early oral nutrition is advocated in AP. Enteral nutrition (EN) can be used “on demand” when patients have no sufficient oral intake after 48 to 72 hours of AP. Early tube feeding within 24 hours holds no health benefits.

11 For infected peripancreatic collections, it is recommended to wait with percutaneous or endoscopic transluminal drainage until the collections have become walled off (which usually occurs after 3 to 4 weeks).

12 In almost 30% of patients, pancreatic (peri)necrosis will become infected, requiring invasive intervention in the vast majority of patients. Upfront open surgical necrosectomy is associated with high morbidity and mortality; it should be avoided if possible.

13 Laparotomy may still be indicated during AP in case of mesenteric ischemia or abdominal compartment syndrome (ACS). In both scenarios it is advised to leave the retroperitoneum intact to prevent spread of activated pancreatic enzymes into the peritoneal cavity and infect sterile retroperitoneal necrosis.

14 The treatment of choice for infected peripancreatic collections is the "step-up approach" in which the necrotic collections are drained mainly by catheter drainage first (percutaneous or endoscopic transluminal), and in the absence of clinical improvement, step up toward minimally invasive necrosectomy (e.g., video-assisted retroperitoneal debridement [VARD] or endoscopic transluminal). For percutaneous catheter drainage, ideally drains are placed just over Gerota fascia trough the retroperitoneum to facilitate retroperitoneal debridement.

15 If technically feasible and available, endoscopic drainage is preferred over the percutaneous route for drainage of (infected) walled-off necrosis (WON).

16 All patients with severe (acute) necrotizing pancreatitis should be treated by a multidisciplinary team consisting of HPB surgeon, gastroenterologist, and interventional radiologist.

EPIDEMIOLOGY

Acute pancreatitis (AP) is one of the most common gastrointestinal diseases requiring acute hospitalization in the Western world. 1 The annual incidence of AP varies from 13 to 45 per 100,000 persons.[1] Approximately 15% to 20% of patients develop a moderate–severe or severe form of the disease. In almost one-third of patients, pancreatic necrosis becomes secondarily infected, which is associated with mortality ranging from 15% to 39%.[2–4]

Approximately half of AP deaths occur within the first 2 weeks of illness, primarily due to multiple organ failure as a result of a severe systemic inflammatory response. The other patients die later due to complications secondary to pancreatic (peri)necrosis infection and subsequent interventions.[5,6]

AETIOLOGY

2 In most Western countries, gallstones and/or bile sludge are the most frequent cause (up to 80%) of AP.[1,7] With approximately 10% to 15% of cases, alcohol is the second most frequent cause of AP in most countries. Less common causes of AP include medication, endoscopic retrograde cholangiopancreatography, hypercalcemia, hypertriglyceridemia, surgery, and trauma (**Table 53.1**). Idiopathic acute pancreatitis (IAP) occurs in around 16% to 26% of patients, requiring additional diagnostic modalities in the follow-up (repeat transabdominal ultrasound, endoscopic ultrasound [EUS] or magnetic resonance cholangiopancreatography).[8] Meta-analyses show that in about 60% of patients with IAP, EUS can establish aetiology. This includes the detection of microlithiasis or biliary sludge (41%), chronic pancreatitis, or pancreatic tumors in up to 7% of IAP.[9]

Table 53.1 Etiology of Acute Pancreatitis

Gallstones
Alcohol
Iatrogenic causes ERCP Abdominal and nonabdominal surgery Cardiopulmonary bypass
Trauma
Neoplasms (e.g., pancreatic cancer, IPMN)
Pancreas divisum
Sphincter of Oddi spasm
Medications
Toxins Parathion Scorpion venom
Hyperlipidemia
Hypercalcemia
Infectious agents Viruses (e.g., mumps and Coxsackie B viruses; HIV) Bacteria (e.g., *Salmonella* and *Shigella* species; hemorrhagic *Escherichia coli*) Biliary parasites (e.g., *Ascaris lumbricoides*)
Genetic causes Cationic trypsinogen *PRSS1* mutations Pancreatic secretory trypsin inhibitor *SPINK1* mutations Cystic fibrosis transmembrane conductance regulator *CFTR* mutations
Autoimmune pancreatitis (lymphoplasmacytic sclerosing pancreatitis)
Vasculitis (e.g., systemic lupus erythematosus and polyarteritis nodosa)
Ischemia

Pregnancy

ERCP, endoscopic retrograde cholangiopancreatography.

AP, both alcoholic and nonalcoholic, may also develop into chronic pancreatitis. This progression may also be related to genetic mutations in the protease gene (PRSS1) that can present an autosomal dominant mutation. Other identified mutations that increase the risk of PC are mutations in the CFTR, SPINK1 and CTRC genes.[10–12]

In rare cases, AP can be the first presentation in patients with pancreatic cancer.[1,2] We recently found a 0.4% risk of pancreatic cancer during a median follow-up of 55 months after the first episode of AP. The median time between the first episode of AP and the detection of pancreatic cancer, in patients free from chronic pancreatitis, was 12 months. After a first episode of AP without a clear cause, physicians should be aware of the possibility of pancreatic cancer as the underlying disease and patients should undergo follow-up with endoscopic ultrasonography and computed tomography (CT).[13–15]

BILIARY PANCREATITIS

The prevalence of gallstones in Western countries is around 20%.[16] In 1901, Opie postulated that obstruction of pancreatic outflow causes pancreatitis, which triggered acinar cell damage.[17] In experimental studies, damage from bile reflux could not be demonstrated in the early stages of AP, only in cases of potentially infected bile.[18–20] Therefore, in acute biliary pancreatitis, sustained obstruction of the ampulla of Vater would ultimately trigger an increase in pressure in the pancreatic duct, which would ultimately be the source of acinar damage in biliary AP.[20–22]

ALCOHOLIC PANCREATITIS

Alcohol consumption is a known risk factor for AP. A meta-analysis showed a high risk of AP with a consumption of more than four alcohol units per day (RR = 2.5, 95% CI: 2.0 to 3.1).[23] Despite this, in animal models it has not

been possible to reproduce acute alcohol-mediated pancreatitis, requiring the addition of other factors such as cerulein, lipopolysaccharide, and ductal obstruction.[23] It is postulated that pancreatic toxicity is mediated by the oxidative and nonoxidative metabolism of ethanol, which ultimately favors the deposition of fatty acid ethyl esters "FAEEs" in acinar cells. This leads to an increase in the release of "Ca^{2+}" from the endoplasmic reticulum, with the activation of a compensatory mechanism of Ca^{2+} entry into the cytoplasm, which increases cellular damage. Similarly, the hydrolysis of the FAEES into fatty acids within the mitochondria favors mitochondrial damage. All of these events trigger cell death.[24,25]

CLINICAL PRESENTATION

AP presents as severe abdominal pain, usually sudden onset which may be associated with vomiting. The pain usually radiates to the back. Most patients seek hospital within 12 to 24 hours of the onset of symptoms. The abdominal examination shows epigastric sensitivity, with signs of peritonitis because of the retroperitoneal location of the pancreas.

PHYSIOLOGY

Following the acinar cells' necrosis, there is a release of activated pancreatic enzymes into the cellular interstitium, activating local vasoconstriction–dilation mechanisms. Infiltration of inflammatory cells occurs in the pancreatic parenchyma with the consequent increase of cellular necrosis.

In the most severe forms of AP, an aggressive cellular and humoral response develops, similar to septic shock, multiple trauma, and extensive burns. The magnitude and continuation of such events are attributed to the development of systemic inflammatory response syndrome (SIRS), which could lead to multiorgan failure in 30% of patients. Within the mediators involved are several cytokines, such as interleukin-1 (IL-1), IL-6, IL-8, tumor necrosis factor (TNF), and platelet activation factor (PAF). All of these mediators are remarkably elevated in the first 24 hours of the disease,

associated with a decrease in anti-inflammatory cytokines (IL-2, IL-10). As a result, activation of neutrophils, monocytes, lymphocytes, platelets, and endothelial cells occurs. There is an increase in the expression of cell adhesion molecules and integrins in neutrophils, favoring distant organ damage (especially the lungs); polymorphonuclear leukocytes appear causing extensive tissue destruction.[26,27]

Regardless of the aetiology of AP, there is an activation in very early stages of the disease of the protease precursor enzymes (trypsinogen). This favors the release of activated enzymes in the cellular cytosol, favoring mechanisms of cellular necrosis.[28–32]

Additionally, in recent years, the "gut-lymph concept" has gained interest, as a factor contributing to systemic multiorgan failure in AP mediated by an increase in the permeability of the intestinal barrier, favoring the translocation of primed neutrophils and intestinal toxic factors through circulation through the thoracic duct, in early stages, promoting multiorgan dysfunction syndrome.[33]

SEVERITY CLASSIFICATION AND PREDICTION

Revised Atlanta Classification

3 Diagnosis according to the 2012 Revised Atlanta Classification (RAC): the diagnosis of AP requires at least two of the following three criteria: (1) abdominal pain compatible with pancreatitis, (2) serum amylase and/or lipase of at least three times greater than the upper limit of the normal value, or (3) findings consistent with acute imaging pancreatitis (contrast-enhanced CT [CECT], MRI, or ultrasound).[34] For typical clinical and laboratory findings, no additional CECT or other imaging is required to confirm the diagnosis. The severity of AP is classified as mild, moderate, or severe: mild when no local or systemic complications are present; moderate in case of local (e.g., collections of peripancreatic fluid) or systemic (e.g., exacerbation of chronic disease) or transient organ failure (48 hours); severe in case of persistent organ failure (more than 48 hours).

Laboratory Test and Scores

Among the methods of predicting the severity of AP are several clinical and laboratory scores. One of the most used is the APACHE-II score (acute physiology and chronic health evaluation II), where a value equal to or greater than 8 is considered a high risk of developing a severe AP. Others are the BISAP score (bedside index for severity AP), the Ranson score, the modified 4 Glasgow/Imrie score, the presence of SIRS, the value of C-reactive protein, and recently the increased in blood urea nitrogen (BUN) and procalcitonin.[35–38] The IAP/APA treatment guidelines advise the use of the SIRS criteria built up from (1) temperature <36°C (96.8°F) or >38°C (100.4°F), (2) heart rate >90/min, (3) respiratory rate >20/min, and (4) white blood cells <4 × 10^9/L or >12 × 10^9/L.[39]

Clinical-Based Classifications: Atlanta Classification and Determinant-Based Classification

The two most accepted classifications are the three-tiered RAC and the four-tiered Determinant-Based Classification (DBC) (**Table 53.2**).[34,40]

In the RAC, severity is divided into three degrees: mild, moderate, and severe, based on the presence of transient or persistent organ failure, as well as the existence or absence of local 5 complications. The DBC includes the presence of organ failure and the existence or absence of necrosis infection, adding a severity level, critical AP, by combining persistent organ failure and infected necrosis. Both systems (RAC and DBC) are capable of accurately classifying the severity of the AP.[41]

TREATMENT

EARLY PHASE

Currently, in the absence of curative treatment, the management of the early stages of AP is based on supportive care, consisting of pain management, adequate fluid resuscitation, as well as optimal nutritional support. Interventions to reduce the inflammatory response have not achieved beneficial results and are therefore discouraged.[39,42]

Table 53.2 Definition of Severity of Acute Pancreatitis According to Current Classification Systems

Revised Atlanta Classification[35]
Mild AP ▪ No organ failure ▪ No local or systemic complications
Moderate severe AP ▪ Transient organ failure (<48 hrs) AND/OR local or systemic complications OR exacerbation of pre-existing comorbidities
Severe AP ▪ Persistent organ failure (single or multiple)
Determinant-Based Classification[36]
Mild AP ▪ No organ failure ▪ No peri(pancreatic) necrosis
Moderate AP ▪ Sterile (peri)pancreatic necrosis AND/OR transient organ failure
Severe AP ▪ Infected (peri)pancreatic necrosis OR persistent organ failure
Critical AP ▪ Infected (peri)pancreatic necrosis AND persistent organ failure

FLUID RESUSCITATION

Adequate fluid resuscitation is justified by the state of a systemic inflammatory response, which increases fluid extravasation to the third space, favoring hypovolemia and organ hypoperfusion, which is associated with organ failure in cases of severe AP.

The use of crystalloid solutions such as Ringer lactate, or balanced saline solutions (Plasmalyte) are currently recommended, since 6 they have advantages over the use of colloid solutions, which have been associated with increased mortality.[39,43,44] On the other hand, all fluid therapy must be closely monitored. The target measures include a heart rate <120/min, mean blood pressure between 64 and 85 mm Hg, and a urine output of at least 0.5 mL/kg/hr, a decrease in serum creatinine and hemoconcentration (less than 44%), the use of rapid or aggressive hydration not being recommended since both are associated with higher mortality and risk of abdominal compartment syndrome (ACS).[45,46]

PAIN MANAGEMENT

Pain is the predominant symptom of AP and should be treated promptly 7 and adequately. Frequent reassessment of pain scores and, if indicated, adjustment of analgesic types and/or dosages is needed to assure proper pain management. Several RCTs compared different types of analgesia in AP.[47–50] A systematic review on opioid use in AP and a recent meta-analysis reported that the quality of most of these RCTs is low, and no particular analgesic strategy is superior.[51,52] As current evidence is limited, pain can be managed according to general state-of-the-art pain protocols.

ANTIBIOTICS AND PROBIOTICS AS PROPHYLAXIS

Secondary infection of pancreatic or peripancreatic necrosis is one of the deadliest complications of AP.[53]

Bacterial translocation from the intestinal barrier is postulated as one of the mechanisms of necrosis infection.[54] Various RCTs have assessed the use of prophylactic antibiotics, without 8 conclusive evidence that this can

reduce the rate of infected necrosis but with increased risk of antibiotic resistant microorganisms.[55–59] Therefore, the use of antibiotics in AP is justified only if there is a documented infection of necrosis or because there is sufficient clinical suspicion.

Several RCTs investigated whether the use of enteral probiotics could influence the intestinal microbiome, reducing bacterial translocation, with initially promising results.[60,61] However, 9 in a subsequent larger multicenter RCT with 296 patients with predicted severe AP, no mortality benefits were found; on the contrary, higher mortality was observed, potentially related to nonocclusive mesenteric ischemia. Currently, the use of probiotics in severe AP is not recommended.[62]

NUTRITION

Enteral Nutrition

The use of enteral nutrition (EN) has been shown to be useful in AP, when compared to routine parenteral nutrition.

EN helps to maintain the integrity of the intestinal barrier, preventing bacterial translocation and bacterial overgrowth, which would ultimately prevent infection of the pancreatic necrosis (INP).[63,64] It is postulated that the benefits of EN are based on an immunomodulatory effect on the intestinal mucosa and on the systemic level, having an effect on the maturation and function of lymphocytes at the level of intestinal epithelial cells (IECs).[65] In experimental models, glutamine infusion decreased inflammatory activity at the IEC level, through the production of cytoprotective enzymes.[66,67]

Benefits have also been shown with respect to the decrease in the rates of multiorgan failure, and mortality, when compared with the use of routine total parenteral nutrition.[68,69]

10 The nasojejunal and nasogastric feeding routes are equivalent, with no differences in adverse effects compared to the nasogastric route.[70–72] In cases of mild AP, the oral route can be used when abdominal pain decreases.[73]

PORTO-SPLENO-MESENTERIC THROMBOSIS IN AP

The incidence of porto-spleno-mesenteric thrombosis (PSMVT) in AP varies from 1.8% to 57%, according to the literature.[74–76] The development of PSMVT is associated with the presence, location, and extent of pancreatic necrosis and the severity of AP. The rate of complications related to the PSMVT over the course of AP, is usually low.[76,77] Complications of PSMVT include: gastric variceal bleeding, splenomegaly, and less frequently, liver failure after progression of portal vein thrombosis. Systemic anticoagulation is advised, however, the recanalization rates vary from 11% to 86%, irrespective of the use of systemic anticoagulation.[75,77,78] It is unknown which patients are at risk to develop a progression of thrombosis; hypothetically, in this group of patients, the use of systemic anticoagulation would have a potential role.[79] Routine splenectomy after splenic vein thrombosis and splenomegaly is not recommended due to the low rate of complications in this group of patients.[74,76]

ENDOSCOPIC RETROGRADE CHOLANGIOGRAPHY IN ACUTE BILIARY PANCREATITIS

Several studies have investigated the role of routine endoscopic retrograde cholangiography (ERC) with sphincterotomy in biliary pancreatitis.[80] It is widely accepted that ERC is indicated in patients with concurrent cholangitis and pancreatitis. In patients with mild AP, early ERC is not indicated because of the lack of potential benefit, compared with the risk for complications.[39,81]

Recently, the results of a multicenter randomized trial showed that in patients with predicted severe acute biliary pancreatitis without cholangitis, early ERC with biliary sphincterotomy within 24 hours after presentation at the emergency department did not reduce the primary end point of death or major complications.[82]

LOCAL COMPLICATIONS OF AP

The RAC classifies local complications into four groups (**Fig. 53.1**).[34]

Collections associated with acute interstitial edematous pancreatitis: (1) acute collections of peripancreatic fluid, which are extrapancreatic and fluid; (2) pancreatic pseudocysts are typically extrapancreatic, encapsulated, contain fluid with no solid components, and develop after 4 weeks; they are rare after severe AP.

Collections associated with acute necrotizing pancreatitis: (3) acute necrotic collections, of early appearance, without clear delimitation, and (4) walled-off necrosis (WON), with encapsulated and thick walled necrosis.

The onset of WON is usually only after 3 to 4 weeks. A recent study found that WON developed in 40% of patients in the first 3 weeks.[83]

Pancreatic necrosis is observed in 5% to 10% of patients with AP and is characterized by the absence of intravenous contrast uptake of the pancreatic parenchyma on abdominal tomography. The computed tomography severity index (CTSI) classifies the percentage of pancreatic parenchymal necrosis and the presence of local alterations, giving a score of 1 to 10, finding an association of higher mortality for scores between 7 and 10.[84]

Extrapancreatic necrosis (EXPN): This involves the involvement of the peripancreatic tissues, generally peripancreatic, retroperitoneal, and mesenteric fat. The presence of EXPN has a better prognosis than pancreatic parenchymal necrosis. However, in cases of EXPN infection, a complication and mortality rate similar to pancreatic parenchymal necrosis was found.[85]

It is recommended that the abdominal CT be carried out 72 hours after the first symptoms of AP because in the first hours the necrosis is unlikely to have been established.

Performing pancreatic magnetic resonance imaging (MRI) can be useful for studying pancreatic fluid collections where the differential diagnosis of disconnection of the pancreatic duct is suspected, in addition to identifying the presence of solid components within the cyst cavity.[86]

MANAGEMENT OF LOCAL COMPLICATIONS

Peripancreatic Fluid Collections

Over the years, the treatment of peripancreatic collections and pancreatic necrosis has evolved. The current best practice is that conservative management should be used in most cases. There is wide acceptance that peripancreatic collections that are infected, or present symptoms that do not subside after a period of conservative treatment, should be drained.[39] Among the symptoms or complications of peripancreatic fluid collection (PFC) are abdominal pain, gastrointestinal obstruction, vascular compression, and biliary obstruction.[53]

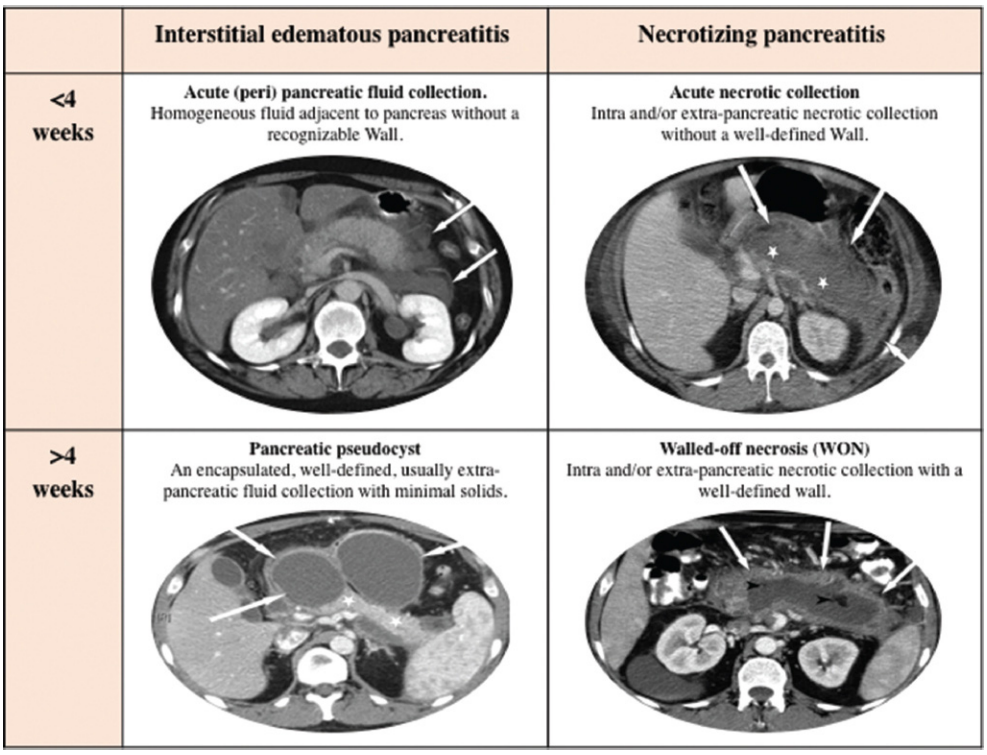

Figure 53.1 Collections associated with AP, according to revised Atlanta classification. (Adapted from Juneja D, Gopal PB, Ravula M. Scoring systems in acute pancreatitis: which one to use in intensive care units? *J Crit Care* 2010;25[2]:358.e9–358.e15.)

Generally, it is recommended to postpone drainage of infected collections until the stage of WON has been reached, this may take several weeks as mentioned earlier. This facilitates the approach of the collection, with a lower probability of bleeding and a greater probability of successful drainage due to greater adherence of the collection to the gastrointestinal

lumen for the endoscopic approach, for example.[87] Early intervention on infected PFC is associated with increased mortality, due to a lowering in the proinflammatory response in critically ill patients, reduced postoperative complications, and reduced number of procedure-related adverse events.[88,89]

Many collections deemed pancreatic pseudocysts on a CT scan in a patient with severe AP actually contain necrosis and should be diagnosed as WON or acute necrotic collection. Ultrasound or an MRI scan is better capable of detecting necrosis in a fluid predominant collection. This is relevant since the treatment of an infected or symptomatic pseudocyst is different from a collection with necrosis as the latter is easily infected when drained sterile.

Pancreatic pseudocysts can often be treated conservatively. Only in case of symptoms or infection is intervention needed. The spontaneous resolution of the pancreatic pseudocysts varies from 8% to 70% and depends on several factors: the presence of multiple locations, location in the pancreatic tail, communication with the main pancreatic duct and coexistence of stenosis, and increase in size during the follow-up.[90–92] There is no absolute size at which intervention is required; however, an increased risk of complications of cysts >5 cm in diameter has been reported, especially in the absence of decreased cyst size for 6 weeks.[34,92,93] Symptoms include persistent abdominal pain, pain in the side or back, partial or complete obstruction of the gastric or duodenal outlet with early satiety, anorexia, weight loss, bloating, vomiting or reflux, biliary obstruction, and jaundice. As mentioned, the most serious complications include infection, bleeding in the cyst, rupture, and erosions of the gastroduodenal and/or splenic artery, where intervention is necessary. Regarding the technique of drainage, the studies comparing different techniques (surgery, endoscopy, percutaneous drainage), do not demonstrate a clear superiority of one technique over another. In general, endoscopic transmural drainage is preferably used, especially when there is a favorable location of the pancreatic pseudocyst (perigastric or periduodenal), in addition to the lower risk of cutaneous pancreatic fistula compared to percutaneous drainage. It has also been described that surgical drainage seems to have a high clinical success rate; however, subsequent studies have shown similar results using endoscopy or percutaneous approaches.[94–96]

MANAGEMENT OF PANCREATIC NECROSIS AND ITS COMPLICATIONS

During the first 3 to 4 weeks after the appearance of acute necrotic 11 collection, it will resolve or encapsulate. Most of the necrotic collections are sterile and will resolve with conservative treatment, but in cases of infection, will mostly require an additional invasive intervention.[39]

Regardless of its size, an asymptomatic WON does not require intervention, since it mostly resolves spontaneously over time.[4,97] A larger size of WON, such as with extension into the paracolic gutter, and the extent of necrosis have been shown to be associated with the need for intervention.[75,90,98,99]

Intervention in a sterile collection carries the risk of secondary iatrogenic infection, with all its associated morbidity and mortality. A sterile necrotic collection without symptoms (e.g., abdominal pain or mechanical obstruction) may require intervention; however, due to the risk of secondary iatrogenic infection, attention should be focused on conservative treatment and interventions should be delayed for 6 to 8 weeks or longer.[4]

12 In almost 30% of patients, peripancreatic collections will become infected, requiring intervention in the vast majority of cases. A small percentage of patients can be treated just with antibiotics.[100,101] Since early open surgery is associated with high morbidity and mortality, it should be avoided whenever possible.[102]

13 There are exceptional indications for early urgent laparotomy such as the presence of mesenteric ischemia and ACS as a direct consequence of AP, which are indications for open surgery.[103]

STEP-UP APPROACH

14 Necrosect omy in the first 2 weeks of AP carries a high risk of morbidity and mortality and should therefore be avoided.[88,89,102] However, percutaneous drainage can be performed early in the course of infected necrotizing pancreatitis.

Previously, a primary open necrosectomy was the preferred treatment. This was associated with high mortality and morbidity rates. Currently, the treatment of choice is the "step-up approach" in which the necrotic collections are drained mainly by less invasive methods (percutaneous drainage, or endoscopic drainage through stents), and in the absence of clinical improvement, there is a "step-up" toward surgical necrosectomy (minimally invasive initially).[104] This intensive approach reduces rates of new-onset multiple organ failure, morbidity, serious adverse events, and lower costs compared to primary open necrosectomy, which has since been largely abandoned.[105] In the step-up approach, almost half of patients can be treated with drains alone, while the other half requires additional different procedures for the final treatment, including percutaneous, endoscopic, open, or minimally invasive surgery.[42,104]

Percutaneous catheter drainage can be a sufficiently definitive treatment in up to 56% of patients.[106] An analysis showed that percutaneous drainage with antibiotics alone was a successful treatment in 50% of patients.[107] Upgrading percutaneous drains toward larger calibers (i.e., upsizing) facilitates the drainage of the collection.[104] Currently, the multicenter POINTER trial is underway to study the immediate drainage by percutaneous catheter of infected necrosis in comparison to the standard conventional approach (step-up approach).[108]

MINIMALLY INVASIVE NECROSECTOMY

If the patient with infected pancreatic necrosis does not recover with drainage alone, a necrosectomy will be required. Traditional open necrosectomy has largely been replaced by minimally invasive techniques. Of these, the most widely used techniques include sinus tract endoscopy and video-assisted retroperitoneal debridement (VARD),[109,110] see **Figure 53.2**. As part of the "step-up approach," a 12- to 14-Fr percutaneous drain is placed in the pancreatic (peri)collection through the left retroperitoneum. If drainage does not lead to clinical improvement, surgical intervention is considered necessary and VARD is proposed. This technique can be considered a hybrid between pure endoscopic retroperitoneal necrosectomy and the open translumbar approach (20-cm incision). In VARD, the small

incision allows the surgeon to remove larger pieces of necrosis, with shorter operation time and less need for repetitive procedures. These minimally invasive techniques showed reduced morbidity and mortality, especially in high-risk patient groups.[111]

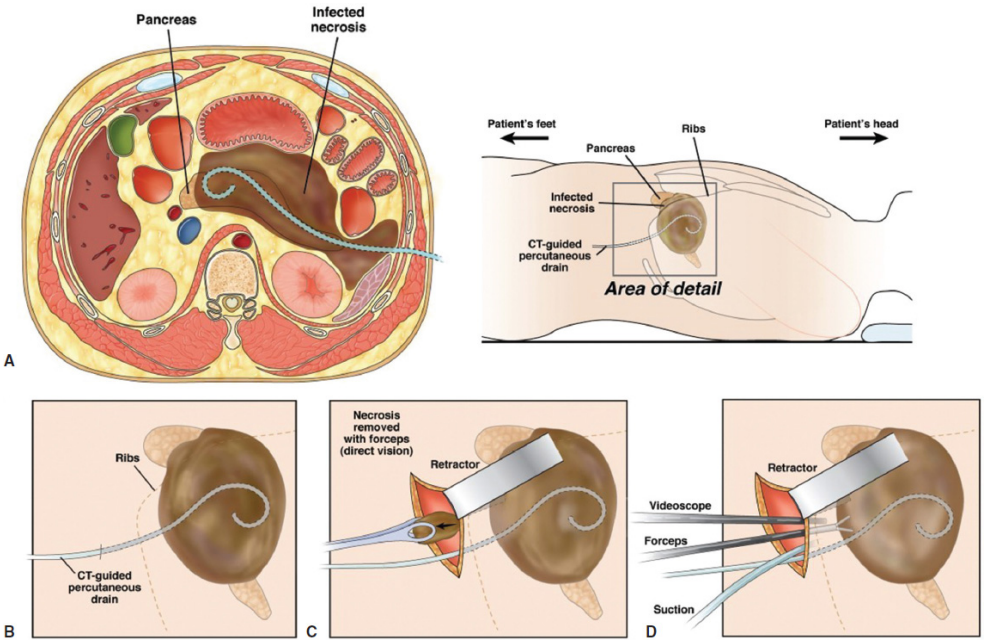

Figure 53.2 Surgical step-up approach. **A:** Cross-sectional image and torso depicting a peripancreatic collection with fluid and necrosis. The first step of the surgical step-up approach is percutaneous catheter drainage. The preferred access route is through the left retroperitoneal space between the left kidney, dorsal spleen, and descending colon. If necessary, percutaneous catheter drainage is followed by a minimally invasive surgical necrosectomy, for example, videoscopic-assisted retroperitoneal debridement. **B:** Enlargement of the area of detail shown in part A of the figure. **C:** A 5-cm subcostal incision is made, and the previously placed percutaneous drain is used as a guide into the retroperitoneum to enter the necrotic collection. The first necrosis is removed under direct vision with a long grasping forceps. **D:** Further debridement is performed under videoscopic assistance. (Reprinted from van Brunschot S, van Grinsven J, Voermans RP, et al. Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis (TENSION trial): design and rationale of a randomised controlled multicenter trial [ISRCTN09186711]. *BMC Gastroenterol* 2013;13[1]:161. *Open access*.)

15 ENDOSCOPIC NECROSECTOMY

In recent decades, transmural (i.e., transgastric) endoscopic management of acute necrotizing pancreatitis is increasingly used. Various endoscopic techniques are used for the treatment of WON, all of which include EUS-guided transmural access to the cavity, **see Figure 53.3**. EUS-guided drainage and/or necrosectomy has had an advantage over the conventional transmural endoscopic approach due to greater technical success.[92,93,107] Compared to surgical necrosectomy, an endoscopic approach significantly reduces the proinflammatory response and improves the clinical outcome in patients with ANP.[112] However, when used as a single-modality approach, it requires more necrosectomy sessions for definitive treatment than in combination with other interventional procedures.[113] A meta-analysis found that endoscopic necrosectomy has a success rate of 81% as a single treatment modality, with a complication rate of 36%.[114] The multicenter randomized controlled TENSION trial, compared the endoscopic step-up approach with the surgical step-approach. Both procedures were found to have similar mortality and morbidity rates. However, the endoscopic step-up group had a lower incidence of pancreatocutaneous fistula and shorter hospital stay.[111]

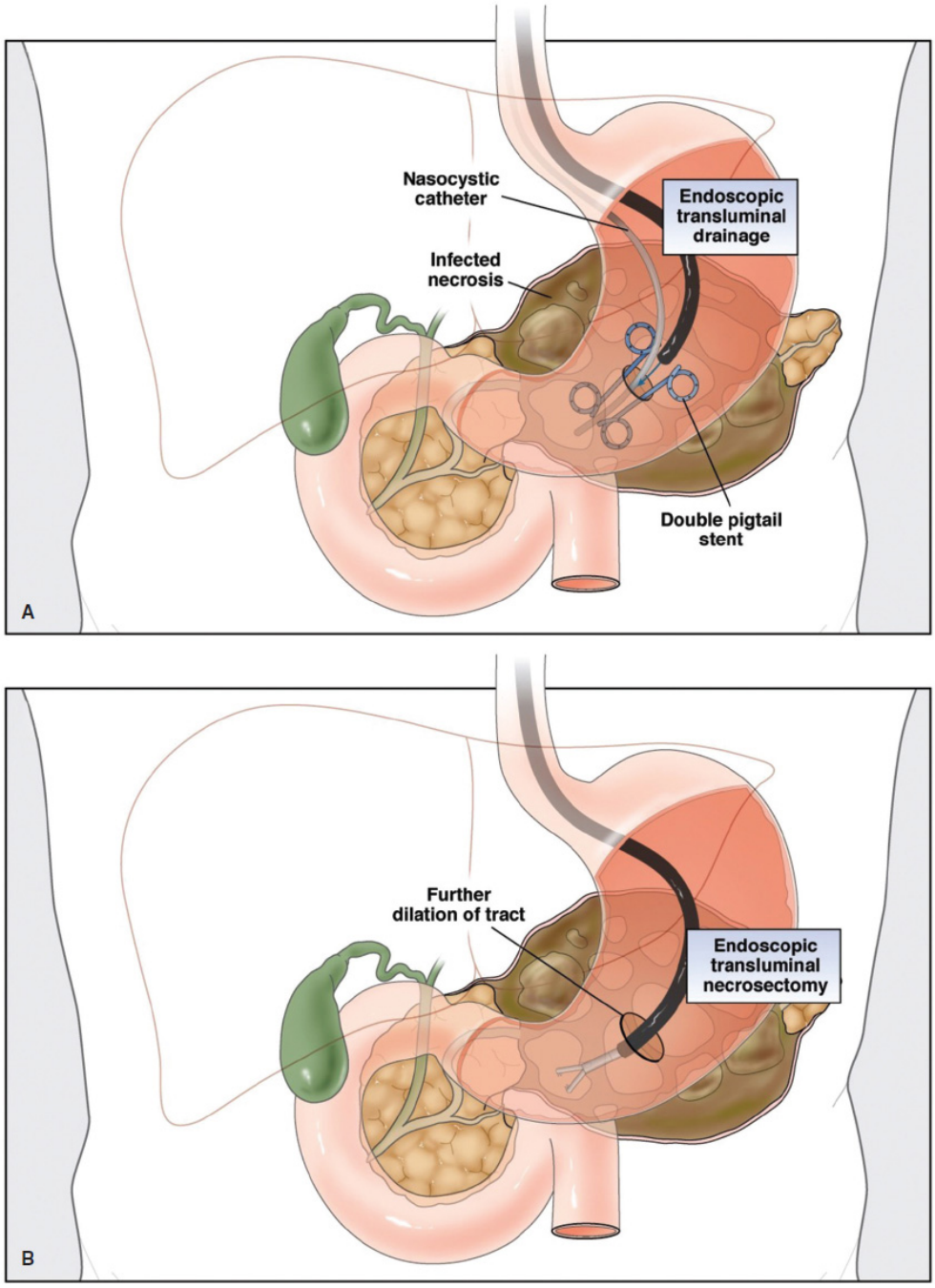

Figure 53.3 Endoscopic step-up approach. **A:** The first step of the endoscopic step-up approach is endoscopic transluminal drainage. The preferred access route for endoscopic transluminal treatment is through the posterior wall of the stomach. The necrotic collection often bulges into the stomach, facilitating endoscopic transluminal treatment. The collection is punctured through the gastric wall, followed by balloon dilatation of the tract. Two double-pigtail stents and a nasocystic catheter are placed for continuous postoperative irrigation. **B:** If necessary, the cystostomy tract is further dilated, the collection is entered by a forward-viewing endoscope, and necrosectomy is performed. (Reprinted from van Brunschot S, van Grinsven J, Voermans RP, et al. Transluminal endoscopic step-up

approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis (TENSION trial): design and rationale of a randomised controlled multicenter trial [ISRCTN09186711]. *BMC Gastroenterol* 2013;13[1]:161. *Open access*.)

Endoscopic drainage of infected pancreatic necrotic collection has evolved, from the use of a small plastic stent to lumen-apposing metal stent (LAMS), with a specific biflanged design that facilitates the creation of a stable and sealed fistula between the gastric or duodenal wall and the WON. Retrospective series showed very promising results with clinical success in up to 89% of cases. However, LAMS is related to a significant rate of adverse events (25.4%).[115,116] The only randomized controlled trial comparing plastic double pigtail stents showed no difference in clinical important outcome parameters. Ongoing trials will show the definite role of LAMS for drainage of WON.[117]

16 All patients with severe (acute) necrotizing pancreatitis should be treated by a multidisciplinary team consisting of HPB surgeon, gastroenterologist, and interventional radiologist.

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54

Chronic Pancreatitis

Katherine A. Morgan

Key Points

1. Chronic pancreatitis (CP) is heterogeneous in etiology with an increasingly recognized role of genetic factors and smoking.
2. The most common indication for intervention in CP is severe, debilitating abdominal pain.
3. Medical and endoscopic therapies are frontline management of CP, but are often unsuccessful.
4. Surgical intervention is aimed at achieving durable pain relief with least perioperative and long-term morbidity.
5. Innovative surgical therapies for CP, including minimally invasive approaches and total pancreatectomy with islet autotransplantation (TPIAT), have gained increasing enthusiasm.

INTRODUCTION

The surgical management of chronic pancreatitis (CP) has evolved significantly in the modern era. The increasing recognition of genetic mechanisms for pancreatitis and the role of smoking in pathophysiology of

CP have changed the patient demographic as well as treatment strategies, including the surgical algorithm. Additionally, potentially field-altering research is currently being undertaken on genetics, molecular pathways, and clinical outcomes in CP.

CP is a benign inflammatory disorder of the pancreas, resulting in progressive fibrotic replacement of parenchyma. The most notable clinical presentation is severe, debilitating, and unremitting abdominal pain, often with associated nutritional failure. CP leads to progressive endocrine failure due to islet loss (type 3c diabetes mellitus)[1] and exocrine failure (malabsorption). Importantly, patients have significant impairments in quality of life.

EPIDEMIOLOGY

CP is a significant public health concern. Its prevalence and annual incidence are estimated at 0.2% to 0.6% and 7 to 10/100,000, respectively in the United States and Europe.[2] The economic impact is notable, with estimated annual healthcare expenditures for pancreatitis in the United States in 2004 at $3.7 billion.[3]

ETIOLOGY

Historically, alcohol use has been the most commonly implicated etiologic factor in CP in the Western world. A more recent multi-institutional observational study by the North American Pancreatitis Study 2 (NAPS2) Group revealed a lesser contributory role for alcohol.[4] Dose and duration of alcohol consumption have been demonstrated to be contributory to CP development, although several more recent studies suggest that alcohol alone is not sufficient to cause CP. Byproducts from ethanol metabolism injure acinar cells and can activate pancreatic stellate cells (PSCs) to form extracellular matrix. Recent investigation suggests an association between alcoholic pancreatitis and a locus on the X chromosome.[5]

1 Smoking is a significant risk factor in the development of CP. Tobacco consumption has been associated with pancreatic calcifications

radiographically.[6] Synergistic effects of smoking and alcohol have been described.[7] More recently, NAPS2 has shown that smoking is an independent risk factor for CP in a dose-dependent fashion.[4] In addition, tobacco use has been shown to be a strong risk factor for the progression of acute pancreatitis to CP, suggesting a role for smoking in pancreatic fibrogenesis.[8]

Genetic causes for pancreatitis have been a major focus of advancement in the evolving understanding of CP in the current era. In 1952, Comfort and Steinberg described hereditary pancreatitis (HP),[9] and in 1996, Whitcomb and colleagues delineated a mutation in the cationic trypsinogen gene PRSS1, which results in the inappropriate activation of trypsin and is responsible for HP.[10] HP is an autosomal dominant disorder with 80% penetrance, marked by recurrent acute pancreatitis beginning in early childhood, progression to CP in many, and a greatly (50×) increased risk of pancreatic cancer beginning in the fifth decade. Since, several other mutations in the PRSS1 gene have been identified. In addition, multiple other genetic foci have been implicated as contributing agents in CP as well, primarily related to the inappropriate activation of trypsin. Pancreas secretory trypsin inhibitor (serine protease inhibitor, Kazal type 1, and SPINK1),[11] cystic fibrosis transmembrane conductance regulator (CFTR) gene, chymotrypsin C (CRTC),[12] calcium-sensing receptor (CASR) gene,[13] and gamma-glutamyltransferase 1 (GGT1) gene[14] have all been elucidated as conferring a susceptibility to CP development. Conversely, the anionic trypsinogen gene PRSS2 may confer a protective advantage against the development of pancreatitis.

Clearly, the etiology of pancreatitis is variable, complex, and incompletely understood.

PATHOPHYSIOLOGY

The pathophysiology of CP is not well elucidated. A theory known as the "three-hit hypothesis" holds that (1) a stochastic event occurs resulting in (2) inappropriate trypsin activation causing acute pancreatitis. The patient then has (3) an unfavorable immunologic response to the inflammation resulting in fibrosis and CP (**Fig. 54.1**).[15] Environmental factors (e.g., alcohol) are

common inciting events in the cascade, with key modulating factors being genetics and the histologic milieu.

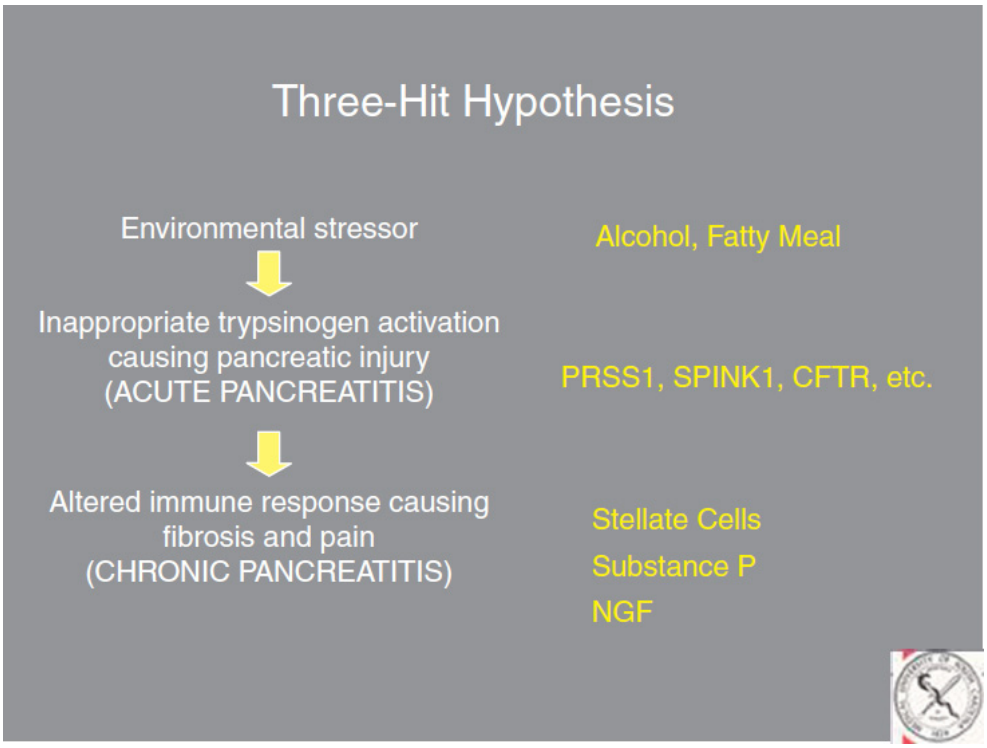


Figure 54.1 Three-hit hypothesis for pathophysiology of chronic pancreatitis. NGF, nerve growth factor. (Adapted from Whitcomb DC. Genetic risk factors for pancreatic disorders. *Gastroenterology* 2013;144:1292–1302.)

Insights into pathophysiology of pancreatitis have occurred through advances in cellular basic science. PSCs are causative in pancreatic fibrogenesis. PSCs are residents of the healthy pancreas that become activated by inflammatory cytokines during pancreatitis to become myofibroblast-like cells, producing extracellular matrix in the interstitial space.[16] In addition, several matrix metalloproteinases are implicated in altering extracellular matrix remodeling and collagen degradation, enhancing fibrogenesis and irreversibly altering the organ architecture to a diseased, fibrotic pancreas.[17]

The CP pain syndrome has complex pathophysiology. Classical theory holds that pancreatic ductal obstruction due to fibrosis results in elevated intraductal and intraparenchymal pressures which cause pain. More recent theories focus on peripancreatic neuropathy. On a histologic level, peripancreatic neuronal hypertrophy as well as infiltration of the periaxonal

tissue with inflammatory cells is evident.[18,19] Increased presence of the "pain neurotransmitters" is identified, including calcitonin gene-related peptide and substance P, stimulated by nerve growth factor.[20] These changes in the peripancreatic neuronal milieu may contribute to peripheral neural remodeling and central neural sensitization that make the CP pain syndrome uniquely severe and vexing to manage.

CLINICAL PRESENTATION

2 The primary presentation of CP is severe, intractable epigastric abdominal pain that radiates into the back. The classic pain is constant with periods of exacerbation. Patients often have associated gut dysfunction, with nausea, emesis, and difficulty tolerating a diet consistently, particularly during pain episodes. Patients may develop endocrine failure (pancreatogenic diabetes, type 3c) and exocrine pancreatic insufficiency (EPI) over time. Less often, patients may present with an acute complication of CP such as biliary or duodenal obstruction, a pancreatic pseudocyst, pancreatic ascites, mesenteric venous thrombosis, or mesenteric arterial pseudoaneurysm (**Table 54.1**).

On physical examination, patients generally appear malnourished. Abdominal tenderness in the epigastrium may be elicited. Significant laboratory values to note include chemistries to assess dehydration and acidosis, a hepatic panel to investigate biliary obstruction or malnutrition, and serum amylase and lipase which may be elevated or may be normal in advanced disease.

RADIOGRAPHIC EVALUATION

Radiography is important in both diagnosis and management of CP. Multiphase, contrast enhanced abdominal computed tomography (CT pancreas protocol) can show pancreatic parenchymal changes of pancreatitis including edema, fibrosis, and atrophy. Pancreatic ductal dilation may be evident, as well as intraductal or intraparenchymal calcifications (**Fig. 54.2**). CT can be helpful in identifying complications of pancreatitis such as biliary

or duodenal obstruction, pseudocysts or ascites, or mesenteric vascular complications. Magnetic resonance pancreatography (MRP) can be useful in revealing parenchymal changes in enhancement and secretion (T1-weighted images) and ductal changes (T2-weighted images), particularly with the addition of secretin stimulation (**Fig. 54.3**). With increased capabilities of MR technology, MR imaging has largely replaced endoscopic retrograde cholangiopancreatography (ERCP) in diagnosis of CP. In the modern era, ERCP is utilized for therapeutic means including endoscopic sphincterotomy, dilation, and stenting. Endoscopic ultrasound (EUS) is useful for evaluation of pancreatic parenchyma and ductal anatomy. EUS has a grading system to objectify and document pancreatitis disease severity, although the system is flawed by interobserver variability (**Table 54.2**).[21]

Table 54.1 Complications of Chronic Pancreatitis

Pain	90%
Pseudocyst	25–30%
Biliary stricture	10–15%
Mesenteric venous thrombosis	5–10%
Duodenal stricture	4–5%
Pseudoaneurysm	2–3%
Pancreatic adenocarcinoma	2–4%[a]
Extrapancreatic malignancy	10–15%

[a]Risk of pancreatic cancer is 2% after 10 years and 4% after 20 years with chronic pancreatitis.

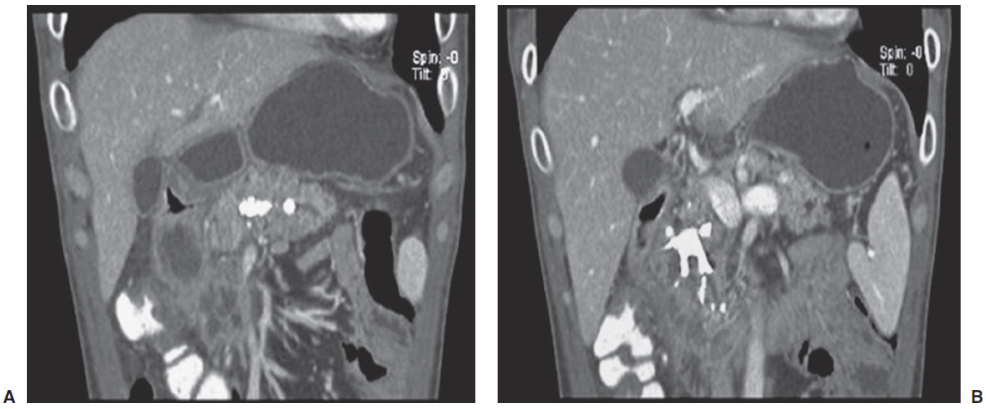


Figure 54.2 Contrasted CT scan in venous phase; coronal images showing (**A**) dilated main pancreatic duct with intraductal stones and (**B**) significant fibrotic disease burden in the head of the pancreas with intraparenchymal and intraductal calcifications.

CONSIDERATIONS IN MANAGEMENT

3 Frontline management of CP includes risk factor modification, such as alcohol and tobacco cessation. Primary medical interventions entail pain management, including adjunctive behavioral therapy, and nutritional optimization, including pancreatic enzyme replacement therapy. Behavioral therapy is a keystone of therapy in CP and is effective in modulating pain perceptions and in managing opioid misuse.[22]

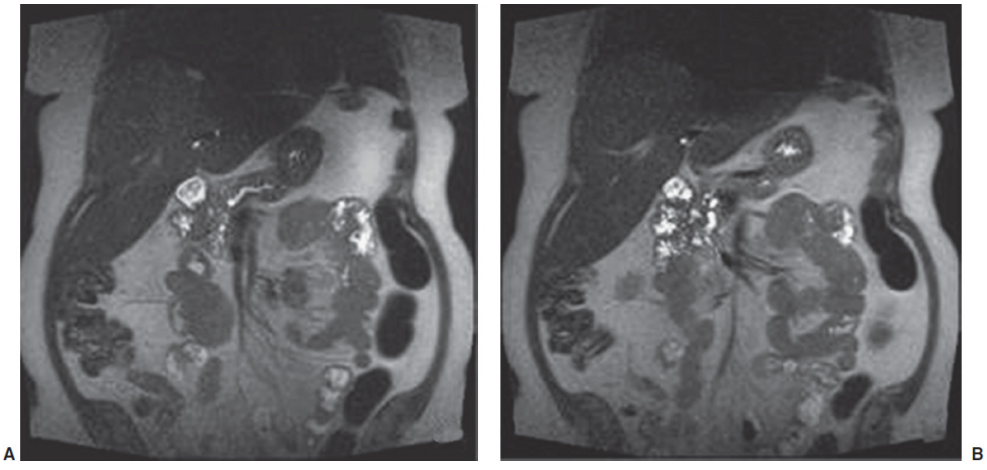


Figure 54.3 T2-weighted magnetic resonance imaging with secretin stimulation demonstrate a pathologically dilated pancreatic duct in the body of the pancreas (**A**) and cystic changes and dilated ducts in a fibrotic and inflammatory head of the pancreas (**B**).

ENDOSCOPIC MANAGEMENT

ERCP is the primary endoscopic modality for therapy in CP, with the goal of relieving obstructive pathology. Potential maneuvers include sphincterotomy, stone extraction, stricture dilation, and stenting.

EUS can be utilized for endoscopic pseudocyst drainage procedures and for celiac plexus neurolysis. Percutaneous and endoscopic-guided celiac nerve blockade has been utilized to manage CP pain. Meta-analysis studies of EUS-guided celiac plexus blockade found short-term pain relief in about one-half of the subjects.[23]

Table 54.2 EUS Criteria for Chronic Pancreatitis

Parenchymal Criteria
Hyperechoic foci
Hyperechoic strands
Hyperechoic lobules, foci or areas
Cyst
Ductal Criteria
Irregular duct contour
Visible side branches
Hyperechoic duct margin
Dilated main duct
Stone
Normal (Low Probability)
0–2 criteria present
Indeterminate (Intermediate Probability)
3–4 criteria present
High Probability
5–9 criteria present

EUS, endoscopic ultrasound.

From Wallace MB, Hawes RH, Durkalski V, et al. The reliability of EUS for the diagnosis for chronic pancreatitis: Interobserver agreement among experienced endosonographers. *Gastrointest Endosc* 2001;53:294–299.

In general, the endoscopic approach is undertaken prior to consideration of surgery, given the perceived advantages of lower morbidity with a less invasive approach. Two prospective, randomized, controlled trials have compared endoscopy and surgery in patients with obstructive CP. Dite and colleagues randomized 72 patients with CP, pancreatic duct obstruction, and pain to endoscopic or surgical intervention. At 5-year follow-up, the surgical group had a greater proportion of patients that were pain free (34% vs. 15%).[24] Cahen and colleagues randomized 39 patients and found the surgical group had a greater proportion of patients that had pain relief (80% vs. 38%, $p = 0.001$), had greater improvements in quality of life, and underwent fewer procedures, despite equivalent morbidity, length of stay, and preserved pancreatic function at 5 years.[25]

SURGICAL MANAGEMENT

Approximately two-thirds of patients with debilitating pain from CP fail medical and endoscopic managements 4 . The goals of surgery are to effectively relieve pain while minimizing morbidity, including minimizing perioperative complications and preserving pancreatic parenchyma. The pancreatic anatomy is the primary determinant in surgical planning. Patients with a dilated (greater than 6 to 7 mm diameter) main pancreatic duct are assumed to have obstructive pathology and are candidates for a drainage-type procedure (lateral pancreaticojejunostomy, Frey procedure). Patients with a small-diameter main pancreatic duct are considered for resection of fibrotic and poorly drained parenchyma. Patients with head-predominant or tail-centered disease can undergo a directed partial resection. In patients with diffuse parenchymal involvement, a TP with islet autotransplantation may be appropriate (**Algorithm 54.1**).

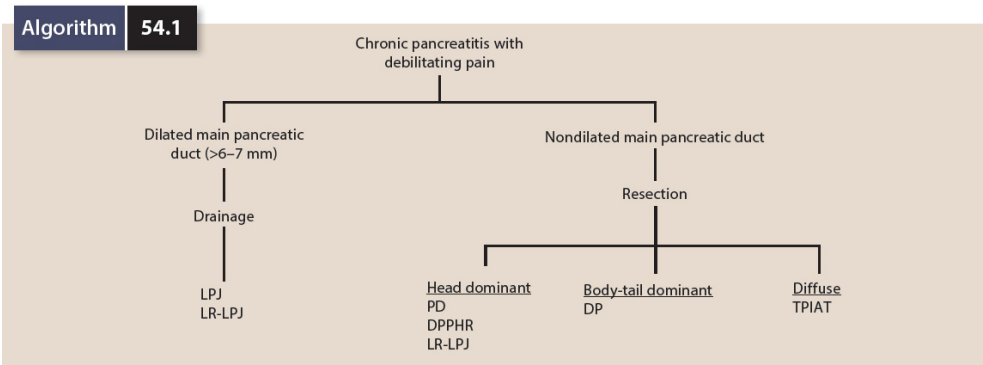
Lateral Pancreaticojejunostomy

Retrograde pancreatic drainage for relapsing pancreatitis was described by Puestow and Gillesby in 1958.[26] A modification of this original drainage procedure that more closely resembles the modern-day technique of the lateral pancreaticojejunostomy (LPJ) was reported by Partington and

Rochelle in 1960.[27] LPJ is the classic operation for pancreatic drainage and entails opening the pancreatic duct anteriorly along its length, medially to the level of the gastroduodenal artery and laterally into the tail. The opened pancreatic duct is then cleared of stones, including into the head, and anastomosed to a Roux-en-Y jejunal limb for drainage.

Procedure-specific complications of note include intraoperative hemorrhage (due to splenic vein or gastroduodenal artery injury), postoperative hemorrhage (often from the gastroduodenal artery), and anastomotic leak (seen in 10% of cases).

Multiple retrospective single-institution case series have been reported evaluating outcomes with LPJ, with pain-relief rates of 48% to 91%.[28–30] Morbidity rates are low (20% on average) and endocrine and exocrine function is often preserved.[31] LPJ is an effective and safe procedure for pain relief in many patients with dilated duct pancreatitis. Recurrent pain does occur after LPJ, however, likely due to pathology in the head of the pancreas. Intraductal stone disease in the head of the pancreas can be cleared with intraoperative pancreatoscopy and electrohydraulic lithotripsy, which has been shown to improve outcomes (reduced readmissions, increased pain-relief rates).[32] Alternatively, combining a localized head resection with LPJ can help to reduce recidivism.



Algorithm 54.1 Algorithm for operative decision-making in chronic pancreatitis. LPJ, lateral pancreaticojejunostomy; LR-LPJ, local pancreatic head resection with lateral pancreaticojejunostomy; PD, pancreatoduodenectomy; DPPHR, duodenum preserving pancreatic head resection; DP, distal pancreatectomy; TPIAT, total pancreatectomy with islet autotransplantation.

Localized Pancreatic Head Resection with Lateral Pancreaticojejunostomy

In 1987, Frey and colleagues described a local pancreatic head resection with lateral pancreaticojejunostomy (LR-LPJ) with the goal of achieving pancreatic ductal drainage, removal of damaged and poorly drained parenchyma in the head of the pancreas, and preservation of the duodenum to minimize postoperative gastrointestinal dysfunction. Frey reported initially on 50 patients, describing a morbidity of 22% and a pain-relief rate of 84%.[33] His outcomes have been validated in modern series, both at his own institution and at others, with pain-relief rates of 62% to 88%.[34,35]

Pancreatic Head Resection

Pancreatoduodenectomy (PD) for CP was described as early as 1946 by Whipple.[36] In the modern era, PD is the operation of choice for patients with complicated CP and head-dominant disease. Patients may present with duodenal or biliary obstruction as well as obstructive pancreatopathy from an inflammatory mass in the head of the pancreas. Outcomes for PD include pain relief in 70% to 89% of patients, morbidity in 16% to 53%, and mortality in less than 5% in high-volume centers.[30–37]

The pylorus-preserving pancreatoduodenectomy (PPPD) was popularized by Traverso and Longmire in an effort to maintain the physiologic benefits of a functional pylorus.[38] PPPD has been well adopted into pancreas surgery although the purported nutritional advantages have not been evidenced.[39–41] Some authors, however, have reported improved professional rehabilitation and quality of life after PPPD as compared to classic PD.[42]

Duodenum-preserving pancreatic head resection (DPPHR) was developed by Beger and colleagues in the 1970s in an effort to decrease the morbidity of pancreatic head resection for CP. Pain relief is reported in 77% to 88% of patients, with professional rehabilitation rates of 63% to 69% (**Fig. 54.4**). Morbidity and mortality are acceptable at 28.5% and 1%, respectively.[43,44] The ChroPac trial, a recent multicenter European trial, randomized 226 patients to PD (or PPPD) versus DPPHR. Perioperative morbidity was lower in the PD group and at 2 years follow-up, there was no difference in

the development of endocrine or exocrine failure or quality of life between the groups.[45]

Distal Pancreatectomy

In patients with CP and disease localized to the body and tail of the pancreas or in patients with a main pancreatic duct stricture in the neck or body, distal pancreatectomy (DP) can be an effective means of pain relief. The majority of CP patients who are candidates for DP have severe inflammatory changes in the region of the splenic hilum, making concomitant splenectomy necessary. Pain-relief rates of 57% to 84% are reported, with 15% to 32% morbidity.[46,47] Postoperative pancreatic fistula after DP is the primary morbidity of this operation and appears to be related to patient-specific factors rather than to operative technique.[48]

Total Pancreatectomy

5 TP for CP was performed as early as 1944 by Clagett at the Mayo Clinic. Perhaps tellingly, his patient died 10 weeks after surgery of a hypoglycemic event. TP can be an effective means of pain relief in patients with diffuse small-duct pancreatitis, as salvage therapy in patients who have failed lesser surgeries, and in patients with genetic pancreatitis. There is a requisite brittle type 3c pancreatogenic diabetes that follows TP, however, with severe, potentially life-threatening hypoglycemic episodes. With TP, there is loss of not only insulin-producing beta cells but also of the alpha cells and other composite cells of the islet that produce hormones to maintain glucose homeostasis. As a result, patients may demonstrate an unpredictable response to exogenous insulin and, importantly, may develop hypoglycemic unawareness.

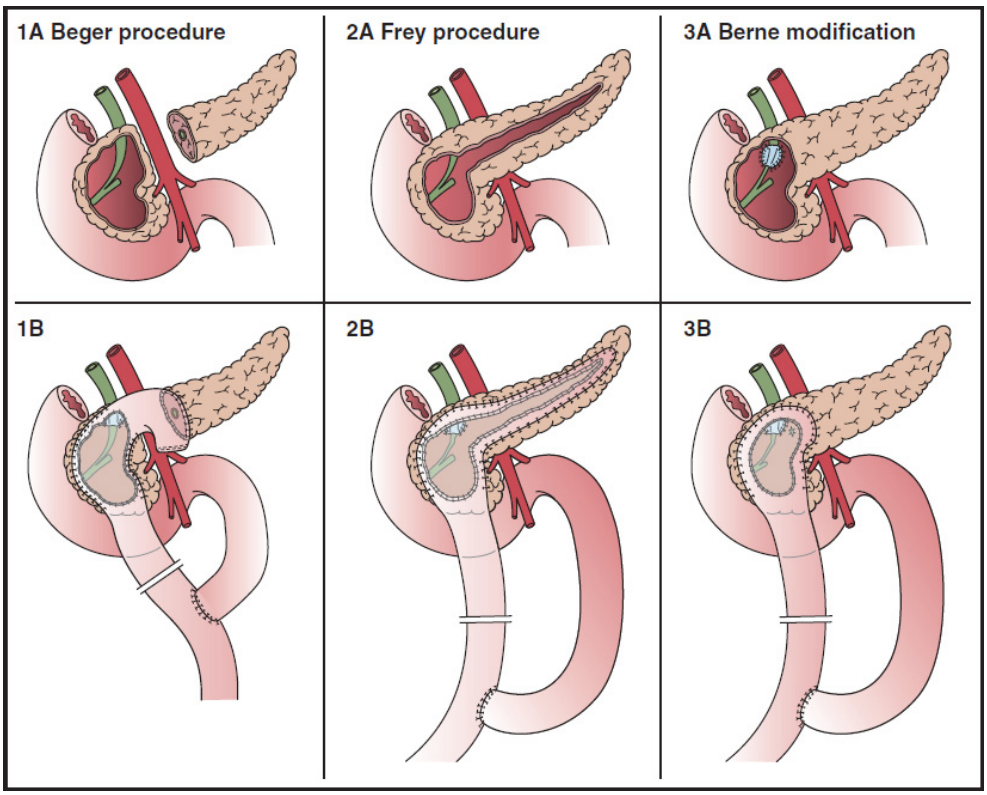


Figure 54.4 Schematic drawings of extent of resection (**A**) and method of reconstruction (**B**) for a Beger procedure (*1*), Frey procedure (*2*), and a Berne modification of the Beger procedure (*3*). (Reproduced from Müller MW, Freiss H, Leitzbach S, et al. Perioperative and follow-up results after central pancreatic head resection (Berne technique) in a consecutive series of patients with chronic pancreatitis. *Am J Surg* 2008;196:364–372.)

Total pancreatectomy with islet autotransplantation (TPIAT) was described by Sutherland and colleagues at the University of Minnesota in 1978, with the goal of ameliorating the brittle diabetes after extensive pancreatectomy.[48] TPIAT has been increasingly accepted over the past decade, and understanding of long-term outcomes is evolving. Pain-relief rates of 72% to 86% have been reported and patients have a significantly improved quality of life. Morbidity rates of 47% to 55% are reported, with 1.4% to 6% mortality, and insulin independence in 10% to 40% long term after islet transplant.[49–51] Insulin independence after TPIAT correlates with the number of islet equivalents per kilogram harvested,[52] and transplanted islet function appears to be durable, with outcomes reported for more than 13 years.[53] Genetic pancreatitis patients have the most favorable outcomes,[51] whereas patients with alcohol-related pancreatitis fare poorly with TPIAT.[54]

A multicenter prospective observational outcomes study evaluating TPIAT is currently in progress.

Minimally Invasive Surgery for Chronic Pancreatitis

Minimally invasive pancreas surgery encompasses laparoscopic and robotic approaches. Laparoscopy began in pancreas surgery with laparoscopic staging for pancreatic cancer. The development of endoscopic stapler technology in the mid 1990s allowed for more complex pancreatic resections to emerge, and the epidemic of incidentally discovered low-grade pancreatic neoplasms allowed for the evolution of laparoscopy as the standard approach to DP. Single and multicenter comparative studies,[55,56] and now several single and multicenter randomized controlled trials[57–59] have demonstrated the efficacy of minimally invasive pancreas surgery. Minimally invasive DP has been shown to have lower blood loss, length of stay, and morbidity compared to open DP, with equivalent operative times and pancreatic fistula rates.[55,57] Minimally invasive PD has been demonstrated to have equivalent outcomes to open DP at expert centers.[56] A recent evidence-based consensus statement on minimally invasive pancreatic surgery reviewed available evidence.[60] Importantly, much of the reported experience in minimally invasive pancreas surgery is for low-grade pancreatic neoplasms and pancreatic cancer. Minimally invasive surgical approaches to CP are technically more challenging due to fibrotic distortion of anatomy and obliteration of normal tissue planes.

CONCLUSIONS

CP is a complex disease, challenging in management. Notable recent progress has been made in understanding the underlying pathophysiology, including genetic causes and cellular and biochemical mechanisms, with much still to be learned. Surgery can be beneficial in many patients with debilitating pain from CP. Evolving surgical therapies, such as TPIAT and minimally invasive techniques, are promising.

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Neoplasms of Exocrine Pancreas

Motaz Qadan and Cristina R. Ferrone

Key Points

1. The incidence of pancreatic cancer continues to rise around the world. Risk factors include smoking, obesity, diabetes mellitus, chronic pancreatitis, and germline mutations in *BRCA2* and *CDKN2A.*
2. The most common mutations identified in PDAC are *KRAS, CDKN2A, TP53,* and *SMAD4*.
3. Intraductal papillary mucinous neoplasms (IPMNs) are important recognized precursor lesions for pancreatic ductal adenocarcinoma and are subclassified as main-duct, branch-duct, or mixed type depending on location.
4. Pancreatic protocol contrast-enhanced computed tomography (CT) is commonly utilized for staging and surveillance. Endoscopic ultrasonography (EUS) with biopsy is essential if neoadjuvant therapy is being considered.
5. A Whipple pancreaticoduodenectomy is performed for head, neck, and uncinate tumors of the pancreas and a distal pancreatectomy (with splenectomy) for body and tail lesions.
6. Systemic therapy utilizing 5-FU/leucovorin/oxaliplatin/irinotecan (FOLFIRINOX) and gemcitabine/abraxane have significantly improved the overall survival of patients with resectable and metastatic PDAC.
7. Palliation of patients with incurable pancreatic cancer may require endoscopic and/or surgical interventions to establish biliary drainage and prevent or relieve gastric outlet obstruction.

INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States in men and women. Overall 5-year survival for patients with pancreatic cancer is 9%.[1] The majority of tumors are exocrine adenocarcinomas (93%) and fewer are pancreatic neuroendocrine tumors

(7%). Surgical resection offers the only chance for long-term cure. Unfortunately, because of the late presentation and early disease dissemination, only 15% to 20% of patients present with resectable disease. Five-year survival after pancreaticoduodenectomy (PD) is improving as systemic therapy becomes more effective. The absence of symptoms associated with early pancreatic cancer, inaccessibility of the pancreas to examination, aggressive tumor biology associated with the disease, and technical difficulties associated with pancreatic surgery render pancreatic cancer as one of the most challenging diseases treated by surgeons and oncologists.

In recent years, significant advances have been made in our understanding of the pathogenesis and clinical management of pancreatic cancer. This chapter reviews the epidemiology and risk factors associated with pancreatic cancer, discuss recent developments in the field of molecular genetics, and provide an update on the current clinical and oncologic management of pancreatic cancer.

EPIDEMIOLOGY AND RISK FACTORS

In the United States, it is estimated that nearly 57,600 new cases of pancreatic cancer will be diagnosed with almost 47,050 people dying of the disease in 2020. Pancreatic cancer accounts for 3% of all cancers in the United States and is responsible for 7% of all cancer deaths. The incidence of pancreatic cancer in the United States is 12.4 per 100,000 populations. The lifetime risk for developing pancreatic cancer is 1.5%.[1] The incidence of pancreatic cancer has slowly been increasing, with an average increase of 0.8% per year over the last 10 years (**Fig. 55.1**). The risk of development of pancreatic cancer is related to age, race, sex, tobacco use, diet, and specific genetic syndromes (**Table 55.1**). The incidence increases with advancing age. More than 80% of cases occur in persons between the ages of 60 and 80 years, and pancreatic cancer is rare in people younger than 40 years. The incidence and mortality rates for pancreatic cancer in African Americans of both sexes are higher than those in whites. The gender differences in pancreatic cancer have been diminishing in recent years with 30,400 cases

predicted in men compared with 27,200 among women. Similarly, 24,640 deaths are predicted in men in 2020 compared with 22,410 among women.

Environmental and dietary factors have also been implicated as risk factors for the development of pancreatic cancer. The most consistently observed environmental risk for the development of pancreatic cancer remains cigarette smoking. It has been estimated that cigarette smoking can increase the risk for pancreatic cancer between 1.5 and 5 times. The mechanism is unknown, but carcinogens in cigarette smoke have been shown to produce pancreatic cancers in experimental studies. In addition, autopsy studies have documented hyperplastic changes in pancreatic ductal cells with atypical nuclear patterns in smokers. Alcohol consumption does not seem to be a risk factor for pancreatic cancer despite conflicting prior data. Recent studies suggest that past studies linking pancreatic cancer to alcohol use may have, in fact, been confounded by tobacco use. Similarly, coffee consumption and exposure to ionizing radiation have been shown not to be associated with an increased pancreatic cancer risk.

Several epidemiologic investigations have suggested that diet may play an important role in the development of pancreatic cancer. An apparent association has been noted between pancreatic cancer and an increased consumption of total calories, carbohydrates, cholesterol, meat, salt, dehydrated food, fried food, refined sugar, soybeans, and nitrosamines. The risks are unproven, however, for the ingestion of fat, beta-carotene, and coffee. A protective effect has been reported for dietary fiber, vitamin C, fruits, and vegetables.[2]

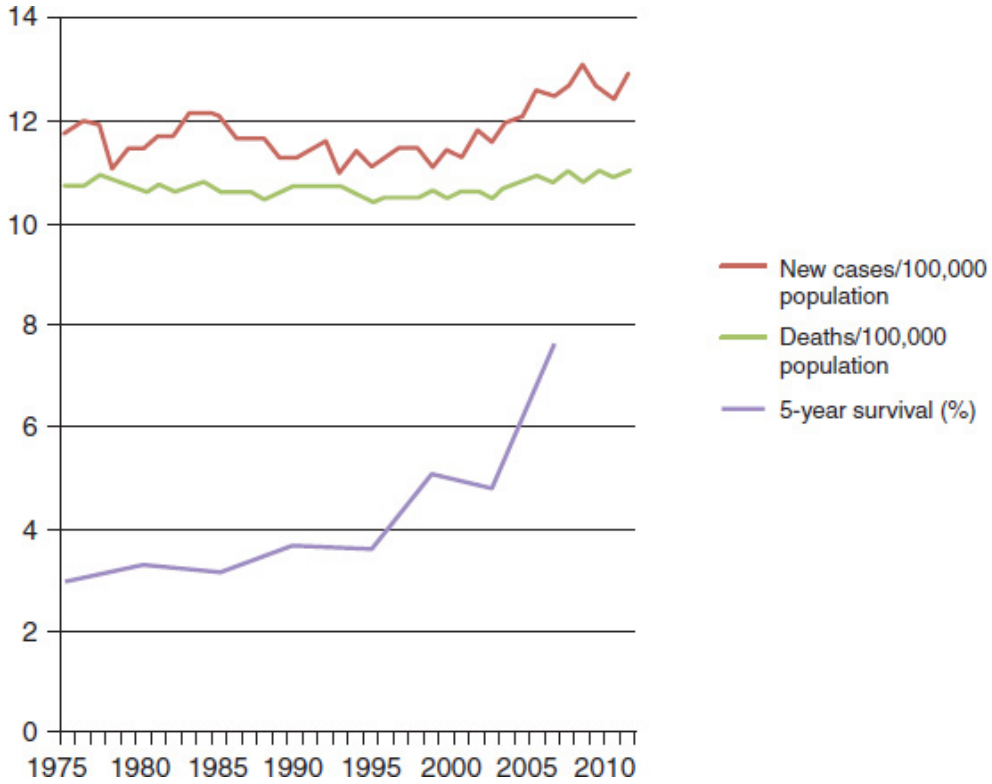


Figure 55.1 U.S. pancreatic cancer new cases, death rate, and 5-year survival. (Adapted from *EER Cancer Statistics Factsheets: Pancreas Cancer*. Bethesda, MD: National Cancer Institute. Available at http://seer.cancer.gov/statfacts/html/pancreas.html. Accessed March 10, 2016.)

In addition to well-defined genetic syndromes, a number of common conditions constitute etiologic factors in the development of pancreatic cancer. An apparent association between diabetes and pancreatic cancer has been suggested. Approximately 80% of patients diagnosed with pancreatic cancer have impaired glucose metabolism, impaired glucose tolerance, or diabetes mellitus. It is unclear if alterations in glucose tolerance/metabolism are a causative factor for pancreatic cancer or represent reaction to an enlarging malignancy in the pancreas. Among patients with newly diagnosed diabetes, 0.85% went on to be diagnosed with pancreatic cancer within 3 years.[3] Type II diabetes of at least 5 years duration has been associated with a twofold increase in pancreatic cancer.

The risk of pancreatic cancer has also been shown to increase as body mass index increases. Examination of data from the Nurses' Health Study and the Health Professional's follow-up study previously demonstrated a 1.72

relative risk (95% CI 1.19–2.48) of pancreatic cancer in patients with a BMI >30 kg/m^2 as compared to individuals with a BMI <23 kg/m^2.

Table 55.1 Risk Factors for Pancreatic Cancer

	Increased Risk	Possible Risk	Unproved Risk
Demographic factors	Advancing age Male sex Black race	Geography	Socioeconomic status Migrant status
Host factors	Hereditary nonpolyposis colorectal cancer Familial breast cancer Peutz–Jeghers syndrome Ataxia–telangiectasia Familial atypical multiple-mole melanoma Hereditary pancreatitis		Peptic ulcer surgery
Environmental factors	Tobacco	Diet Occupation	Alcohol Coffee Radiation

Modified from Gold EB, Goldin SB. Epidemiology of and risk factors for pancreatic cancer. *Surg Oncol Clin North Am* 1998;7:67.

Chronic pancreatitis of any cause has been associated with a 25-year cumulative risk for the development of pancreatic cancer of approximately

4%. Other conditions for which a possible association with pancreatic cancer has been demonstrated include thyroid and other benign endocrine tumors, cystic fibrosis, and pernicious anemia.

Most cases of pancreatic cancer have no obvious predisposing factors. However, it is believed that between 5% and 10% of pancreatic cancers are associated with a familial predisposition. Six genetic syndromes have been associated with an increased risk for the development of pancreatic cancer (**Table 55.2**).

1 MOLECULAR GENETICS

Invasive pancreatic ductal adenocarcinoma (PDAC) tumors are genetically complex, with wide-spread chromosome abnormalities, numerous losses and gains of large segments of DNA, and, on average, more than 60 exomic alterations in each tumor.[4] PDAC harbors an average of 63 genome alterations, of which the majority are point mutations. Four key genes that are frequently altered in PDAC include *KRAS, CDKN2A, TP53,* and *SMAD4* (**Table 55.3**). The most common gene alteration is in *KRAS*, where mutations occur in codons 12, 13, and 61. More than 90% of PDAC tumors possess *KRAS* mutations. Point mutations of the K-*ras* oncogene impair the intrinsic guanosine triphosphatase activity of its gene product. The result is a protein that is constitutively active in signal transduction *and* activates various downstream signaling pathways, including the mitogen-activated protein kinase (MAPK) cascades. Ras proteins are involved in a variety of cellular functions, including proliferation, differentiation, and survival. Cyclin-dependent kinase inhibitor 2A gene (*CDKN2A*) is also inactivated in up to 90% of PDAC due to intragenic mutations in association with allelic loss, homozygous deletion, or hypermethylation of the gene promoter. *CDKN2A* encodes a cyclin-dependent kinase inhibitor that controls G1–S transition in the cell cycle. Inactivation of *CDKN2A* leads to the loss of an important cell cycle checkpoint, thereby resulting in unchecked cellular proliferation. *TP53* is one of the most frequently mutated genes in many cancers, and is inactivated in about 75% of PDAC, mainly due to point mutations or small deletions. The *p53* gene product is a DNA-binding protein that acts as both a cell-cycle checkpoint and an inducer of apoptosis. Inactivation of the *p53*

gene in pancreatic cancer therefore leads to the loss of two important controls of cell growth including regulation of cellular proliferation and induction of cell death. *SMAD4* (*DPC4,* SMAD family member 4 gene). *SMAD4* encodes a transcription factor that mediates signaling of the transforming growth factor-β (TGF-β) superfamily. *SMAD4* is a tumor-suppressor gene that has been identified on chromosome 18q. This chromosome has been shown to be absent in nearly 90% of pancreatic cancers. The *SMAD4* gene is inactive in almost 50% of pancreatic carcinomas. The mutation appears to be a homozygous deletion in 30% of pancreatic cancers, and a point mutation in another 20% of tumors. *SMAD4* mutations are more specific than *p53* or *p16* mutations for pancreatic cancer.

Table 55.2 Genetic Syndromes Associated with Hereditary Pancreatic Cancer

Syndrome	Mode of Inheritance	Gene	Fold Increase in Risk	Manifestation of Pancreatic Cancer
Peutz–Jeghers	AD	*STKll*	140×	Hamartomatous polyps of the gastrointestinal tract; mucocutaneous melanin macules
Hereditary pancreatitis	AD	*PRSSl*	60×	Recurrent episodes of severe pancreatitis starting at a young age
Familial pancreatic cancer	Unknown	Unknown	18×	At least one pair of first-degree relatives with pancreatic cancer
FAMMM	AD	p16	20×	Multiple nevi, atypical nevi, and melanomas
Familial breast cancer 2	AD	*BRCA2*	10×	Breast, ovarian, and pancreatic cancer
HNPCC	AD	*MSH2 HLHl*	Unknown	Colonic, endometrial, and gastric cancers; mutator phenotype

AD, autosomal dominant; FAMMM, familial atypical multiple mole melanoma; HNPCC, hereditary nonpolyposis colorectal cancer.

Germline mutations in *BRCA2* and *CDKN2A,* and less frequently in *BRCA1, PALB2*, and *ATM* have been identified in a small subset of patients with familial pancreatic cancer. The inactivation of *BRCA2,* which encodes a protein involved in DNA damage repair, is associated with a 3.5- to 10-fold increased risk of pancreatic cancer, in addition to the widely referenced increased risk of breast and ovarian cancer. In addition, patients with Lynch syndrome (caused by germline mutation in one of the mismatch repair genes *MLH1, MSH2, MSH6,* or *PMS2*) and Peutz–Jegher syndrome (caused by germline mutation of the *STK11* gene) are at increased risk of pancreatic cancer. Approximately 4% of pancreatic cancers can be characterized by

disorders of DNA mismatch–repair genes with potential implications in responses to immunotherapeutics.[5]

Table 55.3 Genetic Alterations in Pancreatic Adenocarcinomas

Gene	Chromosome Locus	Frequency (%)
Oncogenes	12	90
K-*ras*		
Tumor-suppressor	9p	95
genes	17p	50–75
CDKN2A	18q	55
p53	13q	7
SMAD4		
BRCA2		

2 PATHOLOGY

Tumors of the exocrine pancreas can be classified according to their cell of origin (**Table 55.4**). The most common neoplasms of the exocrine pancreas are ductal adenocarcinomas. Approximately 65% of PDACs arise in the head, neck, or uncinate process of the pancreas; 15% originate in the body or the tail of the gland; and 20% diffusely involve the whole gland.

Table 55.4 Histologic Classification of 645 Cases of Primary Nonendocrine Cancer of the Pancreas

Classification	Number
Duct cell origin	572 (89%)
Duct cell adenocarcinoma	494
Giant cell carcinoma	28
Adenosquamous carcinoma	20
Microadenocarcinoma	16
Mucinous carcinoma	9
Mucinous cystadenocarcinoma	5
Acinar cell origin	8 (1%)
Acinar cell carcinoma	7
Cystadenoma	1
Uncertain histogenesis	61 (9%)
Pancreaticoblastoma	1
Papillary and cystic neoplasm	1
Mixed type—duct and islet cells	1
Unclassified	58
Connective tissue origin	4 (1%)

From Bell RH. Neoplasms of the exocrine pancreas. In: Greenfield LJ, Mulholland MW, Oldham KT, eds. *Surgery: Scientific Principles and Practice*. 2nd ed. Philadelphia, PA: Lippincott–Raven; 1997:901, with permission.

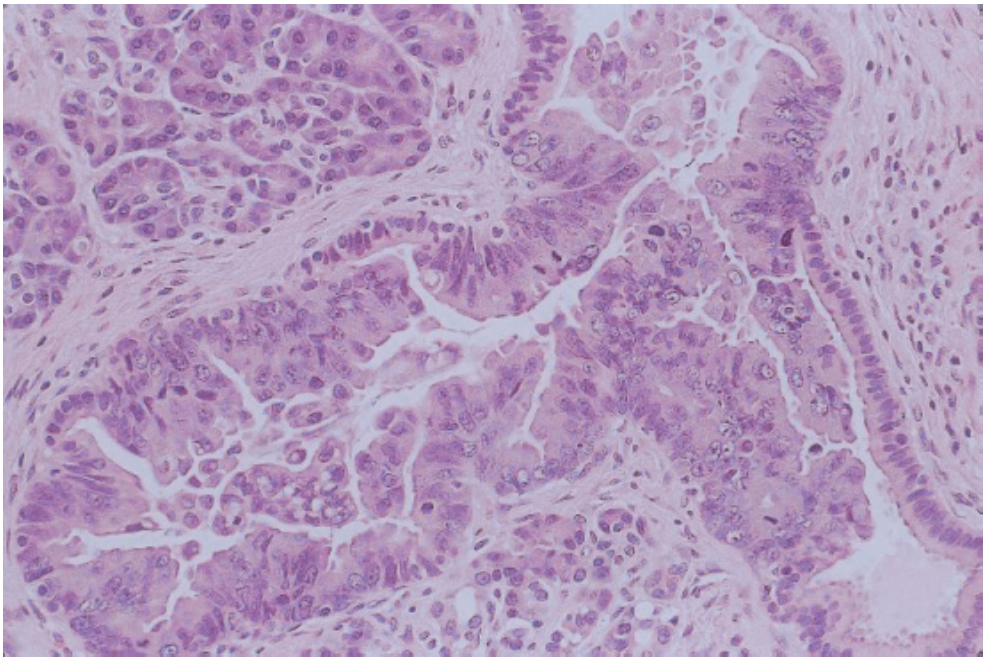


Figure 55.2 Microscopic appearance of ductal adenocarcinoma of the head of the pancreas demonstrating glands from an adenocarcinoma embedded in a fibrous matrix.

Solid Epithelial Tumors of the Pancreas

Ductal Adenocarcinomas

Ductal adenocarcinomas account for more than 75% of all nonendocrine pancreatic cancers. Grossly, they are pale, poorly defined, hard masses that often obstruct the distal common bile duct and/or main pancreatic duct. They are often associated with a biologically-intimate desmoplastic reaction that causes fibrosis and chronic pancreatitis. Microscopically, they contain infiltrating glands of varying size and shape surrounded by dense, reactive, fibrous tissue (**Fig. 55.2**). The epithelial cells sometimes form papillae and cribriform structures, and they frequently contain mucin. The nuclei of the cells can show marked pleomorphism, hyperchromasia, loss of polarity, and prominent nucleoli.

Ductal adenocarcinomas tend to infiltrate into vascular, lymphatic, and perineural spaces. At the time of resection, most ductal carcinomas have already metastasized to regional lymph nodes. In addition to regional lymph nodes, these tumors frequently metastasize to the liver (80%), peritoneum

(60%), and lungs and pleurae (50% to 70%). They also directly invade the duodenum, stomach, transverse mesocolon, spleen, and adrenal glands. Distant nodal involvement is also common.

The histologic examination of a pancreas resected for cancer frequently reveals the presence of precursor lesions in the pancreatic ducts and ductules adjacent to the cancer. This suggests that much like colon cancer, which arises from benign adenoma precursors, pancreatic cancer may also demonstrate progression to malignant disease from benign precursor lesions. Known precursor lesions include pancreatic intraepithelial neoplasia (PanIN). Briefly, PanIN-1A and PanIN-1B are proliferative lesions without remarkable nuclear abnormality that possess flat and papillary architecture, respectively. PanIN-3 is associated with severe architectural and cytonuclear abnormalities, but invasion through the basement membrane is absent. PanIN-2 is an intermediate category between PanIN-1 and PanIN-3 and is associated with a moderate degree of architectural and cytonuclear abnormality.[6] Older data suggest that PanINs are precursors of infiltrating pancreatic cancer: PanINs are often found in association with ductal adenocarcinomas, three-dimensional mapping techniques that demonstrated a stepwise transformation from mild dysplasia to severe dysplasia in pancreatic duct lesions, and PanINs demonstrate some of the same genetic changes seen in infiltrating adenocarcinomas, most notably activating point mutations in codon 12 of K-*ras* and mutations in the *p16* and *p53* tumor-suppressor genes.

Adenosquamous Carcinomas

Adenosquamous carcinoma is a rare variant of ductal adenocarcinoma that shows both glandular and squamous differentiation. This variant appears to be more common in patients who have undergone previous radiation therapy, although the exact etiology is not known. The biologic behavior of adenosquamous carcinoma appears to be similar to that of ductal adenocarcinoma, with similar rates of perineural invasion, lymph node metastases, and distant disease dissemination.

Acinar Cell Carcinomas

Acinar cell carcinomas account for only 1% of pancreatic exocrine tumors. Acinar tumors are typically smooth, fleshy, lobulated, hemorrhagic, or necrotic. Histologically, they form acini, and the cells display an eosinophilic and granular cytoplasm. Immunohistochemical staining demonstrates expression of trypsin, lipase, chymotrypsin, or amylase. These tumors are more common in males with a male-to-female predominance of approximately 3:1. The age of diagnosis is usually in the fifth to seventh decades. These tumors tend to be substantially larger than ductal adenocarcinomas, with improved prognosis compared with patients with ductal carcinoma.[7] Surgical resection is the curative treatment of choice.

Solid-Pseudopapillary Neoplasms

Solid-pseudopapillary neoplasms (SPN), also termed solid and cystic tumors, papillary cystic tumors, *Hamoudi* tumors, and *Frantz* tumors occur primarily in women in their third to fourth decades of life. Grossly, the masses range from 5 to 15 cm in diameter. Radiologically, they present as a well-demarcated heterogeneous mass with solid and cystic components, with a peripheral capsule which rarely shows calcifications. EUS-guided fine needle aspiration (FNA) or core biopsy is often diagnostic, showing uniform cells forming microadenoid structures, branching, and papillary clusters with delicate fibrovascular cores. Most SPNs exhibit benign behavior, and even the less than 20% of tumors that have vascular or perineural invasion, lymph node involvement, or liver metastases frequently have an indolent course. The 5-year overall survival is close to 97% in patients who undergo complete surgical resection.

Pancreatoblastoma

Pancreatoblastomas occur primarily in children ages 1 to 15 years. Pancreatoblastomas contain both epithelial and mesenchymal elements. The epithelial component appears to arise from acinar cells. The tumors are typically larger than 10 cm and often contain areas of degeneration and hemorrhage. The prognosis appears to be more favorable than that for typical ductal adenocarcinoma if the tumor can be resected.

Cystic Epithelial Tumors of the Pancreas

Cystic neoplasms also arise from the exocrine pancreas. Cystic neoplasms are less common than ductal adenocarcinomas; tend to occur in women, and are, on the whole, evenly distributed throughout the gland. Many pancreatic and peripancreatic cysts are still benign inflammatory pseudocysts. It is important to identify cystic neoplasms which require careful surveillance and potential surgical resection. With advancements in imaging technology and increased utilization, cystic lesions of the pancreas are being detected with increased frequency. The majority of pancreatic cysts are often detected incidentally.[8] Although many of these lesions are small and asymptomatic, they can have malignant potential and mucinous lesions are premalignant by nature. The management of these patients is complex, and knowledge of pancreatic cyst natural history and predictors of neoplasia are important.

Serous Cystic Neoplasms

Serous cysts are epithelial neoplasms composed of uniform cuboidal glycogen-rich cells that usually form numerous small cysts containing serous fluid. Serous cystadenomas, or microcystic adenomas, are more common in women than in men (3:1 preponderance). These tumors can vary from a few centimeters to more than 10 cm in size. Twenty-five percent to 30% of patients are asymptomatic. However, most patients present with symptoms such as abdominal or epigastric pain, dyspepsia, nausea, or vomiting. Serous cystadenomas can be located anywhere in the pancreas and usually do not communicate with the pancreatic ducts. Plain computed tomography (CT) shows a honeycomb pattern of microlacunae, with thin septa separating different segments. Serous cystic neoplasms can have a sunburst pattern of central calcification, which is seen in 10% to 30% of cases. Grossly, they appear as spongy, well-circumscribed, multiloculated cysts. Microscopically, they consist of a layer of simple cuboidal cells separated by dense fibrous bands. Serous cystic neoplasms are benign. However, symptomatic cysts or cysts that cannot be differentiated from other potentially malignant cysts should undergo surgical excision.

Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCNs) are neoplasms composed of mucin-producing epithelial cells associated with a pathognomonic "ovarian-type" stroma. These cysts usually do not communicate with the larger pancreatic ducts. MCNs are relatively uncommon but account for almost 30% of all cystic neoplasms. The mean age at diagnosis is between 40 and 50 years. MCNs are more common in women with a female-to-male ratio of 9:1. Most patients with MCNs present with vague abdominal symptoms that include epigastric pain or a sense of abdominal fullness. The majority (70% to 90%) of MCNs arise in the body or tail of the pancreas, and only a minority (10% to 30%) involve the head of the gland. Microscopically, these cysts are lined by tall columnar mucin-producing epithelium. These columnar cells have basal nuclei and abundant intracytoplasmic apical mucin and can form flat sheets or papillae. The stroma is composed of densely packed spindle cells with sparse cytoplasm and uniform elongated nuclei. MCNs are premalignant lesions and should be cleanly resected to prevent progression to malignancy. Variable degrees of premalignant transformation are encountered, ranging from low- to high-grade dysplasia based on the degree of architectural and cytologic atypia of the epithelial cells.

Invasive mucinous cystadenocarcinomas are MCNs that are associated with invasive carcinoma secondary to progression. In surgical series, between 15% and 30% of all MCNs are associated with invasive carcinoma. Naturally, patients with mucinous cystadenocarcinomas tend to be 5 to 10 years older than patients with benign MCNs. The extent of invasive carcinomas and high-grade dysplasia in MCNs can be very focal. Therefore, a benign working diagnosis cannot be established on biopsy alone due to sampling error, and lesions, including precursors, should also be completely excised. The prognosis for patients with resected benign/premalignant tumors is excellent. Patients with mucinous cystadenocarcinoma also perform better than patients with conventional ductal adenocarcinoma, with 5-year overall survival rates nearing 50%.

Intraductal Papillary-Mucinous Neoplasms

Intraductal papillary-mucinous neoplasms (IPMNs) are intraductal mucin-producing neoplasms with tall, columnar, mucin-containing epithelium with or without papillary projections. These neoplasms extensively involve the

main pancreatic ducts (main-duct IPMN) and/or major side branches (branch-duct IPMN). While radiologic distinction from MCNs may be challenging, IPMNs critically lack the ovarian stroma characteristic of MCNs on biopsy sampling, and are therefore distinct lesions. Similar to the well-defined adenoma–carcinoma sequence in PDAC (PanIN to invasive ductal carcinoma), IPMNs seem to follow a similar pattern of progression from IPMN with low-grade dysplasia to high-grade dysplasia to invasive carcinoma. Microscopically, IPMNs consist of papillary projections lined by columnar mucin-secreting cells. They show varying degrees of cellular atypia. Invasive IPMNs are either colloid or tubular, with the latter having a worse prognosis. Further histologic subtyping of epithelial differentiation is based on cell lineage, morphology of the papillae, and immunophenotype, and includes classification into intestinal, gastric, pancreaticobiliary, and oncocytic subtypes with variable prognosis.

IPMNs are subclassified as main-duct, branch-duct, or mixed type depending on their location. Main-duct IPMNs are characterized by involvement of the duct of Wirsung, which is dilated either focally or diffusely throughout the gland. Branch-duct IPMN originates in the side branches of the pancreatic ductal system and appears as a multilobular cystic lesion communicating with a nondilated main pancreatic duct. If the main duct is dilated with synchronous involvement of the branch ducts, it is described as a mixed IPMN.

IPMNs are usually found in individuals in their 60s to 80s. Some patients may experience symptoms that include abdominal pain, steatorrhea, weight loss, jaundice, diabetes, and chronic pancreatitis. However, the majority are detected as incidental findings on cross-sectional imaging studies performed for other indications. Interestingly, the presence of diabetes in IPMNs is more likely to be associated with high-grade dysplasia and invasive carcinoma and is worthy of more aggressive surveillance if no evidence of malignancy is present.[9] IPMNs appear to be more common in the head, neck, and uncinate process of the pancreas but can be found diffusely throughout the whole gland. Computed tomography (CT) scans often provide the initial modality by which these lesions are noted, but are better characterized, and surveillance conducted, using magnetic resonance imaging (MRI). In approximately 20% of lesions, IPMNs may contain areas of calcifications.[10] In a recent report, the presence of calcifications correlated with larger cyst

sizes and were more commonly seen when pancreatic ductal dilatation was found. However, there was no association between presence of calcifications and malignancy, epithelial subtype, or other clinic data, unless the calcification was noted to be "coarse" in nature (compared with punctate or eggshell). On endoscopy, mucin can be seen oozing from the ampulla of Vater in cases of main-duct IPMN with a classic fish mouth opening of the pancreatic duct at the ampulla. Endoscopic retrograde cholangiopancreatography (ERCP) can be used to confirm that the cysts communicate with the pancreatic ducts.

MCNs are the main entity to consider in the differential diagnosis of IPMNs (**Table 55.5**). Aside from the ovarian-stroma of MCNs, two radiologic features distinguish IPMNs from MCNs; IPMNs communicate with ducts whereas mucinous cysts do not. In addition, MCNs are usually seen in the tail of the pancreas and occur in middle-aged women, whereas IPMNs are more frequently seen in the head of the pancreas and occur in older individuals of either gender. Finally, on molecular analysis, MCNs are devoid of *GNAS* mutations compared with IPMNs, and both may possess *KRAS* mutations in their profile, which, importantly, does not necessarily represent an in-situ or invasive malignant component.

Table 55.5 Comparison between Mucinous Cystic Neoplasm (MCN) and Intraductal Papillary Mucinous Neoplasm (IPMN)

	MCN	IPMN
Age (years)	40–50	60–80
Gender	More common in females	More common in males
Location	Body/tail	Head
Communicates with pancreatic duct	No	Yes
Mucin at ampulla	No	Yes
Ovarian like stroma	Yes	No

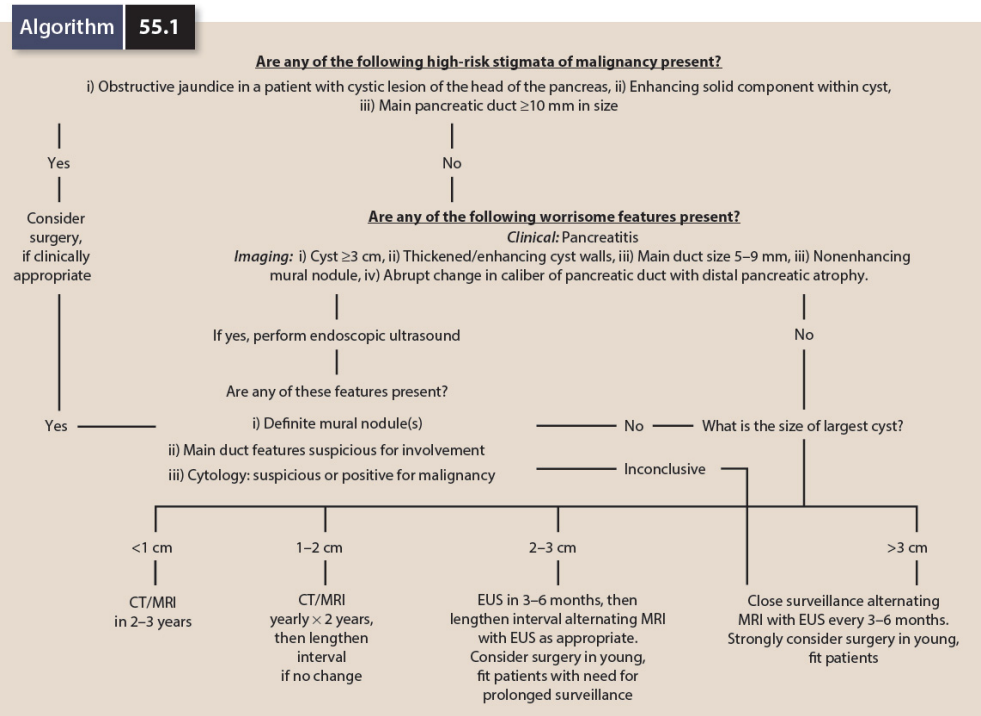
As noted, IPMNs represent a continuum of disease from benign to malignant. In a large series of 851 resected cystic lesions from the Massachusetts General Hospital over a 33-year period, 38% of lesions were noted to be IPMNs.[11] The series also included MCNs, serous cystadenomas, and cystic neuroendocrine tumors. The series highlighted several important findings, including the increase in incidentally-discovered lesions over time, representing the increase in cross-sectional imaging, a decrease in malignancy rate within resected lesions over time, highlighting the ability to detect premalignant lesions more effectively, and an overall high rate of survival for all mucinous lesions (5-year overall survival of 87%).

Several international consensus guidelines for the management of IPMNs have been developed, and range in their assessment of malignant transformation.[12] Traditionally, the International Association of Pancreatology (IAP) guidelines (Sendai and Fukoka) have been followed by surgeons with conservative approaches toward risk of malignant transformation. These guidelines, therefore, incorporate more stringent surveillance recommendations. Conversely, the American Gastroenterology Association (AGA) guidelines underestimate the risk of malignant transformation, and, thus, carry more liberal recommendations for surveillance and discontinuation of long-term follow-up in the event cysts remain unchanged after 5 years.

In attempts to better predict IPMNs with "imminent" malignant potential, IPMNs may possess features of "high-risk stigmata" or "worrisome features." High-risk stigmata in the most recent 2017 iteration include obstructive jaundice in the setting of a cyst in the head of the pancreas, a main duct >10 mm, or a cyst with a solid enhancing component >5 mm in the wall. Worrisome features include cyst >3 cm, thickened and enhancing cyst walls, enhancing mural nodules <5 mm, main duct size between 5 mm and 9 mm, abrupt change in the caliber of the main pancreatic duct with distal pancreatic atrophy, lymphadenopathy, cyst growth >5 mm in 2 years, and elevated serum levels of CA 19-9. All cysts with "worrisome features" should undergo endoscopic ultrasonography (EUS), and all cysts with "high-risk stigmata" should be resected in healthy patients. If no "worrisome features" are present, no further initial work-up is recommended. However, serial surveillance is still necessary (**Algorithm 55.1**). Of note, however, cysts that remain smaller than 1.5 cm for more than 5 years might possess

very low risk for progression to malignancy (<1%) and may be considered for less aggressive surveillance.[13]

The goal of surgical therapy for IPMNs should include complete surgical resection with absence of invasive carcinoma or high-grade dysplasia at the transection margin. In addition, main-duct IPMNs may pose a more challenging situation if disease extends across the entire length of the gland, where total pancreatectomy may be indicated. The presence of focal invasive malignancy and condition of the patient are important determinants of the decision to perform total pancreatectomy. Perioperative management requires specialized care, often with the assistance of endocrinology, and informed discussion with patients in the preoperative phase.



Algorithm 55.1 International consensus guidelines for the management of IPMNs. (From Tanaka M, Fernandez-del Castillo C, Adsay V, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology* 2012;12:183–197.)

Unlike those patients with completely resected noninvasive MCNs (who are routinely cured), patients with completely resected IPMNs should undergo careful follow-up and surveillance for the development of recurrent disease. Furthermore, patients with resected IPMNs should also undergo

careful follow-up and surveillance as they are at higher risk for the development of distinct PDACs elsewhere in the gland.

3 CLINICOPATHOLOGIC STAGING

Accurate pathologic staging of pancreatic cancer is important for providing prognostic information to patients and for comparing the results of various therapeutic trials. The American Joint Committee on Cancer (AJCC) staging for pancreatic cancer evolves every few years (currently 8th edition), and is shown in **Table 55.6**. This system, based on the TNM classification, takes into account the extent of the primary tumor (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastatic disease (M).

Table 55.6 Staging of Pancreatic Cancer

Stage	T	N	M
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1, T2, T3	N1	M0
III	T4 (or any T if N2)	N2 (or any N if T4)	M0
IV	Any T	Any N	M1

Tumor (T)
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
Tis: Carcinoma in situ
T1: Maximum tumor diameter ≤2 cm
T2: Maximum tumor diameter >2 cm but ≤4 cm
T3: Maximum tumor diameter >4 cm
T4: Tumor involves the celiac axis or the superior mesenteric artery

Regional Lymph Nodes (N)
NX: Regional lymph nodes cannot be assessed
N0: No regional lymph node metastasis
N1: Regional lymph node metastasis in 1–3 nodes
N2: Regional lymph node metastasis in ≥4 nodes

Distant Metastasis (M)
MX: Distant metastasis cannot be assessed
M0: No distant metastasis
M1: Distant metastasis

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DIAGNOSIS

Clinical Presentation

Many of the difficulties associated with the management of pancreatic cancer result from an inability to make the diagnosis at an early stage. The early symptoms of pancreatic cancer include anorexia, weight loss, abdominal discomfort, and nausea. Unfortunately, the nonspecific nature of these symptoms often leads to a delay in the diagnosis. Specific symptoms usually develop only after invasion or obstruction of nearby structures has occurred. Most pancreatic cancers arise in the head of the pancreas, and obstruction of the intrapancreatic portion of the common bile duct leads to progressive jaundice, acholic stools, darkening of the urine, and pruritus. Pain is a common symptom of pancreatic cancer. The pain usually starts as a vague upper abdominal or back pain that is often nonspecific, gnawing in nature, worse at night at time, and frequently attributed to some other cause. It is usually worse in the supine position and is often relieved by leaning forward. Pain may be caused by invasion of the tumor into the splanchnic plexus and retroperitoneum, or by obstruction of the pancreatic duct and potential pancreatitis. Other digestive symptoms are also common in pancreatic cancer (**Table 55.7**).

Table 55.7 Symptoms of Pancreatic Cancer

Symptom	Patients (%)
Head	
Weight loss	92
Jaundice	82
Pain	72
Anorexia	64
Dark urine	63
Light stools	62
Nausea	45
Vomiting	37
Weakness	35
Pruritus	24
Diarrhea	18
Melena	12
Constipation	11
Fever	11
Hematemesis	8
Body and Tail	
Weight loss	100
Pain	87
Weakness	43
Nausea	43
Vomiting	37
Anorexia	33
Constipation	27
Hematemesis	17
Melena	17
Jaundice	7
Fever	7
Diarrhea	3

Occasionally, pancreatic cancer may be discovered in an unusual manner. The onset of diabetes may be the first clinical feature in 10% to 15% of patients. An episode of acute pancreatitis may also be the initial presentation of pancreatic cancer if the tumor partially obstructs the pancreatic duct. It is important to consider a pancreatic cancer in patients presenting with acute pancreatitis, especially those without an obvious cause for their pancreatitis (alcohol or gallstones).

The most common physical finding at the initial presentation in head tumors is jaundice (**Table 55.8**). Hepatomegaly and a palpable gallbladder may be present in some patients. In cases of advanced disease, cachexia, muscle wasting, or a nodular liver, consistent with metastatic disease, may be evident. Other physical findings in patients with disseminated cancer include left supraclavicular adenopathy (Virchow node), periumbilical adenopathy (Sister Mary Joseph node), and pelvic drop metastases (Blumer shelf). Ascites can be present in 15% of patients.

Laboratory Studies

In patients with cancer of the head of the pancreas, laboratory studies usually reveal a significant increase in serum total bilirubin and alkaline phosphatase, indicating bile duct obstruction. The transaminases can also be elevated but usually not to the same proportion as the bilirubin and alkaline phosphatase. In patients with localized cancer of the body and tail of the pancreas, laboratory values remain normal early in the course. Patients with pancreatic cancer may also demonstrate a normochromic anemia and hypoalbuminemia secondary to the nutritional consequences of the disease. In patients with jaundice, the prothrombin time can be abnormally prolonged. This usually is an indication of biliary obstruction, which prevents bile from entering the gastrointestinal tract and leads to malabsorption of fat-soluble vitamins (A, D, E, and K) and decreased hepatic production of vitamin K–dependent clotting factors. The prothrombin time can usually be normalized by the administration of parenteral vitamin K. Serum amylase and lipase levels are usually normal in patients with pancreatic cancer.

A wide variety of serum tumor markers have been proposed for use in the diagnosis and follow-up of patients with pancreatic cancer. The most extensively studied of these is CA 19-9, a Lewis blood group–related mucin

glycoprotein. Approximately 5% of the population lacks the Lewis gene and therefore cannot produce CA 19-9. When a normal upper limit of 37 U/mL is used, the accuracy of the CA 19-9 level in identifying patients with pancreatic adenocarcinoma is only about 80%. When a higher cutoff value of more than 90 U/mL is used, the accuracy improves to 85%, and increasing the cutoff value to 200 U/mL increases the accuracy to 95%.[14] The combined use of CA 19-9 and ultrasonography, CT, or ERCP can improve the accuracy of the individual tests, so that the combined accuracy approaches 100% for the diagnosis of pancreatic cancer. Levels of CA 19-9 have also been correlated with distant spread, prognosis, and tumor recurrence. In general, higher CA 19-9 values before surgery indicate an increased size of the primary tumor and increased rates of disease dissemination and localized unresectability. In addition, the CA 19-9 level has been used to monitor the results of neoadjuvant and adjuvant chemoradiation therapy in patients. Increasing CA 19-9 levels usually indicate recurrence or progression of disease, whereas stable or declining levels indicate a stable tumor burden (lack of progression/response), absence of recurrence on imaging studies, and an improved prognosis.

Radiologic Investigations

Radiologic imaging plays a crucial role in the diagnosis, staging, and follow-up of patients with pancreatic cancer. In addition to identifying the primary tumor, the goals of imaging include the assessment of local and regional invasion, evaluation of lymph nodes and vascular structures, identification of distant metastatic disease, and the determination of tumor resectability. Ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) are all useful noninvasive tests in patients suspected of having a pancreatic cancer.

Table 55.8 Signs of Pancreatic Cancer

Sign	Patients (%)
Head	
Jaundice	87
Palpable liver	83
Palpable gallbladder	29
Tenderness	26
Ascites	14
Abdominal mass	13
Body and Tail	
Palpable liver	33
Tenderness	27
Abdominal mass	23
Ascites	20
Jaundice	13
Diarrhea	3

Transabdominal ultrasonography (US) will reveal a pancreatic mass in 60% to 70% of patients with cancer. Pancreatic cancer typically appears as a hypoechoic mass on US. Ultrasonography may also demonstrate dilated intrahepatic and extrahepatic bile ducts, liver metastases, pancreatic masses, ascites, and enlarged peripancreatic lymph nodes. Because helical CT is just as sensitive as ultrasonography and provides more complete information about surrounding structures and the local and distant extent of the disease, transabdominal ultrasonography has been largely replaced by CT.

CT scanning is currently the preferred noninvasive imaging test for the diagnosis of pancreatic cancer. Pancreas protocol CT should be performed with rapid injection of intravenous iodinated contrast. Slices should be reconstructed at less than or equal to 3 mm with overlap. At least two postcontrast acquisitions, in the late arterial (or parenchymal) and venous phases are useful to assess the arteries (celiac, common hepatic, peripancreatic, and superior mesenteric arteries) and veins (portal, splenic,

and superior mesenteric veins [SMVs]). The parenchymal phase best shows the tumor as an ill-defined hypodense mass in the pancreatic parenchyma (**Fig. 55.3**), while the venous phase is best for detecting liver metastases. Neutral enteral contrast, such as water, is used, since this allows for better identification of the duodenal wall and results in artifact-free reformations. In many centers, no oral contrast is used. Coronal and sagittal reformations in both arterial and venous phases increase the sensitivity for determining local invasion. In addition to determining the primary tumor size, CT is used to evaluate invasion into local structures or metastatic disease.

4 In general, MRI offers no significant advantages over CT because of a low signal-to-noise ratio, motion artifacts, lack of bowel opacification, and low spatial resolution. MRI can be considered an alternative preoperative staging examination in patients with allergies to iodinated contrast agents and in patients with renal insufficiency. On MRI, a typical pancreatic adenocarcinoma appears hypointense on T1-weighted, unenhanced images, and has a variable appearance on T2-weighted sequences. The T2 signal of the tumor is often dependent on the amount of desmoplastic response associated with the tumor. On dynamic imaging following a gadolinium contrast injection, an adenocarcinoma enhances relatively less than the background pancreatic parenchyma in the early phase and then reveals progressive enhancement in the subsequent phases. Magnetic resonance imaging with MRCP is currently indicated for noninvasive diagnostic imaging to evaluate the biliary and pancreatic ducts and may be the optimal method to survey patients with IPMN and the pancreatic remnant after surgery.

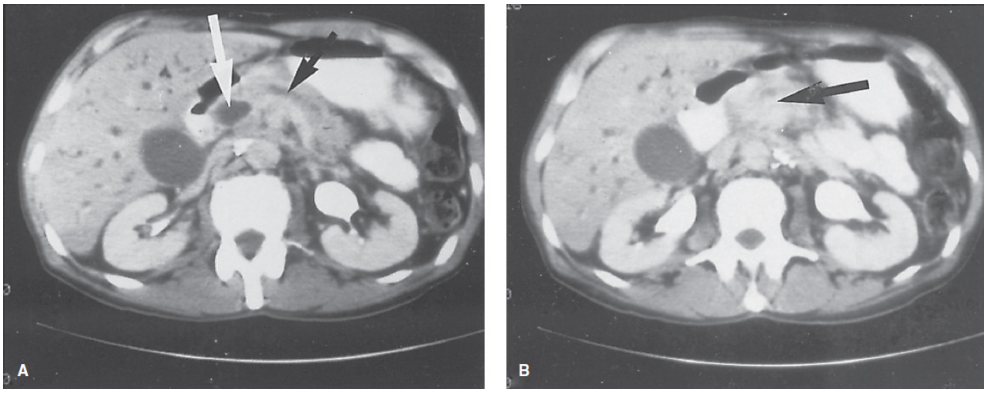

Figure 55.3 Computed tomogram of the abdomen of a patient with adenocarcinoma of the pancreas. **A:** The obstructed and dilated common bile duct (*light arrow*) and pancreatic duct (*dark arrow*) can be seen. In the adjacent cross section **B,** a large mass is present in the head of the pancreas (*arrow*).

Traditionally, the next step in the evaluation of the jaundiced patient has been cholangiography, either by the endoscopic or by the percutaneous route. If the endoscopic approach is used, the duodenum and ampulla can be visualized and biopsy brushing specimens obtained if necessary. In addition, ERCP allows for direct imaging of the pancreatic duct. The sensitivity of ERCP for the diagnosis of pancreatic cancer approaches 90%. The finding of a long, irregular stricture in an otherwise normal pancreatic duct is highly suggestive of a pancreatic cancer (**Fig. 55.4**). Often, the pancreatic duct will be obstructed with no distal filling. Although ERCP is reliable in confirming the presence of a clinically suspected pancreatic cancer, it is not routinely necessary, unless obstructive jaundice is present and relief with stent placement is pursued.

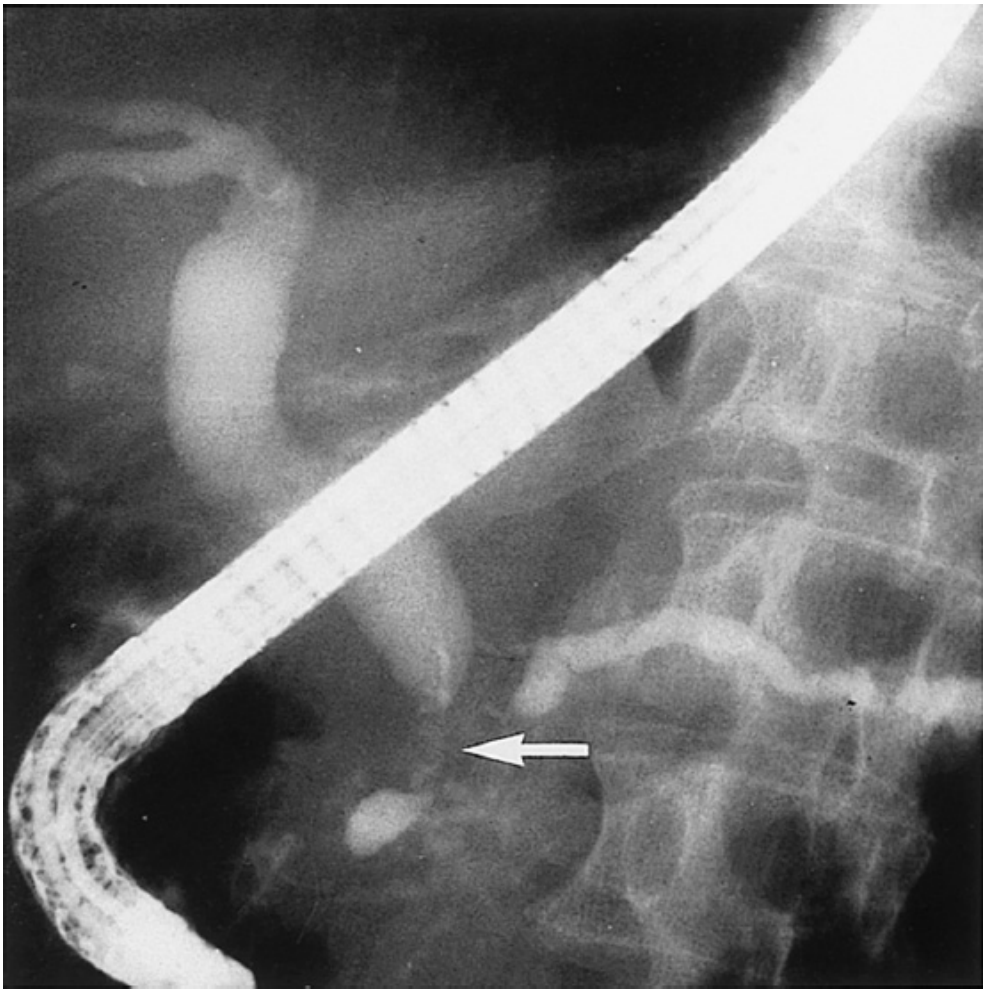

Figure 55.4 Endoscopic retrograde cholangiopancreatography in a patient with adenocarcinoma of the pancreas demonstrates a stricture of both the distal common bile duct and the pancreatic duct (*arrow*).

EUS is a minimally invasive technique in which a high-frequency ultrasonographic probe is placed into the stomach and duodenum endoscopically and the pancreas is imaged. Tumors appear as hypoechoic areas in the pancreatic substance (**Fig. 55.5**). The advantages of EUS for pancreatic cancer include characterization of small lesions (<2 cm) when CT findings are questionable or negative, detection of malignant lymphadenopathy, detection of vascular involvement, and the ability to perform EUS-guided FNA and core biopsies for definitive diagnosis and staging. EUS is not effective in assessing metastatic disease to the liver, although lesions in the left lateral segment overlying the stomach can sometimes be seen and biopsied too. EUS-guided biopsy has been used to

acquire tissue samples for cytologic analysis. This approach may avoid the risks of tumor seeding from percutaneous biopsy. The accuracy of EUS for detection of pancreatic tumors is extremely high at 94%, despite operator dependence, which makes this modality the most sensitive modality for detection, including for subcentimeter lesions where sensitivity is greater than 80%.[15] The addition of FNA biopsy extends sensitivity of detection to up to 92% and specificity up to 98%. Interestingly, while the analysis of regional nodes is frequently unnecessary given the lack of change in management of these tumors, the presence of pathologic celiac or para-aortic disease is different, given that extension of tumor within these nodes is considered nonregional metastatic disease. The sensitivity and specificity of EUS FNA of these nodes is 96.7% and 100%, respectively, highlighting the superior diagnostic power provided by EUS.

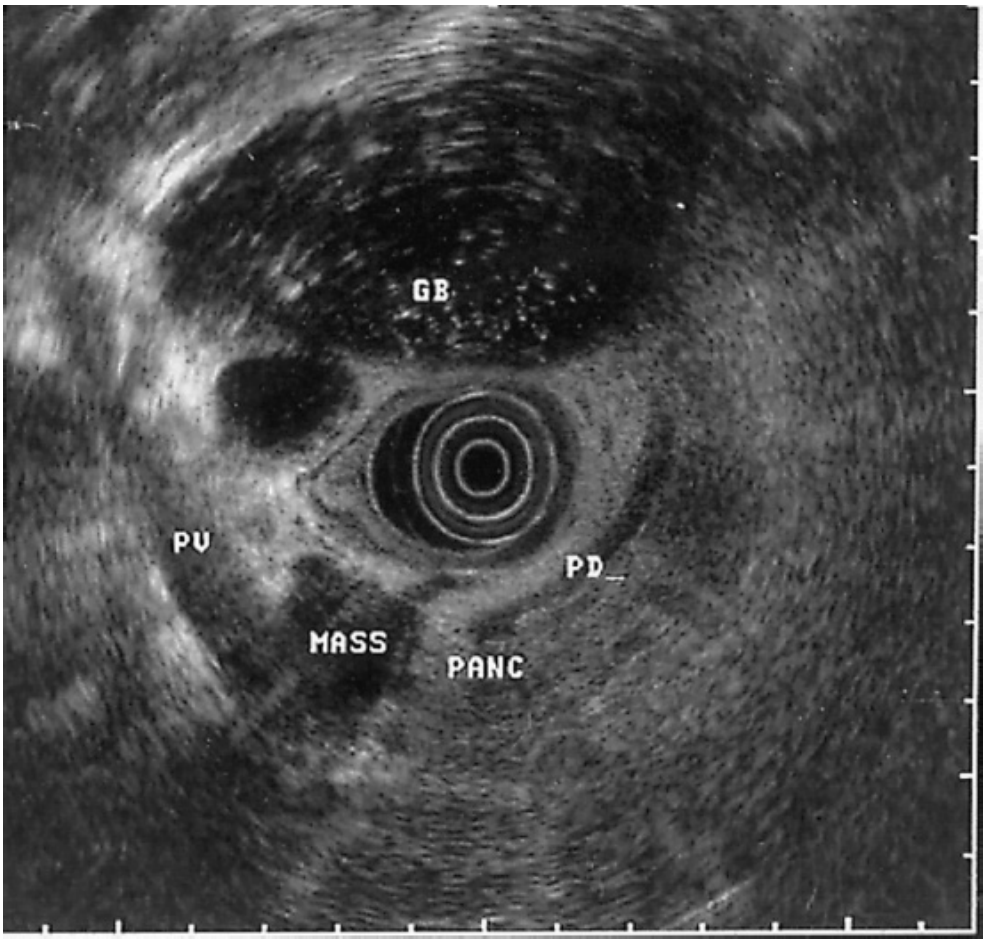

Figure 55.5 Endoscopic ultrasonogram of a 2.2-cm mass in the head of the pancreas. The transducer tip is located in the duodenum. The dilated common bile duct and gallbladder (GB) can be seen at the top of the image. The pancreatic duct (PD) is also dilated. The mass involves the portal vein (PV).

Percutaneous FNA of pancreatic masses is helpful in selected patients. The technique is safe and generally reliable but use of percutaneous biopsy has greatly diminished in recent years, and EUS is the preferred technique when possible. With the advent of EUS in recent years, few lesions of the pancreas today will undergo surgical resection without biopsy first, particularly in the absence of classical signs such as jaundice. This ensures that resection of nonsurgical diseases such as pancreatic lymphoma and autoimmune pancreatitis is avoided. In addition, with the advent of neoadjuvant therapy for treatment of PDAC, tumor biopsy is mandated prior to commencement of chemotherapy and/or radiation regimens.

PREOPERATIVE STAGING

The goal of preoperative staging of pancreatic cancer is to determine the feasibility of surgery and the optimal treatment for each individual patient. Specific anatomy-based CT criteria can stratify patients into four distinct groups (**Table 55.9**): (1) Resectable, (2) Borderline resectable, (3) Locally advanced unresectable, or (4) Metastatic. However, following neoadjuvant therapy, cross-sectional imaging is no longer reliable when determining extent of the local cancer given the inability to distinguish treatment response and fibrosis from tumor.[16]

Table 55.9 Preoperative Staging Based on CT Findings

Metastatic Evidence of metastatic spread (typically to the liver, peritoneum, or lung)
Resectable ▪ No involvement of the SMA, celiac, or CHA ▪ <180° interface between tumor and vessel wall of the PV or SMV and patent portal vein/splenic vein confluence ▪ No evidence of metastatic disease
Borderline resectable ▪ Tumor-vessel interface ≥180° of venous wall circumference and/or reconstructable occlusion ▪ <180° of SMA or celiac wall circumference, or reconstructable short-segment CHA ▪ No evidence of metastatic disease
Locally advanced ▪ Tumor-vessel interface ≥180° of venous wall circumference and/or reconstructable occlusion ▪ >180° of SMA or celiac wall circumference, or reconstructable short-segment CHA ▪ No evidence of metastatic disease

STAGING LAPAROSCOPY

Liver and peritoneal metastases are the most common sites of distant spread of pancreatic cancer. The patient's overall survival continues to be limited once distant intra-abdominal metastases have developed. Currently there is no clinical trial data to support resection of the primary pancreatic cancer and visible metastases. Despite improvements in modern imaging, diagnostic laparoscopy identifies occult metastases in 17% of treatment-naïve patients who appear to be resectable on imaging.[17] These occult metastases are often 1 to 2 mm lesions on the liver or peritoneum. In a series from the Massachusetts General Hospital of 151 patients the median overall survival for the staging laparoscopy group (11.4 months) was significantly longer than the laparotomy group (8.3 months, $p < 0.001$). There was no difference in the 30 day or lifetime incidence of postoperative cholangitis, gastric outlet obstruction, or biliary stent placement between groups, highlighting a role for diagnostic laparoscopy in treatment-naive patients. Patients who only underwent laparoscopy started palliative chemotherapy earlier (17.9 days vs. 39.9 days in the laparotomy group, $p < 0.001$), possibly contributing to the improved survival.

RESECTION OF PANCREATIC CARCINOMA

Carcinoma of the Head, Neck, or Uncinate Process

In 1912, Kaush[18] reported the first successful resection of the duodenum and a portion of the pancreas for an ampullary cancer. In 1935, Whipple[19] described a technique for radical excision of a periampullary carcinoma. The operation was originally performed in two stages. A cholecystogastrostomy to decompress the obstructed biliary tree and a gastrojejunostomy to relieve gastric outlet obstruction comprised the first stage. The second stage was performed several weeks later when the jaundice had resolved, and the nutritional status had improved. During the second stage, an en bloc resection of the second portion of the duodenum and head of the pancreas was performed without reestablishing pancreatic–enteric continuity. Although

earlier contributions had been made, the report by Whipple triggered the modern-day approach to the treatment of pancreatic carcinoma.

5 The operative management of pancreatic cancer consists of 2 phases that include tumor extirpation and then restoration of gastrointestinal continuity with anastomotic reconstruction. After the abdomen has been opened through an upper midline or an extended subcostal incision, a careful search for tumor outside the limits of a pancreaticoduodenal resection should be carried out. The liver, omentum, and peritoneal surfaces are inspected, palpated, and suspect lesions are sampled and specimens submitted for frozen-section analysis. While experience with resection of metastases is growing, the resection of metastatic disease remains unconventional and should be conducted under controlled research or clinical trial settings in specialized centers.

Once distant metastases have been excluded, the primary tumor is assessed for resectability. Local factors that generally preclude pancreaticoduodenal resection include retroperitoneal extension of the tumor to involve the inferior vena cava or aorta or direct involvement or encasement of the superior mesenteric artery, hepatic artery, and celiac axis. Involvement of the SMV or portal vein can be managed with venous resection and reconstruction in select cases. The technical aspects of determining local resectability begin with a Kocher maneuver and mobilization of the duodenum and head of the pancreas from the underlying inferior vena cava and aorta. Once the duodenum and head of the pancreas are mobilized sufficiently, the surgeon's hand can be placed under the duodenum and head of the pancreas to palpate the relationship of the tumor mass to the superior mesenteric artery. Inability of the surgeon to identify a plane of normal tissue between the mass and the arterial pulsation indicates direct tumor involvement of the superior mesenteric artery, and the possibility of complete tumor resection is ordinarily eliminated.

In the setting of resection following neoadjuvant therapy, institutional practice is variable, ranging from no resection when vessels continue to exhibit involvement radiologically to complete vascular resections and reconstructions including both arterial and venous resection. At the authors' institution, the surgical approach involves sampling suspicious areas involving the vessels based on preoperative radiologic assessment to confirm whether viable tumor persists on frozen analysis, including

commencement of surgery with a left-sided SMA first approach if needed to provide biopsies. In the event frozen samples are positive for cancer, palliation is pursed. If frozen specimens confirm only the presence of fibrosis, then planned resection continues, including venous resections and reconstructions as necessary. It should be noted while the principles and steps of the operation are unchanged following neoadjuvant therapy, operations tend to be more complicated due to adhesions and fibrosis, and frequently necessitate tedious and meticulous dissections of the arterial structures to safely resect the specimen.

Following Kocherization of the duodenum, the lesser sac is entered, and the pancreatic body is identified. By separating the mesenteric leaves of the stomach and colon, the right gastroepiploic vein and middle colic vein can be traced to the inferior border of the pancreas. The inferior border of the pancreas should be further dissected and entry of these vessels into the SMV identifies the inferior portion of the SMV–pancreas tunnel. Alternatively, following extensive Kocherization, the first structure that one encounters anterior to the third portion of the duodenum is the SMV, which can be traced toward the inferior aspect of the pancreas. Obliteration of the tunnel by tumor may restrict the surgeon from being able to proceed, although maneuvers such as moving to the left aspect of the field to create a tunnel initially over the splenic vein that is then used to identify the confluence may be helpful. Once the tunnel is exposed from below, dissection of the porta ensues, and early exposure and division of the right gastric artery and gastroduodenal artery expose the portal vein superiorly. It is always important to confirm, before ligation of the gastroduodenal artery, that the structure to be ligated is indeed the gastroduodenal artery and not a replaced right hepatic artery, and that pulses persist in the proper hepatic artery persist on clamping. Once the anterior portion of the vein is cleanly dissected, the tunnel is then completed from above, under the pancreas. The common hepatic duct is then dissected and the gallbladder and cystic duct taken. The stomach is then divided using a linear stapler in the classic approach to include 30% to 40% of its distal component, or the duodenum dissected and divided approximately 2 cm distal to the pylorus in the pylorus-sparing approach. The jejunum is divided 10 to 15 cm distal to the ligament of Treitz. The proximal jejunum and fourth portion of the duodenum are passed under the superior mesenteric vessels to the right, to allow the uncinate process to be dissected from the superior

mesenteric artery clearing all of the tissue along the right border of the artery. The course of the superior mesenteric artery should be clearly identified to avoid injury to this structure. The pancreatic neck is next carefully divided and, subsequently, the common hepatic duct. Once the hepatic duct has been divided, the posteriorly located portal vein can be seen across its length to facilitate dissection of the uncinate process from the vein. Small branches from the SMV should be carefully controlled. Gentle retraction of the specimen away from the vein along with leftward retraction of the vein will ensure that the specimen is meticulously resected in line with the SMA and without leaving behind residual pancreatic, adipose, or nodal tissue.

At this point, the specimen consisting of the gallbladder and common bile duct, the pancreatic head, neck, and uncinate process, and the entire duodenum and proximal jejunum (and the distal stomach for a traditional Whipple procedure) is freed completely and removed from the operative field (**Fig. 55.6**). Margins should be inked to facilitate pathologic analysis of the specimen.

Following resection of the specimen, there are a total of three anastomoses required for restoration of gastrointestinal continuity. These include the pancreaticojejeunostomy, hepaticojejunostomy, and gastrojejunostomy, or duodenojejunostomy if a pylorus-sparing operation is pursued. While reconstruction techniques can vary, our preferred technique is to bring the end of the divided jejunum through the transverse mesocolon in a retrocolic fashion and perform an end-to-side pancreaticojejeunostomy. The anastomosis is carried out in 2 layers, using either an interrupted silk outer layer, or a Blumgart anastomosis that is fashioned using an absorbable monofilament synthetic suture. These techniques rely on an internal duct-to-mucosal anastomosis. A small enterotomy is made in the jejunum to match the size of the pancreatic duct and an inner layer of interrupted 5-0 absorbable monofilament sutures are used to create the anastomosis. Some surgeons prefer to stent this anastomosis with either a short indwelling pancreatic stent or an externalized pancreatic stent when a small duct is encountered. An alternative to this duct-to-mucosa technique is to create an enterotomy approximately the same size as the pancreatic neck and to complete a running anastomosis circumferentially around the entire gland to permit invagination of the neck 1 to 2 cm into the lumen of the bowel by the outer anterior layer of the anastomosis. The biliary–enteric anastomosis is performed 8 to 10 cm

distal to the pancreaticojejeunostomy. An end-to-side hepaticojejunostomy is performed with a single interrupted radial layer of 4-0 absorbable synthetic suture material. Approximately 20 cm distal to the biliary–enteric anastomosis, a 2-layer end-to-side gastrojejunostomy (or duodenojejunostomy) is performed in an antecolic manner with an inner continuous layer of 3-0 absorbable synthetic suture material. The final reconstruction is shown in **Figure 55.6C**.

Several technical aspects of PD remain controversial. These controversies include whether (1) a radical lymph node dissection is necessary, (2) the pylorus should be preserved, and (3) a role exists for minimally-invasive pancreatic resections.

Several nonrandomized retrospective studies have recommended performing a radical (extended) retroperitoneal lymph node dissection to PD in an attempt to improve survival. However, results from four randomized prospective trials (**Table 55.10**)[20–24] have not proven any benefit associated with extended nodal dissections. The prospective trial performed by Pedrazzoli et al.[20] suggested a survival advantage to extended retroperitoneal lymph node dissection in patients with positive lymph nodes. Eighty-one patients with pancreatic adenocarcinoma were randomized to either standard or radical lymphadenectomy over 3 years at six different institutions. While the two groups were similar with respect to preoperative parameters, operative morbidity, and overall survival, a subgroup analysis of the 48 patients with positive lymph nodes showed a statistically significant survival advantage for patients undergoing the extended lymph node dissection. However, the largest prospective randomized trial from the Johns Hopkins Hospital failed to demonstrate a survival advantage for a radical resection compared with a classic PD.[21] Two hundred and ninety-four patients undergoing resection for periampullary adenocarcinoma were randomized between a standard resection (pylorus preserving PD with en bloc resection of the anterior and posterior pancreaticoduodenal lymph nodes, lower hepatoduodenal lymph nodes, and nodes along the right lateral aspect of the superior artery and vein) and a radical resection (standard resection plus distal gastrectomy and retroperitoneal lymph node dissection extending from the right renal hilum to the left lateral border of the aorta and from the portal vein to the inferior mesenteric artery). The groups did not differ with respect to age, gender, site of primary tumor, lymph node status, or margin status.

There were no significant differences in 1-, 3-, or 5-year and median survival when comparing the standard and radical groups (**Fig. 55.7**). However, the radical group had a higher overall morbidity (43% vs. 29%) with significantly higher rates of delayed gastric emptying and pancreatic fistula in addition to a longer postoperative hospital stay.

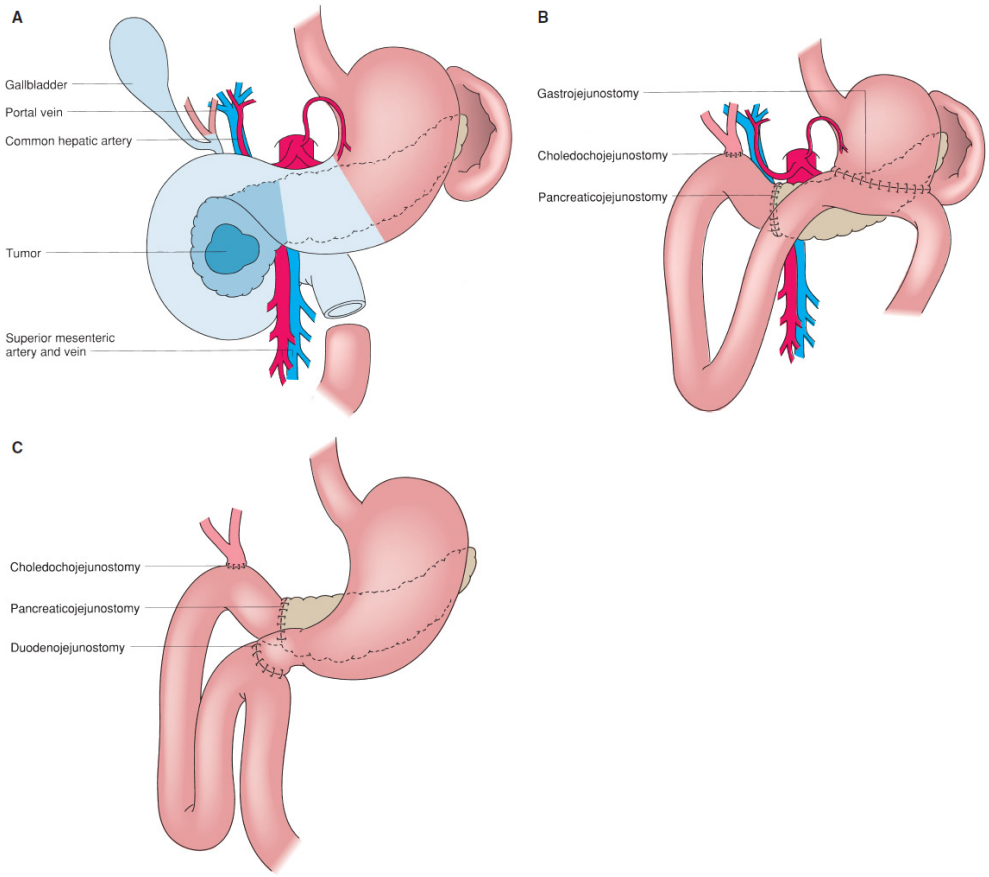

Figure 55.6 Pancreaticoduodenectomy. **A:** The tissue to be resected in a standard pancreaticoduodenectomy. **B:** Reconstruction after a standard pancreaticoduodenectomy. **C:** Reconstruction after the pylorus-sparing variation.

Table 55.10 Randomized Prospective Trials of Standard Versus Extended Lymphadenectomy for Pancreatic Cancer

Author	Year	Procedure	*n*	Op Time (hours)	Morbidity (%)	Mortality (%)	3-Year Survival (%)
Pedrazzoli et al.[18]	1999	Standard	40	6.2	35	5	12
		Extended	41	6.6	45	5	6
Yeo et al.[19]	2002	Standard	146	5.9	29	4	36
		Extended	148	6.4	43	2	38
Farnell et al.[20]	2005	Standard	34	6.2	35	0	41
		Extended	31	7.6	45	2.6	25
Nimura et al.[21]	2012	Standard	51	7.0	12	0	29
		Extended	50	9	20	2	17
Jang et al.[22]	2014	Standard	83	5.9	32	0	25
		Extended	84	7.0	45	2.3	23

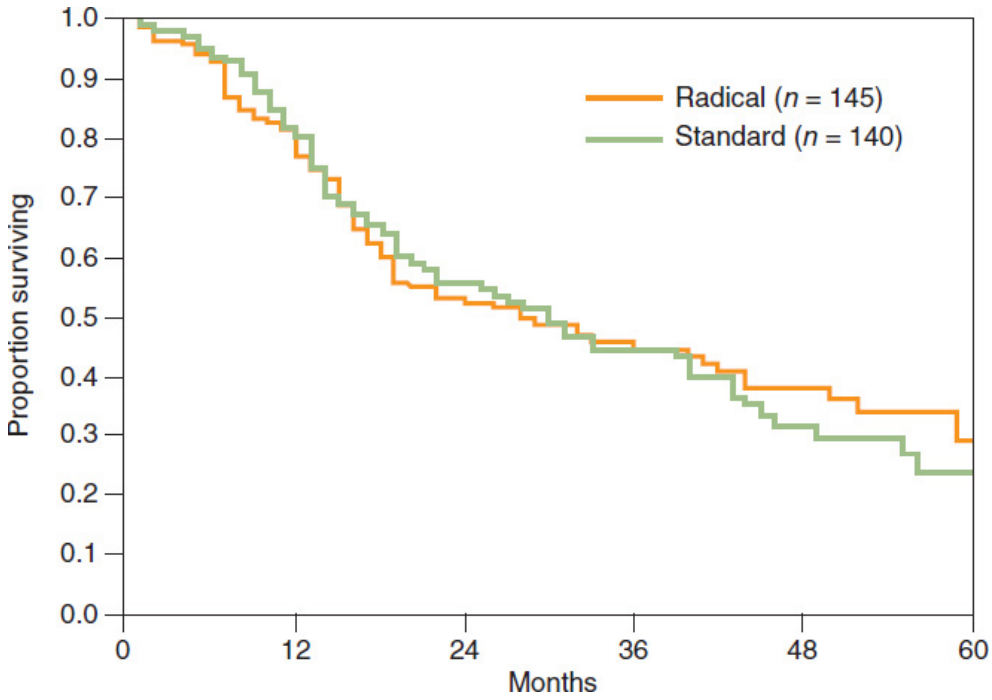

Figure 55.7 Actuarial survival for standard versus radical pancreaticoduodenectomy. (From Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. *Ann Surg* 2002;236:355–366; discussion 366–368, with permission.)

In 1978, Traverso and Longmire[25] popularized the pylorus-preserving modification of the Whipple procedure. Preserving antral and pyloric

function, the pylorus-preserving Whipple procedure reduces the incidence of troublesome postgastrectomy symptoms. A number of studies have documented that gastrointestinal function may be better preserved in the pylorus-sparing modification than in the traditional operation. Concerns exist in the use of the pylorus-preserving Whipple procedure for the management of periampullary tumors because of the possibility of compromising the already small proximal surgical margin of resection in addition to anecdotal increased rates of delayed gastric emptying. This question has been addressed by a number of authors, and no difference appears to be found in survival or emptying rates among those patients treated with the pylorus-sparing Whipple procedure and those managed by the traditional Whipple resection.[26–28]

In recent years, significant advances have been made in the application of minimally invasive techniques to the management of both benign and malignant pancreatic disorders. Initially, laparoscopic pancreatic surgery was limited to diagnostic staging in patients with pancreatic cancer prior to resection. More recently, minimally invasive techniques have been used to manage benign and malignant lesions of the pancreas.[29] Laparoscopic or robotic PD is a technically demanding procedure due to the retroperitoneal location of the pancreas, its intimate association with surrounding gastrointestinal and major vascular structures, and the need for three separate anastomoses to complete the reconstruction. The procedures are performed as either robotic, pure laparoscopic, hand assisted, or as laparoscopic-assisted procedures.

Carcinoma of the Body and Tail

The surgical management of adenocarcinoma of the body and tail of the pancreas may be more limited than that of the head of the pancreas owing to late presentation secondary to the absence of presenting signs such as jaundice. The exploration should be started with a search for evidence of either metastatic disease to the liver or peritoneal implants, which is frequently done using diagnostic laparoscopy. The operation itself is also amenable to a minimally-invasive laparoscopic or robotic approach. In the absence of distant disease, the lesser sac is opened, and the SMV is identified as it passes under the neck of the pancreas in most cases, except if

the tumor is in the very distal portion of the pancreatic tail. The short gastric vessels are ligated sequentially extending to the right diaphragmatic crus, including the superior splenic attachments, and the splenic flexure is then mobilized. These maneuvers completely expose the distal pancreas, and the superior and inferior borders are next dissected. A retropancreatic tunnel is then easily created, and the splenic artery and vein are identified and dissected separately from the pancreas. The splenic artery and then splenic vein are divided near their proximal origins. The splenic vein is ligated close to the SMV or just distal to the insertion of the inferior mesenteric vein (IMV) in order to prevent venous thrombosis and propagation of clot within the vascular stump. The pancreas is divided proximal to the tumor to ensure a negative resection margin. The specimen is removed in a medial-to-lateral fashion above the retroperitoneal plane to remove the distal pancreas and spleen. Removal of the spleen constitutes a complete oncologic resection of tumors of the distal pancreas and associated regional lymph nodes. The transected pancreas is oversewn or stapled, frequently with reinforced staple loads. The bed is carefully inspected for residual disease and bleeding, and hemostasis ensured.

Postoperative Results

During the 1960s and 1970s, many centers reported operative mortality following PD in the range of 20% to 40%, with postoperative morbidity rates as high as 40% to 60%. During the last three decades, a dramatic decline in operative morbidity and mortality following PD has been reported at a number of centers, with operative mortality rates in the range of 2% to 3%.[30–32] The reasons behind this decline appear to be due to (1) increased specialization and expertise of surgeons performing the operation, (2) improvements in preoperative and postoperative care in specialized centers, (3) improvements in anesthetic management, and (4) large numbers of patients being treated at high-volume centers.[33]

Although the operative mortality rates for pancreatic cancer have been reduced significantly, the complication rates approach 40% (**Table 55.11**). Pancreatic fistula remains the most frequent serious complication following PD, with an incidence ranging from 5% to 15% following Whipple resections. In the past, the development of pancreatic fistula after PD was

associated with mortality rates of 10% to 40%. Although the incidence of pancreatic fistula following PD remains stable, the overall associated mortality rate has diminished owing to improved management, which largely includes percutaneous drainage of intra-abdominal collections. Despite many different closure techniques of the pancreatic stump following distal pancreatectomy, the pancreatic fistula rate continues to range from 20% to 30%.[34] Variation in patterns of intraoperative drainage exist, ranging from no drain placement with expectant management postoperatively to placement of dual anterior and posterior anastomotic drains. Similarly, much variation exists with respect to timing of removal of intraoperatively-placed surgical drains. Finally, the role of newer somatostatin analogs has been established in randomized-controlled settings, although widespread adoption has been limited by prohibitive costs across many clinical centers.[35] Most surgeons today continue enteral nutrition with, or without, antibiotics following complete drainage and adequate source control, and are able to manage pancreatic leaks using outpatient surveillance strategies.

Table 55.11 Complications after Pancreaticoduodenectomy

Common
Delayed gastric emptying
Pancreatic fistula
Intra-abdominal abscess
Hemorrhage
Wound infection
Metabolic
Diabetes
Pancreatic exocrine insufficiency
Uncommon
Fistula
Biliary
Duodenal
Gastric
Organ failure
Cardiac
Hepatic
Pulmonary
Renal
Pancreatitis
Marginal ulceration

From Yeo CJ, Cameron JL. Pancreatic cancer. *Curr Probl Surg* 1999;36:61–152, with permission.

Long-Term Survival

Historically, 5-year survival rates for patients undergoing resection for adenocarcinoma of the head of the pancreas were reported to be in the range of 12% to 19% from high-volume centers.[36–38] Factors found to be important predictors of survival in these series were negative margins and nodal positivity on a consistent basis. With the evolution of modern systemic chemotherapy, the median overall survival is 54 months and the 3-year

overall survival is 63% for resected patients who receive adjuvant therapy (**Figure 55.8**).[39]

ADJUVANT AND NEOADJUVANT THERAPY

Surgical and perioperative care after pancreaticoduodenectomy has not changed significantly over the last decade. However, there have been dramatic improvements in systemic therapy. Over the past two decades 5-year overall survival was 15% to 20% for resectable disease, with a median survival of 20 to 24 months.[40] With the development of novel chemotherapeutic regimens the median survival has increased to 54.4 months.[39]

The results of the most important randomized prospective trials of adjuvant therapy for pancreatic cancer are summarized in **Table 55.12**.

Table 55.12 Randomized Prospective Trials of Adjuvant Therapy for Pancreatic Cancer

Study	Treatment Arm	Median Survival (Months)	2-Year Overall Survival (%)	5-Year Overall Survival (%)
GITSG[38]	Surg	11	18	0
	Surg, XRT, 5-FU	18	43	19
EORTC[39]	Surg	13	23	10
	Surg, XRT, 5-FU	17	37	20
ESPAC-1[40]	Surg	17	—	11
	Surg, 5-FU	20	40	21
	Surg, XRT, 5-FU	16	29	10
RTOG[41]	Surg, XRT, 5-FU	17	21 (3 y)	—
	Surg, XRT, Gemcitabine	19	31 (3 y)	—
CONKO[42]	Surg	20	42	12
	Surg, Gemcitabine	22	48	23
ESPAC-4	Gemcitabine	28	—	17
	Gemcitabine, Capecitabine	30	—	28
PRODIGE 24	Gemcitabine	35	49	—
	FOLFIRINOX	54	63	—

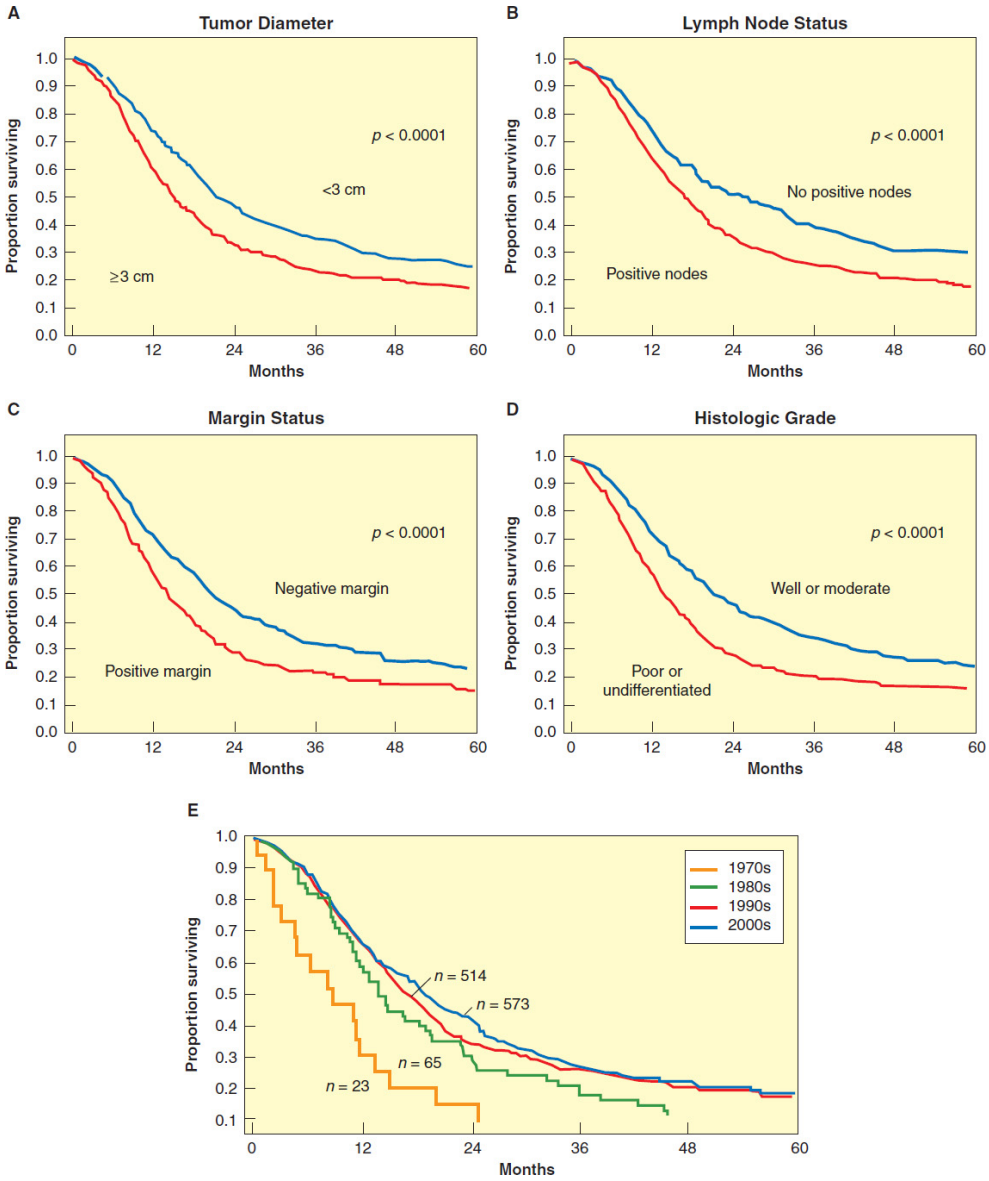

Figure 55.8 Survival of patients with pancreaticoduodenectomy based on tumor size **(A),** lymph node status **(B),** margin status **(C),** histologic grade **(D),** and historical context **(E)**. (From Winter JM, Cameron JL, Campbell KA, et al. 1423 pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. *J Gastrointest Surg* 2006;10:1199–1211, with permission.)

The first randomized clinical trial in PDAC was in 1985 evaluating adjuvant chemoradiation. The role of radiation in the treatment of PDAC continues to be actively debated with significant differences in practice patterns around the world. However, most significantly the landscape of systemic therapy has changed resulting in significant improvements in survival.

In 1985, the Gastrointestinal Tumor Study Group reported encouraging results from a prospective, randomized trial to evaluate the efficacy of adjuvant radiation and chemotherapy following curative resection for adenocarcinoma of the head of the pancreas.[41] Forty-three patients were randomized to either adjuvant therapy with radiation and 5-fluorouracil (5-FU) or no adjuvant therapy. The median survival for the 21 patients who received adjuvant therapy was 20 months, and 3 (14%) survived 5 years or longer. For the 22 patients who received no adjuvant therapy, the median survival was 11 months, and only 1 patient (4.5%) survived 5 years.

The randomized trial conducted by the European Organization for Research and Treatment of Cancer (EORTC),[42] sought to recapitulate the results of the GITSG study in 114 patients with pancreatic head lesions (observation, $n = 54$ and adjuvant treatment, $n = 60$). However, chemotherapy (5-FU) given during radiation was given as a continuous infusion (rather than via bolus) during each radiation sequence, depending on toxicity, for up to 5 days. No chemotherapy was given post chemoradiation. Fifty-six percent of patients received the intended chemotherapy dose during radiation. Patients in the chemoradiation arm had a median survival of 17.1 months versus 12.6 months in the observation arm ($p = 0.099$); 2- and 5-year overall survivals were 37% and 20%, respectively, for the experimental arm and 23% and 10%, respectively, for the control arm.

The first trial evaluating systemic chemotherapy and chemoradiation was the ESPAC-1 trial published in 2004. The trial analyzed 289 patients recruited from 53 hospitals in a 2 × 2 factorial design.[43] The four study groups included (1) surgery only ($n = 69$); (2) chemotherapy only ($n = 73$) consisting of 5-FU, 425 mg/m^2, and leucovorin, 20 mg/m^2, given daily for 5 days every 4 weeks for six cycles of treatment; (3) radiation therapy and 5-FU given ($n = 75$) according to the original GITSG method; and (4) both treatments ($n = 73$, chemoradiation followed by chemotherapy). The major study conclusions were that the 5-year overall survival comparisons between patients who received chemotherapy versus those that did not (21% vs. 8%, $p = 0.009$) and those that received radiation therapy versus those that did not (10% vs. 20%, $p = 0.05$). The authors concluded that adjuvant chemotherapy had a beneficial effect in resected pancreatic cancer, whereas chemoradiation had a deleterious effect. A quality-of-life questionnaire showed no difference between those that received chemotherapy and those

that did not, and those that received chemoradiation and those that did not. Thus, the survival benefit of adjuvant chemoradiation for pancreatic cancer patients remains unclear, and the optimal regimen has yet to be determined.

The RTOG 9704 trial, presented in abstract form in 2006,[44] contained 442 eligible patients who received adjuvant chemoradiation (5,040 cGy) given as continuous fractions with radiosensitizing doses of 5-FU. The comparisons were with the addition of either three cycles of 5-FU (one prechemoradiation, two postchemoradiation for 12 weeks) versus four cycles of gemcitabine (one prechemoradiation, three postchemoradiation). Although the study showed no overall difference in aggregate survival, when pancreatic head lesions only were considered (eliminating study results from resected lesions in the pancreatic body or tail), both median survival (16.7 vs. 18.8 months) and overall survival at 3 years (21% vs. 31%) favored the gemcitabine arm ($p = 0.047$). The study concluded that the addition of adjuvant gemcitabine to postoperative 5-FU chemoradiation was superior to the addition of 5-FU.

The trial which made adjuvant gemcitabine the standard of care for PDAC was the CONKO-1 trial,[45] conducted in Germany and Austria. The trial randomized 368 patients following R0 or R1 resection to either observation or gemcitabine. After a median follow-up time of 53 months, the median disease-free survival was 13.9 months in the gemcitabine arm versus 6.9 months in the observation arm ($p < 0.001$). There was no difference in overall survival for the gemcitabine arm versus the control group; median survival was 22 versus 20 months. Although survival was not different, the authors concluded that postoperative gemcitabine significantly delayed the development of recurrent disease after complete resection of pancreatic cancer compared with observation alone.

The ESPAC-4 trial[46] enrolled 732 patients and compared adjuvant gemcitabine with a combination of adjuvant gemcitabine and capecitabine. After a median follow-up of 43.2 months the median overall survival was 27.9 months for gemcitabine and 30.2 months for the combination ($p = 0.03$).[47] The 5-year survival estimates were 17.1% in the gemcitabine group and 28% in the combination group. Both groups had similar recurrence patterns after a median of 12.7 months with 49.7% presenting with local recurrence, 40.3% with distant only, and 10% with local and distant recurrence.

Phase III trials showing significant improvement in overall survival in patients with metastatic disease utilizing FOLFIRINOX or gemcitabine/abraxane provided the rationale for the most successful adjuvant trial.[9,10,13]

The Phase III PRODIGE 24-ACCORD trial from France and Canada[39] was a landmark trial that consisted of 493 patients with resected PDAC. Patients were randomized to receive modified FOLFIRINOX (oxaliplatin [85 mg per square meter of body-surface area], irinotecan [180 mg per square meter, reduced to 150 mg per square meter after a protocol-specified safety analysis], leucovorin [400 mg per square meter], and fluorouracil [2,400 mg per square meter] every 2 weeks) or gemcitabine (1,000 mg per square meter on days 1, 8, and 15 every 4 weeks) for 24 weeks. After a median follow-up of 33.6 months, the median disease-free survival was 21.6 months in the modified-FOLFIRINOX group and 12.8 months in the gemcitabine group ($p < 0.001$). Disease-free survival at 3 years was 39.7% in the modified-FOLFIRINOX group and 21.4% in the gemcitabine group. This trial demonstrated the longest median overall survival for resected PDAC of 54.4 months in the modified-FOLFIRINOX group and 35.0 months in the gemcitabine group ($p = 0.003$). The overall survival rate at 3 years was 63.4% in the modified-FOLFIRINOX group and 48.6% in the gemcitabine group. This improvement in overall survival does come at a cost to patients with adverse grade 3 or 4 events in 75.9% of patients in the modified-FOLFIRINOX group and in 52.9% in the gemcitabine group. This trial set the new standard of care for PDAC patients.

6 Neoadjuvant strategies for PDAC continue to evolve (**Table 55.13**). Neoadjuvant therapy, which refers to treatment delivered prior to surgical resection, offers several potential benefits including: (1) delivery of treatment to well-oxygenated tissue which may enhance the efficacy, (2) downstaging can enhance the ability to achieve a negative-margin resection and thereby reduce local recurrence, (3) ability to avoid treatment postoperatively, particularly given the high rate of postoperative complications following pancreatectomy, and (4) avoidance of an operation in patients with rapidly progressive disease.

The majority of investigative work performed in the neoadjuvant treatment field has been with chemoradiation therapy. Multimodality treatment was administered to 142 consecutive patients with localized adenocarcinoma of

the pancreatic head.[48] A subset of 41 patients treated by preoperative chemoradiation and pancreatoduodenectomy were compared with 19 patients who underwent pancreatoduodenectomy and postoperative adjuvant chemoradiation. Surgery was not delayed for any patient who received preoperative chemoradiation because of chemoradiation toxicity, but 24% of the eligible patients did not receive their intended postoperative chemoradiation because of delayed recovery following resection. The patients treated with rapid fractionation were reported to have a significantly shorter duration of treatment (median, 62.5 days) than patients who received postoperative chemoradiation (median, 98.5 days). In early follow-up, no patient who received preoperative chemoradiation experienced a local recurrence, and peritoneal recurrence developed in only 10% of these patients. Local or regional recurrence developed in 21% of patients who received postoperative chemoradiation. The overall survival curves were similar for both cohorts.

Table 55.13 Selected Neoadjuvant Trials for Potentially Resectable Pancreatic Cancer

Author	Year	*n*	Regimen	Resected (%)	Median Survival (Months)
Spitz et al.[48]	1997	91	XRT, 5-FU	45	19
Hoffman et al.[49]	1998	53	XRT, 5-FU, Mitomycin C	45	16
Pisters et al.[50]	2002	37	XRT, Paclitaxel	54	19
Wolf et al.[51]	2002	86	XRT, Gemcitabine	73	36
Talamonti et al.[52]	2006	20	XRT, Gemcitabine	85	26
Evans et al.[53]	2008	86	XRT, Gemcitabine	74	34
Turrini et al.[54]	2009	102	XRT, 5-FU, Cisplatin	62	23
Murphy et al.[55]	2018	48	FOLFIRINOX, XRT	67	48.6 for PFS, OS NR
Murphy et al.[56]	2019	49	FOLFIRINOX, Losartan, XRT	69	33
Versteijne et al.[57]	2020	246	XRT/5FU operation Operation	61 72	16 mo 14 mo

Wolff et al.[51] examined 86 patients treated with weekly gemcitabine at a dose of 400 mg/m^2 and 30 Gy of radiation. Sixty-one patients ultimately underwent resection (71%). The median survival in the resected patients was 36 months which is significantly longer than those seen in regimens using 5-

FU or paclitaxel as the radiation sensitizer. Analysis of the specimens revealed two pathologic complete responses and more than 50% nonviable tumor cells in 36 (59%). A gemcitabine-based regimen was also used in a multi-institutional study of 20 patients reported by Talamonti et al.[52] This group used full-dose gemcitabine and limited field radiation to 36 Gy (2.4 Gy/fraction). The authors described 14 patients as resectable and 6 as borderline resectable. Ultimately, all patients were explored and 17 resected (85%), again representing a high rate of resectability. A single pathologic complete response was observed and, in 24% of tumors, greater than 90% of the tumor cells were felt to be nonviable. Also notable was the low incidence (6%) of margin positivity in this trial. The median survival in the resected patients was 26 months. Based on the results of these initial trials, gemcitabine-based neoadjuvant regimens remain of considerable interest.

The most recent Phase III trial evaluating preoperative chemoradiotherapy to immediate surgery in resectable and borderline resectable patients is the Dutch PREOPANC trial.[57] The trial randomized 246 patients. Among patients who underwent neoadjuvant therapy, 61% underwent resection, while 72% of the patients who went directly to the operating room underwent resection. The intent to treat analysis demonstrated no difference in overall survival; 16 months in the neoadjuvant therapy arm versus 14.3 months in the surgery first group, ($p = 0.96$).

The utilization of total neoadjuvant therapy with FOLFIRINOX followed by chemoradiation is expanding. Two Phase II trials have been completed at the Massachusetts General Hospital for borderline and locally advanced disease.[55,56] The Phase II trial for borderline resectable PDAC enrolled 48 patients who received neoadjuvant FOLFIRINOX followed by chemoradiotherapy. Among the 32 patients who underwent resection, the R0 resection rate was 97%, 38% had N1 disease, and median progression-free survival was 48.6 months.[16] The second phase II trial enrolled 49 patients with newly diagnosed locally advanced PDAC who received neoadjuvant FOLFIRINOX and losartan followed by 50.4 Gy of chemoradiotherapy. Among the 34 patients who underwent resection, the R0 resection rate was 88%, 26% had N1 disease, and median progression-free survival was 17.5 months. Median overall survival was 33 months.[17]

UNRESECTABLE PANCREATIC CARCINOMA

For patients with persistently unresectable, but localized pancreatic adenocarcinoma, there are two main treatment modalities including intraoperative high-dose radiation and irreversible electroporation.

Intraoperative therapy is administered with a cone <8 cm in size with an average dose of 15 Gy. No substantial increase in morbidity was identified.[58] For the 64 patients who received TNT with FOLFIRINOX, the median progression-free survival was 14.7 months and the 12-, 24-, 48-, and 60-month survival rates were 98%, 49%, 13%, and 9%, respectively.[59] A gastrojejeunostomy was routinely performed at the time of treatment to avoid gastric outlet obstruction due to edema of the duodenum from radiation of the pancreatic tumor.

Irreversible electroporation is performed utilizing 2 to 6 operator-controlled, monopolar, single-use, disposable electrode probes, with >90 pulses consisting of 80 to 90 ms pulses to transmit energy to the target ablation area.[60] The AHPBA registry collected 152 patients, and after a median follow-up of 19 months from diagnosis, 9 (6%) patients exhibited local recurrence and 27 (18%) patients demonstrated distant recurrence. From diagnosis median overall survival was 30.7 months (range: 0.2 to 68.3 months), median progression-free survival was 22.8 months (range: 0.2 to 68.3 months) and median time to progression was 27.3 months (range: 0.2 to 68.3 months).[61]

PALLIATION

An increasing proportion of patients continue to become resectable as neoadjuvant therapy improves. However, a significant proportion of patients continue to present with locally advanced or metastatic disease that requires palliation. Symptom palliation via operative and nonoperative approaches can significantly improve the quality of life of patients. However, the decision to perform nonoperative versus surgical palliation for pancreatic cancer is influenced by a number of factors, including the patient's symptoms, overall health status, predicted procedure-related morbidity and mortality, location and size of the tumor, and projected survival. Surgical palliation can

be completed with acceptable perioperative morbidity and mortality and postoperative length of stay. The avoidance of late complications of recurrent jaundice, duodenal obstruction, and disabling pain would strengthen the argument in favor of surgical palliation in those patients expected to survive 6 months or more. [7] Nonoperative methods of palliation should be considered for patients in whom life expectancy is short and patients who are not candidates for operative intervention.

Table 55.14 Prospective Randomized Trial of Prophylactic Gastrojejunostomy in Patients with Unresectable Periampullary Cancer

	Patients (No.)	Morbidity (%)	Mortality (%)	Postoperative Length of Stay (Days)	Late Gastric Outlet Obstruction (%)
Gastrojejunostomy	44	32	0	8.5	0
No gastrojejunostomy	43	33	0	8.0	19

Adapted from Lillemoe KD, Cameron JL, Hardacre JM, et al. Is prophylactic gastrojejunostomy indicated for unresectable periampullary cancer? *Ann Surg* 1999;230: 322–330.

Biliary Obstruction

Jaundice, from obstruction of the common bile duct, is often the main presenting sign for patients with pancreatic cancer. Failure to decompress the biliary system can result in progressive liver dysfunction. Symptomatically, deposition of bile salts in the skin and tongue results in significant alterations of taste and refractory pruritus, respectively. Nonoperative palliation with a stent placed during ERCP is the preferred method. If endoscopic stent placement fails, a less desirable option is transhepatic catheter placement with external catheters that are converted to internal stents to permit biliary drainage. With these two options at high volume centers, operative bypass, such as hepaticojejunostomy, has become nearly obsolete.

Endoscopic stents can be plastic, metal or covered metal stents. Plastic stents are thinner stents which are less durable, resulting in more frequent endoscopies and stent changes. Metal stents can be uncovered or covered. In a randomized controlled trial of 119 patients undergoing neoadjuvant therapy for PDAC there was no significant difference in sustained biliary drainage,

however the reasons for stent failure differed significantly.[62] Covered metal stents had a higher rate of stent migration, while uncovered stents had a higher rate of tumor ingrowth. The rate of acute cholecystitis did not differ significantly (4.8% to 9.3%) in patients with their gallbladder in situ.

When patients undergo exploration for possible cure and are found to have unresectable disease, a biliary bypass can be performed or the patient can have an endoscopic metal stent placed. Traditionally, surgeons have performed either choledochojejunostomy or cholecystojejunostomy for the relief of malignant biliary obstruction. Both procedures are effective in relieving jaundice, but it appears that the rate of recurrent jaundice after cholecystojejunostomy is approximately 10%. Therefore, our preference for the palliation of obstructive jaundice is a hepaticojejunostomy or choledochojejunostomy reconstructed with a Roux-en-Y limb of jejunum. The surgical palliation of jaundice can be accomplished safely, with a mortality rate of less than 3% and an overall morbidity rate of 30% to 40%.[63] Nonoperative palliation appears to be associated with lower complication rates, lower procedure-related mortality rates, and shorter initial periods of hospitalization in comparison with surgical palliation. However, the rate of recurrent jaundice is higher.

Duodenal Obstruction

At the time that pancreatic cancer is diagnosed, approximately one-third of patients have symptoms of nausea or vomiting. Although true mechanical obstruction of the duodenum seen by radiologic or endoscopic examination is much less frequent, duodenal obstruction develops in almost 20% of patients before they die as the disease progresses.[64] Duodenal obstruction can be caused in the C-loop by cancers of the head/uncinate or at the ligament of Treitz by cancers of the body and tail. In patients with evidence of duodenal obstruction or impending obstruction, a minimally invasive gastrojejunostomy is indicated for palliation and improvement in quality of life. If patients have a significant burden of disease and a short life expectancy of only a few months an endoscopic duodenal stent can be considered. However, duodenal stents can obstruct due to tumor ingrowth and can jail the ampulla, which prevents exchange of the biliary stent. For patients with a longer life expectancy a minimally invasive isoperistaltic

loop gastrojejunostomy with a loop of jejunum 20 to 30 cm distal to the ligament of Treitz should be performed. If patients have long-standing obstruction and a dilated stomach, it may take weeks before the stomach regains tone and the patient is able to take in adequate calories. This population may benefit from a gastrojejeunal feeding tube which can vent the stomach and feed the jejeunum. This allows patients to avoid a long-term postoperative nasogastric tube and shorten their days in the hospital.

In patients who are explored and found to have unresectable pancreatic cancer we prefer to perform a gastrojejeunostomy. A prospective, randomized trial of prophylactic gastrojejunostomy in 44 patients were randomized and compared to 43 who did not undergo gastric bypass.[65] In this study, no difference was observed in either the complication rate, mortality, or the postoperative length of stay (**Table 55.14**). However, late duodenal obstruction developed in 19% of the patients who did not undergo bypass. A recent multicenter prospective randomized controlled trial has confirmed these results.[66] Therefore, we believe that a prophylactic gastrojejunostomy should be performed in patients undergoing surgical palliation for unresectable pancreatic carcinoma.

Novel approaches to perform endoscopic gastric bypasses using specialized stents are becoming increasingly possible. These procedures provide effective gastric decompression, however, their diameter is significantly smaller than an operative gastrojejeunostomy, limiting the amount and types of food a patient can eat. The endoscopic bypass is twice as likely to require an additional intervention (9%) when compared to a surgical gastrojejeunostomy (19%) in a shorter time interval (64 days vs. 93 days, $p < 0.01$) (Fisher AV HPB in press). Randomized data are required to provide accurate data regarding safety and efficacy.

PAIN

Tumor-associated pain can be incapacitating in patients with unresectable pancreatic cancer. The postulated causes of tumor-associated pain are many and include tumor infiltration into the celiac plexus, increased parenchymal pressure caused by pancreatic duct obstruction, pancreatic inflammation, gallbladder distention resulting from biliary obstruction, and gastroduodenal

obstruction. The management of pain in patients dying of carcinoma of the pancreas is one of the most important aspects of their care. The appropriate use of oral agents can be successful in most patients. Patients with significant pain should receive their medication on a regular schedule and not on an "as-needed" basis. The use of long-acting morphine derivative compounds appears to be best suited for such treatment. Percutaneous neurolytic block of the celiac axis, performed under either fluoroscopic or CT guidance, is also successful in the majority of patients in helping eliminate pain. Patients with unresectable cancer at the time of surgical exploration should receive a chemical splanchnicectomy, with 20 mL of 50% alcohol injected on either side of the aorta at the level of the celiac axis.[67]

CONCLUSION

Pancreatic adenocarcinoma is a complex disease requiring multi-disciplinary care. Significant improvements in the surgical management and systemic therapy have contributed to an improvement in overall survival.

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56

Neoplasms of the Endocrine Pancreas

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Key Points

1. Pancreatic endocrine neoplasms (PENs) originate from multipotent stem cells in pancreatic ductules. Therefore, use of the older terms *islet cell tumor* and *islet cell carcinoma* is now discouraged, in favor of the terms *pancreatic neuroendocrine neoplasms* or *pancreatic neuroendocrine tumors*.
2. PENs have traditionally been classified according to the size and the mitotic rate of the tumor into one of three categories: pancreatic endocrine microadenomas, well-differentiated PENs, and poorly differentiated or high-grade endocrine carcinomas.
3. The most recent World Health Organization classification uses the combination of a proliferative index (Ki-67), mitotic rate, and morphologic features (degree of differentiation) to grade PENs.
4. The best initial imaging technique for a PEN is a high-quality multidetector computed tomography (CT) scan while novel NET-specific positron emission tomography (PET) scans provide important diagnostic and staging information.
5. Insulinomas may present with either neuroglycopenic and/or hypoglycemic-induced symptoms. Ninety percent are solitary, 90% are sporadic, and 90% are benign with their location evenly distributed throughout the pancreas. Ten percent are familial, typically associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome, and commonly multifocal in the pancreas.
6. Most gastrinomas are located in the gastrinoma triangle. Seventy-five percent are sporadic, while 25% are associated with MEN-1 syndrome. They typically have malignant behavior including locally invasive growth and metastatic spread.
7. Glucagonomas usually present with a characteristic severe dermatitis (necrolytic migratory erythema) and are typically large and bulky and often with metastatic disease.
8. The majority of PENs are nonfunctional and surgical resection of localized tumors or those with limited hepatic metastases is standard treatment.

9 Liver-directed therapies including transarterial embolization or ablation may be considered for patients with hepatic metastases that are not amenable to resection.

10 Numerous systemic therapies exist for patients with metastatic PENs including somatostatin analogs, traditional chemotherapy such as temozolomide and capecitabine, targeted therapies such as everolimus or sunitinib, and peptide receptor radionuclide therapy (PRRT).

INTRODUCTION

Epidemiology

Pancreatic endocrine neoplasms (PENs) are rare tumors that account for 3% of pancreatic neoplasms and 7% of all neuroendocrine tumors (NETs).[1] Their incidence has increased nearly fivefold over the past 30 years, corresponding to the dramatic rise in the use of cross-sectional imaging in modern medicine. This has led to an increase in the rate of incidentally diagnosed tumors in asymptomatic patients.[2] First described by Nicholls in 1902 as a tumor arising from pancreatic islet cells, these "islet cell adenomas" were long thought to arise from the islets of Langerhans.[3] Recent investigations have revealed that PENs more likely originate from multipotent stem cells in pancreatic ductules.[4,5] This non–islet cell origin hypothesis has been further supported by the presence of tumors arising in patients with multiple 1 endocrine neoplasia type 1 (MEN-1).[6] Therefore, use of the older terms *islet cell tumor* and *islet cell carcinoma* is now discouraged, in favor of the terms *pancreatic endocrine neoplasms, pancreatic neuroendocrine tumors*, *pancreatic neuroendocrine neoplasms,* or *pancreatic endocrine tumors*.[7,8]

Classification

Traditionally, PENs were classified according to their size and the mitotic rate of the tumor. This system placed PENs into one of three categories: **pancreatic endocrine microadenomas**, 2 **well-differentiated PENs**, and **poorly differentiated** or **high-grade endocrine carcinomas**. PENs are also differentiated by the presence or absence of symptoms due to hormone

production, with nonfunctional PENs (91%) significantly more common than functional tumors (9%).[9,10] The production of certain hormones by functional tumors and their resulting symptoms lead to well-described clinical syndromes, which are detailed later in this chapter.

PENs less than 0.5 cm in diameter are classified as **pancreatic endocrine microadenomas**. Oncologically, they are considered to be benign lesions. Their prevalence is estimated to be as high as 10% of the population in autopsy series.[11,12] Most pancreatic endocrine microadenomas are noted as incidental findings in pancreata resected for other indications and, by definition, produce no neoplastic syndromes (i.e., are nonfunctional). PENs measuring greater than 0.5 cm in diameter but with low-grade histology are referred to as **well-differentiated PENs**. This group comprises the large majority of clinically relevant PENs but are still relatively rare.[13,14]

Table 56.1 2017 World Health Organization Classification of Pancreatic Neuroendocrine Tumors

	Ki67 Index	Mitotic Index
Well-Differentiated NENs	<3%	<2/10 HPF
G1 NET	3–20%	2–20/10 HPF
G2 NET	>20%	>20/10 HPF
G3 NET		
Poorly Differentiated NENs	>20%	>20/10 HPF
NEC G3		
Small Cell Type		
Large Cell Type		

NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NEC, neuroendocrine carcinoma; HPF, high-power fields.

The classification of PENs has in the past been controversial, with no single dominant staging system in existence.[15] Multiple varying staging schemes (including those by the European Neuroendocrine Tumor Society [ENETS] and the American Joint Committee on Cancer [AJCC])[16,17] have been put forward, attempting to establish prognostic characteristics such as size, mitotic count,

presence of necrosis, extrapancreatic invasion, vascular and perineural invasion, 3 nuclear polymorphisms, and nodal involvement.[18–21] In 2017, the **World Health Organization (WHO)** updated their classification of PENs into **well-differentiated NETs** and **poorly differentiated neuroendocrine carcinomas (NECs)** based on tumor morphology with further stratification based on tumor grade as measured by the Ki-67 proliferation index and mitotic rate (**Table 56.1**). By convention, the tumor is assigned the higher grade if the Ki-67 index and mitotic rate differ.

Well-differentiated PENs can also be classified as **functional** or **nonfunctional** based on the presence or absence of a clinically recognizable syndrome (**Table 56.2**). These syndromes are the result of the secretion of biologically active hormones by the tumors and are confirmed by measurable elevations of the hormones in the blood. The most common functional PENs include insulinomas, gastrinomas, vasoactive intestinal polypeptide-omas (VIPomas), glucagonomas, and somatostatinomas. The incidence of these lesions ranges from 1 per 1 million for insulinomas to 1 per 40 million for somatostatinomas.[22] Even less common PENs secreting calcitonin,[23,24] parathyroid hormone–related protein,[25] growth hormone–releasing factor, and adrenocorticotropic hormone[26] have been reported. Nonfunctional PENs are classified as such due to their lack of an associated clinical syndrome. Some of the tumors in this group do secrete elevated amounts of hormones, including chromogranin A, which can be detected in either the serum or in surgical specimens using immunohistochemistry.[27] These secreted hormones either produce no clinical syndromes, as is seen with tumors that secrete pancreatic polypeptide (PP),[28] or secrete hormones in subclinical amounts or inactive forms. Traditionally, functional PENs were reported to comprise the majority of PENs. As methods of detecting these lesions and patterns of presentation have evolved, due primarily to the widespread use of high-quality cross-sectional imaging, nonfunctional PENs now comprise the vast majority of surgically resected cases.[18,29]

MOLECULAR GENETICS

Whole-Exome Sequencing of PENs

In 2011, a seminal whole-exome sequencing study of 68 sporadic PENs[30] identified frequent somatic mutations in *MEN-1* as well as the chromatin-

remodeling complex, *DAXX* (death-domain–associated protein) and *ATRX* (alpha thalassemia/mental retardation syndrome X linked). A subset of samples had mutations in genes involved in the mammalian target of rapamycin (mTOR) pathway including phosphatase and tensin homolog (PTEN), tuberous sclerosis complex 2 (TSC2), and phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit α (PIK3CA). Other studies have correlated *DAXX* and *ATRX* mutations, activation of alternative lengthening of telomeres, and global chromosomal alterations with pathologic features and outcomes.[31] A more recent whole-exome sequencing of 102 PENs samples has clarified four distinct signaling pathways in which somatic mutations were commonly found: (1) chromatin remodeling, (2) DNA damage repair, (3) mTOR signaling, and (4) telomere maintenance.[32]

Familial Syndromes

The majority of PENs are sporadic. Some of them, however, occur as part of inherited familial syndromes such as MEN-1, von Hippel–Lindau (VHL) syndrome, neurofibromatosis (NF-1), and tuberous sclerosis (TS) (**Table 56.3**).[33]

Table 56.2 Classification of Functional Pancreatic Endocrine Tumors

Tumor (Syndrome)	Clinical Features	Extrapancreatic Location	Malignancy Rate
Insulinoma	Hypoglycemia	Rare	10%
Gastrinoma (Zollinger–Ellison)	Peptic ulcer Diarrhea	Frequent	50%
VIPoma (Verner–Morrison; WDHA; Pancreatic Cholera)	Watery diarrhea hypokalemia achlorhydria/acidosis	10%	Most
Glucagonoma	Hyperglycemia Dermatitis	Rare	Most
Somatostatinoma	Hyperglycemia Steatorrhea Gallstones	Rare	Most

WDHA, watery diarrhea, hypokalemia, and either achlorhydria or acidosis.

Table 56.3 Familial Genetic Syndromes Associated with Pancreatic Endocrine Neoplasms (PENs)

Syndrome	Chromosomal Location	Gene Product	PEN Type
MEN-1	11q13	Menin	Gastrinoma Nonfunctional
VHL	3p25-26	VHL	Various
NF-1	17q11.2	Neurofibromin	Somatostatinoma
TS	9q34 (TSC1) 16p13.3 (TSC2)	Tuberin	Various

MEN-1, multiple endocrine neoplasia 1; VHL, von Hippel–Lindau; NF, neurofibromatosis; TS, tuberous sclerosis; TSC, tuberous sclerosis complex.

MEN-1, also known as Wermer syndrome, is an autosomal dominant disorder caused by germline mutations in the tumor suppressor gene *MEN-1*. Chromosomal linkage studies have localized the genetic defect to the 11q13 locus, and studies of DNA markers have localized the MEN-1 gene between PYGM and D11S97. The gene contains 10 exons that code for a 610-amino-acid protein called menin, which is involved in DNA replication, transcription, repair, and chromatin remodeling. Although more than 20 endocrine tumors have been associated with MEN-1 syndrome, the most common include tumors of the parathyroid, anterior pituitary, and endocrine pancreas.

Less frequently than MEN-1, PENs may be associated with **VHL** syndrome. VHL syndrome is another autosomal dominant inheritance disease that includes many clinical disorders[34] including retinal hemangioblastomas, cerebellar and medullary hemangioblastomas, and PENs. PENs are found in a small percentage of patients with VHL syndrome, although pancreatic cysts are commonly encountered. A mutation in the VHL gene, a tumor suppressor located on chromosome 3p25–26, which regulates hypoxia-induced cell proliferation, is responsible. Although germline mutations with loss of heterozygosity (LOH) are associated with this disease, it has been proposed that other tumor suppressors most likely cooperate with VHL in order to form PENs. VHL-mutated PENs

have been shown to have specific defects in angiogenesis and hypoxia-inducible factor pathways.[35]

NF-1 (von Recklinghausen disease) is an autosomal dominant disorder that produces a well-described clinical syndrome characterized by café-au-lait spots and neurofibromas. These patients may develop pancreatic somatostatinomas, often near the ampulla of Vater. The NF-1 gene is a tumor suppressor gene located on 17q11.2 that encodes for neurofibromin, a regulator of the mTOR pathway. Loss of NF-1 results in mTOR activation and tumor development.[36,37]

TS is a rare autosomal dominant disorder associated with mutations in *TSC1* or *TSC2* which encode the protein tuberin. It is a neurocutaneous disorder associated with characteristic skin lesions, central nervous lesions including hamartomas, and rarely PENs. Note that patients may also develop pancreatic angiomyolipomas.

Molecular Targeting of PENs

In summary, PENs are becoming easier to characterize molecularly (and clinically) due to large-scale sequencing efforts and a better understanding of the molecular biologic aspects of these pancreatic tumors. Indeed, the molecular characterization of these tumors have helped to pave the way for clinical trials targeting tyrosine kinases (e.g., sunitinib) and the mTOR pathways (e.g., everolimus). Future molecular interrogation of PENs combined with these types of preclinical targeting approaches should continue to move the field closer to a personalized approach to treating PENs with more effective targeted therapies.

DIAGNOSTIC EVALUATION

Presentation

There are three primary ways by which patients with PENs come to clinical attention: the incidental discovery of a mass in the pancreas during cross-sectional imaging, symptoms secondary to the mass effect of a lesion in the pancreas (i.e., obstructive jaundice or pain), or, as a consequence of the symptoms of a syndrome associated with a functional PEN. As mentioned previously, incidentally detected nonfunctional PENs currently comprise the majority of clinically relevant tumors.

Biochemical

If a nonfunctional PEN is suspected, baseline serum levels of chromogranin A and PP can be useful diagnostic markers prior to surgical resection. Chromogranin A is a 49-kDa protein contained within the neurosecretory vesicles of PENs. The chromogranin A levels can be tracked over time to document tumor recurrence, often before the lesions become visible on cross-sectional imaging studies.[38] PP is secreted by the PP cells of the islets of Langerhans and can also be used to track patients with PENs, though its sensitivity (63%) is lower than that of chromogranin A.[39] Neuron-specific enolase is another tumor marker that is elevated in approximately 50% of PENs, most commonly in patients with pulmonary metastases.[40]

For those in whom a functional PEN is suspected, confirmatory testing of the relevant serum hormone should be performed. Assays are readily available for measuring insulin, gastrin, VIP, and glucagon. Assays for somatostatin, PP, prostaglandins, and other hormonal markers are less commonly available but can be obtained from certain laboratories. Genetic testing may be indicated for those in whom a clinical syndrome is suspected both for diagnostic confirmation but also to guide subsequent personal and family screening.

Computed Tomography

Cross-sectional imaging with thin-cut multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) is typically indicated for all patients with confirmed or suspected PENs.[41] The accuracy of CT in detecting primary PENs ranges from 64% to 82% and depends largely on the size of the tumor.[42,43] PENs are typically hyperdense on arterial phases of imaging. Lesions that are obvious during the early arterial phase can become isodense on later phases of imaging. 4 Therefore, a multiphase approach is typically recommended.[44,45] CT is useful in assessing size and location of the primary tumor, proximity to visceral vessels, peripancreatic lymph node involvement, and the presence or absence of liver metastases (**Fig. 56.1**).

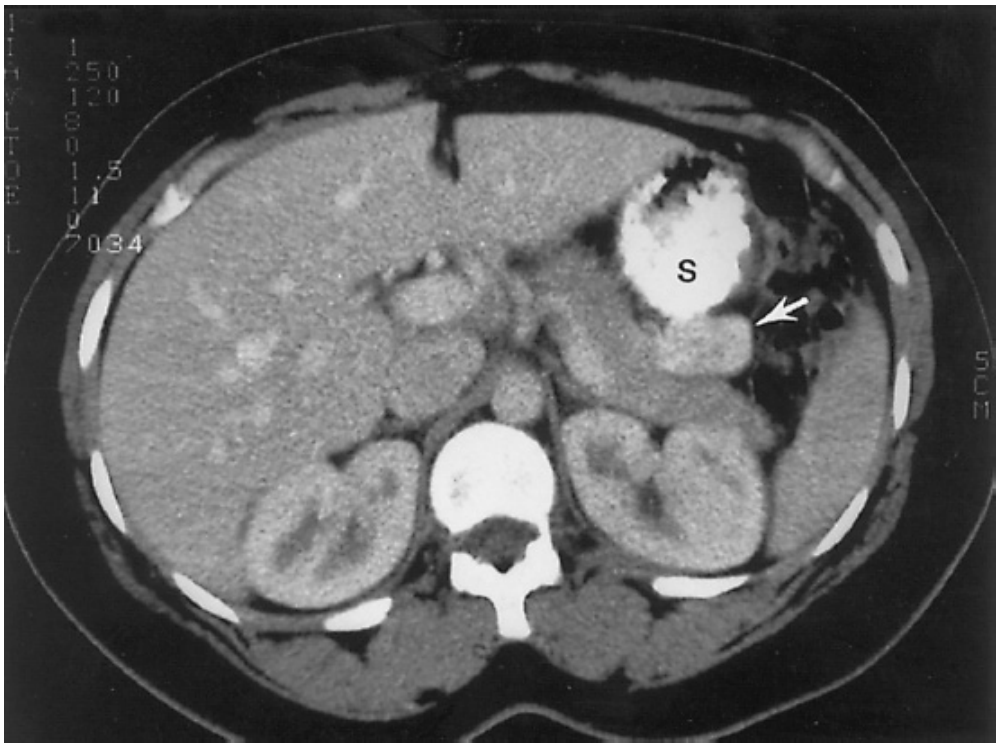

Figure 56.1 Computed tomography with oral and intravenous contrast in a patient with biochemical evidence of insulinoma. The neoplasm (*arrow*) is seen as a contrast-enhancing structure, 3 cm in diameter, in the tail of the pancreas posterior to the stomach (S). (From Yeo CJ. Islet cell tumors of the pancreas. In: Niederhuber JE, ed. *Current Therapy in Oncology*. St. Louis, MO: Mosby; 1993:272, with permission.)

Magnetic Resonance Imaging

MRI is increasingly used in the detection of PENs, particularly small lesions. They are especially well visualized on T1- and T2-weighted images with fat suppression. MRI has the advantage of increased soft tissue contrast without the administration of intravenous contrast when compared to CT.[35] PENs characteristically have high signal intensity on T2-weighted images.[46] On dynamic contrast-enhanced T1-weighted images, the tumors show the same typical enhancement pattern as on CT scan. The sensitivity of MRI has been reported to be between 74% and 100%.[42,43]

Somatostatin Receptor Scintigraphy

Somatostatin receptor scintigraphy (SRS) also plays an important role in imaging patients with PENs given that over 90% of NETs express somatostatin receptors. Traditionally, the octapeptide analog of somatostatin (octreotide)

labeled with indium-111 (known as Octreoscan) was the standard method of staging and characterizing NETs (**Fig. 56.2**).

This imaging modality has been largely replaced by positron emission tomography (PET)–based techniques. The most common used today is gallium Ga-68 DOTATATE which was approved by the FDA in 2016 and offers several benefits compared to traditional Octreoscan including improved sensitivity, less radiation, and enhanced convenience given the shorter scanning time required (**Fig. 56.3**). This method of SRS utilizes 3D PET fused with contrast-enhanced CT to provide improved spatial resolution and better sensitivity. In one seminal prospective study, the addition of Ga-68 DOTATATE to CT/MRI and Octreoscan led to a clinically significant change in management among 33% of the patients.[47]

Consensus guidelines generating appropriate use criteria have suggested that SRS-PET should replace in-pentetreotide scintigraphy for essentially all indications in which the latter was previously being used.[48]

Figure 56.2 Octreotide scan (*anterior view*) in a patient with a large endocrine tumor in the tail of the pancreas (large dark mass, upper right) and several hepatic metastases (upper left quadrant). A small amount of the tracer is seen in the bladder (lower midline).

Endoscopic Ultrasound

Endoscopic ultrasonography (EUS) is an important adjunct in the evaluation and localization of PENs.[49–53] Rösch et al.[51] were able to localize 32 of 39 tumors (82%) correctly with EUS after CT had failed to locate the tumor (**Fig. 56.4**). In their experience, EUS was more sensitive than the combination of CT and visceral angiography. A more recent study by Proye et al.[54] evaluated preoperative EUS and SRS in 41 patients with insulinoma and gastrinoma. The sensitivity and positive predictive value of EUS were 77% and 94%, respectively, for pancreatic tumors; 40% and 100%, respectively, for duodenal gastrinomas; and 58% and 78%, respectively, for metastatic lymph nodes.

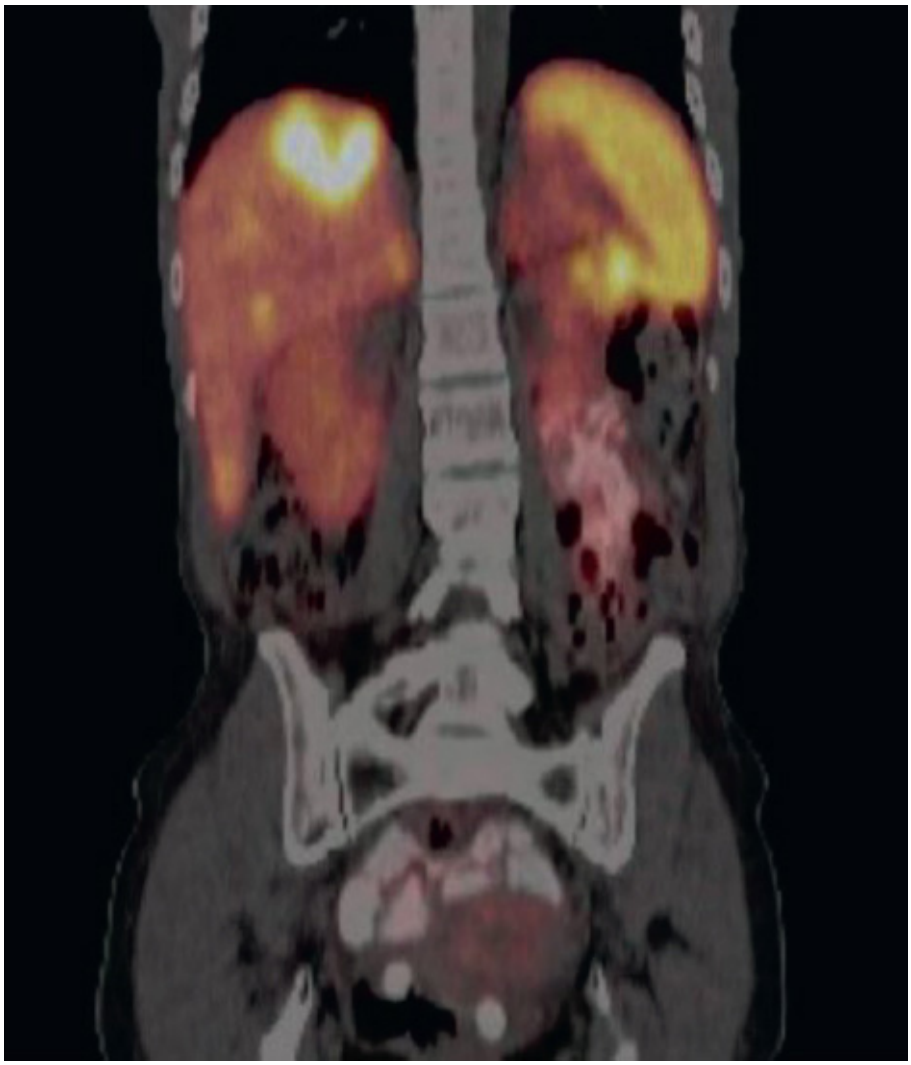

Figure 56.3 Gallium 68 dotatate PET/CT scan of a patient with a pancreatic endocrine tumor with several bulky hepatic metastases.

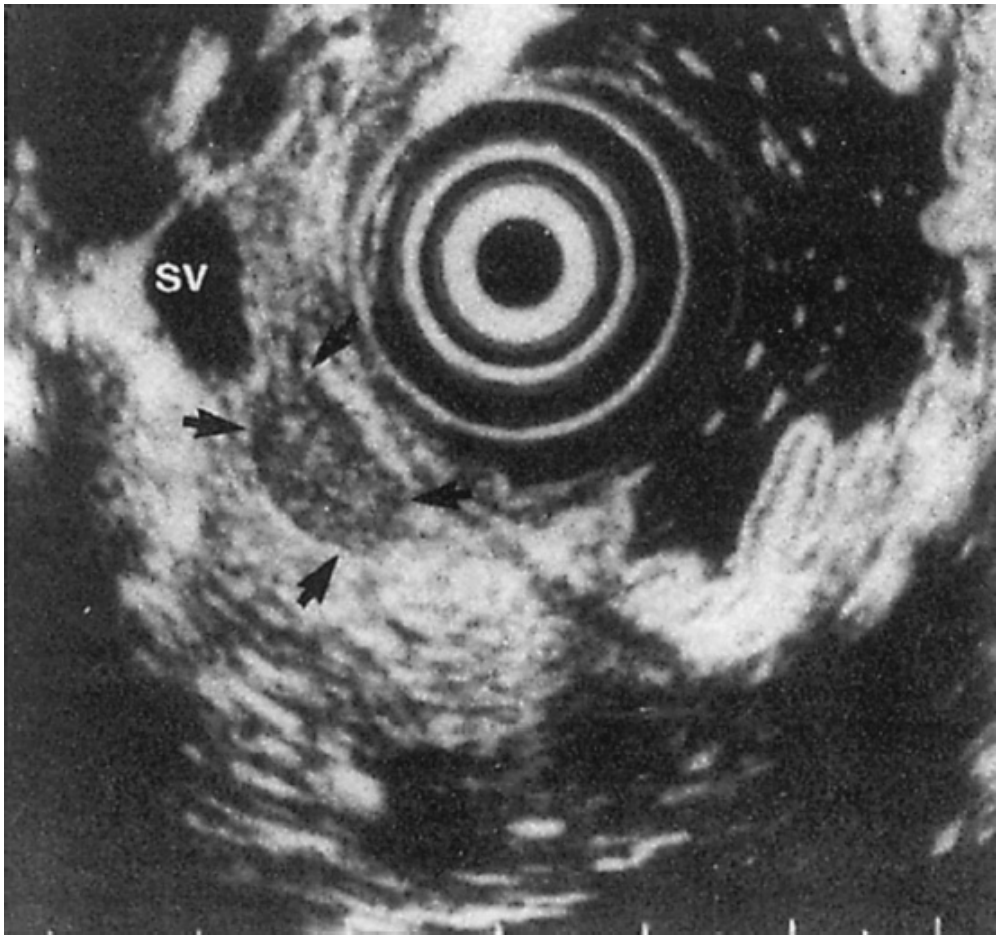

Figure 56.4 Endoscopic ultrasonographic image from a patient with an insulinoma (*arrows*) in the body of the pancreas. SV, splenic vein. (From Rösch T, Lightdale CJ, Botet JF, et al. Localization of pancreatic endocrine tumors by endoscopic ultrasonography. *N Engl J Med* 1992;326[26]:1721–1726, with permission.)

Venous Sampling

Percutaneous transhepatic portal venous sampling (PTPVS) and arterial stimulation with venous sampling (ASVS) are two techniques that are used exclusively for the diagnosis and localization of PENs. Although rarely used, PTPVS and ASVS can be helpful in localizing functional PENs when CT, MRI, SRS, and EUS are unsuccessful. Specifically, when insulinoma or gastrinoma are suspected, PTPVS may help in localizing the occult neoplasm.[55–59] The technique involves placing a catheter percutaneously through the liver into the portal vein and then sequentially sampling for hormone levels in the splenic vein, superior mesenteric vein, and portal vein, thereby regionalizing the location of hormone production (**Fig. 56.5**). The overall accuracy of this test

ranges from 70% to greater than 95% depending on the number of samples obtained, the persistence of autonomous hormone production by the tumor, and the careful handling and assaying of all samples. ASVS involves the selective visceral arterial injection of secretin or calcium with concurrent hepatic venous sampling for either gastrin or insulin.[60,61] Gastrinoma cells are known to respond to secretin by releasing gastrin,[62,63] and insulinoma cells are known to respond to calcium by releasing insulin. The provocative secretogogue is serially injected through an arterial catheter into at least three sites—the splenic, gastroduodenal, and inferior pancreaticoduodenal arteries. Samples are drawn from a hepatic vein catheter before and immediately after each injection. The arterial supply to the occult tumor can then be deduced based on which selective secretogogue injection is followed by a large increase in hepatic vein hormone concentration (**Fig. 56.6**). This technique, particularly when combined with intraoperative ultrasonography, results in a sensitivity of greater than 90%, essentially obviating the need for blind resection in unlocalized insulinomas.[64,65] Additionally, ASVS can differentiate the 5% of patients with nesidioblastosis from those with insulinoma.[66,67]

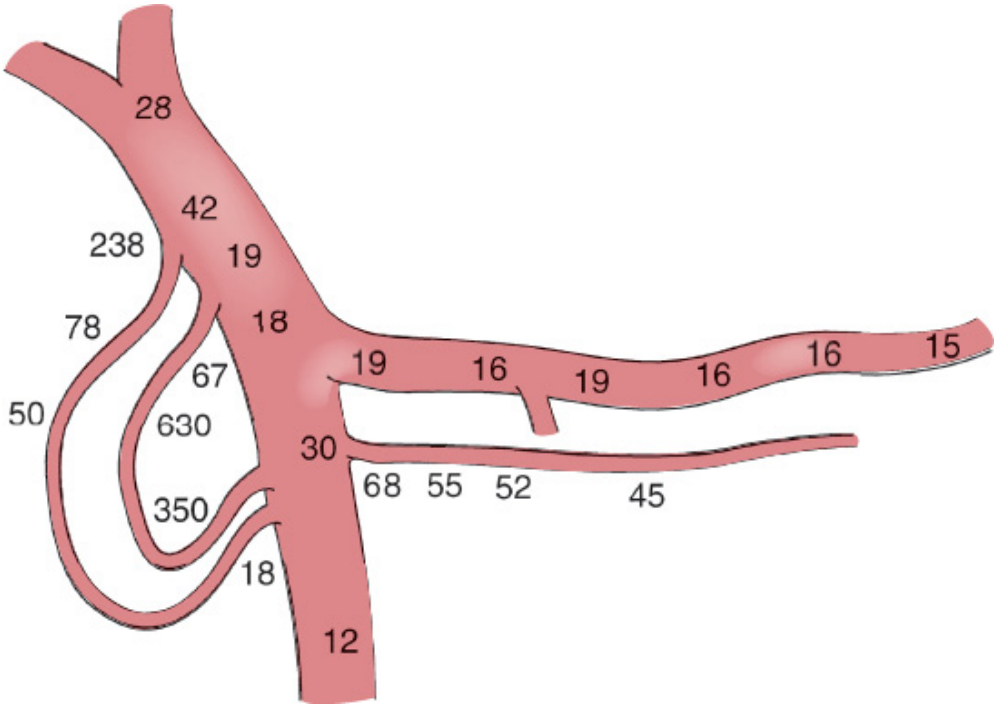

Figure 56.5 Schematic depiction of data from percutaneous transhepatic portal venous sampling (PTPVS) in a patient with an insulinoma. Insulin levels are given in microunits per milliliter. These data localize the neoplasm to the head of the pancreas. (Adapted from Norton JA, Sigel B, Baker AR, et al. Localization of an occult insulinoma by intraoperative ultrasonography. *Surgery* 1985;97:381–384.)

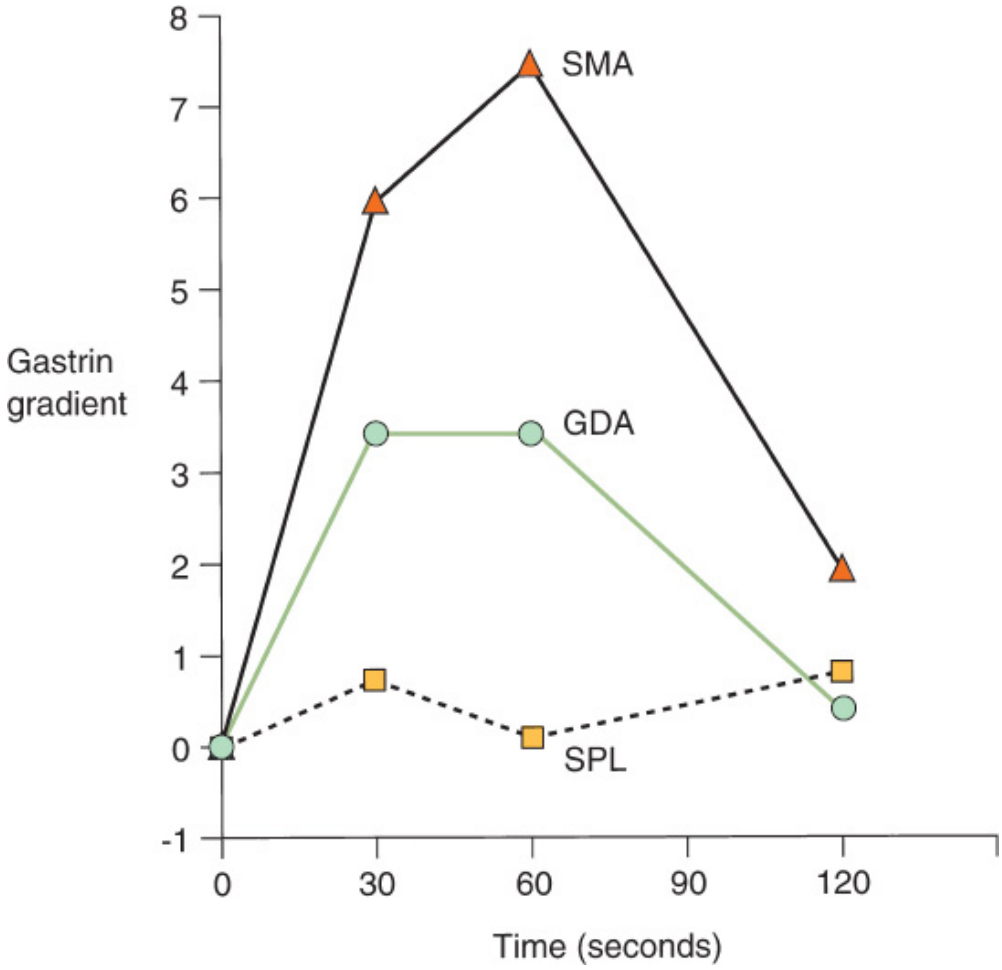

Figure 56.6 Graphic depiction of the results of arterial stimulation with venous sampling (ASVS) in a patient with gastrinoma. The rise in hepatic vein gastrin concentration (gastrin gradient) is plotted on the y-axis, and basal values are plotted on the x-axis: 1, 100% rise; 2, 200% rise; and so forth. A rise in the hepatic vein gastrin concentration observed after the injection of secretin into the superior mesenteric artery (SMA) and gastroduodenal artery (GDA) localizes the neoplasm to the head of the pancreas or duodenum. SPL, splenic artery. (Adapted from Thom AK, Norton JA, Doppman JL, et al. Prospective study of the use of intra-arterial secretin injection and portal venous sampling to localize duodenal gastrinomas. *Surgery* 1992;112:1002–1028; discussion 1008–1009.)

SURGICAL EXPLORATION

With modern diagnostic tools, surgical exploration without preoperative tumor localization is rarely needed. Regardless, at the time of surgical exploration for PEN, a complete evaluation of the pancreas and peripancreatic regions is performed. The body and tail of the pancreas are exposed by dividing the

gastrocolic ligament and entering the lesser sac. This portion of the pancreas can be partially elevated out of the retroperitoneum by dividing the inferior retroperitoneal attachments to the gland. After the second portion of the duodenum has been elevated out of the retroperitoneum by means of the Kocher maneuver, the pancreatic head and uncinate process are palpated bimanually. The liver is carefully assessed for evidence of metastatic disease. Intraoperative pancreatic and hepatic ultrasound can be helpful in identifying occult primaries or metastatic disease with sensitivities reported between 75% and 90%.[64,68]

NONFUNCTIONAL PANCREATIC ENDOCRINE NEOPLASMS

Surgical Resection

Overall, nonfunctional tumors tend to grow more slowly and have a more indolent course than pancreatic ductal adenocarcinoma, yet the 5-year survival rate for PENs after resection remains only 65%, with a 10-year survival of 45%.[10] Size is an important determinant of outcome and can be used to guide surgical decision making. PENs <1 cm typically have low malignant potential and can be safely observed while PENs >2 cm have prohibitive risks for lymph node and hepatic metastases that warrant resection.[69–71] PENs between 1 and 2 cm are controversial and require individualized decision making regarding resection or observation.[72] In general, patients with localized disease who are surgical candidates should undergo formal resection for potential cure via pancreaticoduodenectomy or distal pancreatectomy, depending on tumor location. Tumor enucleation, without formal resection may be appropriate for patients with small tumors in which the lesion is far from the pancreatic duct as to minimize the risks of pancreatic fistula. Patients with locally advanced disease involving the mesenteric vasculature may be candidates for radical mesenteric vascular resection (**Fig. 56.7**) or can be treated with neoadjuvant therapies in an attempt to downstage to resectability. With successful treatment, these patients can expect to enjoy a median survival in excess of 5 years.[73,74]

Lymphadenectomy

The role of lymphadenectomy for PENs remains controversial. PENs frequently metastasize to regional lymph nodes and therefore a lymph node dissection at the time of surgical resection provides important prognostic information as well as local disease control. The rate of lymph node involvement also correlates with tumor size.[75] While consensus guidelines are lacking, most recommend performing a regional lymphadenectomy at the time of resection for most PENs.[72]

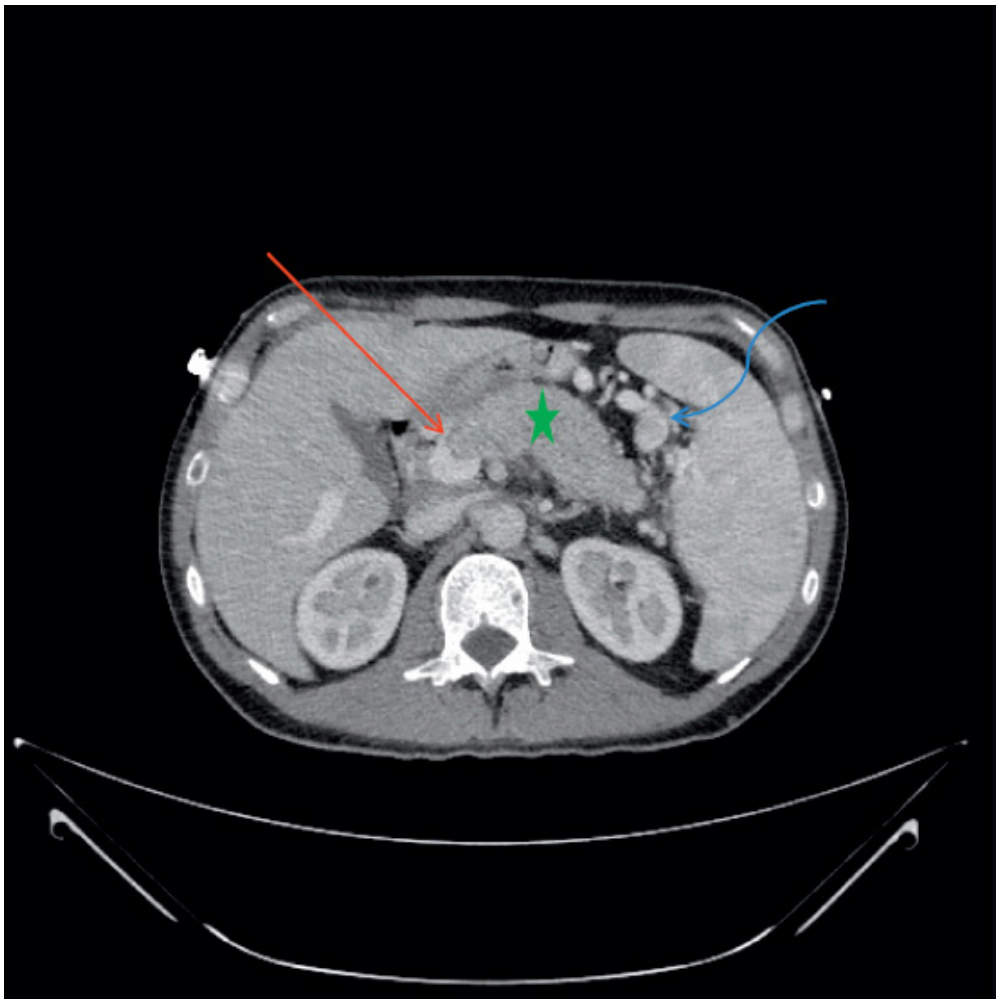

Figure 56.7 Computed tomography of a patient with a large PEN (*green star*) replacing the pancreatic body and tail, with splenic vein occlusion, perigastric varices (*blue line*), and tumor thrombus (*red line*) growing into the portal vein. This patient underwent a distal pancreatectomy, splenectomy, and partial portal vein resection with tumor thrombectomy, with complete surgical extirpation of the malignancy.

Table 56.4 Insulinoma

Parameter	Description
Symptoms	Neuroglycopenia causes confusion, personality change, coma Catecholamine surge causes trembling, diaphoresis, tachycardia Anabolic state: weight gain
Diagnostic tests	Monitored fast Insulin-to-glucose ratio
Anatomic localization	Evenly distributed throughout pancreas

INSULINOMA

5 Insulinoma is the most common functional neoplasm of the endocrine pancreas (**Table 56.4**). Patients typically present with the following features, known as **Whipple triad**[76]:

1. Symptoms of hypoglycemia during fasting
2. Documentation of hypoglycemia, with a serum glucose level typically below 50 mg/dL
3. Relief of hypoglycemic symptoms following administration of exogenous glucose

Autonomous insulin secretion in insulinomas leads to spontaneous hypoglycemia, with symptoms that can be classified into two groups. Neuroglycopenic symptoms include confusion, seizure, obtundation, personality change, and coma. Hypoglycemia-induced symptoms, related to a surge in catecholamine levels, include palpitations, trembling, diaphoresis, and tachycardia. In most cases, patients consume carbohydrate-rich meals and snacks to relieve or prevent these symptoms and typically gain weight.

Insulinoma is most reliably diagnosed by means of a **monitored fast** (via the withholding of exogenous glucose). During a monitored fast, blood is sampled for glucose and insulin determinations every 4 to 6 hours and when symptoms appear. Hypoglycemic symptoms typically occur when glucose levels are below 50 mg/dL, with concurrent serum insulin levels often exceeding 25 microunits/mL. Additional support for the diagnosis of insulinoma comes from the calculation of the insulin-to-glucose ratio at different times during the monitored fast. Healthy individuals have insulin-to-glucose ratios below 0.3, whereas patients with insulinoma typically demonstrate insulin-to-glucose ratios above 0.4 after a prolonged fast.

Other measurable β-cell products synthesized in excess in patients with insulinoma include **C peptide** and **proinsulin**. Elevated levels of both are typically found in the peripheral blood of patients with insulinoma. The possibility of the surreptitious administration of insulin or oral hypoglycemic agents should be considered in all patients with suspected insulinoma. Levels of C peptide and proinsulin are not elevated in patients who self-administer insulin. Additionally, patients self-administering either bovine or porcine insulin may demonstrate anti-insulin antibodies in circulating blood. The ingestion of oral hypoglycemic agents, such as sulfonylureas, can be assessed by means of standard toxicologic screening.

Insulinomas are evenly distributed throughout the pancreas, with one-third found in the head and uncinate process, one-third in the body, and one-third in the tail of the gland.[77] Less than 3% are located outside the pancreas, with these lesions located in the peripancreatic area.[78] Ninety percent are found to be solitary **sporadic** adenomas amenable to surgical cure, while approximately 10% are associated with the **MEN-1 syndrome**. In patients with MEN-1, the possibility of multiple insulinomas must be considered, and recurrence rates following surgery are higher. After the diagnosis of insulinoma has been confirmed biochemically, the appropriate localization and staging studies described earlier are performed (typically CT and EUS). Once the lesion has been localized,[79] patients undergo surgical exploration, where the pancreas is assessed not only by operative palpation but also by intraoperative ultrasonography. This allows for confirmation of preoperative localization and evaluates for the presence or absence of multiple primary tumors. Small tumors that are not close to the main pancreatic duct can be removed by enucleation (**Fig. 56.8**).[80] Larger tumors in the neck or proximal body may be resected via central pancreatectomy.[81–83] In the body and tail of the pancreas, insulinomas

more than 2 cm in diameter and those close to the pancreatic duct are most commonly removed via distal pancreatectomy. Large lesions in the head or uncinate process of the gland may not be amenable to local resection and may occasionally require pancreaticoduodenectomy for complete excision.[84,85] Increasingly, experienced surgeons are utilizing a minimally invasive approach to these tumors. Both laparoscopic and robotic pancreatectomy or enucleation are now performed on a routine basis with good results.[86–90]

Approximately 10% of insulinomas are malignant, presenting with lymph node or liver metastases. In the presence of hepatic metastases, resection of the primary tumor and metastases should be considered to reduce hypoglycemic symptoms and improve long-term survival.[91–93] In patients with unresectable disease, medications such as diazoxide and octreotide can be used to reduce insulin secretion from the tumor, minimizing hypoglycemia. Furthermore, the mTOR inhibitor everolimus, in addition to its antiproliferative effects, may improve glycemic control for patients with metastatic insulinoma.[94] Dietary manipulations, including judicious spacing of carbohydrate-rich meals and the consumption of night-time snacks, can also reduce the number of hypoglycemic episodes. Multiple chemotherapeutic regimens have been used including streptozocin, dacarbazine, doxorubicin, and 5-fluorouracil.[95–97] Combination chemotherapy has yielded the highest response rates but has not been shown to be curative.

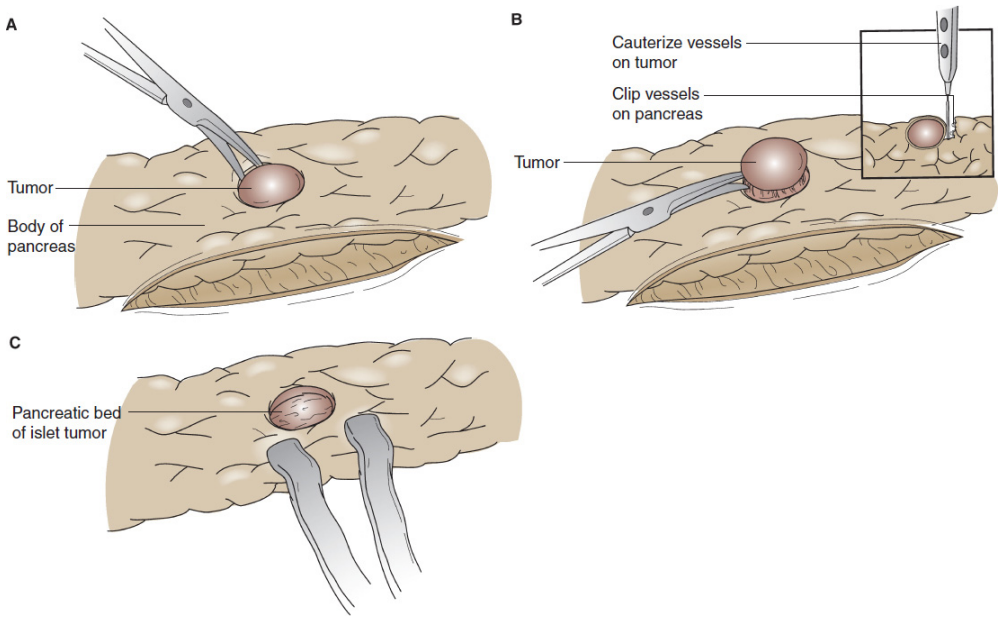

Figure 56.8 The technique for enucleating a benign pancreatic endocrine neoplasm with scissors (**A**) or electrocautery (**B**). **C:** After enucleation, the site of excision is drained.

GASTRINOMA (ZOLLINGER–ELLISON SYNDROME)

In 1955, Zollinger and Ellison described two patients with severe peptic ulcer disease and pancreatic endocrine tumors and postulated that an ulcerogenic agent originated from the pancreatic tumor.[98–100] It has been estimated that approximately 1 in 1,000 patients with primary duodenal ulcer disease and 2 in 100 patients with recurrence after peptic ulcer surgery harbor gastrinomas.[101] Seventy-five percent of gastrinomas occur sporadically, and 25% are associated with the MEN-1 syndrome. Historically, the majority of gastrinomas were found to be malignant, with metastatic disease present at the time of initial workup. With increased awareness and screening for hypergastrinemia, the diagnosis of gastrinoma is made earlier and a higher percentage of patients present with earlier stage and potentially curable neoplasms.[102]

The **clinical symptoms** of patients with gastrinoma are a direct result of increased levels of circulating gastrin (**Table 56.5**). Abdominal pain and peptic ulceration of the upper gastrointestinal (UGI) tract are seen in up to 90% of patients. Diarrhea is seen in 50% of patients, with 10% having diarrhea as their only symptom. Esophageal symptoms or endoscopic abnormalities resulting

from gastroesophageal reflux are seen in up to half of patients. The diagnosis of gastrinoma should be suspected in several clinical settings, including the initial diagnosis of peptic ulcer disease, recurrent ulcer after medical or surgical therapy, postbulbar ulcer, family history of ulcer disease, ulcer with diarrhea, prolonged undiagnosed diarrhea, MEN-1 kindred, nongastrinoma pancreatic endocrine tumors (high association of secondary hormone elevations), and prominent gastric rugal folds on UGI examination. Serum gastrin levels should be obtained in all of these settings.

DIAGNOSIS

Table 56.5 Gastrinoma

Parameter	Description
Symptoms	Peptic ulcer disease Diarrhea Esophagitis
Diagnostic tests	Serum gastrin measurement Gastric acid analysis (or pH testing) Secretin stimulation test
Anatomic localization	Duodenum and head of pancreas (gastrinoma triangle)

In most patients with gastrinoma, the **fasting serum gastrin** level is greater than 200 pg/mL. Gastrin levels greater than 1,000 pg/mL in the setting of documented hyperacidity and ulcer disease are virtually pathognomonic for gastrinoma. Because hypergastrinemia can occur in other pathophysiologic states (**Table 56.6**), fasting hypergastrinemia alone is not sufficient for the diagnosis of gastrinoma. **Gastric acid analysis** (or at least **gastric pH testing**) is critical in differentiating between ulcerogenic (high levels of acid) and nonulcerogenic (low levels of acid) causes of hypergastrinemia. To obtain an accurate gastric acid analysis, patients must not be taking antisecretory medications including histamine (H_2)-receptor antagonists or proton pump inhibitors (PPIs). The diagnosis of gastrinoma is supported by a basal acid output above 15 mEq/hr in nonoperated patients, a basal acid output exceeding 5

mEq/hr in patients with previous vagotomy or ulcer operations, or a ratio of basal acid output to maximal acid output exceeding 0.6.

After documenting that hypergastrinemia and excessive acid secretion exist, provocative testing with secretin should be performed to differentiate between gastrinoma, antral G-cell hyperplasia or hyperfunction, and the other causes of ulcerogenic hypergastrinemia. This is achieved with a **secretin stimulation test** (**Fig. 56.9**). A baseline gastrin level is drawn. The patient is then stimulated with 2 units/kg of secretin as an intravenous bolus and subsequent gastrin samples are collected at 5-minute intervals for 30 minutes. An increase in the gastrin level by more than 200 pg/mL above the basal level supports the diagnosis of gastrinoma.

DIAGNOSIS

Table 56.6 Disease States Associated with Hypergastrinemia

Nonulcerogenic causes (normal to low gastric acid secretion)
Atrophic gastritis
Pernicious anemia
Previous vagotomy
Renal failure
Short-gut syndrome
Ulcerogenic causes (excess gastric acid secretion)
Antral G-cell hyperplasia or hyperfunction
Gastric outlet obstruction
Retained excluded gastric antrum
Zollinger–Ellison syndrome

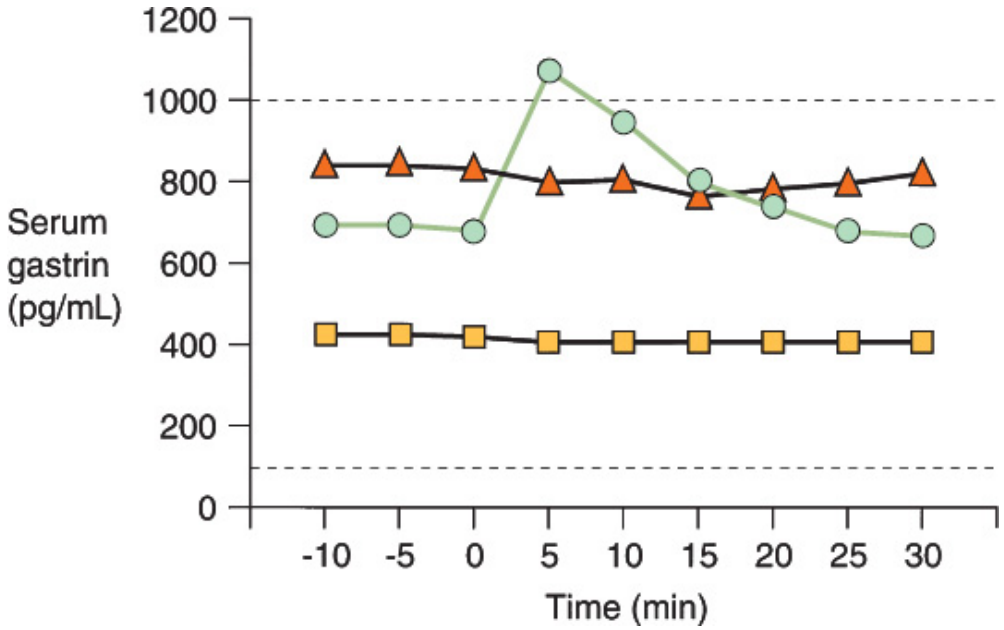

Figure 56.9 Results of intravenous secretin stimulation tests in patients with atrophic gastritis (*triangles*), gastric outlet obstruction (*squares*), and gastrinoma (*circles*). A positive test result, consistent with the presence of gastrinoma, is indicated by an increase over basal serum gastrin levels of at least 200 pg/mL. (Adapted from Wolfe MM, Jensen RT. Zollinger-Ellison syndrome: current concepts in diagnosis and management. *N Engl J Med* 1987;317:1200–1209.)

After the biochemical diagnosis of gastrinoma has been made, the gastric acid hypersecretion should be pharmacologically controlled. PPIs are now considered the drug of choice for this purpose.[103,104] The dose is adjusted to achieve a nonacidic pH during the hour immediately before the next dose of the drug. Typically, PPI doses needed for acid control exceed usual dosing levels. After the initiation of antisecretory therapy, all patients should undergo imaging studies to localize the primary tumor and to assess for metastatic disease.

6 For patients with resectable disease, surgical exploration with curative intent should be offered. On exploration, the entire abdomen should be assessed for areas of extrapancreatic and extraduodenalgastrinomas. Most gastrinomas are found in the **gastrinoma triangle** (**Fig. 56.10**),[77,105] the area to the right of the superior mesenteric vessels, in the head of the pancreas or in the duodenal wall. Both intraoperative ultrasound and intraoperative upper endoscopy may be helpful in tumor localization.

Transillumination of the duodenum may help identify small duodenal gastrinomas.[106,107] If the tumor is still not identified, a longitudinal **duodenotomy** should be performed at the level of the second portion of the duodenum in search of duodenal wall microgastrinomas, which can be palpated

between two fingers.[108,109] Small gastrinomas in the duodenal wall can be locally resected with primary closure of the duodenal defect. The routine use of duodenotomy increases the short- and long-term cure rates in patients with sporadic gastrinoma.[110] In a small percentage of patients, gastrinoma is found only in peripancreatic lymph nodes, with these lymph nodes harboring the apparent primary tumor. Resection of these apparent lymph node primary gastrinomas has been associated with long-term eugastrinemia and biochemical cure in up to half of cases.[111] A review from the National Institutes of Health identified likely primary lymph node gastrinomas in 26 of 176 gastrinoma patients (14.7%), with 69% being eugastrinemic at a mean of 10 years after resection.[112]

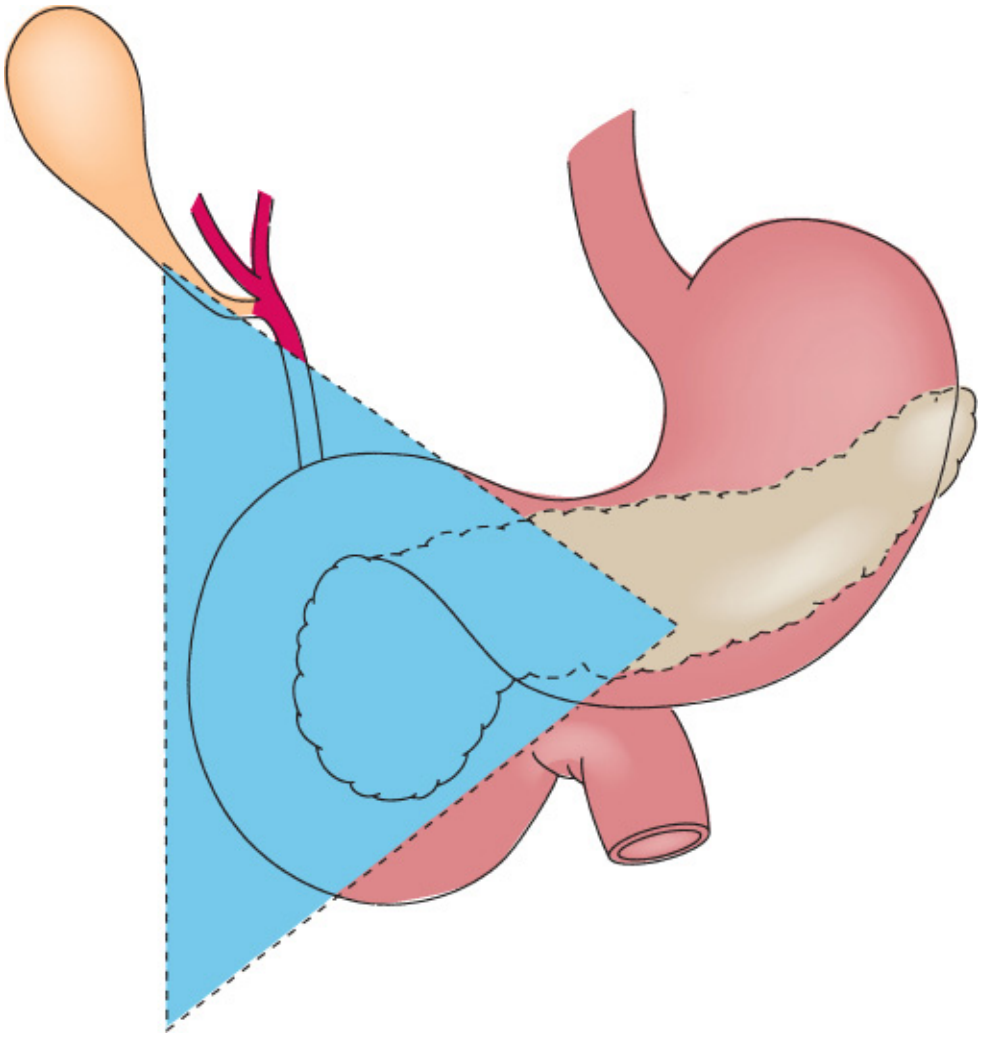

Figure 56.10 Most gastrinomas are found within the gastrinoma triangle.

The management of **gastrinoma in MEN-1** is not as clear given the multifocality of these lesions. Patients with sporadic gastrinomas tend to experience significantly improved disease-free survival following resection compared to those with MEN-1.[113] In patients with MEN-1, gastrin-secreting tumors are often multicentric and associated with lymph node metastases. Although some groups have favored resection only when MEN-1 gastrinoma tumors exceed 3 cm, some have posited that earlier intervention may be warranted.[114,115] The surgical **treatment of hypercalcemia** caused by parathyroid hyperplasia should precede any surgery for hypergastrinemia in patients with MEN-1.

For patients with unresectable metastatic disease, multiple modalities have been used. Chemotherapy including streptozocin, 5-fluorouracil, and doxorubicin provides response rates of less than 50%.[116] Hormonal therapy with octreotide may relieve symptoms, reduce hypergastrinemia, and diminish hyperchlorhydria.[117,118] In patients with hepatic metastases, aggressive surgical cytoreduction,[119–122] hepatic transplantation,[123] hepatic artery chemo- or radioembolization, and interferon therapy have all been used, with variable results.

VIPOMA (VERNER–MORRISON SYNDROME)

Synonyms for VIPoma include WDHA syndrome (watery diarrhea, hypokalemia, and either achlorhydria or acidosis) and pancreatic cholera syndrome (**Table 56.7**). Verner and Morrison[124] characterized this secretory diarrheal syndrome in a 1958 report. Patients characteristically present with intermittent severe, watery diarrhea averaging up to 5 L/d. Hypokalemia results from fecal loss of large amounts of potassium. Low serum potassium levels lead to lethargy, muscle weakness, and nausea. A metabolic acidosis may be present, due to loss of bicarbonate in the diarrhea. Half of the patients may have hyperglycemia or hypercalcemia, and cutaneous flushing can be observed in a minority. The diagnosis of VIPoma is made after other common causes of diarrhea have been excluded (**Table 56.8**)[125] and an elevated serum VIP level is documented.

Table 56.7 VIPoma

Parameter	Description
Symptoms	Watery diarrhea Weakness Lethargy Nausea
Diagnostic Tests	Hypokalemia Achlorhydria Metabolic acidosis Serum VIP levels elevated
Anatomic Localization	Most in body and tail of pancreas, with liver metastases

VIP, vasoactive intestinal peptide.

Table 56.8 Differential Diagnosis of Verner–Morrison Syndrome

Entity	Workup
Villous Adenoma	Lower GI endoscopy
Laxative Abuse	Stool examination for phenolphthalein
Celiac Disease	Fecal fat measurement D-xylose tolerance test Small bowel biopsy
Parasitic and Infectious Diseases	Stool culture Ovum and parasite analysis *Clostridium difficile* toxin assay
Inflammatory Bowel Disease	Lower GI endoscopy Upper GI and small bowel series
Carcinoid Syndrome	Urinary 5′-HIAA Upper GI and small bowel series Abdominal CT Serum serotonin measurement
Gastrinoma	Serum gastrin measurement Gastric acid analysis Secretin stimulation test

CT, computed tomography; GI, gastrointestinal; 5′-HIAA, 5′-hydroxyindoleacetic acid.

VIP secretion can be episodic, so repeated fasting levels should be measured if there is a strong clinical suspicion. Preoperative tumor localization is critical, because 10% of patients may have extrapancreatic tumors located in the retroperitoneum or chest. Most tumors are located in the distal pancreas where they are amenable to resection via distal pancreatectomy. In most cases, hepatic metastases accompany the primary tumor. Therapies directed at these metastases, such as resection or ablative strategies, are appropriate.

Surgical excision is appropriate in nearly all patients with VIPoma. Prior to surgery, fluid and electrolyte imbalances must be corrected. Octreotide can serve as a treatment adjunct, reducing the levels of circulating VIP, with a resultant decrease in the volume of diarrhea. Octreotide is also useful for

symptom control in the setting of unresectable disease. Chemotherapy specific for this disease has not been well studied.

GLUCAGONOMA

7 The most common findings in the glucagonoma syndrome are severe dermatitis, mild diabetes, stomatitis, anemia, and weight loss (**Table 56.9**). The dermatitis manifests as a characteristic skin rash termed **necrolytic migratory erythema**. This rash exhibits cyclic migrations, and it has been theorized that the hypoaminoacidemia accompanying glucagonoma is the cause.

DIAGNOSIS

Table 56.9 Glucagonoma

Parameter	Description
Symptoms	Dermatitis manifested as necrolytic migratory erythema Stomatitis Catabolic state: weight loss
Diagnostic tests	Hyperglycemia Hypoproteinemia Serum glucagon measurement Serum amino acid profile
Anatomic localization	Most in body and tail of pancreas, with liver metastases

The diagnosis of glucagonoma is suggested by the clinical presentation and biopsy of the skin lesions but is secured by the documentation of high fasting levels of serum glucagon. Most glucagonomas are located in the body and tail of the gland. These tumors are typically large and bulky, and surgical resection requires distal pancreatectomy (**Fig. 56.11**). Metastases are found in most patients and safe debulking of these should be considered.[126] As in patients with VIPoma and insulinoma, octreotide can be useful in controlling the signs and

symptoms (hyperglycemia and dermatitis) associated with incurable glucagonoma.

SOMATOSTATINOMA

The somatostatinoma syndrome is the least common of the five generally accepted functional PEN syndromes, occurring in less than 1 in 40 million people. The clinical features are nonspecific including steatorrhea, diabetes, hypochlorhydria, and cholelithiasis (**Table 56.10**). Fasting plasma somatostatin levels of greater than 100 pg/mL can be used to confirm the diagnosis.

Most somatostatinomas are located in the pancreatic head or periampullary region.[127] Tumors are of variable size and are often easily localized. Metastatic disease may be present at the time of diagnosis. Safe resection of the primary tumor (often via pancreaticoduodenectomy) and careful debulking of hepatic metastases are indicated.

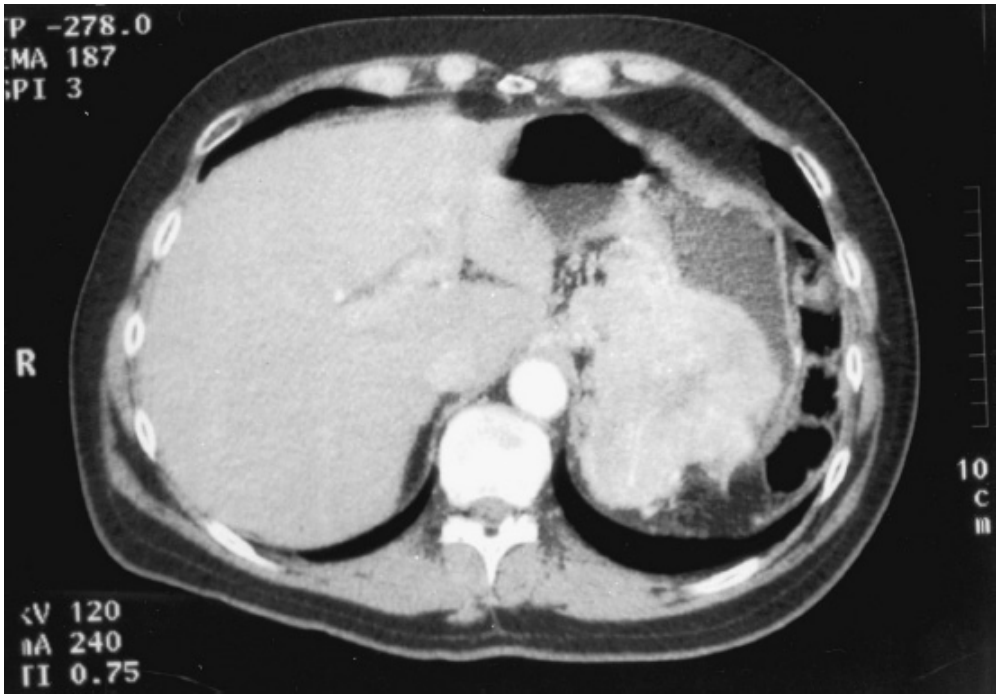

Figure 56.11 Computed tomography with oral and intravenous contrast in a patient with a glucagonoma. The large tumor appears to be posterior to the stomach and to the right of the aorta from the viewer's perspective.

Table 56.10 Somatostatinoma

Parameter	Description
Symptoms	Steatorrhea Right upper quadrant pain
Diagnostic tests	Hyperglycemia Hypochlorhydria Gallstones Serum somatostatin level
Anatomic localization	Most in head or uncinate process of pancreas; often periampullary

METASTATIC PANCREATIC ENDOCRINE TUMORS

Liver-Directed Therapies

At least one-third of patients with malignant PENs present with synchronous liver metastases at the time of diagnosis.[128] A subset of these patients remain asymptomatic and experience 8 prolonged survival even without aggressive therapy.[95] However, overall 5-year survival with liver metastases is less than 50%.[129] PENs are one of the few tumors for which a survival advantage for surgical debulking has been shown.[120,128,130–132] In those selected patients where safe surgical resection of greater than 90% of the tumor burden can be achieved, 5-year survival rates of 60% to 75% have been reported.

Those with unresectable disease to the liver may be candidates for a variety of liver-directed therapies for locoregional control 9 and symptom palliation. Transarterial embolization (TAE), chemoembolization (TACE) or radioembolization (TARE) with yittrium-90 are the most frequently used.[133] For patients with solitary or oligometastatic disease, percutaneous or surgical ablation, either with radiofrequency or microwave ablation techniques, are good options.[134]

Somatostatin Analogs

Since the majority of NETs express somatostatin receptors, somatostatin analogs (SSAs) are widely used for patients with metastatic PENs. SSAs not only lead to effective symptom control of carcinoid syndrome, they are also associated with improved progression-free survival (PFS). Both the PROMID and CLARINET trials were prospective randomized controlled trials demonstrating PFS superiority of long-acting SSAs to placebo among patients with metastatic well-differentiated gastroenteropancreatic NETs.[135,136] Based on these results and the indolent nature of well-differentiated PENs, SSAs are often the initial treatment for patients with slow-growing metastatic NETs. Newer more broadly binding SSAs are being investigated but have not shown superiority compared to traditional SSAs.

Systemic Therapies

A number of systemic therapies have been developed over the past decade for patients with metastatic PENs (**Table 56.11**). 10 While historically only streptozocin-based chemotherapy regimens were available,[96] advances in the molecular understanding of PENs have led to newer targeted therapies which offer improved response rates with better side effect profiles. For example, both **sunitinib malate**, an oral, small molecule, multitargeted tyrosine kinase inhibitor initially approved for the treatment of advanced renal cell carcinoma and refractory gastrointestinal stromal tumors, as well as **everolimus**, an oral inhibitor of the mTOR, are specifically approved for use in metastatic PENs.[137,138] Recent evidence has suggested the combination chemotherapy **temozolomide and capecitabine** is effective for PENs. Finally, **peptide receptor radionuclide therapy (PRRT)** is an exciting therapy recently approved for use in the United States which binds radionuclides to SSAs. In the landmark NETTER-1 trial, PRRT using ^{177}Lu-DOTA^{0},Tyr^{3}octreotate led to improved response rates and overall survival among patients with metastatic midgut NETs.[139] Ongoing research is currently investigating novel radiopharmaceuticals as well as targeted therapies, checkpoint inhibitors, and oncocytic viruses.[140]

Table 56.11 Seminal Randomized Controlled Trials of Systemic Therapies for Patients with Neuroendocrine Tumors

Trial	Intervention	Mechanism of Action	Control	Population	Median PFS Improvement (Mo)
Promid[16]	Octeotide LAR	SSA	Placebo	Midgut NET ($n = 84$)	14.3 vs. 6.0
Clarinet[17]	Lanreotide	SSA	Placebo	GEP-NET ($n = 204$)	38.5 vs. 18.0
Radiant-3[26]	Everolimus	mTOR inhibitor	Placebo	PEN ($n = 420$)	11.0 vs. 4.6
Raymond et al.[137]	Sunitinib	TKI	Placebo	PEN ($n = 171$)	11.4 vs. 5.5
Netter-1[45]	^{177}Lu-DOTATATE	PRRT	Octreotide LAR (60 mg)	Midgut NET ($n = 230$)	NA vs. 8.4

PFS, progression-free survival; SSA, somatostatin analog; NET, neuroendocrine tumor; GEP, gastroenteropancreatic; PEN, pancreatic endocrine neoplasm; mTOR, mammalian target of rapamycin; TKI, tyrosine kinase inhibitor; PRRT, peptide receptor radionuclide therapy.

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Section H: HEPATOBILIARY AND PORTAL VENOUS SYSTEM

57

Hepatobiliary Anatomy

Alice C. Wei

Key Points

1. Couinaud classification divides the liver into eight anatomic segments based on hepatic portal inflow and hepatic vein outflow.
2. Classic hepatic arterial anatomy is present in only approximately 50% of patients, with a replaced or accessory right hepatic artery arising from the superior mesenteric artery and a replaced or accessory left hepatic artery arising from the left gastric artery as the most common variants.
3. The modern Calot triangle (hepatocystic triangle) is bounded by the common hepatic duct medially, the cystic duct inferiorly, and the undersurface of the liver, superiorly. The cystic artery can be identified in this triangle during cholecystectomy.
4. There are three major hepatic veins; most patients have a right hepatic vein that joins the right anterior wall of the inferior vena cava (IVC) and middle and left hepatic veins that converge into a common trunk before joining the IVC.
5. Multiphase computed tomography (CT) with intravenous contrast is the mainstay for preoperative liver imaging. CT scans provide anatomic details of the hepatic vasculature and characterize many hepatic lesions, often without the need for biopsy.
6. Magnetic resonance cholangiopancreatography (MRCP) can be used to visualize intra- and extrahepatic biliary anatomy and provides complimentary information to a CT for indeterminant liver lesions.
7. Intraoperative ultrasonography is used liberally to confirm the anatomy of the hepatic vessels, biliary system and localize lesions during surgery.
8. The steps in major hepatectomy include exposure, vascular inflow control, vascular outflow control, and parenchymal transection.

Liver anatomy is complex, often with variations in the hepatic vessels and biliary tree that may not be apparent at the time of surgery. For safe hepatobiliary surgery, surgeons must have a thorough understanding of each

patient's unique liver anatomy and the relationship of lesions to major structures prior to any operation.

TOPOGRAPHIC AND SURFACE ANATOMY

The liver is a large, wedge-shaped organ situated in the right upper quadrant of the abdomen ventral to the inferior vena cava (IVC). Most of the liver sits in the subcostal space and is bounded superiorly, laterally, and posteriorly by the diaphragm and retroperitoneum, and anteriorly by the abdominal wall. The liver lies anterior to the stomach, gallbladder, hepatoduodenal ligament, and duodenum, and its lower extent lies adjacent to the hepatic flexure of the colon, right adrenal gland, and kidney (**Fig. 57.1**). On the liver's inferior aspect, the gallbladder sits in the gallbladder fossa, and the hepatic portal structures enter encapsulated by the Glissonean capsule by means of the hepatoduodenal ligament. Rouviere sulcus on the right inferior aspect delineates the border between the anterior and posterior right liver. On the left inferior aspect, Arantius cleft runs between the base of the left portal vein and the vena cava, separating the caudate lobe from the left liver. Within the Arantius cleft, the ligamentum venosum (obliterated left umbilical vein) lies between the left portal vein at the base of the falciform ligament and the left hepatic vein.

The visceral peritoneum invests most of the liver surface apart from the posterior bare area and the gallbladder fossa. The bare area is bound by the right triangular and coronary ligament (**Fig. 57.2**). In addition to these ligaments, the left triangular and the falciform ligament, which extends from ligamentum teres to the suprahepatic vena cava, connects the liver to the anterior abdominal wall. The gastrohepatic ligament connects to the ligamentum venosum (obliterated ductus venosus) in Arantius cleft. These ligaments, as well as the hepatoduodenal ligament, which arises between the pancreatic head and the liver hilum (known as the porta hepatis), comprise the ligamentous attachments of the liver. The hepatoduodenal ligament contains the portal vein, hepatic arteries, extrahepatic bile duct, and portal lymphatics (**Fig. 57.3**).

MORPHOLOGIC AND FUNCTIONAL ANATOMY

1 Over the past 100 years, a variety of anatomic models of the liver have been developed and debated. Couinaud classification of liver segments is the most often used by hepatobiliary surgeons (**Fig. 57.4**).[1,2] In this classification, eight segments of the liver are delimited by portal inflow and hepatic venous outflow. The right and left hemilivers are divided by a plane through the middle hepatic vein and the IVC (**Fig. 57.5**) along Cantlie's line. The left and right hepatic veins subdivide their respective hemilivers each into two sectors (alternatively called sections). The sectors are further divided into segments by portal pedicles. This results in the left liver segments II, III, IVa, and IVb and right liver segments V, VI, VII, and VIII. Segment I, the caudate lobe, arises posterior to the portal pedicle and anterior to the IVC. Segment I receives both left and right portal inflow, and caudate veins drain directly into the IVC.

The Glissonean capsule is the connective tissue that invests the hepatic arteries, portal vein, bile duct, nerves, and lymphatics. The structures within the Glissonean capsule enter the liver centrally at the porta hepatis via the hepatoduodenal ligament.

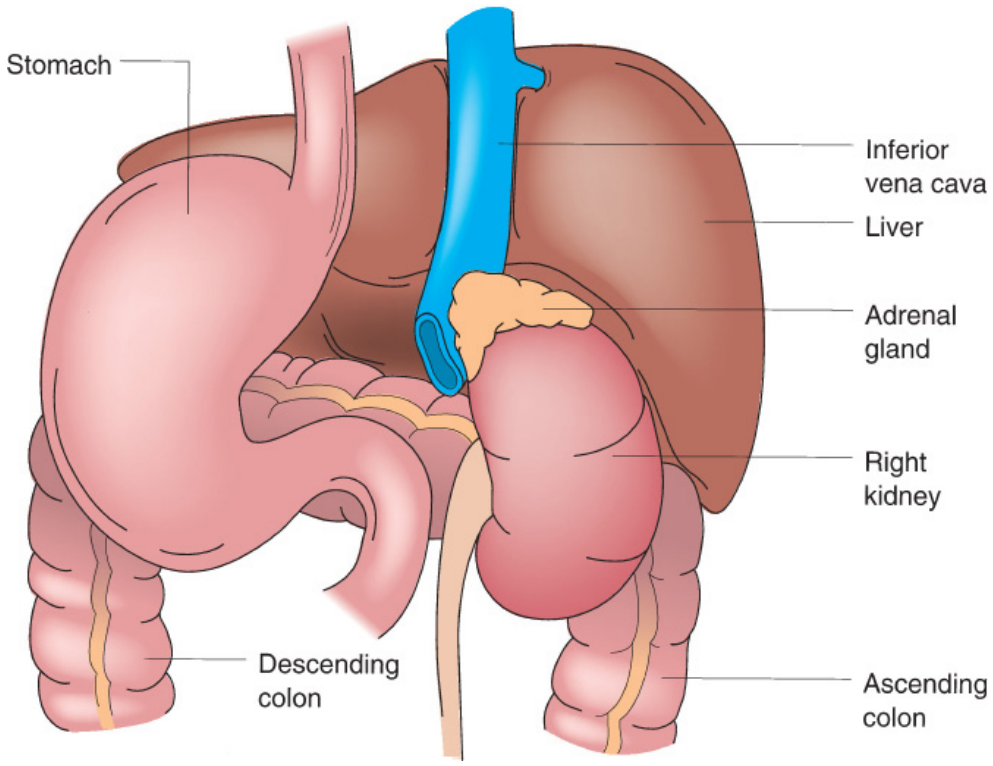


Figure 57.1 Posterior view of the liver, showing organs that produce impressions on its inferior surface.

Variations from the canonical anatomy occur frequently; hepatic artery variation is most common, followed by biliary tract and portal vein variants.[2] Variations often occur concomitantly. When anatomic variation is seen in one of the portal structures, the surgeon should be aware that variation in other structures may be present, and additional investigation to confirm anatomy may be indicated.

Hepatic Arteries

The common hepatic artery arises from the celiac axis and becomes the proper hepatic artery as it turns cephalad in the hepatoduodenal ligament after giving off the right gastric and gastroduodenal artery branches. It lies ventral and medial in the hepatoduodenal ligament and gives off the right and left hepatic arteries. Variations in hepatic artery anatomy are common in up to 40% of individuals (**Fig. 57.6**).[3,4] This variation can be in 2 the origin, branches, or course of the hepatic artery vasculature. Replaced or accessory right and left hepatic arteries occur in 13% and 11% of patients,

respectively.[4] Typically, accessory right hepatic arteries arise from the superior mesenteric artery (SMA) and travel posterior to the common bile duct and lateral to the portal vein. Left accessory or replaced hepatic arteries most often arise from the left gastric artery and course to the liver via the gastrohepatic ligament. The cystic artery can arise either directly from the common hepatic artery or from the right hepatic artery. Variations in the takeoff, size, and number of small vessels, including the cystic artery (**Fig. 57.7**) are common and must be considered when operating. Further, the location, relationship between the hepatic artery branches and other portal and biliary structures, and vessel of origin vary in the anterior and posterior planes with some regularity.

Portal Veins

The main portal vein is formed by the confluence of the superior mesenteric and splenic veins. The coronary vein (left gastric vein) joins the portal vein which travels in the posteromedial aspect of the hepatoduodenal ligament to enter the liver. At the porta hepatis, the main portal vein splits into the right and left portal branches which enter the parenchyma of their respective hemilivers at its first division (**Fig. 57.8**). The short right portal vein enters the liver obliquely and at its second division, gives of the anterior pedicle which supplies segments V and VIII, and a posterior pedicle which supplies segments VI and VII. The longer left portal vein courses outside the liver and turns to lie in the umbilical fissure prior to giving off branches into the left liver. The left second division gives off segment IV branches, also known as the “recurrent branches”; the segment II and III branches supply the left lateral section of the liver (to the left of the falciform ligament). The terminal end of the left portal vein merges with the ligamentum teres as the obliterated umbilical vein. Both the right and left portal veins give off small branches to supply segment I.

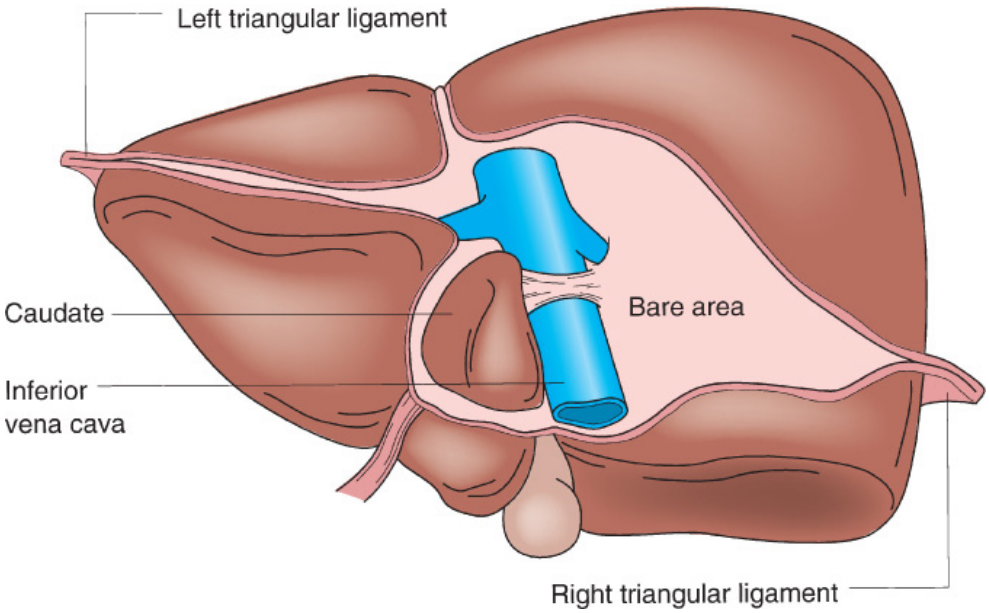


Figure 57.2 Posterior view of the liver, showing the level of peritoneal reflections.

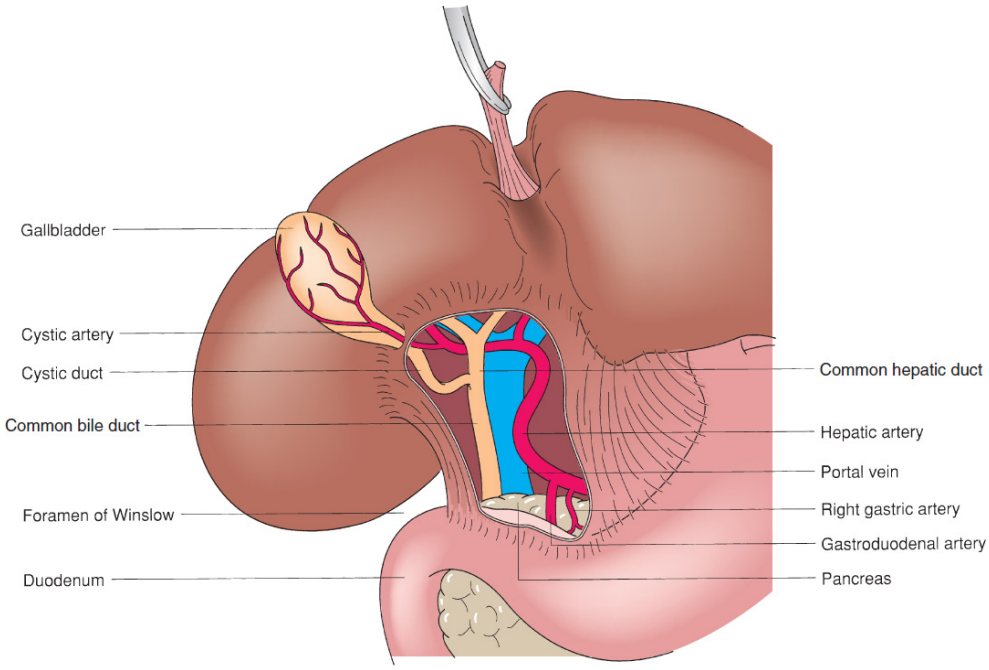


Figure 57.3 Relationship of structures within the hepatoduodenal ligament.

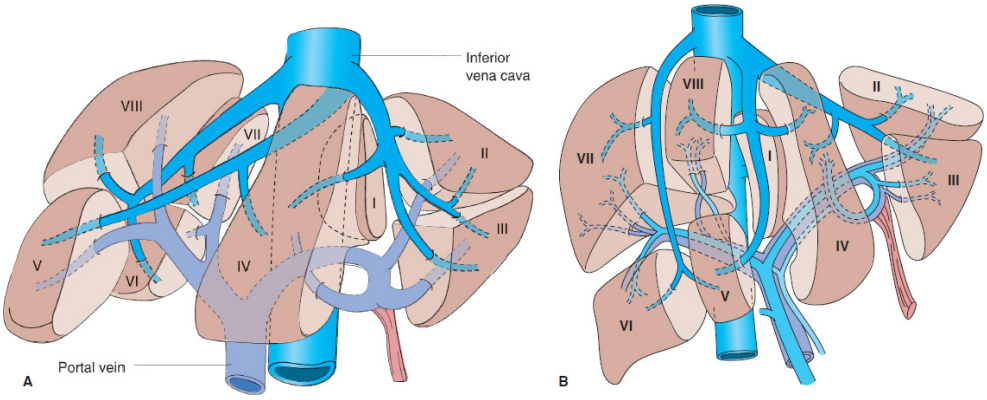


Figure 57.4 Functional divisions of the liver and liver segments according to Couinaud nomenclature with the liver in the natural position (**A**) and after it is mobilized (**B**).

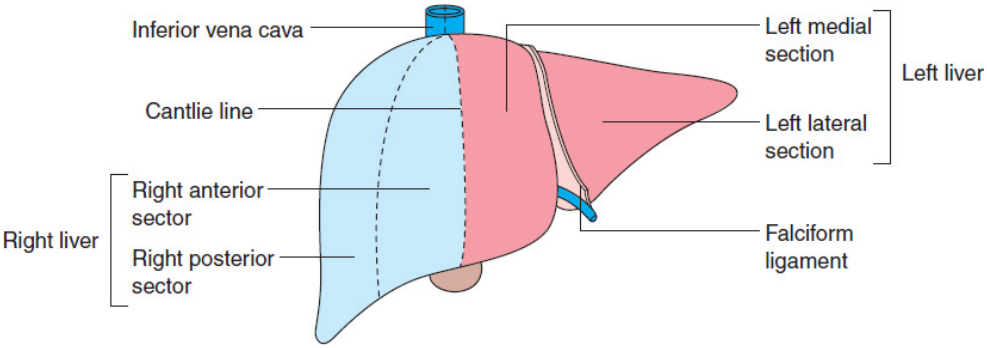


Figure 57.5 Anatomic division of the liver into right and left halves by a plane extending from the gallbladder fossa posteriorly to the inferior vena cava.

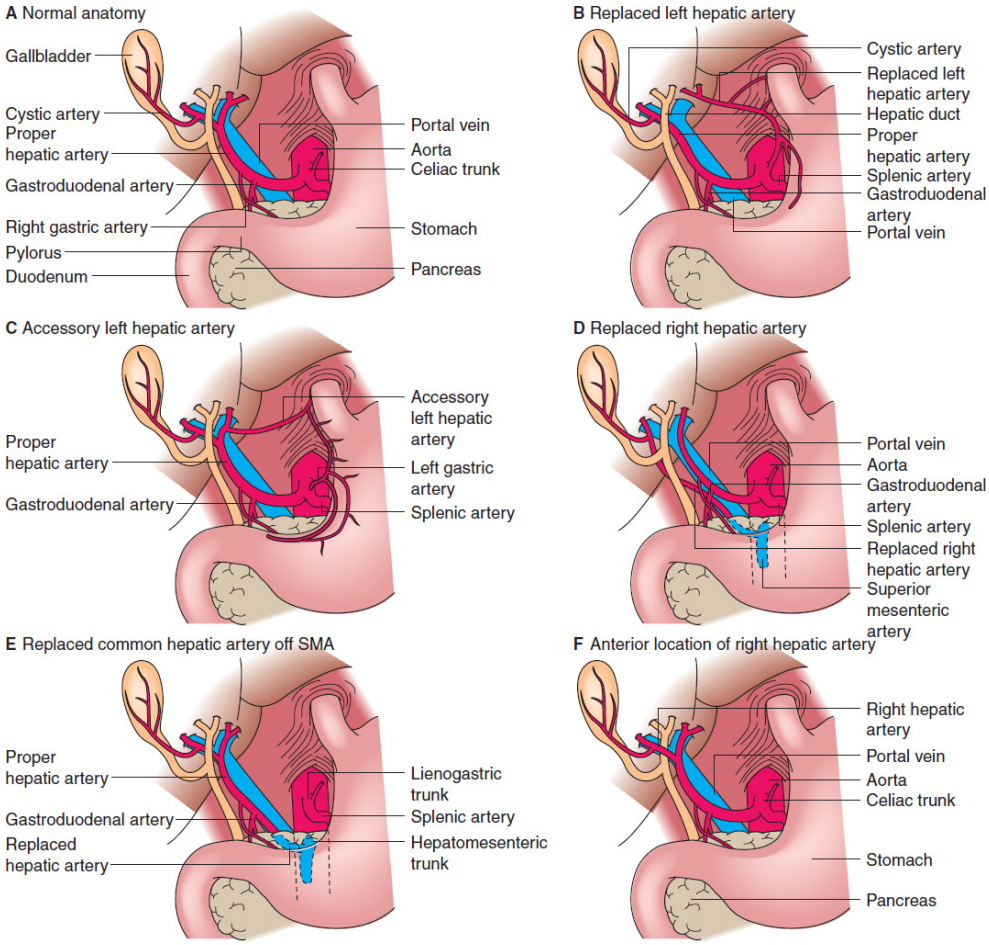


Figure 57.6 Variations in hepatic arterial anatomy.

Biliary System and Gallbladder

The common bile duct lies ventral and lateral in the hepatoduodenal ligament. The right and left liver drain their respective hemilivers into right and left bile ducts which merge to form the common hepatic duct extrahepatically in the liver hilum (**Figs. 57.9** and **57.10**). Variations in the confluence of the biliary system occur with regularity. Common variants include a right posterior (segments VI/VII) duct draining directly into the common hepatic duct, or a right posterior system draining into the left bile duct.

The gallbladder is a pear-shaped organ that lies on the undersurface of the liver and drains into the cystic duct. The cystic duct usually runs parallel to the common hepatic duct for a variable distance before joining the common hepatic duct to form the common bile duct, which then travels through the

pancreatic head and terminates at the ampulla of Vater. The cystic duct can vary in length, and when long, can take a circuitous route, either anterior or posterior, to the common bile duct prior to its insertion on either the lateral or medial side of the common bile duct (**Fig. 57.11**).

Calot triangle was originally described in 1891 as a triangle bound inferiorly by the cystic duct, medially by the common hepatic duct, and superiorly by the cystic artery. In the modern era, the working definition of Calot triangle differs from the original description.[2,3] The modern Calot triangle, should be referred 3 to as the hepatocystic triangle, is larger and is delineated by the cystic duct inferiorly, the common hepatic duct medially, and the undersurface liver superiorly.[3] In this larger triangle the cystic artery can be usually found. Calot's triangle is an important landmark when performing cholecystectomies. Variability in the origin, number, and location of the cystic artery is common (**Fig. 57.7**).

The surgeon should be aware of potential variations when operating in the porta hepatis, regardless of whether the procedure is a simple cholecystectomy or a more complex procedure, such as a living-donor liver transplant. Preoperative and/or intraoperative cholangiography may be required to avoid inadvertent injury to the biliary radicals.

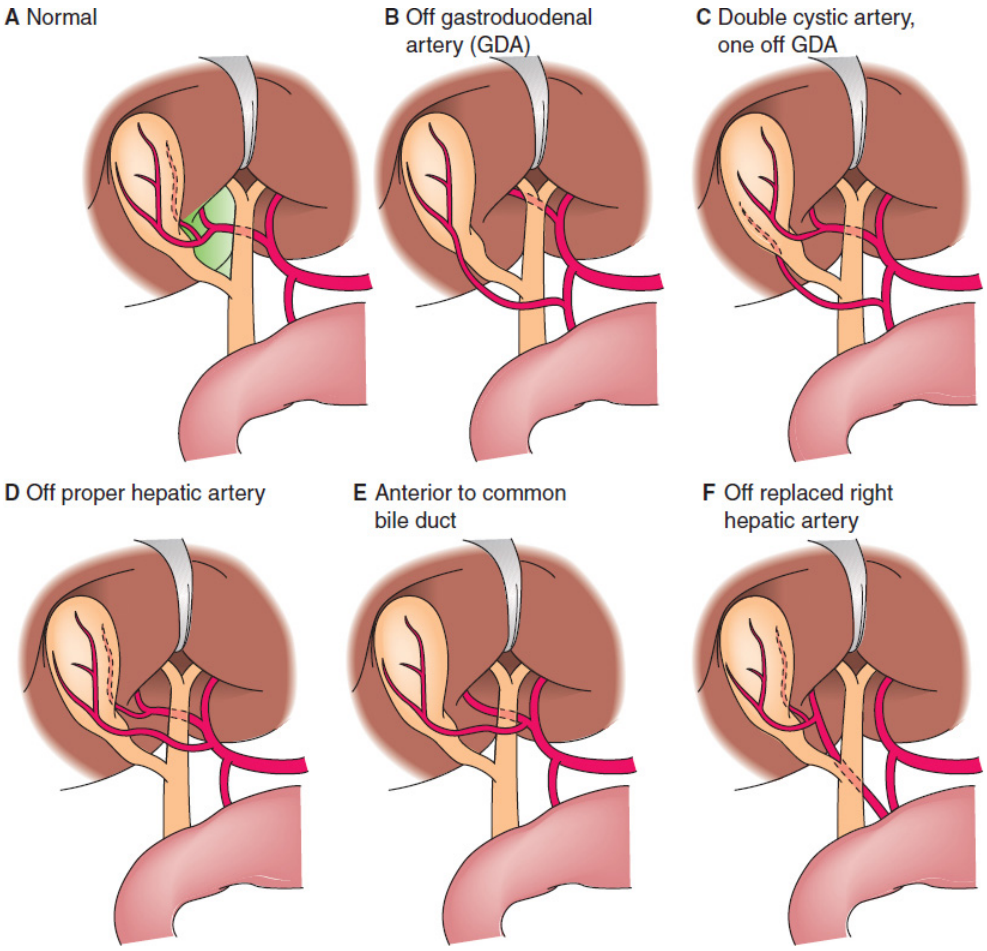


Figure 57.7 Variations of the cystic artery. The modern Calot's triangle (also known as the hepatocystic triangle) is marked in green (**A**).

Hepatic Veins

Liver outflow to the IVC progresses to the suprahepatic IVC via the major hepatic veins, the right, middle, and left hepatic veins. The 4 right hepatic vein usually joins as a single branch on the anterolateral aspect of the suprahepatic IVC. The middle and left veins can either drain individually into the IVC through separate orifices or merge intraparenchymally into a short, conjoined vein prior to entering the IVC.

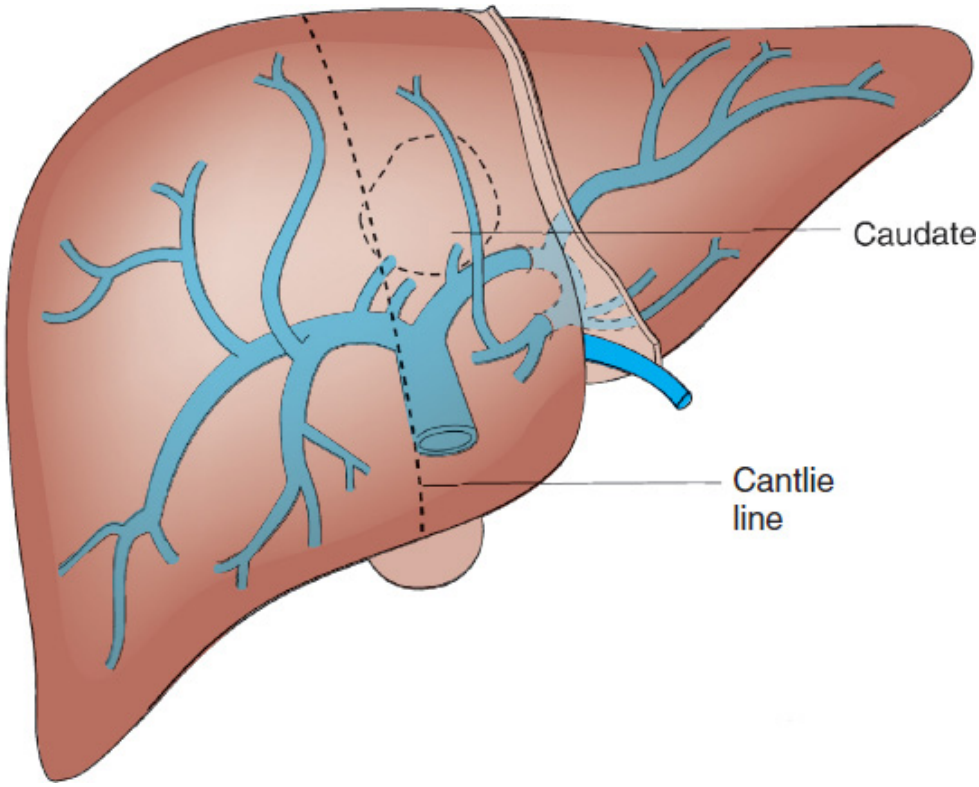


Figure 57.8 Intrahepatic divisions of the portal vein.

The hepatic veins divide the liver into sectors and drain their respective parenchyma. The right hepatic vein separates the posterior sector of the liver (segments VI/VII) from the anterior sector (segments V/VIII) and drains blood from these segments into the IVC (**Fig. 57.12**). Similarly, the middle and left hepatic veins mark the border between the left medial sector segment IV, and from the left lateral sector (segments II/III).

In addition to the named major draining veins, a variable number of accessory veins drain the caudate lobe and right hepatic lobe directly into the retrohepatic IVC. Some accessory veins can be sizable, particularly those from segment VI of the liver. On occasion, an accessory vein may be a major source of liver drainage. When present, large accessory veins must be considered in any planned procedure. For example, in living-donor liver transplantation, major accessory veins may require implantation, and for major liver resections that involve the outflow tract, drainage may be possible through a large accessory segment VI vein (**Fig. 57.13**).

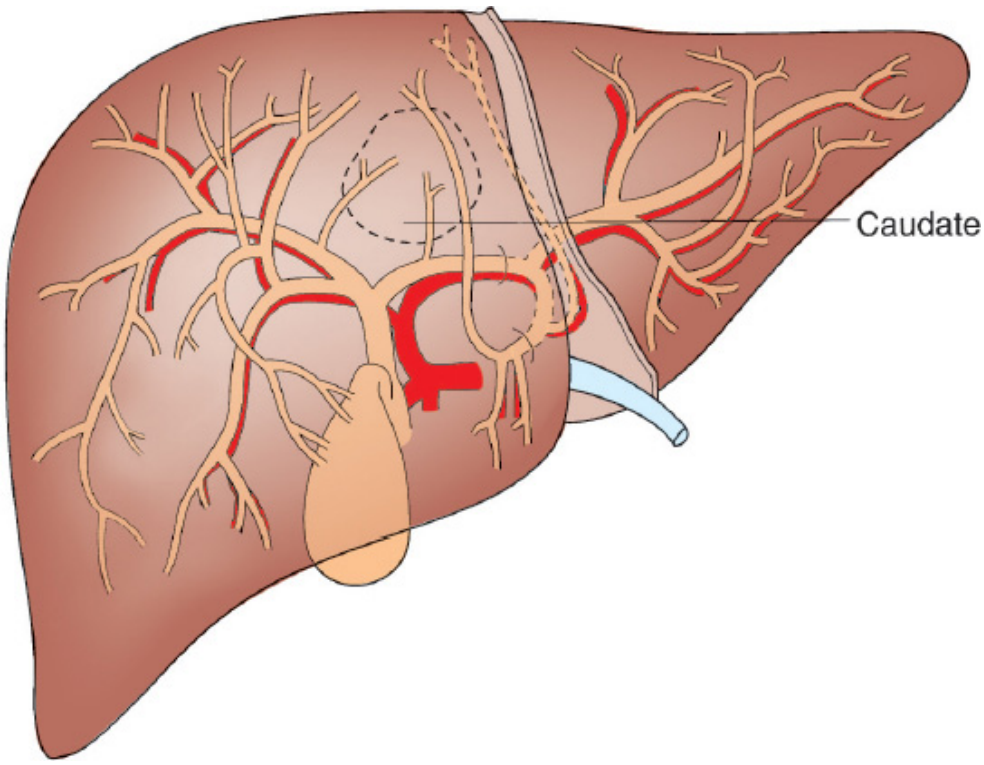


Figure 57.9 Intrahepatic divisions of the bile ducts and hepatic arteries.

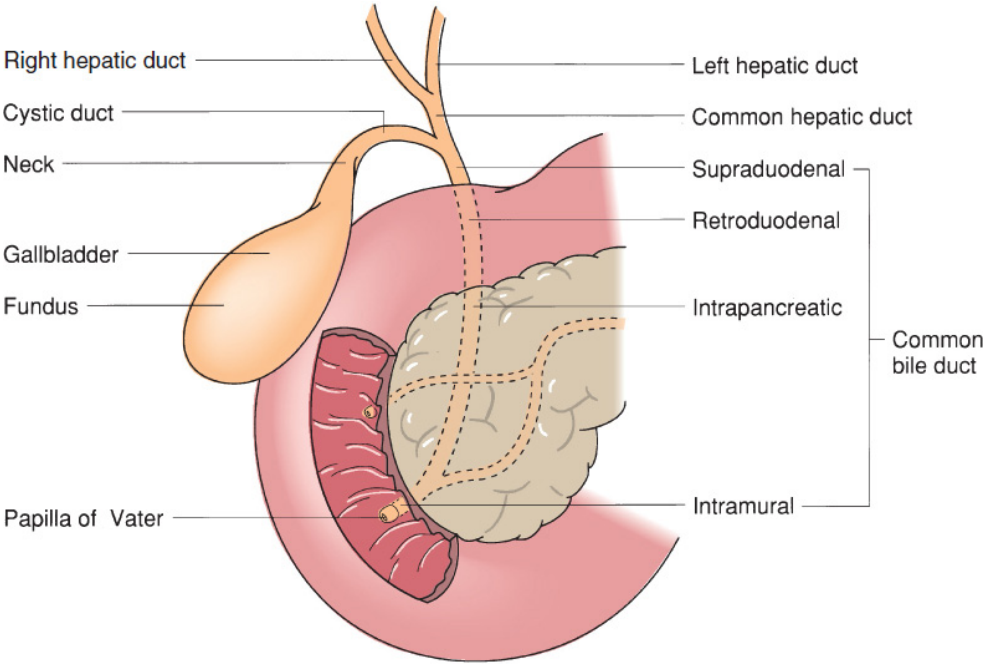


Figure 57.10 Anatomy of the extrahepatic biliary tree and pancreatic duct.

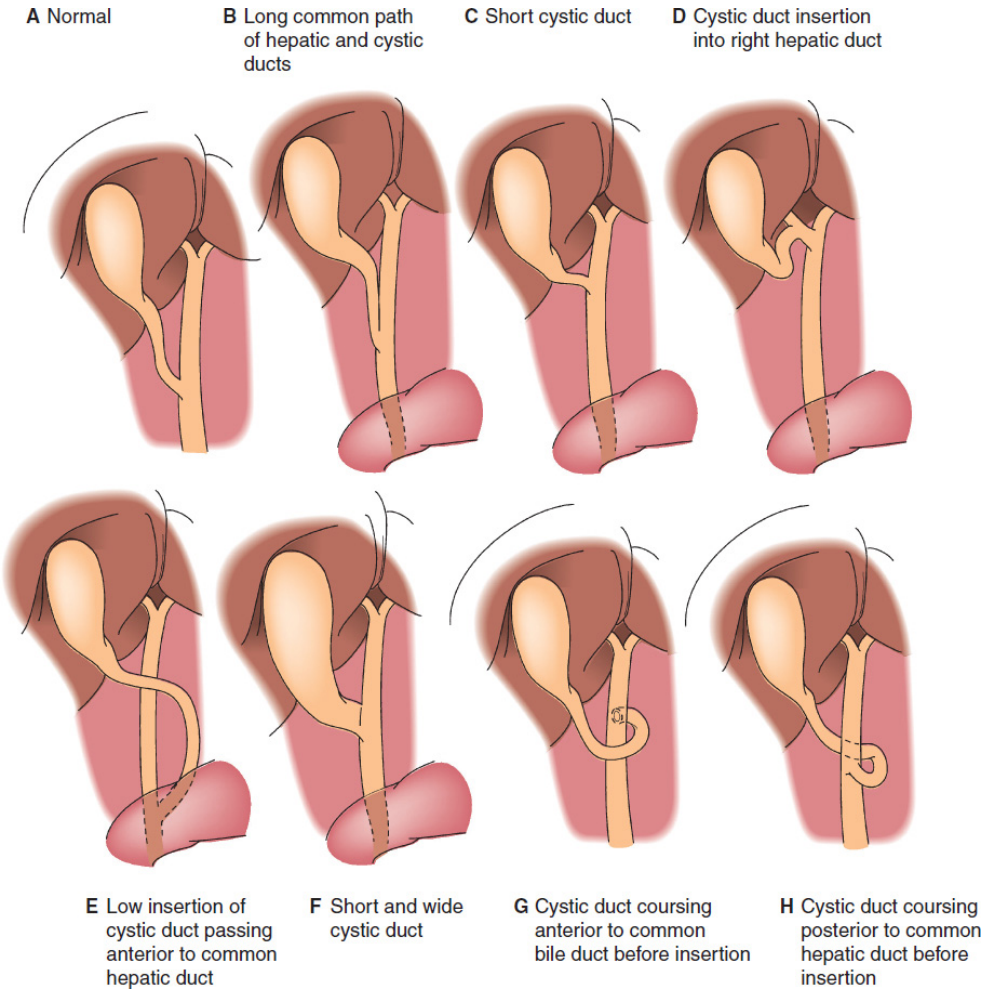


Figure 57.11 Variations in the junction of the cystic duct and common hepatic duct.

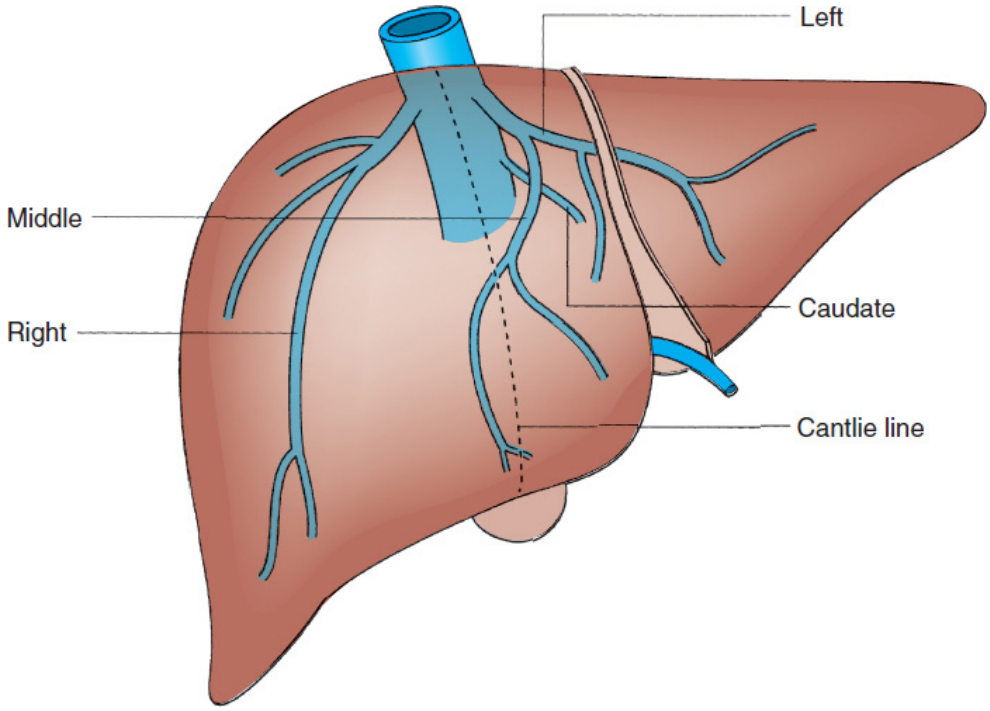


Figure 57.12 Three major hepatic veins drain the liver. The caudate segment of the liver usually drains directly into the inferior vena cava.

LIVER IMAGING

High-quality liver imaging is essential for preoperative assessment of the anatomy of major hepatic structures. The size, number, and location of the intraparenchymal vessels and bile ducts can be mapped preoperatively. Axial, coronal, and/or sagittal reconstruction scans are helpful in providing a three-dimensional model of the liver. For complex procedures, such as living-donor liver resection, careful preoperative mapping of the intra- and extraparenchymal structures are paramount for safe resection and reconstruction. For resections, tumor characteristics and relationship to major structures should be evaluated. Each patient's unique anatomy must be well understood prior to any hepatectomy.

Computed Tomography

Cross-sectional imaging with computed tomography (CT) with liver-specific phases is the mainstay of liver imaging. Well-timed 5 vascular contrast in

the arterial, portal, and venous phases provides excellent detail of the parenchyma and vascular anatomy of the liver (**Fig. 57.14**). In the appropriate clinical context, morphologic and contrast features of the tumor can be diagnostic without the need for liver biopsy (**Fig. 57.15**).

CT angiography plots the arterial anatomy of the liver and should be used liberally to plan complex resections. Three-dimensional reconstructions can be performed for surgical planning. For establishing suitability of living-donor liver transplantation, these reconstructed images are particularly important (**Fig. 57.16**). In addition, specialized CT protocols are available for different tumor types, including hepatocellular carcinoma and cholangiocarcinoma, and can help improve diagnostic accuracy of indeterminate lesions and/or aid in the visualization of small tumors.

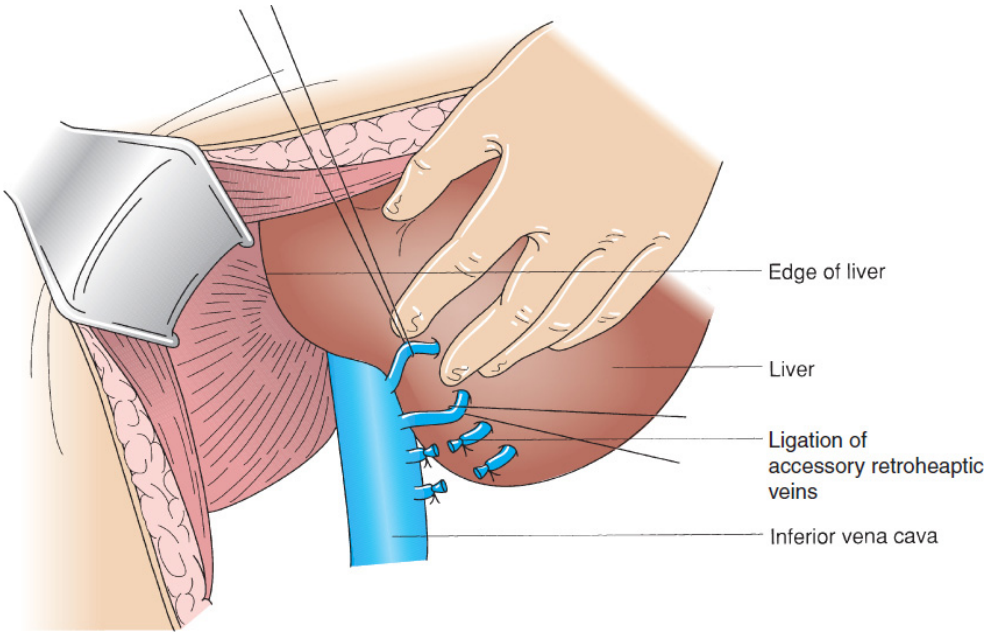


Figure 57.13 Retraction of right liver medially exposes small venous tributaries that drain the right liver directly into the retrohepatic vena cava. Several branches are ligated.

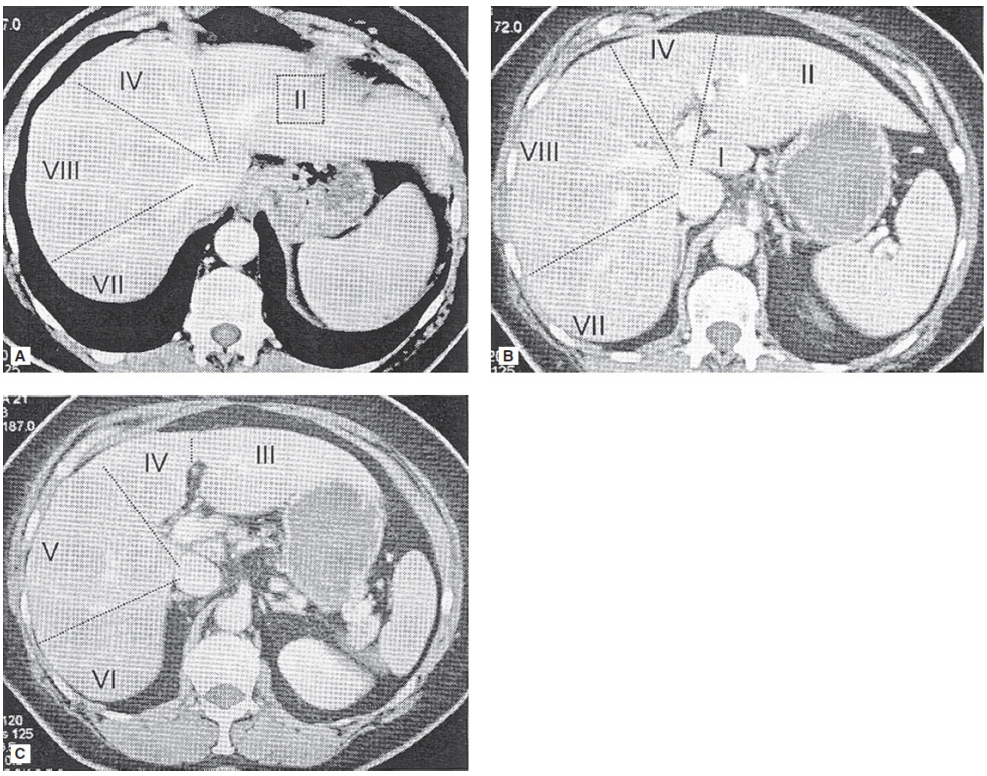


Figure 57.14 Computed tomography scan demonstrating segmental anatomy of the liver with cuts through the dome (**A**), just above the portal bifurcation (**B**), and below the portal bifurcation (**C**).

Further advantages of CT scans are that they can provide staging information to rule out the presence of extrahepatic disease and can provide insight into the presence or absence of underlying liver disease.

Magnetic Resonance Imaging/Magnetic Resonance Cholangiopancreatography

Magnetic resonance imaging (MRI) is a complementary imaging modality to CT and can provide additional information for small or indeterminant liver tumors (**Fig. 57.15**). In particular, MRI with gadolinium-based vascular or hepatobiliary contrast agents has improved sensitivity and specificity for characterizing many liver lesions. Benign lesions, such as hemangiomas, focal nodular hyperplasia, and liver cysts, can often be definitively characterized by MRI. MRI can have higher sensitivity in detecting small tumors in patients with hepatic steatosis or underlying liver disease, particularly if hepatobiliary contrast agents are used.

6 Unlike conventional CT scans, magnetic resonance cholangiopancreatography (MRCP) using T2-weighted imaging has high sensitivity for biliary structures and has largely replaced endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic evaluation of the biliary tree (**Fig. 57.17**). MRCP is noninvasive and can resolve both intra- and extrahepatic biliary structures.

The disadvantages of MRI include the extended time required to obtain the scans, which can be difficult for patients who have claustrophobia or are unable to lie still for long periods of time; the inability to fully stage the other organs in the thoracoabdominal region in the same scan; and the associated additional costs. As a result, MRI should be reserved to provide complementary information that is not obtainable by CT scan.

ULTRASOUND AND INTRAOPERATIVE LIVER ASSESSMENT

Transcutaneous ultrasound (US) can be used as a screening test for liver disease and may be an option for noninvasive surveillance of liver lesions. Routine use of transcutaneous US for preoperative assessment has been supplanted by CT and/or MRI scans.

Nevertheless, US remains an important modality for intraoperative, real-time assessment of liver anatomy (**Fig. 57.18**). US at the 7 time of laparoscopy and/or laparotomy is used in combination with visual inspection and palpation to evaluate the liver. Intraoperative US should be used liberally throughout the procedure for diagnostic purposes and to localize deep lesions and intraparenchymal structures.

Newer modalities, including near-infrared visualization of indocyanine green (ICG) fluorescence, are increasingly being used to provide real-time imaging guidance of anatomic structures. However, experience is still accumulating on the role of these modalities in intraoperative assessment. ICG may be particularly useful in minimally invasive liver resection, as palpation and visual inspection are more limited.

PREOPERATIVE EVALUATION OF HEPATIC RESERVE

Accurate evaluation of the hepatic reserve is imprecise. For patients with underlying liver disease, a variety of different scores and tests have been developed that measure either static or dynamic liver function (**Table 57.1**). However, no single test is able to confidently predict the hepatic reserve of the future liver remnant (FLR) that will remain following liver resection in a patient with impaired liver function.

Liver function and volume of the FLR are the most commonly used methods to evaluate hepatic reserve in North America. For cirrhotic patients, the Child–Pugh score incorporates albumin, bilirubin, INR, as well as the presence or absence of ascites and/or encephalopathy as a measure of hepatic reserve (**Table 57.2**). Only Child–Pugh score A and highly selected B patients are candidates for liver resection. The presence of portal hypertension, manifested by splenomegaly, varices, ascites, or thrombocytopenia, is an independent predictor of postoperative liver failure, and patients with these comorbidities are usually not candidates for resection. Other scores of liver function, including the Model of End-Stage Liver Disease (MELD) score, have limited use for predicting liver failure following resection and are not routinely used to determine suitability for liver resection (**Table 57.3**). For patients with liver cancer or end-stage liver disease, the MELD score is useful for establishing eligibility for liver transplant, and MELD is currently used by the United Network for Organ Sharing (UNOS) for prioritizing organ allocation for liver transplants.

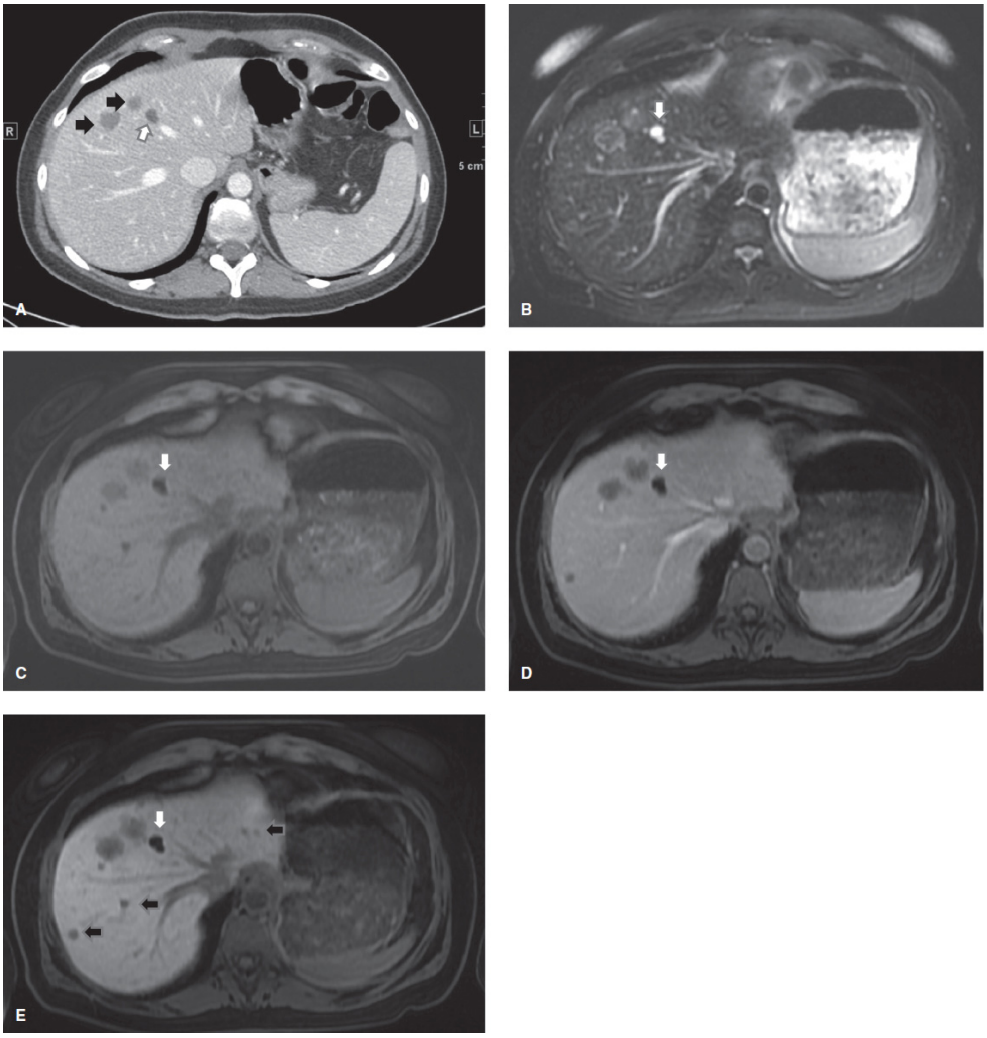


Figure 57.15 Cross-sectional imaging for a patient with colorectal liver metastases and hepatic cysts. The CT scan in portal venous phase (**A**) demonstrates two irregular hypoattenuated lesions consistent with metastases (*black arrows*). A third lesion adjacent to the middle hepatic vein (*white arrow*), lower in attenuation compared to the liver metastases is noted and indeterminant. MRI imaging of the same patient in different phases (**B**–**E**). MRI with fat-suppressed T2-weighted imaging (**B**), and precontrast fat-suppressed T1-weighted imaging (**C**). Same cyst as prior CT (*white arrow*), with markedly T2 bright signal and low T1 signal. MRI with postcontrast fat-suppressed T1-weighted imaging during the portal venous phase (**D**) and delayed hepatobiliary phase with Gd-EOB-DTPA (Eovist) contrast agent (**E**). Same cyst as prior CT (*arrow*). Note the subcentimeter liver metastases now visible on delayed hepatobiliary phase in segments II and VII/VIII (*black arrows*).

Table 57.1 Strategies to Predict Hepatic Reserve

- Child–Pugh score (**Table 57.2**) to assess synthetic ability (albumin, prothrombin time, and ascites), bile conjugation and excretory function (total bilirubin), and metabolic function (changes in mental status from ammonia retention)
- Model for End-Stage Liver Disease (MELD) score estimates 3-mo mortality in patients with chronic liver disease (**Table 57.3**)
- Clearance of galactose or organic anionic dyes, such as indocyanine green
- Volumetric measurements of the liver and prediction of liver remnant after resection based on three-dimensional reconstructions from computed tomography and magnetic resonance imaging

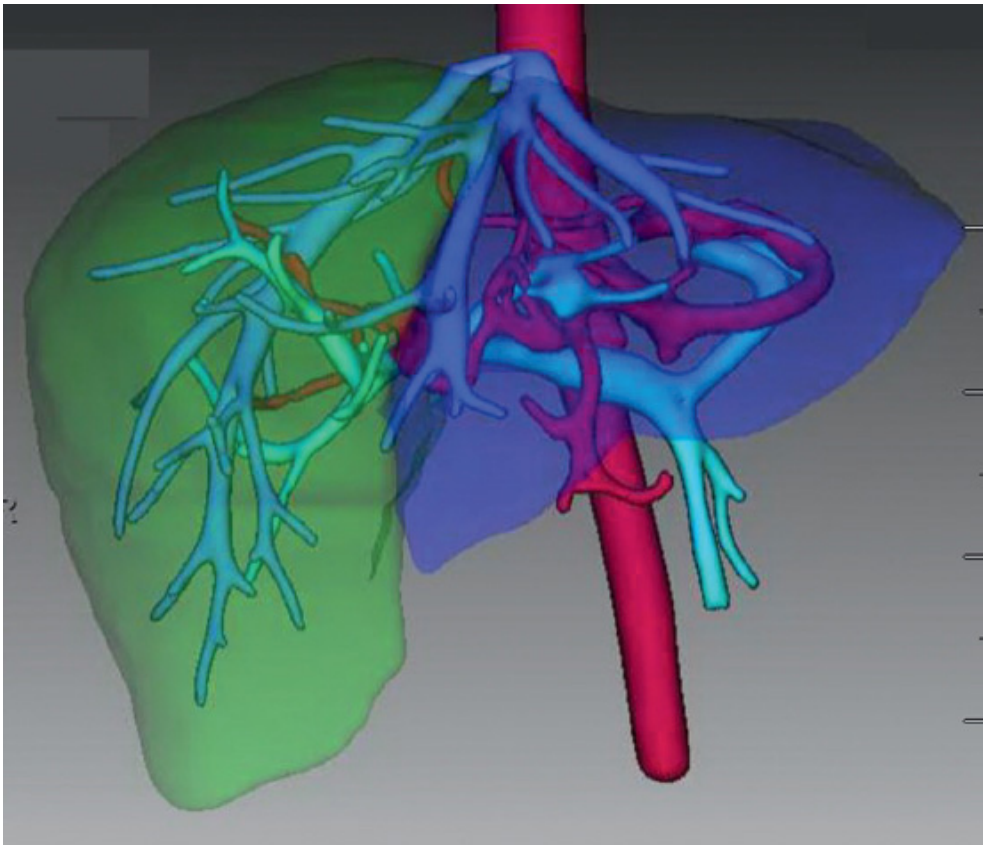


Figure 57.16 Three-dimensional reconstruction of the hepatic vasculature.

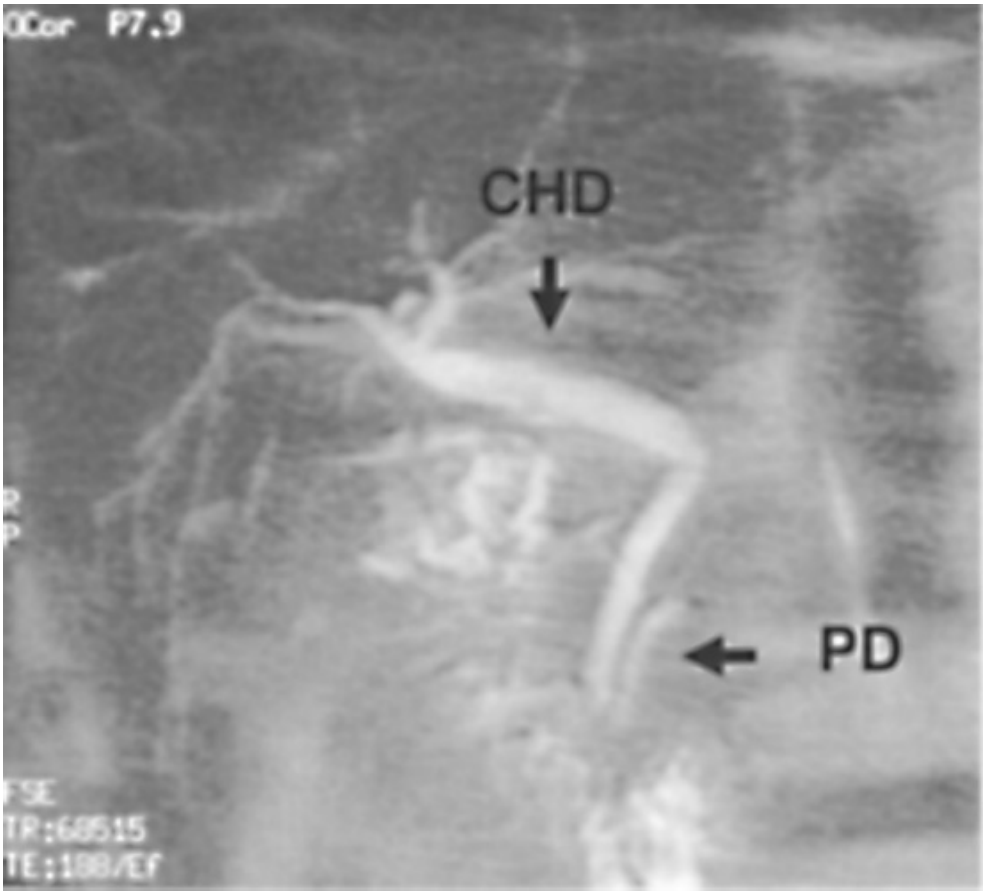


Figure 57.17 Magnetic resonance cholangiopancreatography (MRCP) of a patient after cholecystectomy with mild dilation of common hepatic duct (CHD). The pancreatic duct (PD) is also visible.

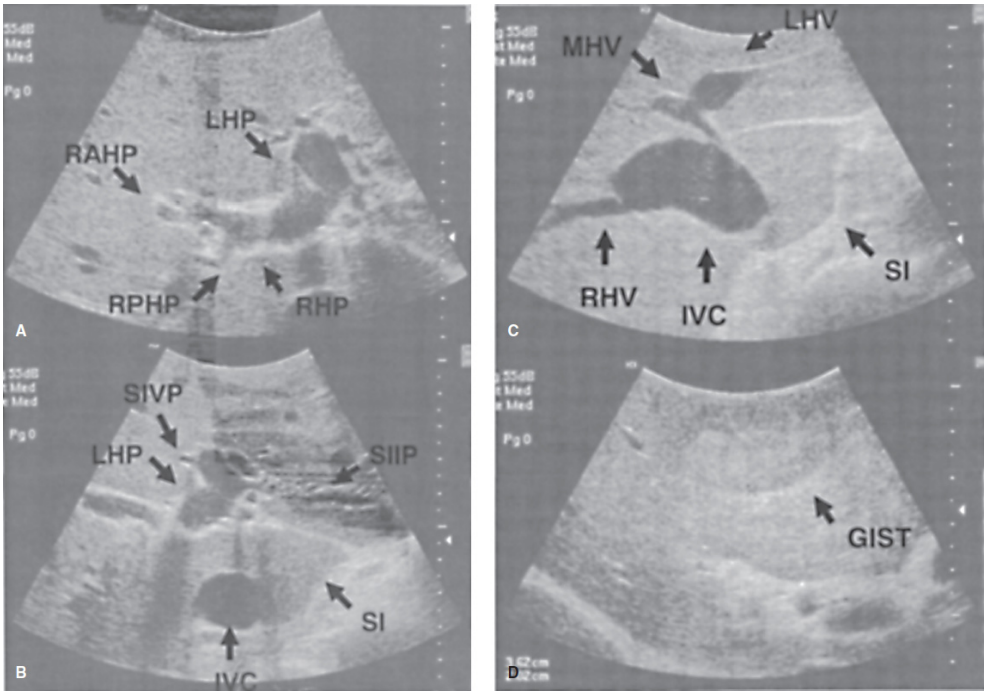


Figure 57.18 **A, B:** Intraoperative ultrasound images of liver demonstrating right hepatic pedicle (RHP), right anterior sector pedicle (RASP), right posterior sector pedicle (RPSP), left hepatic pedicle (LHP), segment II pedicle (SIIP), segment IV pedicle (SIVP), segment I (SI), and inferior vena cava (IVC). **C, D:** Intraoperative ultrasound images of liver demonstrating inferior vena cava (IVC), right hepatic vein (RHV), middle hepatic vein (MHV), left hepatic vein (LHV), segment I (SI), and a metastatic gastrointestinal stromal tumor lesion straddling segments IV and V of the liver.

Table 57.2 Child–Pugh Classification

	1 Point	2 Points	3 Points
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Ascites	Absent	Moderate	Severe
Encephalopathy	Absent	Moderate	Severe
Prothrombin time			
Seconds prolonged	<4	4–6	>6
INR	<1.7	1.7–2.3	>2.3

INR, international normalized ratio; Child–Pugh Class A: 5–6 points; Class B: 7–9 points; Class C: 10–15 points.

Worldwide, ICG retention is a common dynamic test of hepatic reserve. ICG is a tricarbocyanine protein-bound dye that is rapidly eliminated by the liver. Impaired liver function results in slower elimination times, and thus ICG retention provides a dynamic measure of liver function. In a normal liver, ICG retention at 15 minutes (ICG-R15) is 1% to 10%. ICG-R15 of <10% is considered adequate hepatic reserve for major liver resection in cirrhotic patients. The acceptable ICG-R15 must be combined with additional clinical information, including the extent of the planned liver resection, the Child–Pugh score, and the presence or absence of portal hypertension, to estimate the risk of postoperative liver failure for an individual patient.

The volume of the expected FLR is associated with postoperative liver failure. For patients with normal background liver, an FLR >25% is adequate, as long as inflow/outflow and biliary drainage is preserved. For patients with liver disease, including cirrhosis, cholestasis, fatty liver disease, or prior chemotherapy, the threshold suggested for adequate FLR

should be higher, closer to 40%. However, the exact threshold is not agreed upon by all surgeons. For patients with small predicted FLR and/or in cases where there is underlying hepatic dysfunction, augmentation of the FLR is possible. Portal vein embolization or Associating Liver Partition and Portal vein Ligation for Staged hepatectomy (ALPPS) can be used to induce hypertrophy in the FLR prior to hepatectomy. Portal vein embolization on the side of the liver to be resected is performed 3 to 4 weeks prior to planned resection to induce compensatory hypertrophy. ALPPS combines operative portal vein ligation with parenchymal transection to induce rapid FLR hypertrophy. This is followed by planned early hepatectomy, days after ALPPS, once FLR volume is deemed adequate. The ALPPS approach remains experimental due to high rates of morbidity and perioperative mortality compared to percutaneous portal vein embolization.

Table 57.3 MELD Score

MELD = 3.78 × ln[serum bilirubin (mg/dL)] + 11.2 × ln(INR) + 9.57 × ln[serum creatinine (mg/dL)]
40 or more—71.3% 3-mo mortality
30–39—52.6% 3-mo mortality
20–29—19.6% 3-mo mortality
10–19—6.0% 3-mo mortality
<9—1.9% 3-mo mortality

INDICATIONS FOR LIVER RESECTION AND ONCOLOGIC CONSIDERATIONS

The indications for surgery include benign and malignant tumors, biliary conditions, and living-donor liver transplant. The vast majority of liver resections are performed for malignancy for curative intent. Colorectal liver metastases (CRLMs) and hepatocellular carcinoma are the most common malignant indications for hepatectomy. The evaluation of patients for

oncologic indications requires consideration of patient fitness for surgery, as well as oncologic and technical criteria. Oncologic principles for curative-intent surgery are that disease is limited to the liver, the resection can be performed for R0 intent, and an FLR with adequate volume/function, liver inflow, outflow, and biliary drainage can be achieved. The indications for surgery and the principles of surgery remain the same regardless of whether an open or minimally invasive approach is used.

For patients with CRLM, preoperative staging to rule out extrahepatic disease includes a CT scan of the chest, abdomen, and pelvis, and a recent colonoscopy to evaluate disease stage. MRI and PET scans are adjuvant tests that may be helpful to characterize the disease extent but are not routinely required. Also, prognostic variables, such as timing of liver metastases (synchronous vs. metachronous), nodal status of colorectal cancer, CEA levels, and number and size of liver metastases, may guide when or if liver resection is likely to provide a survival advantage.[5] The sequence of liver resection with respect to the timing of chemotherapy and management of the primary colorectal cancer must also be incorporated into a tailored approach for each patient. The goal of resection for CRLM is to obtain an R0 margin, optimally >1 cm, using parenchymal-sparing techniques when possible.[6] The rationale for a parenchymal-sparing approach is that it will preserve liver function and allow repeat liver resection for patients who develop recurrent CRLM. For patients with multiple CRLM, ablation may be combined with resection for small, central tumors where resection is not feasible in order to achieve disease control.

For patients with hepatocellular carcinoma, there is an additional requirement to understand the extent of underlying cirrhosis, which is often present. Poor liver function may preclude liver resection of otherwise technically resectable tumors due to the high risk of postoperative liver failure. As these patients may be candidates for liver transplantation, the decision for resection versus transplantation should be made in a multidisciplinary context. For patients undergoing liver resection for hepatocellular carcinoma, the optimal resection margin is controversial. However, a resection margin aimed at approximately 2 cm is associated with decreased postoperative recurrence rates and improved survival compared with a gross resection margin of 1 cm or less.[7] Some studies favor formal anatomic resections for improved outcomes.

For less common malignancies, a decision-making process analogous to those described above is applicable. Palliative debulking of liver tumors is rare but may be considered for select patients with metastatic neuroendocrine tumors, as these tumors are more indolent than most other malignancies. As a result, liver resection may provide symptomatic control, as well as a survival advantage. Liver metastasectomy for neuroendocrine metastases is based on the ability to debulk tumor volume. The threshold of tumor that needs to be removed for benefit remains controversial; generally, debulking may provide benefit if >90% tumor volume can be debulked safely.

NOMENCLATURE FOR HEPATECTOMIES

Standard terminology should be used to document the extent of liver resection performed. The International Hepato-Pancreato-Biliary Association has endorsed the Brisbane classification as the preferred nomenclature.[8] This naming system sorts liver resections based on first-, second-, or third-order divisions of the hepatic artery and bile ducts. Resections at the level of first-order divisions are termed *hepatectomies* or *hemihepatectomies* (**Fig. 57.19**). Thus, a left hepatectomy involves the removal of segments II, III, and IV, whereas a right hepatectomy involves removal of segments V, VI, VII, and VIII. Resections based on second-order divisions, which remove a named section, are termed *sectionectomies* based on the anatomic sections removed. As a result, there are left lateral (segments II and III), left medial (segment IV), right anterior (segments V and VIII), and right posterior (segments VI and VII) sectionectomies. *Trisectionectomy* is the preferred term for extended hepatectomies. Right trisectionectomy includes removal of three contiguous sections (segments IV, V, VI, VII, VIII), the right posterior, right anterior, and left medial sections. Similarly, left trisectionectomy includes a left hepatectomy and removal of the right anterior sections (segments II, III, IV, V, VIII). Single segment or two contiguous segment resections are termed *segmentectomies* and *bi-segmentectomies,* respectively.

INTRAOPERATIVE CONSIDERATIONS

8 The steps for performing liver resections include exposure and mobilization of the liver, inflow and outflow control, and parenchymal resection. Throughout any hepatectomy procedure, frequent use of US should be used to help map and visualize intraparenchymal structures and tumors, and to ensure the direction of parenchymal transection is appropriate.

Open hepatectomy requires unobscured access to the liver. This can be achieved with a right subcostal incision with or without midline extension. When additional access is required, the subcostal incision can be extended to the left side (**Fig. 57.20**). Retractors are used to elevate the costal margin and provide access to the entire right upper quadrant. On occasion, when suprahepatic access is required, intrathoracic extension or midline sternotomy can be used.

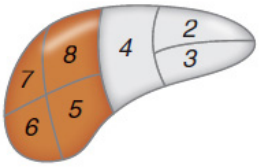
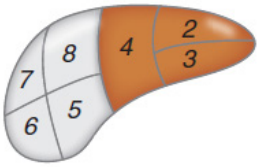
Mobilizing the liver requires dividing its ligamentous attachments between the abdominal wall and retroperitoneum. The liver can then be elevated off of the bare area, if required. The gastrohepatic ligament can also be divided to access the caudate lobe. During mobilization, accessory vessels should be noted and avoided. In particular, care should be taken to avoid an accessory or replaced left hepatic artery that runs in the gastrohepatic ligament. Palpation of the hepatoduodenal ligament can reveal an accessory or replaced right hepatic artery running posterior and medial to the common bile duct.

With the liver mobilized, visual inspection, palpation, and US of the liver and hepatoduodenal ligament should be performed to confirm preoperative findings and identify any new findings which may not have been noted on preoperative evaluation. This includes assessment of the background liver, as well as the number, size, and position of tumors. The location of lesions compared to the known hepatic anatomy should be assessed, and anatomic landmarks should be confirmed by US as the procedure progresses. Occasionally, operative cholangiography can supplement anatomy mapping of the biliary tree.

Safe hepatic surgery depends on the ability to minimize and control hemorrhage from the liver parenchyma during transection. Therefore hepatic arterial and portal venous vascular control are key technical steps in liver resection. Temporary inflow control can be obtained using the Pringle maneuver, which is usually performed in an intermittent manner with occlusion of the hepatic artery and portal inflow with compression of the

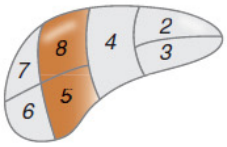
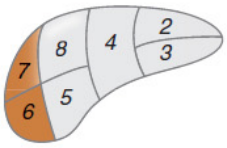
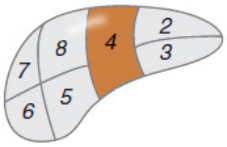
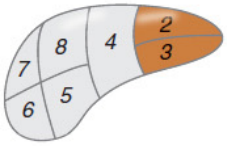
hepatoduodenal ligament. More selective inflow control can be obtained either with an intrahepatic Glissonean or an extrahepatic Glissonean approach to individual pedicles of interest.

Major hepatectomies based on first- or second-order divisions require removal of three or more segments. For these resections, exposure is obtained by taking down the liver attachments to fully mobilize and expose the lobe of interest. Permanent hepatic inflow control is obtained prior to parenchymal transection. For a conventional intra-fascial approach, the hepatic artery, portal vein, and bile duct of interest are exposed by incising the peritoneum of the hepatoduodenal ligament and entering the Glissonean capsule. Early ligation and division are performed to obtain permanent selective inflow control. An endovascular stapler can safely and efficiently divide major vessels and biliary pedicles and should be used liberally in liver surgery. The intra-fascial approach also allows identification of the extrahepatic biliary system. Division of the biliary system can be accomplished either intra- or extrahepatically depending on the length of the involved bile duct. Since the left biliary system has a long transverse-lying extrahepatic segment, it is usually straightforward to divide the left biliary system for a left hemihepatectomy. The right biliary system has a shorter extrahepatic component, and therefore it is sometimes necessary to divide the right bile duct intrahepatically for a right hemihepatectomy. For more extensive hilar dissections, dropping the hilar plate by incising the peritoneum of the hepatoduodenal ligament at the base of segment IV may allow access to the structures at the cephalad aspect of the hepatoduodenal ligament (**Fig. 57.21**).

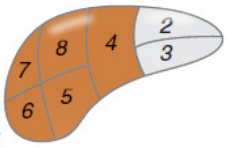
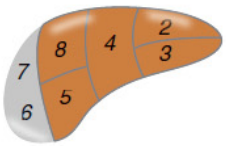
1	*First-order division*		
Anatomical Term	**Couinaud segments referred to**	**Term for surgical resection**	**Diagram (pertinent area is shaded)**
Right Hemiliver **OR** *Right Liver*	*Sg 5–8(+/–Sg1)*	*Right Hepatectomy* **OR** *Right Hemihepatectomy* (stipulate +/–segment 1)	
Left Hemiliver **OR** *Left Liver*	*Sg 2–4(+/–Sg1)*	*Left Hepatectomy* **OR** *Left Hemihepatectomy* (stipulate +/–segment 1)	

Border or watershed: The border or watershed of the first-order division which separates the two hemilivers is a plane which intersects the gallbladder fossa and the fossa for the IVC and is called the midplane of the liver.

2 *Second-order division*
(second-order division based on bile ducts and hepatic artery)

Anatomical Term	Couinaud segments referred to	Term for surgical resection	Diagram (pertinent area is shaded)
Right Anterior Section	*Sg 5, 8*	Add (-ectomy) to any of the anatomical terms as in *Right anterior sectionectomy*	
Right Posterior Section	*Sg 6, 7*	*Right posterior sectionectomy*	
Left Medial Section	*Sg 4*	*Left medial sectionectomy* OR *Resection segment 4* (also see Third order) OR *Segmentectomy 4* (also see Third order)	
Left Lateral Section	*Sg 2, 3*	*Left lateral sectionectomy* OR *Bisegmentectomy 2, 3* (also see Third order)	

Other "sectional" liver resections

Sg 4–8 (+/–Sg1)	*Right Trisectionectomy (preferred term)* or *Extended Right Hepatectomy* or *Extended Right Hemihepatectomy* (stipulate +/–segment 1)	
Sg 2,3,4,5,8 (+/–Sg1)	*Left Trisectionectomy (preferred term)* or *Extended Left Hepatectomy* or *Extended Left Hemihepatectomy* (stipulate +/–segment 1)	

Border or watershed: The borders or watersheds of the sections are planes referred to as the *right and left intersectional planes*. The left intersectional plane passes through the umbilical fissure and the attachment of the falciform ligament. There is no surface marking of the right intersectional plane.

3 *Third-order division*

Anatomical Term	Couinaud segments referred to	Term for surgical resection	Diagram (pertinent area is shaded)
Segments 1–9	*Any one of*	*Segmentectomy*	

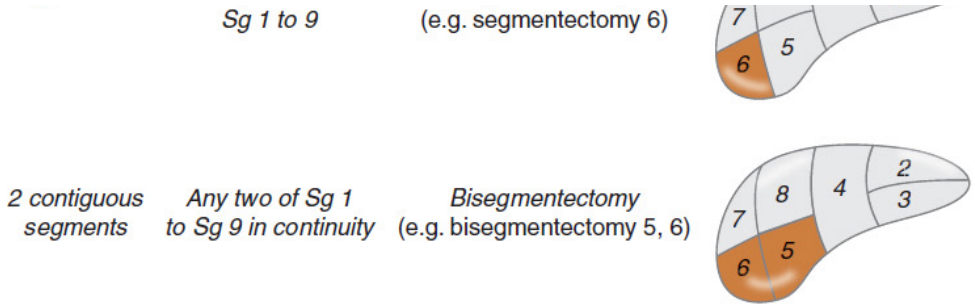


Figure 57.19 The Brisbane terminology of liver anatomy and resections. (Reused with permission from Strasberg SM, Belghiti J, Clavien PA, et al. The Brisbane 2000 terminology of liver anatomy and resections. *HPB (Oxford)* 2000;2[3]:333–339.)

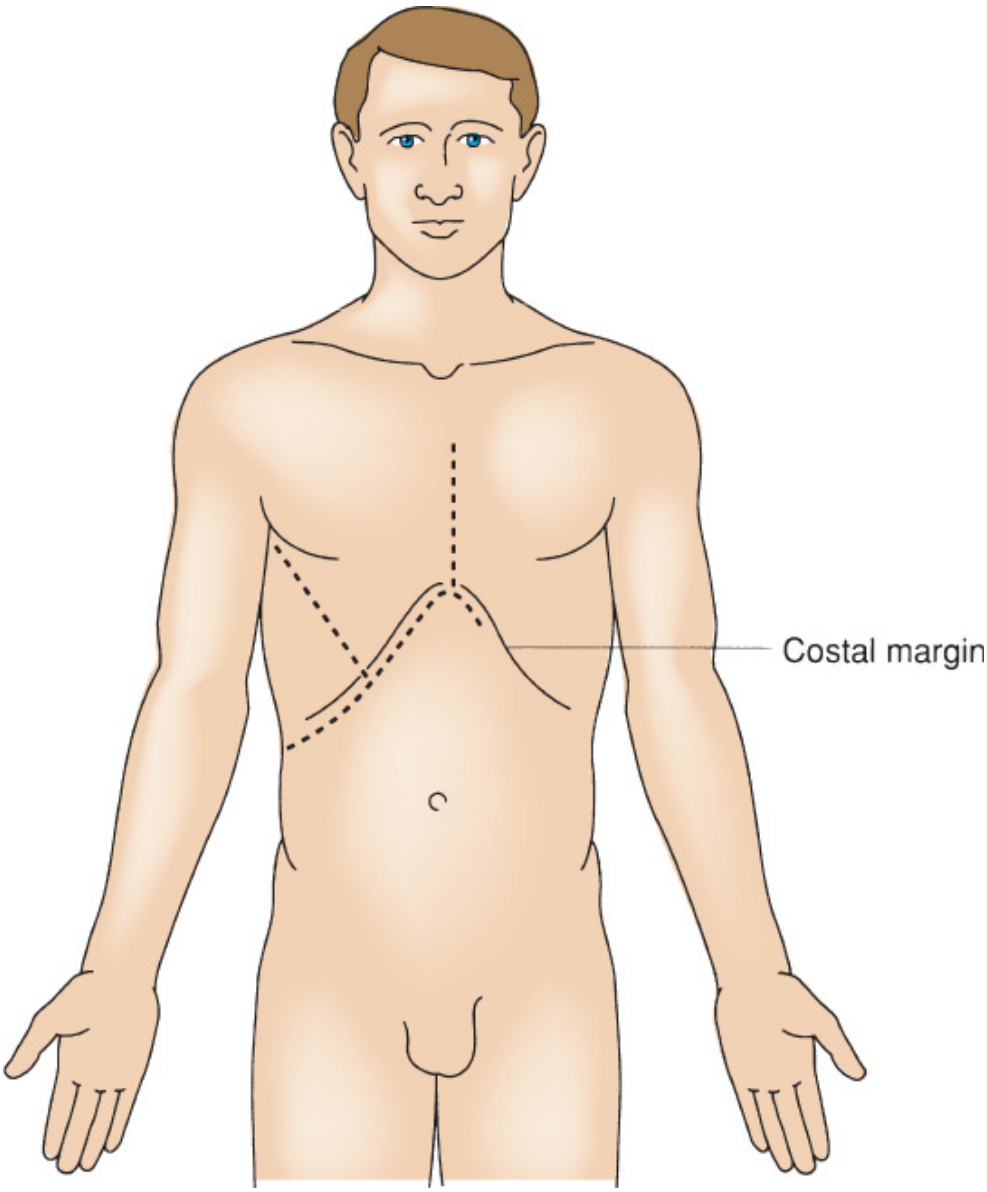


Figure 57.20 Incisions used for open hepatic resection.

Some surgeons prefer an extra-fascial Glissonean pedicle approach to isolate the portal structures. In this method, the portal pedicles are accessed by performing hepatotomies near the hilar plate to encircle the portal pedicles between the Glissonean capsule and Laennec capsule, the membrane that covers the liver parenchyma (**Fig. 57.22**). The extrahepatic Glissonean approach also allows selective inflow control, either on a temporary or permanent basis. In this method, the biliary structures are divided en masse with the vascular pedicle of interest. An advantage of this

approach is that variant biliary and hepatic artery anatomy lies within the Glissonean pedicle and is easily controlled using this method.

Using either approach, early inflow control allows ischemic demarcation of the liver along the anatomic lines, which is helpful to guide the extent of resection required.

Outflow control is then obtained. Small veins from the caudate lobe to the IVC are individually divided to mobilize the liver off of the IVC (**Fig. 57.13**). The hepatic vein of interest can then be encircled and divided with an endovascular stapler (**Figs. 57.23** and **57.24**). For left hepatectomies, formal division of the ligamentum venosum, which runs in Arantius cleft between the posterior left liver and the caudate lobe, provides easy access to the base of the left hepatic vein and facilitates control of this structure.

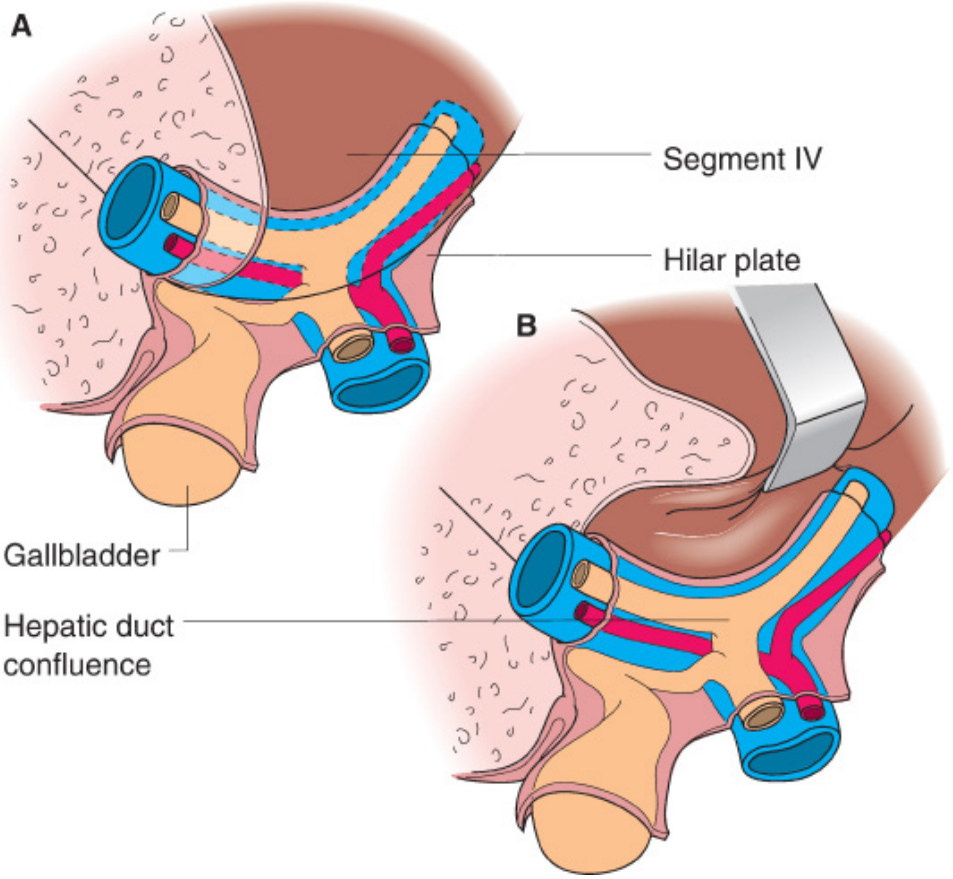


Figure 57.21 Lowering the hilar plate. **A:** The inferior border of segment IV overlies the hepatic duct confluence. **B:** Division of the connective tissue investment allows elevation of segment IV, which results in a "lower" hilar plate and surgical exposure to the hepatic duct confluence.

Parenchymal transection should be performed under low central venous pressure (CVP) conditions (<5 mm Hg) to minimize bleeding from the parenchymal surface.[9] The Pringle maneuver can also be used, either selectively or routinely, to further reduce blood loss and maintain clear visualization of the intraparenchymal structures during transection. Large intraparenchymal structures should be divided formally with sutures, clips, or staples to minimize bleeding and bile leak. A variety of techniques are used for parenchymal transection, including crush clamp, ultrasonic or water-jet dissectors, energy devices (monopolar, ultrasonic, or bipolar), and staplers. No single technique has been demonstrated to be clearly superior; thus, surgeons should use a technique that they are familiar with.

Minor hepatectomies include resection of smaller volumes of liver, but the name is a misnomer, as these resections are often technically challenging and require a more informed understanding of the intraparenchymal structures to ensure safe resection. In the modern era, a parenchymal-sparing approach is favored to preserve the FLR and allow repeat resection in the future and/or preserve liver function. In these cases, exposure and mobilization follow the same principles as discussed above, but unlike major hepatectomies, the vascular inflow and outflow structures are often within the liver. As a result, definitive inflow and outflow control is often not possible prior to parenchymal transection. Since parenchymal transection and vascular control occur concurrently, temporary inflow control with Pringle maneuver and low CVP conditions are even more important for these procedures. Parenchymal transection is performed to allow exposure and control of intrahepatic structures as they are encountered.

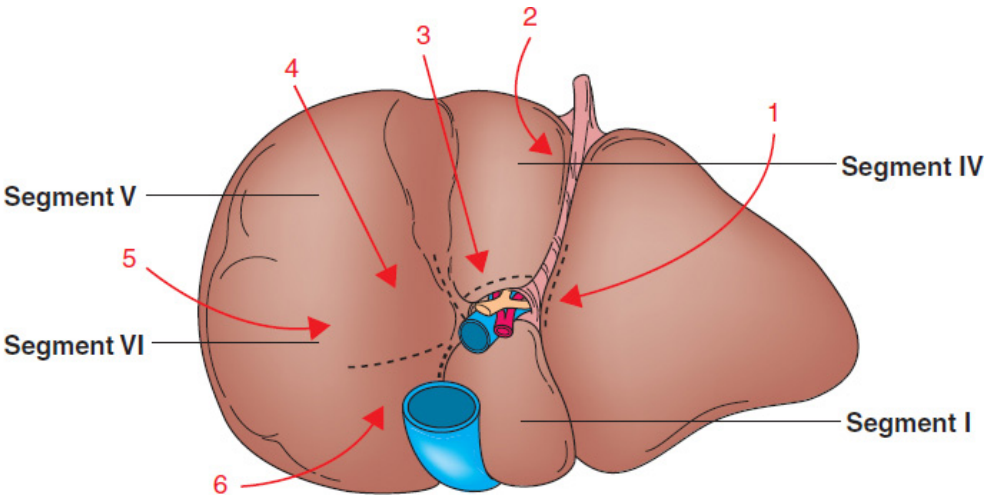


Figure 57.22 Hepatotomies to access pedicles for ligation: right hepatectomy, 4, 5 and 6 left lateral sectionectomy, 1 and 2; left hepatectomy, 1 and 3 right anterior sectorectomy, 4 and 5; and right posterior sectorectomy, 5 and 6.

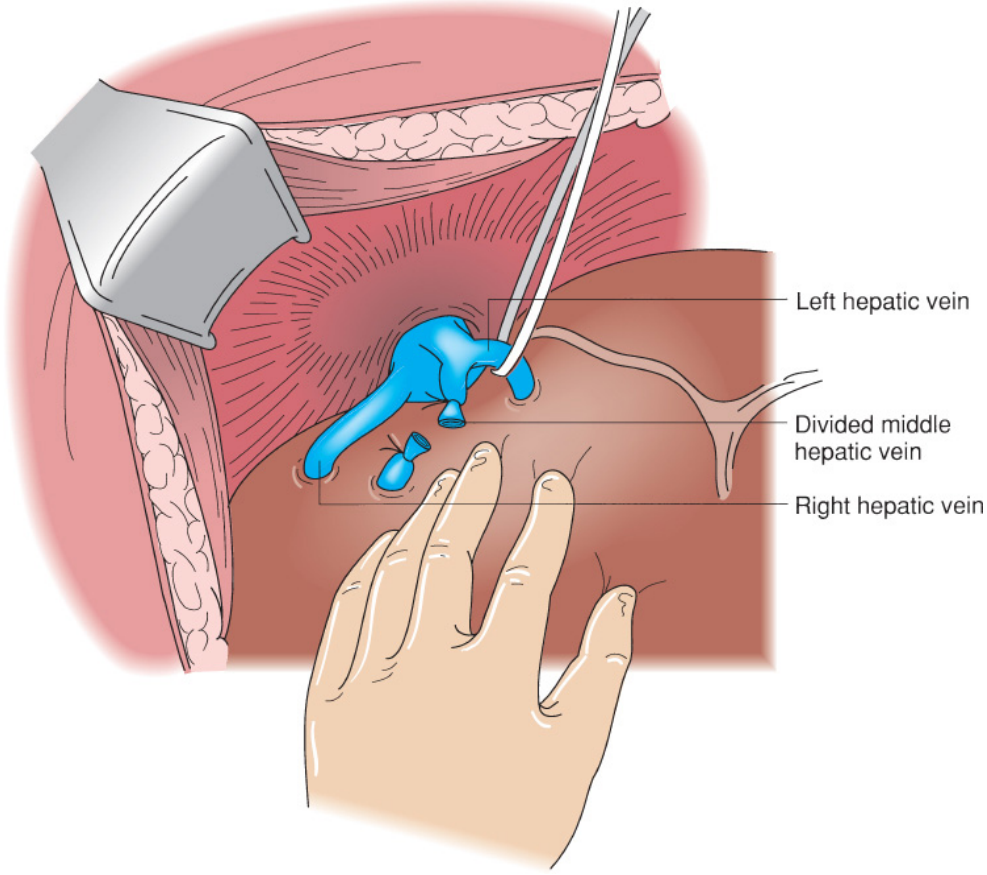


Figure 57.23 Caudal retraction of the left hepatic lobe with division of middle and left hepatic veins during left hepatic lobectomy. Often, the division of the middle and left hepatic veins is intraparenchymal.

Once resection has been completed, the FLR and the cut edge of the liver are inspected. Any bleeding points or open biliary radicals should be oversewn, and hemostasis along the cut surface should be confirmed. The falciform ligament should be reconstructed to avoid postoperative liver torsion.

There has been major advancement in liver surgery technique with the availability of minimally invasive hepatectomy.[10] Minor hepatectomies in safe zone areas—peripherally based lesions in segments II to VI—are now performed using a minimally invasive approach at many centers. As experience is gained, the use of minimally invasive techniques for formal hemihepatectomies, as well as posterior or superior lesions (segments I, IV, VII, VIII) is increasing. However, a minimally invasive approach provides a different anatomic view of the liver. Unlike an open procedure which provides a ventral approach to the liver, the liver is often seen in a caudal–cranial view during minimally invasive right hepatectomy.[11] As a result, surgeons performing minimally invasive major hepatectomies must be intimately familiar with how intraparenchymal structures appear from this perspective. There are several benefits of a minimally invasive approach, including improved postoperative recovery, decreased length of stay, and earlier return to full activity. Minimally invasive surgery can be approached using pure laparoscopic, hand-assisted, hybrid, or robotic-assisted approaches.

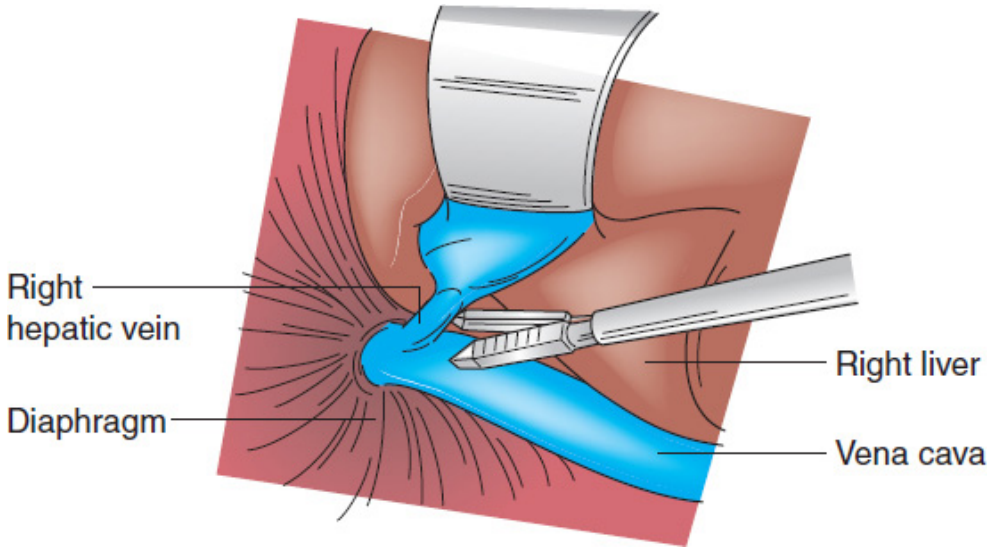


Figure 57.24 A vascular endoscopic stapling device is used to divide the right hepatic vein after the right side of the liver has been mobilized.

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58

Hepatic Infection and Acute Liver Failure

Ola Ahmed and Maria B. Majella Doyle

Key Points

1. Liver abscesses are the most common type of visceral abscess.
2. Acute liver failure (ALF) is characterized by hepatic encephalopathy and impaired coagulation (INR >1.5) in the absence of any underlying or pre-existing liver disease.
3. Liver disease etiology influences management, outcomes, and overall prognosis.
4. Viral and acetaminophen are the most common causes of ALF in adults.
5. While biologic and nonbiologic liver support systems are still under experimentation, liver transplant is the only curative treatment of choice in cases of irreversible liver failure.

PYOGENIC LIVER ABSCESS

Prevalence and Pathogenesis

Pyogenic liver abscesses result from bacterial infections and most commonly develop from intra-abdominal contamination of bowel contents subsequently disseminating to the liver through portal circulation or contiguous spreading following biliary infections. Abscesses may also occasionally arise directly from 1 penetrating wounds or surgical procedures. These specific infections account for 13% of intra-abdominal abscesses, making them the most common type of visceral abscesses, with an annual incidence of 2.3 cases per 100,000 persons and a slight preponderance among male patients.[1,2]

Risk Factors

Common risk factors for abscess development include diabetes mellitus, liver transplantation, pre-existing hepatobiliary or pancreatic disease as well as invasive hepatic and intra-abdominal procedures. Loss of gastric acid production commonly seen in elderly patients or in cases of atrophic gastritis have also been associated with the increased risk of pyogenic infections, largely due to the consequential changes in bowel bacterial flora. Several studies from Taiwan reported a potential link between pyogenic liver abscesses and underlying colorectal cancer.[3–5] In some studies, the incidence of subsequent gastrointestinal malignancy was four-fold higher than in control groups, with *Klebsiella pneumonia* acting as the most implicating pathogen.

Clinical Manifestations

Fever is the most frequent presenting symptom of pyogenic liver abscesses, occurring in up to 90% of patients. Abdominal signs and symptoms occur in 50% to 75% of cases, commonly localizing to the right upper quadrant and manifesting as pain, guarding, and rebound tenderness. Hepatomegaly may occur in some scenarios and jaundice is frequently present. Other common symptoms are nausea, chills, anorexia, weight loss, malaise, and fatigue. Laboratory studies demonstrate leukocytosis and transaminitis with hyperbilirubinemia is evident in over 50% of cases, respectively. Hypoalbuminemia and normochromic, normocytic anemia may also be present.

Diagnosis

Abdominal imaging with ultrasound (US) and computed tomography (CT) are appropriate diagnostic modalities for abscess identification, though a chest x-ray may reveal a right pleural effusion or an elevated hemidiaphragm in 50% of cases. Abdominal US can diagnose pyogenic abscesses in almost 90% of cases and can guide diagnostic or therapeutic drainage. CT is more sensitive than US (95% vs. 85%), will reveal small abscesses, and further differentiate these lesions from other pathologies.[6] When CT scanning is done, intravenous contrast should be used if there are no patient contraindications (**Fig. 58.1**). Alternative diagnostic modalities include magnetic resonance imaging (MRI) or tagged white blood cell scans, which are less common.

Blood cultures are positive in up to 50% of cases and are important diagnostic elements. These should be ideally drawn prior to antibiotic therapy. Standard serum analyses such as complete blood counts, electrolytes, renal profiles, and liver function testing are also performed to determine the degree of systemic infection and for evidence of any potential concomitant organ injury. Serologic and fecal testing of *Entamoeba histolytica* is also considered in the diagnostic workup of patients with epidemiologic risk factors.

Image-guided drainage of suspected abscesses is performed to confirm the diagnosis and the involved bacterial pathogens. Aspirate material is sent for Gram staining and culture to help guide therapy.

Microbiology

Most pyogenic liver abscesses are polymicrobial, consisting of a combination of enteric and anaerobic pathogens. The most commonly identified pathogens are *Escherichia coli* and *K. pneumonia*. Streptococci species are also important causes of liver abscesses as well as *Staphylococcus aureus*. Candida coinfection can also arise in immunocompromised states.

Figure 58.1 Computed tomogram of a pyogenic hepatic abscess in a liver transplant recipient with occlusion of the hepatic artery.

Treatment

Multimodal treatment is essential for resolution of pyogenic liver abscesses. Drainage is both diagnostic and therapeutic and should always be considered when feasible. Drainage can be performed using CT/US-guided percutaneous techniques, surgical via an open or laparoscopic approach or by endoscopic retrograde cholangiopancreatography (ERCP). Drainage catheters should remain in place until output is minimal which is usually up to 7 days. Empiric antibiotic therapy should be administered pending microbiologic culture and sensitivity analysis. Coverage should be broad to include streptococci, enteric gram-negative bacilli and anaerobes and guided by microbiologic expertise. Once culture and sensitivity results are available, directed therapy should be initiated and duration is based on clinical response. A typical

course is 14 days of parenteral therapy followed by oral medication for a total of 6 weeks.[7]

AMEBIC LIVER ABSCESS

Prevalence and Pathogenesis

Amebic liver abscesses are the most common extraintestinal manifestations of amebiasis caused by the protozoan *E. histolytica*. Amebiasis is most prevalent in tropical and subtropical regions with poor sanitation and fecal–oral transmission is the most common route of infection. In developed countries, it can occur in migrants from endemic areas. Most infections are asymptomatic, but amebic dysentery and pulmonary, cardiac, and brain involvement can occur, along with hepatic abscess formation.

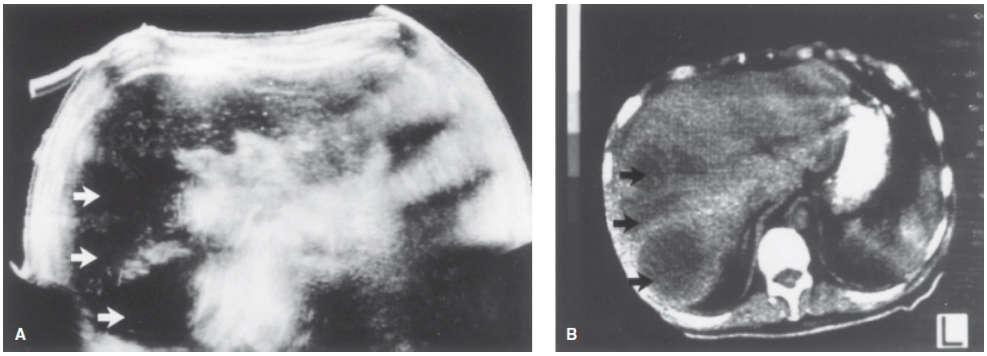

Figure 58.2 Sonogram **(A)** and computed tomogram **(B)** in a patient with multiple amebic abscesses (*arrows*).

Men are affected 10 times more commonly than women, with peak incidence in the third to fifth decade of life, and corticosteroid usage is a risk factor.[8] Ingested cysts pass through the stomach and reach the intestine. There, the cyst wall is degraded and trophozoites are released. These infective particles multiply in the colonic lumen and then may enter mesenteric veins and eventually the liver. Amebic trophozoites then cause obstruction of venules, thrombosis, and infarction of hepatic parenchyma, with resultant abscess formation.

Risk Factors

Risk factors predisposing to amebic liver abscesses are unclear, although immunocompromised states such as HIV may increase the likelihood of invasive disease.

Clinical Manifestations

Clinical presentation usually occurs within 8 to 20 weeks following return from endemic areas, manifesting as right upper quadrant pain and fever. Cough, sweating, malaise, weight loss, and hiccough may also be present. Diarrhea occurs in up to one-third of patients and jaundice is evident in 10%. Abscess rupture occurs in up to 7% of affected patients with direct extension into the peritoneal cavity often resulting in severe peritonitis and systemic infection. Leukocytosis is common with transaminitis and elevated alkaline phosphatase (ALP) levels evident in 80% of cases.

Diagnosis

Several imaging modalities can be utilized, specifically US, CT, or MRI (**Fig. 58.2**). Amebic abscesses are more common in the right lobe and tend to be singular. US typically demonstrates a round, well-defined, hypoechoic mass, while images on CT scan may show a low-density mass with an enhancing rim at it's periphery. On MRI, abscesses appear with a low-signal intensity on T1 weighted images and high signal intensity on T2 weighted images. Elevation of the right hemidiaphragm is evident on 50% of chest radiographs. *E. histolytica* is not always found in stool specimens of infected patients due to the intermittent appearance of organisms and the uncommon occurrence of simultaneous amebic liver and intestinal disease, but diagnostic antibodies are present in the serum 7 to 10 days after the onset of symptoms in over 90% of patients.[9] Needle aspiration with imaging modalities can be both diagnostic and therapeutic for large-sized abscesses. Abscess content is typically described as having an "anchovy paste" consistency and is acellular and proteinaceous in substance. Aspirates can be considered for antigen or PCR testing. Currently, PCR testing is understood to be the most sensitive method in identifying E. histolytica, and the sensitivity for aspirated material ranges from 75% to 100% with specificity rates over 90%, respectively.[10] A study by Parija reported a diagnostic

sensitivity of liver abscess analysis by PCR of 100% before treatment, comparing to 70.6% after treatment.[11] This is likely a result of DNA eradication and parasite destruction following treatment.

Treatment

Treatment is based on amebicidal drugs to eliminate liver organisms and a luminal agent to eradicate intraluminal cysts. Treatment can be initiated empirically pending further evaluation. Metronidazole 500 mg to 750 mg three times a day for 7 to 10 days is typically first line. Tinidazole 2 g orally for 5 days is an alternative treatment that is oftentimes better tolerated. To eradicate intraluminal cysts, the following regimens can be used: paromomycin (25 to 30 mg/kg/day orally three times a day for 7 days), diiodohydroxyquin (650 mg orally three times a day for 20 days), or diloxanide furoate (500 mg orally three times daily for 10 days for adults). Amebic abscesses can almost always be treated with medical therapy alone and abscess drainage can be considered in large abscesses or cases of a low or absent clinical response.

ECHINOCOCCUS (HYDATID DISEASE)

Prevalence and Pathogenesis

Echinococcal infection, also called hydatid disease, is a parasitic infection due to echinococcal tapeworms including *Echinococcus granulosus* or *E. multilocularis* in humans. The liver is most commonly affected by *E. granulosus* but this is typically asymptomatic. Dogs are the definitive host and the life cycle of the organism is such that when the canine host ingests infected viscera (from sheep or cattle) scoleces released in the intestine develop into adult worms. Humans, an intermediate host, acquire echinococcal eggs by ingestion of contaminated foods or with infected animals. The echinococcal egg is digested in the duodenum and yields an embryo (oncospheres). Embryos invade the intestinal wall and reach the liver via the portal circulation. Surviving embryos lodge in the hepatic

capillaries and develop into hydatid cysts. *E. multilocularis* is more commonly associated with alveolar disease.

Risk Factors

The disease is commonly associated with dog and sheep ownership and increasing age.[12]

Clinical Manifestations

Liver involvement with echinococcal cyst can lead to venous obstruction, portal hypertension, sepsis, and cholangitis. The right lobe is involved in most cases (60% to 85%) and symptoms typically develop when the cyst measures at least 10 cm. This can manifest as hepatomegaly, right upper quadrant pain, nausea, and vomiting. Cysts may grow at an annual rate of around 1 to 3 cm/yr. Enlarging cysts can cause symptoms of abdominal pain, biliary obstruction, and jaundice, or less commonly portal hypertension, resulting from mass or pressure effects. Occasionally, cysts may rupture into the peritoneal cavity causing abdominal pain and anaphylaxis.

Diagnosis

Hydatid cysts can be visualized using the previously mentioned imaging techniques: US, CT and MRI. US reaches a sensitivity of 90% to 95%[13] and typically demonstrates a smooth, anechoic, round cyst with a “hydatid sand” on patient movement.[14] CT imaging has an advantage over US through its ability to demonstrate intraperitoneal rupture and concurrent infection while MRI may further delineate the cyst capsule.[15] Serologic testing is also used during the initial diagnosis. Antibody testing with ELISA appears to be the most sensitive modality.[16]

Treatment

Surgical resection is the treatment of choice for large or complicated hydatid cysts (rupture, fistulae, compression). Surgical extirpation aims to remove the cyst intact without spillage of cyst contents. Aspiration of cyst contents

prior to resection may minimize the result of any cyst spillage. After aspiration injection with ethyl alcohol or 20% sterile saline is undertaken to kill remaining scoleces. In cases where the aspirate is bilious and a communication with the biliary tree is thus suspected the cyst should be resected without alcohol injection to prevent the occurrence of sclerosing cholangitis. Surgical excision can be performed through open or laparoscopic techniques depending on cyst features and location. Albendazole should be started 4 days prior to surgery and generally continued for at least 4 weeks postoperatively.[17] Mebendazole may be used as an alternative therapy but is less well absorbed and continued use for at least 3 months post surgery is advised.[18]

SCHISTOSOMA

Prevalence and Pathogenesis

Schistosoma mansoni, S. japonicum, S. haematobium, and *S. mekongi* are species of the trematode fluke that infects humans in endemic areas or visitors to these sites. Liver disease is especially severe with *S. mansoni, S. japonicum,* and *S. mekongi.* The life cycle of *Schistosoma* species alternates between sexual reproduction in humans and asexual multiplication in water snails. Cercariae enter the human host by penetrating the skin. An irritating maculopapular rash that lasts for several days is an early manifestation of infection. Schistosomes live in the intestinal lumen and eggs reach the liver via the portal circulation where they cause an inflammatory reaction manifesting as an inflammatory granuloma surrounding a schistosomal egg. The pathogen is most prevalent in central and subtropical areas of sub-Saharan Africa, the Middle East, India, and Southeast Asia.[19] Hepatocellular carcinoma (HCC), colon cancer, and follicular lymphoma of the spleen have been reported in association with hepatic schistosomiasis.[20]

Risk Factors

Acute schistosomiasis is seen typically in poor and rural communities exposed to infested waters and nonimmune visitors to endemic areas.

Clinical Manifestations

While hepatocellular functioning may not be impaired, physical examination may reveal a firm, nodular liver and features of portal hypertension such as splenomegaly and gastric varices.[21] It is usually asymptomatic until manifestations of portal hypertension declare themselves.

Diagnosis

Diagnosis requires serologic, microscopic, and biochemical analysis to detect infection and parasitic burden coupled with standard imaging modalities. Stool (Kato–Katz smears) and urine analysis can allow for microscopic egg detection while antigen testing can be performed on urine analysis to characterize parasitic burden. Serum transaminases are typically normal. Tissue biopsies are useful in the setting of inconclusive diagnostic tools and will show prominent granuloma formation and severe portal fibrosis. Imaging studies are not typically useful in the diagnosis of acute infection. In chronic cases US may show portal vein wall thickening.[22] Hypertrophy of the left lobe, splenomegaly, and engorged venous collaterals may all be observed as well. CT and MRI may show fibrosis around portal vein branches as well as low attenuation rings through the liver parenchyma.[23]

Table 58.1 Classification of Viral Hepatitis

	The Viral Hepatitides				
Virus	Hep A Picornavirus (RNA)	Hep B Hepadnavirus (DNA)	Hep C Flavivirus (RNA)	Hep D Viroid (RNA)	Hep E Calicivirus (RNA)
Transmission Acute disease Evolution to chronic disease	Fecal–oral Common Never	Parenteral Common Infrequent in adults	Parenteral Uncommon Frequent (70%)	Parenteral Common Yes	Fecal–oral Yes Described in organ transplant recipients
New cases/yr # Infected (U.S.)	1,400,000 6,700	22,100 862,000	44,300 2,400,000	Unknown, found in approximately 5% of cases of HBV infection	300 Unknown, uncommon
Treatment	None	Lamivudine Adefovir Entecavir	Interferon + Ribavirin	Treatment of HBV	Mainly sanitary preventative
Prophylaxis	Vaccine and Ig	Vaccine and Ig	None	Vaccinate against HBV	In development
Fulminant failure	Rare	Yes	Never	With HBV, as coinfection or superinfection	Especially in pregnant women

HBV, hepatitis B virus; Hep, hepatitis; Ig, immunoglobulin.

Treatment

Preferred treatment of schistosomiasis is praziquantel, with a cure efficacy of around 90%. Follow-up stool or urine microscopy should be performed at 6 weeks in endemic areas and 3 to 6 months following treatment in nonendemic areas. Repeat treatment with praziquantel may be warranted in persistent egg detection.

Viral Hepatitis

Viral hepatitis represents an important cause of acute and chronic liver disease, cirrhosis and hepatocellular cancer. In the United States, hepatitis A, B and C account for more than half of acute hepatitis cases with hepatitis C becoming a leading indication for liver transplantation and potential graft loss resulting from its reactivation.[24]

The mechanism of liver injury is largely a host inflammatory response to the virus. **Table 58.1** summarizes the current understanding and characteristics of the five viruses most commonly associated with clinical hepatitis, their modes of transmission, and the consequences of infection.

HEPATITIS A VIRUS

Epidemiology/Risk Factors for Transmission

Hepatitis A is generally self-limiting with no risk of chronic infection. This is usually transmitted via the fecal–oral route. Common risk factors for transmission include international travel, consumption of contaminated food and water, and intravenous drug use. The disease can occur sporadically or in epidemic form and outbreaks are not uncommon. However, incidence in the United States has declined with effective vaccination.

Clinical Features

Fulminant hepatic failure occurs in less than 1% of cases and mostly occurs in patients with underlying liver disease or coinfection. Symptoms are uncommon in children less than 6 years of age and more commonly manifest in adults, occurring in up to 70% of those infected. The incubation period is typically 28 days, ranging from 15 to 50 days. Initial symptoms are fatigue, malaise, nausea, vomiting, anorexia, fever, and right upper quadrant pain. The diagnosis may be missed in cases without jaundice, progressing to bilirubinuria, acholic stools, and jaundice in 40% to 70% of patients. In cases where jaundice becomes manifest, it persists for 1 to 6 weeks. Transaminitis (1,000 IU/mL), hyperbilirubinemia (>10 mg/dL), and elevated ALP (>400 U/L) may also occur (**Fig. 58.3**).

Treatment

Treatment is mainly supportive and infection control measures such as hand washing and isolation should be a top priority to prevent the spread of virus. Complete recovery typically occurs at 6 months in all patients. Vaccine protection for specific patient groups is warranted prior to hepatitis A exposure: all children at age one, individuals travelling to endemic areas, and those with chronic disease and HIV.

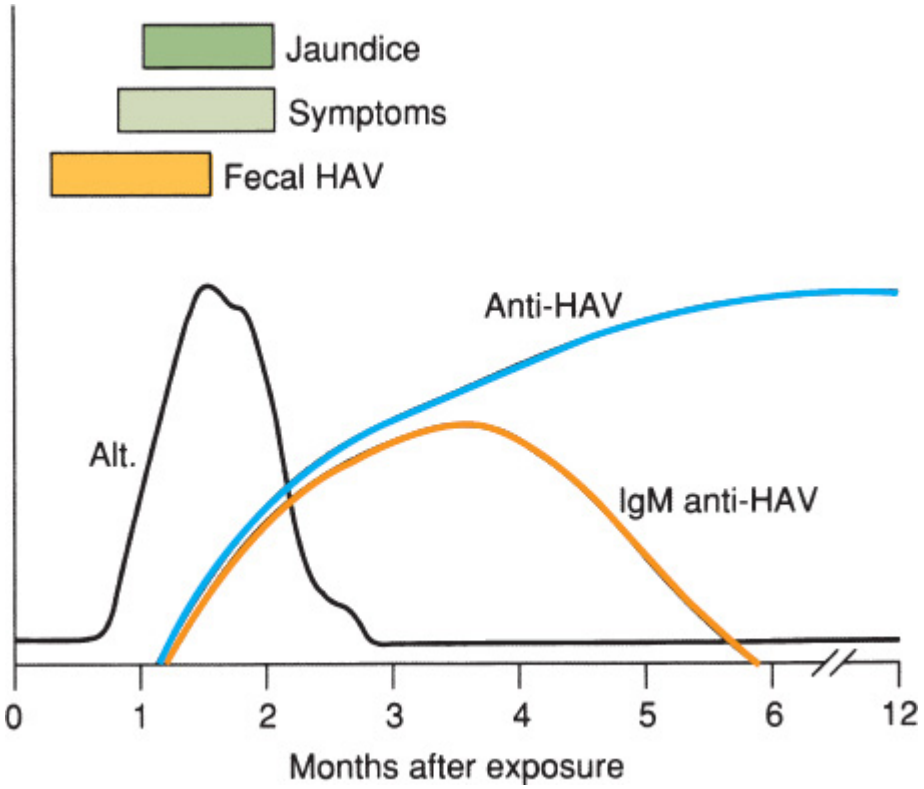

Figure 58.3 Clinical course of hepatitis A infection.

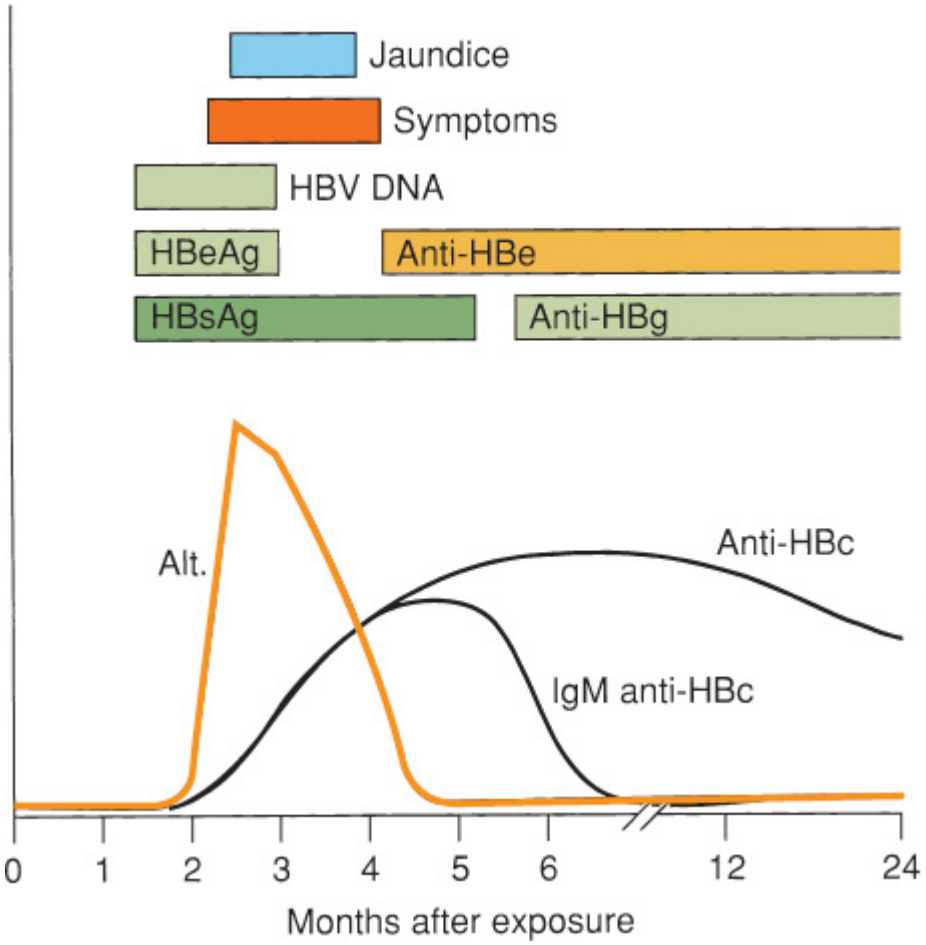

Figure 58.4 Clinical course of acute hepatitis B infection.

HEPATITIS B VIRUS

Epidemiology/Risk Factors for Transmission

It is estimated that nearly 2 billion people worldwide were previously or currently infected with hepatitis B and 248 million are chronic carriers.[25] In the developing world, mother-to-child infection is the most common mode of transmission. In the United States, transmission is primarily through sexual exposure. Infection from intravenous drug use and occupational infections due to percutaneous exposure may also occur. Liver injury is due to the resultant host immune response.

Clinical Features

The incubation period for hepatitis B virus (HBV) can last from 1 to 4 months. Clinical features of the virus vary in acute and chronic disease (**Fig. 58.4**). During the initial acute stage of disease, symptoms can range from subclinical to anicteric hepatitis. Icteric hepatitis occurs in 30% of patients while only 0.1% to 0.5% develop fulminant hepatic failure. The presence of serum hepatitis B surface antigen (HBsAg) may precede jaundice. Acute infection is associated with detectable serum HBV DNA, hepatitis B early antigen (HBeAg), and IgM to hepatitis B core. HBeAg is a useful marker of viral replication except in patients with mutant viruses where it may be undetectable despite active replication. In such cases detection of HBV DNA is diagnostic. The risk of liver failure is proportional to antibody titers of HBcAg and HBsAg. Serum anti-HBc IgM becomes detectable with the onset of jaundice and rapidly reaches peak concentrations. In most patients, when HBV does not develop into chronic hepatitis, anti-HBc IgM becomes undetectable after 6 months and for this reason is considered an accurate marker for differentiating acute hepatitis B from chronic hepatitis B reactivation or exacerbation. Chronic hepatitis can be asymptomatic but may ultimately progress to decompensated cirrhosis and other extrahepatic manifestations of disease such as skin rashes, arthralgias, and glomerular disease (**Fig. 58.5**).

Treatment

Treatment for acute HBV is mainly supportive. Further efforts should be taken to prevent exposure and transmission to other individuals. Vaccinations can be offered to high-risk individuals such as health care workers, visitors to highly endemic areas, men who have sex with men, sex workers, and intravenous drug users. The hepatitis B vaccine is given as a series of three intramuscular doses and has almost 100% efficacy among immunocompetent persons. Hepatitis B immune globulin has a reported efficacy of 90% in the prevention of newborn infections and approximately 75% in cases of needle sticks or sexual infections in people exposed to the virus with no prior immunity. It is administered as soon as possible after exposure together with the first dose of the hepatitis B vaccine series.

Additional treatment options include antiviral therapies such as lamivudine, adefovir dipivoxil, or entecavir as monotherapy. Therapy is

usually directed at HBeAg-positive cases that have an increased risk of cirrhosis and HCC. HBeAg-negative patients with a high viral load may also benefit from treatment. Treatment can be stopped following negative identification of HBsAg on two consecutive tests 4 weeks apart.

Liver transplantation is offered in cases progressing to cirrhosis. Recurrence of viral infection in the allograft can be as high as 80% in HBeAg-positive cases where no postoperative prophylaxis is administered. The combination of lamivudine and hepatitis B immune globulin post transplantation has reduced the reinfection rate to less than 10% and increased the 5-year survival rate to 80%.

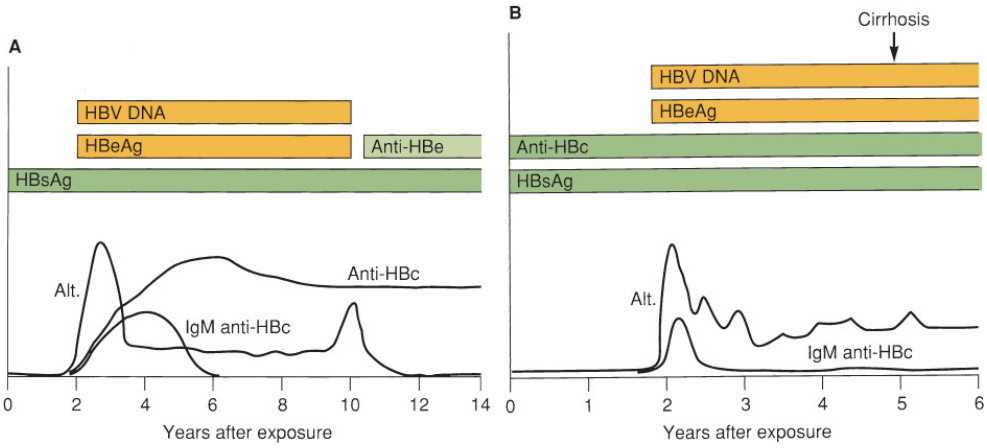

Figure 58.5 Clinical course of chronic hepatitis B. **A:** A benign chronic carrier has continued production of hepatitis B surface antigen but there is an absence of serum markers of viral replication. **B:** A pattern of continuing liver injury and serum markers of active viral replication.

HEPATITIS C VIRUS

Epidemiology/Risk Factors for Transmission

The estimated prevalence of hepatitis C worldwide is 177.5 million, almost 2.5% of the population.[26] In the United States alone, 44,300 new infections arise per year with an estimated 2.4 million people infected. Common risk factors are intravenous drug use, homelessness, incarceration, and sexual contact. In addition, the recent opioid epidemic has resulted in an increase in

hepatitis C virus (HCV) incidence as well as unhygienic and unsafe tattooing and body piercing.

Clinical Features

The HCV incubation period ranges from 15 to 150 days with symptoms commonly developing 5 to 12 weeks following exposure. Up to 80% of cases are asymptomatic. Nonspecific symptoms are seen in the remaining patients including nausea, diarrhea, abdominal pain, myalgia, and weight loss. Extrahepatic manifestations may arise in a subset of patients, including glomerular disease, autoimmune disorders, and dermatologic conditions.[27] Initial laboratory findings may reveal elevated ALT levels (500 to 1,000 IU/mL) and high HCV RNA titers (**Fig. 58.6**). Between 50% and 85% of patients remain chronically infected of which 5% to 30% progress to cirrhosis in the following two or three decades. Cirrhotic patients are at a further risk of developing HCC and decompensated failure.

The diagnosis of chronic hepatitis C is based on the serologic demonstration of persistent HCV RNA and HCV antibodies. HCV RNA can be detected weeks earlier than antibodies, which typically appear 2 to 8 weeks after the initial infection (**Fig. 58.7**).

Treatment

Similar to hepatitis B, treatment approaches include preventative measures for further hepatitis C transmission. Individuals are advised not to donate blood or share a toothbrush and are encouraged to take part in substance-abuse treatment facilities, and counseled regarding safer drug injection practices. Various antiviral treatment regimens are available depending on the viral phenotype and patient risk factors and should be considered in all patients with chronic HCV infection and a detectable HCV viral level for more than 6 months. Eradication is based on achieving a sustained virologic response (SVR) 12 weeks following the completion of therapy.

Interferon (IFN) has long been considered the drug of choice for hepatitis C treatment with its ability to reduce the rate of fibrosis progression. This can be used in combination with ribavirin for either 24- or 48-week courses, depending on the genotype present. SVR rates range from 29% to 62%.

Direct-acting antivirals (DAAs) have also been designed to specifically inhibit HCV proteins. These agents, including simeprevir, ombitasvir, and elbasvir, can be taken orally for 8 to 12 weeks with SVR rates approaching 90%.

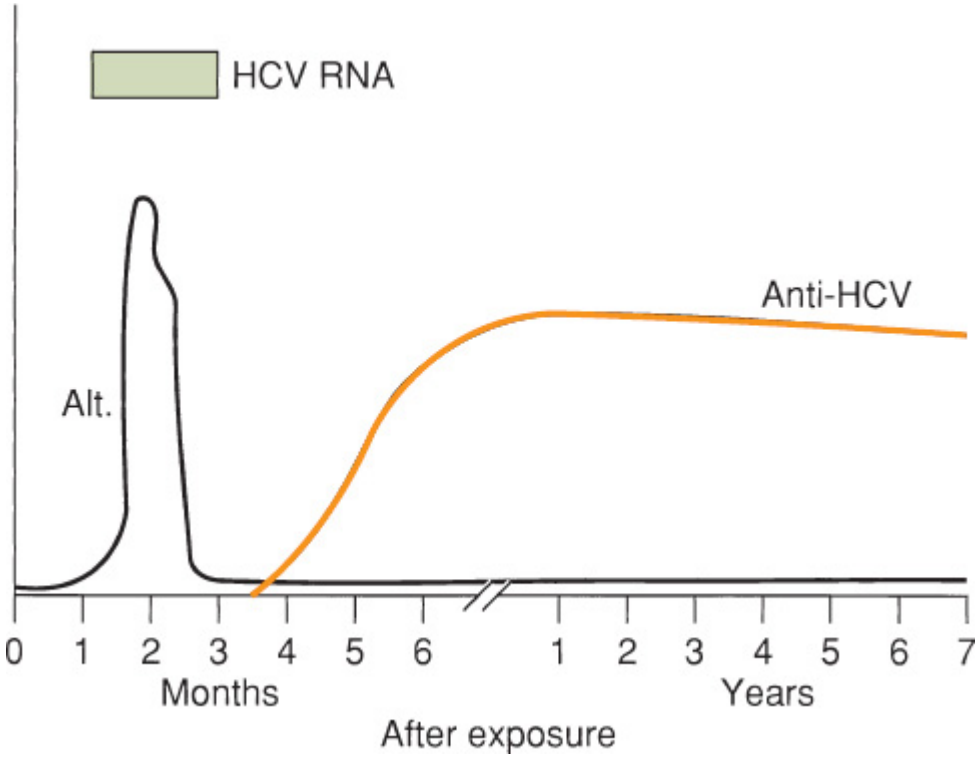

Figure 58.6 Clinical course in acute hepatitis C.

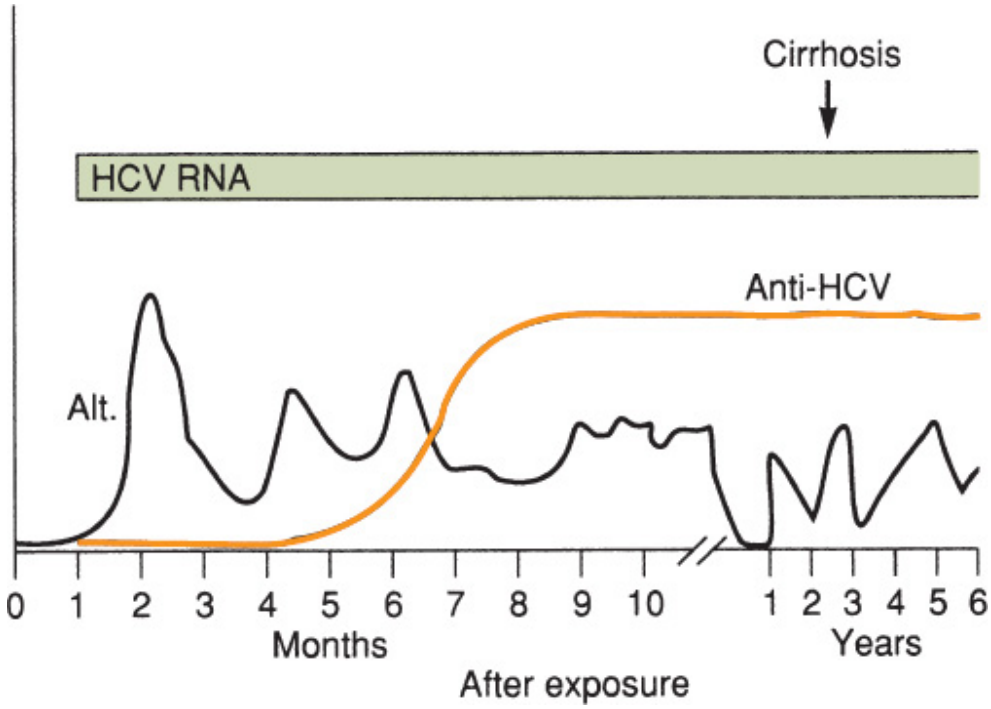

Figure 58.7 Clinical course in chronic hepatitis C.

Hepatitis C cirrhosis is a common indication for liver transplantation. However, reinfection and graft failure are almost inevitable if the virus is untreated during the pre- or posttransplant period. Five-year survival varies between 60% and 80%.

HEPATITIS D VIRUS

Epidemiology/Risk Factors for Transmission

Due to its dependence on HBV, patients with hepatitis D are always coinfected with hepatitis B. Transmission is similar to that of HBV, via parenteral or sexual exposure to blood or body fluids and hepatitis D virus (HDV) only occurs in HBsAg-positive patients.

Clinical Features

Acute infection is diagnosed by the presence of anti-HDV IgM. Coinfection with HBV generally produces a clinically indistinguishable disease with

clinical features similar to the acute hepatitis B infection (**Fig. 58.8**). Anti-HBc IgM distinguishes coinfection from superinfection which may manifest as a severe form of hepatitis or exacerbation of chronic HBV. The diagnosis in patients with chronic liver disease is made by the presence of HBsAg and antibodies against HDV in the serum and confirmed by the presence of HDV antigen in the liver or HDV RNA in the serum (**Fig. 58.9**). Cirrhosis may develop in up to 80% of coinfected patients compared to 15% to 30% of patients solely infected with HBV (**Fig. 58.10**).

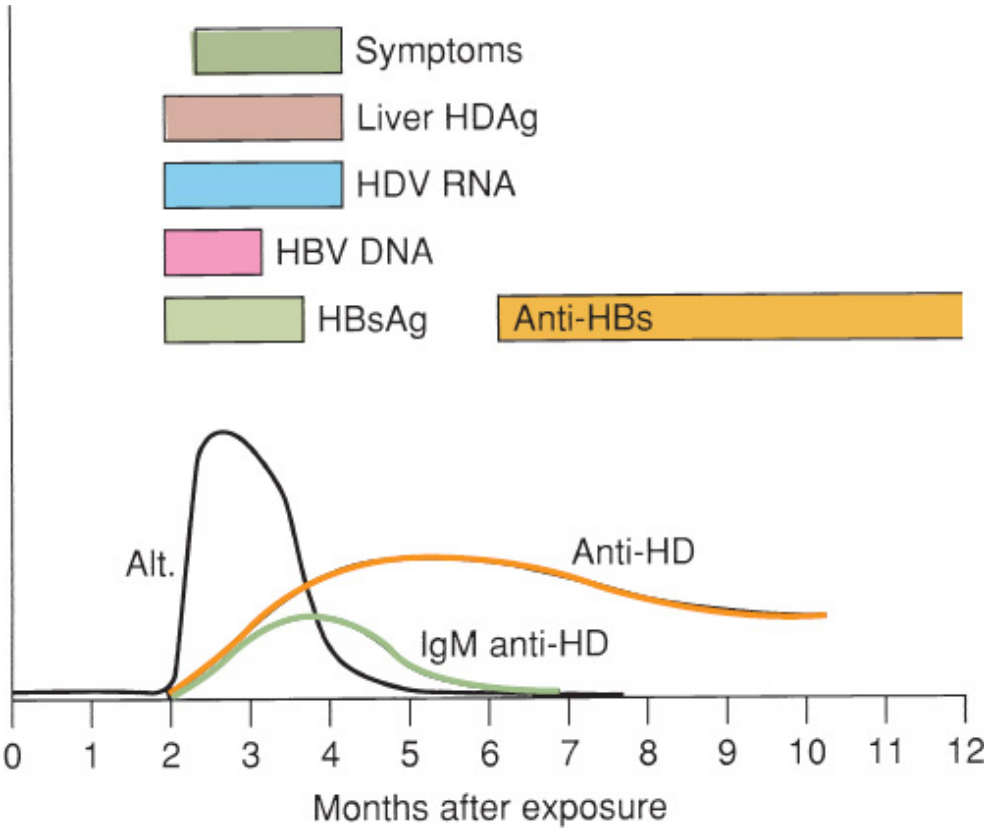

Figure 58.8 Synchronous infection with hepatitis B virus and hepatitis D virus.

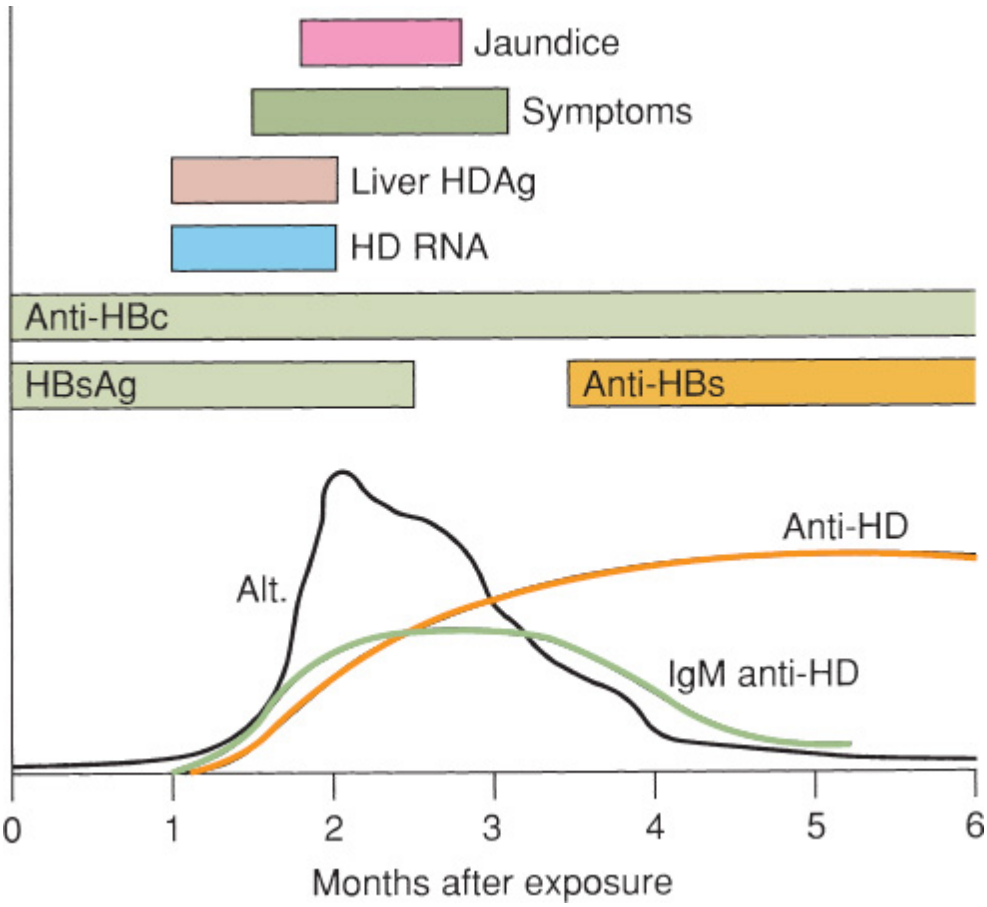

Figure 58.9 Superinfection of chronic hepatitis B carrier with hepatitis D.

Treatment

Treatment and prevention of HDV mirrors that seen with HBV and HCV. IFN is the treatment of choice and may be administered for up to 12 months. Mainstay prevention is dependent on HBV vaccination.

HEPATITIS E VIRUS

Epidemiology/Risk Factors for Transmission

Hepatitis E is one of the least diagnosed etiologies of acute viral hepatitis. There are an estimated 20 million new infections diagnosed every year according to the World Health Organization (WHO) and the virus is

distributed globally. Transmission occurs through the ingestion of fecally contaminated food and water, blood transfusions, and perinatal routes.

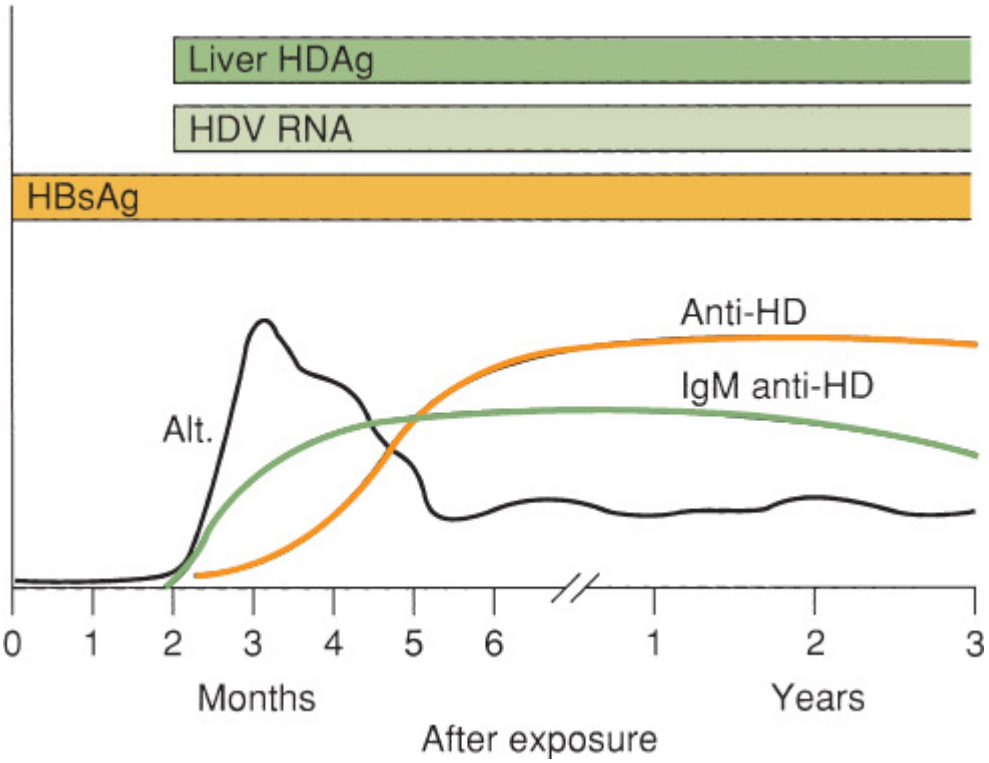

Figure 58.10 Clinical course of chronic hepatitis D infection.

Clinical Features

Most patients remain asymptomatic or develop mild symptoms such as jaundice, malaise, nausea, vomiting, and abdominal pain. The incubation period ranges from 15 to 60 days. In addition, several extrahepatic manifestations have been described including thyroiditis, hematologic anomalies, and neurologic diseases. Common biochemical findings are transaminitis and hyperbilirubinemia with resolution occurring 1 to 6 weeks following onset of the disease. While the disease is generally self-limiting, 0.5% to 4% of infected individuals may progress to fulminant hepatic failure, more likely affecting pregnant women, malnourished patients and those with underlying liver disease.[28]

Treatment

Management of hepatitis E virus (HEV) is mainly supportive, particularly in the acute phase. The disease may persist in immunocompromised patients (transplant recipients) and a 12-week course of antiviral therapy (ribavirin) can be considered. General precautions should be taken when travelling to endemic regions. A vaccine has been developed with a 96% protective efficacy over 12 months, however, this is not widely available.[29]

Cytomegalovirus

Cytomegalovirus (CMV) is a generally asymptomatic disease causing mild nonspecific symptoms in immunocompetent persons. Transmission can occur through close and/or sexual contact, blood exposure, and infected transplanted organs. Hepatic manifestations include mild hepatitis presenting as subclinical transaminitis in infected hosts, and may progress to ALF in immunosuppressed persons. Viral seroprevalence ranges from 30% to 100% and is dependent on age and ethnicity.[30] Infection is lifelong due to the latency of the virus and can be detected in up to 70% of individuals in U.S. cities. The diagnosis is confirmed by the identification of CMV-specific antibodies in serum samples. However, one limitation of this diagnostic technique is that IgM-specific CMV antibodies may be present for up to 6 months making it difficult to distinguish current infection from prior exposure. In addition, CMV antigenemia and PCR to detect CMV DNA have made diagnosis rapid. Histopathologic analysis with a liver biopsy may be necessary to further establish hepatitis.

Treatment is based on clinical course and viral load. The clinical effectiveness of antiviral therapies in immunocompetent persons is unclear and the disease is largely self-limiting. First-line treatment with ganciclovir or valganciclovir should be considered in immunocompromised persons. Treatment should be administered for a minimum 2 to 3 weeks or 2 to 3 months in high-risk patients.[30]

Epstein–Barr Virus

Epstein–Barr virus (EBV) is largely known as an important agent in infectious mononucleosis, but most infections are asymptomatic. The disease is spread through close contact and global seroprevalence rates are over

90%.[31] Deranged liver function tests are not uncommon and are generally self-resolving. In rare instances acute symptomatic hepatitis occurs as a sequelae of infectious mononucleosis. The presence of jaundice may reflect either more severe hepatitis or an associated hemolytic anemia and is present in less than 5% of infected persons.[32] Leukocytosis is usually present, with the presence of atypical lymphocytes being a hallmark. Detection of heterophile antibodies, or the "monospot test" is highly specific but can be negative during the first week of clinical illness. This can be repeated at a later date; however, if the test remains negative, the diagnosis can be further investigated through EBV-specific antibody testing. Treatment is largely supportive to alleviate symptoms. Acyclovir has been considered in the past, however the clinical benefit has not been conclusively established and is not generally recommended.[33]

Herpes Simplex Virus

Acute hepatitis is a rare complication of herpes simplex virus (HSV) infection, although both HSV-1 and HSV-2 have been described as causative agents. Hepatic involvement commonly occurs in immunocompromised patients, neonates, pregnant women, and patients taking steroids. The prevalence of antibodies to HSV-1 is around 75% in most populations and around 20% to HSV-2. Clinical manifestations include high fever, anorexia with nausea, abdominal pain, leucopenia, and coagulopathy.[34] Mortality rates over 70% have been described when the condition occurs and male gender, age over 40 years, coagulopathy, encephalopathy, and the absence of viral treatment are considered increased risks.[35] The diagnosis can be confirmed on histopathology demonstrating diffuse eosinophilic intranuclear inclusion bodies, multinucleated cells, widespread necrosis, and inflammation. Treatment with intravenous acyclovir should be initiated prior to confirmation of etiology given that progression of disease is extremely rapid and lethal.

Varicella Zoster Virus

Varicella zoster virus (VZV) infection is common and frequently presents as primary varicella in children. Hepatitis secondary to VZV infection is rare

but can be deadly, especially in immunocompromised individuals. In these individuals, clinical manifestations include fever, abdominal pain, and rash.[35] Fulminant liver failure may ensue. Reye syndrome may also develop from VZV infection in children leading to progressive encephalopathy and hepatic dysfunction. The diagnosis of VZV hepatitis can be distinguished from other diagnoses and confirmed on a liver biopsy. Disseminated VZV requires prompt treatment with antiviral medication usually in the form of acyclovir to decrease the high mortality rate. Varicella zoster immune globin should also be considered after exposure to the virus in immunocompromised or pregnant patients who lack immunity to VZV combined with strict contact precautions.

ACUTE LIVER FAILURE

Definition

2 ALF is a generally uncommon condition consisting of a rapid deterioration in liver function in the form of coagulopathy (INR >1.5) and hepatic encephalopathy in the absence of pre-existing liver disease. Incidence is low and the condition affects approximately 2,000 individuals in the United States per annum, but can be fatal if untreated. In 2012, a systematic review identified 41 different definitions for ALF, with onset of liver disease and interval between hepatic encephalopathy a largely differentiating factor.[36] Three specific time frames are applied to categorize and distinguish the different forms of ALF; hyperacute (<7 days), acute (7 to 21 days), or subacute (21 days to 26 weeks). The European Association for the Study of the Liver (EASL) characterizes disease duration beyond 28 weeks and before the onset of encephalopathy as chronic liver disease.[37] The most recent definition in hepatic failure nomenclature is “acute-on-chronic” liver failure which is characterized by an acute deterioration in liver function in patients with underlying chronic liver disease.[38,39]

Diagnosis

ALF can be diagnosed and confirmed using a variety of mediums. Following a thorough history and examination assessing for various stigmata of disease, initial testing includes serum liver function tests. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are released when hepatocytes are damaged or killed. ALP is released when the biliary epithelium is injured such as in instances of biliary obstruction or cholangitis. γ-Glutamyltransferase is expressed by both hepatocytes and biliary epithelium and can be elevated in all conditions impacting liver function (**Table 58.2**).[40] A series of standard tests are considered in every patient and when the diagnosis still remains unclear, a liver biopsy is performed provided there are no absolute contraindications.

Table 58.2 Management in Acute Liver Failure: Initial Laboratory Evaluations
Serum chemistries Sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphate, glucose, BUN, creatinine, amylase, lipase
Hepatic panel AST, ALT, alkaline phosphatase, total bilirubin, albumin
Prothrombin time/INR
Complete blood count
Arterial blood gas, lactate, ammonia
Toxicology screen
Viral hepatitis serologies Anti-HAV IgM, Hep B surface Ag, Anti-HBV core IgM, anti-HCV, anti-HEV IgM (if indicated)
Anti-VZV IgM, Anti-HSV IgM
Autoimmune markers ANA, ASMA, IgG levels, SPEP
Pregnancy test
Serum ceruloplasmin level and 24-hr urine copper collection (if Wilson disease is suspected)

Ag, antigen; ALT, alanine aminotransferase; ANA, antinuclear antibody; ASMA, anti–smooth muscle antibody; AST, aspartate aminotransferase; BUN, blood urea nitrogen; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; IgM, immunoglobulin M; INR, international normalized ratio; SPEP, serum protein electrophoresis; VZV, varicella zoster virus.

Etiology

3 The cause of liver failure influences the management approach and prognosis and for this reason ever effort is made to establish the correct underlying cause. ALF can arise from a variety of causes. 4 In the United

States, United Kingdom, and Australia, acetaminophen overdose is the most common cause, accounting for 45.7% to 65.4% of all cases. In Asia, viral hepatitis contributes to the majority of cases.[41] The cause is unclear in 15% of patients.

Drug-Induced Liver Injury

Acetaminophen hepatotoxicity occurs in a dose-dependent manner which can occur following consumption of a single dose or staggered over multiple time points.[42] The former is more commonly seen in suicide attempts rather than instances of therapeutic misadventure.[43] ALF more commonly develops in malnourished patients, a history of alcoholism, or in late presenting cases.[42] Full hepatic recovery is seen in 93% of patients and patients are less likely to proceed to poor outcomes than in instances of non–paracetamol-related hepatic failure.[44]

In contrast to the dose-dependent interactions of acetaminophen, idiosyncratic drug reactions are dose independent and generally occur within 6 months of drug treatment.[45] Stevens–Johnson syndrome caused by phenytoin, amoxicillin-clavulanate, carbamazepine, or halothane is a form of hypersensitivity idiosyncratic responses, while isoniazid, valproate, and amiodarone mainly cause metabolic idiosyncratic reactions.

Viral Hepatitis

Hepatitis A virus infection is generally mild accounting for less than 3% of ALF cases. Up to 70% of cases recover completely with little to no intervention and a better overall outcome is seen than in other causes of viral hepatitis.[46,47] HBV accounts for 8% of all cases of ALF in Europe and the United States.[43] The majority of cases of hepatitis B are caused by new infection while the remaining cases of ALF may develop following reactivation of previously in active disease.[43,48] Hepatitis C does not confer a significant risk of ALF in the absence of hepatitis B coinfection.[49] Similarly, HDV infection can lead to ALF in the setting of concurrent hepatitis B coinfection or pre-existing chronic hepatitis B infection.[50,51] HEV is a worldwide infection and can cause fulminant hepatic failure in specific high-risk groups.[52] Hepatitis E infection accounts for 20% to 40% of ALF

cases in developing countries but is a rare case in Western societies.[53,54] VZV, HSV, and CMV are other rare viral causes (see previous sections).

Other

Other causes of ALF include heat stroke, pregnancy-related injuries (HELLP), metabolic/autoimmune diseases, and hepatic ischemia.[42,43]

Clinical Features, Management, and Treatment

The initial symptoms of ALF are generally nonspecific and may include right upper quadrant pain, nausea, malaise, fatigue, and vomiting.[55] Encephalopathy is one of the hallmarks of ALF and is graded from I to IV (**Table 58.3**). Cerebral edema accompanies 25% to 35% of patients with grade III and 75% of patients with grade IV.[56] Altered mental status in the form of lethargy, confusion, or disturbed sleep may eventually progress to a coma. As liver failure worsens, so does jaundice, transaminase and prothrombin time elevations, and thrombocytopenia. Acute kidney injury occurs in approximately 30% to 70% of patients.[57] Other common electrolyte derangements are hypophosphatemia, hypokalemia, hypomagnesemia, and hypoglycemia.

General management of patients should be in specialist units with liver transplantation services. Up to 40% of patients recover spontaneously. Serial laboratory tests are essential to monitor the patient's clinical course and for the development of any complications. Hemodynamic stability needs to be accurately followed and deviations need prompt responses. Intravascular volume depletion and a low systemic vascular resistance are likely the result of decreased oral intake and fluid extravasation. Hypotension can usually resolve with normal saline and in cases of acidosis, half-normal saline can be considered.[43] In cases of hypoglycemia, dextrose can be added to carefully titrated fluid regimens, avoiding the risk of overhydration that may worse cerebral edema. Mean arterial pressure should be maintained at least 75 mm Hg and if this is not achievable with sole fluid management; norepinephrine with or without vasopressin can be used.[58]

Acetaminophen toxicity can be treated with the administration of N-acetylcysteine, which may also be beneficial in other causes of ALF.[59] Patients with grade III or IV encephalopathy are at a high risk for developing cerebral edema and intracranial pressure monitoring could be utilized to guide treatment. Elevating the head of the bed and prophylactic hypertonic saline should be considered in high-risk patients. In cases of elevated intracranial pressure, mannitol therapy is typically first-line treatment to maintain intracranial pressures below 20 to 25 mm Hg and cerebral perfusion pressures above 50 to 60 mm Hg.[60] Hyperventilation can be considered in patients, although the clinical benefits are transient. It may, however, be effective in patients with impending herniation. Coagulopathy should be monitored and patients should receive stress ulcer prophylaxis to reduce potential gastrointestinal bleeding.

Table 58.3 Stages of Hepatic Encephalopathy

Stage	Clinical Signs
I	Mild confusion, slurred speech, disordered sleep
II	Moderate confusion, lethargy, disorientation
III	Marked confusion, sleeping but arousable, slurred speech
IV	Coma

Table 58.4 King's College Criteria of Poor Prognostic Indicators

Acetaminophen-induced ALF: Arterial pH <7.3 irrespective of coma grade *OR all of the following:* INR >6.5, creatinine >3.4 mg/dL (300 µmol/L), grade III/IV encephalopathy
Non–acetaminophen-induced ALF: INR >6.5 *OR any three of the following:* Age <10 or >40, drug toxicity or undetermined etiology, jaundice >7 days before encephalopathy, INR >3.5, bilirubin >17 mg/dL (300 µmol/L)

ALF, acute liver failure; INR, international normalized ratio.

Liver Transplantation

5 Liver transplantation is the only definitive cure in the setting of irreversible liver failure. Identifying which patients are likely to benefit from liver transplantation and which are likely to spontaneously recover is an important and challenging step. Spontaneous recovery depends on several factors including patient age, degree of encephalopathy, and disease etiology. The King's College criteria are an effective tool applied to determine prognosis in acetaminophen-induced fulminant hepatic failure and is used to predict survival outcomes for alternative etiologies and as an adjunct to prediction tools when proposing candidacy for liver transplantation.[59] Positive predictive values for acetaminophen and non–acetaminophen-induced ALF are 84% and 98%, respectively. Negative predictive values are 86% and 82% for acetaminophen and non–acetaminophen-induced ALF (**Table 58.4**).[61] The model for end-stage liver disease (MELD) system is another validated scoring system commonly used for chronic liver disease severity scoring. In terms of ALF, the King's College criteria appear more specific while the MELD score is more sensitive in predicting mortality. MELD scores greater than 30.5 predict a need for transplantation.[62]

Life Support Systems

Artificial liver support systems have been proposed in an effort to delay or preclude the need for transplantation. The two major categories are biologic and nonbiologic support systems. The mostly commonly investigated systems are the molecular adsorbents recirculating system (MARS) and the Prometheus system. Both systems are based on the removal of albumin-bound toxins. Results in ALF have been variable, and the devices are not widely available outside of clinical trials.

Similarly, bioartificial systems have yet to break into routine clinical practice. In this setting, a patient's blood is perfused through a bioreactor of human or porcine hepatocytes and undergoes detoxification.[63] While these emerging technologies have given some hope and promise to the transplant community, they are still mainly utilized in an experimental setting and liver transplantation remains the only curative option for ALF.

Prognosis

Overall survival rates for ALF are greater than 60% and up to 55% can survive without transplantation.[64] Hepatic encephalopathy development and progression is a key prognostic indicator. However, prognosis can vary between etiologic agents and appears more favorable in acetaminophen-associated toxicity than alternative causes. Mortality also increases with the occurrence of cerebral edema, renal failure, coagulopathy, infection, and mechanical ventilation. Additional indicators of poor prognosis have been further developed in King's College in London to include the presence of three of the following: age less than 11 and greater than 40 years, jaundice present longer than 1 week before encephalopathy occurrence, serum bilirubin greater than 300 μmol/L, prothrombin time greater than 50 seconds, fulminant hepatitis secondary to non–A, B, or C virus, idiosyncratic drug reactions, and halothothane hepatitis.[65]

QUIZ

1. Which of the following is the most accurate regarding the presentation of patients with liver abscesses?

a. Fever is the most common feature of pyogenic liver abscesses caused by bacterial infections.
b. Blood cultures are positive in over 95% of patients.
c. Abdominal ultrasound is rarely diagnostic and always requires an additional radiologic modality to support the diagnosis.
d. Multiple hepatic abscesses is a typical feature of candida infection.

2. The King's College Criteria require the presence of an INR > 6.5 or at least three other variables prior to determining patient candidacy for liver transplantation in nonacetaminophen causes of ALF. Which of the following is not a recognized requirement?

a. Duration of jaundice before onset of encephalopathy >7 days
b. Drug toxicity or undetermined etiology
c. Bilirubin >17 mg/dL (300 µmol/L)
d. Age <10 or >40
e. Hyponatremia

3. Which of the following viruses is likely to proceed to chronic hepatic failure?

a. EBV
b. Hepatitis B
c. Hepatitis C
d. Hepatitis D
e. VZV

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59

Cirrhosis and Portal Hypertension

Russell N. Wesson and Andrew M. Cameron

Key Points

1 Chronic injury and inflammation due to ongoing oxidative stress is a common pathway leading to cirrhosis, regardless of etiology. Removal of the inciting agent can stop progression of disease.

2 Acetaldehyde mediates injury in alcohol-induced liver disease.

3 Nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH) is associated with obesity, hyperlipidemia, and non–insulin-dependent diabetes. It is increasing in incidence and results in a spectrum of change from fatty infiltration to inflammation and cirrhosis.

4 Viral hepatitis is the most common cause of cirrhosis worldwide, accounting for at least 50% of cases. All genotypes of Hepatitis C can now be cured with direct-acting antivirals (DAAs). Hepatitis B is treatable with antivirals.

5 Budd–Chiari syndrome (BCS) is a rare disease characterized by obstruction of the hepatic veins by webs or membranes (most commonly in Asia and Africa) or thrombosis secondary to hypercoagulable states and neoplasms (most commonly in the West).

6 Hepatorenal syndrome (HRS) is a complication of cirrhosis, usually associated with ascites, characterized by progressive renal failure in the absence of intrinsic renal disease.

7 Hepatic encephalopathy is a neuropsychiatric syndrome occurring in the setting of liver disease. It is characterized by variable clinical manifestations ranging from subtle personality changes and sleep pattern derangement to confusion, lethargy, and coma.

8 Portal hypertension is defined as a portal pressure elevated above the normal range of 5 to 8 mm Hg. It is an important complication of cirrhosis (hepatic) and can also occur after portal vein thrombosis (prehepatic), or hepatic venous obstruction (posthepatic). Portal hypertension is responsible for the development of gastroesophageal varices and bleeding.

9 Important scoring systems include the Child–Turcotte–Pugh score which incorporates clinical and laboratory data as a means to assess

the functional status of the liver, estimate hepatic reserve, and predict morbidity and mortality of liver disease. The model for end-stage liver disease-sodium (MELD-Na) score is a highly reliable prognostic marker for cirrhosis, is calculated from standard laboratory tests, and has replaced the Child–Turcotte–Pugh score in liver transplant candidate stratification.

10 Transjugular intrahepatic portosystemic shunt (TIPS) has become first-line therapy for refractory or recurrent bleeding esophageal varices.

11 Surgical interventions for the treatment of variceal bleeding include liver transplantation, shunt procedures, and rarely performed devascularization procedures. Liver transplantation is the definitive treatment for decompensated cirrhosis.

12 Spontaneous bacterial peritonitis (SBP) is a potentially lethal infectious complication of cirrhosis with ascites. It occurs in up to 10% of patients.

CIRRHOSIS

Background and Definition

Cirrhosis is a chronic condition with a high mortality. It constitutes the fifth leading cause of adult deaths and ranks eighth in economic cost among the major illnesses in the United States.[1] A majority of adults with cirrhosis are unaware they have liver disease.

Described in the Greek myth of Prometheus, the ability of the liver to regenerate is legendary. The development of cirrhosis marks the beginning of a disease characterized by a dramatic decrease in the ability of the liver to function effectively and to recover from insults. Cirrhosis is the pathologic end result of repeated, chronic insults to the liver with subsequent repair. This continued cycle causes deranged hepatic architecture defined histologically by marked fibrosis, destruction of vascular and biliary elements with regeneration, and nodule formation (**Fig. 59.1**). It results in a

scarred, distorted nodular cirrhotic liver. Consequences include diminished hepatic function and reserve, portal hypertension, and complications of portal hypertension (**Table 59.1**). Portal hypertension can be prehepatic, intrahepatic, or posthepatic in origin. Importantly, the chronic, ongoing inflammation resulting in cirrhosis is carcinogenic, and hepatocellular carcinoma (HCC) may arise in livers affected by cirrhosis. HCC may occur in the absence of cirrhosis. The complications and causes of cirrhosis may be managed medically or via interventional radiologic techniques, and this may halt progression, improve quality of life, and increase survival. Liver transplantation, however, is the only definitive cure for decompensated cirrhosis at the current time.

1 Pathophysiology

Cirrhosis is caused by a range of pathologic entities. These include viral hepatitis, alcohol, metabolic disorders, drug toxicity, and biliary obstruction, among others (**Table 59.2**). These lead to injury, hepatocyte death, chronic inflammation, fibrosis, and subsequent loss of architectural integrity. The normal regenerative capacity of the liver is overcome, and there is resulting structural distortion. Cellular and molecular mechanisms underlying this shift from physiologic recovery to pathologic distortion after healing continue to be studied, and pathways of hepatic fibrogenesis and cirrhosis remain a central area of investigation in liver biology.[2,3] Significant progress in our understanding of the evolution of liver fibrosis, which ends with cirrhosis, has been gained in recent years.

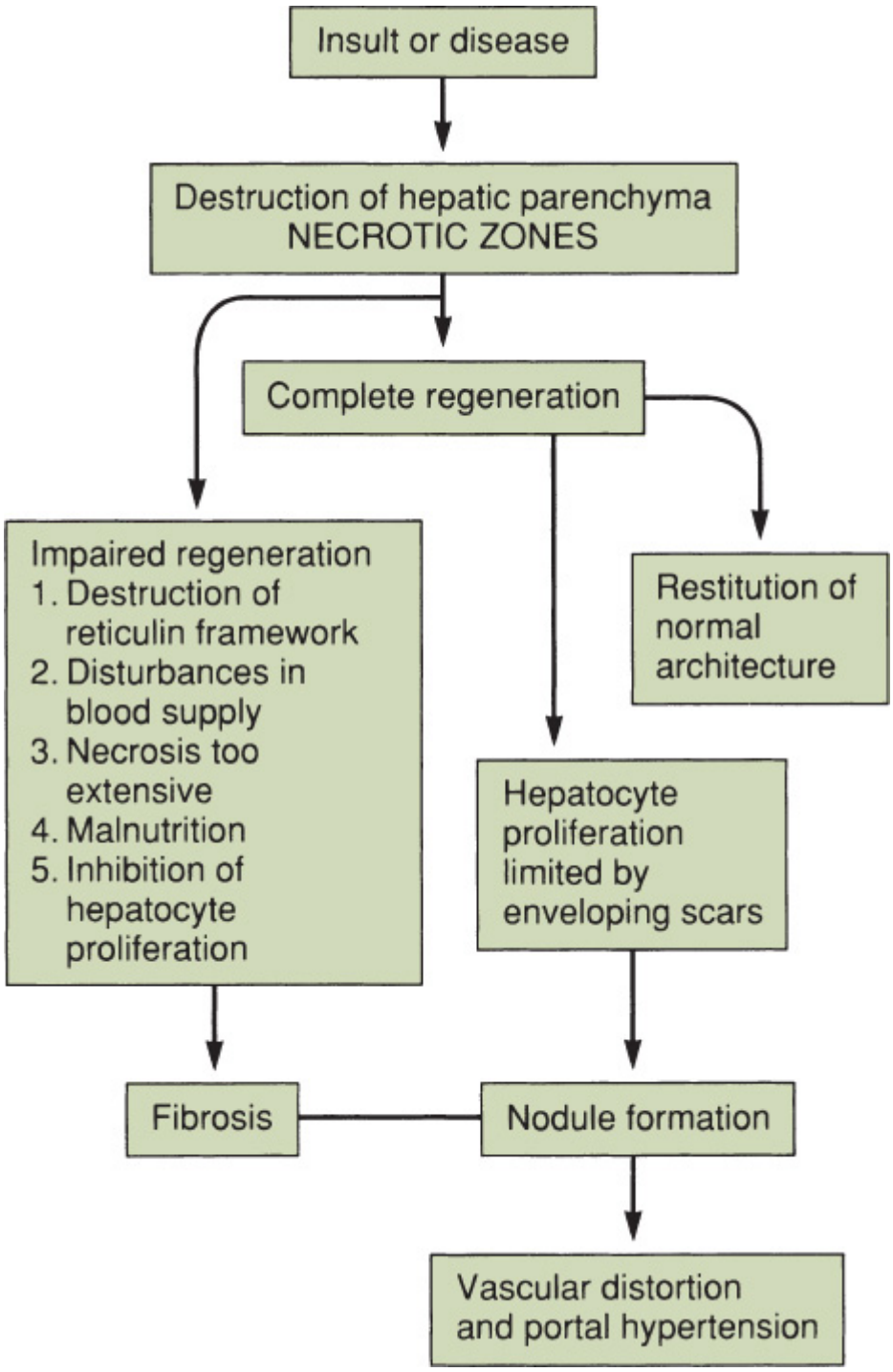

Figure 59.1 Evolution of cirrhosis. Fibrosis develops in nonregenerative necrotic areas, producing scars. The pattern of nodularity and scars reflects the type of response to injury (e.g., uniform vs. nonuniform necrosis) and the extent of injury.

Oxidative stress and chronic inflammation appear to be the final common pathway in the development of fibrosis and cirrhosis. Fibrosis is a wound

healing response in which damaged regions of liver are encapsulated by an extracellular matrix or scar. In chronic liver injury, it develops at variable rates depending in part upon the cause of liver disease and host factors. Fibrosis develops in regions where injury is most severe. For example, pericentral injury (perivenular fibrosis) is a hallmark of alcoholic hepatitis and will progress to panlobular cirrhosis if injury is ongoing.[4] As the liver becomes fibrotic, significant qualitative and quantitative changes occur in the extracellular matrix.[5] A low-density matrix is replaced by a high-density interstitial type matrix with consequences for the function of hepatocytes, hepatic stellate cells (HSCs), and endothelial cells. The high-density matrix activates HSCs leading to loss of hepatocyte microvilli and disappearance of endothelial fenestrations impairing solute transport from sinusoid to hepatocyte.[6]

Table 59.1 Major Complications of Cirrhosis

Portal hypertension and variceal hemorrhage
Ascites and volume overload
Spontaneous bacterial peritonitis
Hepatic encephalopathy
Hepatocellular carcinoma
Hepatorenal syndrome
Hepatopulmonary syndrome

Table 59.2 Causes of Cirrhosis

Most Common Causes (Developed Countries)
Alcohol
Chronic viral hepatitis (hepatitis B and C)
Hemochromatosis
Nonalcoholic fatty liver disease
Less Common Causes
Primary and secondary biliary cirrhosis
Primary sclerosing cholangitis
Veno-occlusive disease
Wilson's disease
Autoimmune hepatitis
Infection (brucellosis, syphilis, echinococcosis)
Drugs and toxins (e.g., methotrexate, isoniazid)
α_1-Antitrypsin deficiency
Cystic fibrosis
Glycogen storage disease
Other metabolic diseases
Sarcoidosis
Copper
Small-bowel bypass
Right-sided heart failure
Hereditary hemorrhagic telangiectasia
Idiopathic

HSCs (previously called the lipocytes, Ito, fat-storing, or perisinusoidal cells) play a central role in fibrogenesis and development of cirrhosis. Activation of HSCs occurs with ongoing inflammation, hepatocyte stress, and death (either via apoptosis or necrosis). These cells are located in the space of Disse between hepatocytes and sinusoidal endothelial cells (**Fig. 59.2**).[7] HSCs, which are normally quiescent and store vitamin A, appear to be the key mediator in the development of fibrosis and are the primary source of

extracellular matrix both in the normal and fibrotic liver.[8] Activated HSCs increase expression of "fibril-forming" collagen types I, III, and V[9] as well as heparan, dermatan, chondroitin sulfate,[10] laminin,[11] and fibronectin.[12]

A number of different stimuli result in initiation and perpetuation of the activation of HSCs. Paracrine stimulation by all neighboring cell types, including sinusoidal endothelium, Kupffer cells, hepatocytes, and platelets initiate activation. Mediators include transforming growth factor beta-1 (TGF-β1), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF).[13] Apoptotic bodies (derived from hepatocytes) play a major role in the activation of HSCs and Kupffer cells.[14] Reactive oxygen species (ROS) are important in activating HSCs and are generated through lipid peroxidation of hepatocytes, macrophages, HSCs, and other cells.[15,16] In alcoholic and nonalcoholic steatohepatitis (NASH), ROS generation in hepatocytes results from induction of cytochrome P450 2E1, leading to pericentral, zone 3 injury.[17,18]

Activation of HSCs leads to further elaboration of proinflammatory and profibrogenic cytokines TGF-β1 and PDGF, creating a self-sustaining cycle.[13,14,19–22] TGF-β1 is derived from both paracrine and autocrine sources and remains the classic fibrogenic cytokine, with downstream signaling converging on Smad proteins resulting in HSC activation.[23,24] Activation of HSCs continues to be explored with roles for toll-like receptors (TLR4) being discovered, direct effects of hepatitis C on HSCs, and effects of hepatitis B on immune cells contributing to HSC activation. Ultimately, degradation and remodeling of the extracellular matrix by matrix metalloproteinases produced by HSCs as well as Kupffer cells occurs.[25,26] Importantly, regression of fibrosis can occur under the influence of certain macrophage subsets as well as dendritic cells. An increasing understanding of the role of inflammatory and immunomodulatory cells in liver disease may have led the way to new therapies in the future.[27–31]

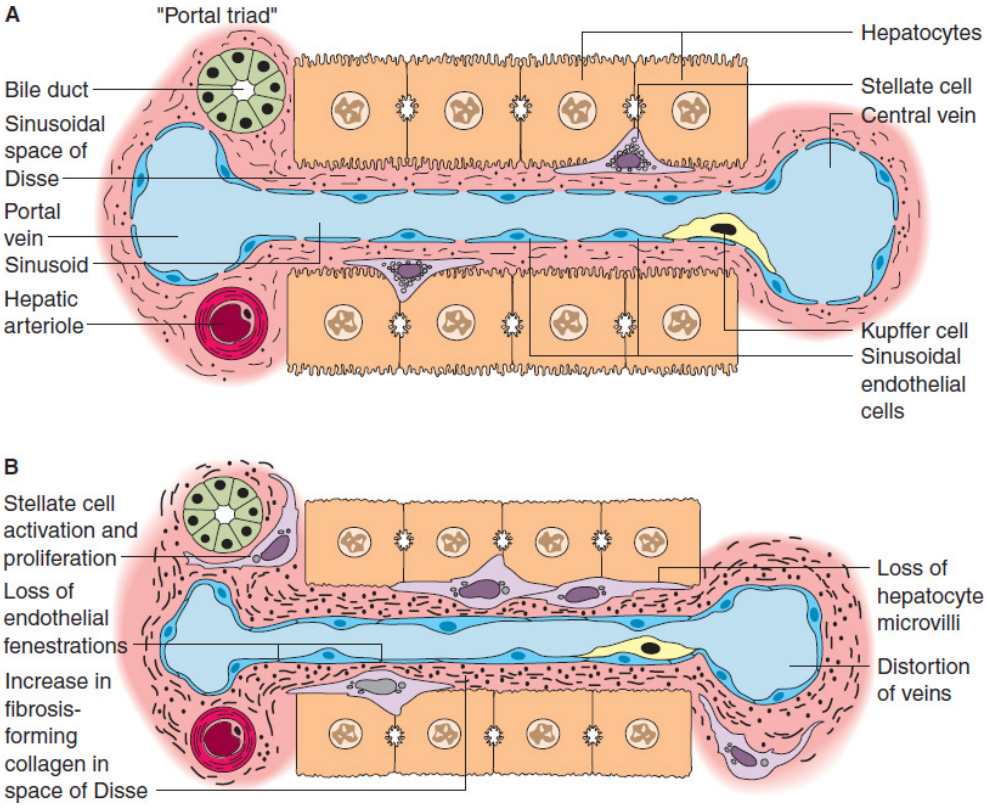

Figure 59.2 Matrix and cellular alterations in hepatic fibrosis. **A:** In normal liver, a modest amount of low-density matrix is present in the subendothelial space of Disse. **B:** In the fibrotic liver, the accumulation of fibril-forming matrix in this region leads to "capillarization" of the sinusoid and functional changes in all neighboring cell types.

Ultimately fibrosis causes architectural and functional disruption of the hepatic acinus. Collagen deposition and extracellular matrix synthesis leads to thickening of the space of Disse. "Capillarization" develops with loss of the fenestrated architecture of the sinusoidal endothelium.[32] This loss of fenestration may be an essential component of hepatocellular dysfunction in cirrhosis, preventing the normal flow of nutrients to hepatocytes and increasing vascular resistance.[33] In addition, endothelial and stellate cells produce endothelin-1, a potent vasoconstrictor, which causes contraction of the myofilaments within HSCs, influencing blood flow to injured areas and contributing to portal hypertension.[34] Fibrosis is reversible early if the inciting agents are removed. Sustained injury leads to irreversibility and progress to cirrhosis.

Treatment of Fibrosis

The point at which fibrosis becomes inexorable is unknown. Dense cirrhosis with nodule formation, portal hypertension, and early liver failure is irreversible, but less-advanced lesions can improve if injury is removed or possibly with therapy. In studies of hepatitis B, hepatitis C, and NASH, up to 70% of patients had reversal of early cirrhosis and fibrosis following successful antiviral therapies, and improvements in NASH and fibrosis after bariatric surgery.[35–37] Growing attention has been given to approaches that might disconnect hepatic injury from the inexorable path of fibrosis.[41] Targeting HSCs and mediators of fibrogenesis may complement therapies that treat the inciting factors of liver injury. **Removal of injurious stimuli** is most effective when initiated early. Examples include the removal of excess iron or copper in hemochromatosis or Wilson's disease, respectively. The potential success of treatment of HBV with **adefovir or entecavir**, treatment of delta hepatitis with interferon therapy, and the success of **direct-acting antiviral** (DAA) therapy against HCV are additional examples.

Suppression of hepatic inflammation has a role to play in some settings and is an active area of investigation. **Corticosteroids** are useful in many inflammatory liver diseases, in particular against autoimmune hepatitis. Duration of use is limited by the extensive side effects associated with prolonged use. **Ursodeoxycholic** acid has clear efficacy in primary biliary cirrhosis.[38,39]

Immune modulation, use of hepatoprotectants (such as hepatocyte growth factor), and the use of farnesoid X receptor ligands hold promise for future investigation. Bile acids such as obeticholic acid and chenodeoxycholic acid act as ligands to farnesoid X receptor. This nuclear receptor transcription factor downregulates HSC activation and contractility and may have other hepatoprotective effects. Cannabinoids and the cannabinoid receptors CB1 and CB2 are involved in fibrogenesis and have emerged as an attractive pathway for antagonizing hepatic fibrosis.

Among the most promising agents currently receiving the greatest attention in the treatment of fibrosis are the antioxidants.[14] A large randomized controlled trial (RCT) studied vitamin E as a therapy to suppress fibrogenesis. It showed benefit in reducing inflammation in adults, but not children.[40,41] N-acetylcysteine, metformin, and silymarin (a natural component of milk thistle that belongs to a group of flavonoid compounds) have been explored without clear evidence of clinical efficacy. Interruption

of the renin–angiotensin system using angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, interference with TGF-beta signaling, and antagonism of endothelin receptors hold promise for decreasing fibrogenesis, but require further investigation.

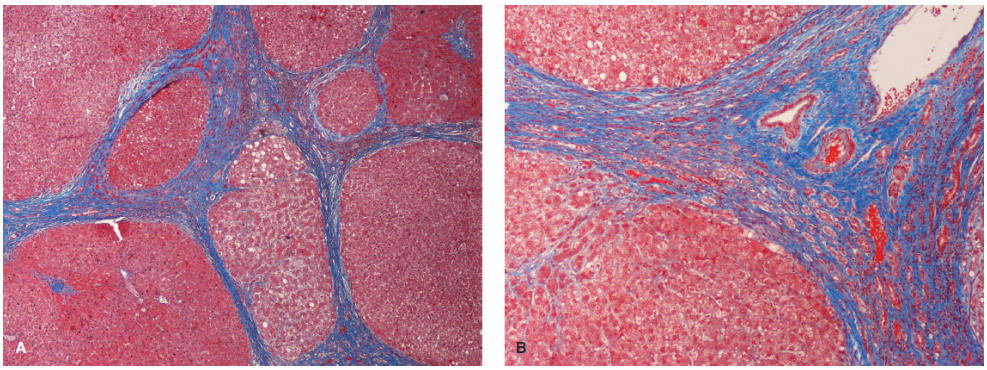

Figure 59.3 Photomicrographs A of cirrhotic liver tissue, showing irregular nodules of regenerating hepatocytes surrounded by dense fibrosis. **A:** Trichrome stain 2× magnification. **B:** Higher magnification (10×) showing portal triad surrounded by fibrosis. (Courtesy of Dr Robert Anders, Department of Pathology, Johns Hopkins Hospital.)

Etiology

Historically, cirrhosis has been divided into micronodular, macronodular, and mixed patterns. However, this World Health Organization (WHO) classification (created in 1977) has little utility in terms of defining etiology due to its low specificity (**Fig. 59.3**).

Alcohol

2 Alcohol abuse is common worldwide, with an estimated prevalence of 18% among adults in the United States. Excessive alcohol intake is associated with a range of liver disease, from fatty liver disease, alcoholic steatohepatitis, and ultimately cirrhosis and HCC. Cirrhosis due to alcohol is the second leading indication for liver transplantation overall, accounting for 19% of all liver transplants in Europe and 30% in the United States.[42,43] Once hepatic decompensation develops, the expected 5-year transplant-free survival rate is 60% for those who stop drinking alcohol and 30% if drinking continues.

Cirrhosis develops in 10% to 30% of heavy drinkers.[44] Consumption of at least 30 g of alcohol per day in women and 50 g of alcohol per day in men over at least 5 years is considered to the minimum threshold alcohol intake for cirrhosis to develop.[45] Why cirrhosis develops in some heavy drinkers but not others is unclear. Genetic predisposition, nutritional effects, concomitant drug use, and viral infection likely interact with alcohol abuse to result in cirrhosis. Advanced disease carries a poor prognosis: more than half of alcoholics with cirrhosis and two-thirds of patients with alcoholic hepatitis and cirrhosis die within 4 years of diagnosis.[46]

Histologic findings: Classically micronodular cirrhosis, the histology of alcoholic liver disease typically begins with the appearance of macrosteatosis of fatty liver disease. This progresses to alcoholic steatohepatitis when inflammation (neutrophil infiltration, generally in association with an elevated peripheral neutrophil count) and necrosis is present. Megamitochondria and Mallory–Denk bodies (eosinophilic accumulations of intermediate filaments with cytokeratin proteins, previously termed Mallory hyaline or Mallory bodies) are also characteristic. As disease duration and toxin exposure progress, fibrosis appears and progresses with architectural distortion occurring.

Alcoholic liver disease has long been known to be associated with consequences of oxidative stress in the liver with failure of homeostatic mechanisms.[47] The toxicity of alcohol is mediated through its metabolic product, acetaldehyde. Alcohol dehydrogenases are isoenzymes that catalyze the oxidation of alcohol (ethanol) to acetaldehyde. ALDH are located predominantly within the cytoplasm of hepatocytes. The microsomal ethanol oxidizing system (MEOS) cytochrome P450 2E1 (CYP2E1) is also responsible for approximately 10% of ethanol oxidation to acetaldehyde. Although alcohol may directly activate HSCs, the key mediator in alcohol-induced liver disease is acetaldehyde. CYP2E1 is largely in the perivenular/centrilobular zone 3 of the hepatic acinus. Zone 3 is also an area of relative hypoxia due of its distance from portal venous and hepatic arterial inflow, and levels of antioxidants such as glutathione are lowest in this zone. Activity of aldehyde dehydrogenases is also lower in zone 3. These factors contribute to the characteristic perivenular location of injury and histologic changes present in alcohol-induced liver disease.

Mechanisms of injury of acetaldehyde include the peroxidation of lipids in cell membrane. Macrosteatosis and the characteristic "ballooning degeneration" of alcohol-induced liver disease results. Acetaldehyde also increases the permeability of the intestinal barrier,[48,49] allowing delivery of bacterial endotoxin (LPS) to the liver. Kupffer cells activation by LPS via TLR4 may set off the inflammatory cascade responsible for the development of alcoholic liver disease.[50] The pathogenesis of alcoholic liver disease continues to be investigated, with roles for tumor necrosis factor-alpha (TNF-α), cyclo-oxygenase 2, dietary fat, oxidative stress, development of antigenic adducts (acetaldehyde binding to proteins creating antigenic adducts) among others being explored. Ultimately, continued alcohol-induced injury results in progression of fibrosis to cirrhosis.

Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis

3 Obesity and metabolic syndrome may produce hepatic injury and may potentiate the effects of viral injury.[51,52] Nonalcoholic fatty liver disease (NAFLD) describes the presence of hepatic steatosis (**Fig. 59.4**) when no other causes for secondary hepatic fat accumulation (e.g., heavy alcohol consumption) are present. NAFLD may progress to NASH and then fibrosis. Up to 20% of patients with NASH may progress to cirrhosis. This disease is now a major health problem in Westernized populations and in particular in the United States.[53] NAFLD is now the most common cause of chronic liver disease in the United States, affecting up to 30% to 46% of the population.[53–55] It is expected to surpass viral hepatitis as the leading indication for liver transplantation by 2025.[56] Initially, the liver becomes infiltrated with fat, with subsequent inflammatory infiltrate. Pathologic features are shared with alcohol-induced liver injury (**Fig. 59.5A,B**). NAFLD is associated with obesity, the metabolic syndrome, hyperlipidemia, cardiovascular disease, and noninsulin-dependent diabetes. Ninety percent of NAFLD patients have at least one of these risk factors and 30% have three or more.[57] Most patients traditionally diagnosed with cryptogenic cirrhosis in fact have NAFLD.[58] NAFLD is major risk factor for primary liver cancer (HCC) and in addition to hepatitis virus infection, accounts for the rapid rise in the incidence of HCC in Western countries.[59] More broadly considered, obesity is a major

risk factor for cancer deaths with a 4.5-fold increase of the relative risk for liver cancer in obese subjects.[60]

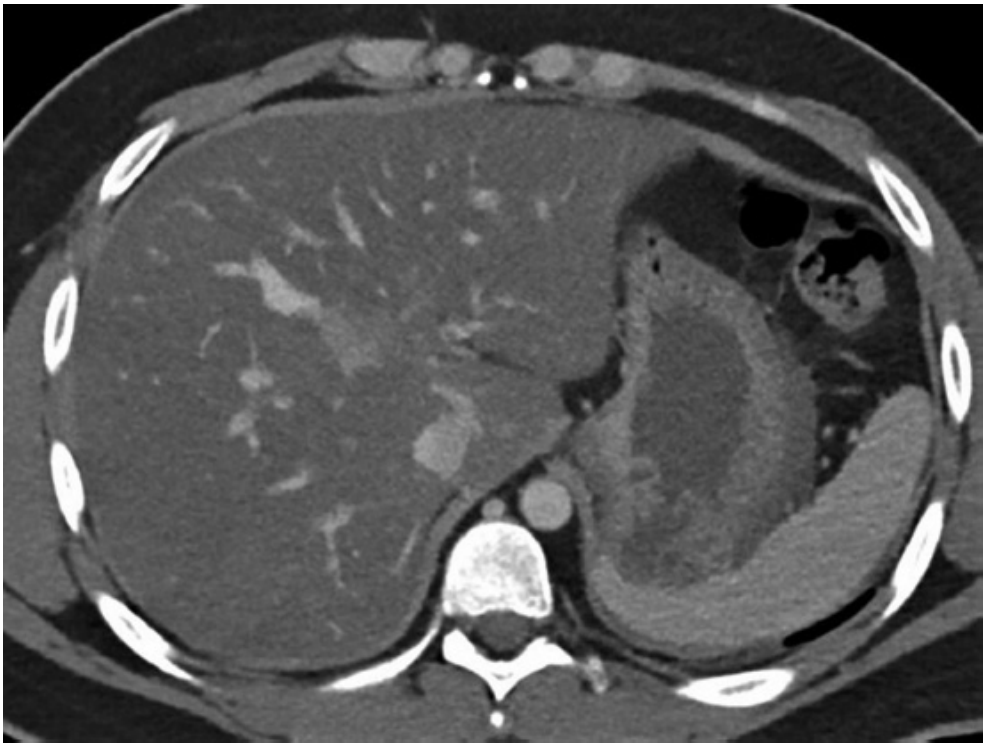

Figure 59.4 Venous-phase contrast-enhanced CT scan demonstrating a hypodense steatotic (fatty) liver. The liver is hypodense relative to the spleen. (Image courtesy of Dr. Ihab Khamel, Department of Radiology, Johns Hopkins Hospital.)

The current understanding of NAFLD with progression to NASH and cirrhosis involves a two-hit model.[56] This model proposes that insulin resistance leads to hepatic steatosis, which sensitizes the hepatic parenchyma to environmental and extracellular insults leading to oxidative injury, inflammation, necrosis, and fibrosis. Dietary fructose is an important culprit in the development of steatosis and steatohepatitis by decreasing intracellular ATP and transforming to lipid in the absence of insulin.[61] Ongoing hepatic insults lead to activation of the inflammasome and secretion of the proinflammatory cytokines IL-1β and IL-18. Inflammasome activation is further increased by gut-derived bacterial endotoxin, with stellate cell activation and fibrosis.[62]

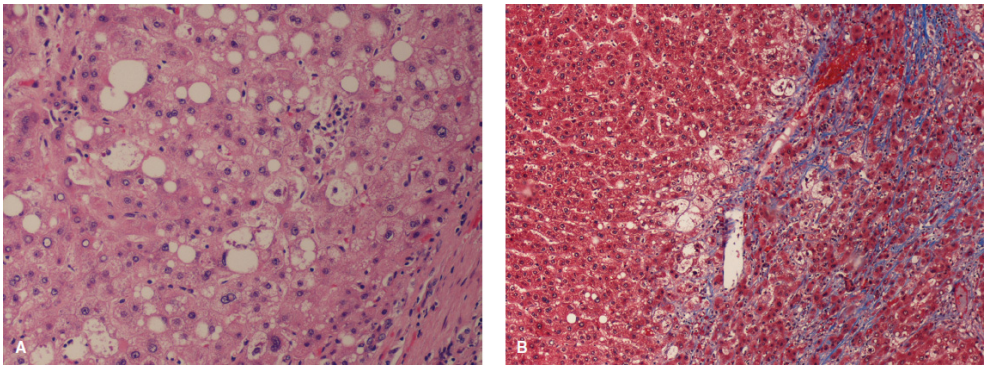

Figure 59.5 **A:** Steatohepatitis 20× magnification. Macrosteatosis, an inflammatory infiltrate and Mallory–Denk bodies are seen. **B:** Trichrome stain demonstrating steatohepatitis and fibrosis (10× magnification). (Images courtesy of Dr. Robert Anders, Department of Pathology, Johns Hopkins Hospital.)

Therapy for NASH centers on lifestyle modification and avoidance of ongoing or additional injury. General measures include avoiding other hepatotoxins including alcohol, and maintaining appropriate vaccinations against viral hepatitis as well as other standard vaccinations (such as against pneumococcus and influenza). Modification of cardiovascular disease risk factors is imperative. Modest weight loss of 5% to 10% is associated with significant histologic improvements in disease severity.[57] Weight loss may be achieved via bariatric surgery if exercise fails. Newer and experimental therapies are also being explored. The role of gut microflora is understood to play a major role in the pathogenesis of NASH (and in other liver diseases) and the use of probiotics, most commonly lactobacilli and bifidobacteria, is being explored in the treatment of NASH. A recent meta-analysis of four RCTs demonstrated probiotics significantly decreased transaminases, total cholesterol, TNF-α, and insulin resistance.[63]

Some, but not all randomized trials support the use of vitamin E as an antioxidant for NASH. A meta-analysis of five trials showed no histologic benefit with vitamin E.[64] This data may be due to heterogeneity of the included trials. The largest RCT included in this meta-analysis showed that patients with NASH without diabetes were more likely to have an improvement in their histology score when compared to placebo, and have an improvement in their ALT levels.[41,65]

Patients with NASH who also have diabetes may benefit from pioglitazone and liraglutide. Metformin use in the setting of NASH has not been shown to improve histology, whereas pioglitazone has been shown to improve fibrosis

as well as inflammation and steatosis in diabetics. Guidelines exist for the follow-up of patients with NASH. Patients should be followed clinically with serial noninvasive assessment of their liver fibrosis score (**Table 59.3**) if biopsy proven NASH is present.

Viral Hepatitis

4 Viral hepatitis is the most common cause of cirrhosis worldwide, accounting for at least 50% of cases. Hepatitis A, B, C, D, and E have all been proved to cause acute hepatitis. Histology is characterized by lymphocytic parenchymal and portal inflammation, focal necrosis, ballooning degeneration, and cholestasis. Kupffer cell and macrophage hypertrophy and hyperplasia are present with lobular disarray. Hepatitis B, C, and D may progress to chronic hepatitis, defined by persistent (>6-month) liver cell necrosis and inflammation.

Hepatitis B Virus: Less than 5% of patients who experience acute HBV infection develop chronic infection, and approximately 10% to 20% of chronically infected persons develop cirrhosis. Hepatitis B remains a major public health problem particularly in Asia and Africa where up to 10% of the population show evidence of chronic infection. Globally, it is estimated there are 248 million HBV carriers in the world, with 600,000 deaths annually from HBV-related disease.[66] In the United States, some data suggests there may be as many as 2.2 million chronically infected residents.[67] Vaccines and antiviral therapies exist. Antiviral medications effective against hepatitis B suppress viral replication to undetectable levels in up to 90% of patients and may reverse fibrosis and even early cirrhosis. Treatment suppresses viral replication, however, HBV remains incorporated into the host genome. This is important as HCC can still develop in the noncirrhotic liver of HBV-infected patients.[68] Public health strategies with systematic vaccination of newborns are able to substantially decrease the incidence of new infections.

Table 59.3 Comparability of Terms in Three Simple Systems for Histologic Grading and Staging of Chronic Hepatitis: IASL, Metavir, and Batts–Ludwig

IASL	Metavir	Batts–Ludwig
Grade (Activity, Inflammation)		
Minimal chronic hepatitis	A1	Grade 1
Mild chronic hepatitis	A1 A2	Grade 2 Grade 3
Moderate chronic hepatitis	A3	Grade 4
Severe chronic		
Stage (Fibrosis)		
Mild—portal fibrosis	F1	Stage 1
Moderate—periportal fibrosis or portal–portal septa	F1 F2	Stage 2 Stage 3
Severe—bridging fibrosis (few)	F3 F4	Stage 3 Stage 4
Severe—bridging fibrosis (many)		
Cirrhosis		

IASL, International Association for the Study of the Liver.

Adapted from Rockey DC, Caldwell SH, Goodman ZD, et al. Liver biopsy. *Hepatology* 2009;49:1017–1044.

Hepatitis C Virus: In contrast, HCV poses a much higher risk of chronic infection: 50% to 85% of persons exposed become chronically infected, and chronic hepatitis develops in 60% of these patients. A systematic review of 111 studies analyzing the natural history of HCV infection estimated the prevalence of cirrhosis 20 years after infection at 16%.[69] Among patients with compensated cirrhosis of viral origin, HCC developed in approximately 20% with HCV, 9% with HBV, and 41% with both HBV and HCV.[70] In the past, standard treatment for HCV was based on the combination of pegylated

interferon and ribavirin (a therapy associated with a high rate of adverse events that limited completion of therapy), with sustained viral response (SVR) rates of up to 80% in patients with genotypes 2 and 3.[71] Results for the more common genotype 1 were only 40% to 50%, with the best reporting an SVR rate of 65%.[72] The discovery of DAAs has revolutionized the treatment of HCV. Choice of antivirals has evolved rapidly and depends on multiple factors, including genotype, treatment history, comorbidities, presence and stage of cirrhosis, and potential drug interactions among other factors. Multiple effective drug combinations exist. Some combinations are effective against multiple HCV genotypes, and a few combinations have pangenotypic activity. Treatment recommendations and guidelines for DAA use are published by the American Association for the Study of Liver Diseases (AASLD) and Infectious Disease Society of America (IDSA) among others (European Association for the Study of the Liver [EASL], and the WHO).

In patients who respond to antiviral therapy, progression to cirrhosis is eliminated and it is generally thought that HCC does not develop. In patients who do not respond to therapy, cirrhosis develops in approximately 40%, and HCC develops in 16% of these patients.[73]

Hepatitis D Virus (Delta virus—HDV): It is an RNA virus. It is unusual in that it requires coinfection with HBV to be pathogenic. Superinfection of HBV-positive patients with HDV may lead to a more rapid clinical course, with progression to cirrhosis in 70% to 80% of patients.[74] The progressive increase in hepatitis-infected individuals in the United States precedes an epidemic in HCC, which has been well documented and is expected to peak over the coming decade.[75]

Cholestasis

Cholestasis may be caused by intrahepatic or extrahepatic biliary obstruction or defects in the ability of hepatocytes to excrete bile. Important causes are biliary atresia, primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC—previously known as primary biliary cirrhosis) (**Table 59.4**). Prolonged biliary obstruction leads to proliferation of bile ducts, formation of bile lakes, fibrosis as a result of the direct toxic effects of

bile salts on hepatobiliary elements, and eventually secondary biliary cirrhosis.

Table 59.4 Causes of Cholestasis

Extrahepatic
Common bile duct stones
Cancers
  Pancreas
  Ampulla of Vater
  Bile duct
Cysts
  Pancreatic
  Choledochal
Infections
  Parasites
  Acquired immunodeficiency syndrome
Chronic pancreatitis
Bile duct strictures
  Benign
  Ischemic
Hodgkin disease
Biliary atresia

Intrahepatic
Primary biliary cirrhosis
Space-occupying lesions
  Primary or metastatic hepatic tumors
  Lymphoma
  Amyloidosis
Vanishing bile duct syndrome
  Allograft rejection
  Graft versus host disease
  Alagille syndrome
Idiopathic adult ductopenia
  Primary sclerosing cholangitis
  Hodgkin disease
Cystic fibrosis

Hepatocellular Cholestasis
Genetic

- α-Antitrypsin deficiency
- Benign recurrent intrahepatic cholestasis
- Byler syndrome
- Cholestasis of pregnancy
- Abnormal bile acid synthesis
- Porphyrias

Acquired
- Viral hepatitis
- Drugs

Alcoholic hepatitis
Bacterial infections
Total parenteral nutrition
- Renal carcinoma
- Hodgkin disease

Postoperative cholestasis

Primary Biliary Cholangitis

Several diseases characterized by cholestasis seem to be caused by underlying autoimmune or inflammatory disorders affecting either small (PBC) or large (PSC) bile ducts. PBC is a chronic, progressive autoimmune cholestatic disease that most commonly affects middle-aged women; family members of affected individuals are at a greatly increased risk of developing the disease. PBC is characterized by a T-lymphocyte mediated attack on small intralobular bile ducts and the bile duct cells. This portal inflammation and destruction of intrahepatic bile ducts ultimately results in cirrhosis. Almost all patients with PBC are women, and almost all of these women have antimitochondrial antibodies present in serum.[76] Antinuclear antibodies are present in up to 70% of patients. Hyperlipidemia, an elevated alkaline phosphatase and bilirubin are also present. In PBC, the autoimmune process directly damages the intrahepatic biliary tree. Toxicity of bile acids contributes to hepatocyte injury.[77]

Presentation is with fatigue, jaundice, and pruritus, however as many as 60% of patients may be asymptomatic.[78] PBC progresses in the majority of patients with median survival of 10 to 15 years in asymptomatic patients and 7 years in symptomatic patients.[79,80] Poor prognostic factors include

advanced age as well as those factors associated with advanced disease (hyperbilirubinemia, hepatosplenomegaly, and symptomatic disease).

Therapy for PBC includes the exogenous bile acid ursodeoxycholic acid. Treatment with ursodeoxycholic acid may reduce the expression of HLA class 1 antigens by hepatocytes and lessen the toxicity of retained naturally occurring bile acids. Complete response, as evidenced by normalization of liver enzymes without histologic progression, is seen in up to 30% of patients and may result in a normal life expectancy. Obeticholic acid (a farnesoid X receptor ligand) is recommended if response to ursodeoxycholic acid is inadequate. Liver transplantation is ultimately required as the definitive treatment in most patients who progress to decompensated cirrhosis. The parameters for liver transplantation and its timing are relatively predictable and have been well studied.

Primary Sclerosing Cholangitis

PSC is a chronic, progressive cholestatic liver disease of uncertain etiology characterized by diffuse segmental intrahepatic and/or extrahepatic biliary strictures with associated fibrosis and inflammation. The disease has no cure and leads to secondary biliary cirrhosis, portal hypertension, and hepatic failure. In addition, it carries a risk of cholangiocarcinoma. Median survival without liver transplantation after diagnosis of PSC is 10 to 12 years. PSC is strongly associated with inflammatory bowel diseases, particularly ulcerative colitis. There is likely a common underlying mechanism involving mucosal autoimmunity to the gastrointestinal (GI) tract. Around 70% of patients with PSC also have ulcerative colitis and up to 90% when rectosigmoid biopsies are routinely obtained.[81] Conversely, only approximately 5% of patients with ulcerative colitis have PSC, though more subtle forms of the disease may be present but asymptomatic. PSC is characterized by elevated levels of autoantibodies and an increased expression of human leukocyte antigen (HLA) class II molecules on biliary epithelial cells.[82,83] As opposed to PBC, in PSC two-thirds of patients are male and younger than 45 years of age at the time of diagnosis.[84] Patients with PSC may be completely asymptomatic with only abnormal liver function tests (up to 44%). Some may have signs of advanced disease at the time of diagnosis.[81] Commonly, the diagnosis is made in symptomatic patients after

endoscopic retrograde cholangiopancreatography (ERCP) has been performed to evaluate elevated liver enzymes, including alkaline phosphatase and γ-glutamyl transferase (GGT). Symptomatic patients have a waxing and waning course and may present with complaints of fatigue (75%), pruritus (25% to 70%), jaundice (30% to 69%), abdominal pain (16% to 37%), and weight loss (10% to 34%).[81] More advanced complications are due to the progression to cirrhosis, but also include episodes of acute cholangitis due to biliary strictures.

The diagnosis of PSC is suggested by a history of inflammatory bowel disease in the setting of elevated liver enzymes. Cholangiography (via MRCP, ERCP, or percutaneous cholangiography) may reveal the characteristic multifocal stricturing and dilatation of intrahepatic and/or extrahepatic bile ducts. Imaging may also reveal a single dominant stricture. Pathologically, bile ductular proliferation, periductal fibrosis and inflammation, ductopenia, and, less commonly, obliterative fibrous cholangitis may be present. Like ulcerative colitis, PSC confers a significant risk of malignant transformation of the biliary mucosa. Cholangiocarcinoma develops in 1% to 2% of patients per year after the diagnosis of PSC, with an overall risk of up to 10%.[85] PSC is a risk factor for both intra- and extrahepatic cholangiocarcinoma as well as gall bladder cancer. HCC risk is increased when cirrhosis is present. Surveillance for cancer with ultrasound, computed tomography (CT), or MRCP, and serum testing of CA19-9 has been recommended. When a dominant stricture, worsening symptoms or cholestasis is present, ERCP with brush cytology and fluorescence in situ hybridization (FISH) may be useful to increase sensitivity of cancer detection.

Unfortunately there is no generally accepted medical therapy effective against PSC. Therapies are directed toward the complications of the disease including biliary obstruction, cirrhosis, and cholangiocarcinoma. Dominant strictures, defined as stenosis less than 1.5 mm in the common bile duct or less than 1 mm in the hepatic duct, are readily treated endoscopically by means of dilation and/or stent placement.[86] A dominant stricture should raise concern for the development of cholangiocarcinoma. Transplantation should be performed before cancer develops. Historically the presence of cholangiocarcinoma was an absolute contraindication to transplantation because of poor outcomes. However, in highly selected patients with

localized tumors, liver transplantation may be achieved with an acceptable survival rate after intensive preoperative therapy radiation and chemotherapy, as proposed by Shaw and implemented on a larger scale by the Mayo group.[87]

Metabolic and Genetic Disorders

A description of all the metabolic and genetic disorders causing liver disease is beyond the scope of this chapter. Some of these diseases are listed in **Table 59.2**.

Hereditary Hemochromatosis: This is an autosomal recessive, inborn error of metabolism most commonly due to mutations in the hereditary hemochromatosis gene *HFE* and results in increased intestinal absorption of iron and subsequent total-body iron overload. Iron accumulates in the periportal regions of the liver and results in hepatotoxicity via lipid peroxidation. Kupffer cells subsequently phagocytose necrotic hepatocytes and activate stellate cells.[88] Over time, the reaction progresses to bridging fibrosis and eventually cirrhosis. Cardiac, endocrine, neurologic, and other systemic manifestations occur. Treatment includes reduction of iron intake, repeated phlebotomy, and liver transplantation.[89] As with other types of cirrhosis, there is a risk of HCC.

Wilson's Disease: Wilson's disease is an autosomal recessive disease caused by a mutation in the Wilson's disease protein resulting in deficient hepatocyte transport of copper into bile. The disease is characterized by a low serum ceruloplasmin level and manifests clinically as Kayser–Fleischer rings (corneal pigmentation), neuropsychiatric disease, and hepatic cirrhosis.[90] Liver manifestations of Wilson's disease vary widely from asymptomatic biochemical abnormalities and steatosis to fulminant hepatic failure, chronic hepatitis and cirrhosis. As copper accumulates in the liver, periportal inflammation develops that leads to piecemeal and lobular necrosis, bridging fibrosis, and ultimately a mixed micronodular–macronodular cirrhosis. A scoring system has been developed to assist with the diagnosis. Treatment options include chelating agents, such as penicillamine, trientine, zinc salts, and orthotopic liver transplantation.

Impaired Venous Outflow or Venous Outflow Obstruction

Cirrhosis may also result from chronic obstruction of the hepatic venous outflow. Causes include chronic right-sided heart failure as a result of severe tricuspid regurgitation, the Budd–Chiari syndrome (BCS), and the sinusoidal obstructive syndrome (hepatic veno-occlusive disease).

Hepatic dysfunction secondary to passive vascular congestion in the setting of right-sided heart failure and elevated right-sided heart pressures is caused by pressure transmission to the hepatic venous system. Sinusoidal congestion occurs and results in perivenular atrophy, hemorrhagic necrosis, and distortion and enlargement of sinusoidal fenestrations.[91] Perisinusoidal edema develops and exceeds the clearance capabilities of hepatic lymphatics, so that ascites develops. Grossly, the liver is described as having a "nutmeg" appearance in which areas of hemorrhage are interspersed with relatively normal yellowish parenchyma.[92] Histologically, perivenular fibrosis progresses to bridging fibrosis that spares the portal regions. This portal sparing is characteristic of "cardiac cirrhosis." In addition to causing ascites, chronic vascular congestion leads to fibrosis in the space of Disse, which compromises nutrient delivery and contributes to portal hypertension and zone 3 hepatocellular injury.[93]

5 **Budd–Chiari Syndrome** (see section on portal hypertension below) is a rare disease more common in women and usually presents in the third or fourth decade of life. It is caused by mechanical obstruction of the hepatic veins (**Table 59.5**). Obstruction may occur at the level of the terminal hepatic veins, the major hepatic veins, or the vena cava and may be caused by obstructing webs or membranes (most commonly in Africa and Asia) or thrombosis secondary to hypercoagulable states and neoplasms (most commonly in the West).

Table 59.5 Etiologic Factors in Budd–Chiari Syndrome

Idiopathic
Hematologic disorders Polycythemia vera Paroxysmal nocturnal hemoglobinuria Myeloproliferative disorders Antithrombin III deficiency Circulating lupus anticoagulants
Oral contraceptives
Pregnancy and postpartum
Tumors Hepatocellular carcinoma Renal cell carcinoma Adrenal carcinoma Leiomyosarcoma of the inferior vena cava
Vena caval webs
Infections Amebic abscess Aspergillosis Hydatid cyst
Phlebitis
Trauma
Veno-occlusive disease

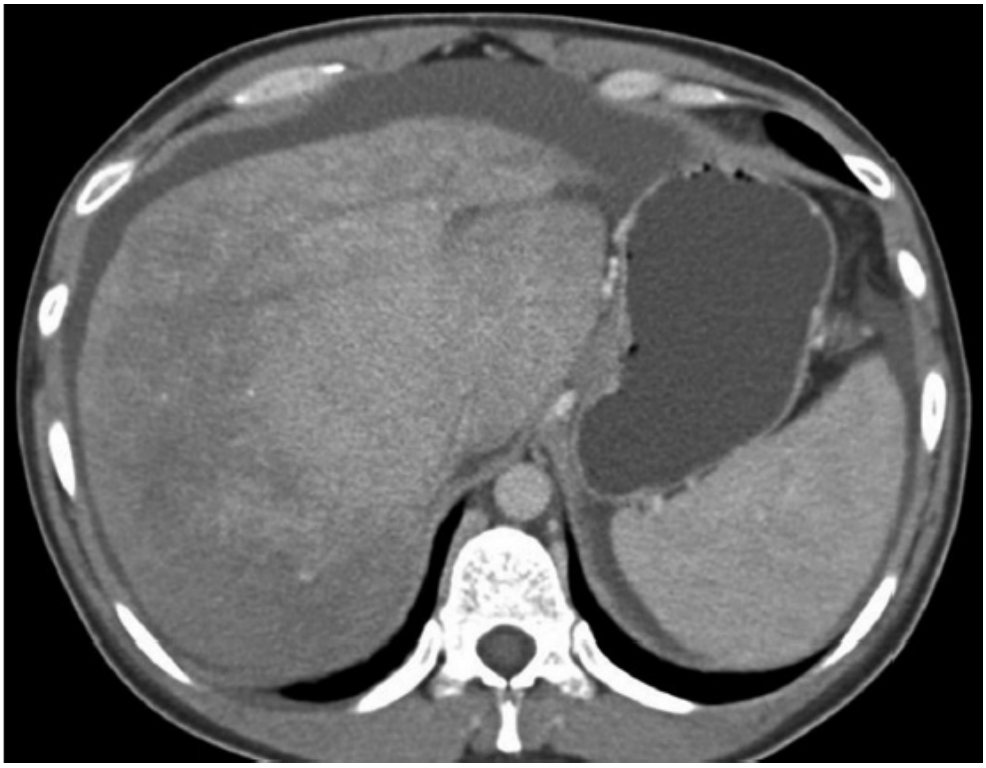

Figure 59.6 Contrast-enhanced CT of a patient with Budd–Chiari syndrome. This patient experienced an unprovoked thrombotic event which was found to be due to a myeloproliferative neoplasm positive for *JAK2 V617F mutation*. Massively hypertrophied caudate lobe is demonstrated. Also visible is ascites, compressed IVC, and splenomegaly. This patient was successfully treated with TIPS and lifelong anticoagulation and continued to have excellent hepatic function.[277] (Image courtesy of Dr. Ihab Khamel, Department of Radiology, Johns Hopkins Hospital.)

The range of presentations is wide: from asymptomatic to acute hepatic failure or cirrhosis.[94] Variation in symptoms and presentation is related to the degree and rate of progression of hepatic outflow obstruction. Patients classically present with abdominal pain, hepatomegaly, and ascites. The diagnosis can be made by duplex Doppler ultrasonography, which has a high sensitivity. Identification of collateral vessels to subscapular or intercostal vessels on ultrasound is a highly sensitive and specific finding.[95] CT and magnetic resonance imaging (MRI) (**Fig. 59.6**) delineate intrahepatic vascular anatomy and are used for the planning of complex interventions.[96] Medical management consists of anticoagulation and management of symptoms. Interventional radiologic procedures have now taken the forefront in management of BCS, in which accessible strictures may be treated with angioplasty or stenting. For patients unsuitable for reestablishment of hepatic

venous outflow through the above means, transjugular intrahepatic portosystemic shunting (TIPS) is able to decompress both the inferior vena cava (IVC) and the portal system. In patients with fulminant BCS or in those who develop chronic decompensated cirrhosis, liver transplantation is lifesaving.

Diagnosis

Although cirrhosis can be asymptomatic for decades, significant information can be obtained by performing a thorough history and physical examination. Symptoms may be nonspecific (anorexia, weight loss, weakness, fatigue). A history of chronic alcohol abuse, hepatitis or risk factors for virus transmission, jaundice, toxin or drug exposure, upper GI bleeding, enlarging hemorrhoids, infections, and alteration in mental status suggests the possibility of liver disease and decompensated cirrhosis. In women, chronic anovulation is common, while in men hypogonadism may develop. Physical findings associated with cirrhosis are listed in **Table 59.6**. In addition to these findings, fetor hepaticus, purpura and bruising, decreased body hair, and white nails (Muehrcke and Terry nails) are common. As cirrhosis progresses, a decrease in blood pressure is often present and contributes to the development of hepatorenal syndrome (HRS). Parotid enlargement may be present in alcoholic liver disease.

Table 59.6 Physical Findings in Cirrhosis

Physical Findings	Incidence (%)
Palpable liver	96
Jaundice	68
Ascites	66
Spider angiomas	49
Dilated abdominal wall veins (caput medusae)	47
Palpable spleen (splenomegaly)	46
Testicular atrophy	45
Palmar erythema	24
Noninfectious fever	22
Hepatic coma	18
Gynecomastia	15
Dupuytren contractures	5

Laboratory tests of liver function are indicated if liver disease is suggested by the history and physical examination. Although levels of bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase may be elevated in hepatic disease, the increases are not specific for liver pathology, and levels may be normal even in the setting of cirrhosis. A very common finding in patients with cirrhosis is thrombocytopenia, caused by hypersplenism and portal hypertension. The platelet growth factor thrombopoietin, which is produced by the liver, is decreased in patients with cirrhosis, and this deficit may lead to thrombocytopenia associated with hepatic disease.

Definitive diagnosis of cirrhosis usually requires biopsy, either percutaneous or operative, or gross inspection during laparoscopy or laparotomy. Regardless of the method selected, it is crucial to obtain a large enough specimen to make the diagnosis. Current recommendations suggest that at least 11 portal tracts need to be assessed.[97] Several staging systems exist for the grading of fibrosis and cirrhosis, including the International Association for Study of the Liver (IASL), Batts–Ludwig, and Metavir systems. The AASLD recommends use of the Batts–Ludwig or Metavir systems due to their simplicity (**Table 59.3**).[97]

Imaging classically reveals an atrophic, nodular liver and an enlarged spleen. Ultrasound is routinely used during the evaluation of cirrhosis. It is well tolerated, widely available, and noninvasive. Ultrasonographic criteria for cirrhosis include the demonstration of multiple nodular irregularities on the ventral liver surface that are clearly separate from the anterior abdominal wall. Parenchymal texture is altered in the setting of fibrosis, though this feature can be subtle. When these criteria are used, ultrasonography has been shown to have a sensitivity, specificity, and accuracy of approximately 90% in the diagnosis of cirrhosis.[98]

CT imaging provides similar information to ultrasound. Contrast administered with imaging during the portal phase can demonstrate the presence of portosystemic collaterals (if portal hypertension is present) and assess patency of the portal vein. MRI provides similar information and may contribute information about liver stiffness when elastography is performed. Contrast-enhanced CT and MRI are important in the characterization of the malignant potential of masses within the liver.

Measures of liver stiffness offer a noninvasive approach to the assessment of degree of fibrosis and may avoid the need to biopsy a liver. Elastography estimates liver stiffness by applying mechanical waves and measuring their propagation speed through tissue. Modalities include ultrasound and MRI among others. Ultrasound-based transient elastography (TE), a measure of liver stiffness, is playing an increasingly large role in the noninvasive assessment of fibrosis, with some studies demonstrating a 95% area under the receiver operating characteristic curve (AUROC) for diagnosing grade IV fibrosis (cirrhosis).[99] MR elastography (MRE) interrogates the whole liver (unlike ultrasound-based TE) and in some reports has a higher technical success rate and better diagnostic accuracy than ultrasound-based TE.

Several laboratory indices have been found to correlate well with histologic grade of cirrhosis.[99,100] The NAFLD fibrosis score, for example, consists of age, BMI, diabetes, platelet count, albumin level, and AST/ALT ratio.[101] The AUROC of this scoring system in diagnosing stage 3 or greater fibrosis was 85% in a recent meta-analysis.[102] The FibroSure (LabCorp) is a patented panel of biomarkers consisting of GGT, haptoglobin, bilirubin, apolipoprotein A1, and α-2-macroglobulin. The AUROC of FibroSure for fibrosis greater than or equal to stage 2 has been shown to be up to 87%.[103] Indirect evidence of cirrhosis includes endoscopically discovered varices of the esophagus and the presence of splenomegaly detected by CT or MRI.

Complications

The occurrence of major complications of cirrhosis signifies the occurrence of decompensated cirrhosis (**Table 59.1**).

Multiple factors can predispose to decompensation in a patient with cirrhosis. Risk factors for decompensation include bleeding, infection, alcohol intake, medications, dehydration, and constipation. In addition, patients with obesity are at increased risk of decompensation. Once decompensation has occurred, patients should be assessed for liver transplantation.

Renal

Renal complications in cirrhosis are intrinsic to functional dysregulation of vascular tone throughout the body.[104] Renal dysfunction is characterized by avid sodium retention despite normovolemia or hypervolemia, dilutional hyponatremia secondary to free water overload, ascites, and ultimately renal failure and the HRS. The paradoxical arterial vasoconstriction of the renal arterial bed in the face of global fluid overload is critical to the pathophysiology of HRS.[105] Among the complications of cirrhosis, HRS confers the highest risk of mortality.[106] Although HRS is the most dramatic renal complication of liver failure, renal dysfunction in patients with advanced liver disease is generally multifactorial.

Much progress has been made in the understanding of the pathophysiology of HRS focusing on the dysregulation of arterial tone in the end stages of

liver disease. Splanchnic arterial vasodilatation, which is triggered by portal hypertension, appears to play a central role in the hemodynamic changes and the decline in renal function in cirrhosis. Empiric observations that support a functional or "secondary effect" theory include the lack of anatomic renal abnormalities in patients with cirrhosis-related renal dysfunction, the normal function of previously dysfunctional kidneys transplanted into otherwise healthy recipients, and resolution of renal abnormalities after successful hepatic transplantation. Recent clinical studies have defined the critical role of optimizing colloid balance and regulating renal blood flow using agents such as terlipressin in counteracting the deranged vascular tone and physiology in cirrhotic patients.[107,108]

Sodium Retention

Patients with cirrhosis who do not have ascites have relatively normal sodium-handling capabilities. Patients in whom ascites develops have a marked inability to excrete sodium. Because of this deficit, sodium intake in excess of renal excretion contributes to fluid overload. The most accepted explanation for this development is the "arterial vasodilation hypothesis," which suggests that hypotension is the primary event. Arterial vasodilation in the splanchnic circulation leads to relative peripheral hypovolemia with activation of the renin–angiotensin–aldosterone and sympathetic nervous systems. This results in the release of antidiuretic hormone (arginine vasopressin), sodium and water retention, and an increase in effective circulating volume, with subsequent edema and ascites.[109–111]

Table 59.7 International Club of Ascites (ICA-AKI) Definitions for the Diagnosis and Management of AKI in Patients with Cirrhosis

Definition of AKI	Increase in sCr ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours; or a percentage increase sCr ≥50% from baseline which is known, or presumed, to have occurred within the prior 7 days		
Staging of AKI	Stage 1: increase in sCr ≥0.3 mg/dL (26.5 μmol/L) or an increase in sCr ≥1.5-fold to twofold from baseline Stage 2: increase in sCr >two to threefold from baseline Stage 3: increase of sCr ≥threefold from baseline or sCr ≥4.0 mg/dL (353.6 μmol/L) with an acute increase ≥0.3 mg/dL (26.5 μmol/L) or initiation of renal replacement therapy		
Progression of AKI	Progression: Progression of AKI to a higher stage and/or need for RRT		Regression: Regression of AKI to a lower stage
Response to treatment	No Response: No regression of AKI	Partial response: Regression of AKI stage with a reduction of sCr to ≥0.3 mg/dL (26.5 μmol/L) above the baseline value	Full response: Return of sCr to a value within 0.3 mg/dL (26.5 μmol/L) of the baseline value

sCr, serum Creatinine.

Adapted from Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *Gut* 2015;64:531–537.

Evidence suggests that nitric oxide and prostaglandins are key mediators. Elevations in portal venous and systemic nitric oxide have been reported in both animal and human studies, and inhibitors of nitric oxide production have been shown to reduce vasodilatation and enhance renal hemodynamics.[112,113] Nitric oxide production may be stimulated by increased absorption of endotoxin from the intestine. Other studies have demonstrated that extracellular fluid volume expansion precedes vasodilation,[114] and that pathologic activation of intrahepatic vascular sensors is the key mediator for renal salt retention.[115] Fluid overload is an important landmark in the natural history of cirrhotic patients and the degree of sodium retention is inversely related to survival.

Water Retention and Hyponatremia

Water excretion is usually normal in patients with cirrhosis before the development of ascites. Patients with cirrhosis and ascites may have a markedly impaired ability to handle free water. An increased production of antidiuretic hormone, decreased delivery of fluid to the diluting segments of the nephron, and reduced renal production of prostaglandins all contribute.[116] Retention of water leads to dilutional hyponatremia (serum sodium 130 mEq/L), which can cause nausea, vomiting, lethargy, and seizures.[117] Severity of hyponatremia correlates with worsening survival.[118–120]

Hepatorenal Syndrome

6 Patients with refractory ascites are at risk for acute kidney injury (AKI). Early diagnosis of AKI is imperative because therapy impacts survival. AKI in cirrhosis can be caused by prerenal azotemia (PRA), HRS, or acute tubular necrosis (ATN). Diagnosis of AKI can be challenging given that patients with cirrhosis often have sarcopenia and a lower baseline creatinine. Criteria for AKI in cirrhosis were revised in 2015 by the International Ascites Club (IAC) (**Table 59.7**). HRS is a unique form of AKI that is a complication of cirrhosis characterized by progressive renal failure in the absence of intrinsic renal disease. It has also been described as occurring in acute liver failure. In patients with cirrhosis and ascites, HRS

occurs in up to 20% of patients at 1 year and 40% at 5 years. Two forms of HRS have been described. HRS-AKI (previously known as type 1 HRS) is characterized by a rapidly progressive decline in renal function associated with a high mortality. HRS-non-AKI (HRS-NAKI—previously known as Type 2) is a more chronic form of renal dysfunction that evolves over weeks to months. The development of HRS is a poor prognostic indicator: If liver transplantation cannot be performed, patients with HRS usually die within months of the development of severe disease.[106] Distinguishing HRS-AKI from other causes of AKI is paramount because treatment differs.

The pathogenesis of HRS is thought to be due to renal cortical vasoconstriction induced by activity of the renin–angiotensin–aldosterone system. The powerful endothelium-derived vasoconstrictor endothelin-1, combined with decreased renal production of vasodilator prostaglandins, also contributes. HRS is usually precipitated by an inciting event. Infection, use of nonsteroidal anti-inflammatory drugs, variceal hemorrhage, or excessive diuretic use may precipitate HRS. Manifestations of the disease include progressive oliguria, rising serum creatinine, increased cardiac output, and decreased arterial pressure.

Differential Diagnosis of HRS: This includes other causes of AKI and PRA. Excessive diuresis may lead to a rise in serum creatinine difficult to distinguish from HRS. A failure to respond to cessation of diuretics and fluid challenge suggests HRS. The disease, however, is virtually indistinguishable by laboratory testing from prerenal uremia. Both prerenal uremia and HRS are characterized by extremely low sodium concentrations in the urine, high urine osmolality, high urine-to-plasma ratios of creatinine, and normal urinary sediment (**Table 59.8**). Criteria for the diagnosis of HRS are listed in **Table 59.9**. Additional diagnostic biomarkers under study include urinary and serum neutrophil gelatinase-associated lipocalin (NGAL), urinary IL-18, urinary kidney injury molecule 1 (KIM-1) and fractional excretion of sodium (FeNa), among others.

Table 59.8 Differential Diagnosis of Acute Azotemia in Patients with Liver Disease

	Prerenal Azotemia	Hepatorenal Syndrome	Acute Renal Failure
Urinary sodium	<10 mEq/L	<10 mEq/L	>30 mEq/L
Urine/plasma creatinine ratio	>30:1	>30:1	<20:1
Urine osmolality	100 mOsm, or more than plasma osmolality	100 mOsm, or more than plasma osmolality	Equal to plasma osmolality
Urine sediment	Normal	Normal	Casts: cellular debris

Table 59.9 International Ascites Club (IAC) Diagnostic Criteria for Hepatorenal Syndrome Acute Kidney Injury (HRS-AKI)

1. Cirrhosis with ascites
2. Diagnosis of AKI according to IAC-AKI criteria
3. No improvement of serum creatinine after 2 days of diuretic withdrawal and volume expansion with albumin (recommended 1 g/kg of body weight per day, maximum 100 g/d)
4. Absence of shock
5. No current or recent treatment with nephrotoxic drugs
6. No macroscopic signs of structural kidney injury,[a] defined as:
   - absence of proteinuria (>500 mg/day)
   - absence of microhaematuria (>50 RBCs per high power field)
   - normal findings on renal ultrasonography

[a]Patients who fulfil these criteria may still have structural damage such as tubular damage. Urine biomarkers will become an important element in making a more accurate differential diagnosis between HRS and acute tubular necrosis.

Adapted from Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *Gut* 2015;64:531–537.

Management of HRS: Often there is a precipitating event that requires treatment. Diuretics should be stopped to prevent further injury. The most common inciting factor is spontaneous bacterial peritonitis (SBP) and infection. Up to 70% of cases of acute HRS have been linked to bacterial infections.[121] Volume contraction from multiple etiologies, including GI bleeding or the excessive treatment of ascites, is another major precipitator. HRS is treated with volume expansion with albumin (**Table 59.9**). Empiric antibiotics should be given until cultures are definitively negative.

Vasoconstrictors (by attenuating splanchnic vasodilatation) combined with albumin (volume expansion) significantly improve renal function in HRS. The vasopressin-analog terlipressin is commonly used outside the United States, and lead to reversal in over 56% of patients in one recent RCT. The oral vasopressor midodrine is commonly used in the United States. Use of terlipressin has not been approved for use by the FDA. Midodrine is sometimes in combination with octreotide, however terlipressin is superior

to the combination of midodrine and octreotide in the reversal of HRS. Others have examined norepinephrine as a substitute for terlipressin with slightly improved reversal rates in the norepinephrine group (43% vs. 39%), although this was not statistically significant.[122] A meta-analysis of all RCTs of vasopressor use in the treatment of HRS has found a reduction in all-cause mortality when vasopressors are utilized.[123] Medical therapy may reverse HRS in some patients, however many will ultimately require liver transplantation or combined liver kidney transplantation.

Pulmonary

Many pathologic processes in patients with cirrhosis affect pulmonary function. Some diseases affect both hepatic and pulmonary systems (i.e., cystic fibrosis, α_1-antitrypsin deficiency); others are primary pulmonary processes, such as interstitial lung disease, primary pulmonary hypertension (portopulmonary hypertension [PPHTN]), and obstructive airway disease. Three important pulmonary manifestations of cirrhosis are discussed: The first relates to the volume effect of ascites and effusion when present: diaphragmatic excursion is reduced, affecting the total lung capacity. Intrapulmonary shunting is less common and is known as the hepatopulmonary syndrome. Finally, PPHTN is another cause of respiratory insufficiency.

Ascites and Hepatic Hydrothorax: The presence of copious ascites can lead to compromised diaphragmatic excursion secondary to increased intra-abdominal and intrapleural pressures. Ascites may also induce hepatic hydrothorax (typically right sided pleural effusion) via transdiaphragmatic lymphatic communication.[124] Compression of lung parenchyma by the effusion impairs gas exchange, and results in ventilation–perfusion mismatch with subsequent hypoxemia. Decreased functional residual and total lung capacity are the end result. Volume removal, either via diuresis, large-volume paracentesis, or thoracentesis can ameliorate symptoms and reduce work of breathing.[125] For patients refractory to the above measures, strategies such as TIPS, indwelling pleural catheter placement, and pleurodesis have been described. Liver transplant is definitive.[125]

Hepatopulmonary Syndrome. HPS is characterized by abnormal arterial oxygenation caused by intrapulmonary vascular dilatations in the setting of

liver disease or portal hypertension. It occurs in patients with mild to severe hepatic disease and is present in approximately 4% to 47% of patients with chronic liver disease (depending on criteria used and population studied).[126,127] Symptoms include dyspnea, platypnea (worsening dyspnea with movement from a supine to an erect position), and orthodeoxia (decreased oxygen tension from supine to erect). The basis for these symptoms is increasing shunt within dilated capillaries in the basal lung that occurs with standing. Spider nevi, clubbing, and cyanosis as well as evidence of impaired oxygenation (peripheral oxygen saturation <96% on room air) may be present on examination. Hypoxemic criteria for HPS in patients with cirrhosis include: 1. PaO_2 <80 mm Hg (<70 mm Hg in patients over the age of 65 years) or 2. Alveolar–arterial gradient ≥15 mm Hg (≥20 mm Hg over the age of 65 years).[128]

Although the underlying mechanism of hypoxemia in these patients is right-to-left intrapulmonary shunting, ventilation–perfusion mismatch and impaired hypoxic vasoconstriction also play a role. Patients usually present with dyspnea and worsening hypoxemia without evidence of a primary pulmonary process. Initial diagnostic tools include pulse oximetry and arterial blood gas analysis. Pulmonary function testing excludes obstructive or restrictive airway disease as a cause of hypoxemia. A definitive diagnosis can be obtained by the use of contrast-enhanced echocardiography (bubble study) or technetium labeled-macroaggregated albumin (MAA) scanning, which will confirm the presence of intrapulmonary vascular dilation.[129,130] Contrast echocardiography is the most sensitive test, whereby intrapulmonary vascular dilation is demonstrated by the late appearance of microbubbles in the left heart three to six cardiac cycles after injection.[131] MAA scanning revealing a shunt of >6% suggests HPS as the major contributor to hypoxemia.[132] The only effective therapy for this disease is orthotopic liver transplantation, and those with HPS and with a PaO_2 <60 mm Hg receive extra priority at listing.[131]

PPHTN refers to pulmonary arterial hypertension that is associated with portal hypertension. It is a complication of portal hypertension due to either chronic liver disease or extrahepatic causes. It is defined as a mean pulmonary arterial pressure of greater than 20 mm Hg at rest, normal or low pulmonary artery occlusion pressure <15 mm Hg at rest, and pulmonary

vascular resistance >240 dyn/s/cm^{-5} on right heart catheterization in the setting of documented portal hypertension.[128] It is a relatively uncommon complication of cirrhosis with prevalence rates of 2% in those with chronic liver disease, to rates of 16% in those listed for transplant. When severe, it carries a substantial risk of mortality and is a contraindication to liver transplantation.[133,134] Doppler echocardiography will suggest elevated right heart pressures (i.e., elevated peak tricuspid regurgitant velocity [TRV] >2.8 m/sec, or those with lower peak TRV but other signs of pulmonary hypertension), which is confirmed by right heart catheterization. The exact pathophysiology behind PPHTN is unknown, but portal hypertension is a necessary component of the disease process. The hyperdynamic state in portal hypertension may be the main contributory factor, although the severity of PPHTN does not correlate with the severity of portal hypertension.[135] Although the high flow state present in cirrhosis elevates right-sided pressures, the fixed obstruction present in the pulmonary microcirculation is highly lethal and is not likely to improve with liver transplantation.

Treatment is nearly identical to that for other types of pulmonary arterial hypertension. Beta-blockers should be avoided when feasible since they can worsen right heart failure and increase pulmonary vascular resistance. TIPS can increase right ventricle preload and worsen heart failure and should be used with caution if indicated for other reasons. Prolonged intravenous infusion of prostaglandins (e.g., epoprostenol) improves pulmonary hemodynamics but does not prolong survival.[134] The oral endothelin receptor antagonists such as bosentan and ambrisentan are also commonly used. Phosphodiesterase-5 inhibitors (sildenafil and tadalafil) are also commonly prescribed. As stated above, severe PPHTN (mPAP >50 mm Hg) is an absolute contraindication to liver transplantation. For patients in whom medical therapy can maintain mPAP under 35 mm Hg and PVR less than 400 dyn/s/cm^{-5}, MELD exception points for priority listing for liver transplantation are available.[136]

Hepatic Encephalopathy

Etiology

7 Hepatic encephalopathy is a neuropsychiatric syndrome due to liver disease that is characterized by variable alterations in mental status. The

manifestations (see clinical features below) range from subtle deficits detectable only by detailed psychometric tests to confusion, lethargy, and ultimately frank coma. The encephalopathy presents in association with acute hepatic failure, as a consequence of progression of chronic liver disease, or after the creation of a surgical portosystemic shunt. Usually, a precipitating event, such as an acute variceal hemorrhage, infection, deterioration in renal function, drugs (e.g., benzodiazepenes), or constipation can be found. Encephalopathy develops in 30% to 45% of patients with cirrhosis and in 10% to 50% of patients with TIPS.

The causative agent in hepatic encephalopathy has been the subject of much debate. Ammonia has been heavily implicated in the development of this condition. However, an elevated ammonia concentration in the serum is not required for diagnostic purposes, nor is it specific. Under normal circumstances, ammonia is produced by bacterial catabolism of nitrogenous sources (protein) in the intestine after which it is absorbed into the portal circulation to undergo degradation in the liver.[137] Ammonia and other bacterial degradation products are theorized to access the peripheral circulation as a result of both poor hepatic metabolism and portosystemic shunting. In patients with cirrhosis, the permeability of the brain to ammonia appears to be increased.[138] Other etiologic agents that have been suggested and include γ-aminobutyric acid (GABA), endogenous benzodiazepines,[139] branched-chain amino acids (BCAAs such as tryptophan),[140] neurotoxic short-chain fatty acids, mercaptans, phenols, and endogenous opiates.[141]

The following observations suggest that ammonia is the key mediator in hepatic encephalopathy: (a) ammonia levels are increased in 80% to 90% of patients with the condition,[142] (b) factors that precipitate hepatic encephalopathy cause increases in ammonia levels, and (c) treatments that relieve hepatic encephalopathy lower ammonia levels.[143] However, contrary to this hypothesis include the following arguments: (a) levels of ammonia correlate poorly with the severity of hepatic encephalopathy, (b) elevated ammonia levels alone do not cause encephalopathy, (c) administration of ammonia to patients with cirrhosis but not hepatic encephalopathy does not cause encephalopathy, and (d) treatments that reduce ammonia levels also reduce levels of other putative toxins.[143]

Clinical Features

A wide range of neurologic symptoms may occur in patients with hepatic dysfunction. Subtle changes may include changes in personality, memory loss, alterations in diurnal sleep variation, and minor decreases in intellectual function. The West Haven criterion describes the range of clinical stages. Neuromuscular impairment present may result in bradykinesia, asterixis, slurred speech and ataxia, and ultimately decerebrate posturing of coma. With progression of disease, asterixis may occur. Stigmata of liver disease are usually evident, including fetor hepaticus and spider angiomas. The combination of asterixis, elevated ammonia levels, and altered mental status in a patient with known liver disease strongly suggests the diagnosis. Electroencephalographic changes are nonspecific and may occur in patients with a variety of other conditions.

Treatment

Treatment options for hepatic encephalopathy include correction of the precipitating factors where possible. Treatments to reduce bacterial load of ammonia from the intestine are also instituted. A search for precipitating infection is extremely important. Pulmonary, urinary, and ascitic infections should be sought via appropriate cultures and ascitic fluid analysis. An assessment of overall volume status and drug history as well as a search for variceal bleed can be made (**Table 59.10**).

Treatment begins with general supportive care including resuscitation and rehydration via volume expansion as well as providing appropriate nutrition and correcting electrolyte abnormalities. The removal of nitrogenous compounds from the small and large bowel is the critical step in decreasing ammonia and other toxic substances from the blood. Orally administered cathartics and enemas can cleanse the bowel of protein and the source of ammonia. However, dietary restriction of protein is no longer recommended as it contributes to the skeletal muscle loss and malnutrition associated with cirrhosis. Dietary supplementation with BCAAs (only necessary in those intolerant of protein) improves the relative deficit of these compared to aromatic amino acids and improves the rate of recovery from episodic hepatic encephalopathy. L-carnitine supplementation has also been demonstrated to improve cognitive deficits and reduce ammonia levels.[144]

Table 59.10 Treatment of Hepatic Encephalopathy

Identify and treat precipitating factors: Disordered carbohydrate metabolism Drugs (benzodiazepines, barbiturates) Infection (spontaneous bacterial peritonitis, other) Hypotension Hypoxia Excess exogenous protein Gastrointestinal bleeding Electrolyte abnormalities Alkalosis Constipation
Supportive therapy: Eliminate dietary nitrogen Purge gastrointestinal tract to remove blood and other nitrogenous compounds Nonabsorbable antibiotics (Rifaximin) Lactulose (or lactitol)
Dopamine receptor agonists: L-dopa and bromocriptine[a]
Branched-chain amino acid[b]
Temporary liver support
Orthotopic liver transplantation

[a] Arousal effect in selected patients may be secondary to enhanced renal function.

[b] High cost and equivocal benefits of intravenous amino acid mixtures make it difficult to justify routine use.

Lactulose is a nonabsorbable disaccharide that acts as a cathartic when administered orally and is a mainstay of therapy. A dose of 45 to 90 g/d divided in two to four doses is generally effective and is adjusted to produce two to three bowel movements per day. Lactulose reaches the distal ileum

and colon where it is metabolized by intestinal bacteria and enhances the bacterial uptake of ammonia.[145] Hourly doses of 30 to 45 mL of lactulose can be administered to induce more rapid improvement during the initial phase of therapy and symptoms may abate within 24 hours to 48 hours. Side effects include flatulence, diarrhea, and electrolyte abnormalities.

Nonabsorbable antibiotics have also been used to decrease the number and concentration of ammonia-forming bacteria in the gut. Rifaximin is a minimally absorbed macrolide antibiotic. The addition of rifaximin to lactulose has been shown to result in a higher proportion of patients experiencing complete reversal of hepatic encephalopathy (76% vs. 50.8%) and decreased mortality (23.1% vs. 49.1%) compared to lactulose and placebo.[146] Based on current evidence, the treatment of hepatic encephalopathy should consist of treatment of any precipitating factors, followed by lactulose administration. Rifaximin should be added for patients without improvement in the first 24 hours. Following an episode of overt hepatic encephalopathy, maintenance therapy with lactulose with or without rifaximin should be administered indefinitely as secondary prophylaxis.[147]

Neomycin and metronidazole are antibiotics active against gram-negative anaerobes such as *Bacteroides*. Some studies have shown that neomycin for 4 days is equally as effective as lactulose,[148] and metronidazole for 7 days is as effective as neomycin.[149] In addition, for chronic hepatic encephalopathy, neomycin for 10 days was equal to lactulose.[150] However, other RCT evidence has shown no difference comparing neomycin versus placebo.[151] Due to the risk of nephrotoxicity and irreversible ototoxicity, neomycin therapy has fallen out of favor.[147] Metronidazole is associated with neurotoxicity.

PORTAL HYPERTENSION

8 Portal hypertension is defined as a portal vein pressure above the normal range of 5 to 8 mm Hg. It may also be defined by a hepatic vein–portal vein pressure gradient (HVPG) greater than 5 mm Hg.[152] Pressures in the portal venous system are usually measured indirectly via the wedged hepatic venous pressure using a technique similar to that used to determine

pulmonary capillary wedge pressure by pulmonary arterial (Swan–Ganz) catheterization.

Current guidelines recommend classification of cirrhosis into compensated and decompensated stages and further substaging compensated cirrhotic patients into those with mild portal hypertension and those with clinically significant portal hypertension (CSPH).[153] CSPH predicts the development of more advanced stages of disease. Patients with CSPH are divided into those with and without gastroesophageal varices. Treatment of portal hypertension differs depending on the stage and substages of cirrhosis, because prognosis, mechanisms of disease, and therapeutic targets are different. Clinically significant portal hypertension is defined by an HVPG equal to or greater than 10 mm Hg (the gold-standard method of assessment). If HVPG is unavailable, noninvasive testing resulting in a liver stiffness >20 to 25 kPa with low platelets, splenomegaly, or presence of portosystemic collaterals on imaging demonstrates CSPH. Ongoing screening endoscopy for varices should be performed in patients with CSPH.

Anatomy

The venous anatomy of the portal system is relatively constant, with the "usual" anatomy present in 98% of the population. The portal vein is formed by the confluence of the superior mesenteric and splenic veins behind the neck of the pancreas. The inferior mesenteric vein most often joins the splenic vein before the portal vein is formed. A third of people have the inferior mesenteric vein joining the superior mesenteric vein. Occasionally, the superior mesenteric vein is not present and the portal vein is formed by multiple smaller mesenteric branches which join the splenic vein.

Portosystemic Collaterals

As portal hypertension develops, portal pressure rises in tributaries of the portal vein. This elevated pressure results in the expansion and dilation of these tributaries as well as of the portosystemic collateral venous communications. The sites of portosystemic communication have important clinical consequences. Dilation of and increased flow through the coronary or left gastric vein becomes highly significant in portal hypertension. The

result is increasing portal blood flow to the veins of the lesser curve of the stomach and the esophagus, leading to the formation of esophageal and gastric varices as well as portal hypertensive gastropathy. The inferior mesenteric vein communicates with rectal branches that distend to form hemorrhoids; the umbilical vein remnant communicates with the left portal vein and dilates in portal hypertension to carry blood through the ligamentum teres of the falciform ligament to veins of the abdominal wall. This paraumbilical plexus dilates and becomes visible on examination as the "caput medusae." Splenic venous flow increases and dilates the short gastric veins further contributing to gastric varices. Retroperitoneal collaterals (**Fig. 59.7**) also form and can create large splenorenal shunts that decompress the portal system but are associated with severe encephalopathy.

Pathophysiology

Increased resistance to portal blood flow may occur at different levels, within the liver (intrahepatic) secondary to cirrhosis, prehepatic in situations of portal vein thrombosis, or posthepatic in hepatic venous obstruction. Normally, the porous hepatic venous sinusoids of the liver offer little resistance to portal flow. Moreover, the liver has limited control over portal blood flow; it is primarily a passive recipient of splanchnic flow which is regulated at the level of the splanchnic arterioles.[154] As discussed above, collagen deposition in the space of Disse and contractile stellate cells cause increased resistance within the liver to portal blood flow. Furthermore, splanchnic vasodilatation and increased splanchnic flow occurs as a response to cytokine and hormonal alterations.

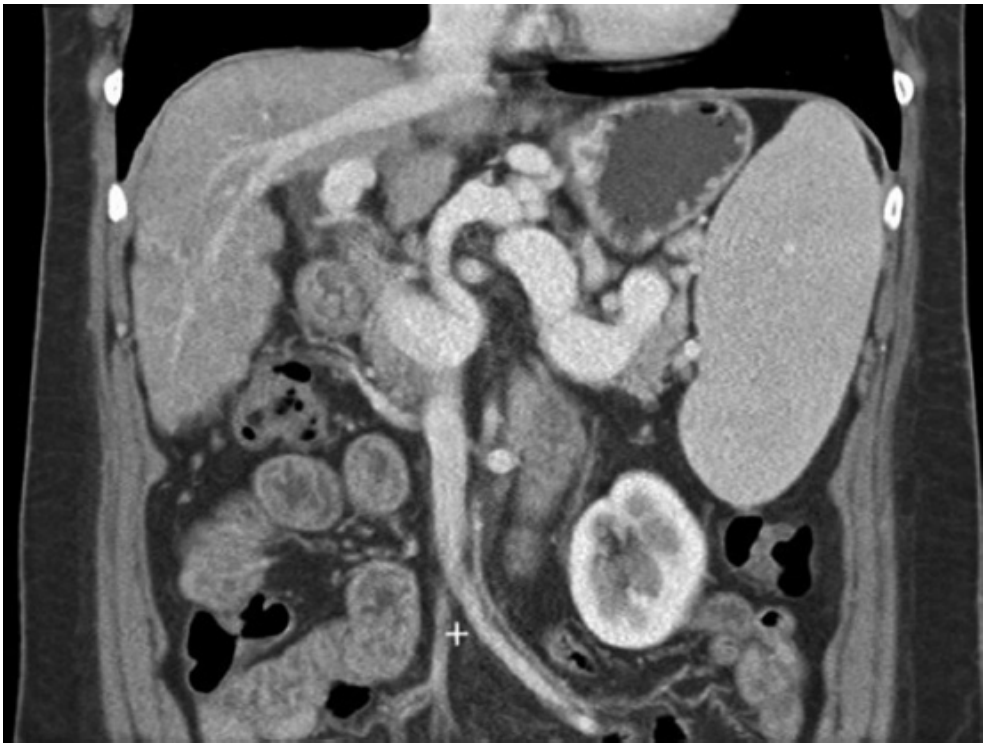

Figure 59.7 Coronal CT of a cirrhotic patient. Portal venous phase is shown demonstrating retroperitoneal collaterals and splenomegaly. (Image courtesy of Dr. Ihab Khamel, Department of Radiology, Johns Hopkins Hospital.)

The increased blood flow through collateral vessels and subsequently increased venous return cause the characteristic hemodynamic features of portal hypertension. An increased venous return via collateral vessels results in a subsequent increase in cardiac output and total blood volume and a fall in systemic vascular resistance.[155] Initially, blood pressure is normal, however with disease progression blood pressure falls.[156]

Nitric oxide, a potent vasodilator, as well as other vasodilators (prostacyclin, endotoxin, and glucagon) are elevated in patients with cirrhosis and portal hypertension.[157,158]

Etiology

Different pathologic processes cause portal hypertension (**Table 59.11**). These are classified as prehepatic, intrahepatic (presinusoidal, sinusoidal, or postsinusoidal), or posthepatic conditions. As noted above, in prehepatic and posthepatic conditions, portal hypertension is the result of mechanical venous

obstruction at the level of the portal or hepatic veins, respectively, whereas cirrhosis is the main cause of hepatic portal hypertension.

Budd–Chiari Syndrome and Veno-Occlusive Disease

Budd[159] described the classic presentation of BCS—abdominal pain, ascites, and hepatomegaly. Chiari[160] described the pathologic characteristics of the liver. Venous obstruction and hepatic venous occlusion causes an increase in pressure in the central veins with centrilobular congestion, necrosis, fibrosis, and cirrhosis with portal hypertension.

Common causes in Western populations are hypercoagulable states associated with polycythemia vera, myeloproliferative disorders, paroxysmal nocturnal hemoglobinuria, and hypercoagulable disorders.[161,162] In Eastern countries, the major causes of obstruction of the vena cava and hepatic veins are membranous webs that directly occlude the vessels. The etiology of these webs is unknown. Veno-occlusive disease is characterized by obliterative endophlebitis of the intrahepatic veins. Causes of veno-occlusive disease include medications, toxins, and pyrrolizidine alkaloids (naturally occurring alkaloids in some plant species).

BCS may present with acute, subacute, or chronic symptoms and is often misdiagnosed. Nearly 50% of patients have had symptoms for more than 3 months.[163] Early treatment prevents the development of hepatic fibrosis and the inevitable progression to end-stage liver disease. Acute symptoms include: hepatomegaly, right upper quadrant abdominal pain, nausea, vomiting, and ascites. Patients may present with the complications of cirrhosis and portal hypertension if presentation is late. In the chronic form, the liver atrophies except for the caudate lobe, which may hypertrophy. This is a classic hallmark of the disease and occurs because the caudate venous outflow into the vena cava is preserved. Compensatory hypertrophy of the caudate then occurs. The hypertrophied caudate lobe narrows the retrohepatic vena cava it surrounds. This may be completely obliterated with total obstruction of blood flow.

Although the diagnosis can be made by ultrasonographic evaluation of the liver and its vasculature with a sensitivity of 85% to 95%,[161] cross-sectional imaging assists in staging and planning therapy. Duplex ultrasound may reveal the location of the obstruction and characterize flow within the vena

cava and hepatic, portal, mesenteric, and splenic veins. Other common findings consistent with BCS include a lack of visualization of the hepatic veins, an enlarged caudate lobe with compressed vena cava, enlarged intrahepatic collaterals, splenomegaly, and ascites.[95] Thrombus within the hepatic veins or IVC may be seen.[164]

Because the vascular obstruction is usually well established at the time of presentation, anticoagulation alone is rarely sufficient therapy for BCS. Historically, major open operations, including mesoatrial shunting,[165,166] and liver transplantation[167] were favored. However, minimally invasive approaches are now preferred with percutaneous portacaval shunting effective in achieving decompression of the portal system.[168]

Table 59.11 Common Causes of Portal Hypertension

Prehepatic
Congenital atresia
Extrinsic compression
Schistosomiasis
Portal, superior mesenteric, or splenic vein thrombosis
Splanchnic arteriovenous fistula

Intrahepatic (Presinusoidal)
Schistosomiasis
Idiopathic noncirrhotic portal hypertension (including nodular regenerative hyperplasia)
Primary biliary cholangitis (PBC)
Sarcoidosis
Congenital hepatic fibrosis
Primary sclerosing cholangitis
Adult polycystic liver disease
Vinyl chloride toxicity
Neoplastic occlusion of portal vein

Intrahepatic (Sinusoidal)
Arsenic poisoning
Vinyl chloride toxicity
Drugs (e.g., amiodarone, methotrexate)

Chronic–Cirrhotic
NASH
Hepatitis B, C
Alcohol
α_1-Antitrypsin deficiency
Cryptogenic
Cystic fibrosis
Hemochromatosis
Wilson's disease

Chronic–Noncirrhotic
Congenital hepatic fibrosis
Focal regenerative hyperplasia

Hepatic veno-occlusive disease Gaucher disease Amyloid or light chain deposition in the space of Disse Mastocytosis Sarcoidosis
Intrahepatic (Postsinusoidal) Budd–Chiari syndrome Sinusoidal obstruction syndrome (veno-occlusive disease) Chronic radiation injury Vitamin A toxicity Epithelioid hemangioendothelioma Sarcoidosis
Posthepatic Cardiac disease (Chronic heart failure, constrictive pericarditis) IVC obstruction (e.g., Budd–Chiari syndrome) Vena cava webs

Creation of a mesoatrial shunt at surgery has been used to achieve decompression in the past in situations when bridging fibrosis was not present and transplant not indicated. This was first described by Cameron and Maddrey and involves decompressing the portal system by bypassing the hepatic veins and narrowed IVC.[165] After abdominal incision, the superior mesenteric vein is exposed. A 16-mm mesoatrial prosthesis (ring reinforced graft) is positioned and tunneled under the sternum into the right chest after a right lateral thoracotomy. The pericardium is opened and right atrium and appendage exposed. This graft is anastomosed first to the superior mesenteric vein and subsequently right atrial anastomosis completed.

Today, decompression of the portal system is achieved percutaneously via transjugular intrahepatic portosystemic shunt (TIPS) procedure. Contrary to TIPS in other settings of cirrhosis and portal hypertension, the rates of postprocedural encephalopathy are usually not increased in patients with BCS, because they have anatomically healthy livers that are able to recover fully if decompression is achieved early, prior to the establishment of cirrhosis. If BCS results in fibrosis and cirrhosis, liver transplantation may

be necessary. Postoperatively, patients require long-term anticoagulation to prevent recurrent thrombosis.

As noted, TIPS may be used as first-line therapy, and it has supplanted surgical shunting in the modern era.[169–171] One- and 5-year survival rates after TIPS have been demonstrated to be 93% and 74%, respectively.[171] Many patients develop shunt occlusion; however, further angiographic manipulation and long-term anticoagulation can be performed and maintain patency.

Portal Vein Thrombosis

Portal vein thrombosis is commonly associated with advanced cirrhosis, and may herald the occurrence of HCC. In children, portal vein thrombosis in the absence of cirrhosis is the most common cause of cirrhosis. However, this spontaneous portal venous thrombosis is uncommon in adults.[172,173] In contrast to patients with cirrhosis-induced portal hypertension, these patients have normal liver function and are not susceptible to the development of complications such as encephalopathy. Causes of portal vein thrombosis include umbilical vein infection (the most common cause in children), coagulopathies (protein C and antithrombin III deficiency), hepatic malignancy, myeloproliferative disorders, inflammatory bowel disease, pancreatitis, trauma, and previous splenorenal shunt.[174] In patients with cirrhosis, a rebalanced hemostasis system prone to hypercoagulability can also contribute. This is mostly due to decreased levels of protein C and elevated levels of factor VIII.[175] Most cases in adults are idiopathic.

Imaging shows an echogenic lesion in the lumen of the portal vein and an absence of portal venous flow on duplex examination. With time, cavernous transformation of the portal vein may occur, in which channels develop within the chronically thrombosed, recanalizing portal vein.[172] CT and MRI are also useful in establishing the diagnosis. Portal vein thrombosis in a noncirrhotic patient may manifest initially with variceal bleeding. Splenomegaly is an important clinical sign.

The initial therapeutic option for the control of hemorrhage caused by portal vein thrombosis is endoscopic esophageal variceal ligation. If unsuccessful, the distal splenorenal shunt has been the traditional surgical treatment for patients with isolated portal vein thrombosis. In patients whose

intrahepatic portal vein is patent (most commonly children), a shunt may be created between the superior mesenteric vein and the patent left portal vein within the parenchyma of the liver (Rex shunt). This may be performed with internal jugular vein and may be the optimal therapeutic procedure for reestablishing physiologic portal flow.[176] This solution reduces portal pressure by restoring blood flow to the liver, preventing chronic hepatic atrophy and dysfunction which would otherwise occur. Many consider the Rex shunt to be the first-line treatment with splenorenal shunting reserved for patients who have no remnant intrahepatic portal system to receive the shunted blood.

Splenic Vein Thrombosis

Splenic vein thrombosis is most often caused by disorders of the pancreas, including acute and chronic pancreatitis, trauma, malignancy and pancreatic pseudocyst. This association is related to the proximity of the splenic vein posterior to and abutting the pancreas. Other causes of thrombosis include retroperitoneal masses, abscesses, and inflammatory bowel disease; the remaining cases are idiopathic. The thrombosis results in isolated "sinistral" or "left-sided" portal hypertension. This increased venous pressure causes the development of gastric varices, which are present in approximately 80% of patients, and esophageal varices in 30% to 40%.[177] Patients, who are expected to have normal liver function, are readily cured with splenectomy, although observation for asymptomatic patients is acceptable. The main indication for splenectomy is variceal hemorrhage.

Complications of Portal Hypertension

9 The most important, potentially lethal complication of portal hypertension is GI bleeding secondary to esophageal and gastric varices. Ascites and hepatic encephalopathy are other debilitating complications. The mortality risk associated with portal hypertension is primarily related to the functional status of the cirrhotic liver. In 1964, Child and Turcotte introduced a scoring system of liver function for the purposes of assessing prognosis after portosystemic shunt surgery in patients with cirrhosis. This has been subsequently modified several times to the *Child–Turcotte–Pugh (CTP)*

score (**Table 59.12**). These indices incorporate clinical and laboratory data as a means to assess the functional status of the liver, estimate hepatic reserve, and predict morbidity and mortality. These criteria were adopted by the United Network for Organ Sharing (UNOS) as a tool for stratifying pretransplant mortality risk for patients on the waiting list for liver transplantation.[178] Over the last decade, the use of these criteria in transplant has been replaced by the model for end-stage liver disease (MELD) score, which uses serum bilirubin, creatinine, and the international normalized ratio (INR) to produce a surprisingly robust prediction of 90-day mortality for patients with cirrhosis on the transplant list.[179] Subsequently, the inclusion of serum sodium to create the MELD-Na score was introduced in 2016 into allocation of livers for transplantation, after it was demonstrated that hyponatremia is associated with increased mortality in patients with end-stage liver disease. Though the CTP score produces a more complete assessment of the patient, its use of subjective clinical components introduces potential variability by clinicians in the assessment of degree of liver disease and therefore makes it unreliable as a verifiable element in assessment of compliance with center behavior in national organ transplant policy.[180,181]

Table 59.12 Child–Turcotte Criteria for Hepatic Functional Reserve

Criterion	Class A	Class B	Class C
Encephalopathy	None	Minimal	Advanced
Ascites	None	Easily controlled	Poorly controlled
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/gL)	>3.5	3–3.5	<3
Nutrition	Excellent	Good	Poor, "wasting"
Child–Turcotte–Pugh Grading of Severity of Liver Disease			
Score	**1**	**2**	**3**
Encephalopathy	None	1 or 2	3 or 4
Ascites	None	Mild	Moderate
Bilirubin (mg/dL)	1–2	2.1–3	≥3.1
Albumin (g/dL)	≥3.5	2.8–3.5	≤2.7
Prothrombin time (s)	1–4	4.1–6	≥6.1
or INR	<1.7	1.7–2.3	>2.3
Grade A, 5–6; grade B, 7–9; grade C, 10–15			

INR, international normalized ratio.

Adapted from Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60(8):646–649, with permission.

While the MELD score was initially developed to determine prognosis of patients after undergoing TIPS, the CTP score has had long-standing use as a reliable predictor of mortality risk for shunt surgery and mortality risk of patients with cirrhosis undergoing other types of abdominal surgery.[182–184] Patients with normal function, termed "Child A," have adequate hepatic reserve and survival rates similar to those of noncirrhotic patients, whereas Child C patients have mortality rates in excess of 50% and may not tolerate any intervention except liver transplantation.

Varices

One of the most life-threatening complications of portal hypertension is bleeding from esophageal varices. Esophageal varices are dilated veins found most commonly in the distal 5 cm of the esophagus. In the normal esophagus, a venous plexus is located in the submucosa; in the distal esophagus, it becomes more superficial within the lamina propria.[185–187] This anatomy gives rise to the known increased incidence of bleeding occurring from distal esophageal varices. In addition, 5% to 33% of patients with portal hypertension have gastric varices.[188]

As portal venous system pressure increases, varices are more likely to develop. Varices generally do not develop in persons with HVPGs less than 12 mm Hg. Pressure gradients above 12 mm Hg are invariably present in patients with varices, but this pressure does not necessarily produce varices in all patients. Gastroesophageal varices are present in 40% of patients with Child A cirrhosis, and in up to 85% of patients with Child C cirrhosis.[153] Varices may also be present in chronic liver disease without frank cirrhosis. For example, 16% of patients with chronic hepatitis C and bridging fibrosis have varices.[189]

Esophageal varices are the cause of upper GI bleeding in approximately 10% of all patients presenting with acute bleeding. Conversely, cirrhotic patients bleed from sources other than varices (e.g., peptic ulcer disease) in up to 40% of cases. Risk of variceal bleeding increases with duration present and variceal size. Approximately half of patient with cirrhosis have esophageal varices, and one-third of all patients with varices will develop variceal hemorrhage with the highest risk during the first year after diagnosis.[153,190–192] Patients with large varices are at the greatest risk for an

initial bleed. Variceal bleeding ceases without intervention in up to 40% of patients, although the risk of mortality and recurrent bleeding remain high.[153] Of patients who survive an episode of bleeding, 30% rebleed within 6 weeks, and 70% at 1 year.[192,194] Mortality from bleeding varies, from 5% for Child's A, less than 25% for Child's B, and more than 50% for Child C patients, respectively.[194]

When combined with clinical data such as the presence of active alcohol consumption, certain endoscopic characteristics of varices have been correlated with initial episodes of bleeding. Variceal size, Child–Pugh class, and the presence of red wale markings (longitudinal dilated venules) are contributing factors. Direct and indirect measurements of portal pressure have been used to predict the likelihood of bleeding, with hemorrhage occurring only in patients with portal–hepatic venous gradients above 12 mm Hg.[195,196]

Diagnosis of Varices and Prevention of Initial Variceal Bleeding

Given the importance of variceal bleeding, methods to diagnose varices and to prevent both initial bleed (primary prophylaxis) as well as recurrent bleeding episodes (secondary prophylaxis) have been developed. Esophagogastroduodenoscopy (EGD) is the gold standard for the diagnosis of gastroesophageal varices, and is indicated upon the initial diagnosis of cirrhosis and after 2 to 3 years if none are present. If small (<5-mm) varices are present, EGD is repeated in 1 to 2 years, and if patients have decompensated cirrhosis, yearly endoscopic screening is recommended by the AASLD. After diagnosis of varices, primary and secondary bleeding prophylaxis is implemented and includes control of the underlying cause of cirrhosis (i.e., alcohol consumption or HCV treatment) and pharmacologic and surgical interventions to lower portal pressure.

Primary Prophylaxis for Prevention of Variceal Bleeding. In early-stage cirrhosis prior to the development of clinically significant portal hypertension, treatment aims to prevent progression, decompensation, and potentially allow for regression of cirrhosis. Elimination of the etiologic agent (e.g., alcohol, virus) at the current time is the mainstay of this strategy.

Beta Blockade: The use of nonspecific β-adrenergic blockade (NSBB) for prevention of variceal bleeding has been studied extensively in RCTs. There is no evidence that NSBB prevents the development of varices in patients without clinically significant portal hypertension.[153] NSBB such as propranolol and nadolol achieve β_1-adrenergic and β_2-adrenergic blockade which decreases cardiac output and increases splanchnic arteriolar vasoconstriction due to diminished β_2-adrenergic mediated dilation.[196,197] The end result is a decrease in portal blood flow and portal pressure (**Table 59.13**).

Whether portal hypertension is due to prehepatic, intrahepatic, or posthepatic conditions, these drugs are effective in pressure reduction.[198] The goal of therapy is to reduce the HVPG to less than 12 mm Hg or to more than 20% below baseline.[199] Meeting these goals decreases bleeding risk as well as the risk of developing ascites, SBP, and death.[200] Two meta-analyses evaluating seven RCTs show efficacy of propranolol or nadolol versus placebo in preventing initial bleeding: risk of bleeding is reduced by 40%, with a bleeding risk of 27% in placebo versus 16% in treated patients.[199,201,202] In patients with cirrhosis, both with and without ascites, who responded to lowering of portal pressure (based on reduction in HVPG), NSBB has also been shown to reduce events (ascites, variceal hemorrhage, SBP, HRS, encephalopathy), reduce mortality and requirement for liver transplantation.[203] Side effects of beta-blockers, however, may limit use, and it has been shown that they do not prevent the formation of varices in patients who do not yet have them.[204]

Surgical Intervention as Prevention. In the 1950s and 1960s, surgeons used surgical portosystemic shunts in an attempt to prevent variceal bleeding. Randomized trials showed that these procedures were effective in preventing variceal bleeding, but were associated with an increased incidence of hepatic failure and encephalopathy and had no effect on overall survival.[205,206] Indeed, these results provided clinical support for the notion that portal diversion accelerates the decline of liver function in patients with cirrhosis. These procedures are no longer performed for this indication.

Endoscopic Sclerotherapy and Variceal Ligation. While previously an accepted practice, due to technical challenges and the incidence of esophageal and pulmonary complications, endoscopic sclerotherapy (ES) as primary prevention of variceal bleeding is no longer practiced. Variceal ligation (EVL) as a method of primary prophylaxis to prevent initial bleeding in high-risk patients with varices initially reported mixed results.[207–209] Consensus recommendations regarding prophylaxis are now published in practice guidelines from the AASLD: patients with cirrhosis with small, high-risk varices (i.e., presence of red whale markings or occurring in a CTP-C patient) should be managed with beta-blocker prophylaxis; patients with medium or large varices should undergo EVL or beta blockade with NSBB or carvedilol as primary prophylaxis.[153]

Table 59.13 Primary Prophylaxis: Management for Patients with Varices That Have Not Bled

Drug	Dose	Therapy Goals	Maintenance/Follow-up
Propranolol	▪ 20–40 mg bid adjusted every 2–3 d to a maximum of 320 mg/d in patients without ascites (160 mg/d in patients with ascites)	▪ Resting HR of 55–60 bpm ▪ Systolic BP should not decrease <90 mm Hg	▪ Monitor HR to ensure on target at every outpatient visit ▪ Continue indefinitely ▪ No need for follow-up EGD
Nadolol	▪ 20–40 mg orally once daily adjusted every 2–3 d to maximum of 160 mg/d in patients with ascites (80 mg/d in patients without ascites)		
Carvedilol	▪ Start with 6.25 mg	Systolic BP should not	▪ Continue indefinitely

	once a day ▪ After 3 d increase to 6.25 mg twice a day ▪ Maximum dose 12.5 mg/d	decrease <90 mm Hg	▪ No need for follow-up EGD
Endoscopic variceal ligation	▪ Every 2–8 wks until the eradication of varices	▪ Variceal eradication	▪ First EGD 3–6 mo after eradication and every 6–12 mo thereafter

HR, heart rate; BP, blood pressure.

Adapted from Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal Hypertensive Bleeding in Cirrhosis: Risk Stratification, Diagnosis, and Management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2017;65(1):310–335.

Esophageal Variceal Bleeding

Initial Management. Esophageal variceal bleeding (**Table 59.14**) is a life-threatening emergency requiring intensive care. Patients who recover from the first episode of variceal hemorrhage have a high rebleeding risk (60% in the first year) with a mortality of up to 33%.

Table 59.14 Guidelines for Management of Patients Presenting with an Acute Bleed

Resuscitation, intravenous access, endotracheal intubation, and ICU care as indicated
Performance of endoscopic evaluation within 12 hrs of bleed, and if variceal hemorrhage is suspected, variceal ligation should be performed
Intravenous vasoactive drugs should be initiated and continued for 2–5 d with addition of nonselective beta blockade once these are discontinued
TIPS is indicated if hemorrhage is not controlled or if bleeding recurs despite pharmacologic therapy and variceal ligation
Prophylactic antibiotics (ceftriaxone) should be initiated

Adapted from: Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017;65(1):310–355.

Initial management is similar to any other emergency due to hemorrhage: The airway is immediately secured, attention is given to ensuring adequate oxygenation and ventilation, and secure large bore iv access is obtained. Laboratory studies aiding resuscitation include measurement of hemoglobin and hematocrit, coagulation status, liver function, electrolytes and renal function.

Resuscitation begins with administration of packed red blood cells (PRBCs), platelets, and fresh frozen plasma as well as intravenous crystalloid as appropriate, and care is transitioned to an intensive care setting. Transfusion using a restrictive strategy (initiating PRBC transfusion at a hemoglobin threshold of 7 g/dL and maintaining it at 7 to 9 g/dL) is associated with a significant decrease in mortality compared to a "liberal" transfusion strategy (initiating PRBC transfusion at a hemoglobin threshold of 9 g/dL and maintaining it at 9 to 11 g/dL). Lower rebleeding and mortality rates were seen in cirrhotic patients randomized to the restrictive strategy.[210] Transfusion and volume expansion in the individual patient should take into account other factors, such as age, cardiovascular disorders, ongoing

bleeding, and hemodynamic status. It should also be noted that INR is not a reliable indicator of coagulation status in the setting of cirrhosis. There are currently no recommendations regarding the administration of platelets or the administration of coagulation factors, while RCTs examining the effect of administration of factor VIIa have not shown a clear benefit.

Cirrhotic patients who bleed are at a high risk of developing bacterial infections, including SBP. RCTs have shown that the use of antibiotic prophylaxis leads to a decrease in the development of infections, recurrent bleeding, and death. Seven days of intravenous ceftriaxone (1 g every 24 hours) is a standard recommendation.

Pharmacologic Therapy. The administration of vasoactive medications should be commenced if variceal bleeding is suggested (**Table 59.15**). A meta-analysis of 30 RCTs shows that the use of vasoactive agents in acute variceal hemorrhage is associated with lower 7-day all-cause mortality and lower transfusion requirements.[211] Vasoactive decrease the rate of bleeding and enhance the endoscopist's ability to visualize the site(s) of bleeding.

Vasopressin (antidiuretic hormone) has potent splanchnic vasoconstrictive properties that decrease portal and collateral blood flow. Continuous intravenous administration of vasopressin has been shown to reduce variceal bleeding, an observation initially made in 1962 and confirmed on several occasions.[212–214] Compared to placebo, vasopressin stopped bleeding in 52% versus 18% of patients. However, rates of rebleeding as high as 45% were noted. Vasopressin should be used in combination with a vasodilator, such as nitroglycerin to protect against coronary artery constriction, decrease cardiac events, and decrease intrahepatic and collateral resistance.[215,216]

Table 59.15 Vasoactive Agents Used in the Management of Acute Variceal Hemorrhage

Octreotide (somatostatin analog)	50-mcg IV bolus (can be repeated in first hour for ongoing bleeding), followed by 50 mcg/h continuous infusion	2–5 d
Vasopressin (with nitroglycerin)	0.2–0.4 U/min can be increased to 0.8 U/min. It should always be accompanied by nitroglycerin IV at a starting dose of 50 mcg/min (max 400 mcg/min) titrated to maintain SBP at approximately 90 mm Hg	24 hrs
Somatostatin	Initial IV bolus of 250 mcg (can be repeated in first hour if ongoing bleeding) Continuous IV infusion of 250–500 mcg/hr	2–5 d
Terlipressin (Vasopressin analog)	Initial 48 hrs: 2 mg IV every 4 hrs until control of bleeding Maintenance: 1 mg IV every 4 hrs to prevent rebleeding	2–5 d

Adapted from Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology* 2017;65(1):310–355.

Somatostatin and octreotide, its longer-acting eight-amino acid derivative, have been used extensively for the treatment of variceal bleeding. These agents decrease splanchnic blood flow indirectly rather than by direct vasoconstriction.[217] Effects of somatostatin are limited to the splanchnic circulation, so that side effects are minimized.[218] In multiple studies, somatostatin and octreotide have proved to be as effective as vasopressin, sclerotherapy, and balloon tamponade.[219–221] A meta-analysis showed octreotide to be more effective than vasopressin in achieving hemostasis.[211] Octreotide is therefore the drug of choice in the United States. Dosing typically consists of a bolus of 50 µg followed by an infusion of 50 µg/hr, to

be initiated as soon as variceal bleeding is suspected and continued for 3 to 5 days after the diagnosis has been verified.[153]

Endoscopic Interventions. Esophageal variceal ligation is performed at urgent endoscopy when varices are the source of bleeding. Signs of variceal bleeding at endoscopy include: a visualized actively bleeding varix, a "white nipple" sign, and blood in the stomach within 24 hours of a bleed without any other evident cause. The endoscopist proceeds to suction the varix into the lumen of a plastic channel and a rubber band is fired over the varix to complete ligation (**Fig. 59.8**). The varix and bleed is controlled and the tissue sloughs after 1 to 3 days, leaving a shallow ulcer.

Success rates for variceal ligation range from 80% to 100%. Ligation compares favorably to sclerotherapy.[222] Sclerotherapy can be used if bleeding is profuse such that visualization is difficult.

Balloon Tamponade. Up to 20% of variceal hemorrhage episodes may be refractory to standard therapy, and in these circumstances balloon tamponade (**Fig. 59.9**) can bridge to a definitive therapy such a TIPS. Tamponade has high success rate in controlling bleeding but is also associated with a high rate of serious adverse events and a mortality rate near 20%. Tamponade entails the placement of a specialized nasogastric tube (the Sengstaken–Blakemore and Minnesota tubes) with two balloons that can be inflated separately to different pressures. These balloons compress varices present at the gastroesophageal junction and the esophagus. Once the mainstay in the initial management of variceal bleeding, use of these tubes is rare and the techniques involved in placing them are becoming a lost art. Incorrect use may cause fatal complications due to esophageal injury. The Sengstaken–Blakemore tube consists of a gastric and an esophageal balloon with a sump port for gastric suctioning. The Minnesota tube has an additional port above the esophageal balloon for aspiration of saliva and other material.

Prior to tube placement, patients undergo endotracheal intubation to maintain a safe airway. The tube is then passed through the nose and into the stomach. Imaging confirms placement of the tip of the tube in the stomach

before balloon inflation. This is critical to avoid inflation of the gastric balloon within the esophagus and subsequent esophageal perforation. The gastric balloon is inflated with 200 mL of air and firmly pulled backward against the gastroesophageal junction to tamponade any proximal gastric bleeding. The esophageal balloon is then inflated to a pressure of 30 to 40 mm Hg, and the tube is secured in position by means of a facemask or helmet to stabilize the tube and prevent inadvertent removal.

Complications of balloon tamponade include aspiration, esophageal and gastric perforation, and necrosis. These may occur in 10% to 20% of patients. Use is restricted to 24 hours to reduce the chance of these complications. Success rates for cessation of bleeding are 70% to 80%, but more than half of all patients rebleed when the balloons are deflated. Although this method is highly effective in the initial control of bleeding, because of its transient effect it is only a temporizing bridge to a more definitive procedure (e.g., TIPS, surgical shunting, or transplantation) and is used only after endoscopic and pharmacologic therapies have failed.

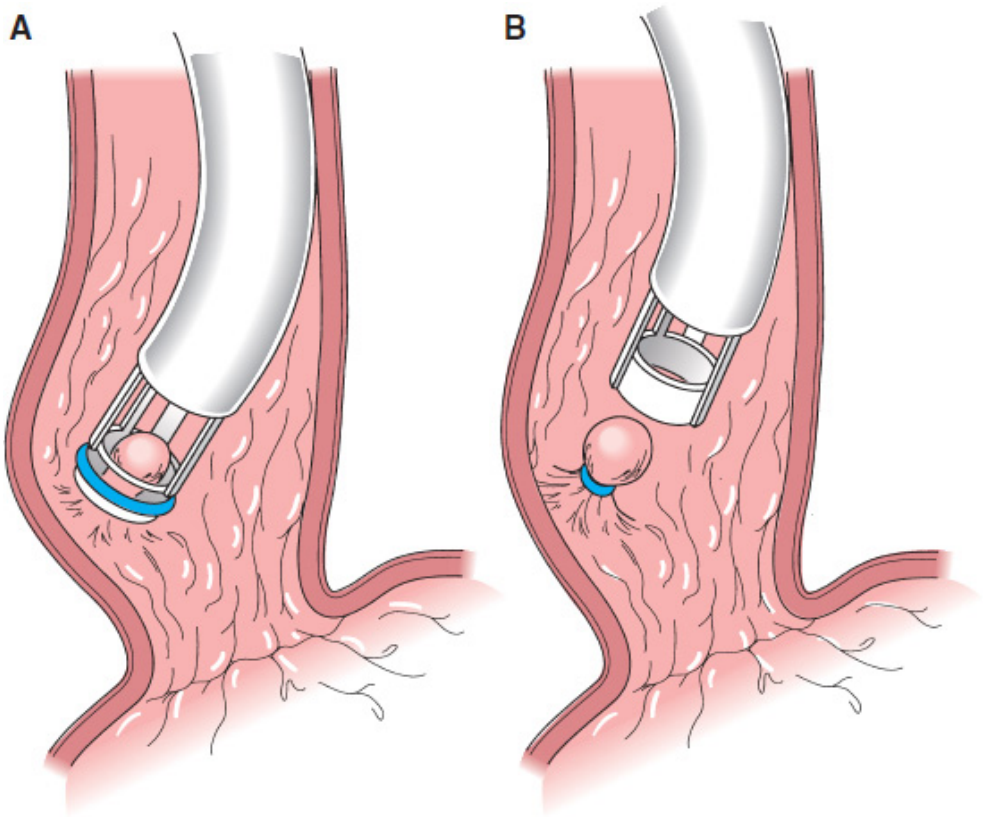

Figure 59.8 Endoscopic ligation of esophageal varices. The device used for ligation is based on the standard Barron-type ligator for the treatment of anal hemorrhoids. The esophageal varix is drawn up into the ligating device with suction (**A**), and the base of the varix is ligated with an O-ring (**B**). Up to six varices can be treated at a single session.

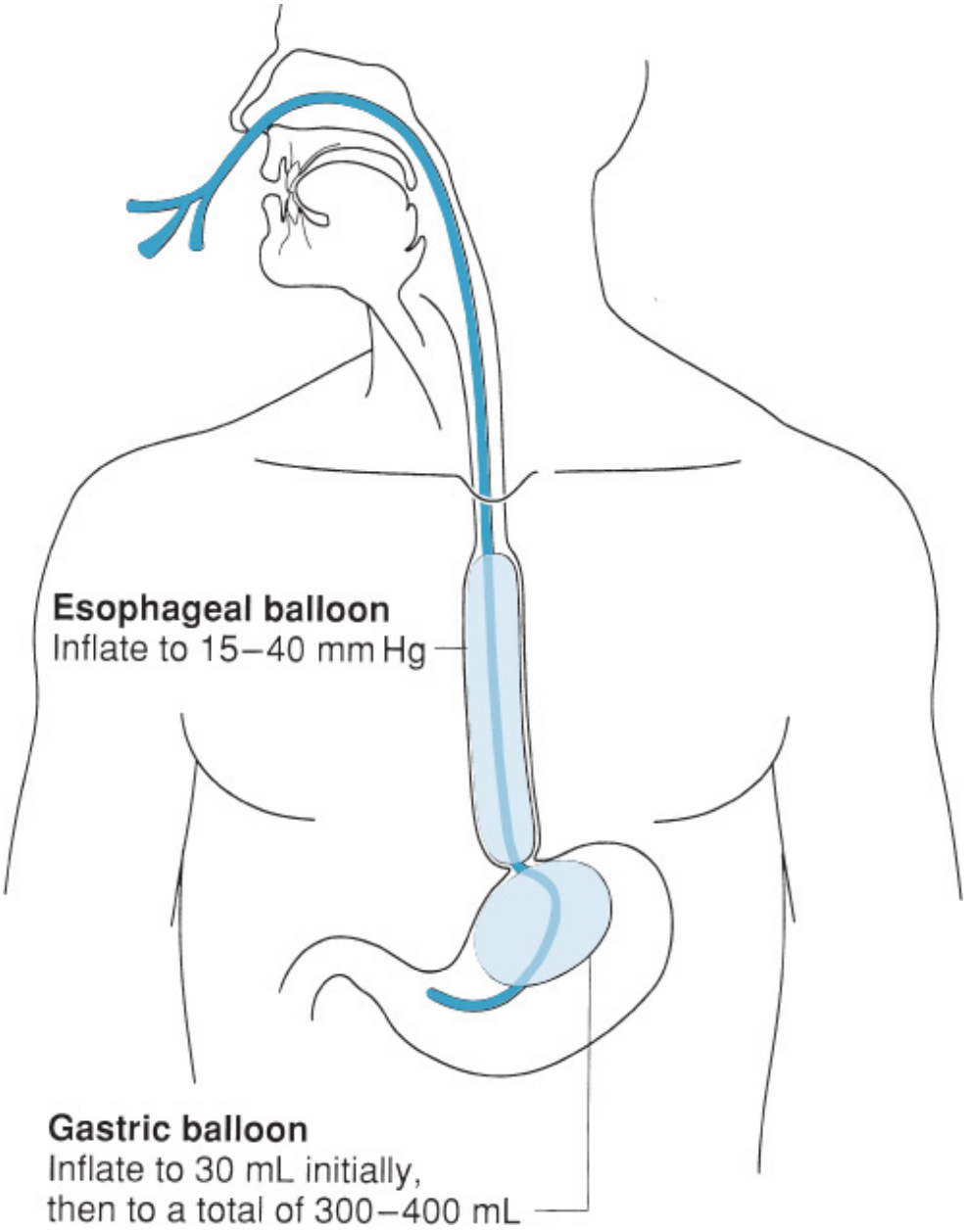

Figure 59.9 The Sengstaken–Blakemore tube is used to tamponade acutely bleeding gastroesophageal varices. The tube has three lumina—one to aspirate the stomach, another to inflate the gastric balloon, and a third to inflate the esophageal balloon. Patients treated with balloon tamponade should be in an intensive care unit, and endotracheal tubes should be placed in almost all to prevent aspiration.

Esophageal Stenting. Another technique that has recently been introduced is the endoscopic placement of self-expanding metal stents. This may achieve better control of bleeding with fewer side effects although no survival benefit has been shown compared to

balloon tamponade. An advantage to stenting is that the stent can stay in place for up to 7 days until definitive therapy.

Transjugular Intrahepatic Portosystemic Shunt. In the 10% to 20% of patients who continue to bleed or who have early rebleeding, additional procedures are indicated. Historically, surgical shunts were performed to bypass the high-pressure hepatic vascular bed. The mortality rate associated with failure to control bleeding can be in excess of 90%, and surgically created shunts in this setting were associated with a high morbidity and mortality rate.

10 TIPS (**Figs. 59.10** and **59.11**) has become first-line treatment for bleeding esophageal varices when the aforementioned attempts fail.[223] Absolute contraindications to TIPS include congestive heart failure, uncontrolled sepsis, multiple hepatic cysts, severe pulmonary hypertension, and uncontrolled biliary obstruction. Relative contraindications include HCC, hepatic vein obstruction, severe coagulopathy or thrombocytopenia, and moderate pulmonary hypertension.[224] After ultrasonographic confirmation of patency of the portal vein, the procedure is performed in the interventional radiology suite, where a stent (8 to 12 mm in diameter) is placed percutaneously over a wire into the jugular vein. The wire is then guided through the superior vena cava, right atrium, and IVC into a hepatic vein, after which the catheter traverses the hepatic parenchyma and connects the hepatic vein to a portal vein (usually the right portal vein). This connection creates a side-to-side portacaval shunt. Success rates in the cessation of variceal bleeding are as high as 90% to 100%, with an incidence of recurrent bleeding of approximately 10%.[225,226]

The ideal portosystemic shunt lowers the portal pressure without critically reducing liver perfusion. This avoids causing hepatic dysfunction, which would accelerate the progression of cirrhosis. It is possible to measure the portal pressure during TIPS, and this can guide optimal management of the TIPS to balance control of bleeding with hepatic perfusion. To control bleeding, the therapeutic goal is to reduce the hepatic venous pressure gradient (HVPG) to below 12 mm Hg. TIPS reduces the HVPG to a mean of approximately 9 to 15 mm Hg (average, 10 mm Hg) or to 40% to 62% below baseline.[227–229] A residual HVPG less than 5 mm Hg has been associated with a deleterious impact on hepatic flow.[230] Since well-validated

instruments predict the survival of patients after TIPS, the procedure should be used with caution in patients with high MELD scores, though TIPS has been used successfully to bridge to transplant.[231] The use of TIPS in massive variceal bleeding in a patient with a high MELD score who has contraindications to liver transplant should be regarded as a palliative intervention.

As with all portosystemic shunts, a significant complication of TIPS is the development of hepatic encephalopathy. The rate of encephalopathy following TIPS is 34%, compared to 19% following EVL for acute variceal bleeding, although the use of covered TIPS stents has reduced the rate of post-TIPS encephalopathy from when bare metal stents were used primarily.[232,233] Early series showed stenosis or occlusion of the TIPS stent developing in up to 50% to 60% of patients in the first year. Long-term patency is now maintained by ongoing surveillance of the shunt with redilatation, thrombolysis, or replacement as required. Current shunts are lined with polytetrafluoroethylene (PTFE) and have a much higher patency than the original permeable wall stents. Primary patency rates are 76% to 89% with shunt dysfunction occurring in 15% of patients at 1 year.[224] Patients are usually followed at 6-month intervals by ultrasonography to assess the patency of the shunt, with HCC screening at the same time. At 6 months of follow-up, 92% of patients had no episodes of rebleeding, and 82% were free of hemorrhage at 1 year. TIPS has become the standard procedure used to halt bleeding in patients who fail medical therapy. The ability to effectively decompress the portal circulation without open surgery in these critically ill patients has transformed clinical hepatology. Patients who become stable can be evaluated for transplantation electively.

Patients Who Have Recovered from an Episode of Acute Variceal Hemorrhage

Patients who recover from the first episode of variceal bleeding have a 60% chance of rebleeding in the first year with a mortality of up to 33%. These patients therefore must receive therapy to prevent rebleeding (**Table 59.16**). First-line therapy in these patients is the combination of NSBB and variceal ligation, with pharmacotherapy the cornerstone.[153] In a recent multicenter RCT, TIPS (using covered stents) when compared to endoscopic variceal ligation or glue injection plus NSBB, showed a lower rebleeding rate (0%

vs. 29%) in patients treated with covered TIPS. However, there was no difference in survival but a higher incidence of early encephalopathy in the TIPS group.[234]

In medically treated patients, the lowest rebleeding rates are observed in patients on secondary prophylaxis who are HVPG responders (defined as a reduction in HVPG below 12 mm Hg or >20% from baseline) on pharmacotherapy. An RCT of covered TIPS versus HVPG-guided therapy (propranolol and isosorbide mononitrate) showed lower rates of rebleeding in patients randomized to TIPS (7% vs. 26%) without differences in survival and with a higher incidence of encephalopathy in the TIPS group.[235] However, HVPG measurement is not available in all centers.

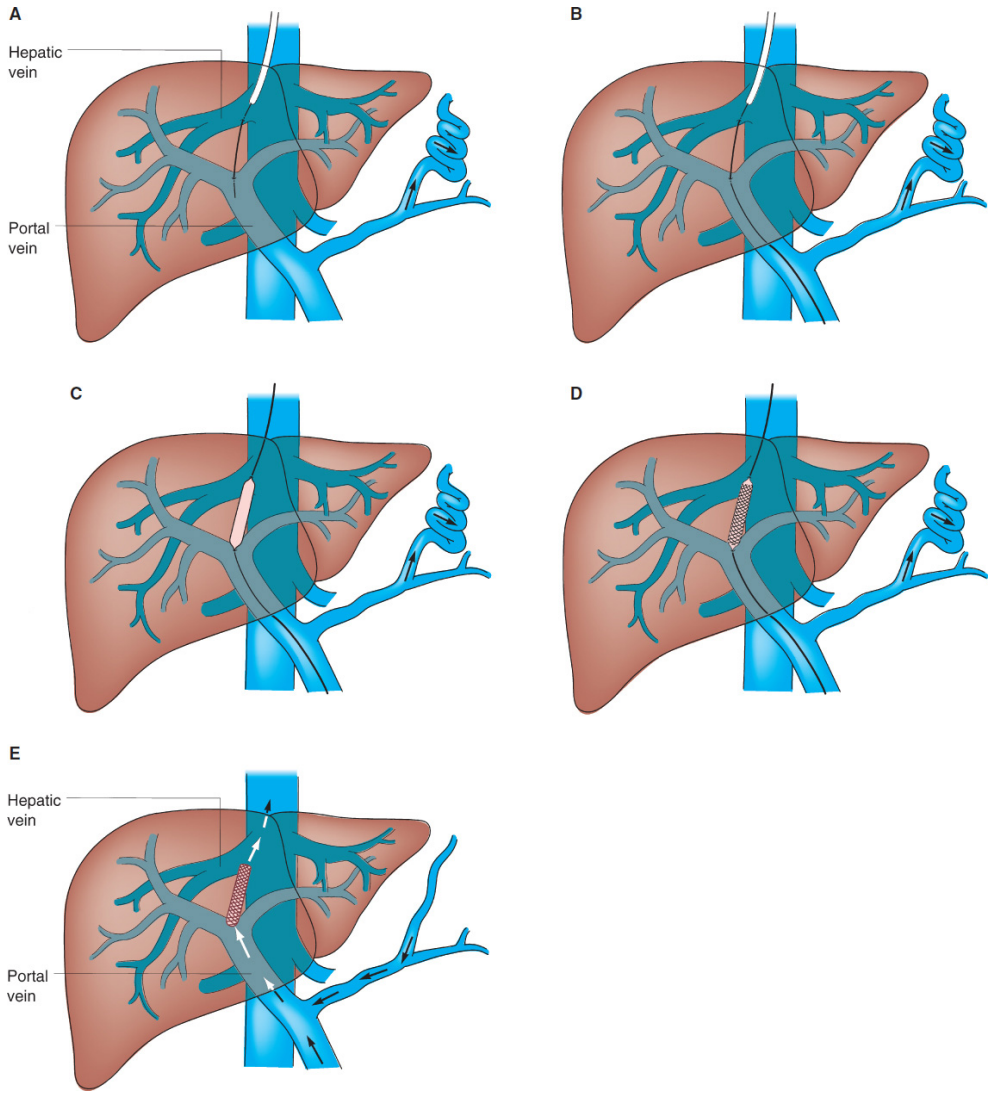

Figure 59.10 Schematic representation of the steps used to create a transjugular intrahepatic portosystemic shunt. **A:** A needle is directed from the IVC or hepatic veins into an intrahepatic portal venous branch. **B:** A guidewire is advanced into the portal venous system. **C:** The resulting tract is then balloon dilated. **D:** A stent is then placed into the dilated tract. **E:** Completed TIPS shunt. *Arrows* indicate direction of blood flow.

11 *Surgical Decompression*

Background. Orthotopic liver transplantation is the definitive treatment for portal hypertension caused by cirrhosis. As discussed above, most patients with bleeding esophageal varices are managed by TIPS or variceal band ligation and NSBB. The introduction and increased use of TIPS has virtually eliminated the need for

emergency portosystemic shunting. There is a small group of patients with portal hypertension whose bleeding cannot be controlled by endoscopy who may be candidates for shunting procedures if they have sufficient hepatic reserve that liver transplant is not indicated, or if patients have portal hypertension due to prehepatic conditions (e.g., portal vein thrombosis).

Shunts. Shunts can be classified by the degree to which they divert blood from the liver, which has important physiologic consequences. Surgical portosystemic shunts include (a) totally diverting (nonselective) shunts, (b) partially diverting shunts, and (c) selective shunts. Total shunts completely divert blood flow from the liver. Examples include both the end-to-side portacaval shunt (Eck fistula) (**Fig. 59.12**) and the large-diameter (>10-mm) side-to-side portacaval (**Fig. 59.13**), interposition mesocaval, and central splenorenal shunts. The mesoatrial shunt is described above in the section dealing with BCS.

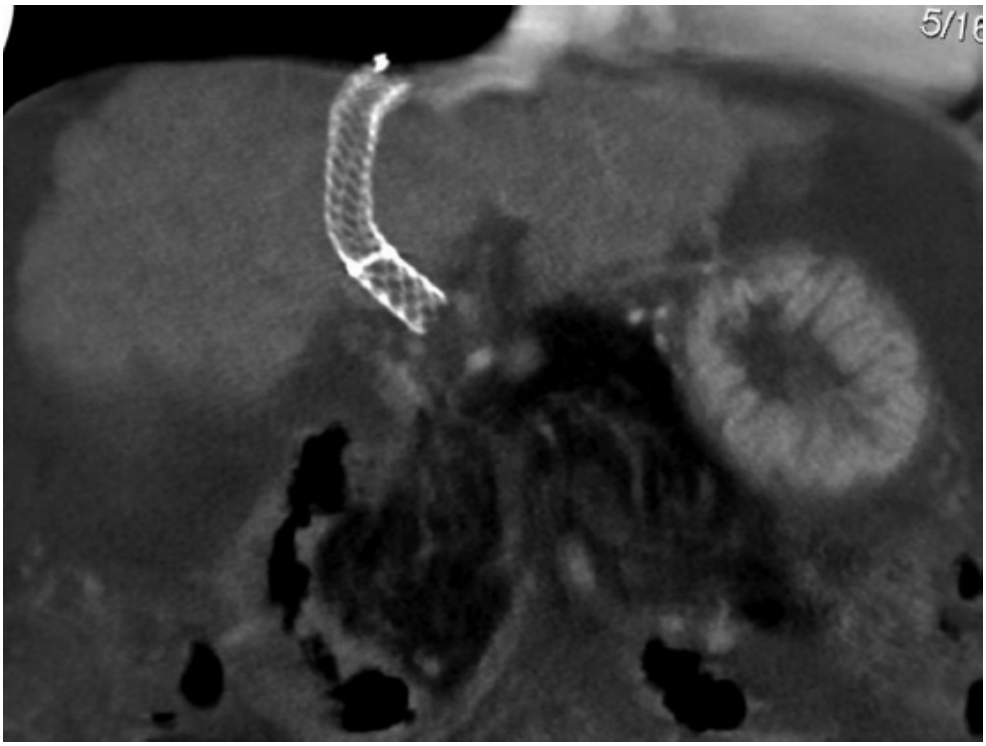

Figure 59.11 Liver MRI, coronal view showing TIPS in situ from right portal vein to right hepatic vein. (Image courtesy of Dr. Ihab Khamel, Department of Radiology, Johns Hopkins Hospital.)

In determining direction and degree of blood flow, the diameter of the anastomosis is critical. Resistance within the portal system in the liver is elevated as a result of cirrhosis. The portal pressure required to overcome this resistance is much higher than that present in the systemic venous system. Because of this pressure difference, large diameter side-to-side shunts divert virtually all blood flow into the low resistance systemic venous system via the IVC. Portal venous blood flow at the level of the liver may become reversed (hepatofugal) and total hepatic perfusion decreased. Ultimately, totally diverting, nonselective shunts result in complete portal blood flow diversion, a lower portal pressure, and are highly effective in treating bleeding varices. They may however accelerate hepatic decompensation via both diminished hepatic flow and removal of hepatotrophic substances present in mesenteric venous flow. Nonselective shunting also leads to hepatic encephalopathy, but may also be used to treat ascites.

When initially proposed, it was suggested that **partially diverting shunts** decompressed the portal venous system sufficiently while maintaining prograde, hepatopetal portal flow into the liver. This contention has been debated extensively. Initial shunts were created with a diameter larger than 10 mm, which maintained some antegrade hepatic flow. After shunt creation, however, in most instances complete or total shunting occurred over time as the shunt dilated and the gradient between portal pressure and IVC pressure disappeared. Smaller shunts were therefore created. Small-diameter (8-mm) side-to-side mesocaval (**Fig. 59.14**) and portacaval (Sarfeh or interposition "H" graft) (**Fig. 59.15**) shunts are performed with an interposition graft made of either expanded PTFE or dacron. The interposition "H" portacaval shunt involves ligation of portasystemic collaterals. The umbilical vein within the falciform ligament, the coronary (left gastric), the gastroepiploic along the greater curve of the stomach and inferior mesenteric veins are usually divided. Bleeding from varices resolves in more than 90% of patients. This smaller-diameter shunt has a higher resistance than the larger shunt, is synthetic and therefore does not dilate, can maintain hepatic perfusion, and is associated with a lower incidence of hepatic encephalopathy. Portal pressure gradients are reduced and hepatopetal flow is maintained in the majority of patients. Shunt thrombosis is a complication which may occurs in up to 16% of patients,[236] but can be treated angiographically.

Table 59.16 Secondary Prophylaxis: Guidelines for Prevention of Rebleeding after Variceal Hemorrhage

Maximal tolerated dosing of nonselective beta blockade with serial EVL until all varices are obliterated is performed, unless TIPS has been placed
Patients should then undergo surveillance EGD every 6–12 mo to evaluate for recurrent varices
Those patients who are candidates should be referred to a transplant center for timely evaluation

Adapted from Garcia-Tsao G, Abraldes JG, Berzigotti A, et al. Portal hypertensive bleeding in cirrhosis: Risk stratification, diagnosis, and management: 2016 practice guidance by the American Association for the study of liver diseases. *Hepatology* 2017;65(1):310–355.

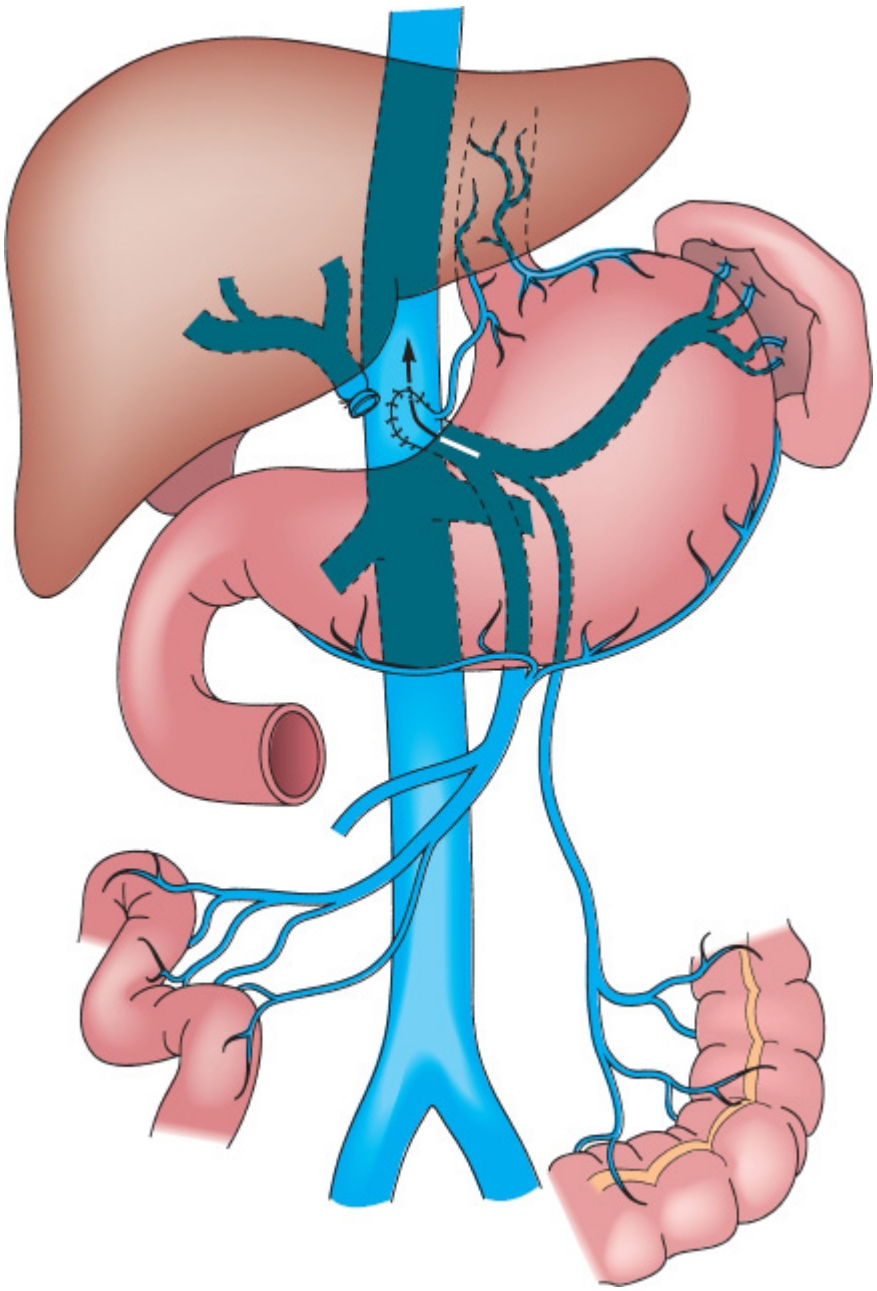

Figure 59.12 End-to-side, totally diverting portacaval shunt (Eck fistula). The portal vein is divided, the hepatic limb of the portal vein is ligated, and the splanchnic end of the portal vein is anastomosed end to side to the IVC. All portal blood is diverted into the IVC, and the hepatic limb of the portal vein cannot serve as an outflow tract.

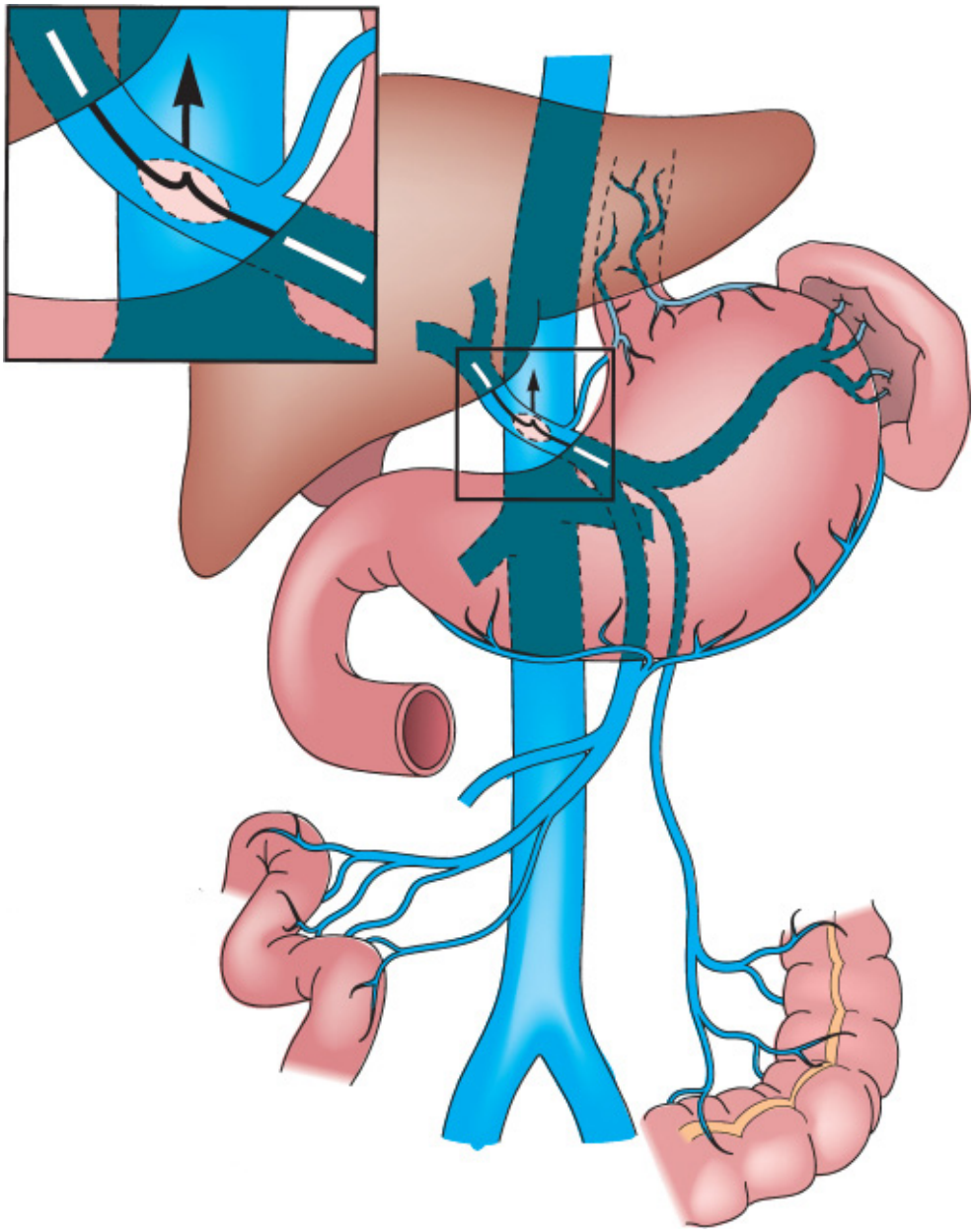

Figure 59.13 Side-to-side portacaval shunt. An anastomosis is made between the side of the portal vein and the side of the inferior vena cava. With a shunt of standard diameter, almost all splanchnic blood is diverted around the liver into the low-pressure vena cava. The hepatic limb of the portal vein serves as an outflow tract from the liver toward the low-pressure vena cava.

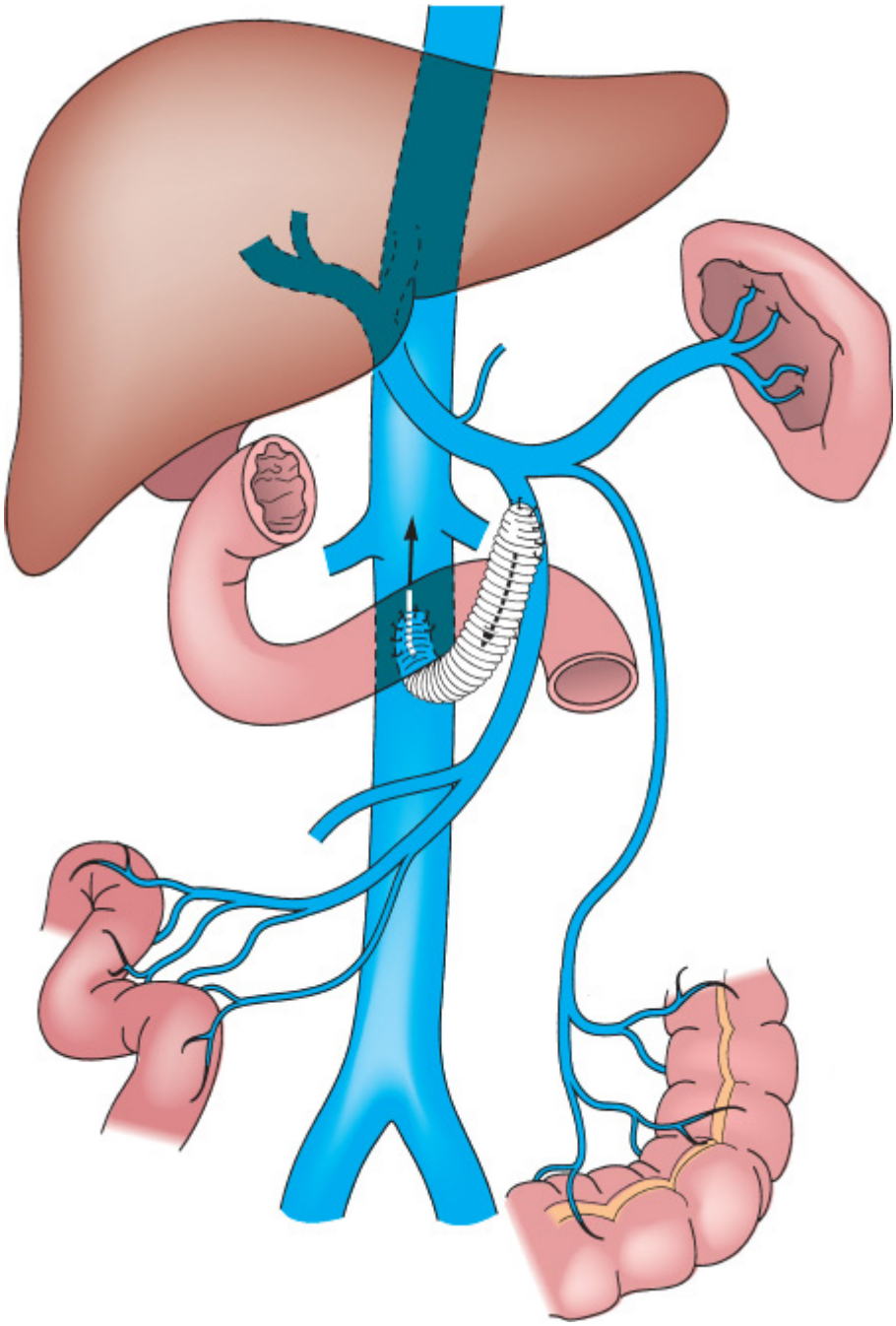

Figure 59.14 Interposition mesocaval shunt. A plastic prosthesis or an autogenous internal jugular vein is used for the shunt. One end is anastomosed to the inferior vena cava, and the other end is anastomosed to the trunk of the superior mesenteric vein. The shunt curves around the lower edge of the third portion of the duodenum and is sometimes called a C-shunt.

Selective shunts are designed to create two separate drainage systems within the portal venous network. High pressure is maintained within the mesenteric system and a low pressure is created in the esophagogastric

system by shunting blood from these varices into the systemic circulation without decompressing the mesenteric network. The most traditional and favored selective shunt is the distal splenorenal shunt. This technically demanding shunt (**Fig. 59.16**) decompresses the gastroesophageal venous system through an anastomosis between the distal splenic vein and the side of the renal vein. Decompression occurs through the vasa brevia (short gastric veins), which are in continuity with the splenic vein. In addition, as in the small side-to-side shunts described earlier, collateral veins must be ligated.

The distal splenorenal shunt was first introduced to reduce the portasystemic encephalopathy that results in some patients after a total shunt. The distal splenorenal shunt controls bleeding in more than 90% of patients and has the advantage of not requiring dissection of the portahepatis. Hepatopetal flow is maintained and the incidence of encephalopathy (5% to 24%) and risk of progressive liver failure are lower.[237,238] Loss of prograde portal flow occurs as a result of either portal vein thrombosis (approximately 10% of patients) or increased flow through collaterals located along the pancreas. It is possible to completely dissect the splenic vein from the posterior pancreas (splenopancreatic disconnection) and prevent flow through the pancreatic collaterals, but this technique adds to the complexity of the operative procedure and to the incidence of complications.[239] Since sinusoidal pressure is not decreased by the distal splenorenal shunt, massive ascites is not treated by the procedure and the distal splenorenal shunt is relatively contraindicated in patients with significant ascites. Ligation of collateral vessels and lymphatics during the procedure increases portal pressures and may actually increase ascites. The presence of a small splenic vein increases the incidence of shunt thrombosis.

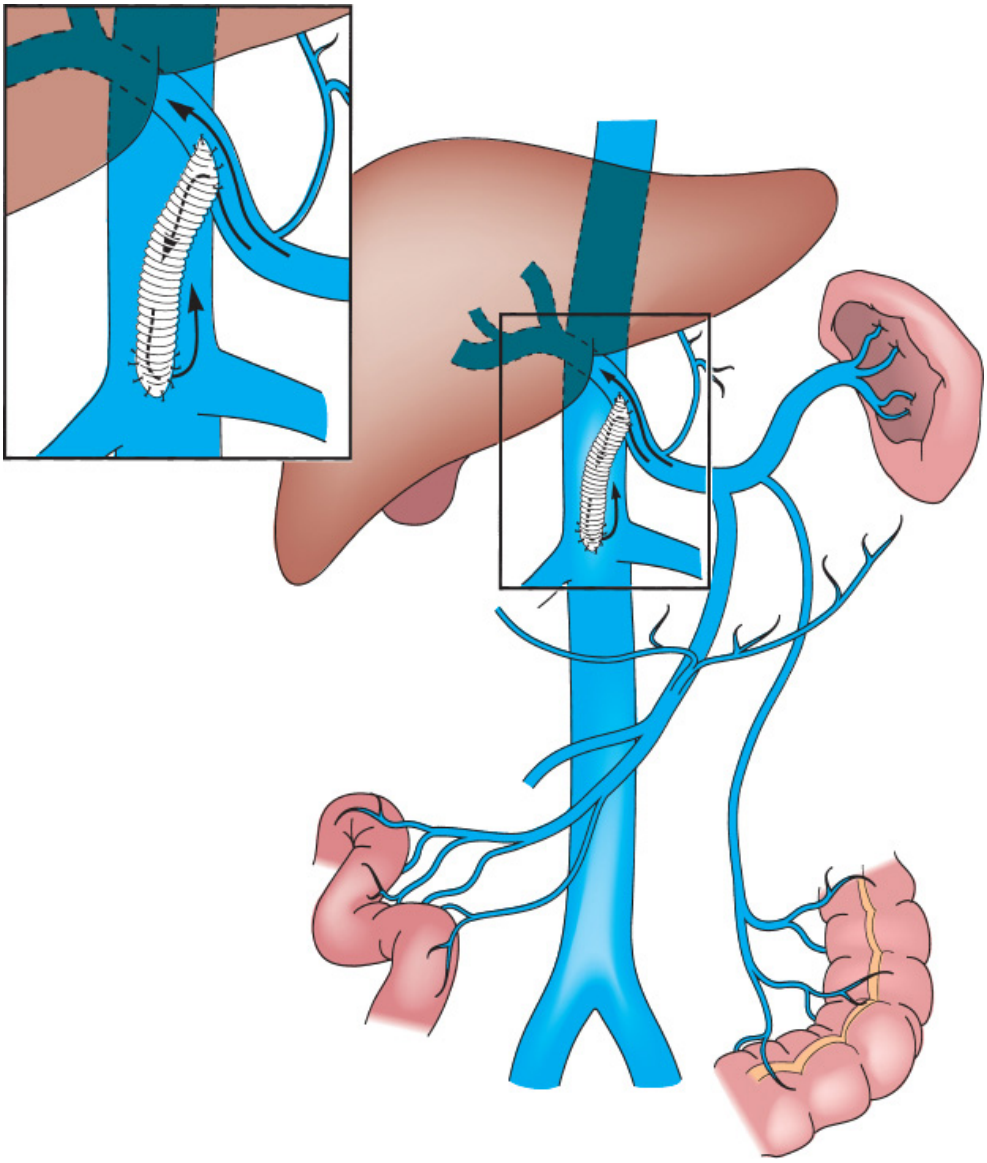

Figure 59.15 Small-diameter interposition portacaval Sarfeh shunt. A vascular prosthesis measuring 8 to 10 mm in diameter is interposed between the side of the vena cava and the side of the portal vein. The goal is to reduce portal pressure partially and thereby prevent variceal hemorrhage but still maintain sufficient pressure to permit the prograde flow of portal blood to the liver. This procedure is simpler to perform than that for the Warren shunt and theoretically avoids the problem of diversion of an increasing proportion of portal blood away from the liver over time, as occurs with the Warren shunt.

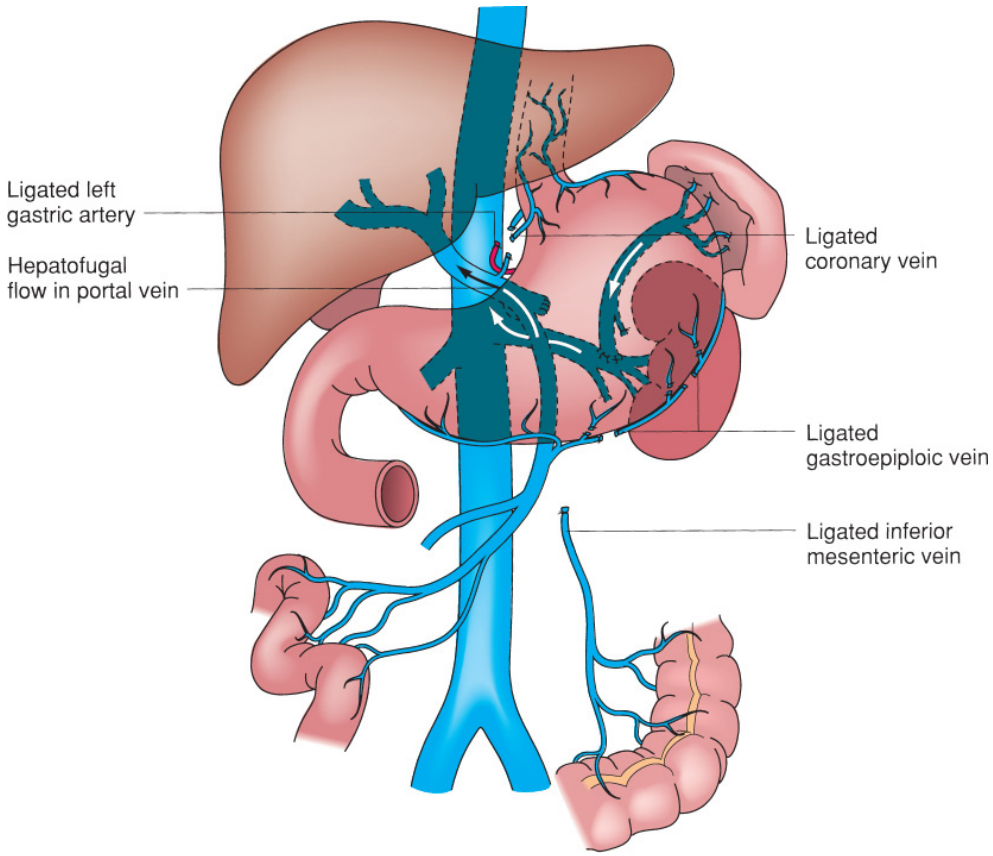

Figure 59.16 Distal splenorenal Warren shunt. The splenic vein is divided near its junction with the superior mesenteric vein. The distal end of the splenic vein is anastomosed to the renal vein. Varices are selectively decompressed through the stomach and short gastric veins into the splenic vein and then into the vena cava through the renal vein. Portal hypertension is maintained in the portal and superior mesenteric veins to provide enough pressure to drive portal blood through the diseased liver.

Trials comparing side-to-side total shunts with the distal splenorenal shunt found that both groups are equally effective (>90%) in the cessation of variceal hemorrhage.[240] The incidence of hepatic encephalopathy is lower after the distal splenorenal shunt, with rates of 36% and 15% for the total and selective shunts, respectively. Rates of rebleeding were similar and ranged from 0% to 30%, with no survival advantage for either procedure.

The side-to-side nonselective total shunt has also been used for the emergent treatment of bleeding varices. Cessation of bleeding occurred in all patients after surgery, and 99% of patients were completely free of episodes of rebleeding. The 5-year survival was approximately 80%, with the majority of deaths occurring during the first year after surgery as a result of

progressive hepatic failure. Hepatic encephalopathy requiring treatment occurred in 8% of patients. Of note, most of these patients had alcoholic liver disease, which recovers on withdrawal of alcohol.

Devascularization Procedures. Devascularization procedures are techniques in which the venous drainage of the stomach and esophagus is disconnected from the liver and intestinal vessels. These procedures are relatively less technically demanding than shunting procedures and can be performed in patients with extensive portal thrombosis. They do not interfere with hepatopetal blood flow and therefore do not increase the incidence of hepatic encephalopathy.

A range of procedures of varying complexity is possible. Esophageal transection with end-to-end reanastomosis (EEA) combined with ligation of the coronary vein (**Fig. 59.17**) is a relatively simple procedure. More complex is the Sugiura procedure (**Fig. 59.18**). This procedure involves splenectomy, devascularization of the proximal stomach and esophagus with esophageal transection and reanastomosis, and ligation of all gastroesophageal collaterals via abdominal and thoracic incisions.[241] A single abdominal incision procedure has been described.[242] Japanese researchers describe bleeding as recurring in fewer than 5% of patients in Japan, but rates of rebleeding are higher and range from 10% to 54% in other countries.[243] Operative mortality rates range from 10% to 35% and outcomes are certainly related to the severity of liver disease. Devascularization procedures are rarely performed today.

Hepatic Transplantation. Orthotopic liver transplantation is the definitive therapy for portal hypertension and cirrhosis. It is indicated for management of end-stage liver disease and has no role in the control of acute variceal bleeding. When successful, transplantation treats both the underlying disease many complications of end-stage liver disease.

In conclusion, open surgical intervention short of liver transplantation for patients with cirrhosis and portal hypertension is becoming a rarity. With the advent of TIPS, surgically created shunts are rarely indicated. While reintervention may be required after TIPS, the overwhelming efficacy and

safety of this procedure has essentially removed almost all need for open portal decompressive procedures.

Gastropathy and Gastric Varices

Approximately 20% of patients with cirrhosis also have gastric varices. The most commonly used classification for risk stratification and management of gastric varices is Sarin classification.[188] Location, size, presence of red spots, and severity of liver dysfunction influence bleeding risk. Cardiofundal varices should prompt investigation for portal or splenic vein thrombosis. Bleeding from gastric varices occurs in approximately 25% of affected patients and is usually more severe than bleeding from esophageal varices with rebleeding occurring in up to 30% of patients.[244] NSBB can be used to prevent bleeding from gastric varices, although data is not as robust. In a meta-analysis of three RCTs, sclerotherapy and EVL were found to be equally effective for initial hemostasis in controlling bleeding gastric varices, however cyanoacrylate injection is better at preventing rebleeding.[245] Other emerging endoscopic tools such as endoscopic ultrasound-guided insertion of coils or cyanoacrylate may provide more effective control but have not been well evaluated yet. Balloon tamponade may also be used as a temporizing measure. TIPS is highly effective as primary therapy for controlling gastric varices in patients who fail or cannot receive endoscopic therapy, with initial hemostasis rates of over 90% reported.[246] The distal splenorenal shunt is reserved for the rare patient who cannot receive TIPS.

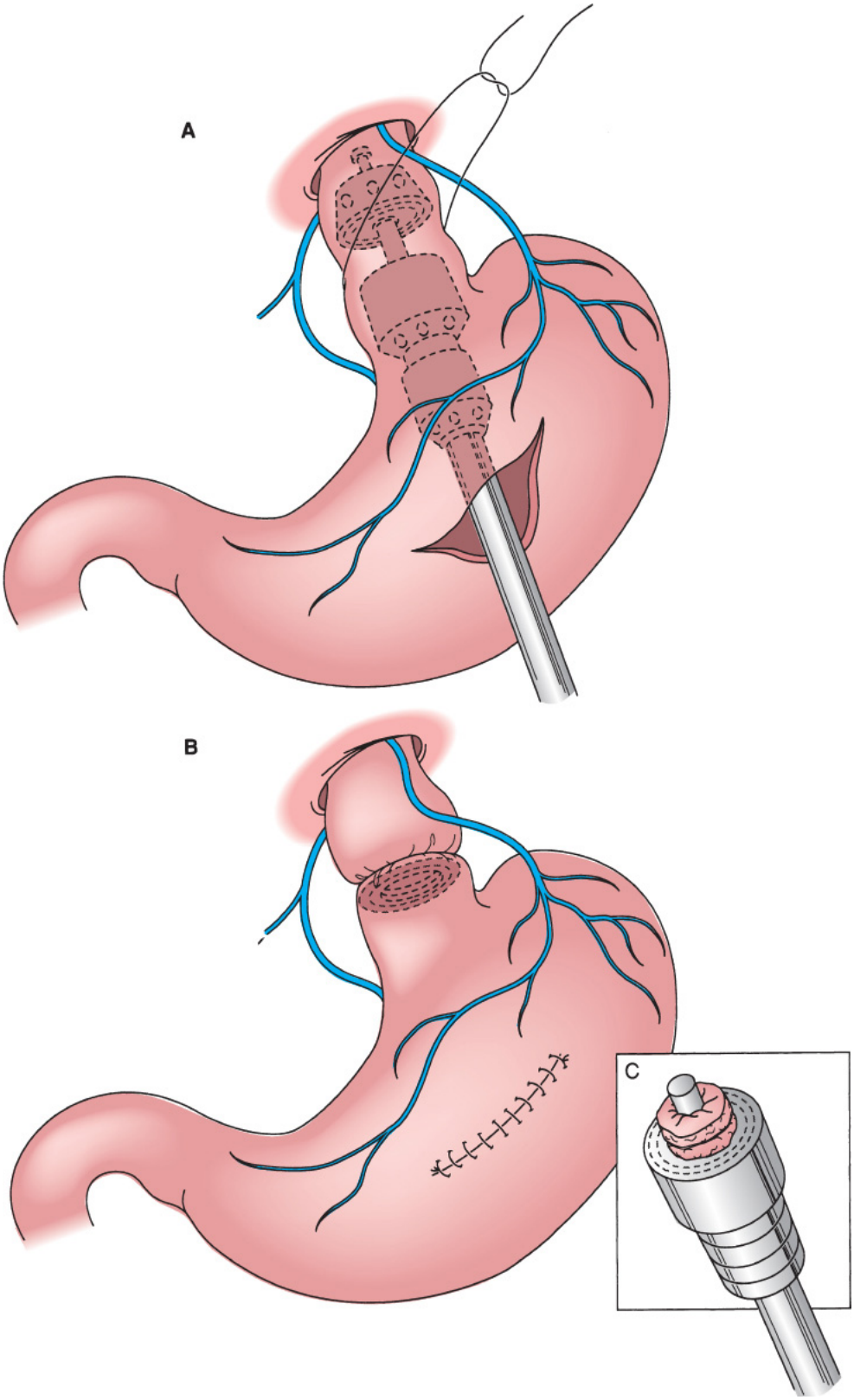

Figure 59.17 Transection and reanastomosis of the distal esophagus with the stapling device to control variceal hemorrhage. **A:** A stapling device is inserted

through a small gastrotomy incision. **B:** When the device is fired, the esophagus is simultaneously transected and reanastomosed with staples. **C:** If the device fires correctly, a complete ring of esophageal tissue is excised.

Balloon-occluded retrograde transvenous obliteration (BRTO) is a procedure for treatment of fundal varices associated with a large gastro/splenorenal collateral. In this procedure, blood flow to the liver is preserved but the large collateral is occluded using various techniques and the fundal varices are decompressed. A recent meta-analysis showed that BRTO and TIPS may have similar success rates in initial control of gastric variceal bleeding, but BRTO was associated with lower rates of rebleeding, hepatic encephalopathy, and mortality at 1 year.[247]

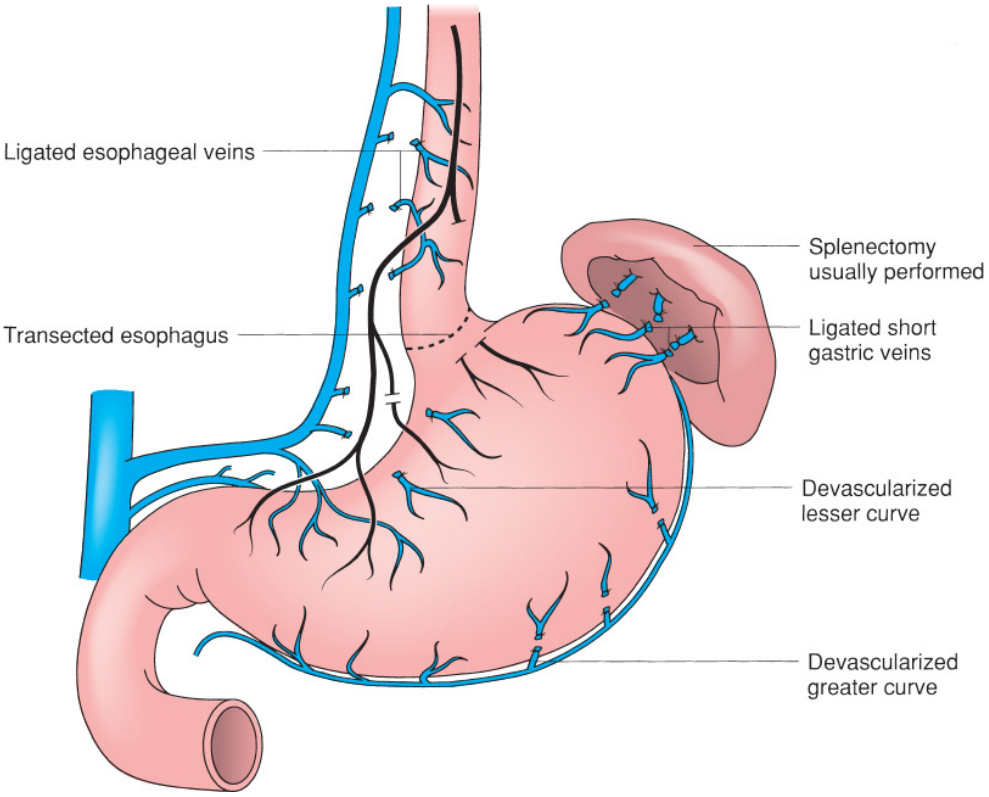

Figure 59.18 Sugiura esophageal transection and devascularization operation.

Portal Hypertensive Gastropathy. Portal hypertensive gastropathy is a condition characterized by dilation of the venules and capillaries of the gastric mucosa without associated inflammation. The major complication of gastropathy is bleeding; gastropathy accounts for 4%

to 38% of all episodes of acute bleeding in patients with cirrhosis.[248] TIPS may provide therapeutic decompression in this setting as well.

Ectopic Varices. Bleeding from ectopic varices is rare in cirrhotic patients, but more common in patients with prehepatic portal hypertension. Location and anatomy are variable, such that case-by-case assessment and management is necessary. Thin slice contrast-enhanced CT with portal venous phase imaging and large-volume diluted oral contrast will assist with diagnosis and delineation of anatomy. Frequent sites of ectopic variceal bleeding are surgically created stomas, duodenum, jejunoileum, and colon. A multidisciplinary approach to management is needed. Endoscopic therapy, TIPS, and BRTO may be useful therapies. Superficial stomal varices may be amenable to ultrasound-guided injection of cyanoacrylate or sclerosants.

Ascites

One of the most important consequences of hepatic dysfunction in cirrhosis and portal hypertension is ascites. Ascites is associated with markedly decreased survival rates. Unfortunately, it does not lead to any increased priority in organ allocation for transplant candidates. Ascites is defined as the accumulation of free fluid within the abdominal cavity (normally <150 mL). Causes of ascites are listed in **Table 59.17**. In cirrhosis, fluid is derived from a combination of hepatic (high in protein) and splanchnic (low in protein) lymphatic fluid that cannot be absorbed as a result of the increased hydrostatic pressures within the liver and splanchnic systems secondary to cirrhosis and capillarization of the space of Disse.[249] Because of the loss of sinusoidal fenestrations and a subsequent decrease in their permeability, splanchnic lymph is more abundant than hepatic lymph in patients with advancing cirrhosis, so that the protein content of ascitic fluid is relatively low.[250] The main underlying pathophysiology in the development of ascites is renal sodium and water retention, which leads to fluid overload.

Clinical and Laboratory Features

Ascites may be present in patients with cirrhosis who have no other overt signs or symptoms. Examination reveals shifting dullness to percussion (1.5

L of ascitic fluid), fluid waves (10 L), and bulging flanks.[251] Respiratory status may be compromised secondary to increased intra-abdominal pressure and pleural effusion (usually right). The progression may be slow or precipitated after an inciting event, such as a bleed or infection. Fluid filled umbilical and inguinal hernias may form and be present on examination.

DIAGNOSIS

Table 59.17 Differential Diagnosis of Ascites

Portal Hypertension
Cirrhosis and other intrahepatic diseases
Hepatic congestion
Congestive heart failure
Constrictive pericarditis
Inferior vena cava obstruction
Budd–Chiari syndrome
Portal vein occlusion
Hypoalbuminemia
Nephrotic syndrome
Protein-losing enteropathy
Malnutrition
Miscellaneous Disorders
Myxedema
Ovarian disease (Meigs syndrome, struma ovarii)
Peritoneal carcinomatosis
End-stage renal disease
Chylous ascites
Bile ascites
Urine ascites

From Sleisenger MH, Fordran JS. *Gastrointestinal disease: Pathophysiology. Diagnosis and Management*. 4th ed. Philadelphia, PA: WB Saunders; 1989:433.

Diagnostic Paracentesis

The differential diagnosis of ascites is presented in **Table 59.17**. Analysis of ascitic fluid obtained from patients with cirrhosis show it to be straw colored and clear; measurements of protein (usually <2 g/dL), quantitative cell counts, and microbiologic culture and determination of pH, amylase, glucose, and albumin levels should be obtained. The serum-to-ascitic fluid albumin gradient (SAAG) is calculated by subtracting the albumin concentration in ascites from the level found in serum and is helpful in determining the cause of ascites; high values (>1.1 g/dL) are associated with portal hypertension, whereas lower levels are associated with other disorders, including malignancy.[252]

Treatment

Initial management includes treating or removing the inciting factor. Where alcohol, autoimmune or HBV-related liver disease is present, ascites can resolve with treatment of these causes. In patients with cirrhosis, lower blood pressure is associated with worse survival. For this reason, and due to the central role of the renin–angiotensin–aldosterone axis in the pathogenesis of the hemodynamic disturbances of cirrhosis, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers should be avoided in patients with ascites. In addition, propranolol may decrease survival in patients with refractory ascites. NSAIDs can inhibit prostaglandin synthesis and impair renal function.

Therapy is directed at renal sodium and water retention. A low-sodium diet is a critical part of the management of patients with cirrhosis (an upper limit of 2,000 mg/d or 45 to 90 mEq/d). Fluid restriction (1,000 to 1,500 mL of fluid/d) is also an essential component of therapy in patients in whom hyponatremia (sodium <125 mEq/L) develops. For the majority of patients who do not respond to fluid and salt restriction alone, diuresis is indicated (**Table 59.18**). Loop diuretics (furosemide) and potassium-sparing diuretic (spironolactone) are the two most widely used agents. They are often required in combination. A ratio of 40-mg furosemide to 100-mg spironolactone generally maintains potassium homeostasis. Diuresis of approximately 500 mL/d is the goal for patients with mild ascites and up to 1 to 2 L/d for patients with both ascites and peripheral edema. More than 90% of patients respond to dietary manipulation and diuretics.[251,253]

Table 59.18 Treatment of Ascites
Bed rest
Sodium restriction 1–2 g/d (45–90 mEq/d)
Fluid restriction 1–1.5 L/d
Diuretics Spironolactone 50 mg PO q8h Maximum of 100 mg q6h Furosemide 40–370 mg/d
Antibiotics Cefotaxime 2 g IV q12h Ofloxacin 400 mg PO q12h Prophylaxis Norfloxacin 400 mg/d while hospitalized Ciprofloxacin 750 mg PO weekly Norfloxacin 400 mg/d for 6 mo Trimethoprim/sulfamethoxazole One double-strength tablet five times a week

Important adverse effects of spironolactone include gynecomastia in males, hyperkalemia, and metabolic acidosis. Complications of furosemide include prerenaluremia, which occurs in approximately 20% of patients as a result of excessive diuresis, and hypovolemia. Additional complications include hyponatremia and encephalopathy.

Large-volume paracentesis (removal of 4 to 6 L of ascitic fluid per day) is performed for patients who are symptomatic due to massive ascites and who do not respond to diuretics. Patients requiring paracentesis usually have severe underlying liver disease and a 1-year survival of 25%.[254] Large-volume paracentesis involves placing a catheter into the abdominal cavity, either in the lower midline or in one of the lower quadrants. Entry lateral to the rectus muscle avoids the inferior epigastric artery. Albumin (6 to 8 g/L of ascites removed) is infused intravenously in the form of 25% albumin (12.5 g/50 mL). Patients who have less than 5 L of ascitic fluid removed do not usually require albumin replacement.[255] Repetitive large-volume paracentesis can be safely performed.

In an Italian multicenter RCT, long-term administration of albumin (40 g twice weekly, then weekly) plus standard of care treatment as chronic treatment of ascites in decompensated cirrhotic patients demonstrated improved transplant-free survival rates at 18 months as compared to standard of care therapy. However, this practice is not yet standard of care in the United States.

Peritoneovenous shunts are surgically placed tubes that connect the peritoneal cavity with the superior vena cava via the internal jugular vein. The two main types are the LeVeen and the Denver shunt. In both, a one-way valve allows unidirectional movement of ascitic fluid from the peritoneal cavity into the systemic circulation. Although these shunts are effective in decreasing the volume of ascitic fluid, a significant number of major complications have been noted, including disseminated intravascular coagulation, heart failure and sepsis, and associated mortality rates are high (approximately 20%).[256] Shunts patency is approximately 50% at 1 year.[254] The use of these shunts has greatly decreased with the development of the TIPS procedure.

Surgically created portosystemic shunts have been used in the past for the treatment of ascites. Because of high morbidity and mortality rates, an increase in encephalopathy and progression to liver failure, and the availability of TIPS as a treatment option, surgically created shunts are now used infrequently for this indication alone. In a study evaluating the use of TIPS for the treatment of medically refractory ascites, the ascites resolved completely in almost 75% of patients, and a partial response was noted in an additional 20%.[271] In addition, renal function improved during the 6 months

of follow-up. TIPS, however, was associated with an increase in encephalopathy.

12 SBP is a potentially lethal complication of portal hypertension with ascites that occurs in up to 10% of patients. The cause of SBP is unknown. Antecedent GI hemorrhage is common, and SBP in this setting may be related to bacterial translocation from the gut. Deficits in immune function, both systemically and within the abdomen, including depressed reticuloendothelial function, low ascitic protein concentration, and deficient ascitic opsonic activity, may play a role.[257–260] Patients often present with abdominal pain and fever, but 10% to 20% of cases are discovered on routine paracentesis.[261–263] In addition, patients may present with other signs not clearly related to SBP, including worsening encephalopathy and deteriorating renal function. The diagnosis is easily made by examination of the ascitic fluid obtained by paracentesis. An elevated absolute polymorphonuclear (PMN) cell count (>250/mm^3) is diagnostic. The majority of cases of SBP are caused by a single species of organism, most commonly a gram-negative enteric bacteria (**Table 59.19**). If more than one organism is present, the diagnosis of SBP should be questioned, and a search for intra-abdominal disease (secondary peritonitis), such as a perforated viscus or diverticulitis, should be performed.

Table 59.19 Bacteria Isolated from Ascitic Fluid in 519 Patients with Spontaneous Bacterial Peritonitis

Organisms	Percentage of Total
Escherichia coli	43
Klebsiella pneumoniae	11
Streptococcus pneumoniae	9
Other Streptococci	19
Pseudomonas	1
Enterobacteriaceae	4
Staphylococci	3
Miscellaneous	10

Adapted from McHutchison JG, Runyon BA. Spontaneous bacterial peritonitis. In: *Gastrointestinal and Hepatic Infections*. Surawicz CM, Owen RL (eds). Philadelphia, PA: WB Saunders; 1995:455.

The treatment of SBP consists of supportive care and broad-spectrum antibiotics. Cefotaxime, a third-generation cephalosporin, is commonly used as empiric therapy. Other antibiotics with proven efficacy include fluoroquinolones. Beta-blockers should be discontinued at presentation, and should not be restarted as they are associated with worse outcomes in patients with a history of SBP. Albumin infusion has been shown to significantly reduce mortality in patients with SBP and to reduce acute renal failure and is complementary to other interventions.[263] Infection-related mortality is low with appropriate treatment, but high if renal failure or septic shock develops, and worse with delay in therapy. Regardless of short-term outcome related to SBP, patients who have liver disease severe enough to develop SBP have in hospital mortality rates of 20% to 40%,[264] and 1- and 2-year mortality rates are approximately 70% to 80%, respectively.[265,266]

Prophylactic antibiotics are indicated for three groups of patients with cirrhosis with ascites: (a) those with GI hemorrhage, (b) those with low ascitic fluid protein (<1.5 g/dL) and either liver failure (defined as CTP score greater than or equal to 9 or a bilirubin above 3 mg/dL) or impaired

renal function (creatinine greater than or equal to 1.2 mg/dL or a BUN greater than or equal to 25, or a sodium below 130 mEq/L), and (c) those who have survived one or more episodes of SBP (recurrence rates are almost 70% at 1 year).[255,264] The preferred antibiotics to be initiated in patients with hemorrhage is 7 days of intravenous ceftriaxone. Norfloxacin, ciprofloxacin, and trimethoprim–sulfamethoxazole are oral alternatives once intravenous therapy is no longer required. These prophylactic antibiotics reduce the incidence of SBP and improve survival.[267–272]

Hernias and Ascites

Hernias of the anterior abdominal wall occur in up to 20% of patients with cirrhosis. The causes include increased intra-abdominal pressure and nutritional deficits, with muscular wasting and thinning of the anterior abdominal wall fascia. Untreated, complications include incarceration, rupture, strangulation, and leakage. Patients with hernias and decompensated cirrhosis need to be evaluated for liver transplantation. In patients with stable liver function, hernias should be treated electively, with pre- or intraoperative paracentesis to decrease intra-abdominal pressure. No increase in complication rates was noted in a study comparing the outcome of umbilical hernia repair in patients with and without ascites. A longer hospital stay and a significantly higher recurrence rate (73% vs. 14%) were noted, however, in the group of patients with ascites. Other studies have shown increased rates of complications with observation without morbidity in those who underwent repair.[273–276] Intra-abdominal drains may be used to remove ascites until the incision has healed, preventing ascites from leaking through the wound. Meticulous fluid management is essential during the postoperative period to prevent early reaccumulation of ascites.

In patients with severe ascites, TIPS may be performed before hernia repair to ensure a good result. Emergency repair of hernias complicated by skin breakdown with ascites leak, incarceration or strangulation is managed in a similar fashion with preoperative large-volume paracentesis, and aggressive control of ascites postoperatively.

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60

Hepatic Neoplasms

Shishir K. Maithel

Key Points

1. Diagnostic principles and key imaging characteristics of benign, pre-malignant, and malignant hepatic neoplasms will be discussed.
2. General management principles and a histology specific guide to treating these neoplasms is provided.
3. The three tenets of surgical management of malignant hepatic neoplasms include assessing oncologic appropriateness, understanding the host condition, and determining technical resectability.
4. Techniques to expand and/or optimize resectability are reviewed.
5. Basic anatomy and classification systems of liver anatomy are discussed and illustrated.
6. A step-by-step approach to five common procedures is detailed.

INTRODUCTION

Improved access to and use of cross-sectional imaging have led to the more frequent discovery of hepatic tumors. In order to differentiate benign, potentially malignant, and malignant histologies, the most up-to-date imaging must be utilized. A complete clinical case analysis is required in order to determine an optimal strategy for patient treatment.

DIFFERENTIAL DIAGNOSIS

1 The most commonly diagnosed benign liver masses are listed in the top of **Table 60.1**. Most incidentally discovered liver masses in otherwise healthy individuals are benign. The most commonly diagnosed neoplasms include cavernous hemangiomas, focal nodular hyperplasia (FNH), hepatocellular adenomas (HCAs), and cystic disease. Cavernous hemangiomas are benign vascular lesions and are the most frequently seen benign liver neoplasms found in all age groups. Most patients are asymptomatic, despite their often large size, with the risk of rupture and hemorrhage being negligible. FNH is the second most common benign lesion and has a predilection in women between the ages of 30 and 50 years. In general, FNH is viewed as a hyperplastic but not neoplastic lesion that does not have malignant potential. The third most common, HCAs are also typically found in women between 30 and 50 years. They can enlarge, particularly with the use of oral contraceptives or during pregnancy. Both situations are associated with estrogen hormone stimulation. Although usually benign at diagnosis, HCAs do have the potential for malignant conversion and hemorrhage. It is this potential that guides indications for resection. While most cysts in the liver are simple, benign, and usually asymptomatic, mucinous cystic neoplasms (MCNs) and intraductal papillary neoplasms of the bile duct (IPNB) do have malignant potential. These cysts are similar to intraductal papillary mucinous neoplasms of the pancreas (IPMN).

Although the majority of liver masses are benign, the possibility of malignancy should be considered as well. These include both primary tumors, namely hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma (IHC), as well as the more commonly seen tumors that have metastasized to the liver. With respect to the most common primary tumor, HCC is the third most common cause of cancer-related death

worldwide. Cirrhosis underlies the development of HCC in nearly 90% of cases, with an annual HCC incidence of 3% to 4% in cirrhotic patients. Chronic infections from hepatitis B and hepatitis C viruses contribute to HCC development, albeit via distinct mechanisms. Excess alcohol consumption also frequently contributes to cirrhosis-related HCC. Nonalcoholic fatty liver disease (NAFLD) is increasingly becoming a risk factor for HCC, particularly in the West, with NAFLD now being the most common reason for liver transplantation in the United States. Patients with human immunodeficiency virus (HIV) represent a higher-risk population, as they have higher rates of HCC that occur at younger ages, and tend to be more frequently symptomatic, progresses more rapidly, and are associated with worse outcomes compared to HCC in non-HIV patients.

Table 60.1 Differential Diagnosis of Hepatic Neoplasms

Benign Liver Tumors
Cavernous hemangioma
Focal nodular hyperplasia (FNH)
Hepatocellular adenoma
Hepatic cysts
Intrahepatic abscess
Focal fat sparing
Primary Liver Malignancies
Hepatocellular carcinoma
Intrahepatic cholangiocarcinoma
Hilar cholangiocarcinoma
Gallbladder cancer
Metastatic Liver Malignancies
Colorectal cancer
Neuroendocrine tumors
Other (breast cancer, reproductive tract cancers, melanoma, adrenocortical carcinoma, renal cell carcinoma, sarcoma)

IHC is the second most common primary liver tumor, and its incidence has been steadily rising in European and North American countries over the last

30 years from 0.1 to 0.6 cases per 100,000. Most patients who present with IHC are asymptomatic and have no known risk factors, which often contributes to its late-stage presentation. Several risk factors have been identified, some of which are common to HCC. Chronic inflammation of the biliary epithelia is the final common pathway among them. These inflammatory conditions include primary sclerosing cholangitis, parasitic hepatic infections, hepatolithiasis, congenital biliary cystic disease, and cirrhosis. Other more general risk factors for IHC include diabetes, obesity, biliary-enteric bypass, and tobacco use.[1]

Metastatic liver tumors can originate from a variety of primary cancers, and should always be considered when evaluating a liver mass, as these are more common than a primary hepatic malignancy. The most common metastatic liver tumor originates from a primary colorectal cancer (CRC). The liver is the most common site for hematogenous spread from CRC. Roughly 25% of CRC patients present with synchronous liver metastases, and nearly 50% of CRC patients develop metachronous liver metastases after resection of their primary tumor. Neuroendocrine tumors (NETs) also commonly metastasize to the liver, usually originating from the midgut (small bowel or appendix) or pancreas and are the second most common source of metastatic liver tumors. Over 80% of patients with metastatic NETs have liver involvement. Noncolorectal, non-NET liver metastases represent a small, but important, group of liver tumors. These most commonly include primary breast cancer, reproductive tract cancers, melanoma, adrenocortical carcinoma, renal cell carcinoma, and sarcoma.

Workup

The algorithm for the evaluation of a patient with a liver mass can be complex. Laboratory evaluation includes a complete blood count, coagulation studies, hepatitis panel, liver function tests, and tumor markers (CEA, AFP, CA 19-9, chromogranin A).

Imaging is a critical part of the workup for liver masses, and various modalities may be used. These include right upper quadrant ultrasound (US), computed tomography (CT) scan, magnetic resonance imaging (MRI), positron emission tomography (PET) scan, and somatostatin receptor (SSR) scintigraphy. Although US can be useful in differentiating a cystic or solid

liver lesion, it is rarely sufficient in isolation to accurately characterize the lesion and make a diagnosis. A CT scan with a triphasic protocol that includes precontrast, arterial, and early and delayed venous images can identify and accurately characterize the majority of liver lesions.

A comprehensive MRI is the most sensitive and specific imaging modality to characterize liver lesions. The various series include fat-suppressed T1 pre- and postcontrast (arterial, portal venous, and 3- to 5-minute delay), T2 with and without fat suppression, MRCP, balanced-gradient sequence, dual-gradient echo in-phase and opposed-phase sequences, and diffusion-weighted images with a high B-value of approximately 800. The sensitivity for detecting small lesions on MRI can be enhanced by using hepatobiliary-specific contrast agents, such as gadoxetate sodium, and the specificity of MRI can be optimized with an extracellular agent. PET scan and SSR scintigraphy have limited use in the initial workup of incidental liver masses and are most helpful for assessing tumor burden, particularly extrahepatic, when metastases from PET-sensitive primary tumors and/or NETs are suspected.

If the diagnosis remains uncertain, a percutaneous core liver biopsy can be obtained. Biopsy should be performed only when the results will change management and should be avoided if HCC is suspected based on patient history and imaging characteristics. If a metastatic lesion is confirmed on biopsy, it is important to identify the primary tumor histology, as prognosis and the role of liver resection will vary greatly depending on tumor origin.

Diagnostic Principles

Upon obtaining adequate imaging, thorough review of all diagnostic studies should be performed. This will allow the most likely diagnosis and determine resectability. Benign lesions are most often associated with normal lab values and low serum tumor markers. Laboratory blood tests—such as elevated bilirubin, LFTs, and INR, as well as a low platelet count—are more suggestive of primary liver tumors that often develop in the background of underlying liver dysfunction and can cause biliary obstruction. Similarly, both primary and metastatic liver tumors can be associated with elevated tumor markers. However, laboratory studies and tumor markers primarily

play a supportive role in the diagnosis of incidental liver masses, and normal values do not exclude the possibility of a malignancy.

General imaging characteristics of liver tumors are shown in **Table 60.2**. Imaging is an integral part of the evaluation of hepatic neoplasms. The combination of radiologic characteristics and clinical features can often identify the etiology without the need for percutaneous biopsy. Specifically, for HCC the diagnosis with imaging in the correct clinical context is widely accepted and is sufficient to initiate both noninvasive and invasive treatments. Alternatively, if adenocarcinoma is detected on biopsy, further staining for specific markers, including TTF-1 (lung), ER/PR (breast), CK-20 (colon), and CK-7 (pancreatobiliary), can help identify the likely site of origin. If the diagnosis remains indeterminate after high-quality imaging and biopsy, excisional biopsy with resection may be necessary, although this is rarely required.

Table 60.2 Radiographic Features of Hepatic Neoplasms on Cross-Sectional Imaging (CT and MRI)

Precontrast Hypoattenuation
Hemangioma
Adenoma
Arterial Enhancement
Hepatocellular carcinoma (HCC)—with venous washout
Neuroendocrine tumors
Melanoma
Renal cell carcinoma
Focal nodular hyperplasia (FNH)
Colorectal cancer (slight)
+/− Hepatocellular adenoma
Early Venous Enhancement
Hemangioma (peripheral nodular enhancement)
Colorectal cancer (slight)
Delayed Venous Enhancement
Cholangiocarcinoma
Hemangioma (diffuse filling)
Colorectal cancer (increasing)
Other Notable Features
Central scar—FNH
Telangiectatic components—inflammatory adenoma

GENERAL TREATMENT GUIDELINES

2 Once a diagnosis is confirmed, an appropriate treatment plan should be developed. When determining the resectability of hepatic lesions, several key considerations should be addressed: the operative/oncologic indication, the surgical fitness of the patient, and the technical resectability of the tumor. In asymptomatic individuals, most benign lesions require no therapy, although this depends on the exact histology. If pain is the only symptom from

a benign liver tumor, in-depth discussion with the patient and careful patient selection are critical before proceeding with resection for this indication. The management of adenomas, however, is generally more aggressive than other benign lesions because rupture and hemorrhage have been reported to occur between 10% and 30%, and malignant transformation into HCC in up to 10% of lesions.

For malignant liver tumors, operative indication is ultimately governed by tumor biology which refers to the oncologic appropriateness of resection. For HCC and IHC, tumor size, multifocality, and vascular invasion should all be considered when determining resectability, however specific cutoffs are inconsistent, and guidelines are variable. HCC tumors, particularly in the background of cirrhosis, that meet the Milan Criteria (MC) should be considered for transplant evaluation. For colorectal liver metastases, hepatic resection has largely become the optimal treatment modality, although only feasible in 20% to 25% of patients. Determining oncologic appropriateness for resection involves balancing synchronous liver disease, primary tumor node status and histology, number and size of liver tumors, CEA level, and disease-free interval. However, there is no perfect stratification system. Liver resection for NETs may be associated with symptom improvement and prolonged progression-free survival, although its role is in flux with the continued expansion and increased efficacy of other management strategies. The role of liver resection for other metastatic tumors, such as breast cancer, melanoma, and sarcoma, is unclear and should be individualized to each clinical scenario. Regardless of the liver tumor being primary or metastatic, the presence of extrahepatic disease can be an indicator of aggressive tumor biology and the value of resection should be questioned. In any case where the oncologic appropriateness of resection is in question, a course of preoperative systemic or liver-directed therapy may help select more biologically favorable tumors prior to subjecting a patient to hepatic resection.

BENIGN/PREMALIGNANT LESIONS

Hemangioma

The prevalence ranges from 3% to 20% in the general population and has a female predominance.[2,3] As stated earlier in the introduction, these are most often "incidental" findings during an examination for some other etiology. Regardless of size, it is important to recognize and accept that most hemangiomas are *not* symptomatic. Even if patients undergo imaging for "pain," the etiology of that pain is usually due to something entirely different. This pain could be a result of biliary colic disease, dyspepsia, ulcer disease, or other similar upper GI ailments.[4] Rarely, a hemangioma can be symptomatic with compression of nearby structures, most commonly the stomach from a large hemangioma in the left lateral sector or diaphragmatic irritation from those located in the dome of the liver. Kasabach–Merritt syndrome, consisting of intravascular coagulation, clotting, and fibrinolysis within the hemangioma leading to systemic fibrinolysis and thrombocytopenia, is an exceptionally rare occurrence.[5]

The diagnosis of hemangioma relies on high-quality multiphase imaging, with a high-quality MRI representing the gold standard of care.[6] Most hemangiomas display "peripheral nodular enhancement with delayed central enhancement" with each progressive phase as the imaging progresses from arterial to venous to delayed venous phase (**Fig. 60.1**).[7] A "flash-filling" hemangioma can occur with small hemangiomas, usually measuring <2 cm, making it difficult to accurately and reliably distinguish from an arterial-enhancing tumor. Regardless, biopsy is not indicated and should be avoided, as imaging is usually diagnostic.

Given their benign, indolent, and asymptomatic nature, observation is the usual treatment strategy for patients with hemangioma. If "pain" is the primary patient complaint, efforts must be made to accurately assign the etiology of that pain and not assume that it is related to the incidentally discovered hemangioma. Most often, the presence of a hemangioma is actually unrelated to the pain.[8] If intervention is required, surgical resection remains the standard of care. Depending on the anatomic considerations of each individual case, both anatomic or nonanatomic resection and enucleation remain viable options.[9] Other liver-directed therapies including radiation, ablation, and arterial embolization have been reported but the lack of data supporting their efficacy makes it impossible to support their routine utilization.[10–12]

Focal Nodular Hyperplasia

FNH is the second most common benign lesion, is typically found in women between the ages of 30 and 50 years, and has a strong predilection in women compared to men approaching 9:1.[13,14] The vast majority of these are asymptomatic and are incidentally found on imaging ordered for some other pathology. Like hemangiomas, even when patients endorse abdominal pain, the etiology is usually something other than the incidental finding of an FNH. In the rare event that an FNH does cause pain, it is usually associated with a left-sided lesion resulting in pressure on the stomach. Additionally it may be a lesion near the surface of the liver that exerts pressure on Glisson capsule, or is pedunculated and is susceptible to intermittent torsion of the pedicle.[15]

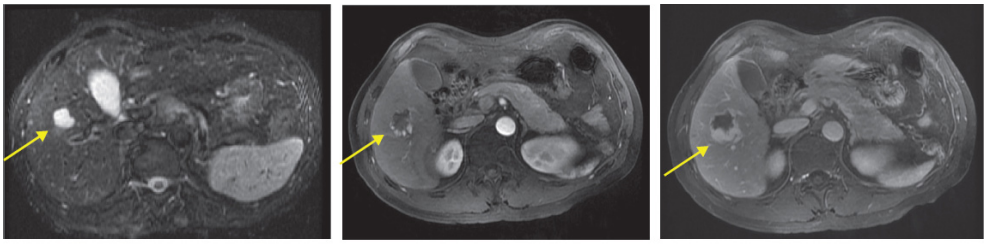

Figure 60.1 Hemangioma demonstrating bright appearance on T2 sequences and progressive peripheral nodular enhancement on delayed venous phase.

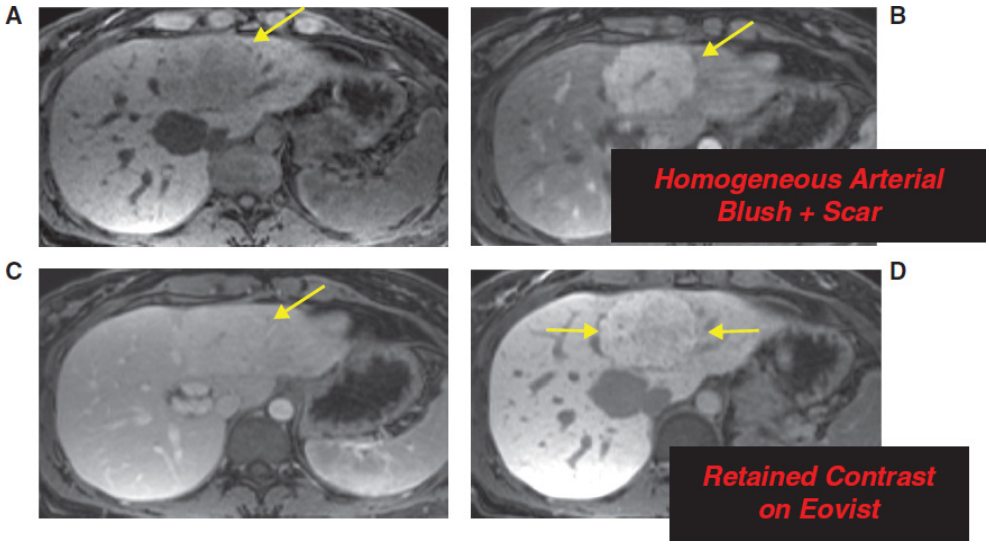

Figure 60.2 Typical appearance of FNH. **A:** Hypointense on precontrast phase. **B:** Bright with central scar on arterial phase. **C:** Homogenous and isointense appearance to liver background on venous phase. **D:** Retained contrast on delayed images with Eovist.

FNH is considered to be a hyperplastic reaction from an arterial malformation in the liver that in essence, hyperperfuses the local surrounding hepatic parenchyma leading to hepatocellular hyperplasia.[16] This phenomenon is usually isolated and thus most frequently presents as a solitary FNH, however multifocal FNH can occur in up to 20% of cases. FNH can also coexist with other benign lesions such as hemangioma or adenoma. Even though they do express estrogen receptors, tumor growth is not associated with oral contraceptive use or pregnancy.[17]

Obtaining the correct imaging is paramount to differentiate an FNH from an adenoma, which is a commonly encountered clinical scenario and carries potentially very different treatment strategies. Replacing the historic sulfur-colloid scan, an MRI with a hepatobiliary contrast agent (e.g., gadoxetate disodium [Eovist®]) is the standard of care to diagnose an FNH. Importantly, these contrast agents can exclude an adenoma. The retention of biliary elements in an FNH is a key distinguishing feature from adenomas that enables this typical imaging characteristic consisting of being hypointense on precontrast T1, isointense on T2, and becoming hyperintense on venous phase T1 images with progressive fading (**Fig. 60.2**).[18] Contrast-enhanced US is another modality that, although rarely utilized, has good diagnostic capability for FNH, particularly for small lesions.[19]

Given the lack of potential for malignant transformation, hemorrhage, or other complications, the treatment for FNH is observation. Patients should be reassured of their indolent nature and be counseled that serial imaging is not necessary. In the exceptionally rare instance of a symptomatic FNH, resection or other liver-directed therapy such as transarterial bland embolization or ablation can be pursued.[20]

Hepatocellular Adenoma

HCA is a rare benign liver neoplasm and similar to FNH; it has a strong tendency to form in women (female/male ratio—9:1).[21] Given this predominance of occurrence in females, the association of HCA with estrogen stimulation has long been studied. While most believe them to be linked, there is no data to support a "causal" relationship between the two.[22] Regardless, decreased size and spontaneous regression have been repeatedly observed in HCAs with cessation of hormonal therapy. This observation has led to cessation still being the first recommendation in patients with HCA. Although the association with estrogen stimulation is believed to be true, studies have demonstrated that most HCAs remain stable during pregnancy. As such, recommendations to avoid pregnancy for risk of growth, bleeding, and rupture are not warranted.[23] Importantly, the association of HCA with obesity and nonalcoholic steatohepatitis (NASH) has increasingly become more apparent. Obesity/metabolic syndrome is emerging as the dominant risk factor for HCA as opposed to oral contraception.[24,25] HCAs are also strongly associated with some rare genetic disorders, such as glycogen storage disease, maturity-onset diabetes of the young type 3, and McCune–Albright syndrome.[21]

Adenomas of the liver represent a heterogeneous disease as our molecular understanding of these lesions continues to evolve. There are four main subtypes, each of which carries its own profile of radiologic characteristics, typical host, and risk of hemorrhage and malignant transformation. The four subtypes include: HNF1α-mutated (HNF1A), inflammatory (telangiectatic—IHCA), β-catenin-mutated (b-HCA), and unclassified.[26] HNF1A has marked steatosis, IHCA is characterized by clusters of small arteries surrounded by extracellular matrix and inflammatory infiltrates, b-HCA contains pseudoglandular formations and cellular atypias such as enlarged, irregular,

and hyperchromatic nuclei. Unclassified adenomas include those not having a characteristic histologic pattern.[24,27]

The best diagnostic test, aside from a difficult-to-interpret tissue biopsy, is a high-quality MRI. As mentioned above, MRI with a hepatobiliary contrast agent will usually reliably distinguish an adenoma from an FNH. HNF1A adenomas are homogeneous and will demonstrate significant fat content. IHCA displays a strong hyperintense signal on T2-weighted images and often has persistent enhancement on the delayed venous phase. The other two types, b-HCA and unclassified, have less distinct imaging features, but usually resemble other hepatocellular tumors with arterial enhancement and venous washout (**Fig. 60.3**).[28,29] Tissue biopsy is best utilized if molecular characterization will inform management.

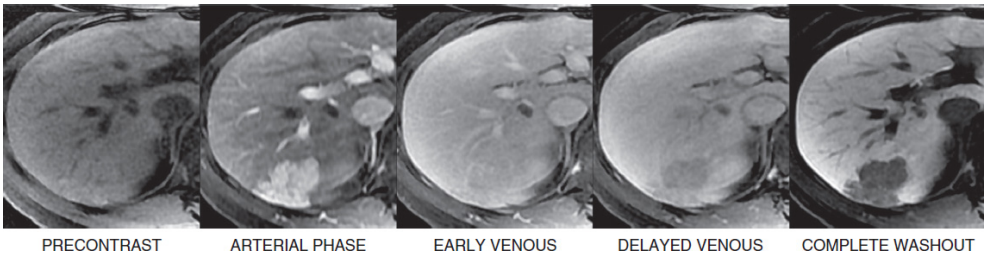

Figure 60.3 Series of images demonstrating the typical appearance of hepatocellular adenoma through the progressive phases of contrast-enhanced imaging.

The management of HCA is closely linked to the potential for complications—namely hemorrhage and/or malignant transformation. The risk assessment for the likelihood of these complications is mainly based on size, gender, and histologic type.[24] Importantly, the number of adenomas is not associated with an increased risk of complications. In general, 5 cm is the accepted "cutoff" for intervention, as the risk for bleeding and malignancy tends to increase with greater size.[24,30] However, these risks are still relatively low—hemorrhage occurs in less than 25% and malignant transformation in approximately 5%. Adenomas in males carry a significantly higher risk of malignant transformation and are most often the b-HCA subtype. As such, although uncommon, adenomas diagnosed in male patients should be removed.[24] When factoring in the histologic subtype, the HNF1A type is very indolent and rarely symptomatic and almost never transforms to HCC. IHCAs have a higher tendency to bleed. Other risk factors for bleeding

include visualization of arteries on imaging, location in the left lateral sector of the liver, and an exophytic growth pattern. The b-HCA subtype is characterized by a much higher risk of malignant transformation, particularly when >5 cm in size.[21,24] In general, size and gender are the main guiding principles for management, with greater than 5 cm and male gender requiring intervention.[24] The histologic subtype can help guide decision making, particularly in a borderline situation, where either resection or observation are equally being considered. For example a 4-cm b-HCA would likely undergo resection while a 5.5-cm HNF1A could likely safely be observed.

In terms of management, if relevant, the first step is cessation of oral contraception. Weight loss can be associated with spontaneous regression of adenomas as well.[24] When indicated, the standard of care for treatment is surgical resection. Bland arterial embolization is another option, particularly in difficult-to-resect lesions or in patients with significant comorbidities.[9,31] Liver transplantation, although previously considered in patients with adenomatosis, has recently fallen out of favor as the risk of complications is not increased with multiple compared to solitary adenomas and these lesions are most often the indolent HNF1A subtype. Instead, isolated treatment of lesions >5 cm can be undertaken and the other smaller adenomas can be observed, often displaying spontaneous regression.[24]

Simple Cysts

Simple cysts of the liver, originally believed to be quite rare, are visualized in up to 25% of patients who undergo MRI evaluation (**Fig. 60.4**). They are cystic formations that contain serous fluid and are lined by a single layer of cuboidal or columnar epithelial cells that resemble biliary epithelium, yet they do not have any direct communication with the biliary tree. Although they can be solitary, most of the time they are multiple. Prior to even considering any intervention, a simple cyst must be differentiated from polycystic liver disease (with or without autosomal dominant polycystic kidney disease—ADPKD), mucinous cysts (discussed below), and infectious etiology (hydatid cysts or echinococcal cysts). All of these other conditions have distinct management strategies that differ from that of simple cysts.

While most simple cysts are demonstrated in females, large, complicated, and symptomatic cysts are almost exclusively seen in women over the age of

50.[32] Outside of this demographic, most simple cysts are asymptomatic and are incidentally discovered during imaging for some other pathology. A carefully detailed history must be obtained in order to exclude other etiologies of pain. Large cysts located in the left lateral sector can compress the stomach. Large exophytic cysts can apply pressure on the liver capsule and/or diaphragm, and sometimes vascular structures and/or bile ducts can be compressed radiographically. The latter is rarely an indication for intervention as the radiographic appearance of compression is not usually clinically apparent or relevant. A trial of cyst fluid aspiration can be utilized to determine if the cyst is truly symptomatic, during which the symptoms should resolve temporarily. However, they will recur as the cyst refills with fluid.[33] Acute hemorrhage into the cyst can be accompanied by severe acute pain that usually resolves over a few days. Simple cysts do not have any malignant potential.

If truly deemed to be symptomatic, management of simple cysts can be pursued with either sclerotherapy or cyst fenestration. Sclerotherapy is most frequently accomplished with a 95% ethanol solution. After the cyst is percutaneously accessed and all the fluid is drained, it is vital to first inject contrast to ensure that no direct biliary or vascular communication is present.[34] Next, approximately 100 mL of 95% ethanol is infused into the cyst cavity and the patient is rolled in different positions to expose the alcohol to the entire cyst surface.[35] The procedure can be quite painful and blood alcohol levels can rise, thus underscoring the importance of limiting the amount of ethanol that is infused. Although the literature is sparse with reports of long-term follow-up after sclerotherapy, the symptomatic recurrence rate requiring additional treatment is believed to be low—less than 5%.[9]

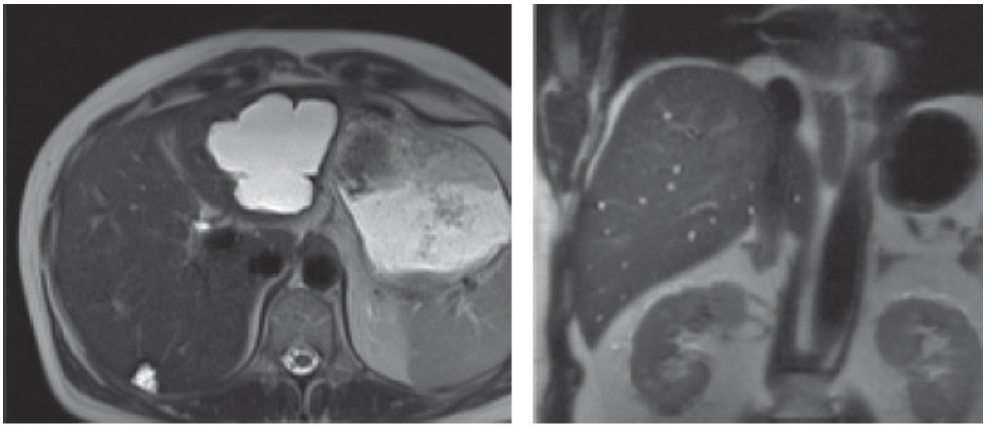

Figure 60.4 Typical appearance of a simple hepatic cyst on MRI T2 sequences.

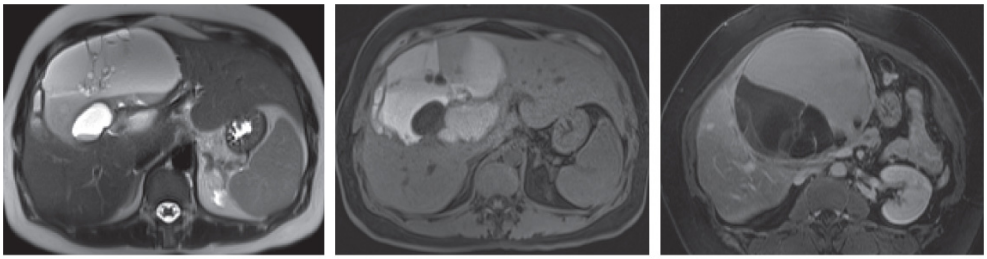

Figure 60.5 T2 sequences of an MRI demonstrating the bright appearance of mucinous cystic neoplasms that highlight the heterogeneous contents, septations, and nodularity that distinguish them from simple cysts.

If intervention is deemed appropriate, laparoscopic cyst fenestration is typically more commonly pursued than sclerotherapy.[36] Although the procedure is simple and straightforward with good results, it should only be utilized when needed. It should not lower the threshold for intervention. The procedure can be likened to taking the "ice cream off the cone." The ice cream represents the protruding cyst from the liver surface, presenting as the interface of the ice cream and the rim of the cone. Importantly, it is not necessary to remove the cyst lining that is embedded within the liver parenchyma. In fact, attempts to do this will greatly increase the risk of complications such as bleeding and bile leak, as these structures are often being compressed just below the cyst wall. Rather, the cyst should be opened approximately 1 cm above the liver surface. The fluid is drained out and then the cyst wall that is exterior to the liver parenchyma is removed with either an energy source or vascular staplers, leaving a crater of sorts. The

epithelium should be carefully cauterized and often an omental flap is created to place inside the cyst cavity. Any persistent fluid secreted from the base of the cyst wall is readily absorbed by the peritoneum and poses no risk to other organs. Success rates are high with this procedure and if done correctly, reintervention rates are low—less than 10%.[37]

Mucinous Cysts (MCN and IPMN-B)

While neoplastic mucinous lesions of the liver are exceedingly rare, it is paramount to differentiate them from simple or infectious cysts. They may have malignant potential and mandate complete resection most of the time. It is important to note that the terminology for these neoplastic cysts has evolved. The previous terminology of "cystadenoma" has been abandoned as the pathophysiologic understanding of these cysts has improved. As such, these cysts in the liver are believed to mirror those in the pancreas with similar rates of malignant potential. The term cystadenoma has been replaced with MCN and intraductal papillary mucinous neoplasm of the bile duct (IPMN-B).[38,39]

Much like MCN of the pancreas, MCNs of the liver are almost always solitary, occurring uniformly in younger women and do not communicate with the biliary tree. They are histologically defined as being lined with ovarian stroma.[40,41] The embryologic decent of the right ovary explains why most MCNs are found in segment IV of the liver, just as they are nearly always found in the body/tail of the pancreas due to the path of decent of the left ovary. Although many are asymptomatic and diagnosed incidentally, most are discovered during a workup of vague epigastric pain. If it reaches a large size, an MCN can progress to cause biliary obstruction and jaundice in the minority of cases.

A good-quality MRI is the best way to radiographically distinguish MCN from other cystic lesions of the liver. Most MCNs present as fluid-containing multilocular cysts with homogenous low or isosignal intensity on T1-weighted images and homogeneous high signal intensity on T2-weighted images (**Fig. 60.5**).[42] Nodularity of the cyst wall may be present as well. Unlike MCN of the pancreas, cyst fluid analysis of the hepatic counterpart is not well defined. Specifically, there is not a characteristic profile of CA 19-9 or CEA levels, partly since hepatic cyst fluid analysis is uncommonly

obtained. If suspected, given its malignant potential, complete resection is warranted, as cyst wall fenestration is not appropriate management.[43] Resection can consist of partial hepatectomy or enucleation, as there is a dissection plane between the MCN and normal hepatic parenchyma.

IPMN-B may macroscopically be divided into two variants: ductectatic type and cystic type. The ductectatic type can resemble main duct IPMN of the pancreas while the cystic type is analogous to side-branch IPMN.[44] The main distinguishing feature from MCN is that IPMN-B directly communicates with the biliary tree. This can often be visualized on MRI (**Fig. 60.6**) or on cholangiography. Given the mucin secretion into the biliary tree, IPMN-B can present with transient obstruction of the bile ducts. Unlike MCN, it is equally diagnosed in both genders and presents in the sixth decade of life. Given its malignant potential, resection is indicated.[39] Unlike the guidelines for resection of IPMN of the pancreas, no such detailed guidelines exist for IPMN-B. Even if malignant transformation has occurred, the prognosis is usually better than after resection of intrahepatic or hilar cholangiocarcinoma.

MALIGNANT LESIONS

3 Determining resectability of hepatic malignancies relies on three key concepts: oncologic appropriateness, host condition, and technical resectability.

Oncologic Appropriateness

Tumor biology dictates oncologic appropriateness. Adequately defining the extent of disease and understanding the nature of the tumor is critical before pursuing operative intervention. The surgeon's first responsibility is to determine those patients most likely to benefit from an operation, which is ultimately governed by tumor biology.

Host Condition

Host condition refers not only to the general health and surgical fitness of the patient, but also to the condition and functional status the liver. In most patients, this can be successfully evaluated through a careful history and physical examination. Other useful tools to further risk-stratify patients include indicated adjunct laboratory values and imaging.

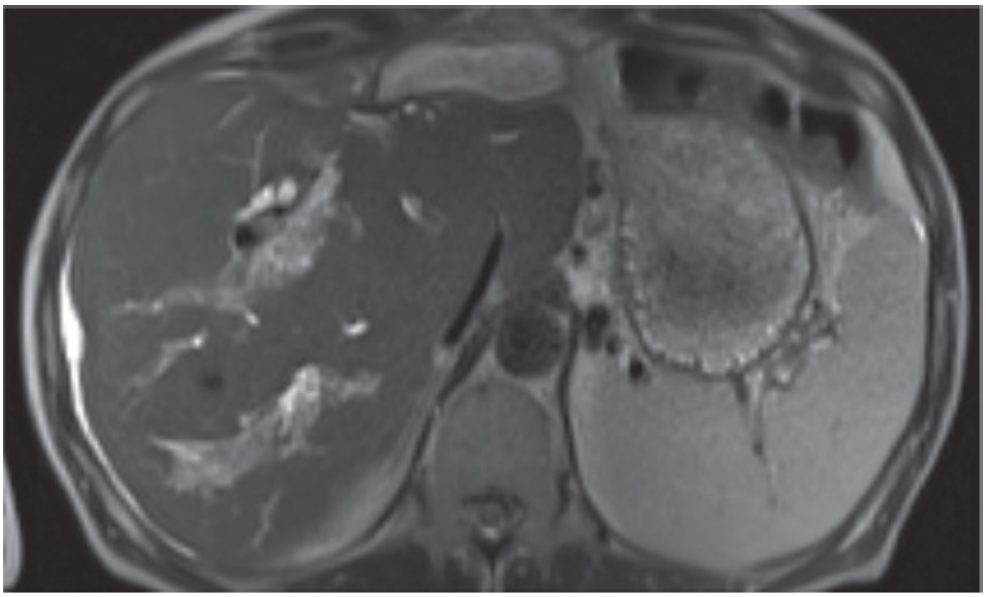

Figure 60.6 T2 sequences of an MRI demonstrating the biliary communication of IPMN-B.

Technical Resectability

Before pursuing any extent of hepatic resection, the remnant liver should be determined to have sufficient inflow, outflow, biliary drainage, and be of adequate quantity and quality to sustain hepatic function postoperatively during the regenerative period.

If surgery is determined to be reasonable from an oncologic perspective, the patient is deemed fit for surgery, and the extent of planned resection leaves an adequate functional liver remnant (FLR); nearly all patients should be candidates for liver resection. These three concepts will be elaborated upon within the context of specific liver tumors, both primary and metastatic, as well as discuss ways by which resectability rates can be potentially increased.

ONCOLOGIC APPROPRIATENESS

Determining resectability of a tumor from an oncologic perspective is paramount and should be the first consideration of any surgeon faced with a cancer patient prior to assessing technical resectability. This is based on the concept of nonmalfeasance, or "first, do no harm." When performed with curative intent, the value of surgery for malignancy is measured by its survival benefit. Tumor biology, however, ultimately dictates patient outcome. Thus, a thorough preoperative evaluation should be performed to assess the extent of spread, which, among other tumor-specific factors, can help predict the nature of disease. Whether a primary or metastatic liver tumor, extrahepatic spread is an indicator of aggressive tumor biology. While not always a preclusion of surgery,[45] the benefit of resection in these cases should be questioned. Improvements in imaging technology and, in appropriately selected patients, staging laparoscopy have increased our ability to identify those patients unlikely to benefit from surgery and avoid unnecessary hepatectomy. In certain cases where the oncologic appropriateness of surgery is in question, a trial of preoperative systemic or liver-directed therapy may help biologically select more favorable tumors for resection.

Preoperative Evaluation

Preoperative evaluation should focus on characterizing the lesion in question, defining the extent of disease, and determining its biologic behavior. Imaging modalities include a staging chest radiograph or chest CT, and either a CT or MRI of the abdomen and pelvis, with preference depending on the type of tumor being evaluated, institutional expertise, and patient-related factors. In many cases, however, both CT and MRI may be necessary.[46] PET scan can be a useful and important tool in evaluating the extent of disease in FDG-avid tumors, particularly when assessing for extrahepatic disease.[47–50] Preoperative biopsy for certain tumor types is often not necessary and should only be pursued in select cases where the information gained will alter the treatment plan, such as administering preoperative therapy.

Despite advances in various high-quality imaging modalities, still roughly 9% to 36% of patients are found to have occult metastatic disease at the time

of surgery.[51–55] Staging laparoscopy has been advocated by some to identify peritoneal metastases not detected on cross-sectional imaging, thereby avoiding unnecessary laparotomy.[54–58] However, its routine use is subject to debate, and may only be of benefit in patients already identified as high risk for having subradiographic metastatic disease.[59–61]

Hepatocellular Carcinoma

HCC is the most common primary liver tumor (**Fig. 60.7**) and the third most common cause of cancer-related death worldwide.[62] Although various nonoperative treatment options exist, surgery remains first-line therapy, with the choice between resection and transplantation generally dictated by the degree of underlying liver dysfunction and tumor burden.[63,64] From an oncologic perspective, four major clinical prognostic indicators have been identified—tumor size, multifocality, vascular invasion, and extrahepatic spread. These indicators serve as the basis for the Tumor–Node–Metastasis (TMN) staging system.[65,66] Since the widespread adoption of the MC, which utilized a selection cutoff using these clinical indicators, the identification of cirrhotic patients with HCC for transplantation has been simplified with consistently favorable results.[67,68] However, translating these clinical indicators into oncologic criteria for resection has proven difficult.

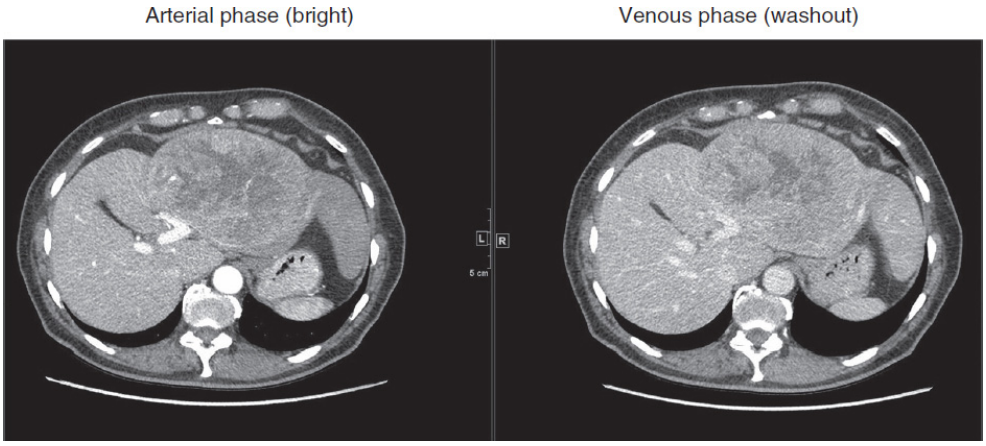

Figure 60.7 Hepatocellular carcinoma (HCC) has a bright appearance on arterial phase and tends to washout on venous phase.

Other clinical staging systems have been proposed using different clinicopathologic parameters with varying success in applicability, cancer-

specific focus, and prognostic value.[69–71] One commonly used system is the Barcelona Clinic Liver Cancer (BCLC) staging system. Stratification under BCLC is based on tumor stage, liver function, and performance status, therefore staging patients with HCC into four categories—early, intermediate, advanced, and terminal making treatment recommendations for each.[72,73] According to this staging system, hepatic resection is only indicated in patients with early-stage HCC (single tumor ≤5 cm or ≤3 tumors all <3 cm, without vascular invasion or extrahepatic spread; satisfactory liver function; and performance score of 0) with the oncologic appropriateness of resection mirroring that of MC.[67,72] While the BCLC system has gained increasing acceptance to guide resection, it continues to be controversial, as conflicting data regarding the prognostic value of these clinical indicators emerge.[74–80]

Historically, tumor size in HCC has been an important predictor of outcome following surgery. Readily measured preoperatively and shown to be inversely correlated with survival, tumors larger than 5 cm and 10 cm in diameter are particularly biologically aggressive.[76,81–84] However, several groups have demonstrated more acceptable and durable long-term survival following resection for large HCC, questioning the prognostic significance of tumor size alone.[77,80,85–87] Furthermore, when controlling for other factors, such as multiple tumors and presence of vascular invasion, size has demonstrated little impact on survival, even in tumors >10 cm in diameter.[65,80,88–90] In fact, the AJCC eighth edition staging classification does not use tumor size alone to stratify patients.[65,66] Increasingly, however, studies focusing on the link between tumor size and vascular invasion have shown that the frequency of microscopic and macroscopic vascular invasion drastically increases as tumor size increases.[78,80,91] This suggests that tumor size, rather than being an independent prognostic indicator, may serve as a surrogate marker for vascular invasion. Thus, while size alone should not dictate treatment, recognizing the link between size and more aggressive tumor biology is critical when discussing the oncologic appropriateness of resection in patients with HCC.

The presence of multiple tumors is another important independent prognostic factor in patients with HCC. The pathogenesis of multifocal HCC is thought to be due to at least two very different biologic mechanisms—multicentric hepatocarcinogenesis, meaning multiple de novo tumors of

independent origin, and intrahepatic metastasis, meaning multifocal dissemination of a common clonal origin.[92–94] While our ability to differentiate between these two pathways may have significant implications for understanding tumor biology and guiding management, reliable biomarkers are lacking and clinical applicability is not yet clear. However, as a whole, multifocal HCC incurs a worse prognosis than equally matched solitary tumors; this is reflected in the current AJCC staging system.[66,89,90] Although acceptable rates of survival have been shown following resection for multifocal HCC ≤5 cm in diameter, the oncologic benefit in patients with larger multifocal HCC is still subject to debate and a trial of preoperative therapy may be prudent prior to selecting these patients for resection.[65,89,90,95]

In multiple studies, vascular invasion has been shown to be one of the best predictors of outcome following surgery for HCC.[65,73,76–80,89–91] Patients presenting with macroscopic or major vascular invasion, defined as tumor involving a major branch of the portal or hepatic vein, have particularly dismal outcomes. This finding is associated with increased risk of intrahepatic and systemic metastases, and poor overall survival.[65,89,90,96–98] Left untreated, the reported median survival of patients with HCC and major vascular invasion is 9 to 10 weeks.[96,97] Several studies have reported an overall 5-year survival of only 10% to 11%, even after hepatic resection for HCC when major vascular invasion was present.[79,89,99,100] Although a small subset of patients may have more favorable outcomes than those previously reported,[79] the benefit of resection in patients with major vascular invasion remains doubtful and controversial, and should be pursued in only highly selected patients. Microscopic vascular invasion has also been shown to be a strong predictor of outcome, with its presence associated with earlier tumor recurrence, metastatic spread, and decreased overall survival.[76–78,80,91] Unfortunately, microscopic vascular invasion is difficult to anticipate and in isolation, is of little use in preoperatively determining resectability.

In patients with HCC, extrahepatic spread, including regional lymph node involvement and distant metastases, is considered stage IV disease. With few exceptions, it is a contraindication to resection in patients with HCC.[64,66,101]

Intrahepatic Cholangiocarcinoma

The second most common primary liver tumor is ICC (**Fig. 60.8**) with rising incidence seen in both European and North American countries.[102,103] Despite the rising occurrence in these countries, no currently available locoregional or systemic therapies have shown generalized therapeutic benefit, although advances in targeted therapy show great promise for select patients. Still, surgical resection remains the only potentially curative treatment for patients with ICC.[104] When the seventh edition AJCC staging system was developed, TMN staging for ICC was based on the same major prognostic criteria of HCC including tumor size, multifocality, vascular invasion, and extrahepatic spread.[105] Given its distinct tumor biology, underlying risk factors, and clinical behavior compared to HCC, several nomograms and staging systems have been developed. These is an attempt to differentiate relevant prognostic indicators and more accurately predict survival in patients with ICC.[106–111] The eighth edition of the AJCC staging system is unique to ICC and does not merely parallel that of HCC.

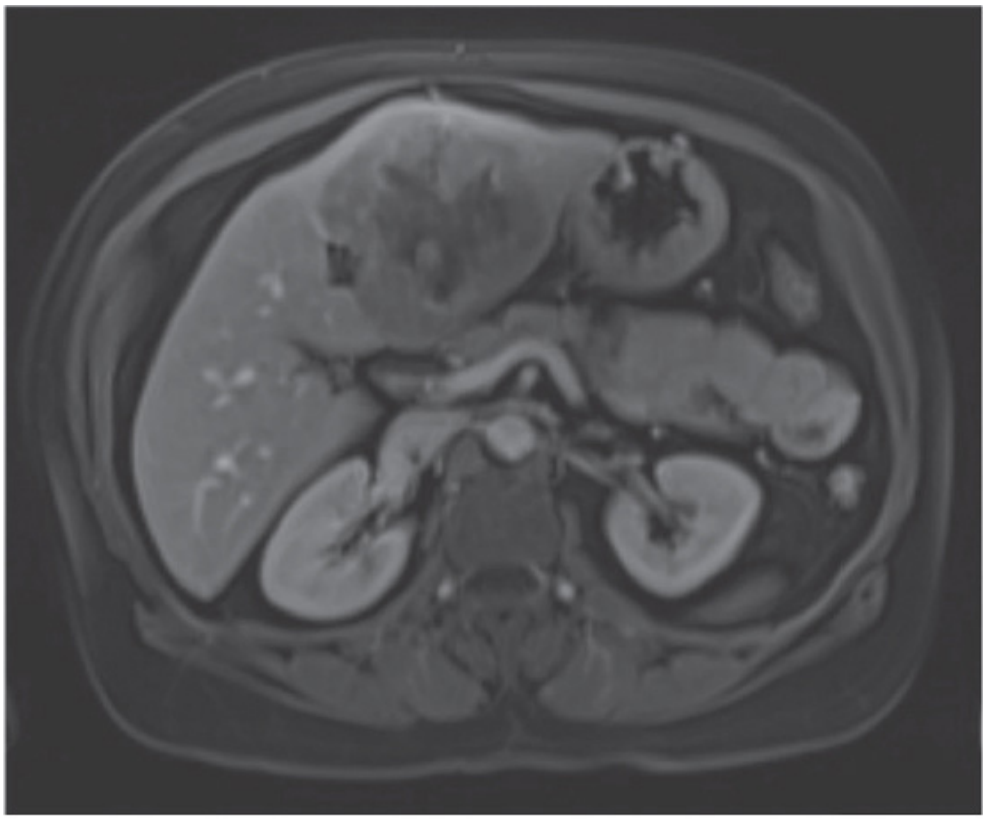

Figure 60.8 Cholangiocarcinoma typically depicts enhancement on delayed venous imaging.

The utilization of tumor size in patients with ICC as a prognostic indicator to stratify patients has been controversial. While used in previous versions of the AJCC staging system, the prognostic value of tumor size was refuted in one of the earliest proposed staging systems for ICC.[107] Supported by several groups, these authors found no independent association between tumor size and survival in ICC.[1,106,112,113] Indeed, tumor size is notably absent in the staging system proposed by Nathan et al., as well as in the seventh edition AJCC staging system addressing ICC independently.[106,110] On the other hand, the Liver Cancer Study Group of Japan (LCSGJ) found a worse prognosis in patients with ICC >2 cm in diameter. This size is used as a cutoff value in their commonly used staging system.[109] Similarly, others have shown a significant negative effect on recurrence and survival with increasing tumor size, particularly in tumors >5 cm and >7 cm. This is reflected by the fact that tumor size has been incorporated in two of the newer proposed nomograms.[108,111,114–116] More recently, increasing tumor size has been found to be associated with an increased incidence of nodal involvement, multiple tumors, vascular invasion, and poorly differentiated tumors.[117,118] The suggestion would be that larger tumor size may be indicative of more aggressive tumor biology. Though perhaps subtle, the role of size in determining resectability should not be entirely discounted. Accordingly, tumor size has been incorporated in the eighth edition AJCC staging system.

Multifocal intrahepatic disease is considered one of the most dominant clinicopathologic factors affecting survival in ICC. The pathophysiology of multiple ICC tumors, similar to HCC, is thought to be due to either satellitosis, multicentric hepatocarcinogenesis, or intrahepatic metastases. However, the clinical significance of these is unclear. Still, there is very little debate that patients with ICC presenting with multiple tumors face a grim prognosis, particularly with ≥3 tumors.[1,108,111,114–117] While most patients with multifocal disease never reach resection, the median survival for the minority that do ranges from 12 to 19 months, with one study observing no survival benefit over patients treated nonoperatively.[1,114,116] Thus, in patients with multiple intrahepatic ICC tumors, nonoperative therapies should be the first consideration. Resection should be reserved for only highly selected cases.

The presence of vascular invasion is often cited as an important risk factor for disease recurrence and decreased survival in patients with ICC.[1,106,108,113]

Its utility as an independent prognostic indicator, however, is less clear. Indeed, when taking into account other factors, such as positive lymph node status and multiple tumors, vascular invasion frequently failed to maintain significance.[1,112,114,117,119] Furthermore, microscopic vascular invasion is difficult to identify on preoperative imaging, giving it little value in determining resectability. Even when faced with major vascular invasion, however, several groups have advocated a more aggressive surgical approach, citing increased resectability rates and comparable or better overall survival when major vascular resection was performed in order to obtain negative margins.[117,119,120] Thus, hepatic resection in the setting of major vascular invasion can be oncologically appropriate in select patients with ICC, particularly after a favorable response to a course of preoperative therapy.

Extrahepatic disease is considered stage IV and these tumors should be deemed unresectable, except in highly select cases. Regional lymph node disease, in the latest eighth edition AJCC staging system, is deemed stage IIIB as opposed to previously being designated stage IV disease.

Figure 60.9 Typical appearance of colorectal cancer liver metastases on venous phase imaging.

Colorectal Liver Metastases

CRC is the most common cancer worldwide and the second most common cause of cancer-related death in the United States.[62] Approximately 25% of patients with CRC present with metastatic disease and 50% will eventually develop metastases, with the majority being located in the liver (**Fig. 60.9**).[121,122] In patients with metastases confined only to the liver, hepatic resection is the goal, with a 5-year survival of approximately 50% in most modern series and a 10-year disease-free survival reaching nearly 20%.[123,124] Unfortunately, resection is only possible in 20% to 25% of patients.

Selecting the patients for resection that are likely to achieve these survival benchmarks, however, has been challenging. Several risk factors have been identified and used in various combinations to develop clinical risk scoring systems to predict long-term survival and guide therapy in patients with

colorectal liver metastases. Examples of these factors include synchronous liver disease, primary tumor node status and histology, number and size of liver tumors, CEA level, disease-free interval, and the presence of extrahepatic disease.

While most studies agree as to the general importance of these factors and their cumulative effect on survival, there is little standardization in their individual cutoff values and prognostic strengths, and no one factor has unanimously been shown to affect outcomes.[125–129] In fact, one study focusing on patients cured of disease at 10 years showed that well over half of them originally had at least one, and 43% had at least three, of these poor prognostic factors—synchronous disease (7%), node-positive primary (51%), CEA >200 (7%), disease-free interval <12 months (37%), multiple hepatic tumors (40%), and size of hepatic tumor >5 cm (36%).[124] Even in the setting of extrahepatic disease, a scenario traditionally considered a contraindication to resection, acceptable 5-year survival rates up to 28% have been shown in select patients undergoing hepatic resection.[130–132] Certainly, there is little question that patients with many risk factors do worse than patients with few to none. However, the line that separates the biologically resectable from the biologically unresectable patients with colorectal liver metastases continues to evade us.

Neuroendocrine Liver Metastases

Although a rare tumor, when metastatic, the liver is involved in the majority of cases, with midgut (small bowel and appendiceal) and pancreatic location being the primary sites of disease.[133] Before considering liver resection, the full extent of disease burden must be evaluated. This can be accomplished with high-quality cross-sectional imaging (**Fig. 60.10**), usually in combination with SSR scintigraphy. While Indium-111 (octreotide scan) is useful, the Gallium-68 Dotatate scan offers greater sensitivity for detecting small-volume disease and is the preferable modality. Indications for resection include not only eradication of disease, but also control of symptoms related to the carcinoid syndrome. Surgical cytoreduction of disease, on the order of 70% to 90%, has been deemed adequate to be associated with improved survival and/or symptom relief.[134,135] As the medical and nonoperative liver-directed therapy armamentarium (including

transarterial embolization, ablation, and transarterial radioembolization) for treating advanced NETs continues to evolve and expand, the role and benefit of resection must be carefully weighed against its potential morbidity. Furthermore, with the FDA approval of Peptide Receptor Radionuclide Therapy (PRRT) with Lutetium 177 Dotatate in January 2018 based on the results of the Netter-1 trial, the role of hepatic resection has been called into question, especially in patients with extrahepatic disease.[136] That being said, liver resection should always be discussed and considered in multidisciplinary tumor boards when determining the therapeutic plan for each individual patient.

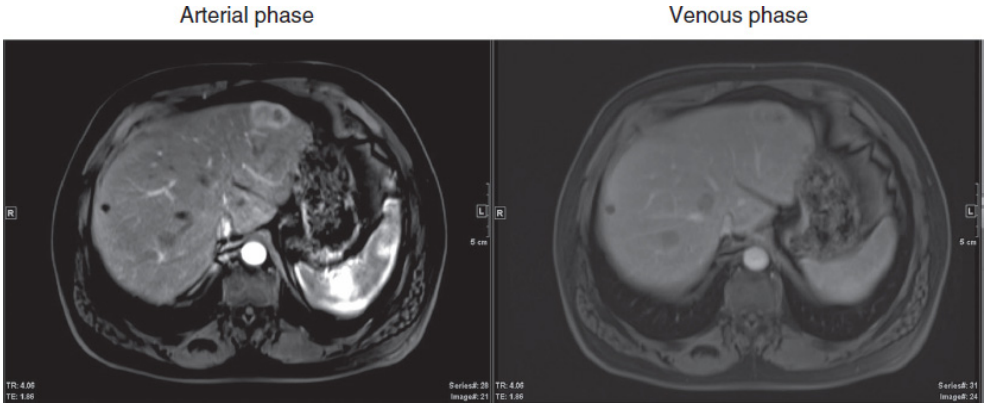

Figure 60.10 Neuroendocrine liver metastases are typically bright on arterial phase imaging and tend to wash out during the venous phase.

Noncolorectal, Nonneuroendocrine Liver Metastases

This group of patients represents a small minority of patients who are candidates for and undergo liver resection. Primary histologies that comprise this cohort of patients include melanoma, renal cell carcinoma, sarcoma, breast cancer, lung cancer, and gynecologic malignancies. Each individual scenario must be evaluated thoroughly in a multidisciplinary setting, as there are no general guidelines that dictate the appropriateness of hepatic resection for this group of patients. One must weigh the magnitude of resection and its potential morbidity, the extent of hepatic and extrahepatic disease, the systemic therapy options and their projected efficacy, and the anticipated survival of the patient.[137]

HOST CONDITION

A patient's general health status and their ability to tolerate surgery, or surgical fitness, is a critical component of determining resectability of hepatic malignancies. A thorough history and physical examination, and any other indicated adjunct workup, should be performed preoperatively on all patients. Because determining the surgical candidacy of a patient is often subjective, several risk indices have been developed to aid in patient assessment, decision making, and provide a more objective way to risk-stratify patients. Those commonly used by anesthesiologist and surgeons include the American Society of Anesthesiologists (ASA) scale, the Eastern Cooperative Oncology Group (ECOG) Performance Status, the Charlson Comorbidity Index (CCI), and the Revised Cardiac Risk Index (RCRI).[138–141] More recently, the concept of frailty has been introduced as an important surgical risk assessment tool and forms the basis of the Hopkins Frailty Score, which was later validated in a large multidisciplinary prospective study examining outcomes of patients undergoing major intraabdominal surgery.[142,143]

TECHNICAL RESECTABILITY

4 In liver surgery, the technical resectability of a tumor is defined not only by what can be removed, but more importantly by what is subsequently left behind. Thus, hepatic arterial and portal venous inflow, venous outflow, biliary drainage, and the quantity and quality of the future liver remnant (FLR) should all be deemed adequate to sustain function and support regeneration in the postoperative period. Patients with underlying liver dysfunction pose a unique challenge when considering hepatic resection and understanding the degree of dysfunction and its effect on prognosis is crucial. In select patients, the use of remnant-optimizing techniques and staged procedures can increase resectability and should be considered whenever possible.

Vascular Inflow/Outflow and Biliary Drainage

One of the major dilemmas in determining the technical resectability of liver tumors is balancing the appropriate operation required in order to completely remove the tumor and obtain negative margins while maintaining adequate vascular inflow, outflow, and biliary drainage of the FLR. Thus, mapping out the tumor location in relation to the patient's hepatic vascular and biliary anatomy is critical. In most patients, this can be done successfully with good-quality cross-sectional imaging, including a CT scan, MRI, or both. Even with centrally located tumors, which more frequently involve major vascular structures close to the hilum, improvements in high-quality cross-sectional imaging have allowed for better visualization and characterization of tissue planes. When biliary obstruction is suspected, cholangiography may help delineate biliary involvement, and can be done endoscopically, percutaneously, or using MRI. Given the advances in imaging, invasive cholangiography is rarely necessary.

Historically, tumor involvement of the portal vein or inferior vena cava has been considered a contraindication to surgery, as resection of these tumors incurred significant perioperative morbidity and mortality risk. However, improvements in surgical technique and perioperative management have expanded our definition of resectability. Indeed, several studies have demonstrated that in select patients, hepatectomy combined with major vascular resection or thrombectomy can be safe, with low postoperative morbidity and mortality, and that major vascular or biliary involvement should not necessarily preclude resection.[79,120,144–148] In highly select patients whose tumor involves the IVC, the hilum, or the confluence of the IVC and hepatic veins, and would otherwise be considered unresectable by any other resection techniques, ex vivo resection with autotransplantation may be an option.[149–153] However, data regarding this approach is sparse, limited to case reports and small series, and the survival benefit is unclear.

FLR QUANTITY AND QUALITY

Volumetric Assessment of the Liver

As the liver has a tremendous capacity for functional compensation and regeneration, healthy livers, without cirrhosis, can tolerate resection of up to

80% of their parenchymal volume. However, the segmental distribution of the liver's functional capacity is not uniform. It can vary from person to person, thus making it difficult to estimate the volume of the FLR needed to sustain function based on traditional anatomic nomenclature.[154] Preoperative volumetric analysis can be an important tool to assess the actual volume and predict the function of the FLR. This is particularly important when considering major and extended hepatic resections.

In the most basic sense, the FLR is standardized to total liver volume (TLV) and is expressed as the percentage of the TLV that is to be left unresected. Various methods for measuring liver volume have been proposed. One method is using CT and three-dimensional CT volumetry. This has been shown to be accurate and reproducible in calculating TLV and FLV values.[155–157] However, direct measurement of TLV on imaging can be problematic as large tumors, biliary dilatation, and underlying liver disease may affect the accuracy of the measurements. In addition, accurately measuring TLV requires that the tumor volume be excluded or subtracted, which can be particularly difficult in the setting of multiple tumors and can lead to user discrepancies and mathematical error.

An alternative approach is to estimate the TLV using a mathematical formula based on body surface area (TLV [cm^3] = −794.41 + 1267.28 × body surface area [m^2]), which has been validated in a meta-analysis and found to be superior to other similar formulas.[158,159] An FLR volume ≤20% has been found to be the strongest independent predictor of postoperative liver insufficiency, as well as a significant risk factor for postoperative liver failure and death.[160–162] Thus, an FLR volume >20% has been proposed as a cutoff for safe hepatic resection in healthy, noncirrhotic livers.

However, many patients undergoing liver resection do not have healthy livers. Although the exact pathogenesis is not entirely understood, liver injury is a known risk of chemotherapy, and increasing duration of preoperative treatment has been shown to increase the risk of postoperative complications.[163–169] Longer durations of preoperative chemotherapy (>12 weeks) have been associated with higher rates of liver injury and postoperative hepatic insufficiency.[167,170] In patients who receive short-duration preoperative chemotherapy, it has been suggested that an FLR of at least 20% to 30% is sufficient to undergo hepatic resection.[170,171] However, those receiving long-duration (>12 weeks) preoperative chemotherapy

should have an FLR volume of at least 30%, although some suggest that an FLR of 40% is necessary to prevent postoperative hepatic insufficiency.[170,172,173] In patients with hepatic fibrosis or cirrhosis, the FLR volume is suggested to be at least 40% to 50% of TLV.[174,175]

Functional Assessment of the Liver

One of the most important assessments when determining resectability of liver malignancies involves the preoperative evaluation of liver function. The perioperative morbidity and mortality risk has been shown to increase with worsening degree of hepatocellular compromise in cirrhotic patients undergoing hepatic resection.[176–179] Although a long list of functional studies, imaging techniques, and serum markers exists, the multiple and diverse functions of the liver make comprehensive evaluation difficult, and no single study has been consistently proven to be the best measurement of preoperative liver function or predictor of postoperative hepatic insufficiency and failure prior to resection.

The model for end-stage liver disease (MELD) is one of two major clinical scoring systems frequently used to evaluate liver function in cirrhotic patients. MELD is based on a patient's bilirubin, international normalized ratio (INR), and creatinine.[180] Traditionally used to predict survival in cirrhotic patients awaiting liver transplantation, the utility of the MELD score has been expanded to a variety of clinical settings, including the assessment of patients being considered for partial hepatectomy.[180–183] For patients with cirrhosis undergoing hepatic resection, a MELD score ≥9 has been shown as an independent predictor of perioperative complications and mortality.[182,183] As such, a MELD score <9 can be considered reasonably safe for hepatic resection.

The other frequently used clinical scoring system, the Child–Turcotte–Pugh (CTP) score, can be used to predict liver-related mortality in cirrhotic patients. CTP takes into account both clinical measures and laboratory values, including presence of ascites, encephalopathy, total serum bilirubin, INR, and serum albumin.[184] An elevated CTP score has been associated with increased morbidity and mortality following liver resection.[177,179,185] In fact, a Child B classification (score 7 to 9) is considered a relative contraindication to resection, particularly for major hepatectomy. A Child C

designation is an absolute contraindication, even for most minor resections.[186] In addition, the presence of encephalopathy, independent of the other factors, is generally considered a contraindication to resection.

An additional method of identifying cirrhotic patients at risk for postoperative complications involves an assessment for the presence of portal hypertension. Splenomegaly and/or varices present on imaging are both reliable signs of portal hypertension. However, they are rarely present in patients being considered for resection, therefore reliance on radiographic evidence of these signs is inadequate. Portal venous wedge pressure can be used for the direct measurement of portal pressure. However, the routine use of this invasive technique is impractical. Alternatively, for patients with underlying liver dysfunction, thrombocytopenia has been shown to be a good surrogate marker for the presence of portal hypertension. It tends to be indicative of increased platelet sequestration due to portal hypertension–induced hypersplenism. Although portal hypertension is not an absolute contraindication to hepatic resection, thrombocytopenia has been associated with increased morbidity and mortality in patients undergoing resection.[187–190] Specifically, a preoperative platelet count <150/nL has been independently associated with major postoperative complications, postoperative hepatic insufficiency, and 60-day mortality in patients with HCC undergoing hepatic resection.[185] In fact, a modified Child score based on this data has been proposed, which replaces encephalopathy in the traditional CTP scoring system with preoperative platelet count. This modified Child score was found to be independently associated with major postoperative complications and 60-day mortality, and the only factor independently associated with postoperative hepatic insufficiency.[185] This modified scoring system is particularly clinically relevant as the presence of encephalopathy is uniformly a contraindication to resection and thus does not contribute greatly to a preoperative risk scoring system. Rather, a simple lab value such as the platelet count can give insight into the presence of portal hypertension. Bone marrow suppression from chemotherapy leading to a decreased production of platelets must also be considered when interpreting the meaning of thrombocytopenia.

Indocyanine green (ICG) clearance is another assessment tool used preoperatively to evaluate liver function in cirrhotic patients being considered for hepatic resection. ICG is an anionic organic dye that is

selectively taken up by hepatocytes and excreted in bile. It is usually measured as a percent serum clearance at 15 minutes and indirectly reflects hepatocyte blood flow and functional capacity.[191] An ICG cutoff of <10% at 15 minutes has been reported to be safe for extended resection, a cutoff of 10% to 20% for hemihepatectomy, 20% to 30% for segmentectomy, and only enucleation for those with >40% ICG clearance.[192] However, the utility of ICG clearance over other well-established functional measures is debated, and it is rarely used in the United States.[188,193]

INCREASING TECHNICAL RESECTABILITY

Portal Vein Embolization

Portal vein embolization (PVE) is a percutaneous procedure performed preoperatively in select patients as a means to increase the volume of the anticipated FLR, which has been shown to subsequently improve liver function, thereby decreasing the risk of postoperative complications associated with small FLR size.[194–197] The portal vein of the intended specimen is embolized and occluded to induce a hypertrophic response in the FLR. The efficacy of PVE has been well documented, with a reported average increase of 12 ± 5% in FLR volume following PVE.[160,161,172,197] In fact, FLR growth due to PVE has been shown to increase resectability in almost 60% of patients who previously would have been considered unresectable due to inadequate FLR size.[171,198] Furthermore, it has been demonstrated that those patients whose FLR growth following PVE enabled them to undergo resection had no difference in postoperative morbidity and mortality compared to those who underwent resection upfront without the need for PVE.[160,198,199] Overall and disease-free survival has also been shown to be similar among these two groups in patients undergoing resection for colorectal liver metastases.[172,198] Thus, it does not seem that increasing technical resectability utilizing PVE sacrifices adherence to the principle of biologic selection.

More recent studies have found the kinetic growth rate of the FLR following PVE to be a strong predictor of postoperative liver insufficiency, liver failure, and death.[200,201] Using cutoff values of ≥2% and >2.66% FLR

growth per week, patients in this group from both studies had significantly lower postoperative morbidity and none developed liver failure or suffered liver-related death. This suggests that growth rate of the FLR, rather than the absolute standard volumetric measurements, may be a better marker for determining resectability of liver tumors following PVE, although further evaluation is still needed.

Although its application is not standardized, studies have warned against the routine use of PVE, citing a large percentage of patients in whom PVE had no effect on morbidity or mortality following hepatic resection.[171,199] Furthermore, PVE is not entirely without risk. Between 2% and 20% of patients fail to demonstrate remnant hypertrophy following PVE, and roughly 10% of patients suffer adverse events following the procedure.[197,202] Tumor progression following PVE may also be a concern, and has been documented in 17% to 25% of patients with colorectal liver metastases.[198,203]

Therefore, it has been suggested that PVE be reserved for an FLR volume ≤20% of TLV in patients without underlying liver dysfunction.[160,171,198,204] Among patients with or at high risk for liver injury (e.g., those who have received extensive preoperative systemic chemotherapy), PVE is recommended for an FLR volume ≤30% of TLV.[160,172,204] In patients with severe hepatic fibrosis or cirrhosis, an FLR ≤40% is the suggested cutoff value for performing PVE.[174,175,204]

Two-Stage Hepatectomy

Initially described by Adam et al. in 2000, a two-stage hepatectomy (TSH) is a potentially curative operative strategy in patients with multiple bilobar colorectal liver metastases that traditionally would be considered unresectable via a single operation, even in conjunction with systemic and local therapies.[205] The first stage of the procedure consists of resection of metastases from only one hemiliver, which is the designated FLR after the second stage is complete. Thus, it is important that parenchymal-sparing techniques be used during the first operation. In most patients, PVE of the contralateral liver is performed following the first stage. During the second-stage operation, all remaining metastases in the contralateral hemiliver are then resected. Although data examining TSHs are limited to single-institution studies with small patient cohorts and widely variable patient selection

criteria, a recent meta-analysis found that in select patients with initially unresectable colorectal liver metastases, TSH resulted in low postoperative morbidity and mortality and acceptable survival outcomes.[206] In particular, these patients fared significantly better than their counterparts who received systemic chemotherapy alone. In one study examining long-term outcomes following TSH, despite higher postoperative morbidity, comparable 5-year survival was seen between patients undergoing completed TSH and those who underwent a single-stage hepatectomy during the same time period.[207]

Associating Liver Partition with Portal Vein Ligation for Staged Hepatectomy

Associating liver partition with portal vein ligation for staged hepatectomy (ALLPS) is a relatively aggressive, and disputed, approach to managing traditionally unresectable liver tumors. More specifically, it was developed to overcome several limitations of PVE, including the potential for disease progression during the 4- to 6-week waiting period, and inadequate FLR hypertrophy following PVE. The procedure involves in situ splitting of the liver with portal vein ligation during the first stage, inducing rapid FLR hypertrophy, followed by a short-interval (<7 days) second stage in which the hemiliver containing the tumor is removed.[208,209] While several case series have reported its technical feasibility, complications can be high. Long-term data is minimal, and its use is highly controversial and debated.[210–216]

ANATOMY AND CLASSIFICATION

5 In order to perform partial hepatectomy, precise knowledge and mastery of the surgical anatomy of the liver, blood vessels, and biliary channels is essential. The liver is divided into sectors that comprise liver segments, each supplied by branches of the portal triads and drained by hepatic veins. Partial hepatectomy involves removal of one or more segments by isolation of the relevant portal venous and arterial inflow, severance of the relevant

hepatic veins and biliary drainage channels, and removal of the associated liver tissue.

The anatomic division between the right and left hemiliver follows a line projected through a plane found at the principal plane or Cantlie line—running from the medial margin of the gallbladder bed to the left of the IVC posteriorly, not at the falciform ligament.[217] Each hemiliver is then subdivided into sectors, sections, and segments.

The Brisbane terminology dictates that the hepatic veins form the boundaries between the different sectors of the liver.[218] Specifically, the medial margin of the right posterior sector is the right hepatic vein and comprises segments VI and VII. The right anterior sector is bordered by the right hepatic vein laterally and middle hepatic vein medially, coursing along the principal plane, comprising segments V and VIII. These are also termed the right posterior *section* and right anterior *section* according to Brisbane terminology. Based on this same terminology system, the area of liver that comprises segments IVa, IVb, and III forms the left medial sector as it is bound by the middle and left hepatic veins. Segment II forms the left lateral sector, because the left hepatic vein divides segment II from III. From a clinically relevant perspective, however, en bloc resection of segments III, IVa, and IVb cannot be performed since this area of liver encompasses the umbilical fissure where the left portal vein is situated. Thus, according to Brisbane terminology, segment IVa/b is referred to as the *left medial section,* and it is bordered by the middle hepatic vein and umbilical fissure. The left lateral sector, according to the slightly modified terminology that is being presented here, is comprised of segments II and III. This represents the portion of liver to the left of the ligamentum teres and falciform ligament and is termed the *left lateral section* according to Brisbane terminology. Essentially, the left liver is divided into a medial and lateral sector along the line of insertion of the ligamentum teres and the falciform ligament. This modified terminology will be utilized for the remainder of this chapter as it is clinically relevant and applicable. The term "section" will not be used. The portal venous and hepatic arterial branches conform to the segmental organization and run within the segments, and the draining hepatic veins converge posteriorly toward the inferior vena cava (**Fig. 60.11**).

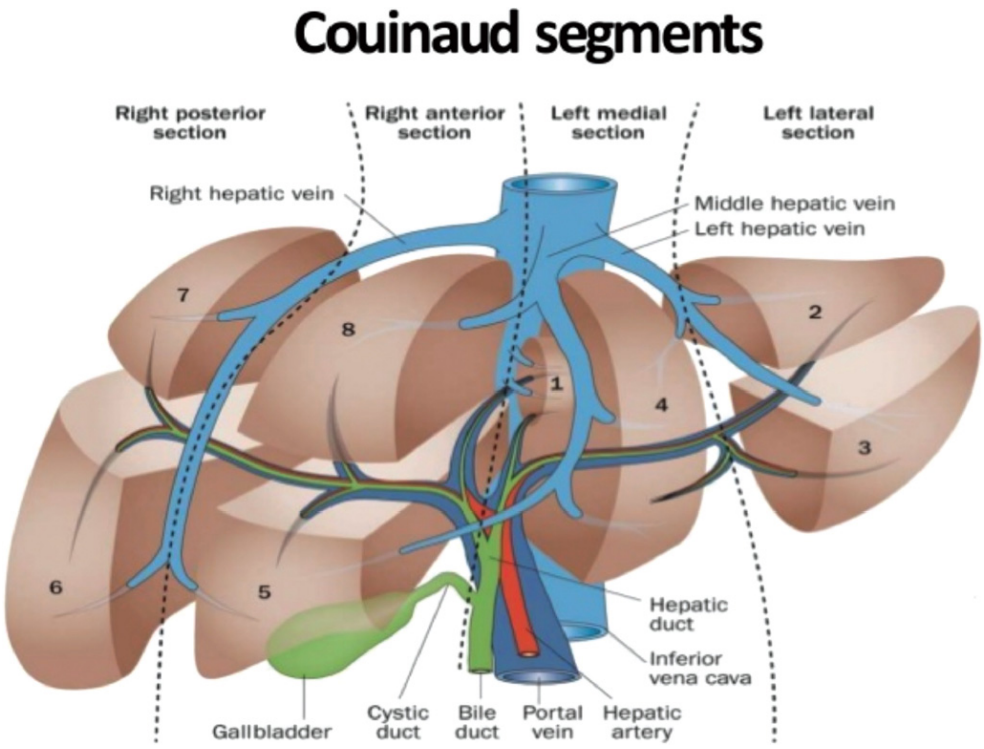

Figure 60.11 Segmental anatomy of the liver utilizing the Brisbane terminology of "sections."

6 Practically, five types of hepatic resections are performed relatively routinely. The five different resections include (1) right hepatectomy, (2) left hepatectomy, (3) left lateral sectorectomy, (4) right posterior sectorectomy, and (5) segmentectomy/nonanatomic resection. A simple step-by-step algorithm for performing these procedures is detailed in **Tables 60.3** to **60.7**. The portal vein and hepatic artery divide into major right and left branches outside the liver parenchyma below the hilus. Here, when the overlying peritoneum is incised, it is usually possible to dissect each major branch beyond its bifurcation, unless significant variations in anatomy exist. The confluence of the right and left hepatic ducts also occurs outside the liver. At the hilum of the portal vein, the right portal vein is short, and often has an early branch to the caudate process prior to its bifurcation into the right anterior and posterior portal veins. In contrast, the left branch of the portal vein and the left hepatic duct pursue a longer, more horizontal extrahepatic course beneath segment IV and are more easily dissected free along their length.

The ligamentum teres (round ligament) runs into the umbilical fissure of the liver, at the base of which the main vascular and biliary pedicles branch to the segments of the left liver (II, III, IVa, IVb). After entering the umbilical fissure, the left branch of the portal vein curves caudally and gives branches not only to the left lateral sector (segments II and III) but together with branches of the left hepatic artery, it also supplies the left medial sector—segments IVa and IVb of the left liver, also known as the *quadrate lobe*. These branches course from left to right, starting in the umbilical fissure and supplying segments IVa/IVb.

Outside of the liver substance, there is not a distinct sheath around the portal triad structures, and they can be dissected separately. The structures of the portal triad—the portal vein, hepatic artery, and bile duct—are covered with Glisson capsule as they enter the liver parenchyma such that within the liver, they are contained in well-formed branching fibrous sheaths often referred to as *pedicles*, each containing a vein, artery, and bile duct. Pedicles are strong structures that contain the constituents of the portal triad, and intrahepatic dissection of these pedicles enables isolation and control of vascular and biliary elements without the need to individually expose each structure outside the liver.

Table 60.3 Right Hepatectomy (Segments V–VIII)

1. Explore the abdomen to ensure no subradiographic metastatic disease.
2. Ligate the round ligament and leave the suture long and place a hemostat on it.
3. Divide the falciform back toward IVC, staying about 1 cm off the surface to enable resuspension of the left liver.
4. Open the lesser sac through the pars flaccidum and clear the area over the caudate lobe and feel for enlarged lymph nodes. This will enable control of the porta hepatis.
5. Ultrasound the entire liver, especially the left liver remnant, to ensure no subradiographic disease.
6. Perform a cholecystectomy, but leave a long tie on the cystic duct stump. This will facilitate a safe dissection in the porta hepatis.
7. Mobilize the right liver. The right phrenic vein will mark the location of the right hepatic vein.
   a. Incise the right anterior coronary ligament.
   b. When visualization becomes difficult, incise the inferior attachments to the liver to drop the kidney and adrenal gland. Stay just lateral to the IVC.
   c. Incise the triangular ligament.
   d. This will give good exposure to retract the right liver toward the left and incise the right posterior coronary ligament.
   e. Do not divide the left coronary/triangular ligament to prevent kinking of the left inflow and outflow vessels postoperatively.
8. Ligate and divide the venous tributaries to the IVC from the caudate lobe to expose and clear off the anterior aspect of the IVC.
   a. Clips, energy devices, or staplers can be used for this depending on the size of the veins.
9. Divide the caval (caudate) ligament with a vascular load stapler.
10. Find and develop the “notch” at the dome of the liver to find space between the right and middle hepatic vein. This will facilitate extrahepatic control of the right hepatic vein.
11. With the cystic duct stump retracted medially to the left, dissect out and control the right hepatic artery. Test clamp to ensure good left hepatic arterial flow before dividing. It can either be tied or stapled.

12. Once artery is divided, dissect out the right portal vein. Test clamp to ensure the left portal vein is intact with US. Place an umbilical tape around the right portal vein and retract to the left to protect the left portal vein. Divide with an endovascular stapler.
13. Now that inflow is controlled, divide the right hepatic vein outflow with an endovascular stapler.
14. Mark out the line for parenchymal transection along Cantlie line, staying just right of the middle hepatic vein.
15. Divide the hepatic parenchyma down to the right bile duct.
16. Encircle the right bile duct intrahepatically, making sure to stay to the right of the cystic duct stump and biliary hilum to avoid injury to the contralateral biliary system. Divide the right bile duct with an endovascular stapler.
17. Complete the parenchymal transection.
18. Hydrate the patient to a status of euvolemia.
19. Ensure hemostasis and biliary stasis along the cut surface of the liver.
20. Resuspend the left liver by sewing the falciform ligament to the diaphragm with interrupted figure-of-eight 2-0 Vicryl sutures.

Table 60.4 Left Hepatectomy (Segments II–IV)

1. Explore the abdomen to ensure no subradiographic metastatic disease.
2. Ligate the round ligament and leave the suture long and place a hemostat on it.
3. Divide the falciform back toward IVC.
4. Open the lesser sac through the pars flaccida and clear the area over the caudate lobe and feel for enlarged lymph nodes. This will enable control of the porta hepatis.
5. Ultrasound the entire liver, especially the right liver remnant, to ensure no subradiographic disease.
6. Perform a cholecystectomy.
7. Mobilize the left liver by incising the left coronary and left triangular ligaments.
   a. Place a laparotomy pad over the stomach and spleen to avoid injury.
   b. Do not injure the diaphragm or left phrenic vein.
8. Divide the entire length of the lesser omentum, being careful to ligate a replaced or accessory left hepatic artery if present.
9. Dissect out the left hepatic artery at the medial aspect of the porta hepatis at the base of the umbilical fissure. Test clamp it to ensure good flow in the right hepatic artery. Divide the left hepatic artery either with ties or an endovascular stapler.
10. Dissect out and control the left portal vein at the base of the umbilical fissure. Test clamp it and ensure good flow in the right portal vein using US. Divide the left portal vein with an endovascular stapler. Divide it distal to the takeoff of caudate lobe branches to preserve caudate inflow.
11. Mark out the plane of transection, staying left of the middle hepatic vein.
12. Divide the parenchyma. Make sure to curve to the left as the transection plane approaches the porta hepatis to prevent injury to the right bile duct or right-sided inflow structures.
13. Encircle the left bile duct at the base of the umbilical fissure and divide it with an endovascular stapler.
14. Complete the parenchymal transection superiorly by dividing the left hepatic vein with an endovascular stapler.
15. Hydrate the patient to a status of euvolemia.

16. Ensure hemostasis and biliary stasis along the cut surface of the liver.

Table 60.5 Left Lateral Sectorectomy (Segments II–III)

1. Explore the abdomen to ensure no subradiographic metastatic disease.
2. Ligate the round ligament and leave the suture long and place a hemostat on it.
3. Divide the falciform back toward IVC.
4. Open the lesser sac through the pars flaccida and clear the area over the caudate lobe and feel for enlarged lymph nodes. This will enable control of the porta hepatis.
5. Ultrasound the entire liver, especially the right liver remnant and segment IV, to ensure no subradiographic disease.
6. Perform a cholecystectomy. This is not absolutely necessary to perform a left lateral sectorectomy but is conventional to perform at the time of liver resection.
7. Mobilize the left liver by incising the left coronary and left triangular ligaments.
   a. Place a laparotomy pad over the stomach and spleen to avoid injury.
   b. Do not injure the diaphragm or left phrenic vein.
8. Mark out the line of parenchymal transection just left of the falciform ligament and umbilical fissure.
9. Divide the parenchyma.
10. Encircle the segment III pedicle as it is exposed during parenchymal transection. Divide it with an endovascular stapler.
11. Encircle the segment II pedicle as it is exposed during parenchymal transection. Divide it with an endovascular stapler.
12. Complete the parenchymal transection superiorly by dividing the left hepatic vein with an endovascular stapler.
13. Hydrate the patient to a status of euvolemia.
14. Ensure hemostasis and biliary stasis along the cut surface of the liver.

Table 60.6 Right Posterior Sectorectomy (Segments VI–VII)

1. Explore the abdomen to ensure no subradiographic metastatic disease.
2. Ligate the round ligament and leave the suture long and place a hemostat on it.
3. Divide the falciform back toward IVC, staying about 1 cm off the surface to enable resuspension of the left liver, should it be necessary.
4. Open the lesser sac through the pars flaccida and clear the area over the caudate lobe and feel for enlarged lymph nodes. This will enable control of the porta hepatis.
5. Ultrasound the entire liver, especially the left liver remnant and right anterior sector, to ensure no subradiographic disease.
6. Perform a cholecystectomy.
7. Mobilize the right liver. The right phrenic vein will mark the location of the right hepatic vein.
   a. Incise the right anterior coronary ligament.
   b. When visualization becomes difficult, incise the inferior attachments to the liver to drop the kidney and adrenal gland. Stay just lateral to the IVC.
   c. Incise the triangular ligament.
   d. This will give good exposure to retract the right liver toward the left and incise the right posterior coronary ligament.
   e. Do not divide the left coronary/triangular ligament to prevent kinking of the left inflow and outflow vessels postoperatively.
8. Divide the caval (caudate) ligament with a vascular load stapler.
9. Find and develop the “notch” at the dome of the liver to find space between the right and middle hepatic vein. This will facilitate extrahepatic control of the right hepatic vein. This step is not always necessary depending on the location of the tumor and whether or not the right hepatic vein needs to be divided to obtain a negative margin.
10. Mark out the line for parenchymal transection along the right hepatic vein using US. The line of transection will be either to the right or left of the right hepatic vein depending on whether or not it needs to be ligated to obtain a negative margin resection. The line of transection is along a transverse plane of the liver.
11. Divide the hepatic parenchyma down to the right posterior sector pedicle.

12. Encircle the right posterior pedicle and test clamp it and ensure preservation of flow in the right anterior pedicle with US. Divide the right posterior pedicle with an endovascular stapler. Extrahepatic control and division of the right posterior portal vein and right posterior hepatic artery is also feasible and commonly performed.
13. If necessary for the procedure, divide the right hepatic vein with an endovascular stapler.
14. Complete the parenchymal transection.
15. Hydrate the patient to a status of euvolemia.
16. Ensure hemostasis and biliary stasis along the cut surface of the liver.
17. If necessary, resuspend the left liver by sewing the falciform ligament to the diaphragm with interrupted figure-of-eight 2-0 Vicryl sutures. Given that the right anterior sector is left in situ, this step is often not necessary.

Table 60.7 Partial Hepatectomy/Segmentectomy

1. Explore the abdomen to ensure no subradiographic metastatic disease.
2. Ligate the round ligament and leave the suture long and place a hemostat on it.
3. Divide the falciform back toward IVC.
4. Open the lesser sac through the pars flaccida and clear the area over the caudate lobe and feel for enlarged lymph nodes. This will enable control of the porta hepatis.
5. Ultrasound the entire liver, especially the future liver remnant, to ensure no subradiographic disease.
6. Perform a cholecystectomy.
7. Depending on what segment or what area of the liver is to be removed, the right or left liver should be mobilized as described in **Tables 60.3** and **60.4**.
8. Mark out the line for parenchymal transection using US to ensure an adequate margin. If a segmentectomy is to be performed, US should be utilized to define the inflow and outflow.
9. Divide and complete the hepatic parenchyma. It is helpful to use US to guide the resection to ensure a negative margin and remnant inflow during the dissection.
10. Complete the parenchymal transection.
11. Hydrate the patient to a status of euvolemia.
12. Ensure hemostasis and biliary stasis along the cut surface of the liver.

The liver straddles the IVC immediately below the diaphragm, and the hepatic veins have a short extrahepatic course to empty into the vena cava. This superior portion of the vena cava with the draining hepatic veins is covered with a fold of peritoneum that extends from the cephalad aspect of the falciform ligament to the right and left triangular ligaments. This fold of peritoneum comprises the anterior and posterior coronary ligaments, which converge to form the right and left triangular ligaments, respectively. The right hepatic vein usually enters the vena cava separately. By contrast, the left hepatic vein runs in the left scissura between segments II and III and is often joined by the middle hepatic vein, which occupies the principal scissura,

before entering the vena cava. Thus, the middle and left hepatic veins most often empty into the IVC as a common trunk. The right and left phrenic veins, which are easily visible on the surface of the diaphragm, empty into the right and left hepatic veins, respectively, and serve as a reliable landmark to mark the location of the right and left hepatic veins. Several smaller veins from the posterior surface of the liver and the caudate lobe drain directly into the IVC, termed the short hepatic veins or "caudate veins."

The umbilical vein runs beneath the falciform ligament and empties into the left hepatic vein. This vein is important in right-sided resections that remove segment IVa because it provides drainage of segment IVb if the procedure mandates ligation of the middle hepatic vein.

OPERATIVE PROCEDURES

Patient Positioning and Incision

For open procedures, the patient should be positioned supine with both arms extended at a right angle to the body. It is not necessary to place the patient in a lateral decubitus position, as adjusting the operating table allows for adequate exposure during the operation. This exposure is adequate for most hepatic resections. The abdomen should be widely exposed from midaxillary line to midaxillary line to allow adequate space for a bisubcostal incision, should one be necessary or preferred. It is the author's preference to do all resections through a simple midline laparotomy incision. A self-retaining retractor to elevate the costal margin provides ample visualization and exposure to complete the procedure safely.

Ultimately, the incision depends on body habitus and tumor location, and the surgeon should not hesitate to extend or enlarge the wound to gain adequate access. For most hepatic resections, a midline incision will suffice with appropriate costal margin and side-wall retraction. A midline incision is often most comfortable for the patient. An extended right subcostal or a bilateral subcostal with a vertical extension are other common incision choices. A slight variation of these incisions that affords excellent exposure for most resections is an upper midline incision from the xiphoid process to approximately 2 to 3 cm above the umbilicus with right lateral extension

toward a point midway between the inferior costal margin and anterior superior iliac spine. A small upper midline incision may be made first to allow preliminary manual and visual exploration to exclude obviously unresectable disease or the presence of extrahepatic spread. Particularly for left-sided resections, a midline incision is adequate. Large tumors of the right side of the liver, especially those lying posteriorly and involving the IVC, may require a right thoracoabdominal approach, but this is rarely necessary. This can usually be avoided with either right lateral extension of an upper midline incision with good costal margin retraction or a generous midline incision.

Exposure, Mobilization, and Assessment

After the abdomen is opened, the entire peritoneal cavity should be explored to assess for evidence of subradiographic metastatic disease. In particular, periportal lymph nodes along the hepatic artery, celiac axis, or in the portacaval groove should be assessed. Exploration of the lower abdomen through an upper abdominal incision may be difficult in patients who have had previous pelvic surgery. When direct access is limited, palpation in conjunction with preoperative cross-sectional imaging (CT or MRI) and/or PET scans is sufficient.

Prior to exploration of the liver, the ligamentum teres (round ligament) is divided, and the falciform ligament is incised and separated from the anterior abdominal wall. The falciform ligament is divided as far cephalad as the subdiaphragmatic IVC. Vessels running within the falciform ligament are usually controlled with bovie electrocautery. When performing a major right-sided resection, the transection plane of the falciform ligament should be approximately 1 cm off the surface of the liver to enable resuspension of the left liver remnant should it be necessary. A long suture should be left on the round ligament to act as a handle during subsequent exploration and dissection for manipulating the liver.

Elevation of the round ligament facilitates examination of the undersurface of the liver, the porta hepatis, and umbilical fissure. Bimanual palpation should be performed, as lesions located deep within the parenchyma may be missed or underestimated with simple surface examination. The transparent tissue of the lesser omentum, or pars flaccida, should be incised to facilitate

manual palpation of the caudate lobe (segment I) and the celiac lymph node basin. If the gastrohepatic ligament needs to be further divided to facilitate an adequate evaluation, attention should be directed to the possible presence of an accessory or replaced left hepatic artery. Complete assessment and palpation of the right lobe requires mobilization of the right liver from the diaphragm and retroperitoneum. This may be delayed until US examination of the liver in conjunction with initial palpation indicates that the lesions are resectable.

Mobilization of the right liver begins with complete division of the falciform ligament and identification of the right hepatic vein as the right coronary ligament is incised. As the falciform ligament fibers begin to splay at the back, one must be careful, as the hepatic vein confluence is in close proximity. Early identification of the right hepatic vein prevents subsequent injury during the lateral and inferior mobilization. The location of the right hepatic vein is marked by the right phrenic vein insertion. Once the right vein is visualized, the anterior and posterior coronary ligaments are incised to expose the entire bare area of the liver until the depth of the posterior ligament prevents adequate visualization. At this point, the inferior peritoneal attachments to the liver are incised, which is usually met with a rush of air, in order to separate and drop the adrenal gland. Releasing the inferior attachments facilitates leftward retraction of the liver and exposure of the triangular ligament. The triangular ligament is incised. With the right hepatic vein already visualized, the dissection can now safely proceed medially to complete the division of the posterior coronary ligament toward the inferior vena cava in order to fully mobilize the right hemiliver.

Next, the short retrohepatic veins draining directly from the caudate lobe to the IVC are serially divided, progressing from the inferior aspect up toward the hepatic veins. Complete exposure of the IVC and right hepatic vein requires division of the fibrous tissue, or the vena caval ligament, which usually obscures the right side or the upper part of the retrohepatic vena cava. This division can be done with an energy device or an endoscopic gastrointestinal anastomosis vascular stapler (Endo GIA; US Surgical, Norwalk, CT). It is the author's practice to routinely divide this ligament with a stapler in order to seal the blood vessels contained within this structure. The vena caval ligament also extends behind the vena cava posteriorly as a fibrous extension from the caudate lobe on the left. Rarely,

the caudate lobe circumferentially wraps around the IVC such that the vena cava runs through a tunnel of liver parenchyma. Although this thin plate of liver tissue can be a source of difficulty, it can similarly be divided to expose the IVC completely with minimal consequence. Dividing this ligament is a necessary step in order to safely gain extrahepatic control of the right hepatic vein.

Similarly for a planned left-sided resection, the left coronary and triangular ligaments are incised to mobilize the left lateral sector. Care must be taken not to damage the stomach and spleen at the far left of the triangular ligament, and placing a laparotomy pad under the ligament helps to protect these structures while incising the ligament. Extrahepatic control of the middle/left hepatic vein confluence is a challenging maneuver. The ligamentum venosum must be divided near its attachment to the left hepatic vein in order to expose the anterior surface of the IVC just proximal to the hepatic vein confluence. The notch in between the right and middle vein is developed and this plane is carefully extended to exit anterior to the IVC at the level of where the ligamentum venosum was divided. Placing an umbilical tape through this space controls the middle/left hepatic vein confluence extrahepatically. This maneuver should only be performed if the location of the tumor mandates extrahepatic division of these veins to facilitate an oncologic margin-negative resection.

Intraoperative Ultrasound

Intraoperative ultrasound (IOUS) is an integral and necessary component for planning and performing hepatic resections. It is used to confirm what was seen on preoperative imaging and to assess for other lesions that may not have been seen previously or have developed in the interval time period between imaging and resection. IOUS also further delineates the exact anatomic relationship of lesions with the major vascular and biliary structures within the liver parenchyma. US guidance is also utilized to perform a needle biopsy of small, deeply placed lesions and for ablative procedures. Examination is carried out with a B-mode, real-time system and a T-shaped probe is the most ergonomic for direct application of the probe to the liver surface and in the author's opinion, provides the best images. Examination should be carried out in a systematic fashion, starting with

assessing the outflow and inflow vessels, the biliary tree, and then finally the hepatic parenchyma. In case of doubt, further examination may be done after mobilization of the right or left liver, particularly for posteriorly located tumors. The probe also may be placed on the inferior surface of the liver. IOUS can help plan and guide large segmental resections traversing narrow planes between the tumor edge and major vascular structures. Thus, it is paramount that the surgeon has the ability to use and interpret IOUS in order to safely maneuver inside the liver.

GENERAL PRINCIPLES OF HEPATIC RESECTIONS

All hepatic resections mandate control of the inflow and outflow vasculature and biliary drainage to the portion of liver to be resected, with preservation of adequate hepatic arterial and portal venous blood supply and intact biliary drainage to the liver remnant. Depending on the type of resection being performed, the inflow and outflow can be controlled either outside the liver substance or within the liver parenchyma. Launois and Jamieson have historically advocated for control of the intrahepatic pedicles when oncologically feasible in order to avoid contralateral injury.[219] In practice, most surgeons use a combination of techniques in hepatic resection, doing both pedicle ligation within the liver and extrahepatic dissection to expose the individual corresponding artery and portal vein. Biliary drainage from the remnant liver must be preserved without injury, including both leakage and stricture, to the biliary tract. The hepatic venous outflow should be controlled after inflow division, and the liver parenchyma must be transected to provide tumor adequate clearance in cases of malignancy.

Inflow Control and Preservation of the Integrity of the Biliary Tree

The hepatic arterial and portal venous blood supply to the portion of liver to be removed can be controlled and ligated either by extrahepatic dissection or by transecting the relevant pedicles within the liver parenchyma.

Extrahepatic vascular dissection may be accompanied by extrahepatic dissection and control of the relevant biliary radicles as well. However, this is associated with a higher risk of biliary injury, particularly during dissection on the right side, where anatomic variations in biliary anatomy are common. Thus, the right hepatic artery and right portal vein are typically divided utilizing an extrahepatic dissection for vascular control of right-sided lesions, while the corresponding biliary structures are divided within the pedicles at the time of hepatic parenchymal transection. This is not possible, however, for tumors that are close to the hilar structures, such as hilar cholangiocarcinoma. In these cases, extrahepatic biliary dissection is required, as making an intrahepatic approach would be impossible without compromising tumor clearance. For left-sided resections, although a pedicle approach is possible, dissection is most often carried out within or at the base of the umbilical fissure, and far left of the hilar bifurcation. Typically, the left hepatic artery and left portal vein are isolated and individually divided and the left bile duct is divided at the base of the umbilical fissure, thus minimizing the risk of injury to the right liver biliary drainage into the common duct.

Outflow Control

When performing a right hepatectomy, intrahepatic control of the right hepatic vein during parenchymal transection is feasible and acceptable for tumors that allow clearance superiorly with adequate tumor margins and with safe intrahepatic access to these vessels. However, extrahepatic control of the right hepatic vein is also safe and provides the added benefit of controlling the main outflow and disconnecting the specimen from the vena cava prior to parenchymal transection. This can potentially help reduce blood loss during parenchymal transection. For the difficult tumors lying high and posteriorly, extrahepatic control and ligation also facilitates an adequate oncologic margin. Because the middle hepatic vein usually merges with the left hepatic vein prior to draining to the IVC, the middle hepatic vein is usually taken within the liver substance when performing an extended right hepatectomy. During an extended left hepatectomy for a superiorly situated tumor, the middle and left hepatic veins are often controlled as a single unit outside the liver. For a standard left hepatectomy, the middle hepatic vein is preserved

and the left hepatic vein is divided within the liver, often as the last step of parenchymal transection. If isolated extrahepatic left hepatic vein control is needed, a small hepatotomy is usually needed to dissect the plane between the middle and left hepatic veins. This is seldom needed or performed.

Parenchymal Transection

Once the inflow and outflow are controlled, parenchymal transection ensues. It is important to maintain a state of low central venous pressure (CVP) in order to minimize bleeding. Central venous access for CVP monitoring is not necessary as long as intravenous fluids are tightly restricted. Several methods may be used to transect the liver parenchyma. The author's preference has been to use a simple crushing technique where Glisson capsule is scored with diathermy along the line of proposed transection, and a Kelly clamp is used to crush the liver tissue and expose small vessels, biliary channels, and larger pedicles. These structures can then be secured and divided using a variety of techniques. The most simple and economic method is to use clips and suture ligation. However, a variety of energy devices can be used that include (1) computer-controlled bipolar cautery (LigaSure; Valleylab, Boulder, CO); (2) a saline-linked radiofrequency ablation monopolar device (TissueLink; TissueLink Medical, Dover, NH), or a bipolar variation (Aquamantys, TissueLink Medical); (3) a Harmonic Scalpel (SonoSurg; Olympus Key Med, New York, NY). All of these devices have been used with success by a variety of investigators.[220–222] They also have been used successfully in the performance of laparoscopic partial hepatectomy. Larger structures can be controlled with sutures or vascular staplers.

The technique of using a Kelly clamp to crush the tissue is rapid and efficient. Although some surgeons choose to apply intermittent inflow occlusion to control blood flow to the remnant, this is most often not necessary if low CVP is maintained.[223] Should inflow occlusion still be necessary, intermittent 15-minute periods of occlusion, interspersed by 5-minute periods of relief to allow perfusion of the remnant and decompression of the bowel, is usually a safe technique. Prolonged occlusion during hepatic resection in patients with jaundice or cirrhosis should be avoided. Prolonged portal inflow occlusion is unnecessary, and for major hepatic resections,

complete parenchymal transection is usually accomplished in 20 to 30 minutes. During the short breaks between applications of the Pringle maneuver, the argon beam coagulator (Force GCU System; Valleylab) can be used to control small vessel oozing on the side of the remnant. Avitene (Davol, Warwick, RI), Surgicel (Ethicon, Somerville, NJ), or fibrin sealants also may be applied to the cut surface of the liver to achieve final hemostasis after transection is complete.

Alternate options for the Kelly clamp technique to expose the intrahepatic vascular and biliary anatomy include an ultrasonic dissector or a water-jet dissector.[224] The ultrasonic dissector has some advantages in dissecting liver parenchyma away from delicate vascular and biliary structures, particularly when a margin-negative resection is dependent on the precise dissection of that area. A disadvantage of the ultrasonic dissector is that it can be time consuming and offers no apparent advantage during the majority of parenchymal transection. No published data are available to indicate that any one technique is associated with decreased blood loss.

Some have described the use of broad coagulation devices, an example of which is the Habib 4X (AngioDynamics, Latham, NY). It uses radiofrequency energy to coagulate liver parenchyma widely along the planned transection plane with or without the use of vascular staplers; this method does not clearly expose the internal structures of the liver. The author does not advocate for such an approach and strongly believes that parenchymal transection should be a controlled dissection to avoid serious damage to the liver remnant and minimize bleeding and risk of bile leak.

The basic steps to performing common hepatic resection procedures are listed in **Tables 60.3** to **60.7**.

CONCLUSION

The nuances of determining resectability for liver tumors can be difficult to master, owing to the variety of primary and secondary malignancies involving the liver, the diversity of patient-specific factors to consider, and the hepatic anatomic and functional variability that represents the norm. The basic principles, however, are simple—if surgery is deemed appropriate from an oncologic standpoint, the patient is in reasonably good health and

can withstand the operation, and the tumor can be safely removed without compromising the viability of the future remnant, nearly all patients will be candidates for resection. However, as our understanding of tumor biology improves, diagnostic and operative techniques evolve, and systemic and local therapies improve, the selection of patients for resection will continue to both expand and simultaneously be refined.

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61

Calculous Biliary Disease

Salila S. Hashmi and Elijah Dixon

Key Points

1. Gallstones are classified by their cholesterol content as either cholesterol (70% to 80%) or pigment (20% to 30%), with pigment stones further classified as black or brown.
2. The pathogenesis of cholesterol gallstones is multifactorial but essentially involves four factors: (a) cholesterol supersaturation in bile, (b) crystal nucleation, (c) gallbladder dysmotility, and (d) gallbladder absorption/secretion.
3. Prophylactic cholecystectomy is generally not indicated in patients with asymptomatic gallstones.
4. Laparoscopic cholecystectomy is a safe procedure even when performed for acute cholecystitis.
5. Choledocholithiasis (Common Bile Duct stones) can have an asymptomatic course or may present with mild biliary colic to fulminant sepsis from acute cholangitis, biliary pancreatitis, or hepatic abscesses.
6. Endoscopic cholangiography with sphincterotomy allows for the diagnosis of CBD stones in the vast majority of cases. It also allows for therapeutic intervention if stones are identified. ERCP with stone extraction is effective in removing stones in 85% to 95% of cases but is associated with postprocedural complications (pancreatitis and cholangitis).
7. Common bile duct exploration may be required to remove stones that cannot be removed via ERCP.

INTRODUCTION

There are two types of gallstones—cholesterol or pigment stones. Cholesterol stones are most common accounting for 70% to 80% of gallstones. The pathogenesis of cholesterol gallstones is multifactorial' essentially involving four factors: (a) cholesterol supersaturation in bile, (b) crystal nucleation, (c) gallbladder dysmotility, [1] and (d) gallbladder

absorption/secretion. These are not purely 2 made up of cholesterol but in fact have a core of calcium salts. The pigmented stones can be black or brown and are made up of calcium bilirubinate. Black stones are exclusively found in the gallbladder whereas brown stones can also be found in the biliary tree (both intra and extrahepatic). While cholesterol stones are more common in the Western world, pigmented stones especially brown stones are more common in Asia.

RISK FACTORS FOR GALLSTONE FORMATION

Cholelithiasis is a result of an interplay between genetic and environmental factors.

Age: The incidence of gallstones increases with age. Most pediatric patients with gallstone disease have an association with a hemolytic disease.

Gender: Females are at a higher risk—mostly secondary to hormonal effects of estrogen, oral contraceptive use or hormonal therapy after menopause. Pregnancy also increases the risk of biliary sludge formation.

Genetics: There has been an implication of a genetic component in up to 30% of patients in some population studies. Cholesterol stones are found in ratios of 3:1 in family members. Genetic mutations have been identified in the hepatic cholesterol metabolism and hemolysis has been identified to play in a role in development of gallstone formation.

Physical activity, diet: Obesity is a major risk factor for gallstone development. Patients receiving parenteral nutrition are also at risk of developing biliary stasis and gallstones.

Other disease processes/medications: Cirrhosis can induce gallstone formation in about 25% to 30% of the patients. Inflammatory bowel disease, ileal resection, cystic fibrosis interferes with bile reabsorption and can lead to cholelithiasis. Medications including estrogen, thiazide diuretics increase biliary cholesterol secretion

whereas ceftriaxone—a third-generation cephalosporin—can also induce biliary stasis and therefore gallstone formation.

NATURAL HISTORY OF GALLSTONES

Eighty percent of people with cholelithiasis will remain asymptomatic. Two percent to 3% per year of those with known gallstones will develop symptoms and 1% to 2% will develop more complex problems (such as cholecystitis, pancreatitis, or cholangitis) annually. Symptoms can be described as right upper quadrant (RUQ) pain, mostly postprandial (usually after a fatty meal) and will often recur. Half of the patients with symptoms will develop a second symptomatic attack within a year. These symptoms correspond to intermittent impaction of gallstones at the gallbladder neck as the gallbladder contracts in order to deliver its contents into the common bile duct (CBD).

GALLSTONES AND GALLBLADDER CANCER

There is limited data to suggest that large gallstones (>3 cm) increase the risk for gallbladder cancer but this may be secondary to chronic inflammation. Therefore, there is no role for prophylactic cholecystectomy for asymptomatic cholelithiasis to 3 decrease cancer risk except for certain populations where the incidence of gallbladder cancer is unusually high (Chileans, Pakistani women, Pima Indians). Calcification of gallbladder is encountered in 0.8% of patients. The risk of gallbladder cancer with porcelain gallbladder was thought to be much higher.[1] The rate of gallbladder malignancy was only 6% compared to 1% in a matched cohort of patients without gallbladder wall calcification. Multivariate analysis identified the presence of a gallbladder mass as the only independent prognostic factor for harboring gallbladder malignancy. Even though it is a small but significant chance of gallbladder cancer with porcelain gallbladder a cholecystectomy is recommended in the setting of a calcified gallbladder.

Table 61.1

Imaging Modality	Findings	Advantages	Disadvantage
Transabdominal US	▪ Gallbladder wall thickening >4 mm ▪ Enlarged gallbladder (long axis ≥8 cm, short axis ≥4 cm) ▪ Pericholecystic fluid ▪ Presence of gallstones/sludge ▪ Murphy sign	▪ Quick, readily available ▪ Inexpensive ▪ No radiation exposure ▪ Sensitivity and specificity 80–85%	▪ User dependent
Biliary scintigraphy (HIDA)	▪ Lack of visualization of gallbladder implies obstructed cystic duct ▪ Ejection fraction <35%—signifies biliary pathology	▪ Sensitivity 95–98% and specificity 90% ▪ Diagnostic yield is higher than US	▪ False positive after prolonged fasting or a after a heavy meal ▪ Not readily available ▪ Radiation exposure
CT	▪ Gallbladder wall thickening ▪ Presence of gallstones ▪ Complications of cholecystitis—gangrenous cholecystitis, liver abscess/perforation		▪ Typically, less helpful for diagnosis for acute cholecystitis ▪ Radiation exposure
MRI/MRCP	▪ Gallbladder wall thickening ▪ Stones in the common bile duct	▪ Sensitivity 86% and specificity 82%	▪ Overestimate the presence of

	gallbladder inflammation ▪ Quality of images depends on patient's cooperation to hold the breath ▪ Radiation exposure

See references [34–36].

CHOLECYSTITIS

Cholelithiasis begets cholecystitis which can present as acute inflammation or more ongoing, intermittent inflammation leading to chronic cholecystitis.

Acute Cholecystitis

Acute cholecystitis develops when the bile flow is obstructed secondary to an impacted gallstone(s) in the gallbladder neck (infundibulum) or in the cystic duct. This obstruction leads to biliary stasis, gallbladder wall edema, venous obstruction, and in extreme cases, eventual arterial obstruction causing necrosis of the gallbladder wall. Acute inflammation may be complicated by secondary biliary infection, gram negatives such as *Klebsiella* and *Escherichia coli* being the most common organisms.

Clinical Manifestations

Clinical course can vary from mild epigastric/RUQ pain with fever/chills to frank sepsis secondary to perforation or development of emphysematous/gangrenous cholecystitis. Inflammation results in midepigastric or RUQ pain with localized peritoneal irritation. Murphy sign which is defined by cessation of inspiration secondary to pain, due to the

presence of an inflamed gallbladder during deep abdominal palpation at the midclavicular line of the RUQ, is pathognomonic for acute cholecystitis.

Imaging

According to the Tokyo guidelines ultrasound (US) is recommended as the first-choice imaging method for the morphologic diagnosis of acute cholecystitis.[2] US findings of gallbladder wall thickening >4 mm, enlarged gallbladder, pericholecystic fluid, presence of gallstones, and/or positive Murphy sign (pain and cessation of inspiration when the probe is pressed over the gallbladder) are consistent with acute cholecystitis.

Criteria for diagnosis of acute cholecystitis on other imaging modalities are listed in Table 61.1. Of note, combined modalities do not appear to add sensitivity or specificity for detection of acute cholecystitis, although they may provide additional morphologic information.

Diagnosis

Criteria for diagnosis for acute cholecystitis are listed in the **Table 61.2**. When compared to pathologic samples the diagnostic accuracy is between 94% and 60%. The World Society of Emergency Surgery guidelines for acute calculous cholecystitis recommend the combined use of clinical, laboratory, and imaging findings for diagnosis.[3]

Table 61.2 Tokyo Guidelines for Diagnosis of Acute Cholecystitis

A. Local signs of inflammation (1) Murphy sign (2) RUQ mass/tenderness
B. Systemic signs of inflammation (1) Fever (2) elevated C-reactive protein (CRP) (3) elevated white blood cell (WBC) count
C. Imaging findings characteristic of acute cholecystitis Suspected diagnosis: one item in A + one item in B Definite diagnosis: one item in A + one item in B and C

See references 2, 41.

Table 61.3 Grades of Acute Cholecystitis (Tokyo Guidelines)

Grade I	Grade II	Grade III
No organ dysfunction and mild inflammatory gallbladder changes	Elevated WBC RUQ tenders/palpable tender mass Duration of complaints >72 hrs Marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis) Duration of complaints >72 hrs	Cardiovascular dysfunction requiring vasopressor support Neurologic dysfunction—decreased level of consciousness Respiratory dysfunction—PaO_2/FiO_2 ratio <300 Renal dysfunction—oliguria, Cr > 2 Hepatic dysfunction Hematologic dysfunction platelets <100,000/mm^3

Three grades of severity have been described with grade III (severe) acute cholecystitis causing systemic symptoms due to organ damage (Table 61.3). These grades have been validated in multiple studies and are significantly associated with prognosis, length of hospital stay, conversion to open surgery and medical costs.[4–6] However, these grades cannot be used to assess surgical difficulty.

Treatment

Initial medical treatment involves parenteral hydration and antibiotics against enteric bacteria. Despite symptom resolution, the patient should undergo

cholecystectomy as the definitive treatment given that the likelihood of a second biliary-related complication is high.

Cholecystectomy is the standard surgical therapy for patients with acute cholecystitis. Laparoscopic and more recently robotic cholecystectomy (at limited centers) has become standard of care. The timing of the cholecystectomy—early versus delayed has been much debated. Early cholecystectomy removes the pathologic source and helps resolve the acute inflammatory response, potentially making the surgery safer with fewer complications and morbidity. No significant differences in patient outcomes between early and delayed surgeries with respect to bile duct injuries, bleeding, laparoscopic-to-open conversions, postoperative infection, and patient death have been reported. However, 4 23% of delayed patients presented with complications requiring emergent cholecystectomy. In addition, total length of stay in the hospital, including the index admission and subsequent admission either for biliary complications and/or later cholecystectomy, was significantly longer for these patients. A 2013 Cochrane Review included six randomized trials with 488 patients; this study compared early (within 7 days of presentation) to late (>6 weeks after initial treatment) cholecystectomy and found similar results.[7] Multiple studies demonstrate that *early* should be within the index admission and the 72-hour limit is a relative rule given improved skills of surgeons with laparoscopic surgery and the understanding that surgery delayed to a different admission could potentially lead to worse complications. Tokyo guidelines recommend early (within 7 days, within 72 hours even better) laparoscopic cholecystectomy for grade I patients. In grade II (moderate) patients, consider urgent/early laparoscopic cholecystectomy if patient performance status is good. If the patient's condition is poor, urgent/early biliary drainage and delayed/elective cholecystectomy should be considered. In grade III (severe) patients with high surgical risk, urgent/early biliary drainage should be performed. In selected patients with no negative predictive factors (total bilirubin ≥2, neurologic dysfunction, respiratory dysfunction) or with cardiovascular or renal system failure that is rapidly reversible after admission early laparoscopic cholecystectomy can be considered.[8]

CHRONIC CHOLECYSTITIS

Cholelithiasis is the causative factor of chronic cholecystitis in most (>90%) patients. This leads to recurrent episodes of cystic duct obstruction manifesting as recurrent biliary colic. These recurrent attacks lead to scarring and a nonfunctioning, noncontracting gallbladder. A patient with chronic cholecystitis presents similarly to those with biliary colic and it is often difficult to distinguish between the two conditions. Diagnosis is accomplished with a US showing circumferential thickened gallbladder wall with gallstones in the setting of recurrent episodes of RUQ abdominal pain. In some patients the gallbladder may be shrunken and small. Chronic cholecystitis is treated with cholecystectomy. A subtype of chronic cholecystitis is called xanthogranulomatous cholecystitis that can present as gallbladder mass. Inflammation of gallbladder wall leads to permeation of bile within the wall, bile in engulfed by macrophages and the resulting lipid-laden macrophages lead to a chronic granulomatous inflammatory response. Histology shows diffuse or focal mural changes in the form of xanthoma cells (foamy histiocytes containing lipids and bile pigment), giant multinucleate histiocytes, and acute or chronic inflammatory cells. Microabscesses may also form in the gallbladder wall and a fibrous reaction may lead to adhesions with adjacent liver, duodenum, and transverse colon.[9] Studies have shown that contrast enhanced US may be a better diagnostic modality in differentiating xanthogranulomatous cholecystitis than gallbladder cancer.[10]

ACUTE ACALCULOUS CHOLECYSTITIS

Acute acalculous cholecystitis presents with major illness and therefore its incidence is significantly higher in intensive care unit patients. It is associated with increased bile stasis and decreased gallbladder emptying and function which leads to bile being inspissated and the formation of biliary sludge. The diagnosis requires a high index of clinical suspicion given that most critically ill patients are sedated and mechanically ventilated which makes reliable physical examination difficult. Late or missed diagnosis may lead to gallbladder ischemia and progression to gangrene and eventual perforation resulting in a mortality rate of up to 15% to 30%. Diagnosis may be made using bedside ultrasonography following similar criteria as used for acute calculous cholecystitis, except for lack of calculi. The sensitivity of US in

this setting ranges from 50% to 100% with a specificity of 90% to 94%. A hepatobiliary iminodiacetic acid (HIDA) scan with morphine amplification can be used to increase bile secretory pressure and allow bile to reflux through a contracted gallbladder neck, thereby decreasing false-positive rates, providing sensitivity rates of 67% to 100% and specificity rates of 69% to 100%. A negative US in a patient with a high clinical suspicion for acute acalculous cholecystitis may benefit from a HIDA scan to improve diagnostic yield. Treatment includes a percutaneous cholecystostomy (PC) tube in critically ill and/or unstable patients and a cholecystectomy for a stable patient. PC tube may be the definitive treatment for acute acalculous cholecystitis given there is no mechanical obstruction secondary to cholelithiasis.

OTHER CONDITIONS

Gangrenous Cholecystitis

Gangrenous cholecystitis is more commonly found in diabetic patients who have acute cholecystitis. The most common site for necrosis is the fundus as it is the furthest from the blood supply. Usually full-thickness necrosis is present in patients with gangrenous cholecystitis, but this does not necessarily result in frank perforation in all cases. CT findings include irregular thickening of the gallbladder wall, poor contrast enhancement of the wall (interrupted rim sign), increased density of fatty tissue around the gallbladder, gas in the gallbladder lumen or wall, membranous structures within the lumen (intraluminal flap or intraluminal membrane), and peri-gallbladder abscess.[11] Contrast enhanced CT or MRI are recommended for diagnosing gangrenous cholecystitis as these findings may be under appreciated on US alone.[12]

Emphysematous Cholecystitis

Emphysematous cholecystitis results from gas-forming bacteria in the bile. This can result in perforation, intra-abdominal abscess, generalized peritonitis, necrotizing fasciitis of abdominal wall. Given that intramural gas can be difficult to identify on US, CT is the modality of choice for diagnosis

and can also help to assess perforation and/or intra-abdominal abscess. Treatment includes antibiotic coverage for Clostridium and cholecystostomy tube placement for unstable, sick patients and a cholecystectomy for clinically stable patients.[2]

Of note the grading severity according to the Tokyo guideline classifies bother gangrenous and emphysematous cholecystitis as moderate.

Mirizzi Syndrome

Biliary obstruction secondary to cholecystitis is called Mirizzi syndrome. There are two types of Mirizzi syndrome. Type I involves compression of the CBD secondary to an impacted stone in the infundibulum or cystic duct. Type II involves a cholecystocholedochal fistula. Open cholecystectomy is the standard of care given that high laparoscopic to open conversion rates have been reported. Given the degree of inflammation a subtotal/partial cholecystectomy or a biliary reconstruction may also be required.

Cholecystoenteric Fistulae

Cholecystoeneteric fistula formation is a rare complication which occurs in approximately 1% to 2% of all patients with cholecystitis. The most common site of fistula is to the duodenum or transverse colon. This happens when the gallbladder decompresses into a bowel loop during an episode of cholecystitis. Complications of a cholecystoenteric fistula are rare, but a large gallstone may pass into the bowel and cause a mechanical bowel obstruction, usually distally in areas of narrow caliber, such as the ileocolic valve or sigmoid colon. This obstruction is known as a *gallstone ileus*. If this complication occurs, the initial management involves removal of the gallstone through an enterotomy with possible bowel resection. Decision to proceed with removal of the biliary enteric fistula and cholecystectomy at the time of index operation depends on patient's clinical condition and the degree of tissue inflammation. An association between the presence of a cholecystoenteric fistula and gallbladder cancer has been suggested, therefore clinical suspicion for cancer is warranted in this scenario.

CHOLECYSTECTOMY

Laparoscopic cholecystectomy was first performed in 1985 and is now the most common gastrointestinal surgical procedure performed in the U.S. and Canada. It is the gold standard operative technique given significant decreases in operative time, patient comfort, length of stay, and overall costs. True contraindications to the laparoscopic approach to cholecystectomy include (i) patient inability to tolerate pneumoperitoneum, (ii) bleeding diatheses, (iii) decompensated cirrhosis with ascites and varices.

TECHNIQUE—LAPAROSCOPIC CHOLECYSTECTOMY

The abdomen is typically entered near the umbilicus. This can be done with an open Hasson or a closed veress needle technique. We prefer the open Hasson technique and recommend a good finger sweep before inserting the Hasson port. This helps to sweep away any bowel or adhesions. The abdomen is then insufflated with CO_2. Even a blunt finger can injure bowel and therefore once the camera is placed through the port a thorough look in this area should be performed to rule out any inadvertent injuries before proceeding to the RUQ. If the patient has had a previous midline surgery or there are significant adhesions in the midline one should consider entering the peritoneal cavity under direct vision using optiview in the right or the left upper quadrant and then place the other ports under direct vision. Three additional operating ports are placed under direct visualization: one 10-/12-mm port in the epigastric/subxiphoid area, one 5-mm port in the RUQ in the anterior axillary line, in a position to grasp the fundus of the gallbladder and retract it cephalad and another 5-mm port in the midclavicular line in a position to grasp the infundibulum. Care should be taken to place ports at least a hands breadth away from each other to operate without the instruments clashing with each other.

Typically, the fundus is retracted cephalad (10 o'clock position), however depending on the length of the gallbladder this retraction may be appropriate

to apply below the fundus. The infundibulum is grasped and needs to be retracted toward the right lower quadrant to expose the triangle of Calot.

A few minutes should be spent to orient to the anatomy at this time. The dissection in the triangle should be performed above the Sulcus of Rouviere to avoid being too close to the duodenum. The hepatic artery may or may not be clearly visible but spending a few seconds may delineate a pulsation. Usually part of the bile duct can also be seen. Also, if the dissection will be below the umbilical fissure this means that one is too far out to the left in the porta and need to readjust retraction.

Hook cautery is used for dissection on the surface in the triangle and separate the lymphatic and fatty tissue. The blunt tip of the laparoscopic suction device is also a great tool especially in an inflamed field, allowing for dissection and suctioning of blood at the same time. Dividing the peritoneum on either side of the gallbladder wall helps expose the triangle even better. We recommend doing this before dissecting deep in the triangle. The goal is to identify two distinct structures entering the gallbladder (the cystic artery and cystic duct) creating the critical view of safety (Strasberg). This is done with a combination of hook cautery, suction catheter, and Maryland forceps. Sometimes the artery is very anterior to the triangle and may need to be clipped to complete the dissection in the triangle before the cystic duct can be clipped and divided confidently, especially if the dissection is difficult secondary to inflammation. This should be done with extreme caution and only in select cases. We recommend placing two clips on the staying side of the artery and the duct and one clip toward the gallbladder and then divided.

The peritoneum surrounding the gallbladder is then incised further and using electrocautery the gallbladder is then taken off the cystic plate. If bleeding is encountered electrocautery should be used to control it immediately before the visibility is lost once the gallbladder has been taken off the cystic plate. Inadvertent excursion into the deep plane here can lead to bleeding from tributaries of the middle hepatic veins.[13]

Once the gallbladder is free it is placed in an impermeable bag and removed through the umbilical port. This may need to be enlarged in the setting of large calculi. All ports are removed under direct visualization. The fascia at the umbilical port site is then closed using 0-Vicryl sutures and then the skin is closed with Monocryl sutures.

Intraoperative Cholangiogram

If the anatomy is unclear, a cholangiogram is a useful adjunct. This can be performed laparoscopically via access of the proximal cystic duct. A ductotomy is made on the anterior wall of the proximal cystic duct. The duct proximal to this is ligated with a clip. A cholangiocatheter is then threaded through this ductotomy and a radio-opaque contrast agent is injected, and under fluoroscopy the biliary ductal anatomy is defined. The role of routine cholangiography in prevention of bile duct injury is controversial. A complete and adequate cholangiogram includes identification of the cystic duct, visualization of both the right and left hepatic ducts, smooth tapering of the CBD, and presence of contrast into the duodenal lumen.

Newer techniques of fluorescent-assisted biliary system identification using systemically injected near-infrared dyes, such as indocyanine green, may assist in identification of the critical structures without requiring intraoperative catheter placement. Fluorescent imaging requires a special camera system and allows continuous biliary mapping throughout the procedure. Intraoperative US is another adjunct that can be utilized to define anatomy during laparoscopic cholecystectomy.

OTHER APPROACHES TO CHOLECYSTECTOMY

Single-Incision Laparoscopic Approach

The desire for minimally invasive surgery led to the development single-incision approach to laparoscopic cholecystectomy (SILS). This is generally performed by placing a multiport access device through the umbilicus and inserting various instruments through the single port in order to dissect the critical structures and the gallbladder. The safety of SILS in elective cholecystectomies has been proven in various clinical trials, however increased operative time and hernia rates have been reported.

Robotic Cholecystectomy

With the emerging use of robot technology in various surgical procedures, robotic cholecystectomy has also been gaining popularity. Studies have shown that even though this is a safe approach and the outcomes of robotic and laparoscopic approach are comparable, the cost to the healthcare system continues to be an issue. Further investigations are needed to determine its role in acute settings and its cost-effectiveness.

Open Cholecystectomy

Open cholecystectomy is now a rare operation. It is usually performed if there is another concurrent procedure or when a laparoscopic cholecystectomy is converted to an open procedure. This may be due to inability to identify anatomy or an inadvertent injury. Conversion to open cholecystectomy in the setting of acute cholecystitis is not protective of bile duct injury. Open cholecystectomy can be performed through either an upper midline or right subcostal (Kocher) incision. Typically, dissection is performed in a top-down fashion, from the fundus toward Calot triangle with identification of the cystic artery and duct at the gallbladder neck. Dissection can still be started in the triangle as described above to obtain the critical view, divide the duct and the artery. The duct and artery can be divided between clips and sutures. The gallbladder is then taken off the cystic plate using electrocautery either in a top-down approach, or from the infundibulum upward to the fundus.

SUBTOTAL CHOLECYSTECTOMY

Subtotal cholecystectomy is an option to avoid biliary tract injury in cases where anatomy cannot be delineated clearly or when there is an impaction of a large stone at the cystic duct. This can be performed with laparoscopic or open approach. It involves opening the gallbladder above the neck, removing all the stones leaving the neck of the gallbladder in situ to protect the critical structures. In some cases, the posterior wall of the gallbladder may be left attached to the liver bed as well. The neck of the gallbladder may be closed with suture or stapler (subtotal reconstitution). If left open the lumen of the cystic duct is closed with a purse-string suture (subtotal fenestration).

Omentum can be placed within the neck of the gallbladder as well. While the reconstituting technique can lead to stone reformation and recurrent symptoms, the fenestrating technique has a higher likelihood of bile leak or biliary fistula. A similar proportion of patients have been shown to require reintervention after fenestrating versus reconstituting subtotal cholecystectomy (32% vs. 26%), more completion cholecystectomy was required after fenestrating subtotal cholecystectomy (9% vs. 4%). A closed suction drain should be placed in the gallbladder fossa after a subtotal cholecystectomy to evacuate any bile leak, which will generally resolve spontaneously.

Percutaneous Drains after Cholecystectomy

There is no current evidence in support of leaving drains after an uncomplicated cholecystectomy or even open cholecystectomy. They seem to increase harm to the patient without providing any additional benefit. Drain placement should be deferred onto a case-to-case basis and can be considered if the gallbladder is necrotic or in cases of subtotal cholecystectomy with high risk for bile leak postoperatively. Even in these cases drains may assist in the early diagnosis of bile leaks but do not prevent it.[14,15]

COMPLICATIONS OF CHOLECYSTECTOMY

Serious complications of laparoscopic or open cholecystectomy are rare and the associated mortality rate is <0.3%. The most severe complication of cholecystectomy is a biliary duct injury. The incidence of bile duct injury following laparoscopic cholecystectomy is between 0.3% and 0.6% (vs. 0.2% to 0.3% for open surgery). Cystic artery stump leak is rare but may happen if the clips are dislodged. Major vascular injuries, especially to the right hepatic artery, may occur in association with bile duct injuries due to their close anatomic relationship. Spillage of stones into the peritoneal cavity during laparoscopic cholecystectomy occurs in 5% to 40% of cases. Intra-abdominal abscess, subcutaneous abscess, and fistulation of stones through the abdominal wall have all been described and therefore every attempt

should be made to remove spilled stones. Large stones or massive spills should be removed as best possible to prevent delayed complications.

PROPHYLACTIC CHOLECYSTECTOMY

Asymptomatic cholelithiasis can be managed expectantly without surgical intervention. Prophylactic cholecystectomy may, however, be indicated in certain circumstances (Table 61.4). Patients who have a higher risk of cancer in the setting of gallbladder disease, such as Native Americans, presence of large gallstones (>2.5 cm), or calcification of gallbladder wall ("porcelain gallbladder") are commonly offered prophylactic cholecystectomy. Patients who are more likely to have recurrent symptoms or complications secondary to gallstone disease may also undergo prophylactic cholecystectomy; examples of these conditions include hereditary spherocytosis, sickle cell disease, other hemoglobinopathies, the bariatric patients, and pediatric patients.

Table 61.4 Indications for Prophylactic Cholecystectomy

Pediatric gallstones associated with sickle cell disease
Congenital hemolytic anemia
Gallbladder polyp >10 mm
Calcifications
Acalculous cholecystitis/biliary dyskinesia
Concern for gallbladder malignancy
Cholelithiasis and no access to medical care

PERCUTANEOUS CHOLECYSTOSTOMY

PC tubes can be used as a bridge to cholecystectomy or a definitive treatment of acute cholecystitis in critically ill patients or those who are not good

surgical candidates. There is no data to suggest any difference in outcomes for transhepatic versus transperitoneal cholecystostomy tube placement.[16] The technical success for radiologically guided cholecystostomy tubes is 98% to 100%. Potential complications include intrahepatic hematoma, pericholecystic abscess, biliary peritonitis, and biliary pleural effusion. Once the patient is doing clinically better a cholangiogram should be performed to ensure there is no obstruction at the level of the cystic duct and if no evidence of obstruction the tube can be clamped for 10 to 14 days to confirm that the patient will tolerate removal. If clamping is tolerated it can be safely removed. If clamping trial is not tolerated a cholecystectomy should strongly be considered or the tube may need to be left for a longer duration.[17] Patients who have a persistent obstruction secondary to gallstones and are still not good surgical candidates may need upsize of tube and/or removal of stones percutaneously.

It is recommended to wait at least 8 weeks after placement of PC tube before proceeding with laparoscopic cholecystectomy. Early cholecystectomy (less than 8 weeks) has been shown to be associated with higher risk of complications and longer hospital length of stay.[18,19] This may be secondary to maximal medical optimization preoperatively.[20] When doing a laparoscopic cholecystectomy with a cholecystostomy tube in place it is usually easier to remove the cholecystostomy tube at the outset of the operation so that the fundus can be retracted normally. The suction catheter can be used to remove all the bile to prevent leakage. Alternatively, a clip can be placed at the site where the tube was entering the gallbladder, or a grasper can be used retract the fundus cephalad and cover the hole to prevent leakage of bile, sludge and stones. There is data to suggest that the rate of CBD injury during a subsequent laparoscopic cholecystectomy after PC tube may be higher than general population.[17] There is no difference in risk of CBD injury in the early cholecystectomy versus late group after placement of PC tube.

Other Therapies

Ursodeoxycholic acid (ursodiol) works by dissolving cholesterol crystals and decreasing hepatic secretion of biliary cholesterol thereby decreasing the number of stones and is thought to decrease the number of biliary colic

attacks. Unfortunately, most stones recur (>50% at 5 years) and in a prospective randomized study of ursodiol therapy the authors found that it did not decrease the number of attacks nor gallstone-related complications during the waiting period for cholecystectomy. An additional therapy is extracorporeal shock wave lithotripsy (ESWL). This therapy uses energy ("shock") waves to dissolve stones. ESWL can dissolve small calculi or decrease the size of larger calculi and make them potentially extractable by endoscopic or percutaneous techniques, especially if in the CBD or distal cystic duct. It is a relatively safe procedure with rare complications, including hematoma (biliary or otherwise), bowel perforation, and necrotizing pancreatitis.

SPECIAL CONSIDERATIONS

Gallstone Pancreatitis

Gallstone pancreatitis is the most common form of acute pancreatitis, thought to be secondary to obstruction of the ampulla secondary to a stone and reflux of bile into the pancreatic duct. In most cases the obstruction is transient and urgent biliary decompression is needed. Once the pancreatitis is settled these patients should undergo cholecystectomy. There is no data to support any differences between early endoscopic retrograde cholangiopancreatography (ERCP) and conservative management of pancreatitis of any severity. However, in patients with concurrent cholangitis or continuous biliary obstruction early ERCP reduced mortality and systemic complications.[21]

Gallbladder Cancer

A gallbladder containing an unsuspected cancer is removed in 0.2% to 2% of all laparoscopic cholecystectomies. If cancer is suspected preoperatively a complete staging workup with CT of chest, abdomen/pelvis or CT chest, and MR abdomen should be completed before cholecystectomy and better still the patient should be referred to a specialist hepatobiliary surgeon. During surgery extreme caution should be taken to avoid bile spillage as this is associated with worse outcomes if cancer is found on final pathology.[22,23] If

the suspicion is very high then an en bloc hepatic resection (parts of segment 4b and 5) should also be performed. This can be done with laparoscopic energy (Harmonic or Ligasure) devices. The gallbladder is taken off with the cystic plate in continuity, being careful to ensure a negative margin. If suspicion is high a portal lymphadenectomy should be performed as well. This is all done for appropriate staging. The gallbladder with en bloc liver should be extracted in an impermeable bag to reduce the risk of seeding the peritoneum and/or port sites. If a gallbladder cancer is incidentally discovered on pathology, these patients should be referred to hepatobiliary surgery expertise for further management. They will require additional hepatic resection, portal lymphadenectomy, and possible bile duct resection (if cystic duct margin is positive). The optimal time interval for re-resection for incidentally discovered gallbladder cancer appears to be between 4 and 8 weeks after the initial cholecystectomy.

Cholecystitis during Pregnancy

After appendicitis, biliary disease is the second most common gastrointestinal disease requiring surgical consideration during pregnancy. The safety of laparoscopic cholecystectomy is well established in the second trimester. Chances of spontaneous abortion and preterm labor prohibits this procedure being undertaken in the first and third trimester. If acute cholecystitis cannot be managed with antibiotics in either of these trimesters, PC tube should be considered as a bridge to cholecystectomy in second trimester or post delivery. The periumbilical port site may need to be adjusted based on the gestational age.

Cholecystitis and Cirrhosis

Cholecystitis in the presence of liver cirrhosis should generally be treated with PC tube placement. Even though incidence of complications may be higher in these patients this does not preclude them from getting a cholecystectomy in selected patients. Higher MELD score, Child's B and C, operative time, intraoperative blood loss, lower platelet count, and high INR are all prediDifferent Techniques for Common Bile Duct Explorationolecystectomy in patients with cirrhosis. Laparoscopic approach

is associated with shorter operative time, reduced length of stay, and reduced complication rates.[24–26] Therefore, patient selection is of utmost importance; elective surgery in patients with varices and ascites should be avoided. They should be treated with PC tubes if they develop acute cholecystitis. If varices are found on the gallbladder wall intraoperatively subtotal cholecystectomy and stone retrieval is an option to avoid bleeding.

CHOLEDOCHOLITHIASIS

Choledocholithiasis is defined as the presence of stones in the extrahepatic biliary tree. CBD stones can be defined as primary or secondary stones based on the location of their origin. Primary CBD stones originate within the bile duct. These tend to develop in conditions associated with bile stasis, such as: (i) benign biliary strictures, (ii) bile duct cysts (choledochal cysts), or (iii) sphincter of Oddi dysfunction. They can also occur in patients with congenital 5 absence of gallbladder or those whose CBD was clear at the time of cholecystectomy. These are predominantly brown-pigment (calcium bilirubinate) stones. Secondary stones originate from the gallbladder and migrate into the bile duct. They are the most common type of CBD stones. Majority of these stones are cholesterol stones. Ten percent to 15% of patients with symptomatic gallstones will have CBD stones and the vast majority of patients with secondary CBD stones will have gallstones.[27]

Clinical Presentation

Clinical presentation of CBD stones can vary from an asymptomatic course to biliary colic, jaundice, cholangitis, and pancreatitis. CBD stones can pass spontaneously into the duodenum without clinical consequence. The incidence and frequency in which this occurs is unknown. In patients with a low index of suspicion (nonjaundiced patients with nondilated bile ducts on US), the incidence of CBD stones at the time of cholecystectomy is approximately 5% with one-third of these patients passing the stone(s) spontaneously. Biliary colic is the most common presentation. Intermittent obstruction of CBD and passage of stones can also cause varying fluctuations in the bilirubin and liver function enzymes. Persistent CBD obstruction can lead to cholangitis and

present as Charcot triad—fever/rigors, jaundice, RUQ pain or Reynaud pentad—hypotension and mental status changes in addition to Charcot triad. Pancreatitis is the second most common presentation of CBD stones. CBD stones can be found in about 50% of patients with pancreatitis depending on the timing of the cholangiography. If left untreated symptomatic CBD stones can lead to serious complications therefore diagnosis and ultimately their treatment is of utmost importance.

Diagnosis

Without the presence of any clinical signs (cholangitis or pancreatitis) the diagnosis rests on a combination of biochemical and radiologic tests. Numerous studies have assessed the predictive value of serum liver biochemical tests. Although liver biochemical tests have a strong negative predictive value (97%), they only have a positive predictive value of 15% to 50% when they are abnormal in patients with suspected CBD stones. ϒ-Glutamyltransferase has been suggested to be the most sensitive and specific.[28] Imaging modalities consist of both invasive and noninvasive techniques. Transabdominal US alone has a poor sensitivity of 22% to 60% in detecting CBD stones and is highly operator dependent. Presence of gallstones or CBD diameter greater than 6 mm can be predictive of CBD stones. Like US, computed tomography (CT) scans also have a low sensitivity. Magnetic resonance cholangiopancreatography (MRCP) is the gold standard noninvasive imaging modality to detect duct stones. It has a sensitivity of 81% to 100% and specificity of 92% to 100%. Small stones less than 5 mm can still be missed with MRCP. Its accuracy is comparable to ERCP and an intraoperative cholangiogram (IOC). Certain treatment algorithms recommend an endoscopic ultrasound (EUS) as first approach prior to ERCP in patients at intermediate risk of CBD stones, when the diagnosis of choledocholithiasis is unclear, or in patients with severe gallstone pancreatitis. If no stones are seen on EUS, an ERCP can be avoided. Laparoscopic intraoperative US using a high-frequency probe allows for successful evaluation of the CBD in 88% to 100% of cases with a sensitivity of detecting CBD stones of 71% to 100%. In addition, laparoscopic US, like EUS, allows for the adequate evaluation of the distal bile duct for stones. Given the invasive nature of ERCP and the risks of

bleeding, perforation, ascending cholangitis, and postprocedure pancreatitis it is now best reserved as a therapeutic measure rather than a diagnostic test. When routine IOC was being performed at the time of open cholecystectomy choledocholithiasis was discovered in 10% to 15% of patients and those that were clinically significant were even less. Use of IOC at the time of laparoscopic cholecystectomy has yielded similar results. It has been shown that only 2.2% of patients with positive IOC required ERCP 6 weeks post cholecystectomy for symptomatic choledocholithiasis.[27]

The American Society for Gastrointestinal Endoscopy has proposed a risk stratification scheme to detect duct stones based on common predictive factors previously identified (Table 61.5).[29] This has been validated in a large cohort of multi-institutional patient cohort.

Management

Management of choledocholithiasis includes endoscopic, surgical (open and/or laparoscopic), and percutaneous approaches. Sequence of events for management of choledocholithiasis varies depending on the local expertise of a multidisciplinary team (surgery, gastroenterology, and radiology). For acutely sick patients with cholangitis or severe gallstone pancreatitis and persistent choledocholithiasis ERCP prior to cholecystectomy should be performed.

Table 61.5 The American Society for Gastrointestinal Endoscopy Predictors of Choledocholilithiasis

Predictors of Choledocholithiasis	
Very strong	
CBD stone on transabdominal US	
Ascending cholangitis	
Bilirubin >4 mg/dL	
Strong	
Dilated CBD (>6 mm) on US	
Bilirubin elevated (1.8–4 mg/dL)	
Moderate	
Abnormal liver biochemical test (other than bilirubin)	
Age >55	
Clinical gallstone pancreatitis	
Likelihood	
Presence of any very strong predictor	High
Presence of both strong predictors	High
No predictors	Low
All other patients	Intermediate

See reference 29.

Table 61.6 ERCP Prior to Cholecystectomy vs CBD Exploration for Choledocholithiasis

ERCP prior to cholecystectomy for suspected choledocholithiasis	▪ High-risk group, especially those needing decompression for cholangitis ▪ Severe gallstone pancreatitis and persistent choledocholithiasis
Common bile duct exploration at the time of cholecystectomy	▪ Large, impacted stones ▪ Multiple failed endoscopic attempts ▪ Anatomy precluding endoscopy such as previous gastric bypass ▪ Intermediate preoperative risk for choledocholithiasis with IOC confirming choledocholithiasis

ERCP, Endoscopic retrograde cholangiopancreatography; CBD, common bile duct; IOC, intraoperative cholangiogram.

Table 61.6 elicits timing and sequence of interventions based on some relevant clinical scenarios.

There is some evidence to support a single-stage laparoscopic cholecystectomy with IOC and CBD exploration in those with choledocholithiasis versus preoperative ERCP followed by laparoscopic cholecystectomy. Prospective randomized trials have concluded equivalent duct clearance rates, 6 morbidity, but shorter length of stay with single-stage procedure.[30] This 7 is dependent on the surgeon's comfort level with laparoscopic or open CBD exploration. Management of patients with high and low risk of choledocholithiasis is generally agreed upon. It is the management of patients with intermediate risk that poses a challenge. Randomized clinical trial has shown shorter length of stay and difference in morbidity with upfront cholecystectomy and IOC compared to preoperative ERCP and subsequent ERCP.[31]

Endoscopic Approach

A cholangiogram is performed after a deep biliary cannulation to define anatomy and confirm choledocholithiasis. Endoscopic sphincterotomy is the first therapeutic step in stone extraction. If there is a large impacted stone sometimes a precut sphincterotomy is required to complete the sphincterotomy. Balloon baskets and Fogarty-type balloon catheters are employed for stone extraction. Large stones may also mandate dilatation of the papilla using endoscopic balloon dilation. Mechanical lithotripsy, intracorporeal lithotripsy with laser or electrohydraulic probes can help reduce stone size and facilitate retrieval. ERCP is successful in about 90% of cases, the chances of retention increase with stone size >15 mm. Complications of ERCP include acute pancreatitis, cholangitis, bleeding from sphincterotomy, perforation (duodenal and biliary).

Percutaneous Approach

This involves (i) a rendezvous procedure and (ii) a complete percutaneous procedure. Rendezvous involves passage of a guidewire percutaneously through the bile ducts and into the duodenum. This guidewire is then used by endoscopists for an ERCP. This is beneficial is cases with altered anatomy (Bilroth II) or large duodenal diverticulum precluding ERCP. Complete percutaneous approach requires multiple sessions. A transhepatic fistula is created, allowed to mature for 7 to 8 days and then used for stone retrieval.

Table 61.7 Different Techniques for Common Bile Duct Exploration

	Transcystic	Transcholedochal
Success	80–90%	83–96%
Morbidity	Bile leak 1% Acute pancreatitis 0.5% Cystic duct rupture 6.8%	Bile leak 14% Pancreatitis 7.3% Reoperation 7.3% Mortality 1%

Refs. [37–40].

7 SURGICAL TECHNIQUES FOR CHOLEDOCHOLITHIASIS

Laparoscopic Surgical Approach

Laparoscopic Common CBD Exploration (LCBDE)

Concomitant LCBDE at the time of laparoscopic cholecystectomy allows for management of choledocholithiasis as a single stage procedure. It is ideal for patients with CBD stones incidentally identified at the time of IOC. LCBDE can be performed via a transcystic or transcholedochal technique (Table 61.7). Transcystic LCBDE is used for small stones (1 cm). Usually the same port sites as a laparoscopic cholecystectomy can be used, with potentially an additional 5-mm port along the midclavicular line on the left. The gallbladder is left in situ for traction. A cystic ductotomy is made like the one for IOC. To relax the Sphincter of Oddi 1 mg of glucagon is administered intravenous and after 3 minutes with the guide wire in place, a cholangiocatheter is advanced from the ductotomy into the CBD, which is then saline irrigated to flush small stones and debris out of the bile duct under fluoroscopic guidance. A choledochoscope can be used for direct visualization and stone extraction can be accomplished with the use of a basket. The ampulla may need dilatation which can be performed with a long ureteral balloon over a guide wire. This technique can also be used for cystic duct dilatation if needed. At the completion the cystic duct can be ligated using an Endoloop, clips or suture.

CBD exploration via choledochotomy is performed only when CBD >1 cm in diameter and it is typically reserved for larger stones (>1 cm). An anterior longitudinal choledochotomy below the cystic duct is made between two stay sutures on the CBD using fine absorbable sutures. The same techniques as mentioned above can be used for stone retrieval. If all the stones are removed and CBD is clear the choledochotomy should be closed primarily. However, if there are concerns for recurrent/retained stones, the choledochotomy should be closed over a T-tube. The T-tube preparation and management is detailed below.

Laparoscopic Biliary Enteric Bypass

If there is risk of recurrent stones or distal biliary stricture (malignancy excluded) a choledochoduodenotomy or a Roux-en-Y hepaticojejunostomy should be considered. In the past there were concerns for sump syndrome with choledochoduodenotomy, which implied food debris blocking the bile flow. But it is really thought to be a technical error secondary to narrow anastomosis. This anastomosis allows for easy endoscopic access to the biliary tree if needed. In cases where duodenum cannot be mobilized secondary to inflammation a Roux-en-Y hepaticojejunostomy should be performed. The downside is that in future direct endoscopic access to the biliary tree is not available with this anastomosis.

Laparoscopic-Assisted Endoscopic Retrograde Cholangiopancreatography

Patients who have had previous Roux-en-Y gastric bypass accessing the ampulla can be difficult even with balloon endoscope. In this situation laparoscopic access to the gastric remnant can provide an easier access for ERCP. Stomach is brought up to the wall, a gastrostomy is made, and a radially dilating trocar is placed through the gastrostomy. An endoscope is then passed down through this trocar to perform ERCP.[32] Once ERCP is completed the gastrostomy can be closed with sutures or an endoscopic stapler.

Open Surgical Approach

Open Common Bile Duct Exploration

In the current era open CBD exploration is infrequently performed, mostly when other approaches fail. Presence of large impacted stones causing Mirizzi syndrome, patients in whom anatomy precludes endoscopic treatment such as prior gastric resection/bypass, duodenal diverticula, or presence of biliary enteric fistula, are some of the instances where open CBD exploration may be required.

A wide Kocher maneuver is performed to allow for exposure and palpation of the entire bile duct. A supraduodenal longitudinal choledochotomy is made between two stay sutures with fine absorbable sutures. This should be as distal as possible; this (i) allows easy creation of

an anastomosis if needed, (ii) leaves maximal amount of CBD for additional future procedures, (iii) allows the use of a rigid choledoscope since it measure about 7 cm. Fogarty cannulation is performed, passing the catheter into the duodenum (can be easily palpated with fingers). The balloon is then inflated very carefully while the catheter is being retracted against the papilla so the stones from the duct can be cleared. Care is taken to avoid passage of stones into the proximal duct. This can be done for stones in the proximal duct as well. Inflation in balloon needs to be precise—where underinflation can miss stones overinflation can lead to duct damage. After a choledochotomy is made a choledoscope (rigid or flexible) can also be used to remove stones. Use of rigid instruments including grasping forceps should be avoided as they can damage the bile duct and lead to late strictures. The duct should be flushed with saline; this allows for small stones and sludge to be flushed out. Use of T-tubes is falling out of favor and therefore the choledochotomy can be closed with interrupted fine absorbable sutures but if needed (high risk patients) a 12-French T-tube can be left in place and secured with interrupted fine absorbable sutures, taking care not to catch the T tube with the sutures.

A T-tube needs to be prepared before being placed in the CBD. This involves cutting the two limbs and removing half the diameter of the part that will be in the CBD. This will prevent obstruction in the bile duct and allow easy removal. Once the T tube is placed completion cholangiography should be performed to assess for CBD clearance. The T-tube it is left to straight drainage until postoperative day 5 to 7 when a T-tube cholangiogram is performed. If no obstruction is present the tube can be clamped and eventually pulled after 4 to 6 weeks (once the tract has matured). T-tubes do not prevent bile leakage and should usually be deployed with a closed suction drain in proximity. If retained stones are identified, the biliary tree can be accessed percutaneously via the T-tube, once the tract has matured, and the stones can be removed.

Transduodenal Sphincteroplasty

Patients with impacted stones at the ampulla or with primary bile duct stones, recurrent stones, intrahepatic stones, or a benign distal bile duct stricture may require an open biliary drainage procedure, such as a transduodenal sphincteroplasty. This involves a wide Kocher maneuver followed by a

lateral duodenotomy. A transcystic Fogarty can be helpful in identify the papilla if not readily visible. If the papilla is identified a Fogarty can be passed through it to be used as a guide for the sphincteroplasty. The sphincteroplasty is then performed for 4 to 5 mm at 11 o'clock position superiorly to avoid the duct of Wirsung which is present medially; this is done with sharp electrocautery. Sphincteroplasty in then extended to a longer length to allow instrumental exploration of the CBD with forceps for extraction of stones. Sutures are placed on the outer wall between the duodenal mucosa and the CBD wall, taking care to avoid the duct of Wirsung. Stones can also be removed using Fogarty, saline irrigation, and a choledoscope.

Choledochoduodenostomy and Roux-en-Y Hepaticojejunostomy

The consideration for one versus the other are the same as described above in the laparoscopic biliary enteric bypass section.

T-TUBES

Historically T tubes were commonly used after CBD exploration. However, these appear to increase operating time and hospital length of stay without any evidence of benefit after open or laparoscopic CBD exploration. The increased complication rate is primarily attributed to the placement of the T-tube, and is due to (i) bile leakage, (ii) wound issues at T-tube insertion site, (iii) dislodgement or displacement of T-tube leading to biliary obstruction, and (iv) persistent biliary fistula. Therefore, their use has decreased over the years. A Cochrane Review in 2013 called for more randomized trials to be conducted with low risk of bias and assessing the risk–benefit effect of these tubes.[33]

INTRAHEPATIC STONES

Hepatolithiasis or intrahepatic stones are defined as stones present above the confluence of the left and right hepatic ducts. The etiology remains unknown

in most patients, but these can occur secondary to chronic biliary stasis and in the presence of choledochal cysts, biliary strictures, and/or biliary parasites. Majority of these patients (70%) do not have gallstones. The two most commonly referred classifications are listed in **Table 61.8**, these are based on distribution of stones and presence of biliary stricture.

Most patients with hepatolithiasis present with cholangitis with wide range of severity. According to a Japanese survey 20% of patients with hepatolithiasis can remain asymptomatic. There are numerous diagnostic modalities including US, CT, MRCP. Endoscopic and percutaneous cholangiography are invasive and therefore used less readily. Initial management for symptomatic patients revolves around resuscitation and treatment for cholangitis. Biliary drainage can be performed via percutaneous or endoscopic technique depending on the location of stricture and distribution of stones. Definitive treatment may require hepatectomy especially if there is concern for cholangiocarcinoma. Depending on the location of strictures hepatectomy and hepaticojejunostomy with anchoring jejunal limb to the abdominal wall may also be performed. This allows percutaneous access in the future if stone retrieval may be needed. Recurrence rates are high even when intrahepatic stones are completely removed. Recurrence rates are variable (0% to 50.8%) and depend on presence of bile duct strictures and treatment modality. Incidence of intrahepatic cholangiocarcinoma in patients with hepatolithiasis has been reported to be 5% to 10%.

Table 61.8 Classification of Intrahepatic Stones

Japanese Classification	Takada Classification
Type I: Intrahepatic stones alone	Type I: No stricture, mild biliary dilatation
Type IE: Intra- and extrahepatic ductal stones	Type II: Distal CBD/ampullary stricture
Type L: Left-sided intrahepatic ductal stones	Type III: Hilar stricture
Type R: Right-sided intrahepatic ductal stones	Type IV: Unilateral hepatic duct stricture
Type C: Caudate stones	Type V: Multiple bilateral strictures

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62

Biliary Injury, Strictures, and Sclerosing Cholangitis

Rory L. Smoot and Sean P. Cleary

Key Points

1. Bile duct injury remains a common complication of cholecystectomy.
2. The method and timing of bile duct injury repair depends on he location and extent of the injury, presence of concomitant vascular injury, the presence of sepsis and the timing of recognition.
3. Management of benign biliary strictures is dependent on etiology. Treatment strategies include medical management, endoscopic stenting as well as surgical bypass or resection.

While the etiology of injuries and acquired or autoimmune-based strictures of the bile ducts are diverse (see Table 62.1), a basic understanding of biliary anatomy and physiology as well as its impact on liver homeostasis can guide management decisions. The recognition and initial management of biliary injury and/or stricture are important skills for general surgeons to have, as appropriate initial therapeutic approaches can have a significant impact on the outcome of definitive management. Based on the published frequency of biliary injuries and the ubiquitous nature of cholecystectomy,

statistics suggest that the majority of general surgeons will face a biliary injury over the course of their career.[1] While the acute and chronic nature of injuries and strictures, respectively, impacts their presentation, the principles of management remain similar: (1) control any associated infection/sepsis (due to intraperitoneal leak or cholangitis); (2) restoration of biliary drainage (internally or externally); (3) assessment of malignant potential; (4) timely definitive management; and (5) continue appropriate surveillance and reintervention. For each subset of conditions, the options are slightly different and will be discussed in detail further. As with the majority of medical/surgical care, the approaches have become less invasive over time.

BILE DUCT INJURY

1 Bile duct injuries have been reported at a frequency of up to 0.6% and 0.1% for laparoscopic and open cholecystectomy, respectively.[2] Less well recognized is the potential for bile duct injury during other RUQ operations including distal gastric/proximal duodenal procedures and liver resection. This chapter will focus on cholecystectomy as the initiating factor; however the workup and management listed can be applied regardless of the index operation. For cholecystectomy, factors that have been implicated as elevating the risk of associated injuries include obesity, acute inflammation, and anatomic abnormalities among others (Table 62.2). The etiology of bile duct injuries are variable but generally fall into one of two categories: (1) misinterpretation/misidentification of pertinent anatomy[3] or (2) aberrant anatomy. Misinterpretation of visual cues during cholecystectomy can result in the "classic" pattern of injury in which the surgeon visualizes/interprets the common bile/hepatic duct as the cystic duct secondary to excessive cranial traction, adherence of the cystic duct to the common hepatic duct in parallel, or initiation of dissection in an inappropriate plane medial to the common bile/hepatic duct (Fig. 62.1). In this scenario, the common duct is clipped and divided. Alternatively, aberrant biliary anatomy including either low cystic duct insertion and parallel course of the cystic duct and common bile duct has been reported in up to 25% of patients, and aberrant drainage of the right posterior sectoral duct directly into the common bile duct occurs up to 6% of the time; this unconventional segmental biliary drainage pattern can

place these ducts at risk for injury (Fig. 62.2).[4] Finally, other mechanisms such as traction injury or inadvertent dissection into the common hepatic duct have been described more commonly with open procedures and a "top-down" approach, respectively. Independent of the underlying etiology, classification systems for bile duct injury have been developed. The most commonly utilized classification used historically to describe location rather than extent (Table 62.3).[5] Practically speaking, classification of biliary injuries is important only in that the ultimate definitive management is dependent on the pattern of injury. A special category of injury that bears mentioning is combined vascular and biliary injury, typically termed vasculobiliary injuries.[6] These most commonly involve stricture or occlusion of the right hepatic artery, although portal vein injuries are also described. Vasculobiliary injuries significantly increase the risk of stricture following definitive surgical management due to the resulting compromise in biliary blood supply.

Several strategies for mitigating the risk of bile duct injury have been proposed including obtaining the "critical view of safety," intraoperative cholangiogram, and various forms of subtotal cholecystectomy. The critical view of safety describes the view obtained following clearance of tissue within the triangle of Calot such that only two structures (cystic duct and artery) are connecting the gallbladder to the central hepatoduodenal structures. An important aspect in obtaining this view is initiating dissection on the infundibulum of the gallbladder, not on the triangle of Calot itself. This minimizes the possibility of inadvertently initiating the dissection on the medial side of the common duct, which can lead to misinterpretation of the common duct as the cystic duct. The routine use of IOC during cholecystectomy is practiced by a minority of general surgeons, and the most recent population-based data would suggest it does not impact the rate of bile duct injury, but may be beneficial in selected use.[7–9] However, identification of a biliary injury is facilitated at the index operation when IOC is performed which may expedite management and reduce morbidity.[10] Finally, while conversion to an open procedure should be considered in all patients in whom anatomic landmarks cannot be clearly defined, this may not provide significantly reduced risk of biliary injury if the operating surgeon is not accustomed to routine open cholecystectomy. Two alternative strategies have been described; the perforating and fenestrating partial cholecystectomy.[11]

Partial cholecystectomy has gained in acceptance as an alternative to conversion for surgeons less comfortable in open gallbladder surgery who are confronted with significant portal inflammation and difficulty identifying relevant structures. The risk of postoperative biliary fistula is relatively low and emphasis should be placed on clearing all stones to prevent recurrent symptoms.

Table 62.1 Causes of Benign Biliary Strictures

Postoperative Strictures

Post-Biliary Surgery/Intervention

Laparoscopic Cholecystectomy

- Transection
- Occlusion (w/ clip)
- Laceration
- Thermal injury

Open Cholecystectomy

- Traction injury

Transection/Laceration

Common Bile Duct Exploration

ERCP

Injury During Other Procedures

Liver Resection

- Ischemic/thermal injury
- Post biliary leak
- Stapler/ligation of major biliary structures

Gastrectomy

Portal–Caval Shunt

Trauma-Blunt/Penetrating

Vascular/Ischemic

- Secondary biliary cirrhosis

Postradiation

Stricture of Biliary–Enteric or Biliary–Biliary Anastamosis

Strictures Secondary to Inflammatory Conditions

Cholecystitis, Choledocholithiasis, Mirrizzi Syndrome

Primary Sclerosing Cholangitis

Primary Biliary Cirrhosis

Stricture/Stenosis of Sphincter of Oddi

Duodenal Ulcer

Crohn Disease

Autoimmune (IgG4-cholangiopathy)

Viral

Drug

Table 62.2 Factors Associated with Intraoperative Bile Duct Injury
Chronic Inflammation
Anatomic Abnormalities ▪ Low insertion of right posterior duct ▪ Short cystic duct
Narrowing of the Angle between GB and Falciform
Long Parallel Cystic Duct
Obesity
Emergency Surgery
Previous Upper Abdominal Surgery
Failure to Identify the Cystic Duct/Critical View
Intraoperative Hemorrhage

Figure 62.1 Classic laparoscopic bile duct injury. The common bile duct is mistaken for the cystic duct and transected. A variable extent of the extrahepatic biliary tree is resected with the gallbladder. The right hepatic artery, in background, is also often injured.

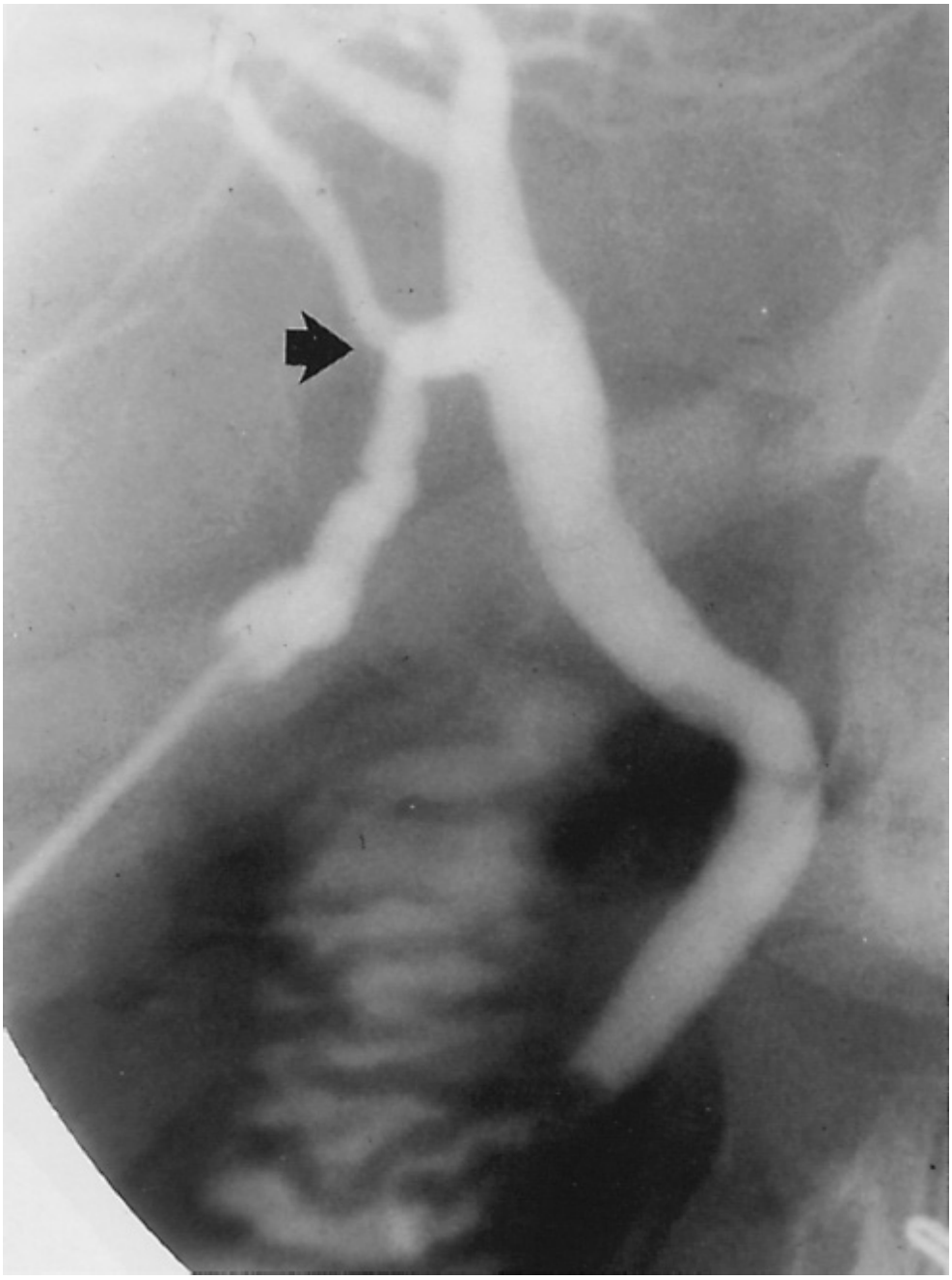
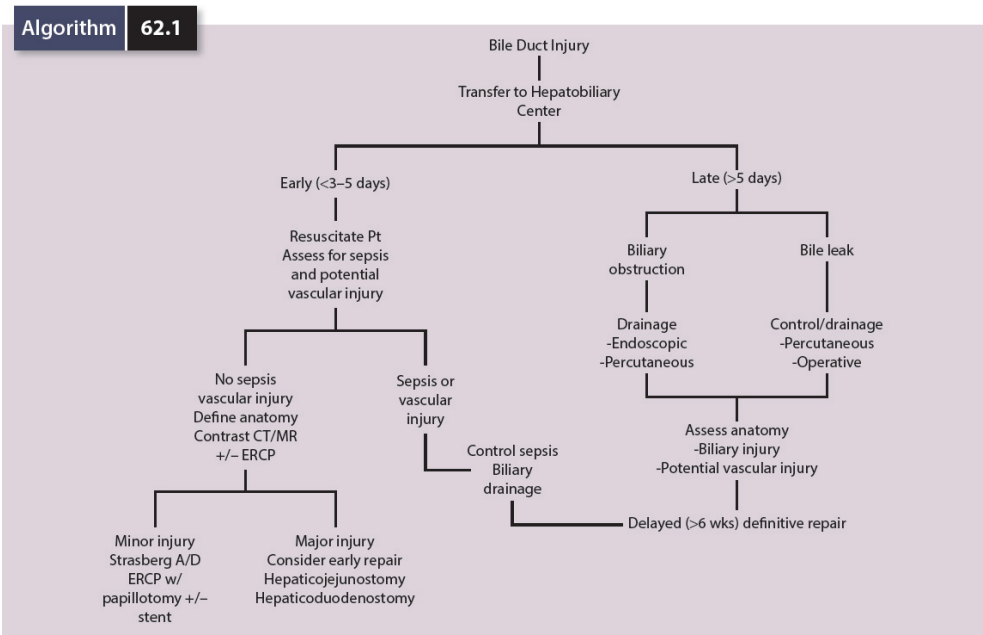


Figure 62.2 Operative cholangiogram demonstrating a right lobe segmental bile duct entering the cystic duct (*arrow*). Division of the cystic duct proximal to this insertion can result in a bile leak or obstruction of bile flow from a significant segment of the liver.

Table 62.3 Strasberg Classification of Bile Duct Injury
A Cystic Duct Stump Leak or Minor Leak from Gallbladder Fossa
B Right Posterior Sectoral Duct Occlusion
C Right Posterior Sectoral Duct Leak
D Main Duct Leak with Intact Duct
E1 Transected Main Duct with Stricture >2 cm from Confluence
E2 Transected Main Duct with Stricture <2 cm from Confluence
E3 Stricture of Common Hepatic Duct with Right and Left Hepatic Ducts Still in Communication
E4 Stricture of Common Hepatic Duct with Right and Left Hepatic Ducts Separated
E5 Stricture of the Common Hepatic Duct and Right Posterior Sectoral Duct Occlusion



Algorithm 62.1 Bile duct injury.

Clinical Presentation

The presentation of biliary injuries varies considerably from intraoperative identification, to acute presentation secondary to bile leak or jaundice, and subacute presentations related to stricturing, cholestasis, and/or cholangitis. The timing of presentation, signs and symptoms are frequently linked to the type of injury (i.e., partial vs. complete, occlusion vs. transection, and the presence of ischemic injury). Intraoperative identification of biliary injury occurs when bile leakage is noted or when identification of a third structure emanating from the gallbladder is noted after transection of the duct, typically indicating that the common duct has been mistaken for the cystic duct. Acute presentations can occur several hours to several days following surgery. The presenting signs and symptoms can include nausea, fever, increasing pain, and/or jaundice. Patients in whom symptoms are worsening following cholecystectomy should be evaluated with the possibility of biliary injury in mind. Subacute presentations can occur months to years later when stricturing can lead to obstructive jaundice and/or cholangitis. Patients with significant delay in identification can present with biliary cirrhosis from chronic obstruction and the sequelae of advanced liver disease including portal hypertension.

Evaluation

Evaluation of the patient with a suspected biliary injury begins with a focused history and physical examination. Intraoperative details of the index operation including approach, structures identified, placement of clips, and hemostatic techniques used should be clearly documented. Ideally, confirmation of the details of the case and intraoperative events with the primary surgeon should take place by direct communication. The timing of their symptoms as it relates to cholecystectomy should be noted and signs of systemic illness (sepsis) such as fever, tachycardia, and hypotension should be assessed. Basic lab testing including complete blood count, liver transaminases, alkaline phosphatase, and coagulation parameters should be obtained. Imaging studies typically consist initially of CT scanning with IV contrast. Images are evaluated for the presence of dilated biliary tree, undrained fluid collection, and whether the inflow vasculature of the liver is intact. Assessment of the biliary tree continuity and the level of injury can be obtained by ERCP or MRI/MRCP. If delayed repair is planned and undrained collections are present, then image-guided drainage is performed. Drainage of collections or bilomas should be performed prior to ERCP if bile leak is suspected to reduce the risk of postprocedural sepsis, ideally via percutaneous route. If a tangential injury is suspected, then ERCP has the advantage of providing not only diagnostic information, but also the ability to intervene therapeutically typically with sphincterotomy with or without stenting. If a complete transection/occlusion is suspected, then ERCP will have little diagnostic value and has the disadvantage of being an invasive modality. In these scenarios, MRI with MRCP is the preferred diagnostic modality.

Treatment

2 For complex injuries identified intraoperatively or early postoperatively, where there is no significant sepsis, transfer to a hepatobiliary surgeon and evaluation can be performed expeditiously, and early repair within the first 3 to 4 days can be considered. For injuries recognized >4 to 5 days postoperatively or if there is significant associated sepsis, delayed repair should be given strong consideration (**Algorithm 62.1**). The principles of

delayed management are as follows: (1) control sepsis/drain undrained collections, (2) establish biliary drainage, and (3) definitive management/repair by a surgeon with significant hepatobiliary experience once sepsis and inflammation has resolved. As noted above, patients with undrained fluid collections in the porta hepatitis should have image-guided drainage often after initiating fluid resuscitation and broad spectrum antibiotics targeting enteric organisms. For partial injuries, most typically a lateral laceration of the duct and/or cystic duct stump leak, then endoscopic stenting is often successful as definitive management. For complete transection +/− occlusion with delayed presentation, percutaneous biliary drainage is required. Occasionally if the duct has not been occluded, PTC cannulation of unobstructed ducts can be challenging. If the duct can be cannulated, ideal management would be to span the defect with a PTC, otherwise external drainage of the duct alone can improve the control of bile flow and sepsis. If the duct is occluded, the establishment of external drainage is achieved with a catheter secured at or above the level of the injury. If an ongoing bile leak is present, this will most typically stop following biliary drainage and the biloma drainage catheter can be removed while continuing external drainage of the biliary tree via PTC. The patient will need to be instructed on care of the biliary drainage catheter, and furthermore the patient will need to be cautioned about the risk of dehydration and instructed to increase oral fluid intake while the external drain is in place. The timing of definitive management will depend on several factors but typically can be considered from 6 to 12 weeks following control of the local sepsis. Factors affecting timing include the presence of significant infection/inflammation at the index operation in which the injury occurred, the overall medical condition of the patient, the presence of a concomitant vascular injury, and tolerance of external biliary drainage. For patients with significant infection/inflammation and/or a concomitant vascular injury at the index operation, delaying definitive management until 12 weeks may be prudent given the significant risk of postoperative anastomotic stricture.

Definitive surgical management most typically consists of a biliary–enteric anastomosis. This can be performed to the duodenum if mobility will allow it, but most typically is performed to a Roux-en-Y limb of the jejunum. Perioperative planning and optimization considerations include the potential

for nutritional deficiencies with extended external biliary drainage including vitamin K deficiency which may impact the risk of perioperative hemorrhage. The position of the right hepatic artery in relation to the bile duct must be noted as this typically runs posterior to the duct, however can course anteriorly, and in this position is at high risk for injury during subsequent definitive operative repair as the porta hepatis can be scarred and the structures obscured. Therefore location as well as patency of the right hepatic artery should be confirmed on imaging prior to definitive repair. Identification of the bile duct can be aided by intraoperative ultrasound with identification of the PTC catheter marking the bile duct. Utilization of a small gauge needle and a syringe to probe with aspiration of bile can also be used to definitively identify the duct. After identification, the anterior wall of the duct can be opened longitudinally as the arteries run at the 3 and 9 o'clock positions laterally. If the injury is near or at the biliary confluence, then a right angle or probe can be inserted into the bile duct and the ductotomy extended onto the left hepatic duct to provide for a larger anastomosis. The biliary–enteric anastomosis can be done in a side-to-side fashion if the posterior wall of the bile duct cannot be safely mobilized or in an end-to-side fashion if it is mobilized. Surgeon choice dictates interrupted versus running stitches, however absorbable monofilament sutures are typically utilized. It may be helpful to leave the PTC across the anastomosis if this is possible and it is common to place a drain near the anastomosis. Optimal long-term outcomes are obtained when the repair of bile duct injuries is undertaken by a surgeon with significant hepatobiliary training and/or experience, with risks of poor long-term results highest when the repair is undertaken by the index surgeon.[12,13] The timing of repair is a subject of significant controversy, with early (<3 to 5 days) and late (>6 weeks) repair associated with the better outcomes than repairs attempted in the intermediate period (6 days to 6 weeks) or in the presence of sepsis.[14,15]

The management of concomitant biliary and vascular injury requires special consideration. The most common concomitant vascular injury is to the right hepatic artery, with injury to the hepatic artery proper and portal vein less common. Of note, arterial collaterals exist through the hepatic duct confluence so that arterial supply to the right biliary tree may be maintained in the presence of the right hepatic artery injury if the confluence is not disrupted. Repair of arterial injuries is rarely successful unless identified

and repaired immediately, but repair of significant portal vein injuries should be considered. Early repair of biliary injury in the presence of isolated right hepatic artery injury can be considered, however, if vascular integrity of the biliary system is in question, delayed repair is preferred and in the most dramatic cases may require hepatic resection.

Outcomes

The short- and mid-term outcomes of definitive operative repair have been reported in a number of retrospective series.[12–15] There remains debate regarding the optimal timing of repair, however a recent large systematic review and meta-analysis evaluating data pooled from 32 individual studies demonstrated a benefit to early referral and delayed repair. Repair failure, which was typically defined as diagnosed stricture or need for imaging/intervention secondary to suspected stricture/cholangitis, was noted to be 37.7% in repairs undertaken before 6 weeks and 8.9% in repairs after 6 weeks. Early referral to a hepatobiliary surgeon was associated with a decrease in postoperative complications and biliary stricture.[16]

Follow-Up

Following definitive repair, the patients are at risk long term for stricture of the anastomosis. We recommend annual ultrasound and liver function testing to assess for the development of strictures which may be associated with a rising alkaline phosphatase level or the development of progressive intrahepatic duct dilatation. Early identification of strictures is essential and can typically be dilated either endoscopically or percutaneously prior to the development of secondary biliary cirrhosis and liver failure.

BILIARY STRICTURE

3 The etiology of benign biliary strictures include iatrogenic/postoperative and various other infectious/inflammatory conditions (Table 62.1). Postoperative biliary strictures due to bile duct injuries have been addressed above. The approach to nonneoplastic biliary strictures is dependent on the

etiology and location within the biliary tree and ruling out neoplastic processes are a vital component of the evaluation.

Clinical Presentation

Patients with benign biliary strictures often present with either cholangitis or jaundice. Patients with cholangitis typically present with some combination of fever, right upper quadrant pain, and jaundice. Patients with sepsis secondary to cholangitis will have hypotension and tachycardia at presentation. This may be in the setting of known predisposing factors such as recurrent pancreatitis, previous biliary surgery, and primary sclerosing cholangitis (PSC). Alternatively patients may present absent known risk factors.

Evaluation

Similar to patients with bile duct injury, evaluation begins with a focused history and physical examination with special attention to predisposing factors including a history of biliary intervention/surgery, recurrent pancreatitis, and history of inflammatory bowel disease. Laboratory evaluation includes complete blood count, liver function testing, and coagulation profile. IgG4 levels should be considered, however negative results do not rule out this as a diagnosis, as tissue IgG4 levels are far more sensitive than serum levels for diagnosis. For patients with signs and symptoms of cholangitis and/or sepsis, fluid resuscitation and broad spectrum antibiotics should be initiated as part of the evaluation and the remainder of the workup performed while hospitalized. Patients without infection/sepsis can be evaluated as an outpatient. Typically the next step in evaluation includes CT scan of the abdomen with IV contrast. The presence of a mass requires evaluation for neoplastic processes. Without an obvious mass, the typical next step in a combination of ERCP, EUS, and biliary endoscopy (if available). EUS is performed to further assess for neoplastic changes, while ERCP is performed for both diagnostic (cholangiography and brushings) as well as therapeutic reasons as stenting is often required. Brushings should be evaluated by cytology and, if available, fluorescence *in situ* hybridization (FISH). If endoscopic stenting with drainage of as many

relevant hepatic segments as possible cannot be achieved, percutaneous biliary drainage (PTC) should be considered.

Treatment

The treatment for benign biliary strictures is dependent on the etiology and ranges from medical management to endoscopic and/or operative management. Conditions that can be treated medically include IgG4 cholangiopathy or pancreatitis which can typically be temporized with stenting and treated with corticosteroids. Duodenal Crohn's is another condition that may be able to be managed medically with stenting to temporize until the inflammation improves, and similarly nonneoplastic duodenal ulcers leading to ampullary/biliary stricture can be treated medically while temporized with endoscopic biliary drainage. Patients with pancreatitis-related biliary strictures may be managed with stenting if the stricture is related to acute inflammation. For patients with chronic inflammatory changes and stricturing, definitive management may require operative intervention. In this setting, two options for benign strictures are possible including Whipple pancreaticoduodenectomy or biliary bypass typically to a Roux limb. The choice of approach depends whether or not there is head-dominant pancreatitis likely to benefit from resection and the ability to safely perform such an operation. A resective approach should be considered if malignancy cannot be excluded. PSC represents a unique situation that will be discussed in detail in the next section. Postoperative biliary strictures can be balloon dilated and stented, which is successful in select patients, however definitive management often will require operative bypass which can be accomplished by bilioenteric anastomosis as described above.

Outcomes

The data regarding successful outcomes following endoscopic management of biliary strictures reports variable rates depending on retrospective versus prospective evaluation, plastic versus fully covered self-expanding metal, and etiology (most commonly pancreatitis vs. posttransplant anastomotic stricture vs. postcholecystectomy). In a prospective trial of metal versus

plastic stenting, the stricture resolution rate (at 12 months) was 92.6% versus 85.4% and fewer procedures were required during the treatment period (2.14 vs. 3.24).[17] Similarly, a meta-analysis also demonstrated fewer ERCPs required with metal stenting and a stricture recurrence rate of 16%.[18] As might be expected, longer-term follow-up of prospective stenting trials with covered metal stents have demonstrated stent-free probabilities of 61.6% for chronic pancreatitis at a median of 58 months, and 84.6% in postcholecystectomy strictures at 5-year poststent follow-up. The stent dwell time at the index treatment was 10 to 12 months in these studies.[19,20]

Follow-Up

Patients undergoing endoscopic stenting +/− balloon dilation for biliary stricture may require repeated procedures, the timing of which typically will be dictated by the choice of plastic versus covered metal stenting. For patients undergoing bilioenteric bypass, we recommend annual ultrasound and liver function testing as discussed above.

Table 62.4 Causes of Secondary Sclerosing Cholangitis

Pancreatitis with biliary obstruction
Choledocholithiasis Recurrent pyogenic cholangitis Postoperative stricture Hepatic ischemia
Tumors

SCLEROSING CHOLANGITIS

Sclerosing cholangitis can be primary (PSC) or secondary. Secondary sclerosing cholangitis is most commonly associated with recurrent episodes of cholangitis from a variety of causes (Table 62.4) which can lead to scarring and strictures. Management of the underlying etiology is required for treatment/prevention of secondary sclerosing cholangitis and may include

medical, endoscopic, or operative intervention based on the etiology. In contrast, PSC is an autoimmune disease without a known inciting factor. It is associated with ulcerative colitis (approx. 2/3 of patients with PSC will have ulcerative colitis), and carries a markedly increased risk of cholangiocarcinoma (400- to 1,000-fold increase compared to the general population).[21] A finding of diffuse strictures throughout the biliary tree is pathognomonic of the disease (although segmental involvement is possible) and progressive disease often leads to chronic cholestasis and eventual liver failure requiring transplant. The presence of a dominant stricture with or without an associated mass in a patient with PSC requires workup to rule out cholangiocarcinoma. Surgical intervention on the biliary tree other than transplant or cholecystectomy is uncommon while endoscopic management is the mainstay of therapeutic and surveillance strategies.

Clinical Presentation

Clinical presentation is a spectrum from incidental findings (alkaline phosphatase/bilirubin elevations and/or imaging changes), to painless jaundice, to cholangitis and sepsis. The initial diagnosis of PSC may be at the time of cholangiocarcinoma diagnosis.

Evaluation

The initial evaluation is similar to those noted above for biliary stricture, with a focused history and physical examination, followed by bloodwork, resuscitation as indicated, and imaging studies. Specific to PSC, the diagnosis is made based on clinical presentation and imaging findings. Either ERCP or MRCP can be utilized to evaluate the biliary anatomy, and diagnostic features include diffuse areas of structuring/beading throughout the biliary tree. Imaging characteristics of cirrhosis and/or portal hypertension should also be assessed. ERCP allows stenting and brushing/biopsy of any dominant strictures. Evaluation of cytology for malignancy is complicated in the setting of PSC and adjunctive studies such as FISH specifically evaluating the specimens for polysomy is recommended. A high index of suspicion should be maintained for malignancy in these patients and surveillance should be undertaken at a specialized center.

Treatment

For secondary cholangitis, treatment is targeted at the underlying etiology. In this setting, endoscopic and/or operative intervention on the liver/biliary tree may be undertaken. For example, in patients with recurrent pyogenic cholangitis (RPC), there often is selective involvement of the left lateral sector of the liver with progressive sclerosis and recurrent episodes of cholangitis secondary to intraductal stone formation. Resection of the involved liver segments can provide durable management. For other indications, such as IgG4 cholangiopathy, the treatment is medical. For PSC, the treatment modality for symptomatic strictures is endoscopic dilation, brushing, and stenting with close surveillance; the timing of which is dictated by the findings on cytology and FISH. Progressive liver failure or cholangiocarcinoma are treated with liver transplant in appropriately selected patients with PSC, although recurrence of PSC in the transplanted liver is possible.

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63

Biliary Neoplasms

Kaitlyn J. Kelly, Yuman Fong, and Sharon Weber

Key Points

1. Surgery remains the only curative option for biliary malignancies.
2. Gallbladder cancer is a rare malignancy with a dismal prognosis because of its insidious onset, propensity for local invasion, and rapid disease progression.
3. The association of gallstones with carcinoma is probably related to chronic inflammation.
4. Patients with choledochal cysts have an increased risk of carcinoma developing anywhere in the biliary tree, but the incidence is highest in the gallbladder.
5. The only curative option in patients with gallbladder cancer is complete surgical resection.
6. Nonoperative palliative biliary decompression can be accomplished with percutaneous or endoscopic stenting, depending on the level of obstruction.

INTRODUCTION

1 Tumors arising in the gallbladder and biliary tree are rare, with approximately 10,650 cases per year in the United States and 140,000 per year worldwide.[1,2] These tumors are often asymptomatic until late in the course of the disease. Consequently, these tumors commonly present in an advanced, often unresectable stage. Surgery remains the only curative option for biliary malignancies. Complete resection of biliary neoplasms, however, often requires radical resections and complex biliary reconstructions that are only routinely safe at specialized, high-volume centers. Both the late diagnosis and the complex operative techniques required for potentially curative resection contribute to the challenge of these cases. This chapter reviews the incidence, diagnosis, and therapy of these malignancies as well as the outcomes of treatment.

GALLBLADDER CARCINOMA

2 Gallbladder cancer is a rare malignancy with a dismal prognosis because of its insidious onset, propensity for local invasion, and rapid disease progression. Overall, most series report a 5-year survival of less than 5%.

Incidence

Gallbladder cancer is the most common biliary tract malignancy, but there are only 6,000 to 7,000 new cases diagnosed nationally each year. Attesting to the rarity of this lesion, after routine screening of abdominal ultrasounds in asymptomatic patients in Japan, only 19 out of 194,767 patients (0.01%) were found to have gallbladder cancer.[3] This tumor occurs more frequently in women (female:male ratio = 3:1), and peak incidence is in the seventh decade.[4] There is a tremendously increased risk of gallbladder cancer in particular indigenous populations, including Mapuche Indians in South America (12.3 cases/100,000 males and 27.3/100,000 females), and Native Americans in New Mexico (8.9 cases/100,000 people).[5,6]

The increased risk of gallbladder cancer with cholelithiasis is well established; 70% to 90% of all patients with carcinoma also have gallstones. However, less than 0.5% of patients with gallstones are found to have gallbladder cancer.[5] In recent series of patients undergoing elective

cholecystectomy for gallstones, gallbladder cancer is found incidentally in <0.5% of patients.[7] The association of gallstones with carcinoma is probably related to chronic inflammation. Larger stones (>3 cm) are associated with a 10-fold increased risk of cancer.[6,8]

3 The association of gallbladder cancer with gallstone disease has led some investigators to question whether all patients with gallstones should undergo cholecystectomy. The argument against this approach is that the use of cholecystectomy only for symptomatic patients, thus leaving the gallbladder in place in patients with asymptomatic gallstones, has not led to an increase in the prevalence of gallbladder cancer over time. Also, epidemiologic studies have found that the 20-year risk of developing cancer in patients with gallstones is less than 0.5% for the overall population and 1.5% for high-risk groups.[5] Thus, routine cholecystectomy for asymptomatic gallstones because of concern for gallbladder cancer does not appear to be warranted.

In the past, the finding of a calcified gallbladder wall, called "porcelain gallbladder" (**Fig. 63.1**), was associated with a high risk of cancer, in some series ranging from 25% to 60%.[9] Thus, the recommendation was for all patients with porcelain gallbladder to undergo open cholecystectomy, even if asymptomatic. Recent series evaluating this issue suggest that the risk of gallbladder cancer in patients with porcelain gallbladder has likely been greatly overestimated. In fact, although patients with limited areas of calcification of the wall may have a higher incidence of gallbladder cancer (7%), patients with diffuse calcification of the gallbladder wall, the classic presentation for porcelain gallbladder, do not appear to have an increased risk of cancer.[10,11]

4 Patients with choledochal cysts have an increased risk of carcinoma developing anywhere in the biliary tree, but the incidence is highest in the gallbladder. This risk increases with age. Therefore, cholecystectomy is recommended for all patients with choledochal cysts at the time of diagnosis.

Pathology and Staging

More than 80% of gallbladder cancers are adenocarcinomas; there are several histologic subtypes, including papillary, nodular, and tubular. Papillary tumors, which grow predominantly into the gallbladder lumen,

have an improved prognosis compared with the other subtypes.[12] Poor prognostic signs in gallbladder cancer include grade, and vascular invasion.[12,13] The most important prognostic factor may be lymph node status, although 5-year survivors with nodal involvement have been documented.[14,15] Less than 5% of cases are squamous cell carcinomas, with the remaining 10% being anaplastic lesions.

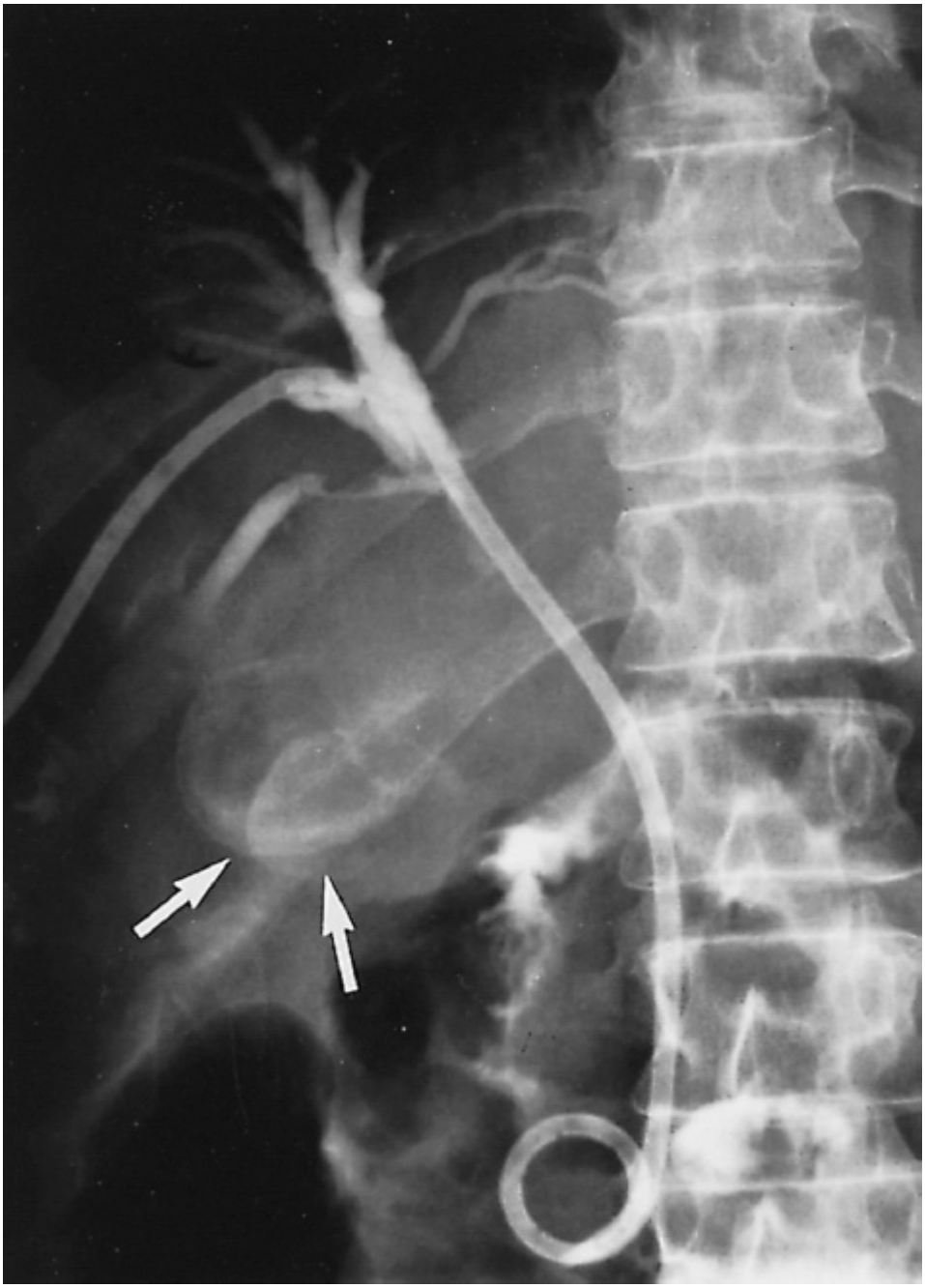

Figure 63.1 Unresectable gallbladder cancer demonstrating palliative transhepatic percutaneous stent placed to relieve jaundice. Porcelain gallbladder is present (*arrows*).

Gallbladder cancer spreads via the lymphatic and venous drainage. Because of drainage of the cholecystic veins directly into the adjacent liver, these tumors often involve hepatic parenchyma, most often portions of segments IV and V. Lymphatic spread is first to the cystic duct (Calot) node,

then to pericholedochal and hilar nodes, and finally to peripancreatic, duodenal, periportal, celiac, and superior mesenteric artery nodes. Nodal disease in the porta hepatis often causes common bile duct (CBD) obstruction and resultant jaundice, which is the first clinical symptom in 30% of patients. Jaundice may also be caused by tumors arising in the infundibulum, which may spread directly to the cystic duct and common hepatic duct. Although peritoneal metastases are frequent, distant extraperitoneal metastases are not.

Limited information exists regarding the genetic changes in gallbladder cancer. Recently reported gene abnormalities associated with gallbladder cancer include p53, K-ras, CDKN2 (9p21), FGFR, and PI3 kinase pathway aberrations.[16–20] The finding that patients with an anomalous pancreaticobiliary junction have a greater frequency of K-ras mutations has led investigators to believe that reflux of pancreatic enzymes into the biliary tree may contribute to the development of cancer.[16] Because of our limited knowledge of the sequence of molecular changes, there are no known detectors of early disease or of risk assessment. Clearly, this is an area that needs improvement, particularly in endemic areas.

The American Joint Committee on Cancer's (AJCC) eighth edition of its tumor, node, metastasis (TNM) staging system (**Table 63.1**) reflects prognostic characteristics of tumor depth, regional nodal disease, and distant spread. The gallbladder differs histologically from the rest of the gastrointestinal tract in that it lacks a muscularis mucosa and submucosa. The gallbladder wall is composed of (a) a single layer of columnar cells, the mucosa, and lamina propria; (b) a fibromuscular layer; (c) a perimuscular, subserosal layer containing lymphatics and neurovascular structures; and (d) a serosal surface, except where the gallbladder is embedded in the liver. Because lymphatics are present in the subserosal layer only, tumors invading less than the full thickness of the muscular layer have minimal risk of nodal spread. Thus, disease invading into, but not through, the muscular layer of the gallbladder is T1b disease (stage I), whereas invasion into the perimuscular connective tissue is T2 (stage IIa or b). If on the peritoneal side, it is T2a, and if on the hepatic side, T2b. Stage III disease includes tumors that have perforated the serosa or have directly invaded the liver or other surrounding structures (T3), which are clearly more advanced but still potentially resectable. Tumors that invade the main portal vein, hepatic artery, or two or

more extrahepatic organs/structures are classified as T4 (stage IVA) and are typically unresectable. Lymph node metastasis to one to three regional nodes is N1, and to four or more regional nodes is N2. N1 nodal metastasis is classified as stage IIIB and N2 as stage IVB. In line with other pancreaticobiliary malignancies, the stage III grouping refers to locally advanced disease and stage IV indicates locally advanced unresectable or metastatic disease.

Clinical Findings and Diagnosis

Most patients are found to have gallbladder cancer during workup or treatment of cholelithiasis or choledocholithiasis. In patients with symptoms, abdominal pain consistent with biliary colic or acute cholecystitis is most common. Patients also present with jaundice, weight loss, anorexia, or an increase in abdominal girth secondary to ascites. Physical findings may include right upper quadrant tenderness or a palpable mass, hepatomegaly, and ascites. Laboratory investigation, if abnormal, is most often consistent with biliary obstruction. Because of its nonspecific presentation and the lack of reliable screening tests, gallbladder cancer is not diagnosed preoperatively in more than half the cases.

Imaging evaluation often reveals a thickened gallbladder wall or a mass within or replacing the gallbladder on ultrasound examination. Because polyps, asymmetric wall thickening from cholecystitis (especially xanthogranulomatous type), and carcinoma can have an echogenicity similar to the gallbladder wall, these lesions are often difficult to distinguish. This is even more difficult when inflammation is present from gallstones. At times, ultrasound can visualize invasion of the liver, adjacent adenopathy, and a dilated biliary tree. The ability of ultrasound to differentiate benign from neoplastic disease is enhanced using endoscopic ultrasound, and may be more specific than computed tomography (CT) or magnetic resonance imaging (MRI).[21–23]

A dynamic contrast-enhanced CT scan may identify a gallbladder mass or invasion into the liver parenchyma or adjacent organs. The classic finding in a patient with gallbladder cancer is asymmetric thickening of the gallbladder wall. Staging of gallbladder carcinoma using CT, however, is limited by poor sensitivity in identifying nodal spread.[24]

In patients who are jaundiced, direct cholangiography may be useful to delineate the extent of biliary involvement as well as to palliate symptoms of biliary obstruction. A mid–bile duct obstruction not caused by gallstones is gallbladder cancer until proved otherwise (**Fig. 63.2**). More recently, with improvements in MRI technology, diffusion-weighted imaging and magnetic resonance cholangiopancreatography (MRCP) have evolved into a single, noninvasive imaging modality that allows complete assessment of biliary, vascular, hepatic parenchymal, and nodal involvement, as well as involvement of adjacent organs (**Fig. 63.3**).[25–27]

STAGING

Table 63.1 American Joint Committee on Cancer, 8th Edition, Staging System for Gallbladder Carcinoma

Stage	Tumor	Nodes	Metastasis
0	Tis	N0	M0
I	T1	N0	M0
IIA	T2a	N0	M0
IIB	T2b	N0	M0
IIIA	T3	N0	M0
IIIB	T1–3	N1	M0
IVA	T4	N0–1	M0
IVB	Any T	N2	M0
	Any T	Any N	M1

Definition of TNM	
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T2a	On peritoneal side, without involvement of serosa
T2b	On hepatic side, without extension into liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach,

	duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades two or more extrahepatic organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis to one to three regional nodes
N2	Metastasis to four or more regional nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

Used with permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.

Figure 63.2 Endoscopic retrograde cholangiopancreatogram obtained from a patient with gallbladder cancer. Mid–bile duct obstruction (*arrow*) is caused by direct extension of tumor to the cystic and common hepatic duct.

In patients who present with incidentally discovered gallbladder cancer following cholecystectomy, staging should be performed with high-quality CT or MRI of the chest, abdomen, and pelvis. There is no clear role for PET/CT in this setting.[28]

Surgery

5 It is clear that the only curative option in patients with gallbladder cancer is complete surgical resection. It is essential for optimal patient care that patients with gallbladder cancer be recognized before laparoscopic cholecystectomy is performed, because of the risk of bile spillage, with its potential for subsequent carcinomatosis.[29]

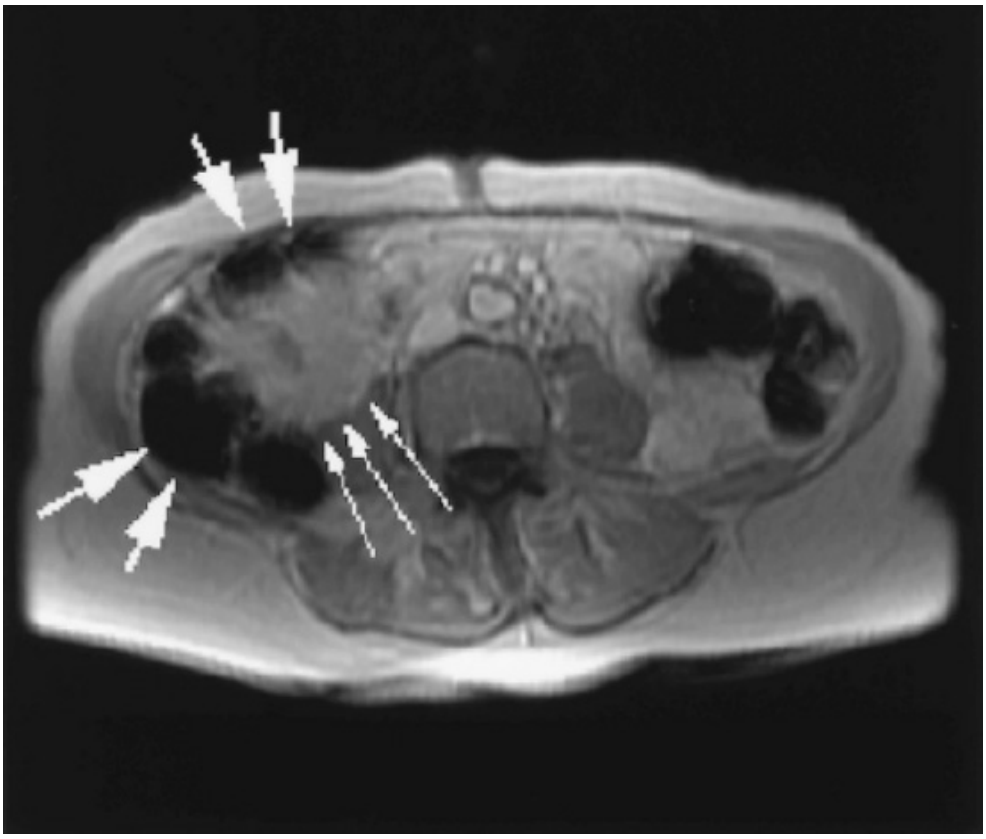

Figure 63.3 T1-weighted magnetic resonance imaging scan of a patient with gallbladder cancer (*small arrows*) with extension into the duodenum and the hepatic flexure of colon (*large arrows*).

Role of Staging Laparoscopy

Because a large percentage of patients with gallbladder cancer are found to have occult, unresectable disease at the time of surgical exploration, several authors have investigated the use of initial staging laparoscopy for this disease.[30–33] Because gallbladder cancer has such a propensity to spread intra-abdominally, this tumor is ideal for detection of intra-abdominal metastases with laparoscopy. This is demonstrated by the fact that up to 50%

of patients are found to have unresectable disease at the time of laparoscopy.[34,35] Patients who are found to have unresectable disease at laparoscopy can begin other forms of systemic therapy earlier and may undergo the procedure as an outpatient. Particularly because patients with unresectable disease have a median survival of only 6 months, the impact on quality of life, including decreased length of stay in the hospital, cannot be overemphasized.

Cholecystectomy with or without Partial Hepatectomy

Gallbladder cancer, if not completely surgically removed, results in rapid local progression and death. In a collected review of 5,836 patients with gallbladder cancer, the overall mean survival was between 2 and 5 months, whereas the 5-year survival was 4%.[5]

There is little doubt that the results of treatment, as well as the scope of operation, are related to depth of tumor penetration (**Table 63.2**). For tumors limited to the muscular layer of the gallbladder (T1), there is near-universal agreement that simple cholecystectomy is adequate.[15,36–38] T1 tumors have not yet invaded the subserosal layer, which contains lymphatics, and therefore lymphadenectomy is not required. Attesting to the fact that early gallbladder carcinoma is completely curable, simple cholecystectomy has resulted in 90% to 100% survival when early cancer is an incidental finding after elective cholecystectomy.[15,39]

The extent of surgical resection for T1b tumors is controversial, with recommendations ranging from simple cholecystectomy to radical excision, including hepatectomy. For T2 or greater tumors, extended resection with cholecystectomy combined with resection of liver segments IVb and V and portal lymphadenectomy is recommended.[40]

To understand the rationale for extensive resections, it is also important to understand the pattern of spread of gallbladder cancer. Direct extension to the adjacent liver parenchyma often occurs first, followed by adjacent organ involvement, including duodenum, colon, and stomach (**Fig. 63.2**). Lymphatic spread of gallbladder cancer is routine, often involving nodes in the porta hepatis, peripancreatic region, celiac axis, and the aortocaval nodal basins. There is currently no consensus on the extent of lymphadenectomy that is appropriate for gallbladder cancer. Extensive lymphadenectomy including

para-aortic nodes is advocated in the East, but is not universally accepted. Recently, a technique of intraoperative nodal staging was proposed that entails sampling the highest peripancreatic lymph node for frozen section. This is the lymph node situated between the N1 and N2 nodal stations at the junction of the bile duct and the superior border of the head of the pancreas (**Fig. 63.4**). Metastatic disease to this node has been shown to be a poor prognostic factor.[41]

Dissection of lymph nodes should include all tissues from the bifurcation of the hepatic ducts to the distal CBD. Proponents of this approach advocate liver resection on the basis that it is the only way to obtain an adequate margin on the hepatic side of the gallbladder and resection of the regional nodes allows the best chance for complete tumor clearance. For all of these reasons, simple cholecystectomy is inadequate for T2 or greater tumors. When larger anatomic hepatic resections have been performed in patients with T2 tumors, it has increased the 5-year survival from 25% to 40% after simple cholecystectomy to 70% to 100% after radical resection.[14,36–38,42,46,47,49,50]

RESULTS

Table 63.2 Five-Year Survival after Resection for Gallbladder Cancer

	T1 or T2 Tumors		T3 or T4 Tumors	
Author	Simple Cholecystectomy (%)	Radical Cholecystectomy or Segmental Resection (%)	Simple Cholecystectomy (%)	Radical Cholecystectomy or Segmental Resection (%)
Wanebo et al.[42]	33	—	3	13
Ouchi et al.[38]	57	100	0	23
Nakamura et al.[43]	—	100	—	15
Donohue et al.[36]	—	—	0	29
Shirai et al.[15]	—	72	—	37
Fong et al.[44]	—	58 (T2)	—	25
Wakai et al.[45]	100[a] (10-year survival, T1b only)	75[a] (10-yr survival, T1b only)	—	—
Kai et al.[46]	25	60 (T2)	—	—
Jensen et al.[47]	29	42	—	—
Mayo et al.[48]	16	53	8	11

[a]No significant difference.

For T3 and T4 lesions, there is a high likelihood of intraperitoneal and hematogenous spread and significant morbidity from the radical procedures that are often necessary for excision of local disease. Recent series, however, support an aggressive approach to resection of these large tumors, particularly if no indication of nodal involvement is found (**Table 63.3**) and negative margins can be achieved. For T3 and resectable T4 tumors, a minimal resection includes segments IVb and V, and in many cases an extended right hepatectomy (segments IV, V, VI, VII, and VIII) may be necessary to obtain complete resection. With aggressive resection, long-term survival can be achieved even for patients with these more advanced tumors.[14,15,36,37,43,51]

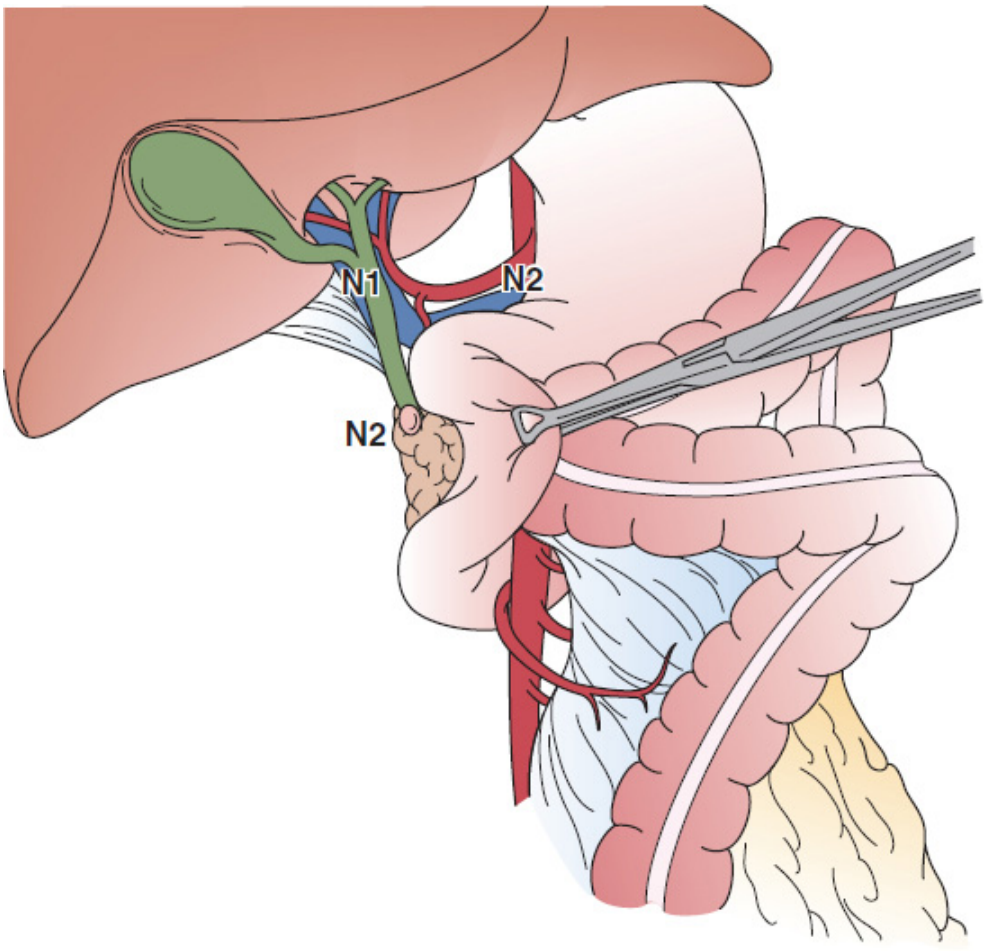

Figure 63.4 Illustration of the highest peripancreatic lymph node.

Surgical exploration should be performed for all patients without medical contraindications. If a T1 tumor is suspected, a cholecystectomy and biopsy of regional nodes should be performed after thorough examination of the abdominal cavity for any signs of tumor dissemination. The pathology and depth of penetration should be confirmed by frozen section, and the procedure terminated if a T1 tumor with negative margins is confirmed. For T2 lesions, a radical cholecystectomy (with resection of segments IVb and V) with lymphadenectomy should be performed.[14] For T3 lesion and resectable T4 lesions, a segment IVb and V resection or extended right hepatectomy is performed if needed to obtain negative margins. Similarly, bile duct resection should only be performed if necessary to achieve negative margins.

RESULTS

Table 63.3 Results after Radical Resection for Gallbladder Cancer

Author	Number Resected	Mortality (%)	5-Year Survival (%)
Nakamura et al.[43]	15	0	25
Donohue et al.[36]	42	2	33
Ogura et al.[37]	1,686	5	51
Shirai et al.[15]	40	0	65
Bartlett et al.[14]	102	4	58
Fong et al.[44]			
Taner et al.[40]	131	2	13
Kai et al.[46]	90	2	40
Jensen et al.[47]	443	—	42
Mayo et al.[48]	202	2	—

Complete regional lymphadenectomy should be performed, skeletonizing the CBD, hepatic artery, and portal vein. Short-term postoperative outcomes following resection of gallbladder cancer have remained relatively stable over time, with postoperative morbidity occurring in 30% to 40% of patients, and mortality occurring in <5% (**Table 63.4**).

Table 63.4 American Joint Committee on Cancer, 8th Edition, Staging System for Intrahepatic Bile Duct Carcinoma

Stage	Tumor	Nodes	Metastasis
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
II	T2	N0	M0
IIIA	T3	N0	M0
IIIB	T4	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1
Definition of TNM			
Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ (intraductal tumor)		
T1a	Solitary tumor 5 cm without vascular invasion		
T1b	Solitary tumor >5 cm without vascular invasion		
T2	Solitary tumor with intrahepatic vascular invasion or multiple tumors, with or without vascular invasion		
T3	Tumor perforating the visceral peritoneum		
T4	Tumor involving local extrahepatic structures by direct invasion		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis is present.		

Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

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Incidentally or Laparoscopically Discovered Gallbladder Cancer

Gallbladder cancer is often discovered during pathologic examination after cholecystectomy for presumed benign disease. Because of the popularization of laparoscopic cholecystectomy in the past decade, an increasing number of patients with gallbladder cancer are found incidentally. The role of reresection in this setting is controversial. In a series of 135 patients who underwent re-exploration following laparoscopic cholecystectomy, 61% of all and 36% of those with T1b primary tumors were found to have residual disease.[52] In this study, survival following reresection of residual locoregional disease was extremely poor and was not different from that of patients with metastatic disease. Improved survival has been demonstrated following reresection to achieve negative margins, however, especially in patients with T2 or T3 disease.[49,53,54] While laparoscopic port-site recurrence has been reported, it is associated with peritoneal-based disease. Port-site excision at the time of re-exploration is no longer recommended as recent data have shown that it is not associated with decreased recurrence or improved survival.[55,56]

Reresection after recent cholecystectomy is often technically challenging. Postoperative inflammation in the right upper quadrant often hinders distinction of tumor from normal tissue. Determination of ductal or nodal involvement by tumor is always difficult at the time of reoperation. In addition, postoperative fibrosis often encases the right hepatic artery, which crosses behind the bile duct in most patients. Because of this, during a second operation for incidentally discovered gallbladder cancer, an extended right hepatectomy along with excision of the extrahepatic biliary tree and portal lymphadenectomy is often necessary. This resection allows adequate exposure for lymphadenectomy and greater confidence of a negative margin

on the bile duct, and also permits biliary reconstruction to only one side of the liver. The disadvantage is that a large portion of normal liver parenchyma is sacrificed, and consequently, transient postoperative liver dysfunction is common. Although it may be more difficult to curatively resect disease in patients with incidentally discovered gallbladder cancer after laparoscopic cholecystectomy, there is no difference in overall survival between patients with incidentally discovered gallbladder cancer who are submitted to curative resection and those patients who undergo initial curative resection.[57]

When a patient presents with T1a gallbladder cancer discovered after simple cholecystectomy, the pathology should be reviewed to determine if the entire gallbladder has been removed and if the cystic duct margin is clear of tumor. If all margins are negative, no further therapy is warranted. If the tumor is proved to be T1b or greater, and in the absence of metastatic disease, patients should be counseled regarding reresection to attempt complete staging and margins, chemotherapy with or without radiation, or observation. Patients with a known or suspected early gallbladder carcinoma should be referred to an experienced center where curative-intent resection can be performed at the initial operation.

Neoadjuvant and Adjuvant Therapy

Very few randomized trials have been completed to inform the role of neoadjuvant and adjuvant therapy for gallbladder cancer. Given the relative rarity of these malignancies in the United States, large-scale, randomized trials are feasible only in the context of a multi-institutional or cooperative group setting. Consensus guidelines state that neoadjuvant therapy should be considered for patients with locally advanced gallbladder cancer, although there is little data supporting any one regimen. Commonly used regimens include combinations of gemcitabine with oxaliplatin, cisplatin, or capecitabine, or 5-fluorouracil-based regimens. A meta-analysis published in 2019 identified 474 patients with gallbladder cancer treated in 8 studies with neoadjuvant therapy and surgery or surgery alone and concluded that data were insufficient for routine use of neoadjuvant therapy.[58]

In 2002, a randomized phase III trial of adjuvant chemotherapy with 5-fluorouracil and mitomycin C versus surgery alone for patients with pancreaticobiliary malignancies having resection found that in the subset of

patients with gallbladder cancer (n = 112), the 5-year survival rate was significantly better in the adjuvant group (26%) versus the control group (14%).[59] Similarly, the 5-year disease-free survival rate was 20.3% versus 11.6%, clearly favoring the adjuvant therapy group. A recent review of the SEER database also reported an association between adjuvant chemoradiation therapy and improved survival in patients with locoregionally advanced disease.[60] This finding prompted a multi-center phase II trial of adjuvant capecitabine and gemcitabine followed by concurrent capecitabine and radiation therapy for patients with resected gallbladder cancer or extra hepatic cholagiocarcinoma. The results of this study were published in 2015 and showed promising findings of 65% 2-year survival.[61] These studies suggest that patients with gallbladder cancer with high risk for recurrence (T2 or greater, node-positive, or margin-positive) should be considered for adjuvant treatment with systemic chemotherapy or chemoradiation.

Prognosis

The 5-year survival rate for all patients with gallbladder cancer is less than 5% in most series, with a median survival of 6 months. This is primarily because most patients present with unresectable disease. Of those patients undergoing resection, survival is dependent on depth of penetration and nodal status. Nearly 100% survival is reported after simple cholecystectomy for T1a disease, whereas patients with T2 and T3 tumors without nodal disease have a 5-year survival greater than 50%.[14,15,43,50] Node positivity is an ominous finding, with few series reporting 5-year survivors.

Follow-up after Resection for Gallbladder Cancer

The most common sites of recurrence after resection of gallbladder cancer include carcinomatosis, intrahepatic metastases, or nodal recurrence in the retroperitoneum. For most tumors, local recurrence is found synchronously with diffuse intra-abdominal spread. When jaundice or cholangitis is the presenting symptom of possible recurrence, a nonsurgical palliative

approach using percutaneous transhepatic cholangiogram (PTC) and stenting is usually favored unless a benign postsurgical stricture is suspected. Because of the rapid growth of tumor in patients with recurrence, the hospitalization and recovery time from a surgical bypass is usually not justified for recurrences resulting in biliary obstruction.

The routine follow-up of a patient after resection of gallbladder cancer includes office visits every 3 months with physical examination and measurement of liver function tests, and cross-sectional imaging every 3 to 6 months for the first 2 years. In patients who remain free of disease at 2 years, follow-up should be continued on an individualized basis. Although CA19-9 may be elevated in patients with gallbladder cancer, the sensitivity and specificity are poor and, thus, is optional for screening for recurrence.[62] If recurrence is identified, systemic therapy with gemcitabine and cisplatin should be considered as it has been shown to prolong survival in the setting of metastatic disease.[63] For patients who cannot tolerate this regimen, alternatives include single-agent gemcitabine or gemcitabine plus capecitabine.[64] Lastly, molecular profiling to identify targeted agents, including immunotherapy, that may be effective is recommended.

Issues for the Future

Clearly, improving our ability to recognize early gallbladder cancer in high-risk geographic areas would have an important impact on outcome in these patients. This will likely require implementation of screening programs in high-risk areas, which could result in prophylactic cholecystectomy.[65] Additionally, standardization of minimum pathologic assessment of gallbladder specimens in high-risk areas is important to allow for accurate diagnosis, staging, and treatment of patients.

Further studies on characterization of molecular aberrations in gallbladder cancer by next generation sequencing and other technologies may lead to the discovery of targetable mutations and lead to the development of novel therapies. Additionally, there is a theoretical role for neoadjuvant therapy for patients with locoregionally advanced gallbladder cancer given their poor prognosis following surgery. Clinical trials in this area are needed.

BILE DUCT CARCINOMA

Bile duct carcinomas may arise within the liver (intrahepatic cholangiocarcinoma [ICC] or peripheral cholangiocarcinoma), at the liver hilum (hilar cholangiocarcinoma or Klatskin tumor), or in the extrahepatic bile duct (extrahepatic cholangiocarcioma [ECC]). While all arise from the biliary epithelium, the location of these tumors affects prognosis as well as the potential for curative resection.

Resection of biliary neoplasms, particularly hilar cholangiocarcinoma, often requires radical resections and complex biliary reconstructions that should be performed only at high-volume, experienced centers. There is also a role for surgery in palliation for these cancers by providing biliary bypass for jaundiced patients with unresectable tumors. Because disease is often diagnosed late in the course and because complex operative techniques are required for potentially curative resection, these tumors represent one of the greatest challenges for definitive treatment.

INCIDENCE

The incidence of ICC in the United States is approximately 0.7/100,000 with a similar mortality. During the last 30 years, it appears that both the incidence and mortality in the United States are increasing.[66] The overall incidence of hilar cholangiocarcinoma, the most common type, is 1.0/100,000 per year in the United States, although rates are higher in other geographic regions such as Israel and Japan.[67] Recent population studies have noted a trend toward a relative increased incidence of ICC compared to ECC.[4,68,69] Using the Surveillance, Epidemiology and End Results-Medicare databases, Welzel et al.[69] noted HCV infection, chronic nonalcoholic liver disease and obesity, and smoking being associated only with ICC and not ECC, possibly explaining the divergent trends in incidence. Cholangiocarcinomas arise slightly more often in males, with a male-to-female ratio of 1.3:1 and an average age of 50 to 70 years.

Known risk factors for cholangiocarcinoma include primary sclerosing cholangitis, ulcerative colitis, choledochal cysts, and biliary tract infection, either with *Clonorchis* or in chronic typhoid carriers.[70] Some industrial

chemicals (e.g., nitrosamines, dioxin, asbestos, and polychlorinated biphenyls) have also been implicated in the pathogenesis of cholangiocarcinoma. Although there has been some suggestion of an increased risk of cholangiocarcinoma arising after transduodenal sphincteroplasty,[71] it is difficult to determine if this is caused by the surgical intervention or the underlying disease leading to sphincteroplasty.

Pathology and Staging

More than 90% of bile duct cancers are adenocarcinomas. They are morphologically described as nodular, which is the most common, scirrhous, diffusely infiltrating, or papillary. Histologic subtypes include acinar, ductular, trabecular, alveolar, and papillary. Papillary tumors have an improved outcome. Much less common types of bile duct tumors include cystadenocarcinomas, hemangioendotheliomas, and mucoepidermoid carcinomas. In patients with ICC, negative prognostic signs include vascular invasion, multiple tumors, and lymph node metastases.[72]

Historically, ECCs have been classified according to their location in the upper (60%), middle (15% to 20%), or lower third (15% to 20%) of the bile duct. Middle-third lesions arise between the cystic duct and the superior border of the duodenum. Lower-third lesions are found below the superior border of the duodenum but above the ampulla. The problem with this classification is that the anatomic landmarks are somewhat arbitrary and not clinically useful. A more useful classification is to divide these lesions into upper-half or lower-half tumors, based on the location of the cystic duct as it enters the common duct (in the case of normal anatomy). The usefulness of this classification scheme is that it allows the surgeon to delineate whether a hepatic or pancreatic resection will be required for clearance of tumor. The AJCC TNM staging system (eighth edition) for bile duct cancers is described in **Tables 63.4** to in **63.6**.

Table 63.5 American Joint Committee on Cancer, 8th Edition, Staging System for Perihilar Bile Duct Carcinoma

Stage	Tumor	Nodes	Metastasis
0	Tis	N0	M0
I	T1	N0	M0
II	T2a–b	N0	M0
IIIA	T3	N0	M0
IIIB	T1–3	N1	M0
IVA	T4	N0–1	M0
IVB	Any T	N1–2	M0
	Any T	Any N	M1

Definition of TNM	
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ/high-grade dysplasia
T1	Tumor confined to bile duct, with extension up to the muscle layer or fibrous tissue
T2a	Tumor invades beyond the wall of the bile duct to surrounding adipose tissue
T2b	Tumor invades adjacent hepatic parenchyma
T3	Tumor invades unilateral branches of the portal vein or hepatic artery
T4	Tumor invades main portal vein or its branches bilaterally; or the common hepatic artery; or the second-order biliary radicals bilaterally; or unilateral second-order biliary radicals with contralateral portal vein or hepatic artery involvement

Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three positive lymph nodes typically involving the hilar, cystic duct, common bile duct, hepatic artery, posterior pancreatoduodenal, and portal vein lymph nodes
N2	Four or more positive lymph nodes from the sites described for N1
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

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Table 63.6 American Joint Committee on Cancer, 8th Edition, Staging System for Distal Bile Duct Carcinoma

Stage	Tumor	Nodes	Metastasis
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1–3	N1	M0
III	T4	Any N	M0
IV	Any T	Any N	M1
Definition of TNM			
Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma in situ/high-grade dysplasia		
T1	Tumor invades the bile duct wall with a depth of <5 mm		
T2	Tumor invades the bile duct wall with a depth of 5–12 mm		
T3	Tumor invades the bile duct wall with a depth of >12 mm		
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery		
Regional lymph nodes (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis to one to three regional nodes		
N2	Metastasis to four or more regional nodes		

Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

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Other staging systems have been created that attempt to incorporate clinically important indicators of resectability for hilar cholangiocarcinoma that are defined preoperatively, including hepatic lobe atrophy or portal vein involvement.[73] With the increasing acceptance of major hepatic resection for these tumors, this preoperative staging system attempts to define whether there is ipsilateral involvement alone, because tumors with bilateral extension past the primary biliary radicles are not resectable.

Clinical Findings and Diagnosis

The presentation of patients with cholangiocarcinoma is variable. Patients with hilar or extrahepatic tumors most commonly present with painless jaundice. Symptoms of mild right upper quadrant pain, pruritus, anorexia, malaise, and weight loss may also be reported. Cholangitis is the presenting symptom in 10% to 30% of patients. Some patients, particularly those with ICC may be asymptomatic and have their tumors discovered incidentally or on evaluation for elevations of alkaline phosphatase and gamma-glutamyl transferase. Many of these patients will present to the surgeon with a biopsy showing adenocarcinoma without a known primary tumor. The standard evaluation in these patients should include tumor markers including carcinoembryonic antigen (CEA) or α-fetoprotein (AFP); upper and lower endoscopy to evaluate for a gastrointestinal source; CT scan to assess for a primary tumor in the gastrointestinal tract or pancreas; and, in women, a mammogram. If no site of primary disease is found, in most patients, the diagnosis is ICC.

On CT, cholangiocarcinomas most often appear as hypodense masses with irregular margins on precontrast phase images, with peripheral rim enhancement on arterial phase, followed by progressive hyper-attenuation on venous and delayed phases.[74] Intrahepatic lesions often exhibit associated

capsular retraction and segmental/lobar atrophy and ductal dilatation. Hilar and proximal extrahepatic lesions demonstrate dilated intrahepatic biliary ducts with a normal, collapsed gallbladder, and, depending on the level of the tumor, a nondilated or partially dilated extrahepatic biliary tree (**Fig. 63.5**). While conventional CT is useful for assessment for extrahepatic, metastatic disease and perihilar adenopathy, high-resolution CT and/or MRI are required for accurate assessment of the tumor and for determination of respectability (**Figs. 63.6** and **63.7**).[74] Portal vein patency can be determined with ultrasound, CT, or MRI. Particularly for hilar tumors, signs of hepatic lobar atrophy should be carefully sought, because this indicates ipsilateral portal vein involvement by tumor. MRCP offers the potential of evaluating parenchymal, vascular, biliary, and nodal involvement with a single noninvasive examination.[25,27,75]

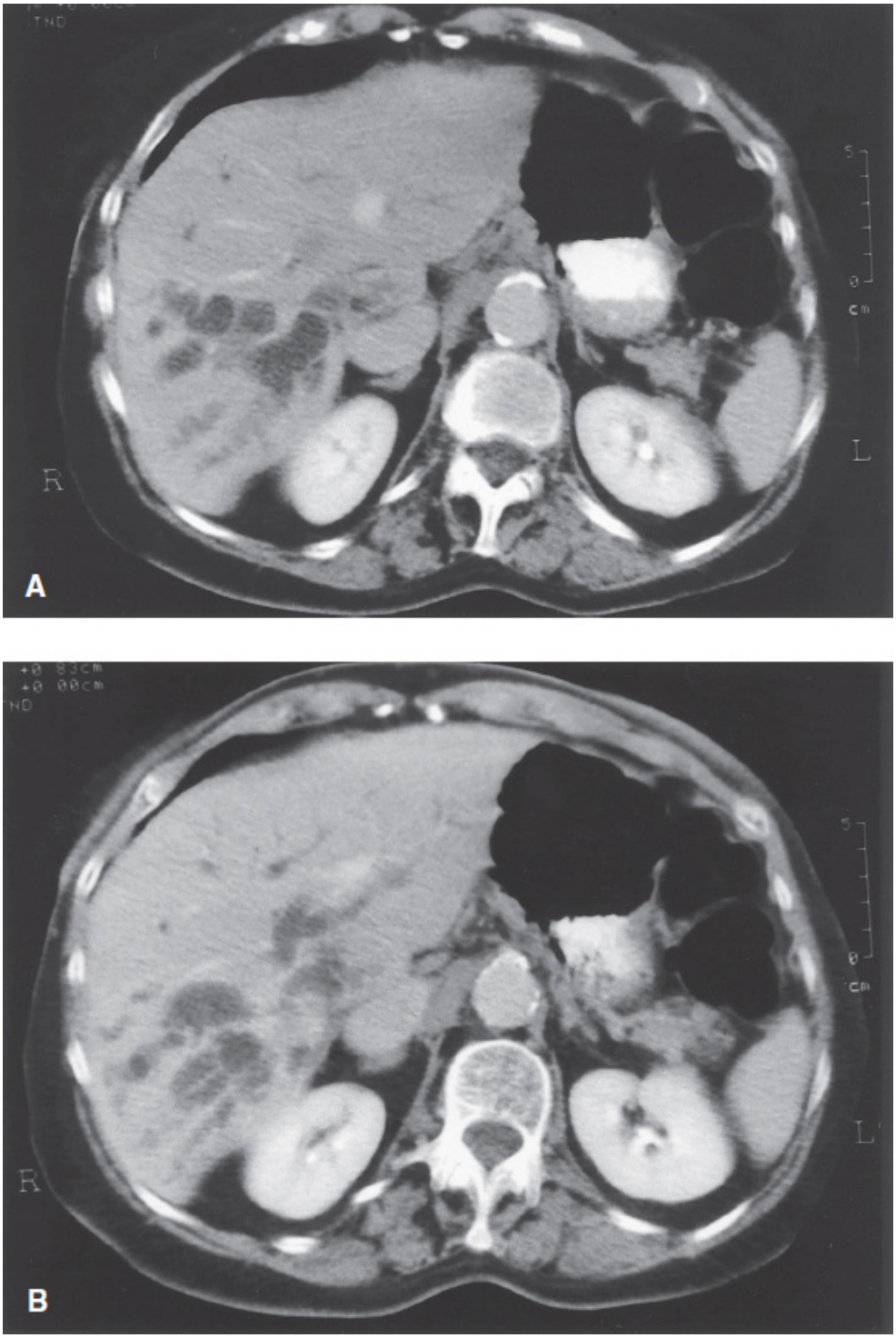

Figure 63.5 Computed tomography scan in a patient with hilar cholangiocarcinoma, demonstrating dilated intrahepatic ducts in the right lobe (**A** predominantly posterior sector, **B** both anterior and posterior sectors) but inability to directly visualize tumor.

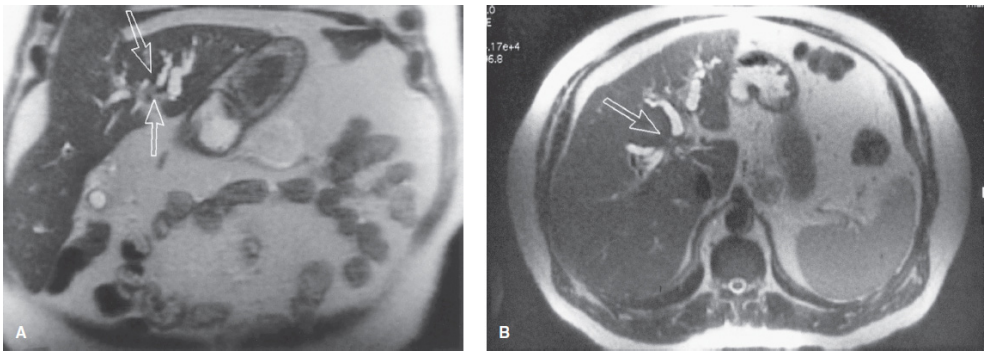

Figure 63.6 Coronal (**A**) and axial (**B**) magnetic resonance imaging in a patient with hilar cholangiocarcinoma. Dilated intrahepatic ducts are present with a soft tissue density consistent with tumor (*arrows*).

In most centers, direct cholangiography is used to evaluate the extent of biliary involvement and provide palliation for jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) has little role to play in high biliary obstruction because opacification of the proximal biliary tree is difficult. ERCP, however, can be effectively used to image more distal lesions. At the time cholangiography is performed, some authors advocate the routine preoperative placement of biliary drainage catheters to aid in intraoperative identification of the bile ducts.[76,77] Others have found a higher incidence of infectious complications and mortality, and a longer hospital stay, after preoperative placement of biliary drainage catheters.[78–80] The difficulty in making the decision regarding preoperative stenting is that many patients are severely symptomatic because of jaundice and pruritus and require palliation, thus if the operation is delayed, many patients require palliation.

In many cases, it is difficult to obtain pathologic confirmation of cholangiocarcinoma, even with the use of biliary brushings and cytology obtained at the time of direct cholangiography. Oftentimes, patients are offered surgical therapy based on clinical suspicion and radiographic appearance. In patients with ICC, cross-sectional imaging with CT scan is usually sufficient. Tumors may be mass-like or may have cystic areas.

Surgery

Untreated, most patients with bile duct cancers die within a year of diagnosis.[80,81] Surgical excision is the treatment of choice, with no other

potentially curative therapy available. The immediate causes of death are most commonly hepatic failure or cholangitis related to tumor growth and inadequate drainage of the biliary tree.[82] Therefore, the goals of surgery are complete removal of tumor with R0 margins while leaving a sufficient liver remnant, and establishing adequate biliary drainage. Patients with ICC require additional consideration. Those patients with multifocal and especially bilobar intrahepatic tumors, even if technically resectable with negative margins and adequate remnant liver, should not be considered for resection. These patients have very poor prognosis indicating that bilobar hepatic spread represents hematogenous metastasis.[83] What remains controversial is whether peritumoral satellite lesions also represent metastatic disease. Because this is unknown and surgery is the only potentially curative therapy for these patients, satellite lesions are not currently considered an absolute contraindication to resection.

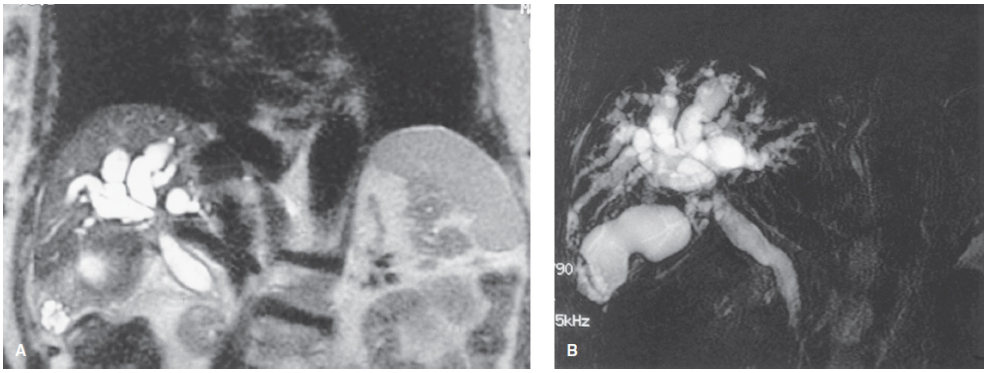

Figure 63.7 Coronal (**A**) magnetic resonance imaging and magnetic resonance cholangiopancreatography (**B**) in a patient with hilar cholangiocarcinoma, demonstrating dilated intrahepatic ducts narrowing at the area of obstruction.

Hilar cholangiocarcinoma is often unresectable due to local factors. These include invasion of the main portal vein or both the right and left portal veins and hepatic arteries and tumor extension into second-order biliary radicals of both right and left hepatic lobes. By contrast, tumors extending into second- or third-order biliary radicles on one side of the liver without vascular involvement can be resected for cure. It has become clear over the last three decades that curative treatment for patients with tumors of the hilum or those involving the upper half of the bile duct depends on aggressive excision that often requires a major liver resection. Until as recently as one decade ago,

treatment of hilar cholangiocarcinoma was associated with mortality as high as 30%.[84–88] Recently, major improvements in the safety of these operations have been demonstrated, and resection of hilar tumors now results in mortality of less than 10%, even when liver resections are required.[84,85,87,89]

Role of Staging Laparoscopy

Because of the potential morbidity of a laparotomy that has no therapeutic benefit, staging laparoscopy has been advocated to save patients from unnecessary laparotomy. In patients with hilar cholangiocarcinoma, up to 25% will benefit from staging laparoscopy because of detection of occult extrahepatic disease.[33,34] Laparoscopy is a very sensitive means to detect peritoneal metastases or additional intrahepatic disease through the use of laparoscopic ultrasound but is less sensitive in detecting nodal metastases or locally invasive tumors.

Partial Hepatectomy with or without Bile Duct Resection

The extent of hepatectomy required for resection of cholangiocarcinoma is dependent on the tumor location in relation to the portal inflow and venous outflow of the liver. Intraoperative ultrasound is a useful adjunct for assessment of tumor extent and for small satellite lesions that may not be apparent on cross-sectional imaging.

Small ICCs may be removed by segmentectomy or sectorectomy, but these tumors are often large and require extended right or left hepatectomy. For hilar and proximal hepatic duct lesions, complete resection usually requires combined biliary and hepatic resection with or without major vascular reconstruction. Additionally, caudate resection is often required because of direct extension into caudate biliary radicles or parenchyma.[73,88,90] Resection of the extrahepatic bile duct with Roux-en-Y hepaticojejunostomy to the remnant duct is required in these cases. Intraoperative assessment of the bile duct resection margin should be performed if additional duct can potentially be taken. If not, assessment on permanent sectioning is sufficient.

Lymphadenectomy

Regional lymphadenectomy is essential for accurate staging of cholangiocarcinoma, and may be important for locoregional disease control, but has historically been underperformed for intrahepatic and hilar tumors.[72,91] Recent data have shown that lymph node metastases are present in 30% to 40% of patients.[72,91–93] Regional lymph nodes include those along the porta hepatis, the hepatoduodenal ligament, the hepatic artery for essentially all patients. In addition, for those with primary tumors of the right hemiliver, retropancreatic nodes should be removed. For those with primary tumors of the left hemiliver, perigastric lesser curve nodes (levels 1, 3, and 5) should be removed.[94] A recent study utilizing the SEER database found that removal of at least six lymph nodes is recommended for accurate staging of ICC.[95]

Pancreaticoduodenectomy

For cholangiocarcinoma of the lower half of the extrahepatic bile duct, pancreaticoduodenectomy is requiring for complete tumor extirpation. The proximal bile duct margin should be assessed by frozen section to ensure tumor clearance. Regional lymphadenectomy is inherent in this procedure.

Liver Transplantation for Hilar CC and the Mayo Protocol

Orthotopic liver transplantation (OLT) was thought to hold promise for patients with hilar CC, because of the ability to achieve adequate margins by complete hepatectomy. Unfortunately, when used as a single treatment modality, results have been poor. Three- and 5-year survival rates have been reported at 25% to 30%.[96–98] Because of this poor outcome, the Mayo Clinic developed a protocol combining neoadjuvant therapy with liver transplant, based on a strategy initially developed by the University of Nebraska. This protocol uses high-dose neoadjuvant 5-fluorouracil and brachytherapy followed by liver transplantation.[99,100] Inclusion criteria include (i) locally advanced unresectable disease with either positive intraluminal brush cytology, positive intraluminal biopsy, or CA19-9 $\geq$100 in the setting of a radiographic malignant stricture; (ii) primary sclerosing cholangitis with resectable disease; and (iii) absence of medical contraindications for OLT. Since 2003, biliary aneuploidy as demonstrated by digital image analysis

(DIA) and fluorescent in situ hybridization have been considered equivalent to cytology.[101,102] Exclusion criteria include (i) extrahepatic disease including regional lymph node involvement; (ii) uncontrolled infection; (iii) prior attempt at resection; (iv) prior treatment with radiation or chemotherapy; and (v) previous malignancy within 5 years. In this protocol, patients receive external beam radiotherapy to a target dose of 4,500 cGy with concomitant fluorouracil (5-FU). Following this, transcatheter iridium-192 brachytherapy with a target dose of 2,000 to 3,000 cGy is administered. Thereafter, patients receive oral capecitabine as tolerated until transplantation. It is important that, prior to transplantation, patients undergo a staging laparotomy, at which time biopsy of perihilar lymph nodes as well as any lymph nodes or nodules suspicious for tumor is performed. Only patients with negative staging operations remain eligible for transplantation.[99]

The prolonged course of neoadjuvant therapy, staging laparotomy, and time on the OLT waiting list provides an opportunity to exclude patients demonstrating disease progression. This highly rigorous selection bias in favor of patients with biologically favorable disease is reflected in the early outcomes published from the Mayo group. In a recent review of 71 patients enrolled in this transplant protocol, only 38 underwent transplantation (38%). These patients were compared to 26 patients (of 54 explored, 48%) who underwent successful resection. When compared to those undergoing resection (some with node-positive disease), patients undergoing transplantation were younger ($p < 0.001$) and more likely to have inflammatory bowel disease ($p < 0.03$) and PSC ($p < 0.001$). It is important that only 58% of patients had histologically proven cancer. In these highly disparate groups, 5-year survival was 82% after transplantation (38 patients) compared to 21% after resection of 26 patients ($p = 0.022$).[103] There were also fewer recurrences in the transplant patients (13% vs. 27%), and recurrences became apparent later after transplantation than after resection (mean 40 months vs. 21 months). Direct comparisons are difficult with this study given the differences between groups. A recent meta-analysis of patients with unresectable hilar cholangiocarcinoma reported 5-year overall survival of 65% for those who underwent neoadjuvant therapy followed by transplantation, versus 32% for those who had transplantation alone.

At present, OLT cannot be considered a standard form of therapy for hilar cholangiocarcinoma for patients with resectable disease, but it does offer a potential option for patients with underlying PSC or those with unresectable tumors who fit the rigorous inclusion and exclusion criteria of these protocols.

RESULTS

Table 63.7 Results after Resection for Hilar Cholangiocarcinoma

Author	*N*	Percent Resected	Postoperative Mortality (%)	5-Year Survival (%)	Survival (Months)	
					Mean	Median
Cameron et al.[75]	96	55	2	8		18
Hadjis et al.[87]	131	21	7	12	25	
Altaee et al.[83]	70	21		19		12
Baer et al.[84]	48	44	4	23	34	
McMasters et al.[104]	91	44	0	26		22
Klempnauer et al.[105]	151		10	28		24
Nagino et al.[106]	173	80	10	26		
Nakeeb et al.[107]	72	57		34		
Jarnagin et al.[108]	225	71	10	27		35
Rea et al.[97]	46		9	26		28
Jang et al.[109]	48		0	48		
Konstadoulakis et al.[110]	73	81	7	35		
Yubin et al.[111]	115	100	2	22		40

Prognosis after Resection

Results of major studies on resection of hilar cholangiocarcinoma are summarized in **Table 63.7**. In patients amenable to curative resection, the median survival is 35 months with a 5-year survival rate of 10% to 30%.[78,86,87,96,100,112] Surgical resection provides both improved survival and improved quality of life. The greatest risk factors for recurrence include the presence of positive margins, and node-positive tumors.[113]

In patients with ICC, expected 3-year survival rates as high as 60% have been reported, with 5-year survival rates of 30% to 45%.[35,113,114] Patients with unresectable disease have a median survival of 12 months.[35,115] Thus,

completely resected ICC appears to have an improved prognosis over proximal (hilar) cholangiocarcinoma. Patients with cholangiocarcinomas arising in the distal bile duct have both an increased resectability rate and improved prognosis over those with hilar cholangiocarcinomas.[89] Patients with resectable distal bile duct cancer have a 5-year survival rate of 30% to 50%, with a decreased survival if nodes are involved with tumor.[116,117]

Unresectable Cholangiocarcinoma

6 For patients with unresectable hilar cholangiocarcinomas, biliary drainage is necessary.

Nonoperative palliative biliary decompression can be accomplished with percutaneous or endoscopic stenting, depending on the level of obstruction. Proximal lesions are usually approached percutaneously with placement of expandable stents or drainage catheters (**Fig. 63.8**). Internal stents result in fewer electrolyte abnormalities and improvement in patient comfort, although morbidity and mortality occurs in up to 30% of patients and stent occlusion is common.[118–120] There is a significant risk of cholangitis with external and internal drainage, occurring in more than 90% of patients with metallic expandable internal stents in one series.[119] Bleeding and bile leaks are also frequent complications. More recent techniques (e.g., photodynamic therapy) have been used to palliate patients with biliary obstruction and may hold some promise for the future.[121]

Palliative surgical bypass can also be performed, however is less often necessary with current availability of advanced endoscopic and percutaneous techniques. A partial excision of the left lateral segment and biliary-enteric anastomosis to the left hepatic duct (Longmire procedure) was used commonly in the past, but more recently surgical techniques have become less complicated and do not require hepatic parenchymal transection. One technique involves biliary decompression through the left duct, approached through the round ligament, a segment III bypass (**Fig. 63.9**). Opening the bridge of tissue just beneath the ligamentum teres allows access to the duct. In this position, a long anastomosis can be performed from the segment III duct to a jejunal limb because of the horizontal course of the duct in this location. Although less commonly used, the right hepatic duct can be

approached at the base of the gallbladder fossa. This is technically more difficult and results in a higher rate of late bypass failure.[122]

Because patients with unresectable disease have a relatively short median survival, those whose disease is clearly unresectable on preoperative imaging should undergo percutaneous internal or external drainage. In patients who undergo exploratory surgery and whose disease is found to be unresectable, surgical bypass offers fewer episodes of cholangitis, with an improved quality of life. In some series, surgical bypass for patients with unresectable disease is the only biliary drainage procedure ever required by the patient.

In patients with unresectable distal cholangiocarcinomas, palliation can be achieved with surgical bypass, percutaneous biliary drains, or ERCP-placed stents. The simplest and most effective way to relieve jaundice is usually with an ERCP stent. Although surgical bypass offers improved patency and fewer episodes of cholangitis, the morbidity of the procedure is not warranted in patients with these aggressive tumors.

Liver-directed therapies such as transarterial chemoembolization (TACE), transarterial radioembolization (TARE), and ablation are also potential treatment options for patients with ICC who are not candidates for resection. These therapies have not been evaluated in the format of a randomized prospective trial, but have shown promising results in both retrospective and early phase prospective studies (REFS).

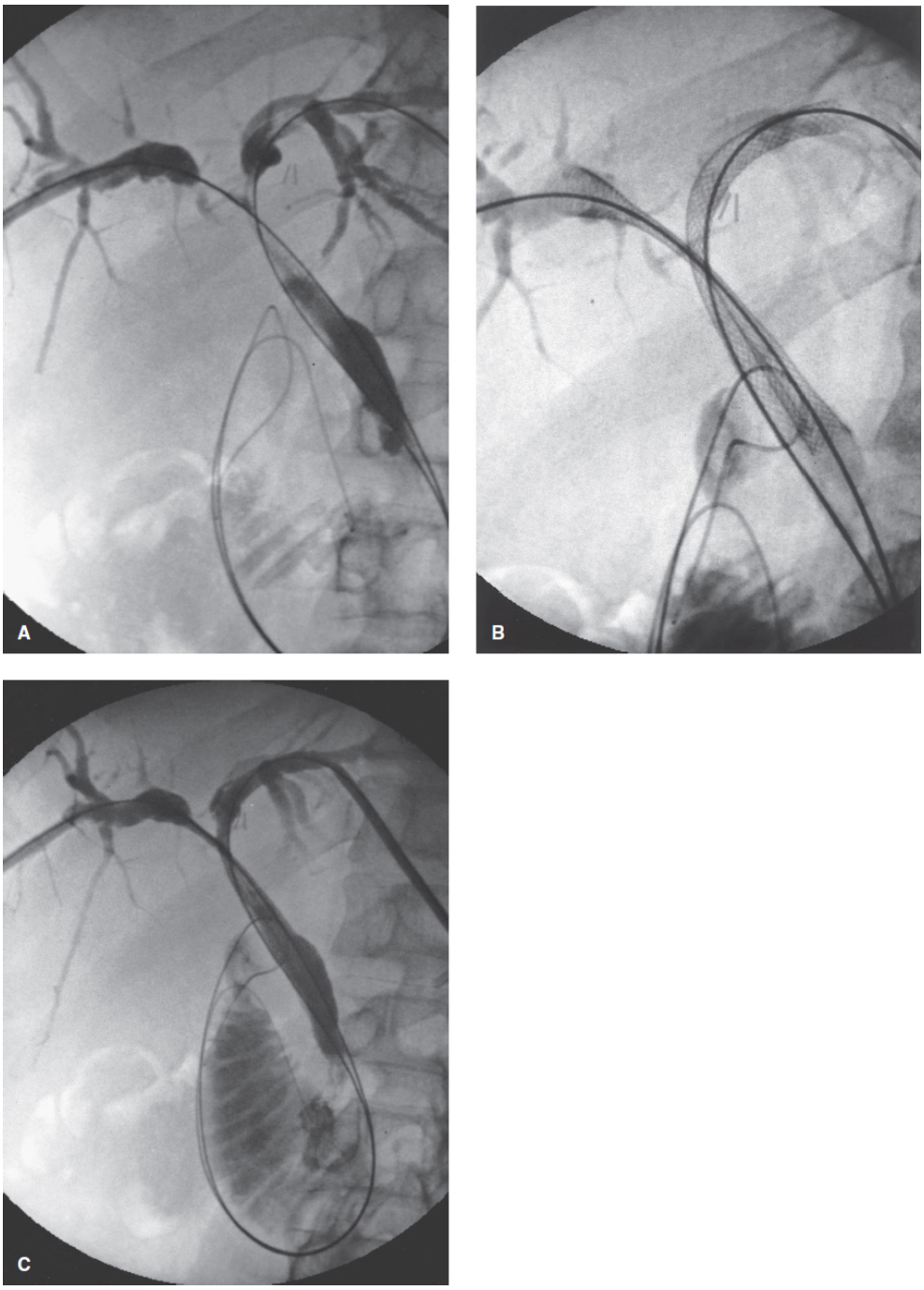

Figure 63.8 **A:** Percutaneous transhepatic cholangiogram in a patient with hilar cholangiocarcinoma, demonstrating biliary obstruction at the confluence. The patient has previously had placement of internal/external stents for biliary drainage. **B:** Film demonstrates appearance of wall stents after deployment into the left and right biliary ducts. **C:** After stenting, the cholangiogram demonstrates adequate biliary drainage, with contrast filling the duodenum.

Adjuvant Therapy

To date, no chemotherapeutic regimen has consistently shown activity against cholangiocarcinoma. Many of the issues that pertain to chemotherapy trials in gallbladder cancer are directly relevant to the interpretation of trials for cholangiocarcinomas. Studies performed to date have typically been small, single-institution trials, including patients with both gallbladder and bile duct cancers.[123]

Although 5-fluorouracil (5-FU)–based chemotherapy is often offered to patients with unresectable disease, the likelihood of response is less than 10%. Capecitabine as a single agent may have some modest activity in cholangiocarcinomas.[124] When capecitabine was used in combination with gemcitabine in a recent prospective study, overall survival was 14 months.[64] Gemcitabine and cisplatin combination therapy has also been tested in phase II studies of patients with advanced biliary tract carcinoma.[125,126] Results of these studies demonstrated response rates of 27% to 34.5%, and overall survival of 9.7 to 11 months. The use of mitomycin C and doxorubicin (Adriamycin), in combination with 5-FU, has resulted in combined response rates of less than 30%, with higher toxicity than 5-FU alone.[127]

With the exception of extrahepatic disease, there is no clear role for adjuvant chemotherapy in the treatment of cholangiocarcinoma. The previously mentioned phase II trial from 2015 showed a promising 2-year survival for patients with extrahepatic cholangiocarinoma treated with adjuvant capecitabine/gemcitabine and concurrent capecitabine and radiation therapy.[61] Aside from this study, however, previous data suggested no difference in overall survival (36% vs. 42%, $p = 0.6$) or loco regional recurrence (38% vs. 37%, $p = 0.13$) in patients who underwent R0 resection alone versus those with high loco regional recurrence risk who received adjuvant chemoradiation therapy.[128] Similar to the recommendations for gallbladder cancer, patients with extra-hepatic cholangiocarcinoma who undergo R0 or R1 resection should be considered for adjuvant capecitabine/gemcitabine and concurrent capecitabine and radiation therapy.

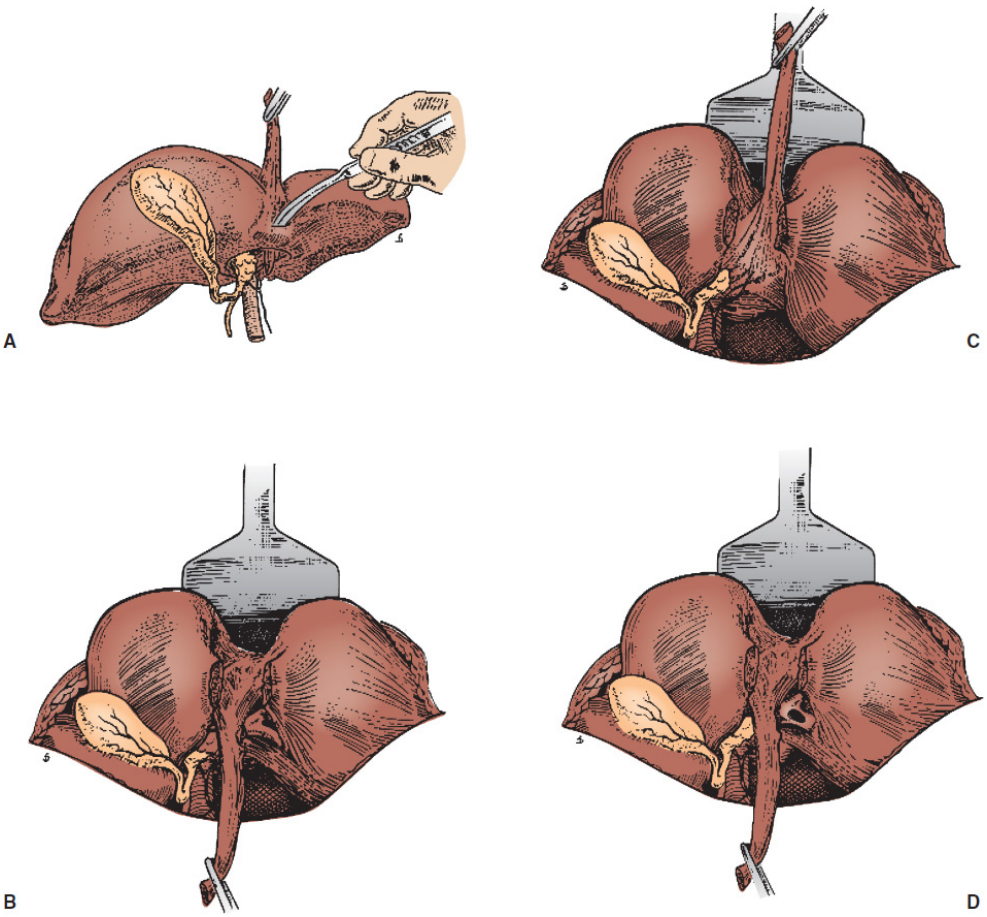

Figure 63.9 Surgical approach to segment III duct. **A:** The bridge of tissue present at the base of the liver is divided. **B:** The ligamentum teres is held superiorly to expose the tissue overlying the segment III duct. **C:** The segment III duct is exposed. **D:** The duct is opened in preparation for anastomosis with a Roux-en-Y jejunal limb. (Courtesy of Dr. L. H. Blumgart.)

In cases of unresectable cholangiocarcinoma, the use of external beam radiation therapy has been explored.[90,129–132] To date, no study has clearly demonstrated efficacy for this modality. Anecdotal reports of long-term survivors after external beam radiotherapy show that some individuals may benefit from such treatment, but this must be weighed against the potential complications (e.g., duodenal or bile duct stenosis and duodenitis). The most encouraging results involve use of intraoperative or interstitial radiation.[129,130,132,133] In patients whose disease is resected and have node- or margin-positive disease, systemic therapy with gemcitabine or 5-FU, or 5-FU–based chemoradiation, or enrollment in a clinical trial should be strongly encouraged.

Follow-up after Resection of Cholangiocarcinoma

Recurrence following resection of ICC is within the liver in 60% of patients. While data are lacking, there is some evidence to suggest that there is a role for reresection in highly selected patients. The most likely site of recurrence after resection of hilar cholangiocarcinoma is locally within the bile duct, regional lymph nodes, or liver. Therapy for recurrence is palliative. Surgical re-excision is usually impossible because of the challenging anatomic location and the radical procedures that are required for resection of the primary tumor. The main symptoms of recurrence that demand palliation are pruritus or cholangitis associated with jaundice. For biliary drainage to relieve jaundice or cholangitis, either surgical drainage or drainage by PTC can be effective. Endoscopic drainage has little role in the relief of jaundice in patients who have had Roux-en-Y biliary reconstruction. For limited recurrences, intraluminal brachytherapy or external beam radiotherapy may improve palliation and, potentially, survival.[134]

Routine follow-up consists of office visits every 3 months with physical examination and measurement of liver function tests. Although a rising alkaline phosphatase level is a reliable indicator of evolving biliary obstruction, patients recovering from liver resection and biliary obstruction can have persistent elevations of alkaline phosphatase. Up to 10% of patients with biliary surgical reconstruction, however, may develop a benign anastomotic stricture. Most patients with recurrence or a benign stricture will present with jaundice or cholangitis. Surveillance cross-sectional imaging is recommended every 3 to 6 months for the first 2 years following resection and should be individualized thereafter.

Issues for the Future

Further studies are needed to develop effective adjuvant, and potentially neoadjuvant, therapies for cholangiocarcinoma. Continued assessment of novel drugs and radiosensitizers, and biologic agents is warranted. A better understanding of the molecular pathogenesis and genetics of bile duct cancers

may lead to new therapeutic strategies and possibly preventive strategies for high-risk populations.

BENIGN GALLBLADDER NEOPLASMS

Incidence

Benign tumors of the biliary tract are rare, but have been reported more frequently as imaging modalities (e.g., ultrasound and CT scan) have come into widespread and frequent use. In patients undergoing cholecystectomy, the reported incidence of benign gallbladder tumors is less than 3%.

Pathology

Polyps and Pseudotumors

Benign gallbladder tumors are most frequently polyps or polypoid lesions. The incidence of polyps in asymptomatic patients is about 5%.[3] Cholesterol polyps (cholesterolosis), accounting for half of all gallbladder polypoid lesions, result from epithelium-covered, cholesterol-laden macrophages in the lamina propria.[135] These lesions are likely a result of an error in cholesterol metabolism. They extend from the mucosa on a narrow stalk, grossly appearing as yellow spots on the mucosal surface. Nearly all are multiple, and most are less than 10 mm in size.[135,136] When a polyp is pedunculated, it is benign in most cases; alternatively, sessile "polyps" are more often malignant (**Fig. 63.10**). Inflammatory polyps result from chronic inflammation and extend by a narrow vascularized stalk into the gallbladder lumen. None of these lesions are considered premalignant, although isolated cases of cholesterolosis associated with in situ carcinoma have been reported.[137]

Figure 63.10 T2-weighted magnetic resonance imaging scan showing a sessile polyp within the gallbladder (*arrow*) that was malignant on histologic examination.

Adenomas

Gallbladder adenomas are found infrequently. They may be tubular or papillary, both arising from the epithelial layer of the gallbladder. Multiple papillary adenomas, or papillomas, are called *papillomatosis*. A direct association between benign adenoma, adenoma containing carcinoma in situ, and invasive carcinoma has been demonstrated; thus these lesions are considered premalignant.[138] Malignant transformation, however, has only rarely been reported, primarily from large adenomas. In one series, all benign adenomas were less than 12 mm in diameter, whereas the adenomas with cancerous foci were greater than 12 mm.[137]

Adenomyomatosis

Adenomyomatosis of the gallbladder is characterized by localized or diffuse hyperplastic extensions of the mucosa into, and often beyond, a hypertrophied gallbladder muscular layer. Hyperplasia occurs at outpouchings of the

mucosa of the gallbladder through the wall (Rokitansky–Aschoff sinuses) and through the crypts of Luschka. This can result in focal thickening of the gallbladder wall, resembling gallbladder adenocarcinoma. The etiology is unknown. This lesion may be premalignant, because cases of adenocarcinoma arising in or near adenomyomatosis have been reported, but this relationship is unclear.[129,139,140]

Other Benign Gallbladder Tumors

Other benign lesions include tumors arising from the tissue of the gallbladder wall, such as leiomyomas, lipomas, hemangiomas, granular cell tumors, and heterotopic tissue, including gastric, pancreatic, or intestinal epithelium.

Clinical Findings

Patients with benign gallbladder tumors typically present with symptoms consistent with choledocholithiasis, including right upper quadrant pain, fatty food intolerance, and nausea. Many benign gallbladder lesions are also discovered incidentally after elective cholecystectomy. Therefore, symptoms caused by benign lesions are difficult to separate from those caused by gallstones. Most lesions, however, are asymptomatic and are discovered incidentally during imaging for other abdominal conditions.

Diagnosis

Diagnosis of benign gallbladder polyps is usually made when an ultrasound study is obtained to evaluate a patient for symptoms consistent with gallstones. On ultrasound, a filling defect that does not change with position is likely a polyp or carcinoma and not a gallstone. Cholesterol polyps are typically small, submucosal, multiple, and hyperechoic on ultrasound because of their high cholesterol content. Other than this typical appearance and the fact that malignant polyps are usually more than 1 cm in size, it is difficult to differentiate benign from malignant polyps.

Both intravenous contrast-enhanced and unenhanced CT may be important in distinguishing benign from malignant polyps. In a recent series examining 31 polypoid lesions of the gallbladder, contrast-enhanced CT detected all of

the lesions. Benign polyps were not visualized with unenhanced CT, unlike neoplastic tumors, thus improving the ability to distinguish these lesions when both enhanced and unenhanced CT scans were obtained.[9] Endoscopic ultrasound has also been used to image these lesions, and may be more accurate than transabdominal ultrasound in differentiating benign from malignant tumors.[22]

Treatment

Large polyps, greater than 10 mm, have the greatest malignant potential.[9,135,136] Without the evidence of invasion or metastatic disease, however, no radiologic test can reliably differentiate benign from malignant lesions. Therefore, if large (>1 cm) polyps are present, even in asymptomatic patients without stones, cholecystectomy is warranted.[141] Additionally, resection is recommended for smaller pedunculated lesions with evidence of a vascularized stalk. Small pedunculated lesions with the gross characteristics of a benign cholesterol polyp may be observed and resected only if symptomatic. Although these lesions have routinely been followed with ultrasound, a recent prospective study suggested that polyps smaller than 1 cm do not progress to carcinoma.[142] Cholecystectomy, however, is still considered the standard of care if there is any increase in size.

BENIGN BILE DUCT NEOPLASMS

Incidence

Benign bile duct tumors, at times clinically resembling hilar cholangiocarcinoma, are less common, occurring in less than 1% of patients.[4]

Pathology

Attesting to the rarity of these lesions, only two cases of benign extrahepatic bile duct disease occurred in 4,200 biliary tract operations in one institution.[143] The most common benign tumors of the extrahepatic biliary tree arise from the glandular epithelium lining the ducts; about two-thirds of benign tumors are polyps, adenomatous papilloma, or bile duct adenomas.

Most are found in the periampullary region, but they can be distributed throughout the entire biliary tree (**Fig. 63.11**). Multiple papillomas also have been reported throughout the intrahepatic and extrahepatic biliary tree, termed *multiple biliary papillomatosis.* Although local recurrence and progression to death from obstructive jaundice and cholangitis occur frequently in these rare cases, these tumors have little, if any, malignant potential. Other benign tumors (e.g., cystadenoma, granular cell myoblastoma, leiomyoma, heterotopic tissue) have also been reported.

One condition that deserves consideration is the case of "malignant masquerade," an inflammatory, fibrotic lesion clinically resembling hilar cholangiocarcinoma, but pathologically consisting only of extensive fibrosis and inflammatory cells without evidence of dysplasia or preneoplastic change.[144–146] In patients being considered for palliative treatment alone with presumed hilar cholangiocarcinoma, it is essential to obtain a tissue diagnosis. It is inappropriate to treat benign lesions by percutaneous stenting because of the excellent outcome after resection of these lesions.

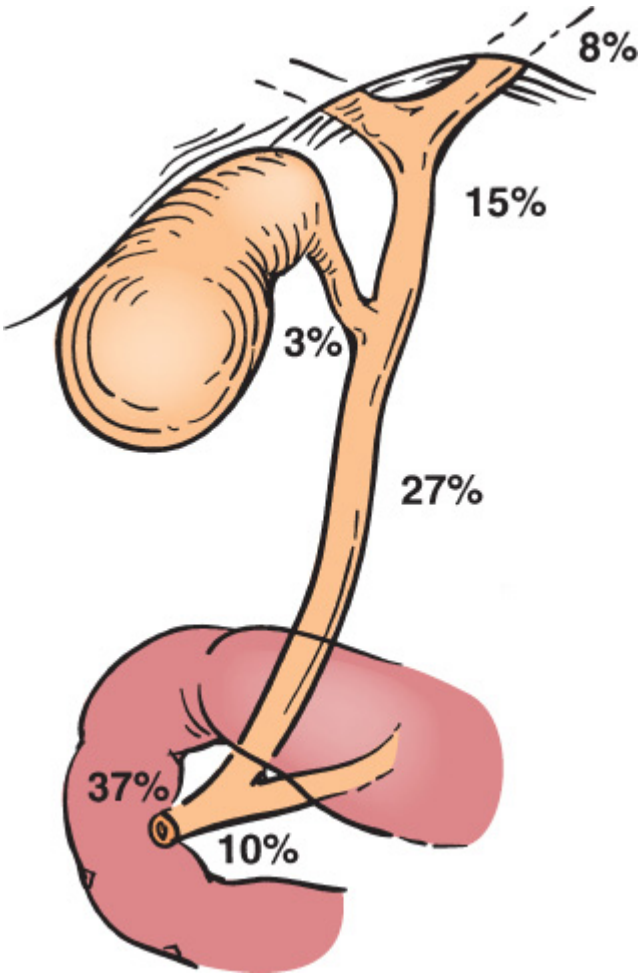

Figure 63.11 Distribution of papillomas and adenomas of the biliary tree. The ampulla and common bile duct are the most frequent sites.

Clinical Findings

Biliary obstruction, with resultant jaundice or cholangitis, is frequently the presenting symptom in patients with benign bile duct tumors. Symptoms may also include epigastric pain or nausea. Because these tumors are indolent, symptoms may be intermittent or gradually progressive.

Diagnosis

Because of the presence of jaundice, benign bile duct tumors are usually initially evaluated with ultrasound. Many patients then undergo ERCP or PTC and CT scan. A diagnosis of malignant masquerade should be suspected

in patients with mass lesions that resemble hilar cholangiocarcinomas, but without lobar atrophy or portal vein involvement.

Treatment

Resection and reconstruction are performed to relieve jaundice and cholangitis. The preferred reconstruction is a Roux-en-Y choledochojejunostomy to decrease the risk of postoperative biliary stricture or recurrent cholangitis.

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Section I: COLON AND RECTUM

64

Anatomy and Physiology of the Colon, Rectum, and Anus

Elise H. Lawson and Elizabeth C. Wick

Key Points

1. The mesorectum is invested by the fascia propria of the rectum.
2. The ileocolic branch of the superior mesenteric artery supplies the right colon and the proximal transverse colon.
3. The inferior mesenteric artery supplies the distal transverse colon, sigmoid colon, and rectum.
4. The inguinal lymph nodes drain the lymphatics from the anal canal below the dentate line.
5. The colon has 10^{13} bacteria, which promote mucosal immunity, help digest complex nutrients, and protect against pathogenic organisms.
6. Alterations in the colonic flora have been associated with inflammatory bowel disease and colorectal cancer.

INTRODUCTION

While the complex coordination of stool through the colon, rectum, and anus is the main function of the colon, it also plays a role in the complex digestion and absorption of carbohydrate and protein residue, creates a balanced environment for bacteria, and lubricates stool for transit. Understanding the anatomy and physiology of the colon, rectum, and anus is important to treating the pathology associated with it.

EMBRYOLOGY

Knowledge of embryologic origins is helpful for understanding gastrointestinal function as well as pathophysiology. In addition, it is useful to remember when mobilizing the colon in order to identify appropriate planes of dissection and prevent injury to retroperitoneal structures. The primitive gut is derived from endoderm and is divided into three segments (foregut, midgut, and hindgut) by the third week of gestation. The small intestine distal to the ampulla of Vater and the colon proximal to the splenic flexure are formed from the midgut, while the remaining colon (distal to the splenic flexure), rectum, and anal canal (proximal to the dentate line) are formed from the hindgut. This has implications for arterial blood supply, as structures formed by the midgut are supplied by the superior mesenteric artery, while structures formed by the hindgut are supplied by the inferior mesenteric artery.

The midgut undergoes a three-stage process of rotation and fixation starting in the sixth week of gestation. In the first stage, the midgut elongates over the superior mesenteric artery, herniates out of the abdominal cavity through the umbilical cord, and then rotates 90 degrees in a counterclockwise direction. In the second stage, which starts in the tenth week of gestation, the midgut returns to the abdominal cavity while continuing to rotate an additional 180 degrees counterclockwise around the superior mesenteric artery. This results in the colon lying anterior to the duodenum. In the third stage, the cecum migrates inferiorly to the right lower quadrant, and then fixation of the ascending and descending colon begins. Major anomalies of rotation typically occur during the second stage, and include nonrotation, malrotation, reversed rotation, omphalocele, and internal hernia.

The terminal end of the hindgut is termed the cloaca. During development, the intestinal and urogenital tracts are joined at the cloaca until the urorectal septum migrates caudally, dividing the cloaca into the urogenital plate anteriorly and the anal plate posteriorly. The dentate line represents the fusion plane of the endodermal and ectodermal tubes, with the anal transition zone referring to the cloacal part of the anal canal which includes both endodermal and ectodermal components.

GROSS ANATOMY

The colon is a tubular organ measuring on average 150 cm, though overall length is highly variable. Typically, the colonic diameter decreases over its course, with the cecum measuring about 7.5 to 8.5 cm and the distal sigmoid colon about 2.5 cm. As described above, the ascending and descending colon are fixed to the lateral peritoneal wall, with the posterior aspects fused to the retroperitoneum. In contrast, the transverse and sigmoid colon are intraperitoneal strictures that are fixated only at their proximal and distal aspects.

The colon is distinguished from the rest of the gastrointestinal tract by three unique anatomic features: taeniae coli, haustra, and appendices epiploicae (**Fig. 64.1**). The three taeniae coli are continuous condensations of the outer longitudinal muscle layer of the colon and are named according to their attachments: taenia mesocolica (posteromedial, attached to the mesocolon), taenia omentalis (posterolateral, attached to the greater omentum), taenia libera (anterior, no attachments). The three taeniae originate at the base of the appendix, course along the length of the colon, and then converge at the rectosigmoid junction, marking the anatomic beginning of the rectum. They are one-sixth shorter than the rest of the bowel wall, resulting in outpouchings between the taenia called sacculations or haustra, which are separated by the plicae semilunares. Finally, the appendices epiploicae are antimesenteric fat appendages that protrude from the colonic serosa and vary in size.

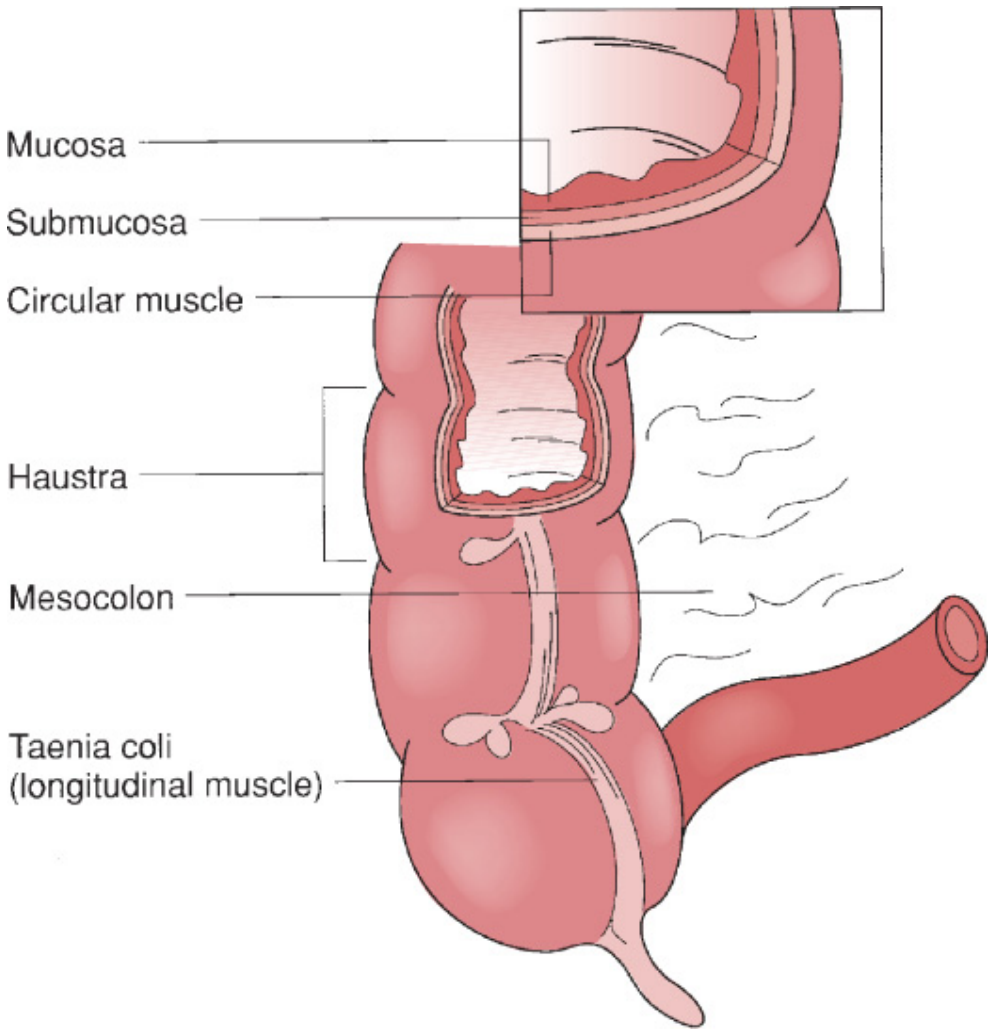

Figure 64.1 Layers of the colonic wall.

The colon begins in the right lower quadrant with the cecum. The cecum extends approximately 6 to 8 cm below the ileocecal valve, which is located at posteromedial aspect of the cecum (**Fig. 64.2**). The ileocecal valve is formed by angulation between the ileum and cecum via the superior and inferior ileocecal ligaments and prevents reflux of stool back into the ileum.[2] The cecum is the widest portion of the colon, has the thinnest wall, and is entirely enveloped by peritoneum.

The origin of the appendix can be identified by following the converging taeniae at the most proximal portion of the cecum. In the vast majority of people (85% to 95%), the appendix lies posterior to the cecum, lateral and in line to the terminal ileum. Other variants in position include retrocecal (toward the psoas muscle), pelvic, and retroileal.[3] Visualization and

documentation of the appendiceal orifice and ileocecal valve is important for ensuring complete colonic examination during colonoscopy.

From the cecum, the right colon ascends approximately 15 cm to the hepatic flexure, which is anterior to the inferior pole of the right kidney and overlies the second portion of the duodenum. When the right colon and mesentery are mobilized during a colectomy, care must be taken to visualize and avoid injury to the underlying duodenum and right ureter. Only the anterior surface of the right colon is invested with peritoneum; laterally, the white line of Toldt marks the extent of the peritoneal covering and serves as an important landmark during surgical mobilization of the colon.

The transverse colon stretches from the hepatic flexure to the splenic flexure and is the longest segment of colon (between 30 and 60 cm). The transverse colon is suspended by the transverse mesocolon and is completely intraperitoneal. It is the most mobile portion of the colon and may descend to the level of the iliac crests or deep into the pelvis. The greater omentum descends from the greater curve of the stomach in front of the transverse colon and then ascends to attach to the transverse colon on its anterosuperior edge. To mobilize the transverse colon or enter the lesser sac, the fusion plane of the omentum to the transverse colon must be dissected.

The splenic flexure is situated high in the left upper quadrant, more cephalad than the hepatic flexure, and abuts the lower pole of the spleen. There are attachments from the colon to the diaphragm at the level of the 10th and 11th ribs and spleen (phrenocolic and splenocolic ligaments), and these must be carefully divided during mobilization of the flexure to avoid splenic injury.

The descending colon is approximately 25 cm long and courses from the splenic flexure to its junction with the sigmoid colon at the pelvic brim. It lies anterior to the left kidney and, like the right colon, the anterior, lateral, and medial portions of the descending colon are covered by peritoneum.

The sigmoid colon extends from the pelvic brim to the sacral promontory, where it continues as the rectum and generally measures 15 to 50 cm in length. It is completely invested by peritoneum. The sigmoid colon is extremely mobile and has a generous mesentery that extends along the pelvic brim from the iliac fossa across the sacroiliac joint to the second or third sacral segment. Because of its mobile mesentery, the sigmoid colon can twist, forming a volvulus which causes obstruction. The left ureter runs in the

intersigmoid fossa, which is at the base of the mesosigmoid. When a high ligation of the inferior mesenteric artery is performed during a cancer operation or the sigmoid colon is being mobilized along the white line of Toldt, the left ureter should be identified to avoid inadvertent injury. Preoperative placement of urinary stents can be useful for locating the ureter intraoperatively in complex, reoperative pelvic surgery.

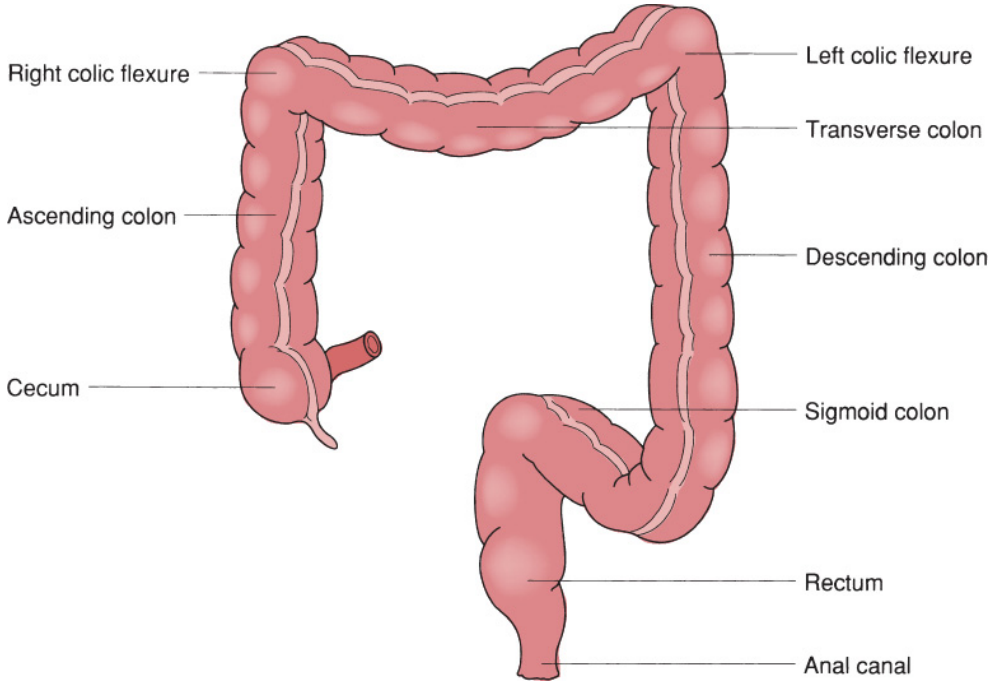

Figure 64.2 General anatomic components of the colon.

At the sacral promontory, the colon becomes the rectum. The rectosigmoid junction is marked by the convergence of the colonic taenia. The outer layer of the rectal wall is composed of the longitudinal muscle, where the three teniae splay. The rectum measures 12 to 15 cm in length. It proceeds posterior and caudal along the curvature of the sacrum and coccyx, passing through the levator ani muscles, at which point it turns abruptly caudal and posteriorly at the anorectal ring, becoming the anal canal. Anterior to the rectum are the uterine cervix and posterior vaginal wall in women, and the bladder and prostate in men. Posteriorly, the rectum occupies the sacral concavity where the median sacral vessels, presacral veins, and sacral nerves run, all of which are invested in the presacral fascia. The rectum is marked by three curves. The upper and lower curves are convex and to the

right, while the middle is convex and to the left. Within the lumen, these correspond to the valves of Houston, which separate the lower third, middle third, and upper third of the rectum—important landmarks when the location of a rectal abnormality is established endoscopically (the lower rectal valve is at 7 to 8 cm from the anal verge, middle rectal valve at 9 to 11 cm, and upper rectal valve at 12 to 13 cm).[4] The valves do not contain all layers of the bowel wall and thus biopsy at this location carries minimal risk of perforation. The middle valve of Houston is the internal landmark corresponding to the anterior peritoneal reflection. The anterior and lateral surfaces of the upper third of the rectum are intraperitoneal, whereas only the anterior surface of the middle third of the rectum is intraperitoneal in location. The lower third of the rectum is entirely extraperitoneal. The mesorectum is 1 the term used to describe the areolar tissue surrounding the rectum that contains nerves, lymphatics, and terminal branches of the superior hemorrhoidal branch of the inferior mesenteric artery. Although it invests the rectum circumferentially, the mesorectum is most prominent posterior to the rectum. It is invested by the fascia propria of the rectum, a continuation of the parietal endopelvic fascia (**Fig. 64.3**). The fascia propria (investing fascia) includes the distal two-thirds of the posterior rectum and the distal one-third of the anterior rectum, where it is no longer intraperitoneal. A total mesorectal excision entails removal of the entire rectum without violating the fascia propria of the rectum. This is accomplished by mobilizing the rectum using the plane between the fascia propria of the rectum and the presacral fascia. Anterior to the investing fascia (fascia propria) is a delicate layer of connective tissue known as Denonvilliers fascia, which separates the rectum from its anterior structures. Waldeyer fascia (rectosacral fascia) is the presacral fascia that is an extension of the parietal pelvic fascia from the periosteum of sacral segment four to the posterior wall of the rectum. It contains branches of the sacral splanchnic nerves. Below Waldeyer fascia is the supralevator or retrorectal space.

The surgical anal canal begins at the anorectal ring or levator ani muscles and extends to the anal verge. It measures 2 to 4 cm and is usually longer in men than in women. The internal anal sphincter (continuation of the circular smooth muscle of the rectum) and the external anal sphincter (continuation of the puborectalis muscle) encircle the anal canal and control fecal continence.

The internal anal sphincter relies on autonomic innervation, while the external anal sphincter uses somatic innervation. The median length and thickness of the female anterior external sphincter are 11 and 13 mm and thus a small tear sustained during vaginal delivery may cause fecal incontinence.[5] There are three layers of the external sphincter—subcutaneous (traversed by the conjoined longitudinal muscle with some fiber attachments to the skin), superficial (connective tissue attaches posteriorly, forming the anococcygeal ligament), and deep (continues with the puborectalis muscle). Between the internal and external anal sphincters, the longitudinal muscle of the rectum joins fibers of the levator ani and puborectalis muscles to form the conjoined longitudinal muscle.

The dentate line marks the transition between the columnar epithelium of the intestine and the squamous epithelium of the anal canal. The transition between these two epithelia is called the anal transitional zone. The Columns of Morgagni are the 6 to 14 longitudinal folds located at the dentate line. Small pockets between these columns called anal crypts contain glands, which may become obstructed with foreign material to cause an infection. Below the dentate line is the anoderm, which extends to the anal verge and does not contain accessory skin structures, such as hair, sebaceous and sweat glands. The autonomic nervous system innervates proximal to the dentate line and the somatic nervous system supplies the anoderm and distally.

Pelvic Floor

The perineal body is the tendinous insertion of the external anal sphincter, bulbocavernosus, and superficial and deep transverse perineal muscles. It supports the perineum and separates the vagina from the anus. Three striated muscles that attach to the pubic bone make up the pelvic floor or levator ani muscles: iliococcygeus, pubococcygeus, and puborectalis. The pelvic floor muscles are supplied by branches from the third sacral nerve, while the external anal sphincter is supplied by nerve fibers traveling with the pudendal nerve on the levator's undersurface.

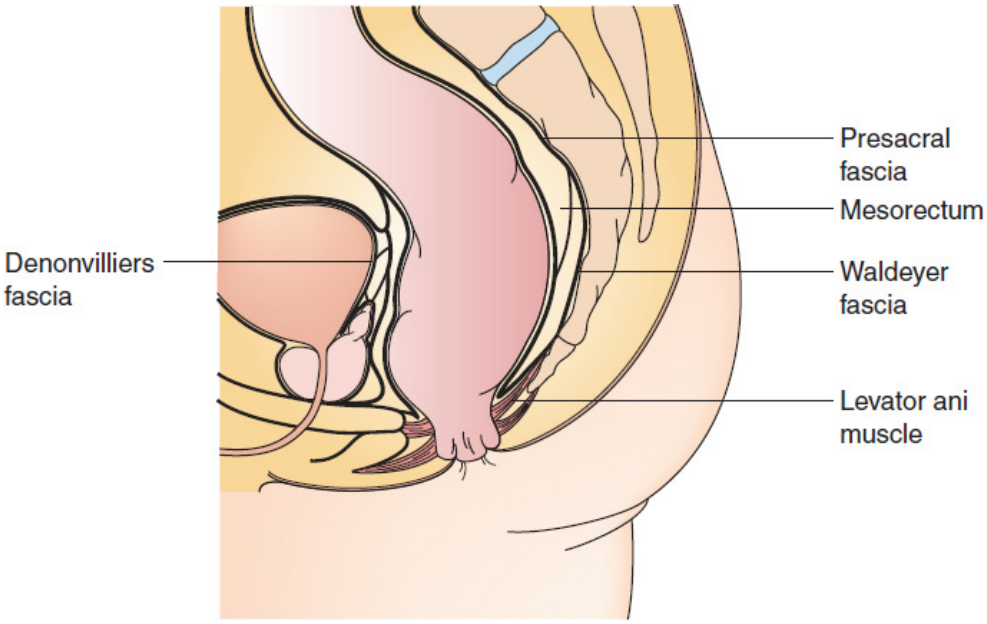

Figure 64.3 Fascial relationships of the pelvis.

The puborectalis originates from the back of the symphysis pubis and forms a U-shaped sling as it joins the opposite muscle posteriorly. The iliococcygeus muscle arises from the ischial spine and posterior part of the obturator fascia and travels inferiorly, posteriorly, and medially to insert into the last two segments for the sacrum and coccyx. The pubococcygeus muscle arises from the anterior half of the obturator fascia and the posterior pubis. Its fibers are directed backward, downward, and medially, where they decussate with fibers of the opposite side. The decussation is called the anococcygeal raphe.

Anorectal Spaces

The perianal space surrounds the anal canal superficially and contains the external hemorrhoidal plexus. The ischioanal space extends laterally and goes superiorly to the levator ani from the skin on the perineum. The levator ani and external sphincter muscles form the medial boundary, while the lateral wall is formed by the obturator fascia. The superficial postanal space connects the perianal spaces with each other posteriorly below the anococcygeal ligament, while the deep postanal space lies above the anococcygeal ligament. The ischioanal and perianal spaces make the ischioanal fossa. The deep postanal and ischiorectal spaces form a horseshoe

configuration that may be involved in a horseshoe abscess. Below the perianal space between the sphincter muscles is the intersphincteric space. The submucosal space contains the internal hemorrhoidal plexus and lies between the internal anal sphincter and the mucosa distal to the dentate line. Proximally, it becomes the submucosa of the rectum. Above the levator complex is the supralevator space, which extends superiorly to the peritoneum at the rectosacral fascia. The retrorectal space extends above the rectosacral fascia and lies between the upper two-thirds of the rectum and sacrum.

Arterial Blood Supply

The arterial blood supply to the colon, rectum, and anus is highly variable. The superior mesenteric artery typically arises from the aorta, runs posterior to the pancreas, and passes anterior to the third portion of the duodenum (**Fig. 64.4**). In addition to supplying the small bowel 2 through jejunal and ileal branches, the superior mesenteric artery gives rise to the ileocolic, right colic, and middle colic branches that supply the cecum, ascending colon, and proximal transverse colon. The right colic arterial anatomy is particularly variable and can be absent or arise from the ileocolic or the superior mesenteric artery. The middle colic artery has a right branch that supplies the hepatic flexure and the right portion of the transverse colon, while the left branch supplies the left 3 portion of the transverse colon. The inferior mesenteric artery arises from the anterior surface of the aorta, typically 3 to 4 cm above the aortic bifurcation, and supplies the distal transverse colon, descending colon, sigmoid colon, and upper rectum. The inferior mesenteric artery gives rise to the left colic artery and sigmoidal branches, then continues in the sigmoid mesentery, and after crossing the left iliac vessels, is renamed the superior rectal/hemorrhoidal artery. The inferior mesenteric artery may also function as an important collateral vessel to the lower extremities during instances of distal aortic occlusion. The superior hemorrhoidal artery descends behind the rectum and splits into right and left branches in the mesorectum. It is the main blood supply of the rectum. The middle and inferior rectal/hemorrhoidal arteries arise from either the internal pudendal arteries or the hypogastric arteries and supply the distal two-thirds

of the rectum. The presence of the middle rectal artery, in particular, can be variable.

Venous Drainage

The veins that drain the large intestine bear the same terminology and follow a course similar to that of their corresponding arteries (**Fig. 64.5**). The veins from the right colon and transverse colon, along with the veins draining the small intestine, drain into the superior mesenteric vein. The superior mesenteric vein runs slightly anterior to and to the right of the superior mesenteric artery. The superior mesenteric vein courses beneath the neck of the pancreas, where it joins with the splenic vein to form the portal vein. The inferior mesenteric vein is a continuation of the superior rectal vein and drains blood from the left colon, sigmoid colon, rectum, and superior anal canal. The inferior mesenteric vein follows a course of its own, starting at the left colic artery, and ascends over the psoas muscle in a retroperitoneal plane. The vein courses under the body of the pancreas to drain into the splenic vein. During an anterior resection of the rectum, division of the inferior mesenteric vein at the inferior border of the pancreas can provide additional mobility of the left colon to facilitate a coloanal anastomosis. The superior hemorrhoidal (rectal) veins drain blood from the rectum and upper part of the anal canal, where the internal hemorrhoidal plexus is situated, into the portal system via the inferior mesenteric vein. The middle hemorrhoidal (rectal) veins drain the lower part of the rectum and upper part of the anal canal into the systemic circulation via the internal iliac veins. The inferior hemorrhoidal (rectal) veins drain blood from the lower rectum and anal canal, where the external hemorrhoidal plexus is located, via the internal pudendal veins into the systemic venous circulation via the internal iliac veins. In the setting of portal hypertension, the superior, middle, and inferior hemorrhoidal veins interact to shunt venous blood from the portal system into the systemic circulation.

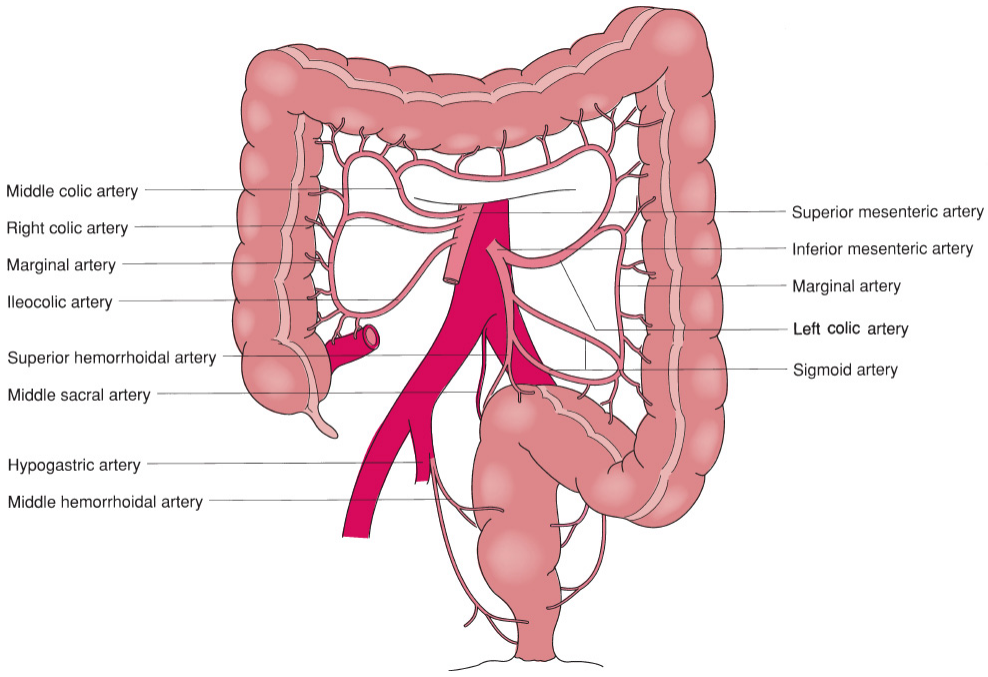

Figure 64.4 Arterial blood supply of the colon.

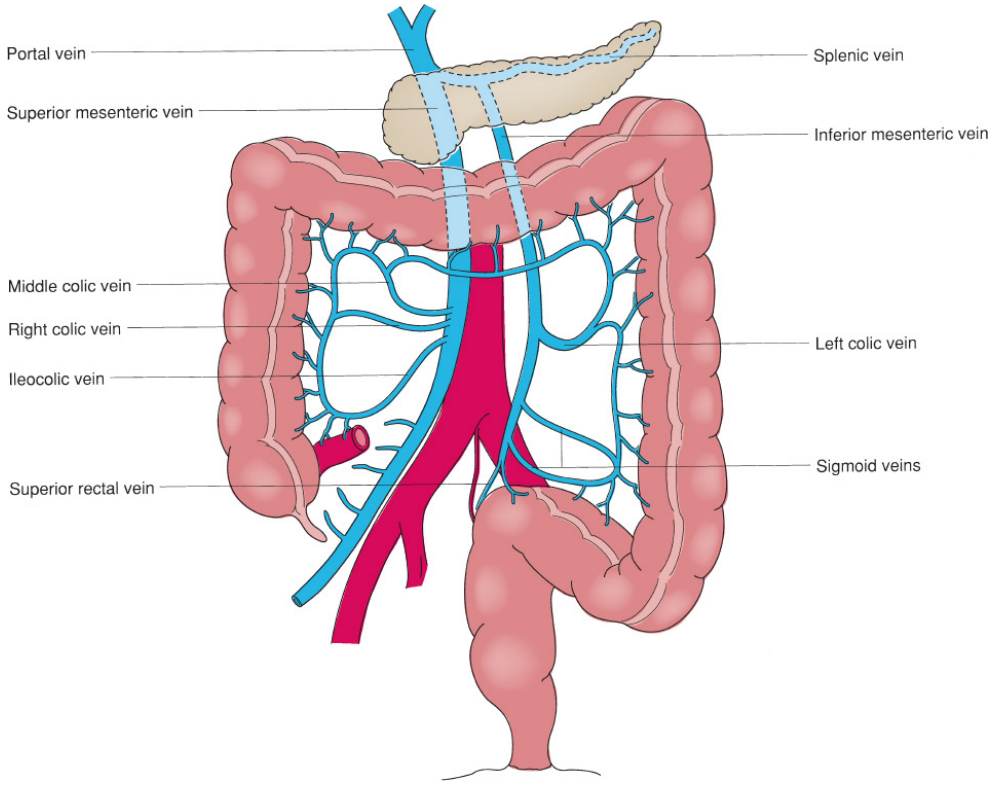

Figure 64.5 Venous drainage of the colon by the portal vein.

Lymphatic Drainage

4 Lymphatic drainage generally follows the arterial blood supply of the colon and rectum. As such, performing a high ligation of the feeding artery during oncologic segmental colon resection should ensure adequate lymph node harvest. In the anal canal, lesions above the dentate line drain into the inferior mesenteric lymph nodes while lesions below the dentate line drain into both the internal iliac lymph nodes and the inferior mesenteric lymph nodes.

Neural Components

The colon possesses extrinsic and intrinsic (enteric) neuronal systems. The extrinsic system consists of sympathetic and parasympathetic nerves that inhibit or stimulate colonic peristalsis, respectively. The sympathetic innervation to the right colon originates from the lower thoracic segments of the spinal cord and travels in the thoracic splanchnic nerves to the celiac and superior mesenteric plexuses. Postganglionic fibers emerge from here and course along the superior mesenteric artery and its branches to the right side of the colon. The parasympathetic nerves originate from the right vagus nerve and travel along with the sympathetic nerves to the right side of the colon. The left side of the colon and the rectum receive sympathetic fibers that arise from L1 through L3 segments of the spinal cord. This passes through the ganglionated sympathetic chains and leaves as a lumbar sympathetic nerve to join the preaortic plexus. It extends along the inferior mesenteric artery as the mesenteric plexus and then becomes the presacral nerve or superior hypogastric plexus. These hypogastric nerves are identified at the sacral promontory 1 cm lateral to the midline. The key zones of sympathetic nerve damage are during ligation of the inferior mesenteric artery and during initial posterior rectal mobilization adjacent to the hypogastric nerves. The parasympathetic supply to the left side of the colon and the rectum comes from S2 through S4 spinal cord segments. The sacral nerve fibers become the nervi erigentes, which join the pelvic plexus at the pelvic side walls. To prevent injury during full mobilization of the rectum, the lateral ligament should be cut close to the rectal side wall. Both the sympathetic and parasympathetic nervous systems play a role in erection, in that damage to

the parasympathetics can lead to erectile dysfunction, while retrograde ejaculation can occur with damage to sympathetic nerve injury.

The intrinsic, or enteric, nervous system consists of two groups of plexuses that are identified by their location within the colon wall. This system can function independently of the central nervous system and controls motility as well as exocrine and endocrine functions of the gut, and is involved in intestinal immune regulation and inflammatory responses. The Meissner plexus is located in the submucosa between the muscularis mucosae and the circular muscle of the muscularis propria and is important in secretory control. The myenteric plexus, also known as the *Auerbach plexus,* is located between the inner circular muscle and outer longitudinal muscle layers of the colon and primarily controls intestinal motility.[4]

The internal anal sphincter is supplied by the sympathetic and parasympathetic nerves that supply the lower rectum. The parasympathetic nerves are inhibitory. The external sphincter is supplied by the inferior rectal branch of the internal pudendal nerve and the perineal branch of S4. Sensation of the anal canal is from the inferior rectal nerve, which is a branch of the pudendal nerve.

PHYSIOLOGY

Nutrient digestion and absorption primarily occurs in the small bowel. The primary function of the colon is to absorb water, electrolytes (sodium and chloride), undigested starches and bile salts. The physiologic control of colonic water and electrolyte transport requires careful integration of neural, endocrine, and paracrine components. Although colonic epithelium does not actively absorb glucose or amino acids as the small-intestinal epithelium does, the colon does absorb short-chain fatty acids and vitamins that are produced by bacterial breakdown of nonabsorbed carbohydrates and amino acids. These short-chain fatty acids, which include acetate, butyrate, and propionate, are absorbed in a concentration-dependent fashion. They are a major energy substrate for colonic epithelial cells and represent the major fecal anions.[6]

Approximately 1,500 mL of ileal effluent reaches the cecum in a 24-hour period, 90% of which is reabsorbed in the colon. The colon has a

tremendous capacity that allows it to absorb as much as 5 to 6 L of water within a 24-hour period. When colonic capacity is exceeded, diarrhea results.[7] Normally formed feces consists of 70% water and 30% solid material. Almost half of the solid material is made up of bacteria and the other half is composed of undigested food material and desquamated epithelium. Water absorption in the colon is a passive process that depends primarily on the osmotic gradient established by the active transport of sodium across the colonic epithelium. The composition of ileal effluent and luminal flow rates also plays an important role in water absorption. Upsetting the balance of these three factors results in diarrhea. The absorptive capacity is not the same throughout each segment of the colon. Salt and water absorption is greatest in the right colon. Patients undergoing a right hemicolectomy should therefore be counseled preoperatively that they may experience loose bowel movements in the early postoperative period. Patients should also be reassured that this will resolve with time as the remaining colon adapts.

Colonic Flora

The bacterial flora of the colon is established soon after birth and is largely dependent on dietary and environmental factors. 5 The colon is populated by approximately 10^{13} commensal bacteria.[10] The vast majority of the normal colonic flora consists of anaerobic bacteria, with *Bacteroides* species being most prevalent, particularly *Bacteroides fragilis*.[11] Aerobic colonic bacteria are mainly coliforms and enterococci, with *Escherichia coli* being the most predominant coliform. The colonic flora is important for (a) digestion and absorption of complex macromolecules, (b) protecting the colon against invasion by noncommensal bacteria, and (c) development of mucosal immunity. Fermentation of carbohydrates generates short-chain fatty acids, including acetic acid, propionic acid, and butyrate, which is the primary nutrient for the colonic mucosa. Colonic bacteria also produce certain vitamins, such as vitamins K and B_{12}, which are absorbed by the host. The enterohepatic circulation of bilirubin and bile acids depends on bacterial enzymes produced by fecal flora. The degradation of bile pigments by colonic bacteria gives stool its characteristic brown color. Colonic bacteria

also play an important role in preventing infection by controlling the growth of potentially pathogenic bacteria such as *Clostridium difficile*.

Host and colonic flora have a mutualistic relationship; however, disturbances of this coexistence can lead to human disease.[12] [6] Changes in diet and use of antibiotics can dramatically alter the microbiome. Dysregulation of the flora has been implicated in the pathogenesis of inflammatory bowel disease, obesity and, to a lesser extent, colorectal cancer. Increasingly, dysregulation has also been linked to nongastrointestinal diseases including autism and other neurologic conditions. In animal studies, mice with certain immune deficiencies that make them prone to colitis fail to develop colitis when raised under germ-free conditions. Analysis of the microbiota of patients with inflammatory bowel disease revealed markedly different flora compositions in ulcerative colitis, Crohn disease, and healthy control patients. Similarly, certain genetically altered mice with a propensity to develop colorectal cancer fail to develop tumors in germ-free conditions. Although studies of human flora and colorectal cancer are limited, preliminary studies have raised interest in modulating the colonic flora as a way to treat and/or prevent colitis and other diseases of the colon.

Colonic Motility

Motor activity varies greatly throughout the colon. There are two patterns of colonic motility: segmental contractions, which are single or clustered contractions, and propagated activity, which is either high-amplitude (>100 mm Hg) propagated contractions (HAPCs) or low-amplitude (<60 mm Hg) propagated contractions (LAPCs). *Segmental contractions* are intermittent contractions of the longitudinal and circular muscles that result in the segmented appearance of the colon.[13] These contractions propel luminal contents in a back-and-forth pattern over short distances, slowing aboral transit and allowing for water reabsorption.[14] *Propagated activity* consists of strong, propulsive contractions of the smooth muscle that involve a long segment of colon.[15] The LAPCs move luminal contents forward at a rate of 0.5 to 1.0 cm/s and typically last for 20 to 30 seconds.[13] HAPCs occur three to four times per day, primarily after awakening, exercise, and after meals.

The orderly progression of colonic luminal contents from cecum to anus requires the coordination of smooth muscle contractions. Calcium-dependent

cyclic depolarization and repolarization of the colonic smooth muscle cell membrane generates a basic electrical pattern of slow-wave activity. This activity allows each smooth muscle cell to control its own contraction and to couple with adjacent smooth muscle cells.[16] The extrinsic (autonomic) and intrinsic (enteric) neuronal systems also interact to influence colonic motility.

Defecation

When fecal matter enters the rectum, the internal anal sphincter relaxes (rectoanal inhibitory reflex, or RAIR), while the external anal sphincter contracts to maintain continence. Distention of the rectum in this setting is the primary stimulus for defecation to begin. At this point, the urge to defecate may be suppressed by conscious contraction of the external anal sphincter. Receptive relaxation of the rectal ampulla accommodates the fecal mass and the urge to defecate passes unless the volume of feces is extremely large or the sphincter mechanism is impaired. If the subject voluntarily accedes to the urge to defecate, a Valsalva maneuver occurs, which increases the intra-abdominal pressure to overcome the resistance of the external anal sphincter. Relaxation of the pelvic muscles causes the pelvic floor to descend and the anorectal angle to straighten. Conscious inhibition of the external anal sphincter then allows passage of the feces. On completion, the pelvic floor returns to its resting position and the anal sphincter muscles return to their resting activity, closing the anal canal. Under normal circumstances, this process occurs once every 24 hours; however, the interval between bowel movements may vary between 8 and 12 hours and 2 to 3 days in normal subjects.

Anal Continence

There are varying degrees of anal continence, with a spectrum from complete control to complete lack of control. Maintaining continence is complex, as both voluntary and involuntary mechanisms play a role in anal continence. The most important mechanisms involve the internal anal sphincter, which contributes 52% to 85% of the pressure generated to maintain continence.[17,18] The remaining anal basal pressure is comprised of the external anal sphincter (30%) and the hemorrhoidal cushions (15%). The internal sphincter is

supplied by dual extrinsic innervation: sympathetic outflow (S5) via the hypogastric nerve provides motor supply and parasympathetic outflow (S1–S3) provides inhibition. The external sphincter nerve supply is dependent on the pudendal nerve (S2–S4) and maintains tonic activity at rest. When stool enters the rectum, the contents of the rectum are sampled by sensors in the anal canal to determine whether the contents are solid, liquid, or gas. By discriminating between the consistency of the stool, the pelvic floor and sphincter muscles are able to coordinate a complex mechanism through angulation of the pelvic floor and contraction of the anal sphincter muscles. Other mechanisms contributing to continence include stool consistency and volume.

CONCLUSIONS

Understanding the basic principles of colorectal anatomy and physiology is an essential foundation for proficiency in colorectal surgery. Many of the colorectal diseases represent derangements in colorectal physiology such as colonic pseudo-obstruction, colonic inertia, pelvic floor dysfunction, or fecal incontinence. Furthermore, much of the foundation of optimal colorectal oncologic surgery is related to the anatomy of the colon and rectum.

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65

Gastrointestinal Bleeding

Richard H. Turnage and Benjamin L. Davis

Key Points

1. Gastrointestinal (GI) bleeding is classified as upper, lower, or mid-GI bleeding based on the accessibility of the bleeding site to endoscopic imaging.
2. Esophagogastroduodenoscopy (EGD) is the initial diagnostic test of choice in almost all cases of upper GI bleeding.
3. Hemodynamically stable patients with hematochezia should undergo colonoscopy after resuscitation and bowel preparation.
4. As many as 15% of hemodynamically unstable patients presenting with hematochezia will be bleeding from an upper GI source.
5. About 70% of patients with overt GI bleeding in whom an EGD and colonoscopy failed to identify a site of hemorrhage will be bleeding from the small intestine.
6. Video capsule endoscopy is the diagnostic test of choice for hemodynamically stable patients suspected to be bleeding from the small intestine.
7. Endoscopic therapy significantly reduces the rate of recurrent bleeding and the need for urgent surgical intervention in patients with high-risk lesions, such as those that are actively bleeding or have a nonbleeding visible vessel.
8. Patients bleeding from lesions not amenable to endoscopic therapy or who fail endoscopic therapy are managed by angiographic embolization or surgery.

NOMENCLATURE

Bleeding from the gastrointestinal (GI) tract is classified as overt or occult based on the presence or absence of visible signs of blood loss. Patients with overt GI bleeding present with hematemesis (the vomiting of blood), melena (the passage of black tarry stools), and/or hematochezia (the passage of bright red blood). Patients with occult GI bleeding present with iron

deficiency anemia and/or a positive fecal occult blood test without signs of overt bleeding. This chapter focuses on the clinical features, evaluation, and management of patients with overt GI bleeding.

1 Traditionally, overt GI bleeding has been classified as upper or lower based on the location of the bleeding relative to the ligament of Treitz. Advances in endoscopic imaging of the small bowel and the distinct nature of small bowel bleeding have established a new model of nomenclature for GI bleeding that is based on accessibility of the bleeding site to endoscopic imaging. Bleeding proximal to the ampulla of Vater, and within reach of a standard esophagogastroduodenoscope (EGD), is termed upper GI bleeding. Bleeding from the colon, rectum, or anus and within reach of the colonoscope is defined as lower GI bleeding and bleeding between the ampulla of Vater and the ileocecal valve, visualized by video capsule endoscopy (VCE) and/or device-assisted enteroscopy (DAE), is defined as mid-GI (or small bowel) bleeding.[1,2] The term "obscure GI bleeding" is used to identify those instances in which no source of bleeding is found despite endoscopic examination of the entire GI tract.

About 40% to 60% of patients hospitalized with overt GI bleeding are bleeding from the upper GI tract, 5% to 10% are bleeding from the small bowel, and 25% to 32% are bleeding from the lower GI tract. The site of bleeding is unknown in 29% to 35% of patients.[2–4] The most common causes of overt GI bleeding and their relative frequencies are shown in Table 65.1.

EPIDEMIOLOGY

Bleeding is the most common indication for hospitalization for GI diseases in the United States. In 2014, GI bleeding caused more than 500,000 hospitalizations, 2.2 million days of hospitalization, $5 billion in direct costs, and nearly 11,000 deaths. Overall, the mortality rate for patients hospitalized with GI bleeding is about 2%, although the number varies widely based on the severity of bleeding and the patient's comorbidities.[3]

The incidence of upper GI bleeding in the United States is about 67 cases per 100,000 population.[5] Worldwide, the incidence varies from 48 to 160 cases per 100,000 population.[14] The incidence of upper GI bleeding has declined over the past 30 years.[5,15–17] For example, a study in the United

States documented a 21% reduction in the incidence of upper GI bleeding between 2002 and 2012[5]; changes attributed to decreased bleeding from peptic ulcer disease and gastritis.[4,15]

The incidence of lower GI bleeding (as traditionally defined) is about 33 cases per 100,000 population. The age- and sex-matched incidence of hospitalizations for lower GI bleeding decreased by 15% in the United States between 2001 and 2009.[4] In contrast, Lanas et al. reported an increased incidence of lower GI bleeding in Spain between 1996 and 2005.[16]

Although overt GI bleeding can occur at any age, it is particularly prevalent in the elderly. The median age of patients hospitalized for upper and lower GI bleeding is 67 and 74 years, respectively.[5,10] Upper GI bleeding is slightly more common in males (55%)[5,17] and lower GI bleeding is slightly more common in females (52%).[10]

CLINICAL PRESENTATION

A thorough medical history, physical examination, and basic laboratory tests provide important information regarding (1) the site and cause of bleeding, (2) risk factors for GI bleeding, and (3) the severity of bleeding. Clinical scenarios associated with various causes of GI bleeding are shown in Table 65.2.

Table 65.1 Causes of Overt Gastrointestinal Bleeding and Their Relative Frequencies

Cause	Relative Frequency (%)
Upper GI Bleeding[4–7]	
Peptic ulcer disease	27–68
Erosive disease (gastritis, esophagitis, duodenitis)	11–30
Mallory–Weiss tear	4–8
Esophageal/gastric neoplasm	3–5
Vascular lesions (angioectasias, Dieulafoy lesion)	2–10
Gastroesophageal varices/portal gastropathy	2–9
Mid-GI Bleeding[8,9]	
Vascular lesions (angioectasias, telangiectasias)	16–20
Ulcerations/erosions	11–18
Small bowel neoplasm	4–11
NSAID enteropathy	4–8
Crohn disease	3–5
Small bowel diverticulum (diverticulosis, Meckel's)	1–3
Other disease	2–9
Obscure GI bleeding	39–48
Lower GI Bleeding[10–13]	

Diverticulosis	26–31
Internal hemorrhoids	14–19
Neoplasm	6–20
Colon ischemia	6–12
Postpolypectomy	3–8
Inflammatory bowel disease	2–9
Angioectasias	1–6
Rectal ulcer	0–6
Infectious colitis	0–2
Radiation colitis/proctitis	0–3

GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug.

Site and Cause of Bleeding

Patients with upper GI bleeding will usually present with hematemesis or melena. Hematemesis is the vomiting of bright red blood or dark heme-positive material, termed coffee-ground emesis. The latter is blood that has been partially degraded and suggests that the bleeding has stopped. The vomiting of bright red blood suggests recent or ongoing bleeding. Melena is the passage of black, tarry stools with a characteristic pungent odor. It is caused by bacterial degradation of blood and occurs with as little as 50 mL of blood in the upper GI tract, small bowel, or proximal colon. Clinical findings most suggestive of an upper GI source of bleeding include melena, nasogastric lavage fluid containing blood or coffee grounds, and a serum urea nitrogen to creatinine ratio of more than 30.[18]

Hematochezia is the passage of bright red blood, maroon-colored blood, or blood clots from the rectum. It is usually caused by bleeding in the colon or rectum, but may occur with rapid blood loss anywhere in the GI tract. Fifteen percent of patients with hematochezia will have severe upper GI bleeding,[19] most of whom are hemodynamically unstable. The clinical finding most predictive of lower GI bleeding is the passage of blood clots per rectum.[18]

Risk Factors for GI Bleeding

Important risk factors for overt GI bleeding include advanced age, nonsteroidal anti-inflammatory drug (NSAID), and aspirin (ASA) use, treatment with antiplatelet agents and anticoagulants, and the presence of chronic illnesses, especially renal failure, cirrhosis, and cardiac disease.[2,5,10,14,15] Many risk factors have a synergistic effect on a patient's risk of bleeding. For example, the combination of NSAIDs and anticoagulants is more than double the risk of upper GI bleeding compared with NSAIDs or anticoagulants alone.[15] GI bleeding is also an important complication of patients hospitalized for common acute and chronic illnesses such as sepsis, stroke, myocardial infarction, renal failure, cirrhosis, and cancer.[10,15,20,21]

Table 65.2 Clinical Scenarios Associated with Various Causes of Overt Gastrointestinal Bleeding

Upper GI Bleeding
Peptic ulcer disease
Epigastric pain followed by hematemesis/melena in a person taking aspirin or NSAIDs
Esophagitis/esophageal ulceration
Hematemesis/melena in a person with a history of gastroesophageal reflux, heartburn, and/or odynophagia
Mallory–Weiss tear
Vomiting/retching followed by hematemesis and/or melena
Gastroesophageal varices
Painless, massive bleeding in a cirrhotic
Mid-GI Bleeding
Angioectasias
Recurrent GI bleeding in an elderly patient with chronic renal failure or aortic stenosis
Meckel diverticulum
Painless, large-volume GI bleeding in a child or young adult
Aortoenteric fistula
GI bleeding in patient with a history of abdominal aortic aneurysm repair
Lower GI Bleeding
Diverticulosis
Painless, intermittent large-volume hematochezia
Internal hemorrhoids
Intermittent low-volume bleeding with bright red blood on the tissue or dripping into the toilet water
Colon ischemia
Abdominal pain and hematochezia in an elderly patient with cardiovascular disease
Hematochezia or bloody diarrhea shortly after abdominal aortic aneurysm repair

GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs.

Severity of Bleeding

GI bleeding varies from minor, self-limited episodes of blood loss to massive hemorrhage with shock. The medical history, physical examination, and basic laboratory tests provide important information regarding the severity of bleeding and the patient's hemodynamic response. Basic laboratory tests should include a complete blood count with platelet count, electrolyte measurements, liver function tests, a basic coagulation profile, and a type and crossmatch.

In addition to hematemesis, melena, and/or hematochezia, patients with GI bleeding may present with symptoms of acute blood loss including light-headedness, dizziness, orthostatic syncope or near syncope, shortness of breath, and/or tachycardia. Severe bleeding is associated with the physical features of hypovolemic shock including cool, clammy, mottled skin, tachycardia, tachypnea, flat jugular veins, oliguria, and perhaps hypotension. Advanced age, chronic illnesses, and various medications may obscure these hemodynamic responses. Clinical findings most predictive of severe upper GI bleeding include bright red blood in the nasogastric lavage fluid, tachycardia with a heart rate greater than 100 beats per minute, and a hemoglobin level less than 8 g/dL.[18]

Table 65.3 Clinical Variables Used in Risk Assessment Tools for Patients with Upper GI Bleeding

Glasgow-Blatchford Score[22]	Admission Rockall Score[23]	AIMS65 Score[24]
Systolic blood pressure	Systolic blood pressure	Albumin
Heart rate	Heart rate	INR
Hemoglobin	Liver failure	Mental status
Melena at presentation	Renal failure	Systolic blood pressure
Syncope at presentation	Disseminated malignancy	Age
Blood urea nitrogen	Other major comorbidities	
Hepatic disease	Age	
Cardiac disease		

GI, gastrointestinal; INR, international normalized ratio.

RISK ASSESSMENT AND TRIAGE

Most patients with overt GI hemorrhage will stop bleeding spontaneously. Those who do not stop and those who rebleed are likely to require endoscopic, angiographic, or surgical intervention and are at a high risk to suffer a complication or die. Accurate estimation of the severity of bleeding and the patient's hemodynamic response guides the triaging of patients for diagnostic studies and therapeutic interventions. Minor, self-limited bleeding in hemodynamically normal patients may be managed in an ambulatory

setting whereas patients with ongoing or severe bleeding require urgent endoscopic evaluation and treatment in an intensive care unit. A number of tools employing clinical and endoscopic criteria are used to estimate the severity of bleeding and the likelihood of continued or recurrent hemorrhage and death.

Risk Assessment Tools for Upper GI Bleeding

The most widely validated risk assessment tools for predicting recurrent upper GI bleeding and mortality are the Glasgow-Blatchford score (GBS),[22] Rockall score,[23] and the AIMS65 score.[24] The clinical variables used in these risk assessment tools are shown in Table 65.3. The GBS is superior at predicting a combined endpoint of hospital-based intervention or death compared with the other two tools[25] and is promulgated by clinical guidelines from the European Society of Gastrointestinal Endoscopy,[26] the International Consensus Group,[27] and the Asia-Pacific Working Group.[28] A GBS score ≥7 predicts the need for endoscopic control of bleeding and a score ≤1 allows for the safe discharge and outpatient management of patients at very low risk of adverse outcomes.[25–29]

Risk Assessment Tools for Lower GI Bleeding

Unlike upper GI bleeding, there is no generally accepted risk prediction tool for patients with lower GI bleeding. A number of tools have been studied; however, heterogeneity of populations and outcomes has limited comparison and generalizability. The primary outcomes examined included severe bleeding, 30-day mortality, and adverse events.[30–32] The Oakland score[33] predicts safe discharge from the emergency department. The GBS has also been used to identify patients with lower GI bleeding who are at risk for adverse outcomes (rebleeding, need for transfusion, and in-hospital death).[34] As shown in Table 65.4, there is considerable overlap in the variables used in these models, particularly with regard to measures of blood loss and patient hemodynamics, the presence of comorbidities, and the use of

antithrombotic drugs. Unfortunately, the predictive ability of most of these tools for their primary outcome is only fair.[35]

RESUSCITATION

Airway Management

The initial step in the resuscitation of an acutely bleeding patient is to ensure that the airway is secure. Patients with severe GI bleeding who are inadequately ventilating or who are unable to protect their airway should undergo endotracheal intubation to optimize gas exchange and reduce the risk of aspiration. Prophylactic endotracheal intubation is not indicated as it is associated with the development of cardiopulmonary complications such as pneumonia.[36]

Table 65.4 Clinical Variables Used in Risk Assessment Tools for Patients with Lower GI Bleeding

Strate et al.[30]	Sengupta and Tapper[31]	Kollef et al. (BLEED)[32]	Oakland[33]
Heart rate	Age	Ongoing bleeding	Age
Systolic blood pressure	Dementia	Systolic blood pressure	Gender
Syncope	Metastatic cancer	Prothrombin time	Prior admission for lower GI bleeding
Nontender abdominal examination	Chronic renal disease	Altered mental status	Blood on digital rectal examination
Bleeding in first 4 hrs of hospitalization	Chronic lung disease	Unstable comorbid disease	Heart rate
Aspirin use	Anticoagulant use		Systolic blood pressure
>2 comorbid conditions (Charlson Index)	Admission hematocrit Admission albumin		Hemoglobin

GI, gastrointestinal.

Volume Resuscitation

Intravenous access is obtained by placing two large-bore catheters into antecubital veins. Intravascular volume resuscitation is started with an isotonic saline solution. Most patients will stop bleeding spontaneously and crystalloid resuscitation is all that is required. The decision to transfuse

blood or blood products depends on the specific needs of the patient. A number of randomized controlled trials[37,38] and published clinical guidelines[26–28,39,40] support a restrictive transfusion strategy which withholds the transfusion of packed red blood cells (PRBC) until a hemoglobin threshold of 7.0 to 8.0 g/dL is reached. A higher threshold (8 to 10 g/dL) is used for patients with ischemic cardiac disease. Patients with massive GI bleeding should receive a balanced hemorrhagic resuscitation regimen (e.g., a 1:1:1 ratio of PRBC, fresh frozen plasma, and platelets) to restore intravascular volume, oxygen-carrying capacity, and coagulation factors.

Hemodynamic Monitoring

Prompt, adequate resuscitation and diligent observation are the cornerstones of managing these potentially critically ill patients. Patients with evidence of active bleeding, those who have sustained significant blood loss, and those with risk factors for adverse outcomes should be admitted to an intensive care unit for close monitoring of their vital signs and evidence of continued or recurring blood loss. The placement of a urinary catheter and frequent monitoring of heart rate, blood pressure, oxygen saturation, urine output, and mental status are minimum necessary to monitor patients who have suffered significant GI bleeding. The presence of comorbidities such as cardiac, renal, or hepatic disease may necessitate invasive cardiac monitoring in order to optimize intravascular volume replacement therapy.

Nasogastric Lavage

The placement of a nasogastric tube in patients with suspected GI bleeding is controversial and the practice is highly variable.[18,26,27] Blood or coffee grounds in the nasogastric lavage fluid increases the likelihood of upper GI bleeding and the presence of bright red blood in the lavage fluid increases the probability of severe bleeding requiring urgent endoscopic hemostasis.[18] However, nasogastric lavage does not affect mortality, length of hospital stay, or the need for transfusions or surgery.[41] Furthermore, nasogastric tube insertion is an uncomfortable procedure with patients rating its discomfort comparable to fracture reduction or abscess drainage.[42]

Management of Antithrombotic Drugs

Twenty-nine percent to 44% of patients with severe GI bleeding are taking antithrombotic drugs (antiplatelet agents, anticoagulants).[10,43] The management of these patients balances the effect of the antithrombotic drug on the severity of bleeding with the risk of thromboembolic events should the agent be withdrawn. The treatment of patients who develop severe GI bleeding while receiving antithrombotic medications is the subject of numerous evidence-based guidelines[26–28,39,40] including those promulgated by the American Society for Gastrointestinal Endoscopy[44] and a joint task force of the Asian Pacific Association of Gastroenterology, and the Asian Pacific Society for Digestive Endoscopy.[45] Selected recommendations from these guidelines are shown in Table 65.5.

Table 65.5 Management of Patients with Overt Gastrointestinal Bleeding Who Are Taking Antithrombotic Medications

Patients receiving vitamin K antagonists (e.g., warfarin)

1. Patients with overt GI bleeding should have their anticoagulation managed in consultation with a cardiologist[26,40,44,45]
2. Patients with serious, life-threatening bleeding should have their coagulopathy corrected with 4-factor prothrombin complex concentrate (PCC) plus vitamin K or fresh frozen plasma if PCC is unavailable[26,28,40,44,45]
3. Endoscopy and endoscopic hemostasis should not be delayed awaiting correction of the coagulopathy,[27,28,45] especially if the international normalized ratio is less than 2.5[26,29,39,44]
4. Patients at high risk for thromboembolic events (e.g., patients with a mechanical mitral heart valve) should resume warfarin once hemostasis has been achieved.[29,45] These patients should receive unfractionated heparin as a bridge to anticoagulation with warfarin[44,45]

Patients receiving direct oral anticoagulants (DOACs; e.g., apixaban, dabigatran, rivaroxaban, edoxaban)

1. Patients with overt GI bleeding should have their anticoagulation withheld.[26,27,44,45] Because of their short half-lives and predictable loss of anticoagulant effect, “time is the most important antidote against DOACs”[26]
2. Endoscopy and endoscopic hemostasis should not be delayed by treatment of the coagulopathy[27,28]
3. Idarucizumab may be administered to patients with life-threatening bleeding who are anticoagulated with dabigatran[28,45]
4. Once the bleeding has been controlled, the DOAC should be resumed within 1–2 days and in consultation with the patient’s cardiologist[28,45]

Patients receiving single agent antiplatelet therapy with aspirin

1. Antiplatelet therapy for cardiovascular prophylaxis should be managed in collaboration with a cardiologist, neurologist, or cardiovascular specialist[28,29,44]
2. Patients receiving aspirin monotherapy for primary cardiothrombotic prophylaxis[a] should have the aspirin withheld at

least temporarily, with consideration given to permanent discontinuation[26,29,46]

3. Patients receiving aspirin monotherapy for secondary cardiothrombotic prophylaxis[b] should have the aspirin continued.[40,46] If it is stopped, it should be resumed upon obtaining hemostasis[28] or at least within 72 hours of achieving hemostasis[26,29,45]

Patients receiving dual agent antiplatelet therapy (aspirin, clopidogrel, prasugrel, ticlopidine, ticagrelor, vorapaxar)

1. Antiplatelet therapy for cardiovascular prophylaxis should be managed in collaboration with a cardiologist, neurologist, or cardiovascular specialist[26,28,29,40,44]
2. Patients at high risk for cardiothrombotic events should have both antiplatelet agents continued because of the high risk of thrombosis and death[29,40,45,46]
3. Patients at low risk for continued or recurrent bleeding (e.g., those with low-risk endoscopic stigmata) should have both antiplatelet agents continued[28]
4. Patients with severe bleeding and lower risk for cardiothrombotic events should have at least one of the agents continued, generally aspirin[26,28,40,45] with the P2Y12 receptor inhibitor restarted within 5 days of achieving hemostasis[26,28,40,45,46]

[a]In the absence of known cardiovascular disease.

[b]In the presence of known cardiovascular disease.

DIAGNOSTIC ALGORITHMS

Upper GI Bleeding

2 The initial diagnostic test in almost all cases of upper GI bleeding is EGD. This procedure will identify the site of bleeding in 95% of cases, provide information regarding the likelihood of continued or recurrent bleeding, and be therapeutic. Multiple evidence-based clinical guidelines recommend that patients undergo EGD after appropriate resuscitation and

within 24 hours of presentation.[26–28] Early endoscopy allows for the safe discharge of low-risk patients, improves outcomes for high-risk patients, and reduces resource utilization. Patients with ongoing bleeding and persistent hemodynamic instability despite volume resuscitation should undergo EGD within 12 hours.[26,28] Patients with cirrhosis and suspected variceal bleeding should also undergo EGD within 12 hours of presentation.[47,48] Patients must be appropriately resuscitated prior to endoscopy as inadequate resuscitation is associated with adverse outcomes, including in-hospital mortality.[49]

Computed tomographic (CT) angiography is an appropriate diagnostic test in those instances in which (1) the patient is actively bleeding and remains hemodynamically unstable despite volume resuscitation or (2) EGD has documented evidence of hemorrhage but the site of bleeding could not be identified.[50] CT angiography can be performed expeditiously and will detect rates of bleeding as low as 0.3 mL/min. It will also identify sources of bleeding outside the reach of a standard endoscope thus facilitating therapeutic endoscopic or angiographic interventions. In actively bleeding patients, the sensitivity and specificity of CT angiography is 85% and 92%, respectively. The sensitivity of CT angiography is only about 50% in patients with lower rates of bleeding.[50,51]

Visceral angiography is indicated in those instances in which endoscopy or CT angiography has identified a site of active bleeding that is not amenable to endoscopic hemostasis. In this setting, visceral angiography has a high diagnostic accuracy and is effective in achieving hemostasis with catheter-based embolization techniques in about 80% of cases.[50,52] Visceral angiography will detect arterial or capillary bleeding at rates of 0.5 to 1.0 mL/min, a rate of bleeding that correlates with the need for ongoing volume resuscitation to maintain hemodynamic stability. If the bleeding has stopped, or is intermittent, the bleeding site will not be visualized by angiography, an important limitation of this study.

Lower GI Bleeding

The timing and manner of diagnostic studies for patients with lower GI bleeding depends upon the severity of bleeding and the hemodynamic status of the patient. A diagnostic algorithm for the evaluation of patients with lower GI bleeding is shown in Figure 65.1. Patients with minor self-limited

episodes of bleeding and no other indication for hospitalization (such as those with an Oakland score ≤8) may be discharged from the emergency department and evaluated by colonoscopy in an outpatient setting.[39,40]

3 Hemodynamically stable patients with suspected lower GI bleeding should undergo colonoscopy. The timing of the procedure is controversial. Two systematic reviews found that colonoscopy performed within 24 hours of presentation was associated with improved detection of a definite site of bleeding, increased rates of endoscopic treatment, and shorter hospital stays.[53,54] However, a recent multicenter, randomized controlled trial comparing early versus elective colonoscopy failed to demonstrate a difference in the rate of rebleeding or the ability to identify stigmata of recent hemorrhage.[55] Patients should undergo bowel preparation prior to colonoscopy in order to optimize visualization of the colonic mucosa and improve diagnostic yield which is 42% to 100% in patients with hematochezia.[10,39,40] CT angiography is indicated in those instances in which colonoscopy documents evidence of bleeding but is unable to identify the source.

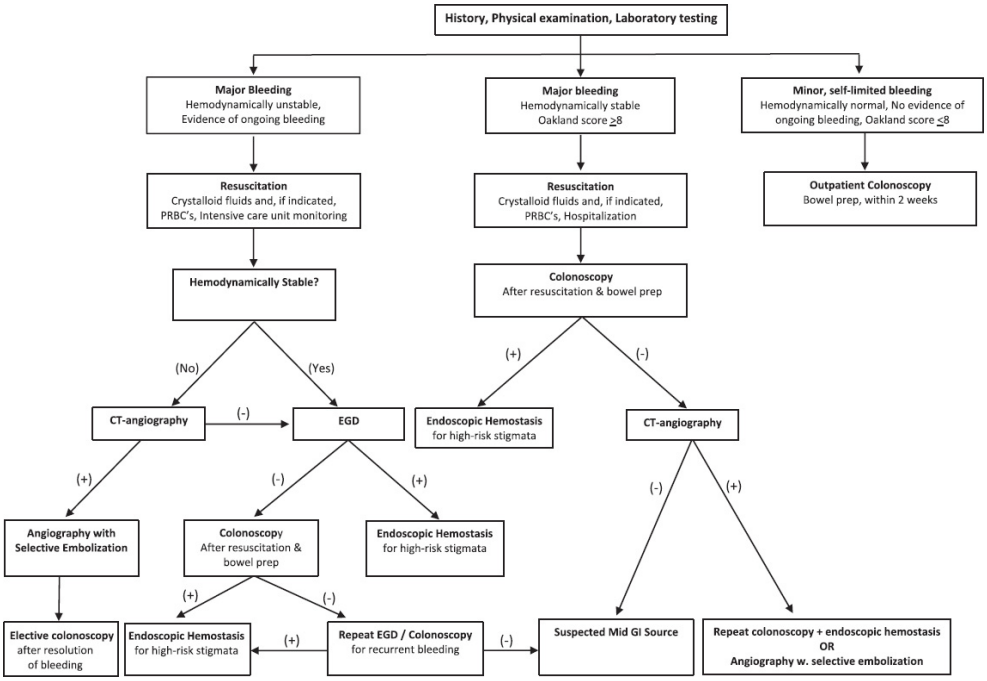

Figure 65.1 Diagnostic algorithm for patients presenting with hematochezia. PRBCs, packed red blood cells; EGD, esophagogastroduodenoscopy; GI, gastrointestinal; CT, computed tomography; (+), diagnostic; (−), nondiagnostic.

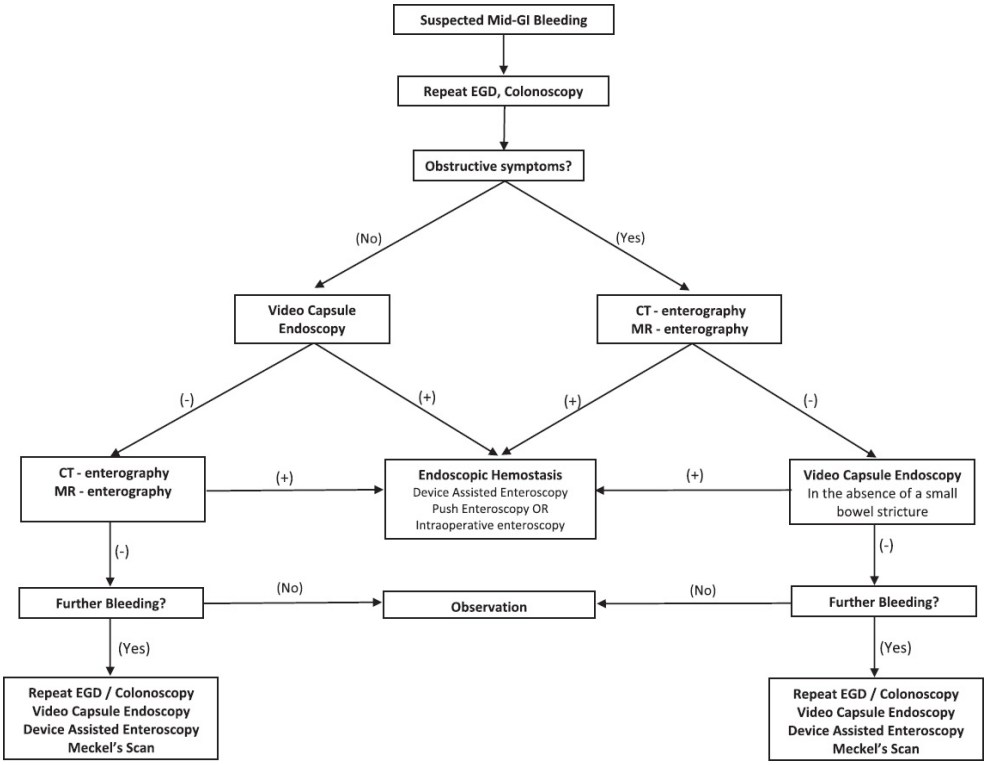

Figure 65.2 Diagnostic algorithm for hemodynamically stable patients with suspected overt mid-gastrointestinal bleeding. GI, gastrointestinal; CT, computed tomography; MR, magnetic resonance; (+), diagnostic; (−), nondiagnostic.

Hemodynamically unstable patients with hematochezia who have not responded to volume resuscitation should undergo urgent CT angiography as the initial diagnostic test since these patients are unlikely to tolerate bowel preparation and colonoscopy.[39,40] If a source of bleeding is identified by CT angiography, the patients should undergo visceral angiography with superselective embolization of the bleeding site. If a source of bleeding is not identified by CT angiography, an EGD 4 should be performed given the high rate of upper GI bleeding in unstable patients presenting with hematochezia (15%).[19,39,40,46,56]

Mid-Gastrointestinal Bleeding

5 About 70% of patients with overt GI hemorrhage in whom an EGD and colonoscopy fail to identify the source of bleeding are bleeding from the small intestine.[57] A diagnostic algorithm for the evaluation of patients with mid-GI bleeding is shown in Figure 65.2. If the patient is hemodynamically unstable, he/she should undergo CT angiography to identify the site of

bleeding and guide subsequent endoscopic or angiographic hemostasis. Hemodynamically stable patients with potential small bowel bleeding should undergo repeat EGD and/or colonoscopy since these studies will identify a site of bleeding in 30% to 40% of instances.[58]

6 VCE is the diagnostic test of choice for hemodynamically stable patients with potential small bowel bleeding. It allows the noninvasive examination of the entire length of small bowel in 80% to 90% of cases and has a diagnostic yield of 80% in patients with suspected small bowel bleeding, especially if performed within 2 to 3 days of the hemorrhage.[2,58,59] Recurrent bleeding after a negative VCE is infrequent (6% to 11%).[59,60] The primary risk of VCE is capsule retention which occurs in about 1% of examinations.[61] The most common cause of capsule retention is a small bowel stricture. Thus patients with suspected small bowel bleeding and obstructive symptoms should undergo CT enterography prior to VCE.[58,59]

DAE includes balloon-assisted enteroscopy and spiral enteroscopy. The diagnostic yield of DAE in patients with suspected mid-GI bleeding is about 60% and increases to 75% in the setting of a positive VCE.[62,63] DAE facilitates the endoscopic treatment of patients in whom VCE has identified a site of bleeding within the small intestine. A detailed description of the role of DAE in the management of patients with small bowel disorders is provided in Ref. [64].

Multiphase CT enterography uses intravenous contrast and large-volume oral contrast to detect inflammatory lesions, neoplasms, and vascular abnormalities within the small bowel. The diagnostic yield of CT enterography for patients with suspected small bowel bleeding is 40% to 57%.[65,66]

Pertechnetate scintigraphy is performed in young adults or children suspected to be bleeding from a Meckel diverticulum. Intravenous Technetium-99m pertechnetate is taken up by the mucoid cells of ectopic gastric mucosa located within the Meckel diverticulum and presents as a focus of abnormal radioactivity in the right lower abdomen. The diagnostic accuracy is greater than 90% in children[67] but is less than 50% in adults.[68]

7 **Table 65.6** Endoscopic and Medical Management of Patients with Peptic Ulcer–Related Upper GI Bleeding According to the Endoscopic Appearance of the Ulcer[26–29]

Endoscopic Stigmata	Type[a]	Endoscopic Treatment	Medical Management
High-Risk Stigmata			
Spurting ulcer	Ia	Endoscopic hemostasis	High-dose PPI (bolus + continuous infusion) for 72 hrs
Oozing ulcer	Ib	Endoscopic hemostasis	High-dose PPI (bolus + continuous infusion) for 72 hrs
Nonbleeding visible vessel	IIa	Endoscopic hemostasis	High-dose PPI (bolus + continuous infusion) for 72 hrs
Adherent clot	IIb	Clot removal + endoscopic hemostasis if underlying high-risk stigmata	High-dose PPI (bolus + continuous infusion) for 72 hrs
Low Risk Stigmata			
Flat pigmented spot	IIc	None	Once daily oral PPI
Clean ulcer base	III	None	Once daily oral PPI

[a]Forrest classification.[72]

GI, gastrointestinal; PPI, proton pump inhibitor.

UPPER GASTROINTESTINAL BLEEDING

Peptic Ulcer Disease

Peptic ulcer disease is the most common cause of upper GI bleeding, accounting for about 50% of cases. *Helicobacter pylori* and gastroerosive drugs, especially NSAIDs and ASA, are independent and synergistic risk factors for peptic ulcer–related bleeding and account for about 80% of cases.[15,69] NSAIDs potentiate the effect of other risk factors for peptic ulcer–related bleeding such as advanced age, anticoagulants, corticosteroids, and selective serotonin reuptake inhibitors.[15] About 30% of patients will present with bleeding as the initial symptom of their disease and about 50% of patients will have antecedent upper abdominal pain.[70,71]

The Forrest Classification is an endoscopic scoring system that identifies patients at high risk for continued or recurrent bleeding and death.[72] High-risk endoscopic stigmata include active ulcer bleeding and a nonbleeding visible vessel. Low-risk endoscopic stigmata includes ulcers with flat pigmented spots or clean ulcer base. An adherent clot is defined as a blood clot over an ulcer that is resistant to jet water irrigation. The management of patients with peptic ulcer–related bleeding based on the endoscopic appearance of the ulcer is shown in Table 65.6.

Endoscopic hemostasis can be achieved with injection, thermal or mechanical methods.

Thermal devices (contact and noncontact), injectable agents (i.e., sclerosing agents, thrombin/fibrin glue), and endoscopic clips are all effective methods for achieving hemostasis, with no single modality being superior.[26,27,29,73] Epinephrine injection alone is effective at achieving primary hemostasis, but is associated with a high rate of rebleeding.[74] Therefore, if epinephrine is used to treat peptic ulcer bleeding, it should be used in combination with another endoscopic modality.[26]

Following successful endoscopic therapy, patients with ulcers with high-risk endoscopic stigmata should receive high-dose proton pump inhibitor (PPI) therapy administered as an intravenous bolus followed by continuous infusion for 72 hours post endoscopy. This regimen has been demonstrated to reduce rebleeding, the need for surgery, and mortality.[26,73] Daily oral PPI therapy is then continued for 4 to 8 weeks.[75] Patients with low-risk lesions

(clean base, flat spot) should receive oral PPIs once a day from the time of diagnosis.[29] All patients should be tested for *H. pylori* in the acute setting and appropriate antibiotic therapy initiated if *H. pylori* is detected.[26]

Patients who rebleed following initial endoscopic control should undergo repeat endoscopic hemostasis.[26,29] One randomized controlled trial comparing endoscopic re-treatment to surgery found that endoscopic re-treatment controlled bleeding in 73% of patients and was associated with a lower rate of adverse events compared with surgery.[76] Emerging data suggest that hemostatic powder may provide temporary hemostasis in patients in whom standard endoscopic techniques are unsuccessful.[26,28,77] Additionally, over-the-scope clips, which are much larger than standard endoscopic clips, may allow successful treatment of some ulcers in which standard endoscopic treatment has been unsuccessful.[26,78]

8 If the bleeding is unable to be controlled at the second endoscopy or if the patient rebleeds, the patient should undergo angiographic embolization or surgery.[20,26,79,80] Three meta-analyses have compared embolization to surgery in patients who failed endoscopic hemostasis. All three studies found that embolization is associated with higher rates of rebleeding and two of the three reported a trend toward higher mortality rates with emergency surgery. These data are summarized in Table 65.7.[81–83]

The surgical choice depends on the location and extent of the ulcer, the patient's medical status, and the experience of the surgeon. For favorably located gastric ulcers, such as those along the greater curvature, excision of the ulcer with closure of the gastrotomy will suffice. If the ulcer is unfavorably located, for example, near the gastroesophageal junction, simple oversewing of the bleeding vessel may adequately control the hemorrhage. Biopsy of the ulcer margin, either at the time of operation or at follow-up endoscopy in 4 to 8 weeks, is important to rule out malignancy. Extensive gastric resections such as subtotal or total gastrectomy are generally not performed in these potentially medically complex and unstable patients.

Table 65.7 Results of Three Meta-Analyses Comparing Embolization to Surgical Hemostasis for Remedial Treatment of Bleeding Peptic Ulcers[81–83]

	Angiographic Embolization (% of Events)	Surgery (% of Events)
Rebleeding	25–35	15–18
Mortality	19–24	22–25
Need for additional intervention	18–33	8–18
Complications	31	50

Most duodenal ulcers requiring surgical control are large, posterior lesions bleeding from the gastroduodenal artery. A longitudinal incision in the duodenal bulb will allow visualization of the bleeding gastroduodenal artery in the base of the ulcer which should be oversewn proximally and distally to the bleeding site with figure-of-eight stitches. A U-stitch is placed underneath the bleeding site to control the transverse pancreatic artery which enters the gastroduodenal artery posteriorly. The performance of a vagotomy and drainage procedure (usually a Heineke-Mikulicz pyloroplasty) is associated with lower mortality rates compared with oversewing the ulcer alone.[84] Operations for peptic ulcer disease including truncal vagotomy and pyloroplasty are described in detail in Chapter 44.

Stress Ulceration

Stress ulceration is characterized by diffuse bleeding from erosions and superficial ulcers in the stomach, and to a lesser extent the duodenum, of critically ill patients. The clinical spectrum of this disease varies from asymptomatic, superficial gastroduodenal erosions to deep mucosal and submucosal ulcerations with overt upper GI bleeding and hemodynamic instability.

The incidence of overt upper GI bleeding in critically ill, hospitalized patients is between 0.9% and 5.0%.[20,85,86] The risk is much higher in critically ill patients requiring specialized care such as mechanical ventilation, renal replacement therapy, and extracorporeal life support.[20,87] The risk of stress-related upper GI bleeding in hospitalized patients who are not critically ill is much lower (0.29%).[88]

The most salient factor in the pathophysiology of stress ulcerations is disruption of the gastroduodenal mucosal barrier. Critical illness or injury reduces gastric blood flow and causes mucosal ischemia and reperfusion injury. This in turn impairs mucosal barrier defenses and ultimately disrupts mucosal integrity. The pathophysiology of stress ulcerations is reviewed in Ref. [20].

The principal nonpharmacologic method to decrease stress-related upper GI bleeding is the administration of enteral nutrition. It is postulated that enteral nutrition buffers gastric acid, enhances protective mucosal prostaglandin production, and improves regional perfusion.[20] Acid suppression with PPIs is the predominate means of prophylaxis against stress ulceration.[20,85,88,89] PPIs significantly reduces the risk of upper GI bleeding in critically ill patients when compared to no prophylaxis or placebo, histamine H_2-receptor antagonists, or sucralfate.[20] There is increasing evidence linking acid suppression with the occurrence of nosocomial infections in critically ill patients, especially ventilator-associated pneumonia and *Clostridium difficile* colitis.[90,91] These observations and others have created a growing concern that the adverse effects of acid suppression outweigh the risk of stress-related upper GI bleeding. At the very least, it calls into question the use of acid suppression in patients at low risk for stress ulceration, such as hospitalized patients who are not critically ill or those patients in the intensive care unit who lack well-defined risk factors for GI bleeding.[20]

The management of patients with stress-related upper GI bleeding is similar to that of patients with other nonvariceal causes of upper GI bleeding. Endoscopy should be performed within 12 to 24 hours of presentation depending on the severity of the bleeding. The presence of high-risk endoscopic stigmata identifies lesions that may be amenable to endoscopic hemostasis. Hemostatic powders may be useful for diffusely bleeding lesions. High-dose PPI therapy is the mainstay of treatment for patients

whose lesions are not amenable to endoscopic hemostasis. It is also prescribed after successful endoscopic therapy.

The need for surgical management of severe bleeding from stress ulceration is extremely rare. Most of the published experience is more than 40 years old. A number of surgical procedures have been used to control bleeding ranging from suture ligation of specific bleeding sites to total gastrectomy for diffuse hemorrhage. Rebleeding is common for procedures less extensive than total gastrectomy and the mortality rate is high regardless of the operative approach. Stress-related upper GI bleeding is further discussed in Chapter 44.

Esophagitis

Severe esophagitis causes 6% to 15% of cases of upper GI bleeding[5,6,92,93] with an adjusted incidence of 4 to 12 cases per 100,000 population per year.[3,5] Gastroesophageal reflux disease is the most common cause of esophagitis associated with overt upper GI bleeding. Fungal (candida) and viral (herpes simplex, Cytomegalovirus) esophagitis may also cause upper GI bleeding in immunocompromised individuals. Gastroesophageal reflux disease and esophagitis are discussed in Chapter 41.

Patients bleeding from esophagitis present with hematemesis (43% to 86%) and/or melena (38% to 52%).[6,92] A minority of patients will have symptoms of gastroesophageal reflux such as heartburn (23% to 38%).[92,94] Massive bleeding with hematochezia (2%) and hemodynamic instability (5%) is uncommon.[92,94] In general, patients bleeding from esophagitis have more stable vital signs, higher hemoglobin and hematocrit levels, and lower Rockall scores than patients with other causes of upper GI bleeding.[92]

Most patients respond well to treatment with PPIs with few requiring endoscopic hemostasis (3%). These patients have an extremely low risk of rebleeding and mortality. Many patients with bleeding from esophagitis can be triaged to early discharge once the diagnosis is made with endoscopy. Patients with cirrhosis who are bleeding from severe esophagitis are at higher risk for rebleeding (17%) and mortality (33%).[92]

Mallory–Weiss Syndrome

Mallory–Weiss syndrome is upper GI bleeding caused by a longitudinal laceration of the distal esophagus and proximal stomach after vomiting, retching, coughing, or straining. Extension of the laceration into the submucosa disrupts esophageal venous and arterial plexuses with hemorrhage. A history of heavy alcohol use is commonly described, as is the presence of a hiatal hernia.

Patients characteristically have an episode of nonbloody emesis, retching or coughing followed by hematemesis. This "classic" presentation occurs in slightly more than 50% of cases.[95] About 10% of patients will present with melena in the absence of hematemesis.[96] The amount of bleeding is variable with severe bleeding described in patients with cirrhosis and portal hypertension.

The mortality rate associated with bleeding from a Mallory–Weiss tear is about 5%. Risk factors for poor outcomes include advanced age, medical comorbidities, and active bleeding at the time of endoscopy.[6,97] Endoscopic mechanical hemostasis is effective in controlling active bleeding and preventing rebleeding.[26,98] Patients without high-risk stigmata are treated with high dose PPIs as are those patients whose bleeding is controlled endoscopically.[26] Surgical treatment, consisting of oversewing the bleeding site through an anterior gastrotomy, is rarely necessary.

Dieulafoy Lesion

A Dieulafoy lesion is an abnormal enlarged artery that courses through the submucosa of the stomach (70%), duodenum (15%), esophagus (8%), colon (2%), rectum (2%), or small intestine (1%).[99] Severe GI bleeding is caused by erosion of the arterial wall through a small superficial defect in the overlying mucosa.

Dieulafoy lesions typically occur in older individuals with 90% of patients more than 60 years of age. Males are affected more commonly than females and medical comorbidities are common. The use of NSAIDs, aspirin, or anticoagulants is also common among patients with bleeding Dieulafoy lesions.[99–101]

Patients present with hematemesis and melena. Most patients are actively bleeding at presentation. One-third of patients are hemodynamically unstable

and two-thirds require blood transfusions. Recurrent bleeding occurs in about 20% of patients.[99,100]

Greater than 90% of patients with bleeding Dieulafoy lesions can be managed endoscopically.[26,102] There is similar efficacy with thermal, mechanical, or combination hemostasis techniques.[100,103] Recurrent bleeding after initially successful endoscopic hemostasis is managed with repeat endoscopic therapy.

Patients who fail endoscopic hemostasis are treated with angiographic embolization or surgery. The operative management of gastric Dieulafoy lesions is laparoscopic or open wedge resection of the lesion after preoperative endoscopic localization. Lesions in the small bowel or colon are treated with resection of the involved bowel and lesions in the rectum are managed by oversewing the bleeding vessel.

Gastroesophageal Varices

Cirrhosis is the fifth leading cause of adult deaths in the United States and ranks eighth in economic cost among major illnesses.[104] About 50% of patients with cirrhosis develop gastroesophageal varices (GEV)[105] and 10% to 15% of these patients will bleed from their varices each year.[106]

Cirrhosis may be classified into two main prognostic stages, compensated and decompensated, depending on the presence or absence of decompensating events such as ascites, variceal bleeding, or encephalopathy.[48] Up to 85% of patients with decompensated cirrhosis will have GEV compared with 30% to 40% of patients with compensated cirrhosis.[105] Patients with compensated cirrhosis develop varices at a rate of 7% to 8% per year[107] and progress from small to large varices at a rate of 10% to 12% per year.[108]

Portal hypertension is an early and important consequence of cirrhosis and is responsible for the majority of its complications, including variceal hemorrhage. The development of portosystemic collaterals, such as those through the coronary and short gastric veins which cause GEV, is an early consequence of portal hypertension. The risk of variceal bleeding depends on the severity of liver disease, size of the varices, and the presence of red wale marks, which are due to thinning of the variceal wall.

The risk of variceal bleeding and death directly relates to the degree of elevation of portal venous pressure. Each 1 mm Hg increase in portal pressure predicts a 3% increase in the risk of death with a median follow-up of 19 months.[109] The relationship between portal pressure and complications of portal hypertension[48,110,111] is shown in Table 65.8.

Patients with variceal bleeding present with effortless and recurring hematemesis of large volumes of dark red blood. The history and physical examination will identify risk factors for cirrhosis (e.g., alcoholism, obesity, hepatitis) and associated physical findings (e.g., jaundice, ascites, spider angiomas, palmar erythema, gynecomastia, ascites, and visible portosystemic collaterals within the abdominal wall, termed "caput medusa"). Splenomegaly is a sensitive, but nonspecific sign of portal hypertension and may be identified on physical examination and/or imaging with ultrasound or CT. Thrombocytopenia is the most common laboratory sign of portal hypertension, although it lacks the accuracy to either diagnose or exclude clinically significant portal hypertension or GEV. Other laboratory tests may document evidence of hepatic synthetic dysfunction (prolonged prothrombin time, hypoalbuminemia, hyperbilirubinemia) and/or hypersplenism and bone marrow suppression (thrombocytopenia, leukopenia).

Table 65.8 Relationship between Elevated Portal Pressure and Complications of Portal Hypertension[48,110,111]

HVPG[a] (mm Hg)	Complication of Portal Hypertension
3–5	Normal
5–10	Mild portal hypertension
>10	Clinically significant portal hypertension
>12	At risk for variceal bleeding
>16	At higher risk of death
>20	Predicts failure to control bleeding, early rebleeding, and death

[a]Portal pressure is most commonly estimated by catheterizing the hepatic vein with a balloon catheter and measuring the difference between the wedged (or occluded) hepatic venous pressure and free hepatic venous pressure (hepatic venous portal gradient, HVPG).

Noncirrhotic causes of portal hypertension include schistosomiasis, extrahepatic portal vein thrombosis, and idiopathic portal hypertension. Additionally, as many as one-third of cirrhotics with upper GI hemorrhage will be bleeding from a cause unrelated to portal hypertension, the most common of which is peptic ulcer disease.[112]

The immediate goals of therapy for patients bleeding from GEV is to control the hemorrhage, prevent early recurrence, and prevent 6-week mortality.[48] Acute variceal bleeding is a medical emergency requiring prompt, intensive care. A restrictive PRBC transfusion strategy (described earlier) is associated with lower rates of early rebleeding and mortality in cirrhotics with upper GI bleeding than are more liberal transfusion strategies.[37,48] Patients with cirrhosis who present with upper GI bleeding are at a high risk of developing bacterial infections. The administration of prophylactic antibiotics decrease the risk of infections, recurrent hemorrhage, and death.[113] The antibiotic of choice in most centers is ceftriaxone administered for a maximum of 7 days.[48] The intravenous infusion of vasoactive agents (such as octreotide) should be started as soon

as possible and before diagnostic endoscopy in patients suspected of bleeding from GEV. A recent meta-analysis of 11 trials showed that the administration of octreotide significantly improved control of acute variceal bleeding.[114]

Endoscopy should be performed as soon as possible following resuscitation and not more than 12 hours after presentation. If a variceal source of bleeding is confirmed or suspected, endoscopic variceal ligation (EVL) should be performed. Once EVL have been performed, "early" transjugular intrahepatic portosystemic shunt (TIPS) has been shown to lower treatment failure and mortality rates in high-risk patients. For patients in whom early TIPS is not performed, intravenous vasoactive drugs (e.g., octreotide) should be continued for 2 to 5 days and nonselective beta blockers (e.g., propranolol) should be started once the vasoactive drugs have been discontinued. Rescue TIPS is indicated in those patients in whom hemorrhage cannot be controlled by vasoactive drug infusion and EVL, or if bleeding recurs.[48]

Patients who recover from the first episode of variceal hemorrhage have a 60% chance of rebleeding in the first year and a mortality rate of up to 33%. Patients who had TIPS performed during the initial bleeding episode do not require additional specific therapy, but should be referred for liver transplant evaluation. The first-line therapy for patients who do not undergo TIPS initially is nonselective beta blockers plus EVL.[48] If the patient bleeds while on first-line therapy, he/she should undergo TIPS. A multicenter randomized controlled trial comparing TIPS to EVL plus nonselective beta blockers found that TIPS was associated with a significantly lower rate of rebleeding but had a higher rate of early encephalopathy. There were no differences in survival.[115] The evaluation and surgical management of patients with complications of cirrhosis is discussed in Chapter 58.

Clinical Outcomes for Upper GI Bleeding

Overall, the mortality rate for patients with upper GI bleeding is 2.0% to 2.5%.[3,5,17] The mortality rate for patients bleeding from GEV is more than twice that of patients bleeding from nonvariceal causes.[17] Patients who develop upper GI bleeding while they are hospitalized for another condition

have a mortality rate that is 3 to 4 times higher than that of patients who present to the hospital with GI bleeding.[21]

LOWER GASTROINTESTINAL BLEEDING

Diverticular Disease

Diverticular disease is the most common cause of lower GI bleeding, accounting for about 30% of cases.[10,11,116] The age- and sex-adjusted incidence of diverticular bleeding in the United States is 19 to 24 cases per 100,000 population per year.[4,117] The cumulative incidence of lower GI bleeding in patients with known diverticular disease is 2.2% at 5 years.[117]

Diverticular bleeding originates most commonly from the right colon despite the fact that in Western population diverticular disease predominantly affects the left colon. Bleeding is caused by perforation of a vasum rectum located at the neck or apex of the diverticulum. The vasa recta penetrate the colon wall through obliquely oriented connective tissue septa. Protrusion of the mucosa and submucosa through this tissue plane forms the diverticulum and causes apposition of the colonic mucosa and the vasum rectum. This is illustrated in Figure 65.3. Ulceration of the mucosa of the diverticulum and disruption of the arterial wall cause hemorrhage into the bowel lumen.

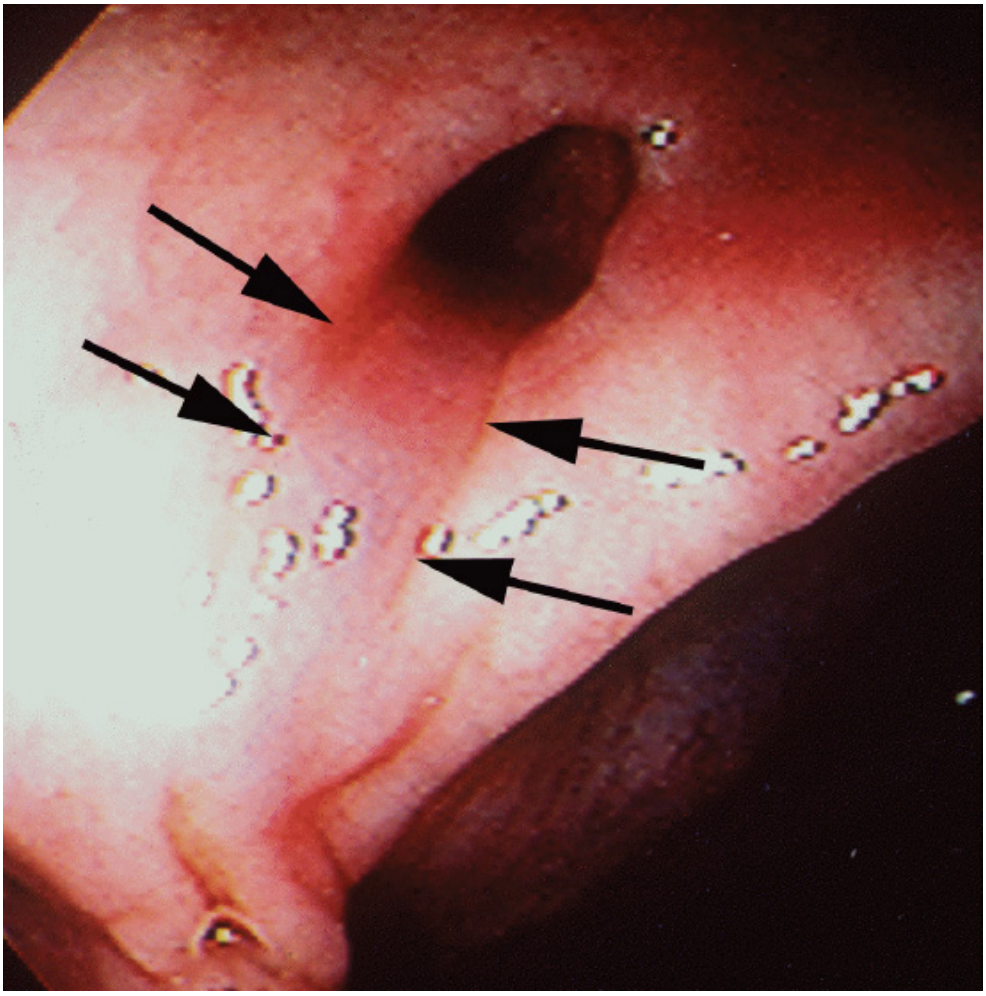

Figure 65.3 Endoscopic view of a colonic diverticulum showing a vasum rectum underneath the colonic mucosa at the neck of the diverticulum (*arrows*).

Patients with diverticular bleeding present with painless, intermittent, large-volume hematochezia. The color of the blood varies from dark maroon to bright red blood clots depending on the location and intensity of the bleeding. Patients with diverticular bleeding do not typically exhibit small amounts of bleeding. Important risk factors for diverticular bleeding are age greater than 70 years, pancolonic disease, the use of NSAIDs, ASA, or anticoagulants, and a previous episode of diverticular bleeding.[117–119]

Most patients (75% to 80%) with diverticular bleeding will stop bleeding spontaneously, although recurrence is common. The incidence of a second episode of bleeding is 3,626 per 100,000 person-years and the median time between the first and second episodes is 1.2 years. The incidence of recurrent bleeding is higher for individuals who have the index bleed at an

older age and those individuals taking antiplatelet agents. If a person has had two prior episodes of diverticular bleeding, the annual risk of recurrent hemorrhage is about 11%.[117]

Endoscopic hemostasis is an effective treatment for patients with diverticular bleeding and high-risk endoscopic stigmata (active bleeding, nonbleeding visible vessel). The particular technique depends upon the location of the bleeding, the ability to access the bleeding site, and the operator's experience.[53,120] The use of endoscopic clips (with or without epinephrine injection) has the advantage of reducing the potential for transmural injury and perforation associated with contact thermal modalities, especially in the thin-walled right colon.[53,120] A review of endoscopic treatment of 137 patients with diverticular bleeding reported successful hemostasis in 92% of patients and no reported complications.[12]

Patients with severe bleeding who cannot tolerate colonoscopy should undergo CT angiography to identify the site of bleeding followed by selective visceral angiography. Superselective embolization with microcoils, polyvinyl alcohol particles, or water-insoluble gelatin (gel foam) has improved the success rate of this procedure and reduced the risk of adverse events, especially bowel infarction. Reports of embolization as first-line therapy for patients with overt lower GI bleeding documented successful initial hemostasis in 85% to 96% of patients with early rebleeding in 22% of patients.[12,121]

The indications for surgical treatment of patients with diverticular hemorrhage include: (1) bleeding that has been unresponsive to endoscopic hemostasis and angiographic embolization, (2) recurrent bleeding that is refractory to endoscopic or angiographic hemostasis, and (3) massive hemorrhage in which the patient has been unresponsive to resuscitation. Preoperative localization of the bleeding site is important and allows the surgeon to limit the extent of resection to a partial colectomy, reduces the likelihood of recurrent bleeding, and improves short- and long-term outcomes. A subtotal colectomy is indicated in rare instances in which the site of bleeding cannot be localized. The rate of recurrent bleeding after a subtotal colectomy is less than 4% and the perioperative mortality rate is 2% to 6%.[122,123] The surgical management of complications of diverticular disease is discussed in Chapter 69.

Internal Hemorrhoids

Hemorrhoids are dilated submucosal veins located in the anus above (internal hemorrhoids) or below (external hemorrhoids) the dentate line. Although usually asymptomatic, patients with first-degree hemorrhoids (i.e., internal hemorrhoids bulging into, but not out of, the anal canal) may present with painless, recurrent episodes of bleeding that cause coating or streaking of the stool with bright red blood, the dripping of blood into the toilet, or staining of tissue with blood. Severe bleeding requiring transfusion is uncommon except in patients taking anticoagulants and those with portal hypertension.

Anoscopy should be the initial diagnostic study for all patients with lower GI bleeding. It will identify internal hemorrhoids as the cause of rectal bleeding and facilitate their treatment by banding. Even if internal hemorrhoids are present, colonoscopy is still necessary to exclude another more serious source of bleeding.

Mild hemorrhoidal bleeding can be successfully managed with diet and lifestyle modification. Dietary changes include fiber supplementation and increased water consumption with the goal of reducing straining during defecation. Other lifestyle modifications include the avoidance of prolonged sitting or straining on the toilet, improved perianal hygiene, and avoiding triggers of constipation or diarrhea.

Banding is effective in controlling hemorrhoidal bleeding in more than 90% of patients. Patients who have failed banding or other forms of endoscopic treatment, those with symptomatic combined internal/external hemorrhoids (grades III/IV), and patients who are coagulopathic may require operative treatment. Although more effective than endoscopic hemorrhoidal banding, operative treatment is associated with a higher rate of complications such as anal stenosis and postoperative bleeding. The management of complications of hemorrhoids is discussed in Chapter 70.

Colon Ischemia

Colon ischemia (also referred to as ischemic colitis) is an acute condition caused by transient ischemia and reperfusion of a segment of the colon that leads to localized inflammation, mucosal ulceration, and bleeding. The

severity of the injury ranges from reversible localized inflammation to transmural infarction and necrosis. In the United States, colon ischemia accounts for 7% to 12% of hospital admissions for lower GI bleeding.[11,116] The left colon is most commonly affected (33%).[124] The vascular watershed areas of the colon, such as the splenic flexure and the sigmoid colon, are particularly susceptible to ischemic injury.

Colon ischemia is more common in females (57% to 76%) than males and the prevalence increases with age.[125,126] Colon ischemia typically presents with sudden cramping, mild, left lower abdominal pain, an urgent desire to defecate, and the passage of bright red or maroon-colored blood or bloody diarrhea.[127] Abdominal pain (87%), rectal bleeding (84%), and diarrhea (56%) are the most common symptoms.[128] Physical examination demonstrates a soft abdomen with tenderness and voluntary guarding over the affected segment of colon. Peritonitis suggests full-thickness ischemia, perforation, or an alternate diagnosis. The acute onset of symptoms is an important feature of colon ischemia and distinguishes it from other causes of colitis in which the onset of symptoms is more gradual.

Risk factors for the development of colon ischemia include cardiovascular and pulmonary diseases, irritable bowel syndrome, diabetes mellitus, and collagen vascular diseases.[125,126,129] Vasoactive drugs, including cocaine and amphetamines, have also been associated with the development of colon ischemia.[125] Surgical procedures, especially those that require ligation or occlusion of the inferior mesenteric artery such as abdominal aortic aneurysm repair, are also associated with the development of colon ischemia.[126] The rate of colon ischemia following abdominal aortic aneurysm repair is about 2%.[130]

Most episodes of colon ischemia are benign, self-limited, and cause mild rectal bleeding. Severe hematochezia occurs in about 12% of patients and is more frequent in women and in patients with severe lung disease, elevated creatinine and glucose levels, and those receiving anticoagulants.[131] Severe bleeding is also more commonly associated with gangrenous colon ischemia (10%) and fulminant pancolitis (2%).[126,127]

Patients with suspected colon ischemia should undergo CT with intravenous and oral contrast as the initial diagnostic test. This study can suggest the diagnosis, identify areas of affected colon, and exclude other serious (and more common) causes of abdominal pain (e.g., diverticulitis,

appendicitis). CT findings (segmental wall thickening, mucosal thumbprinting, and pericolonic fat stranding) are not specific enough to differentiate colon ischemia from other causes of colitis such as diverticulitis, infectious colitis, or inflammatory bowel disease.

Colonoscopy should be performed within 48 hours of presentation. On endoscopic examination, the colonic mucosa will appear erythematous, edematous, and friable. Mucosal ulcerations may also be present. In instances of gangrene, the bowel wall will appear dusky with blue-black nodules.[126,127] The mucosa should be biopsied except in instances of gangrene. Patients with peritonitis or evidence of irreversible ischemic injury should not undergo colonoscopy.

Most cases of colon ischemia resolve spontaneously without diagnosis or specific treatment. Patients with more significant clinical findings require hospitalization for general supportive measures including fasting, intravenous fluid resuscitation, and broad-spectrum antibiotics. Patients with rectal bleeding usually respond to medical treatment alone. Surgical management is required in about 14% of patients.[131] The most common indications for surgery are peritonitis, clinical deterioration, fulminant colitis, or other evidence of necrotic bowel. The mortality rate for patients needing operative management is 37% to 47%.[126]

Inflammatory Bowel Disease

Clinically significant GI bleeding is rare in patients with inflammatory bowel disease. Overt GI bleeding is more common in patients with Crohn disease (1.2%) than ulcerative colitis (0.1%).[132] In patients with Crohn disease, the site of bleeding is equally distributed between the small bowel, ileocolonic region, and the colon. Severe bleeding from ulcerative colitis is usually caused by pancolitis.[132,133] There are no specific clinical or epidemiologic factors predictive of severe bleeding in patients with either Crohn disease or ulcerative colitis.

Colonoscopy will identify the site of bleeding in 60% to 80% of cases. In most instances, the bleeding originates from diffuse areas of active inflammation or ulcerations.[132–134] Most patients respond favorably to fluid resuscitation and medical treatment of their disease (89%) although recurrent bleeding is common (26%). Relatively few of these lesions are amenable to

endoscopic therapy (10% to 15%).[132,133] The need for surgical treatment for initial control of the bleeding or for recurrent bleeding is common in patients bleeding from Crohn disease (20%) and uncommon for patients with ulcerative colitis.[132,134] The clinical presentation, diagnostic evaluation, and management of complications of inflammatory bowel disease are discussed in Chapters 49 and 65.

Infectious Colitis

Overt lower GI bleeding can occur with infections caused by *Campylobacter jejuni*, *Salmonella*, *Shigella*, Shiga toxin–producing *Escherichia coli*, Cytomegalovirus, or *C. difficile*. Diarrhea along with fever and bloody stools suggests an invasive bacterial etiology (e.g., *Salmonella*, *Shigella*, *Campylobacter*, Shiga toxin–producing *E. coli),* enteric viruses (e.g., Cytomegalovirus), or a cytotoxic organism such as *C. difficile*. Immunocompromised patients, such as those receiving chemotherapy or immunosuppressants, are particularly susceptible to Cytomegalovirus colitis. Treatment consists of fluid resuscitation and targeted antibiotics or antiviral agents.

MID-GASTROINTESTINAL BLEEDING

Five percent to 10% of patients with overt GI bleeding will be bleeding from lesions in the small intestine. The bleeding is vascular (24%), inflammatory (16% to 18%), or neoplastic (11%) in etiology.[2] Recurrent bleeding is common, occurring in about one-third of patients.[135] The differential diagnosis is strongly influenced by the patient's age and medical history. Patients under the age of 40 years are more likely to be bleeding from Crohn disease or a Meckel diverticulum, whereas patients older than 40 years are more likely to be bleeding from angioectasias and NSAID ulcers. A history of a bleeding diathesis (such as von Willebrand disease), medication usage (such as ASA, NSAIDs, anticoagulants, and other antiplatelet agents), valvular heart disease, chronic renal failure, and cirrhosis are important risk factors for small bowel bleeding.[2,136]

Angioectasia

Vascular lesions of the GI tract may be classified into three broad categories: (1) vascular tumors, which may be benign (e.g., hemangioma) or malignant (e.g., Kaposi sarcoma, angiosarcoma), (2) vascular anomalies associated with congenital or systemic diseases (e.g., Klippel–Trenaunay–Weber syndrome, hereditary hemorrhagic telangiectasias), and (3) acquired and sporadic lesions (e.g., angioectasias, gastric antral vascular ectasias, radiation-induced vascular ectasias, and Dieulafoy lesions).

Angioectasias are the most common vascular abnormality of the GI tract. They are characterized by abnormal, ectatic, dilated, tortuous, and usually small blood vessels located within the mucosa and submucosa of the GI tract. The affected vessels are lined by vascular endothelium with little or no smooth muscle. There is no associated inflammation or fibrosis. They are most commonly located in the jejunum (80%) followed by the duodenum (51%), stomach (23%), and right colon (11%). Sixty percent of patients with angioectasias will have lesions in multiple sites within the GI tract.[137]

Most angioectasias are asymptomatic and discovered incidentally during endoscopy for other indications. For example, Fouch et al. reported finding angioectasias in 8 of 964 healthy, asymptomatic patients undergoing screening colonoscopy for colon cancer. None of these patients bled from these lesions when followed for 3 years.[138] Most symptomatic patients present with clinical evidence of chronic well-compensated occult blood loss. Patients with overt GI bleeding may present with hematemesis, melena, or hematochezia depending on the location of the lesion and the intensity of the hemorrhage. Most patients with angioectasias are 60 years of age or older. Risk factors include advanced age, chronic renal disease, and cardiovascular disease.[137] Bleeding from angioectasias in patients with aortic stenosis, termed Heyde syndrome, is postulated to result from an acquired von Willebrand factor deficiency.[8]

VCE is the preferred first-line diagnostic test for patients suspected to be bleeding from the small bowel. Patients with active bleeding on VCE are treated with endoscopic hemostasis using DAE and argon plasma coagulation.[2,58,59] Unfortunately, recurrent bleeding is common (34% to 45%). Risk factors for recurrent bleeding include the number of vascular lesions, age over 65 years, presence of lesions in the jejunum, cardiac

valvular disease, chronic renal disease, use of anticoagulants, and the need for transfusion.[139]

A number of medical treatments have been proposed for patients bleeding from angioectasias. Octreotide has been shown to reduce the transfusion requirements of patients bleeding from angioectasias as has low-dose thalidomide.[139–141] Hormonal therapy (estrogen plus progesterone) has been abandoned because of lack of efficacy in randomized controlled trials.

Hemodynamically unstable patients with active bleeding should undergo CT angiography followed by angiographic embolization of the bleeding site. Superselective embolization will control the bleeding in 70% to 80% of cases, with recurrent bleeding in about 12% of cases.[142,143] Surgical management is reserved for those instances in which endoscopic and angiographic hemostasis have been unsuccessful. Laparotomy with intraoperative enteroscopy will identify the site of bleeding in patients with overt hemorrhage and facilitates endoscopic hemostasis.[144] Aortic valve replacement reduces the risk of bleeding from angioectasias in patients with Heyde syndrome.[8]

Meckel Diverticulum

Meckel diverticulum is the most common GI congenital anomaly, occurring in 0.3% to 2.9% of the population.[145] About 4% of Meckel diverticula are symptomatic.[145–148] Symptomatic Meckel diverticula can present at any age but predominantly occur in children and young adults. More than half of all symptomatic patients are younger than 10 years of age[149–151] and most are males (1.5:1 to 4:1).[145,152] Twenty-five percent to 35% of symptomatic patients present with GI bleeding[145,152] in which case it is postulated that heterotopic gastric oxyntic glands located within the Meckel diverticulum cause peptic ulceration of adjacent small bowel mucosa with resulting hemorrhage.

A Meckel scan (pertechnetate scintigraphy) will detect a bleeding Meckel diverticulum with a high degree of accuracy in children (>90%).[67] Unfortunately, the diagnostic accuracy of a Meckel scan in adults is less than 50%.[68] The diagnostic accuracy of balloon-assisted enteroscopy in patients with bleeding Meckel diverticula is 85% to 90%.[68,153] Treatment consists of

resecting the diverticulum with adjacent bowel. Diverticulectomy alone will allow persistence of the ulcer and possibly recurrent bleeding.

Small Bowel Diverticula

Diverticular disease of the small intestine is an uncommon cause of GI bleeding. About 80% of small bowel diverticula are located in the jejunum and multiple diverticula are common (67%). Small bowel diverticula are pseudodiverticula (like colonic diverticula) and may be complicated by diverticulitis, obstruction, and bleeding. The pathogenesis of bleeding is the same as that of colonic diverticula with erosion of a vasum rectum through the diverticular wall with the acute onset of massive hemorrhage.

Patients present with hematemesis, melena, or hematochezia depending on the location of the diverticulum and the intensity of bleeding. CT angiography will localize the site of bleeding in actively bleeding patients and DAE or visceral angiography will facilitate endoscopic hemostasis or selective microembolization, respectively. Surgical resection of the involved bowel is the treatment of choice in those instances in which endoscopic hemostasis or angiographic embolization is unavailable or has been unsuccessful.

Aortoenteric Fistula

Although communication between the aorta and the intestine may occur as a result of aneurysmal disease or infectious aortitis (*primary aortoenteric fistula*), most aortoenteric fistulas result from erosion of an aortic vascular prosthesis through the wall of the distal duodenum (*secondary aortoenteric fistula*). The incidence of aortoenteric fistula following aortic reconstructive surgery is about 1% with most of these fistulas arising from the proximal graft anastomosis. This may occur after open or endovascular aortic procedures.

Patients may present with massive GI hemorrhage and exsanguination. Others may have an initial episode of GI bleeding (i.e., herald bleed) that is followed in hours, days, or weeks by catastrophic hemorrhage. Patients may also complain of back or abdominal pain and less commonly have fever or signs of sepsis from infection of the graft.

The diagnosis of an aortoenteric fistula must be considered in any patient with an aortic prosthesis or an abdominal aortic aneurysm who presents with GI hemorrhage. If the patient is hemodynamically stable, the initial diagnostic study should be CT angiography. This test may demonstrate evidence of an aortoenteric fistula such as perigraft infection. If CT angiography is negative or nondiagnostic, EGD should be urgently performed to identify evidence of the aortoenteric fistula (such as the blood, clot or graft material in the distal duodenum) or another cause of bleeding, such as peptic ulcer disease. Care should be taken to avoid dislodging fresh thrombus in the distal duodenum as it can induce massive hemorrhage. In patients who are actively bleeding, exploratory laparotomy with exposure of the proximal graft should be undertaken. Identification of an aortoenteric fistula requires repair of the duodenal wall and resection of the graft with aortic reconstruction or extra-anatomical bypass. The complications of abdominal aortic operations including aortoduodenal fistulas and their management are discussed in Chapter 94.

Gastrointestinal Stromal Tumors

Gastrointestinal stromal tumors (GISTs) are infrequent causes of overt GI bleeding. These tumors occur most commonly in the stomach (36%) and small intestine (18%), but may be found anywhere within the GI tract. The age-adjusted incidence of GISTs is 0.7 to 1.2 cases per 100,000 population per year. The median age of patients with a GIST is 65 years with a slight predominance in females (M/F ratio = 0.8). Most GISTs (97%) are sporadic and associated with a mutation of the C-kit (71%) or platelet-derived growth factor receptor alpha (15%) gene.[154]

GI bleeding is a common and important clinical manifestation of GISTs.[155,156] About one-third of patients with GISTs will present with evidence of GI bleeding such as hematemesis, hematochezia, or the passage of melena. Fewer patients will present only with occult blood loss, for example, iron-deficiency anemia or a positive fecal occult blood test.[156,157] CT (e.g., CT angiography, CT enterography) or endoscopy (e.g., EGD, VCE, DAE, colonoscopy) is diagnostic in the majority of cases. The specific diagnostic modality depends upon the suspected site and magnitude of hemorrhage.

The treatment of choice for patients bleeding from a GIST is surgical resection with a 1- to 2-cm macroscopically normal margin. Postoperative tyrosine kinase inhibitor therapy with imatinib is useful for patients at high risk of recurrence. The molecular biology, clinical presentation, and management of patients with a GIST are discussed in detail in Chapter 50.

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Ulcerative Colitis

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Key Points

1. Ulcerative colitis (UC) is a form of inflammatory bowel disease (IBD) characterized by mucosal and submucosa inflammation of the colon and rectum. This process is continuous and homogenous, beginning in the rectum, and extending proximally for a variable distance.
2. The acute indications for surgical intervention include fulminant disease, toxic megacolon, and uncontrolled bleeding. Failure of medical management, dysplasia, and cancer are indications for elective surgery.
3. Intestinal and some extraintestinal manifestations of UC can be cured by complete removal of the colon and rectum.
4. Current surgical options depend on the acuity of presentation of the disease; minimally invasive methods should be employed when clinically indicated and technically feasible.
5. Ileal pouch-anal anastomosis (IPAA) can provide patients with a continent reservoir for stool; however, permanent end ileostomy remains a viable option for patients who do not qualify or do not wish to undergo pouch construction.
6. Although perioperative and late complications after IPAA are common, the vast majority of patients enjoy a high quality of life after surgery.

INTRODUCTION

Ulcerative colitis (UC) is a nonspecific and idiopathic inflammatory bowel disease (IBD) affecting nearly 600,000 Americans of both sexes and all ages groups, although peak onset occurs between the second and fourth decade of life.[1] Unlike Crohn disease (CD)—a related, but distinct entity affecting the entire gastrointestinal (GI) tract—UC primarily affects the mucosa and submucosa of the colon and rectum through recurrent episodes of inflammation, ulceration, and healing. While chronic UC increasingly has

been managed successfully via medical and biologic therapy, surgery continues to play a role in the treatment of acute severe disease, medically refractory disease, dysplasia, and cancer.

EPIDEMIOLOGY

Although the exact incidence and prevalence of UC remains difficult to determine due to its relative infrequency and the fact that mild cases might never be reported, several trends have emerged. First, the disease appears to demonstrate a North/South gradient, with the highest incidence and the prevalence occurring in northern Europe (24.3 per 100,000 person-years and 505 per 100,000 people) and Canada (19.2 per 100,000 person-years and 248 per 100,000 people) and the lowest in Asia and the Middle East.[2–4] American estimates indicate a slightly lower prevalence than Europe or Canada, ranging from 214 to 238 per 100,000 people.[5,6] Second, despite slightly higher rates of CD among women, there appears to be no sexual predominance in UC.[2,6] Third, the age-specific incidence of UC appears to be bimodal with the largest peak between 15 and 40 years old followed by a separate, smaller peak at 50 to 75 years old (**Fig. 66.1**).[6,7] Finally, after a steady increase throughout the industrialized world over the last 20 years, both the incidence and prevalence of UC appear to have stabilized in North America and Europe, with continued growth being limited to newly industrialized areas in Africa, Asia, and South America.[3,8]

ETIOLOGY AND RISK FACTORS

The etiology of UC remains unknown. Extensive investigations have failed to isolate a specific gene, environmental exposure, or immunologic dysfunction.[9] Instead, the origin is believed to be multifactorial. That is, patients are born with an underlying genetic predisposition that is activated via the interaction or dysregulation of a variety of environmental and microbial risk factors.

Genetics

Familial clustering has been identified since the earliest descriptions of UC. Between 10% and 20% of UC patients have at least one other family member with IBD, particularly UC as opposed to CD, further suggesting the two diseases represent separate clinical entities.[10] Interestingly, parent–child and sibling–sibling pairings appear to be more common than pairings involving more distant relatives despite no clear Mendelian inheritance pattern.[11] Monozygotic twin concordance varies, but has been reported to be between 10% and 19%.[12–14] In addition, certain ethnic groups, particularly Ashkenazi Jewish populations, have significantly higher rates of UC compared to geographic controls.[15] Overall, first-degree relatives of a patients with UC have a four-fold increase in their risk of developing the disease.[16]

Over 200 separate gene loci have been associated with an increased risk of developing IBD. The vast majority are located in genes involved in inflammatory signaling or mucosal barrier function and confer a risk for both UC and CD, although several disease-specific relationships have been identified.[17–19] For example, certain human leukocyte antigen haplotypes and alteration in cell–cell junction signaling appear to be more associated with UC than CD.[20–22] However, currently identified genetic features explain only 7.5% of disease variance in UC and do not reliably predict disease activity.[23,24]

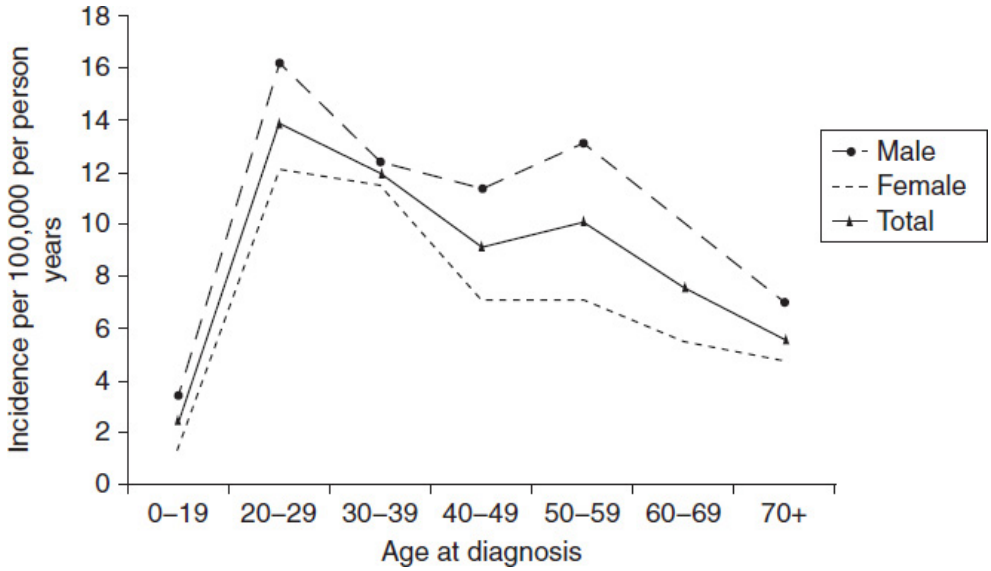

Figure 66.1 Age-specific incidence of UC in Midwestern U.S. population. (Adapted from Loftus CG, Loftus EV Jr, Harmsen WS, et al. Update on the incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted County, Minnesota, 1940–2000. *Inflamm Bowel Dis* 2007;13[3]:254–261.)

Environment

Although none have proven causal, multiple environmental exposures have been associated with a higher incidence of UC. Diets high in fats, meats, and refined sugar or low in vegetables appear to be associated with an increased risk of developing UC.[25–28] There is some evidence that breast feeding is protective against the development of both UC and CD, including a dose-dependent response with the lowest rates among children who were breastfed for at least 12 months compared to 3 or 6 months.[29]

Exposure to microorganisms and antibiotics also appears to play some role given that both the temporal and geographic incidence of IBD parallel trends in urbanization.[30] The odds of developing IBD are 2.9 times higher among children exposed to antibiotics within their first year of life and 2.8 times higher among children treated at least once for otitis media between 2 and 5 years old.[31,32] Whether the trigger is the exposure to a pathogenic bacteria or the lack of exposure to normal, nonpathogenic bacteria that promote immune regulation—the so-called "hygiene hypothesis"—remains unknown.[33]

Cigarette smoking plays a complex role in the development of IBD. In contrast to CD, active smokers have a lower incidence of UC than nonsmokers. Former smokers, however, are at higher risk than individuals who have never smoked.[34–36] The apparent protective effect of smoking extends to some of the extraintestinal manifestations of UC, in particular lower rates of primary sclerosing cholangitis (PSC).[37,38] Interestingly, appendectomy also appears to be protective against developing UC, with up to a 30% to 45% risk reduction in large, retrospective studies.[39–43] Although the mechanism remains unknown, some have suggested that responding to an inflammatory process like appendicitis stimulates the immune system to perform self-regulatory functions that prevent the inappropriate inflammatory cascade that characterizes UC.

Microbiome

The newest line of inquiry into the pathogenesis of IBD involves the influence of the microbiome, both on its own and through its interaction with other risk factors. Animal studies have demonstrated that mice with a genetic susceptibility do not develop colitis if kept in a germ-free environment while healthy mice that are inoculated with microbiota from IBD patients go on to develop colonic inflammation.[44,45] Humans predominantly develop IBD in areas of the body with high bacterial loads (colon) and fecal stasis (terminal ileum and rectum).[30] Moreover, fecal diversion, the use of antibiotics, and even fecal microbial transplantation have been associated with disease remission in select UC patients.[46–49]

In addition, the microbiome appears to mediate the influence of other epidemiologic risk factors. Patients with defects in NOD2, the gene encoding an intracellular pattern recognition receptor that interacts with bacterial peptidoglycan, appear to have both higher levels of proinflammatory bacteria and a more aggressive phenotype of CD.[50–52] Breast milk contains anti-inflammatory microbiota as well as prebiotic oligosaccharides that promote immune tolerance. Similarly, cigarette smokers have more proinflammatory and less anti-inflammatory bacteria in their gut lumen when compared to nonsmokers and there is some evidence of normalization upon smoking cessation.[53]

CLINICAL FEATURES

UC symptoms are dynamic and typically parallel the severity of disease. Inflammation classically begins in the rectum and extends proximally in a homogenous and continuous fashion. The degree of colonic involvement is variable, ranging from the rectum alone (proctitis) to the rectosigmoid (proctosigmoiditis) to the entire colon and rectum (pancolitis) in approximately 20% of patients.[54] Unlike in CD, the small intestine is spared, aside from the final few inches of the terminal ileum, which can experience a reversible "backwash ileitis" from the reflux of diarrheal stool (**Table 66.1**). Heterogenous inflammation, rectal sparing, and significant ileal or proximal small bowel disease raise the possibility of CD and require further evaluation.

The classic symptoms of UC are diarrhea and rectal bleeding, although patients may present anywhere along the spectrum from chronic low-grade disease to fulminant colitis. The diarrhea is typically small volume, consisting of mostly blood and mucus, and can be as frequent as every 1 to 2 hours. Paradoxically, patients with isolated rectosigmoid disease may experience constipation and incomplete evacuation (tenesmus) as a result of rectal spasm.[24] The bleeding is also typically a slow, low-volume ooze from diseased mucosa rather than the massive hemorrhage that can be seen with vessel injury. Many patients experience diffuse, crampy abdominal pain, especially in the left lower quadrant, that is relieved or improved by defecation.[55] Persistent or severe pain is uncommon and should raise concern for severe disease with inflammation extending to the serosa.[56]

Disease severity is typically calculated using the Mayo Clinic Score, although other scales exist (**Table 66.2**).[57] Worsening abdominal distention along with signs of systemic involvement, including fever, tachycardia, and leukocytosis, are worrisome for fulminant colitis or toxic megacolon and require immediate surgical evaluation. Chronic signs of illness, including weight loss, fatigue, anemia, and anorexia, must be identified and addressed as a part of a comprehensive treatment plan, ideally prior to any surgical intervention, if possible.

Table 66.1 Clinicopathologic Features of Ulcerative Colitis versus Crohn Disease

Common Clinicopathologic Characteristics of IBD		
Manifestation	**UC**	**CD**
Bleeding	Common	Rare
Crypt abscesses	Common	Rare
Rectal involvement	Common	Rare
Small bowel involvement	Rare	Common
Transmural inflammation	Rare	Common
Bowel wall fissures	Rare	Common
Fibrosis	Rare	Common
Fistulas	Rare	Common
Perianal disease	Rare	Common
Ulcers	Rare	Common
Cobblestoning	None	Common
Pattern of involvement	Continuous, distal to proximal, mucosal	Skip lesions, transmural

Table 66.2 The Mayo Clinic Score

Stool Frequency (3-day average)
(Total number of stools/day)
0 = Normal number of stools for this patient
1 = 1–2 stools/d more than normal for this patient
2 = 3–4 stools/d more than normal for this patient
3 = >5 stools/d more than normal for this patient

Rectal Bleeding (3-day average)
0 = No blood seen
1 = Streaks of blood with <50% of stools
2 = Obvious blood seen with >50% of stools
3 = Blood alone passed

Physician's Global Assessment (PGA)
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

Finding of Flexible Proctosigmoidoscopy (Endoscopic Subscore)
0 = Normal or inactive disease
1 = Mild disease (erythema, decreased vascular pattern, mild friability)
2 = Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3 = Severe disease (spontaneous bleeding, ulceration)

Table 66.3 Extraintestinal Manifestations of UC by Disease Activity

Parallel Disease Activity	Independent of Disease Activity	Variable Course
Erythema nodosum	Polyarticular peripheral arthritis/arthropathies	Primary sclerosis cholangitis
Pauciarticular peripheral arthritis/arthropathies	Axial arthropathies (sacroiliitis, ankylosing spondylitis)	Pyoderma gangrenosum
Acute synovitis	Uveitis/iritis	
Episcleritis	Aphthous ulceration	

Adapted from Vavricka SR, Schoepfer A, Scharl M, et al. Extraintestinal manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2015;21(8):1982–1992.

Extraintestinal Disease

Hepatobiliary

Asymptomatic transaminitis is the most common hepatobiliary abnormality in UC, affecting nearly 50% of patients. Although much less common—occurring in only 3% to 7% of UC patients—PSC is the most feared hepatobiliary manifestation of UC since there is no effective medical therapy short of liver transplantation.[58,59] PSC is independent of colonic disease activity, may precede colonic symptoms of UC by up to 7 years, and persists even after proctocolectomy (**Table 66.3**). In addition, PSC patients are at four to five times higher risk of developing colorectal cancer than patients with UC alone; as such, they require more intensive endoscopic surveillance.[60]

Cutaneous

Erythema nodosum is the most common cutaneous manifestation of IBD, occurring in 10% to 15% of cases.[61] Patients develop tender, raised, and red-violet nodules in their subcutaneous tissue that represent

lymphohistocytic infiltrates responding to an unknown antigen. The number and severity of lesions tightly parallels colonic disease activity and persistence can be interpreted as a sign of inadequate disease control.[62] Pyoderma gangrenosum occurs less frequently, but is more difficult to treat and does not reliably parallel disease activity. Lesions begin as erythematous plaques in the pretibial region, but progress into ulcerative, painful wounds with ragged borders (**Fig. 66.2**). Topical or intralesional steroids, topical tacrolimus, and systemic tumor necrosis factor-alpha (TNF-α) antagonists produce some response, although aggressive wound care is essential to healing.[63,64] Peristomal lesions can be particularly difficult to treat. Although occasionally necessary, re-siting should be performed with caution as lesions are known to recur at the new stoma site.[65]

Musculoskeletal

Peripheral and axial arthropathies occur in a minority of UC patients, but can be particularly debilitating.[66] Pauciarticular peripheral arthritis is acute and parallels colonic disease activity while polyarticular disease persists and follows an independent course.[67] Patients with a family history and the HLA-B27 haplotype are at higher risk of developing axial disease, including sacroiliitis and ankylosing spondylitis, which can unfortunately progress to significant disability. NSAIDs and exercise programs remain the mainstays of management, although anti-TNF and, more recently, anti-IL-17 agents appear to provide some relief in severe cases.[68,69]

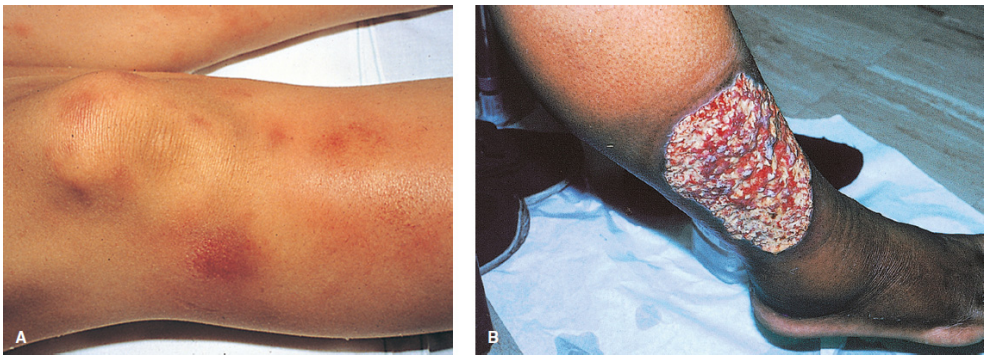

Figure 66.2 **A:** Erythema nodosum. **B:** Pyoderma gangrenosum. (Reproduced with permission from Goodheart HP. *A Photoguide of Common Skin Disorders: Diagnosis and Management*. Baltimore, MD: Lippincott Williams & Wilkins; 1999.)

Ophthalmologic

Although UC patients frequently report ophthalmologic symptoms, fewer than 10% actually develop ocular inflammation, including, episcleritis, iritis, and uveitis.[70,71] Episcleritis is the most common and is characterized by redness without vision changes. Both iritis and uveitis are less common, but can produce pain, blurry vision, and eventually blindness if not treated promptly with steroids or immunomodulatory medications.[72]

DIAGNOSIS

Physical examination is often nonspecific, although worsening abdominal distention and generalized abdominal pain are often indicators of severe disease. As with other septic conditions, the triad of tachycardia, fever, and leukocytosis suggests systemic toxicity and should prompt rapid resuscitation and surgical evaluation.

Laboratory Testing

There is no specific diagnostic test for UC. In the acute setting, a complete blood count will evaluate for systemic toxicity and anemia. Serum albumin and prealbumin provide a measure of protein loss and malnutrition. Erythrocyte sedimentation rate or C-reactive protein levels can be drawn and followed as markers of disease activity. Stool studies and a *Clostridium difficile* assay should be sent to rule out bacterial and parasitic infections.

Calprotectin, a calcium-binding protein expressed by neutrophils, can be measured in the stool as a marker of colonic mucosal inflammation. Meta-analyses report an 80% to 95% sensitivity and a 76% to 96% specificity for distinguishing IBD from non-IBD diagnoses, including patients with irritable bowel syndrome.[73–75] In fact, patients with levels of <50 μg/g have only a 1% to 4% chance of having IBD. Fecal calprotectin levels also appear to correlate with endoscopic findings, degree of mucosal healing, and risk of relapse at 3 and 6 months.[76]

Serum antibodies, such as anti–*Saccharomyces cerevisiae* antibody (ASCA) and atypical perinuclear antineutrophil cytoplasmic antibody

(pANCA), are often elevated in IBD, but do not reliably distinguish UC from CD or predict disease activity in UC, although ASCA+ may be a marker for complex disease in CD. Patients who are ASCA+/pANCA−have the highest positive predictive value for UC (77% to 95%), although the sensitivity for this combination is only 30% to 38%.[77]

Imaging

Conventional x-rays are quick and can be useful in the rare case of frank perforation or toxic megacolon. Classically, barium enema was performed in the diagnosis of chronic UC, although it has largely been replaced by more modern imaging modalities. Colonic foreshortening, loss of haustral markings, and linear, "collar button ulcers" are signs of long-standing colonic inflammation (**Fig. 66.3**).

Computed tomography (CT) of the abdomen and pelvis with IV and occasionally oral and/or rectal contrast has become the technique of choice in evaluating acute disease. CT can be obtained rapidly, can demonstrate the extent and severity of inflammation, and can rule out extraintestinal air or other signs of perforation.

Magnetic resonance imaging (MRI), especially specialized enterographic protocols involving biphasic oral contrast agents (magnetic resonance enterography; MRE), is often used for evaluating chronic disease (**Fig. 66.4**).[78]

Both MRE and its CT equivalent (CTE) can document both intra- and extramucosal disease activity, including the presence of fistulae, phlegmons, masses, or abscesses that might suggest a disease process other than UC.[79] Importantly, MRE and CTE are both 90% to 95% sensitive for small bowel CD, a diagnosis that must be excluded, if at all possible, prior to any elective surgical intervention.[80,81] MRI has the advantage of limiting ionizing radiation exposure, which can benefit younger patients who may require multiple imaging studies over their lifetime.

Figure 66.3 Abdominal x-ray of megacolon. (Beck DE, Roberts PL, Saclarides TJ, et al. *ASCRS*. New York: Springer; 2011.)

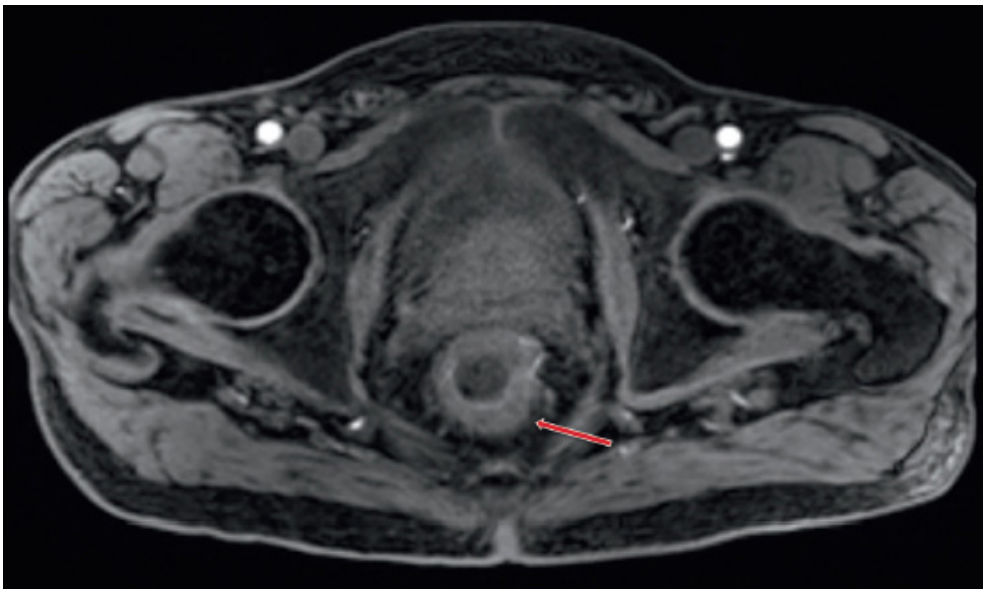

Figure 66.4 MRI demonstration of active UC with rectal wall thickening, increased vascularity, and inner layer hyperenhancement. (Courtesy of Dr. William Reed.)

Endoscopy

Endoscopy with biopsies remains the gold standard for the diagnosis of UC. Limited evaluation with flexible sigmoidoscopy or rigid proctoscopy is often sufficient given the near universal involvement of the rectum and may be safer in the setting of acute inflammation when full colonoscopy may pose an increased risk of perforation. Mucosal inflammation is typically graded on the Mayo Endoscopic Subscore, a component of the Mayo Score (**Table 66.3**), which has shown strong correlation with microscopic findings and good interrater reliability.[82–84] Biopsies should also be taken to confirm histologic evidence of IBD, rule out concomitant cytomegalovirus (CMV) infection, and evaluate for dysplasia.

Surveillance and management of dysplasia in IBD has evolved in recent years. In short, surveillance colonoscopy should begin within 8 to 10 years of the onset of symptoms and should be performed every 1 to 2 years. Patients with a family history of colorectal cancer or PSC should be surveilled more frequently.[85] At least 32 random biopsies must be performed throughout the colon—typically eight each in the right, transverse, left, and sigmoid colon—to achieve a 90% sensitivity for ruling out dysplasia.[86] Any polyps that are discovered should be removed endoscopically, if possible, and biopsies should be taken of the surrounding tissue to rule out persistent dysplasia.[87]

Pathology

Macroscopic Appearance

UC starts in the rectum and progresses proximally in a continuous fashion, with the most severe inflammation typically occurring in the most distal regions (**Fig. 66.5**). Inflamed mucosa generally appears granular, friable, and congested when viewed endoscopically. This pattern can dissipate either gradually or abruptly as one moves proximally, but is never interrupted by areas of normal mucosa ("skip lesions"). Rectal mucosa in UC may be "burned out" or may demonstrate local treatment effect, but it is never spared, as in seen in CD.

Ulcers, superficial fissures, and pseudopolyps may be present in more severely inflamed areas, however, unlike in CD, fibrosis and strictures are uncommon (**Table 66.2**). In fact, the presence of stricturing disease in

suspected UC should raise concern for malignancy until proven otherwise, especially if symptomatic, proximal to the splenic flexure, or late in the course of the disease.[88] The presence of fistulizing disease indicates CD rather than UC.

Microscopic Appearance

Histology should confirm evidence of both colitis and chronicity. Biopsies demonstrate inflammation, including neutrophils within the surface epithelium, lamina propria, and crypts. Although inflammation in UC is traditionally confined to the mucosa and submucosa, the colon wall can be inflamed transmurally in the setting of acute severe disease, mimicking CD. Neutrophilic infiltration of the crypts ("cryptitis") can lead to aggregation ("crypt abscesses") and eventually ulceration (**Table 66.2**). As these findings are also present in acute non-IBD colitis, additional evidence of chronicity (irregularities in crypt size, shape, and spacing) or regeneration (mucin depletion, hyperchromatic nuclei, Paneth cell metaplasia) is required to make the diagnosis of UC.

Differential Diagnosis

Bloody diarrhea is a hallmark of acute colitis from any etiology. Infectious sources, such as *C. difficile,* Campylobacter, Salmonella, *Escherichia coli* 0157:H7, and Entamoeba, should specifically be excluded via stool studies. Biopsies should be tested for CMV, regardless of whether an underlying diagnosis of IBD is made. Persistent diarrhea with a normal or relatively normal colonoscopy warrants biopsies to rule out microscopic colitis. Segmental inflammation may be due to ischemic colitis (splenic flexure or rectosigmoid) or diverticular disease (sigmoid colon).

In nearly 10% of the cases, it is impossible to definitively classify the source of the colitis. Over time, a portion of these cases will declare themselves as either CD or UC, while others will remain indeterminate, especially if the serologic assessment is inconclusive.[89] As has been mentioned throughout, distinguishing UC from CD can be a challenge, particularly in the setting of CD colitis (25% of CD cases).[90] Upper GI symptoms, small bowel involvement, perianal disease, and patchy colonic

involvement should elicit some pause before proceeding with definitive surgical interventions.

MANAGEMENT

Medical Management

Medical therapy for UC is separated by disease severity. In general, patients with mild-to-moderate colitis are treated in the outpatient setting with oral and/or rectal medications while patients with fever, tachycardia, or significant abdominal tenderness are admitted to the hospital for intravenous resuscitation and steroids. All treatment regimens have the same goals, regardless of the medications used: induction of clinical remission with improvement or elimination in symptoms, promotion of mucosal healing ("endoscopic remission"), maintenance of steroid-free remission, and prevention of complications and, where possible, colectomy.

Mild-to-Moderate Colitis

Aminosalicylates continue to be the first-line treatment of mild UC and can be used both for induction and maintenance of remission.[91] Mesalamine (5-ASA) is the active compound, but is metabolized by proximal intestinal cells and requires either specialized coating or azo bonding to another compound to reach more distal disease. Alternatively, oral and rectal preparation can be used concomitantly.[92] Noncompliance with 5-ASA maintenance therapy is associated with a five-fold increase in disease recurrence.[93] Occasionally, budesonide, a topical corticosteroid, is required to help achieve remission, however, it appears to be less effective as monotherapy than 5-ASA alone and is typically weaned in favor of other immunomodulatory medications during maintenance.[94,95]

Moderate-to-Severe Colitis

Patients with more severe disease (Mayo Clinic Score 6–12 with Mayo Endoscopic Subscore 2–3) are at higher risk of failure, recurrence, and colectomy, if remission cannot be achieved and maintained medically. Younger patients (<40 years old), more extensive disease, deep ulcers on

endoscopy, steroid dependence, and infection with either *C. difficile* or CMV have all been identified as predictors of increased 3-month colectomy rates.[96–100] Although the evidence is limited, experts have moved toward recommending more aggressive upfront treatment in moderate-to-severe disease rather than waiting to start immunomodulatory medications or biologics until after a patient has failed 5-ASA.[101] This shift in management partially reflects increasing evidence for "top-down" as opposed to "step-up" medical management in CD, but also the lack of evidence for 5-ASA in severe UC and the concern that any delay in achieving remission may increase both the likelihood and risks of surgery due to prolonged inflammation and progressive physiologic decline.

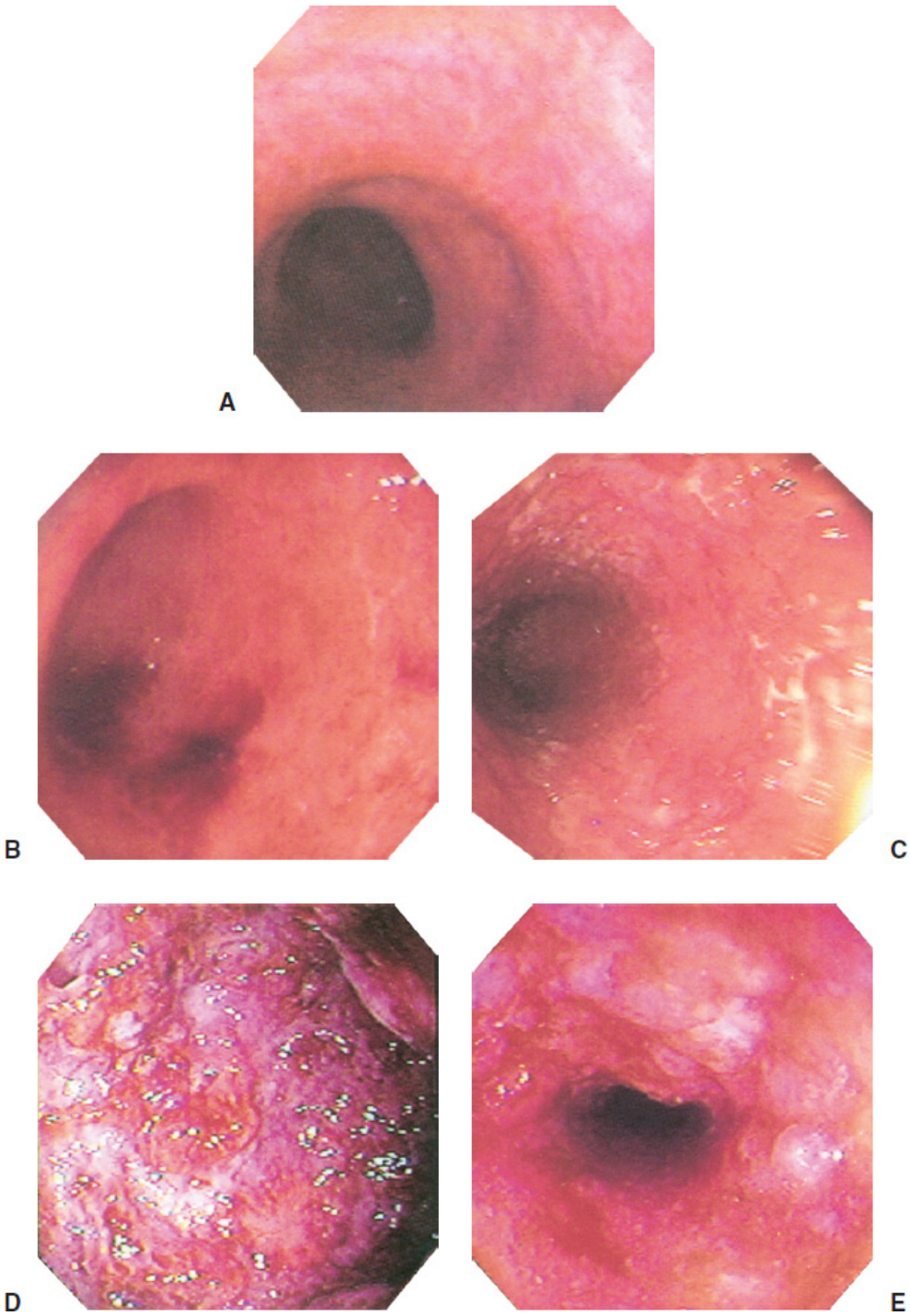

Figure 66.5 UC endoscopic findings with (**A**) Loss of normal vascular pattern. **B:** Contact bleeding. **C:** Granularity. **D:** Ulceration and friability. **E:** Colonic stricture. (Reproduced with permission from Corman ML. *Colon and Rectal Surgery*. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

Corticosteroids remain the primary treatment of acute UC flares, with remission rates approaching 70%.[102,103] In the outpatient setting, oral

prednisone doses of 40 mg or higher per day are common and are typically followed by either a short or more prolonged taper as symptoms improve and other medications are introduced. Overall, the use of corticosteroids has decreased in recent years, largely due to the increase in the number and effectiveness of available biologic agents. Corticosteroids should not be used for maintenance of remission due to their side-effect profile, including osteoporosis, diabetes, glaucoma, and an increased risk of infection, among others. In fact, long-term corticosteroids use in IBD is associated with an increase in mortality.[104]

Thiopurines, including 6-mercaptopurine and its prodrug azathioprine, have been used extensively in the treatment of moderate-to-severe UC, however, their slow onset of action makes them more appropriate for maintenance therapy than for induction. In fact, azathioprine was found to be superior to 5-ASA in maintenance of remission and may be equivalent to some biologics, although no head-to-head trials exist.[105] Skin cancers, lymphoma, and severe infections have been reported with the use of these medications.[106,107] Liver enzyme elevations, pancreatitis, and cholestasis have also been seen, although the most commonly reported side effects are headaches, hypersensitivity, and abdominal pain.

Infliximab, a chimeric mouse–human monoclonal antibody targeting TNF-α, was approved for the treatment of CD in 1988 and shortly afterward for UC. Infliximab successfully induced remission in over 60% of patients in the ACT 1 and 2 trials and significantly increases the likelihood of mucosal healing on endoscopy.[108,109] Extended follow-up has demonstrated that 15% of patients who initially respond to infliximab subsequently have to discontinue therapy due to side effects or loss of efficacy.[110] Newer TNF-α antagonists, including adalimumab, certolizumab, and golimumab, have also been shown to induce and maintain remission in UC, although none seem as effective at inducing remission as infliximab.[108,111,112] Vedolizumab, a monoclonal antibody targeting integrin α4β7, prevents neutrophilic translocation in intestinal capillaries, thereby modulating the immune response in a gut-specific fashion. In head-to-head trials, vedolizumab was more successful than adalimumab at inducing clinical remission, at least among biologic naïve patients.[113] There was no difference among patients who had previously been treated with a TNF-α antagonist. Based on this evidence, the American Gastroenterological Association recommends initial

biologic treatment with either infliximab or vedolizumab followed by ustekinumab, a monoclonal antibody targeting IL-12 and IL-23, in primary nonresponders.[101]

Overall, biologic agents are well tolerated. Infection, including reactivation of dormant mycobacterial and fungal infections, as well as certain autoimmune reactions remains a persistent concern.[114–116] The data regarding malignancy risk with anti-TNF agents are mixed, although there appears to be an increased risk of lymphoma.[117] More recently, biologics have been used in combination with either thiopurines or methotrexate as "dual therapy" in order to improve their pharmacokinetics (higher drug levels) and decrease their immunogenicity (lower rates of antidrug antibodies). A multiarmed randomized controlled trial found no difference in corticosteroid-free remission or mucosal healing between azathioprine and infliximab monotherapy, but did find significantly better rates among patients receiving both medications.[118] Patient selection is key, however, as combination therapy also appears to increase the rate of adverse drug reactions.[119]

Acute Severe Colitis

Patients with acute severe colitis require hospitalization for bowel rest, fluid resuscitation, pain control, and intravenous immunosuppression. IV corticosteroids, such as methyl-prednisolone, are first-line therapy with daily doses of 40 to 60 mg or higher being common. There is no evidence to support any particular steroid preparation, dose, or dosing strategy over another. Antibiotics are not required unless there is evidence of perforation.[101] All patients with IBD are at substantively increased risk for venous thromboembolism and should be treated during a flare with prophylactic heparinoids unless contraindicated.

Failure to improve within 48 to 96 hours of appropriate medical therapy should prompt reevaluation with either the addition of a second-line "rescue" medication or surgery. As mentioned previously, infliximab induces remission in roughly 60% of patients and may allow up to 90% of steroid-refractory patients to avoid colectomy in the urgent setting.[120] Cyclosporine can also be used as a second-line medication and may be more effective that steroids alone, however, serial lab draws to determine levels and close

monitoring for toxicity is required.[121] Two randomized controlled trials demonstrated no difference in short-term colectomy rates for steroid-refractory patients treated with infliximab versus cyclosporine.[122,123] Both medications have mean response times of 5 to 7 days, after which surgery should strongly be considered as sequential "rescue" therapy is ineffective.[124]

Surgical evaluation should take place early in the course of the hospitalization to ensure that important discussions regarding the risks and benefits of surgery are not rushed.[125] If available, an enterostomal therapist should also meet with patients to answer questions, discuss stoma care, and begin the adjustment process.

SURGERY

Indications

Approximately 20% to 30% of UC patients will ultimately require surgery.[126,127] While the short-term colectomy rate appears to have decreased in the biologic era,[128] the long-term rate remains roughly the same, suggesting that current medical therapies may be more successful at shifting surgery to an elective setting than at obviating it completely.[120,129] Two population-based studies report conflicting data on changes in the indication for surgery in the biologic era, with one Japanese study finding a relative increase in surgery for dysplasia and cancer while a Finnish study found no significant differences over time.[130,131]

Whether prior exposure to biologics increases the risk of surgery remains somewhat debatable. Daily prednisone doses of >40 mg clearly increase the risk of infection, anastomotic leak, and pelvic sepsis in patients undergoing proctectomy or ileal pouch-anal anastomosis (IPAA).[132] There is mixed evidence with respect to TNF-α antagonists, with some studies finding higher short-term infectious and anastomotic complications while others do not.[133–135] Meta-analyses separating patients by their underlying diagnosis found a trend toward higher postoperative complications for CD patients on anti-TNF-α agents, but not for UC.[136,137] Several experts have postulated that this effect may be moderated by higher drug levels among CD patients and

observational studies appear to demonstrate a dose–response effect.[138] There is no evidence to suggest that vedolizumab exposure increases postoperative complications rates.[139–141] Given the conflicting data, some authors support performing IPAA regardless of biologic exposure while others recommend waiting at least 4 weeks after anti-TNF-α dosing and 4 to 8 weeks after vedolizumab dosing before performing elective surgery.[142,143]

Fulminant Colitis and Toxic Megacolon

Fulminant colitis, as defined by Truelove and Witts, is an aggressive form of acute severe colitis characterized by fever, tachycardia, abdominal tenderness, greater than 10 bloody bowel movements per day, anemia requiring transfusion, elevated erythrocyte sedimentation rate, and colonic dilatation on radiography.[144]

Toxic megacolon occurs when severe colonic inflammation results in dilatation of the transverse colon beyond 6 cm (**Fig. 66.3**). Toxic megacolon is not specific to UC and can occur in the setting of colitis from other sources, including infection and ischemia. Toxic megacolon from UC is seen most often in new diagnoses, but can occur in acute exacerbations of chronic UC. As with fulminant colitis, patients experience severe colonic and systemic inflammation, as demonstrated by high fevers, tachycardia, severe abdominal pain, and leukocytosis or leukopenia.

Aggressive resuscitation and broad-spectrum antibiotics should be started immediately. All opiates and antidiarrheal agents should be discontinued to avoid worsening colonic distention. Steroids should be started as soon as an infectious source is ruled out. Primary nonoperative treatment should not be prolonged due to high risk of perforation and decompensation. In one study, patients experiencing more than eight stools per day or three to eight stools per day with a C-reactive protein >45 mg/mL after 3 days of rescue therapy had an 85% chance of requiring colectomy during their hospitalization.[145] Moreover, early surgical intervention is associated with a decrease in the mortality rate among patients failing medical therapy.[146,147]

Uncontrolled Bleeding

Less than 5% of UC patients have life-threatening GI bleeding. In this rare circumstance, a total abdominal colectomy is necessary to remove the

inflamed and friable mucosa. Operations for bleeding represent only 10% of emergent colectomies performed in UC patients.[148]

Dysplasia and Cancer

Patients with UC are at an increased risk of developing colorectal cancer compared to the general population, with younger patients and patients with pancolitis, longer disease duration, family history of IBD, or PSC at the highest risk. Meta-analyses report 10-, 20-, and 30-year rates of colorectal cancer at 2%, 8%, and 18%, respectively,[149] although newer population-based cohorts suggest that the actual risk may be lower.[150,151]

Cancer in the setting of UC appears to have the same stage-specific prognosis, but is often detected at a later stage than in the general population. In fact, nearly 20% of colorectal carcinomas in the setting of UC are unresectable at the time of diagnosis.[152,153] Given the fact that patients with UC undergo colonoscopy more frequently than the general population, such a pattern of disease indicates that cancer development in UC patients may be accelerated or may follow a different progression from dysplasia to carcinoma.

As mentioned above, the guidelines have changed in response to growing evidence that the majority of dysplasia is visible and potentially resectable, even in the setting of IBD.[154] The traditional recommendation for total proctocolectomy in the setting of dysplasia was based on elevated risk of malignant transformation throughout the colon or rectum. Under the new guidelines, visible polypoid lesions that are completely removed endoscopically with biopsies of the surrounding tissue that demonstrate no evidence of dysplasia can be managed as they would in patients without IBD.[154] In addition, rather than mandating colectomy, “invisible” dysplasia on random biopsies may instead be followed using close-interval chromoendoscopy, which has demonstrated higher detection rates and lower incidence of metachronous colorectal cancer when compared to white light.[87,155] Still, any dysplasia in the setting of UC warrants further evaluation by a specialist and may still prompt total proctocolectomy in the setting of unresectable, unsurveyable, or multifocal disease.

Failure of Medical Management

Inability to fully control UC symptoms or to do so without the chronic use of steroids remains the most common indication for surgery. Proctocolectomy can also improve many of the extracolonic manifestations of UC and can be considered in particularly debilitating or recalcitrant cases of erythema nodosum, large joint arthritis, aphthous ulceration, or episcleritis.[156]

Surgical Management

Unlike for CD, surgery with total proctocolectomy is curative for UC. Multiple surgical options are available and the ultimate choice of operation should be determined by the indication, urgency, continued need for immunosuppressive medications, and medical and nutritional condition of the patient. In general, the decisions regarding colectomy, proctectomy, and IPAA should be made independently, given that proctectomy can often be postponed safely after abdominal colectomy and that patients with permanent end ileostomy have both lower long-term complication rates and can have equivalent quality of life to those with a restorative IPAA.[157,158]

Total Abdominal Colectomy with End Ileostomy

For urgent indications, including fulminant colitis, toxic megacolon, uncontrolled bleeding, and perforation, the operation of choice is a total abdominal colectomy with preservation of the rectum and an end ileostomy (**Fig. 66.6**). Resection of the rectum in the urgent setting should be avoided, if possible, to both allow for continent reconstruction at a later time and to avoid a perineal dissection under conditions in which the perineal wound is likely to break down or become infected. Mobilizing the rectum unnecessarily disrupts the mesorectal planes, making later reconstruction more difficult. In addition, active inflammation and anasarca can obscure dissection planes, putting the ureters and pelvic nerves at unnecessary risk. In addition, consideration should be given to the level of ileal transection proximally, keeping in mind that pouch reach is dependent on the available bowel and the length of its mesentery. Under certain circumstances, the ileocolic artery must be preserved to allow for back filling of the arcades if the superior mesenteric artery must be divided to enable the ileal pouch to reach the anus.

The location of stoma should be marked preoperatively by an enterostomal therapist, if possible. Managing a poorly placed stoma is a major source of preventable frustration for patients. If there is concern regarding visualization of the ureters, stents should be placed prior to beginning the operation. Although they do not reduce the rate of ureteral injury, they do aid in intraoperative identification of any injury and can help facilitate prompt repair.[159]

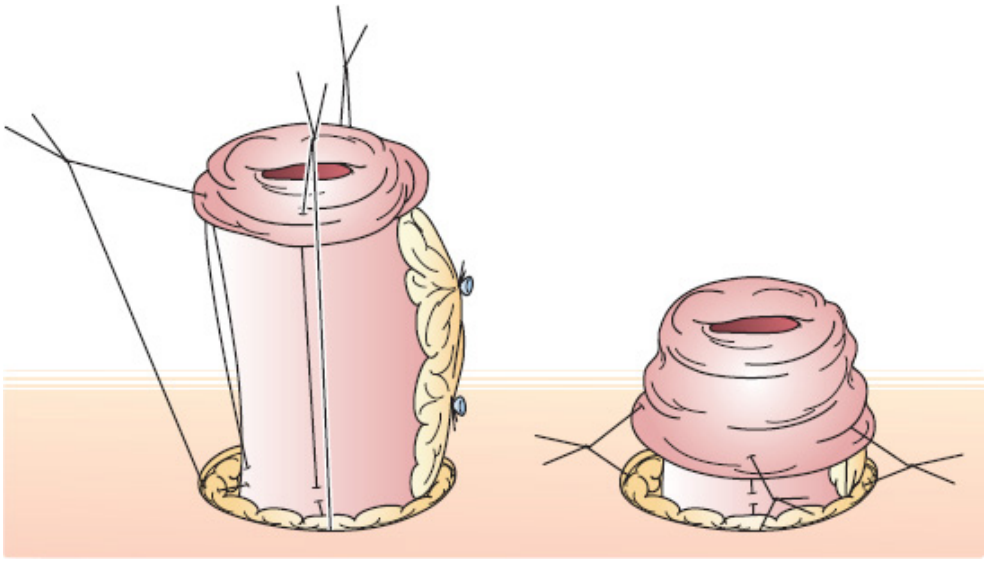

Figure 66.6 Brooking ileostomy.

A minimally invasive approach should be attempted, if the patient is stable and the surgeon is sufficiently comfortable with such an approach.[160,161] After establishing pneumoperitoneum and placing additional ports, the colon is mobilized systematically in either a medial-to-lateral or lateral-to-medial fashion (**Figs. 66.7** and **66.8**). Although the sequence of the operation varies from surgeon to surgeon (e.g., right colon first vs. left colon first), a systematic technique should be employed. Unless there is concern for cancer, the vessels can be transected close to the bowel wall to avoid the risks of high ligation. Particular attention should be paid to the splenic flexure, as a splenic tear will unnecessarily complicate the operation.

Once the colon has been completely mobilized and the vessels divided, the rectosigmoid junction can be transected, either laparoscopically or through a Pfannenstiel or lower midline incision. The distal ileum is either similarly divided and the specimen is extracted through the lower incision, or the

entire specimen is extracorporealized through the ileostomy aperture, with division of the terminal ileum, followed by creation of an end ileostomy (**Fig. 66.6**). It is critical to make sure that the small bowel mesentery is not twisted before maturing the ileostomy.

Depending on the level of inflammation, the rectal stump may be at substantial risk of staple line disruption and leakage. If possible, it is prudent to leave a long enough rectal stump to be able to tack it anterior to the fascia but deep to the skin. In the event of a rectal stump leak, tacking to the fascia effectively creates a mucous fistula rather than allowing leakage of stool into the pelvis or peritoneal cavity. Other strategies for managing the rectal stump include oversewing the staple line, decompressing the rectum from below with a soft drain that is removed several days postoperatively, or purse-stringing the proximal end around a transabdominal drain, if an early return to the operating room is anticipated.

Completion Proctectomy/Total Proctocolectomy

Hospitalized patients who do not respond to medical management, cannot achieve steroid-free remission, or are medically or nutritionally depleted should undergo total abdominal colectomy (rather than proctocolectomy) to remove the bulk of disease, break the inflammatory cycle, and allow time for rehabilitation prior to considering any additional surgery. After recovery, patients who have persistent rectal symptoms (pain, tenesmus, bleeding, discharge), do not want to undergo continued surveillance, or desire restoration of continuity can proceed with completion proctectomy with or without IPAA. Short of persistent symptoms requiring steroids, an inability to perform surveillance of the rectum, or evidence of dysplasia/cancer, proctectomy is not mandatory and patients can live full lives with a permanent ileostomy and their remaining rectum in place, as long as they continue surveillance.[157] Unfortunately, proctectomy is required for restoration of continuity as ileorectal anastomosis has not demonstrated favorable outcomes in UC and should be avoided outside of specific clinical situations (e.g., palliation and young women considering future pregnancy).[162]

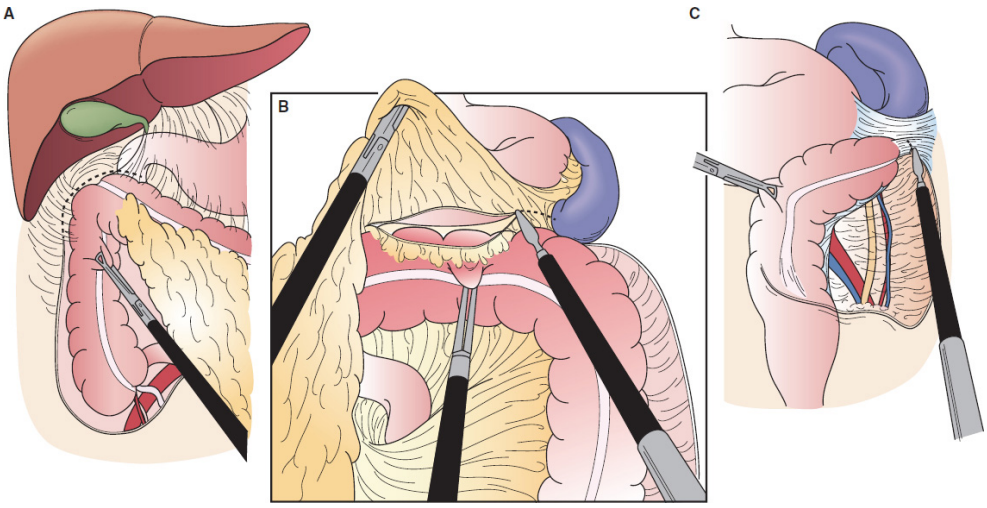

Figure 66.7 Colon mobilization. **A:** right colon. **B:** transverse colon. **C:** left colon.

Abdominal colectomy is performed as above, either at a prior operation or during the initial phase of total proctocolectomy. As with total abdominal colectomy, proctectomy can be performed via an open or minimally invasive approach, depending on the surgeon's training and comfort. The patient is placed in a steep Trendelenburg position and the small bowel is displaced into the upper abdomen. The remaining sigmoid and rectum are placed on tension and the peritoneum is incised over right side of the rectum, medial to the ureters and the pelvic nerves. The embryologic plane between the mesentery and the retroperitoneum is followed cephalad just posterior to superior rectal artery to identify the inferior mesenteric artery (IMA). Careful dissection near the IMA pedicle toward the left pelvic sidewall will reveal the left ureter through the retroperitoneal fascia; its location is almost always higher than expected. After the ureter is identified, the IMA can be skeletonized and divided. In the absence of neoplasia, it is unnecessary to perform a high (proximal) ligation of the IMA.

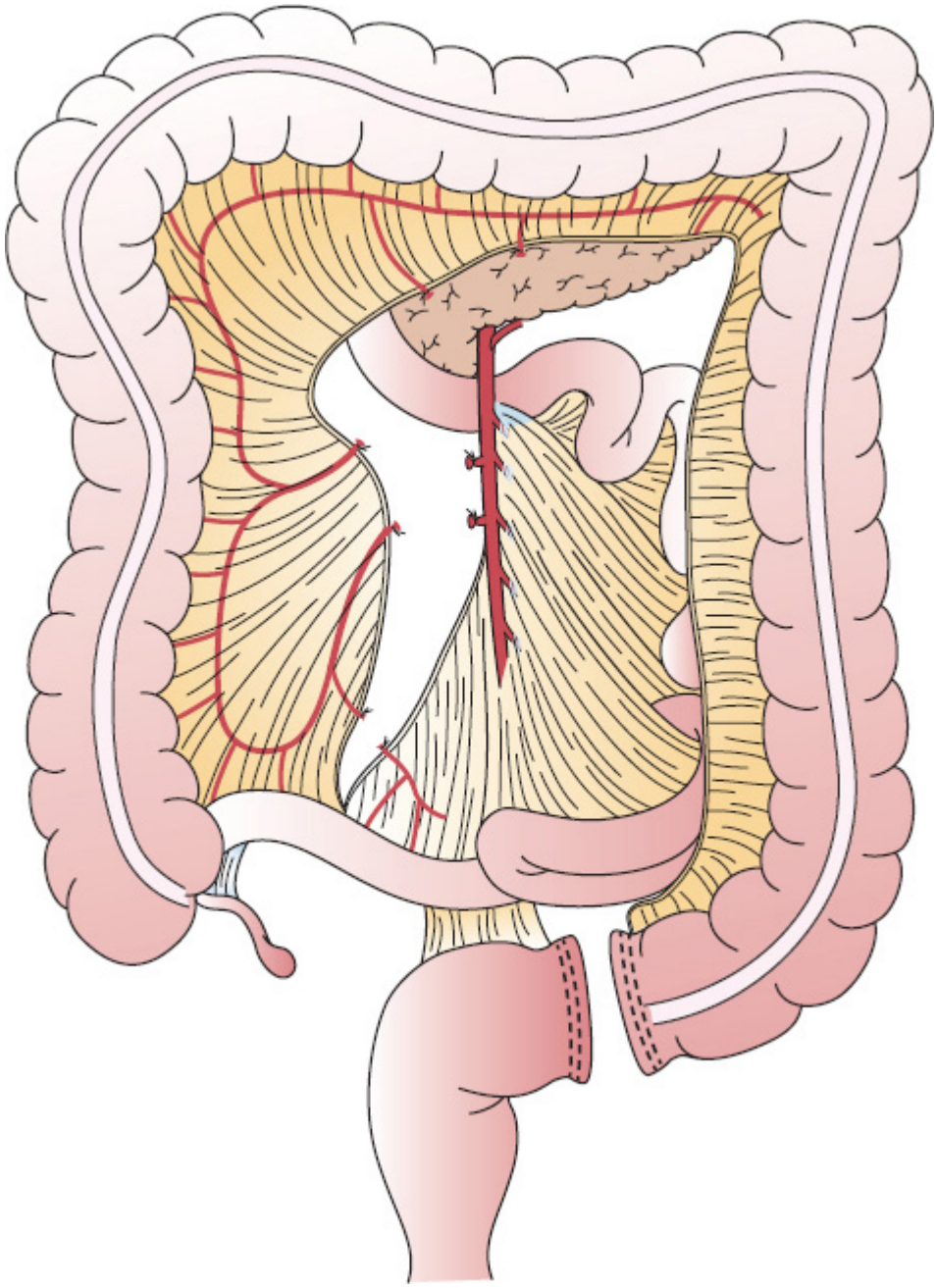

Figure 66.8 Mobilized colon with vessels divided, and stapled at the rectum. This specimen is ready for extraction; the ileum can be transected intracorporeally, or after specimen is extracorporealized.

The dissection is carried distally into the pelvis along the posterior mesorectal plane. The "wishbone" of the superior hypogastric plexus should be clearly identified and protected. Meticulous dissection can be done relatively bloodlessly as long as one stays in the correct embryologic plane. Dissection posteriorly through the presacral fascia risks injuring the

presacral veins, which can result in troublesome and sometimes life-threatening bleeding. All effort should be made to complete the dissection posteriorly, prior to dividing the anterior peritoneal reflection and entering either the rectovaginal or rectoprostatic plane. Denonvilliers fascia should not be violated in order to avoid contributing to sexual dysfunction, particularly in men.

Once the dissection is carried down to the pelvic floor circumferentially, the distance from the anal verge can be assessed via digital rectal examination. In patients undergoing IPAA, the rectum is transected using a stapler and removed from the field. In patients undergoing total proctectomy and permanent ileostomy, a perineal dissection is begun, either in the lithotomy or prone position. Unlike an abdominoperineal resection for cancer, the perineal dissection begins in the intersphincteric groove and extends proximally in the relatively bloodless plane between the sphincters until the abdominal cavity is entered. Performing an intersphincteric dissection leaves the external sphincter in situ, allowing it to be incorporated into a layered perineal closure thereby improving the chance of complete wound healing.

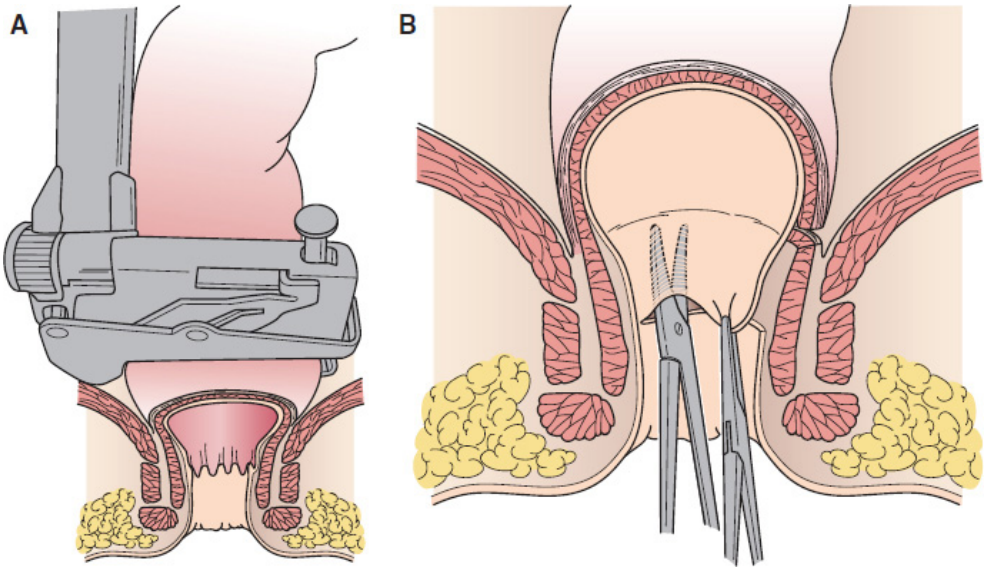

Figure 66.9 Distal rectal transection, (**A**) stapled above the dentate line, or (**B**) a mucosectomy in preparation for a hand-sewn anastomosis.

Ileal Pouch-Anal Anastomosis

Total proctocolectomy with IPAA is the most commonly performed elective operation for UC, typically in the setting of persistent mild-to-moderate disease or dysplasia. While higher than end ileostomy, IPAA has an acceptable morbidity rate (20% to 30%) and produces a quality of life that approaches normal controls.[125] IPAA is not appropriate in patients with poor anal sphincter function, a history of anorectal disease, or an inability to tolerate the increased risk of pelvic sepsis that exists in the setting of an ileoanal anastomosis. All prior pathology should be reviewed to confirm the diagnosis of UC as IPAA in CD carries a higher risk of post-operative complications and pouch failure.[163–165]

Colectomy and mesorectal mobilization are performed as described above except the rectum is transected approximately 1 cm above the anorectal ring with the stapler (**Fig. 66.9A**). Alternatively, a mucosectomy can be performed from below, although this necessitates hand-sewn ileoanal anastomosis (**Fig. 66.9B**). Overall, there is no difference in perioperative complications between double-stapled and hand-sewn IPAA anastomoses.[166–169] Some studies suggest leaving a small rectal cuff improves defecatory function,[170] although any residual rectal mucosa poses some risk of dysplasia or recurrent proctitis ("cuffitis").[171,172]

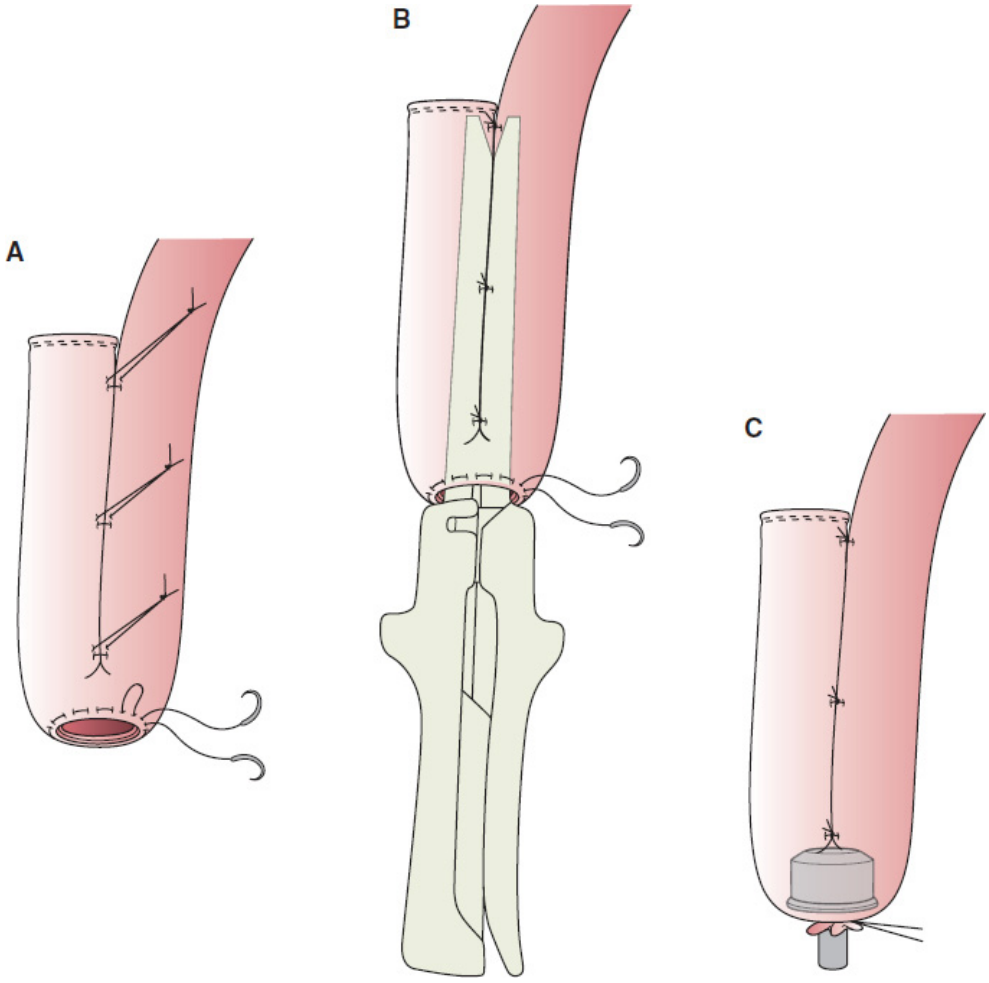

Figure 66.10 IPAA construction and anastomosis, (**A**) terminal ileum alignment for (**B**) common channel creation. **C:** EEA anvil attachment at the apex of the pouch.

After the proctectomy has been completed, a pouch is fashioned from the terminal ileum. Multiple pouch configurations exist, although there is no evidence to support one over another[173,174]; the double-loop J-pouch configuration is the most popular in the United States (**Fig. 66.10**). A portion of the distal or terminal ileum is pulled toward the anus to align the bowel in a "J" configuration. Before committing to pouch formation, it is necessary to confirm that the apex will reach the rectal cuff or anus without tension, which is typically done by stretching the apex slightly beyond the pubic symphysis. Multiple maneuvers can be performed to "lengthen" the reach of the pouch, if necessary, and are beyond the scope of this discussion. Once the apex location is decided on, the two limbs of the ileum are aligned with interrupted suture to create a pouch of 15 to 20 cm in length. An enterotomy

is made at the apex of the pouch and a GIA stapler is used to fashion a common channel between the two limbs. The pouch can then be anastomosed to the distal segment either by using an EEA stapler (placing the anvil in the J pouch and firing pin through the rectal pouch) or via a hand-sewn anastomosis (**Fig. 66.11**).

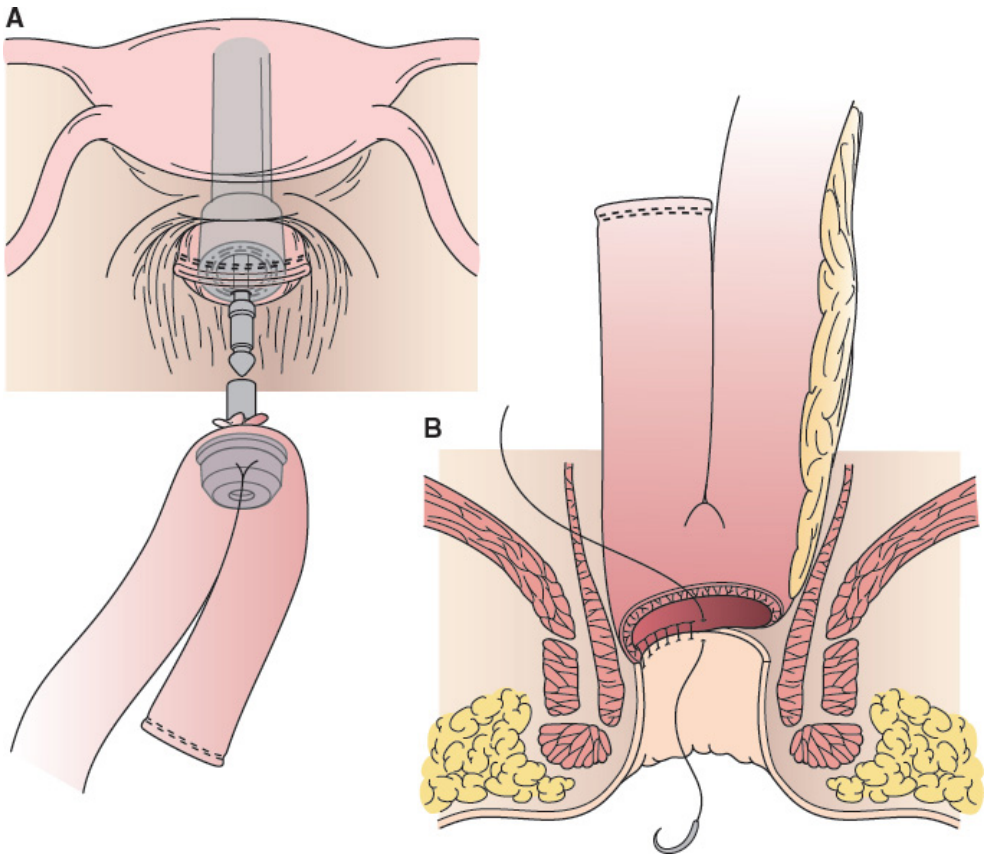

Figure 66.11 Anastomosis of the J-Pouch with (**A**) stapled anastomosis and (**B**) hand-sewn anastomosis.

IPAA-Postoperative Complications

The majority of patients who have an IPAA report a high quality of life after surgery. As with any abdominal or pelvic operation, patients are at risk for bleeding, infection, bowel obstruction, sexual or bladder dysfunction, and changes to fertility. Up to 60% of IPAA patients experience a perioperative complication.[175] Small bowel obstruction occurs in 15% to 20% of patients and is most commonly managed nonoperatively.[176] Sexual function after surgery is variable.[177] Between 10% and 20% of patients describe an increase in dyspareunia while 2% to 19% of men report retrograde

ejaculation or erectile dysfunction.[178–180] Women with UC who have surgery appear to have lower conception rates and higher rates of infertility or need for fertility treatment compared to women with UC who do not have surgery, although there is no difference between patients with IPAA versus end ileostomy.[181]

Recent series have also called into question the long-term bowel function of IPAA patients. In a large U.S. study, the majority of IPAA patients reported having between 6 and 10 bowel movements per day after a median follow-up of 4 years, however, 90% still reported difficulties delaying a bowel movement for 15 minutes, 56% reported having to have a second bowel movement within 15 minutes of evacuating, and 19% reported fecal leakage on some to most days.[175]

Pouch-specific complications include persistent, nonspecific inflammation of the pouch ("pouchitis"), and anastomotic issues, including stricture, abscess, fistula, and pelvic sepsis. Pouchitis occurs in 40% to 50% of the patients and is the most common complication after IPAA.[175,182] It is generally treated with oral antibiotics (ciprofloxacin or metronidazole), but may require evaluation with endoscopy and biopsy, if symptoms persist. Other medications that have been shown to help treat pouchitis include corticosteroids, budesonide, 5-ASA, and allopurinol.[183] Up to 10% of IPAA patients experience a frank anastomotic leak and 12% develop a persistent fistula tract. Antibiotics, drainage, and salvage procedures can be performed, however, between 7% and 8% eventually require pouch excision.

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67

Colonic Polyps and Polyposis Syndromes

Emily Steinhagen and Neil Hyman

Key Points

1. Colonic polyps are common and may have adenomatous, serrated, hyperplastic, or inflammatory histology; dysplasia is inherent to adenomas and serrated polyps.
2. Colorectal cancer may develop in polyps via the classical pathway, driven by APC gene mutations, the microsatellite instability pathway, or the CpG island methylation pathway.
3. Screening and surveillance decrease the risk of colorectal cancer by detecting and removing polyps before they develop into cancer with colonoscopy representing the gold standard.
4. Multi-disciplinary management of hereditary polyposis syndromes is optimal.
5. Patients with hereditary polyposis syndromes require screening and surveillance for colonic and extracolonic malignancies as they have increased risks that vary by genetic syndrome.
6. The role for prophylactic surgery in adenomatous polyposis syndromes should be individualized to patients and disease phenotype.

Polyps occur frequently in the colon and rectum, and may represent precursor lesions to colorectal cancer (CRC). As such, identification and removal of these lesions may decrease an individual's risk of developing CRC. There are three main pathways through which CRC can develop, and each involves a precursor lesion. The classical pathway, characterized by chromosomal instability, is most common and consists of adenomas developing progressive mutations eventually leading to CRC. The microsatellite instability (MSI) pathway and hypermethylation pathways occur due to failure to repair DNA errors of replication, and are associated more frequently with serrated type polyps (**Fig. 67.1**).

Approximately 5% to 10% of CRC has a hereditary basis.[1] For patients and families with a hereditary predisposition to CRC, there are typically other at-risk organ systems for neoplasia, and progression to cancer may

occur more quickly compared to sporadic cases. Recognition of these syndromes enables appropriate screening and surveillance.

Polyps may be classified by their shape as well as their histology. Polyps may be sessile, protruding directly from the bowel wall with a broad base; pedunculated, on a fibrovascular stalk; or flat, which may be the most difficult to recognize endoscopically (**Fig. 67.2**). Polyps may also be considered as neoplastic, with malignant potential, or nonneoplastic. Neoplastic polyps typically include adenomas and serrated lesions. Nonneoplastic polyps include hyperplastic polyps (HPs), hamartomatous polyps such as juvenile polyps or inflammatory polyps. Submucosal lesions such as lipomas, leiomyomas, lymphoid aggregates, or other lesions may appear polypoid as well.

COLONIC POLYPS

Adenomatous Polyps

1 Adenomas are epithelial lesions that typically appear smooth but may become nodular as they grow and their histology advances. They are generally asymptomatic and are found in up to half of individuals who undergo screening colonoscopy. Because they are by definition precancerous, removing them via screening and surveillance is generally thought to be the major factor accounting for the decreasing incidence of CRC in the United States.

Epidemiology

Traditionally, adenoma rates have been higher in the United States and Western countries compared to parts of Asia, South America, and Africa. However, as the "Western" lifestyle has spread, the incidence of adenoma and CRC has increased in these regions. Studies evaluating the incidence of adenomas on screening or surveillance colonoscopies suggest that the rate may approach 50%.[2] The incidence of adenomas increases with age in all populations. It is estimated that in a patient with an adenoma, there is a 30% to 50% chance that they have at least one additional adenoma.[3]

Even outside of defined hereditary syndromes that predispose to polyps and CRC, heredity plays a role in adenoma and CRC risk. There is a two- to threefold risk of CRC among those with a first-degree relative who has adenomas or CRC. The more affected family members, the higher the risk. However, the risk may be impacted by the shared environment as well as shared genetics.

It was previously thought that adenomas were uniformly distributed throughout the colon with larger polyps more prevalent on the left side. However, the reported incidence of right-sided polyps has increased over time.

Histology

Adenomatous polyps are characterized by their physical features, size, glandular structure, and degree of dysplasia (**Fig. 67.3**). Tubular adenomas consist of at least 80% dysplastic tubules that are arranged in a tightly packed network and extend toward the normal lamina propria. Villous adenomas have at least 80% villous fronds that consist of a core of lamina propria surrounded by adenomatous epithelium; these fronds are elongated crypts. Tubulovillous adenomas have features of both.

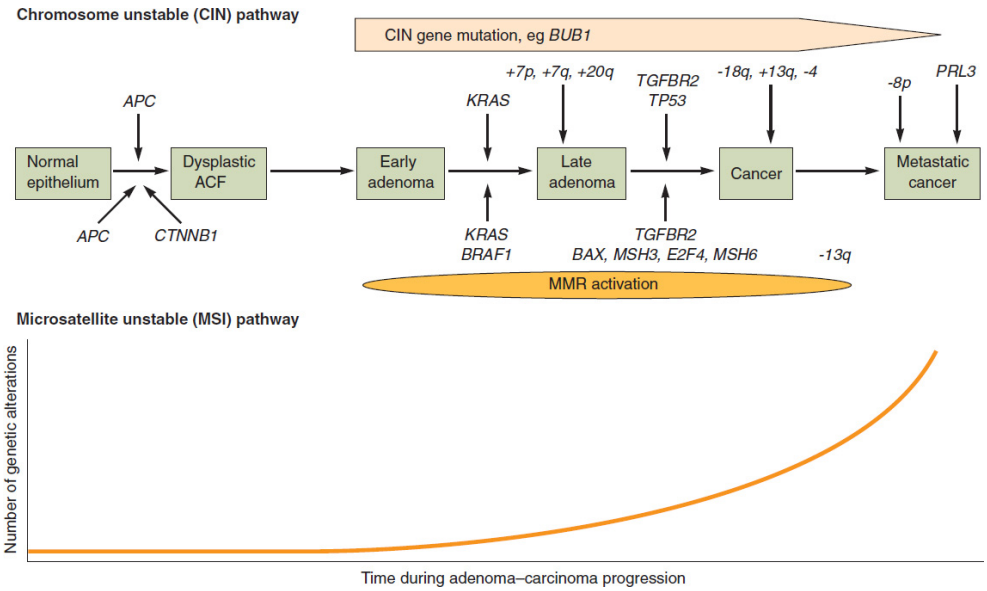

Figure 67.1 Proposed sequence of genetic events in the development of colon cancer. Carcinomas arise from an accumulation of events whose sequence has been defined for two of the carcinogenesis pathways. Tumors progress through the adenoma-to-carcinoma sequence along pathways marked by chromosomal instability (CIN) or microsatellite instability (MSI). At least one more pathway, characterized by promoter methylation of tumor-suppressor genes, serrated polyps, and cancers with variable degrees of microsatellite instability, is incompletely understood, and not shown here. ACF, aberrant crypt focus; TGF, transforming growth factor.

Adenomas are, by definition, dysplastic. The degree of dysplasia depends on the degree of abnormality in the crypt architecture as well as the appearance of the nuclei. Abnormalities in crypt architecture may be described as irregular branching, crowding, or "back-to-back" configurations (**Fig. 67.4**). Signs of nuclear atypia include larger size, pleomorphism, and hyperchromatic appearance. There may be multiple mitoses and pseudostratification within the cells. Dysplasia is graded as mild, moderate, or severe. Severe, or high-grade dysplasia, indicates that the basement membrane has not yet been invaded; extension into the lamina propria defines intramucosal carcinoma; invasion into the muscularis mucosa denotes invasive carcinoma. Polyp size often correlates with the extent of villous morphology and degree of dysplasia and is therefore associated with an increased risk of cancer.

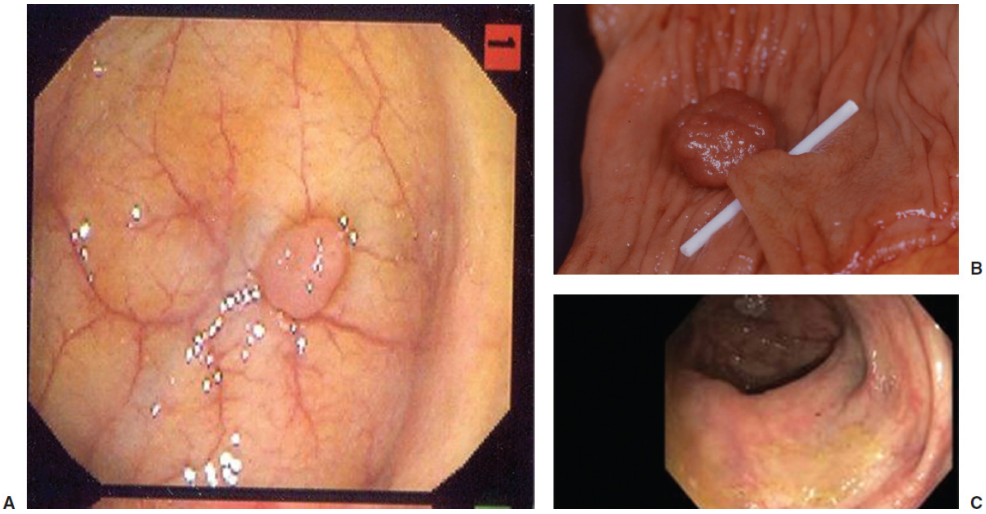

Figure 67.2 Appearance of (**A**) sessile polyp, (**B**) pedunculated polyp, and (**C**) flat polyp.

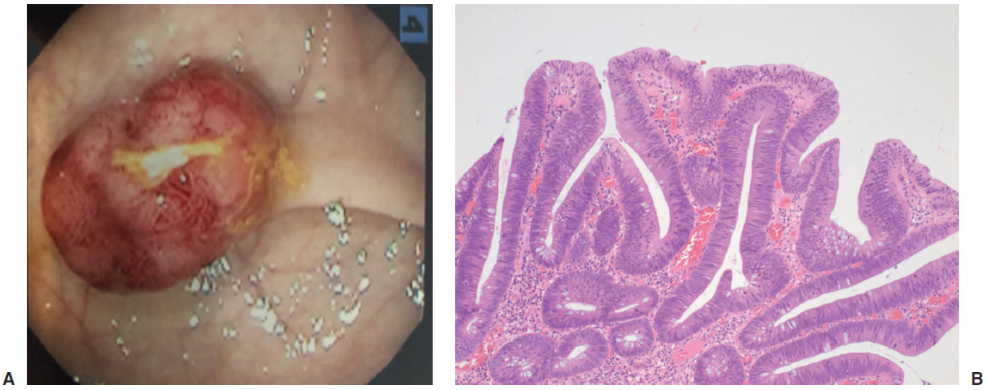

Figure 67.3 Adenomas. **A:** Colonoscopic appearance. **B:** Histologic appearance.

Etiology/Molecular Pathways

Classical Pathway

2 Adenomas develop through a progressive sequence of molecular alterations that lead to proliferation, cellular accumulation, and atypia. The vast majority of CRC develops along this chromosomal instability, or classical pathway, during which there is a process of multistep carcinogenesis. In sporadic cases (those not associated with a hereditary mutation), there are spontaneous changes that occur during DNA replication. The frequency of CRC compared to other types of cancer is likely a result of frequent cell turnover. Mutation of the *APC* gene, located on chromosome 5q, is an early event in the adenoma to carcinoma sequence. This tumor

suppressor gene can act as a gatekeeper of sorts, and once it is mutated, cellular proliferation can occur without regulation.

The protein produced by the *APC* gene is β-catenin. Once *APC* is mutated, there is a loss of phosphorylation of β-catenin, which is important for crypt proliferation. Mutations in *KRAS*, the prototypical oncogene in CRC, are frequently seen in polyps as well; as they become more advanced, *KRAS* mutation frequency increases. Proto-oncogenes function in signal transduction to regulate normal cell growth; they turn on when growth is stimulated and turn off when sufficient growth has occurred. When mutated, there is unregulated growth signaling and excessive cellular proliferation. The tumor suppressor gene *p53* must be inactivated to transition from adenoma to carcinoma. The *p53* gene typically prevents cells with DNA damage from replicating by stopping mitosis progression from the G1 to S phase.

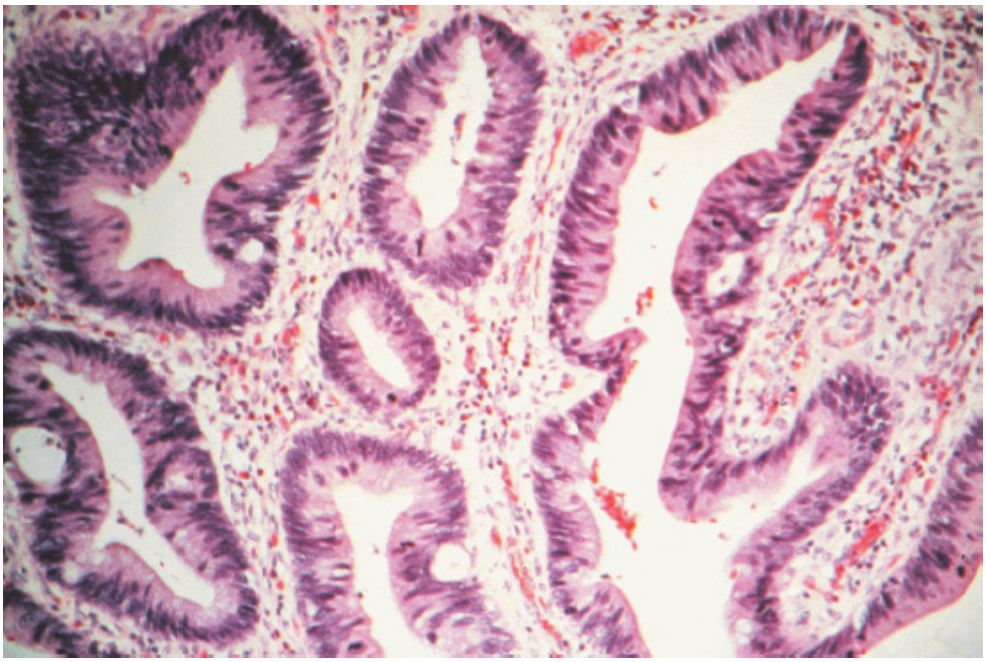

Figure 67.4 Histologic appearance of adenoma. There are crowded, irregular glands and cells. The nuclei are hyperchromatic and nonuniform in size and shape.

Microsatellite Instability Pathway

Approximately 15% to 20% of adenomas and carcinomas develop along a different molecular pathway; the so-called MSI pathway. This occurs when there is hypermethylation of one of the genes controlling the mismatch repair

(MMR) pathway. The most frequent MMR genes are *MLH1, MSH2, MSH6,* and *PMS2*. While in Lynch syndrome (LS) these genes have germline mutations, sporadic methylation of the promoter gene of *MLH1* (sometimes referred to the *BRAF* V600E mutation) accounts for the majority of sporadic MSI-high CRCs. The normal function of MMR genes is to repair DNA damage that occurs as a consequence of replication; without it, MSI can occur. Specific genes that maintain normal cellular behavior may be affected such as *transforming growth factor B receptor II (TGF-BII)*. When TGF-β receptors are inactivated, cells no longer have normal growth regulation control. One of the more notable features of the MSI pathway is that the progression may occur more rapidly (1 to 2 years) compared to the classical pathway. Cancers that develop along this pathway are more likely to occur on the right side of the colon, with histology notable for poor differentiation, signet ring or mucinous tumor subtypes, and an abundance of tumor-infiltrating lymphocytes. Compared with tumors developing along the classical pathway, prognosis is improved.

CpG Island Methylation Pathway

The CpG island methylator pathway (CIMP) describes a subset of CRC that develops along a pathway of epigenetic instability. The hallmark of this mechanism is hypermethylation of CpG islands, which inactivates tumor suppressor genes. More than half of human genes are regulated by promoters; CpG islands represent one type of promoter. When they are hypermethylated, the genes are inappropriately silenced and this can deregulate key genes involved in carcinogenesis.

Figure 67.5 Large polyp harboring invasive carcinoma.

Cancers with a high degree of methylation represent a clinically distinct group of tumors with a different histology and potentially different behavior. Typically, promoter regions of tumor suppressor genes are involved. Tumors notably have high rates of mutations in *KRAS* or *BRAF*, wild type p54, are located in the proximal colon, have mucinous features, are poorly differentiated, occur at an older age, and are more frequent in female patients.[4]

Progression to Cancer

Though nearly all CRCs originate from adenomas or serrated lesions, most polyps do not develop into cancer. Malignant potential is related to size and histology, with larger size and villous components in adenomas representing higher-risk lesions for progression. Adenomas that are 0.5 cm or less very rarely contain severe dysplasia or carcinoma (<0.5%) and only 1% to 2% of

adenomas less than 2 cm contain carcinoma (**Fig. 67.5**). In autopsy studies, up to 40% of adenomas >2 cm harbor an associated cancer. The risk of cancer in adenomas larger than 1 cm, with villous components, and severe dysplasia are estimated at 3%, 17%, and 37%, respectively, but may increase with age. The rate of transition to cancer is estimated at 2.6% in patients aged 55 to 59, and 5.1% in those over 80.[5] It is generally estimated that it takes 5 to 10 years to go from normal mucosa to cancer. This explains the findings of The National Polyp Study, which demonstrated the protective effect of screening colonoscopy for at least 10 years.

Clinical Features

Most patients with adenomatous polyps are asymptomatic. However, hematochezia may be present when larger polyps are in the distal colon or rectum, and right-sided polyps may cause melenic stools. In addition, iron deficiency anemia (with or without associated systemic signs and symptoms) can result from occult bleeding related to polyps. Polyp size is directly related to bleeding risk and volume; those less than 2 cm typically lose less than 1 mL of blood daily. Secretory diarrhea may be associated with large, villous adenomas in the distal colon and rectum and can also be associated with hypokalemia and hypochlorhydria. When polyps are particularly large, they can also lead to obstructive symptoms or alterations in bowel function.

Serrated Polyps

Incidence

Serrated polyps appear to be less common than other histologic types, occurring in approximately 5% of individuals undergoing screening and making up only 7% of polyps detected on colonoscopy.[6] They occur more frequently on the right side of the colon and are frequently flat and covered with a mucous cap, which can make them difficult to identify endoscopically (**Fig. 67.6**). Over 75% occur on the right side of the colon.

Histology

Serrated polyps are characterized by the saw-tooth pattern of the colonic crypts. The crypt base is serrated and dilated, and the proliferative zone has migrated to the side of the crypt rather than the base. Sessile serrated adenomas (SSAs) represent 3% to 20% of serrated polyps. The two most frequent serrated polyps, traditional serrated adenomas and SSAs, are associated with *BRAF* mutations and the CIMP or MSI pathways.

Progression to Cancer

Serrated lesions follow MSI or hypermethylation pathways to evolve into carcinoma. The time sequence appears to be shorter than that of traditional adenomas, but has not been well described.

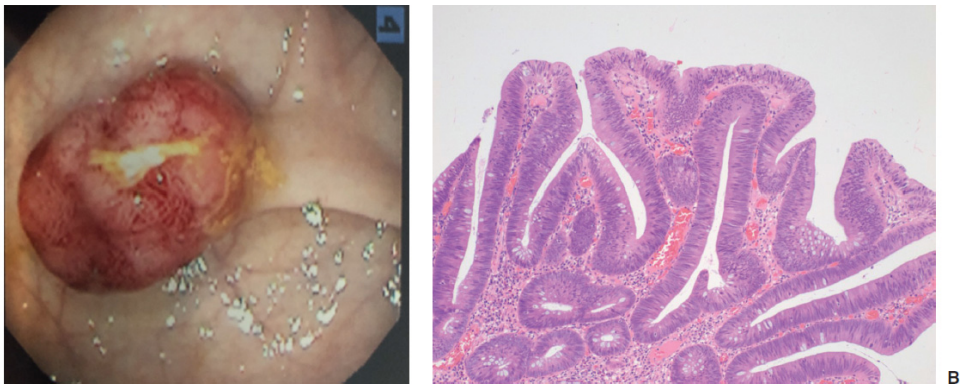

Figure 67.6 Sessile serrated adenoma (SSA), (**A**) colonoscopic appearance; this is a flat lesion that often has a mucous cap and can be difficult to identify on colonoscopy. **B**: Histologic appearance of SSA.

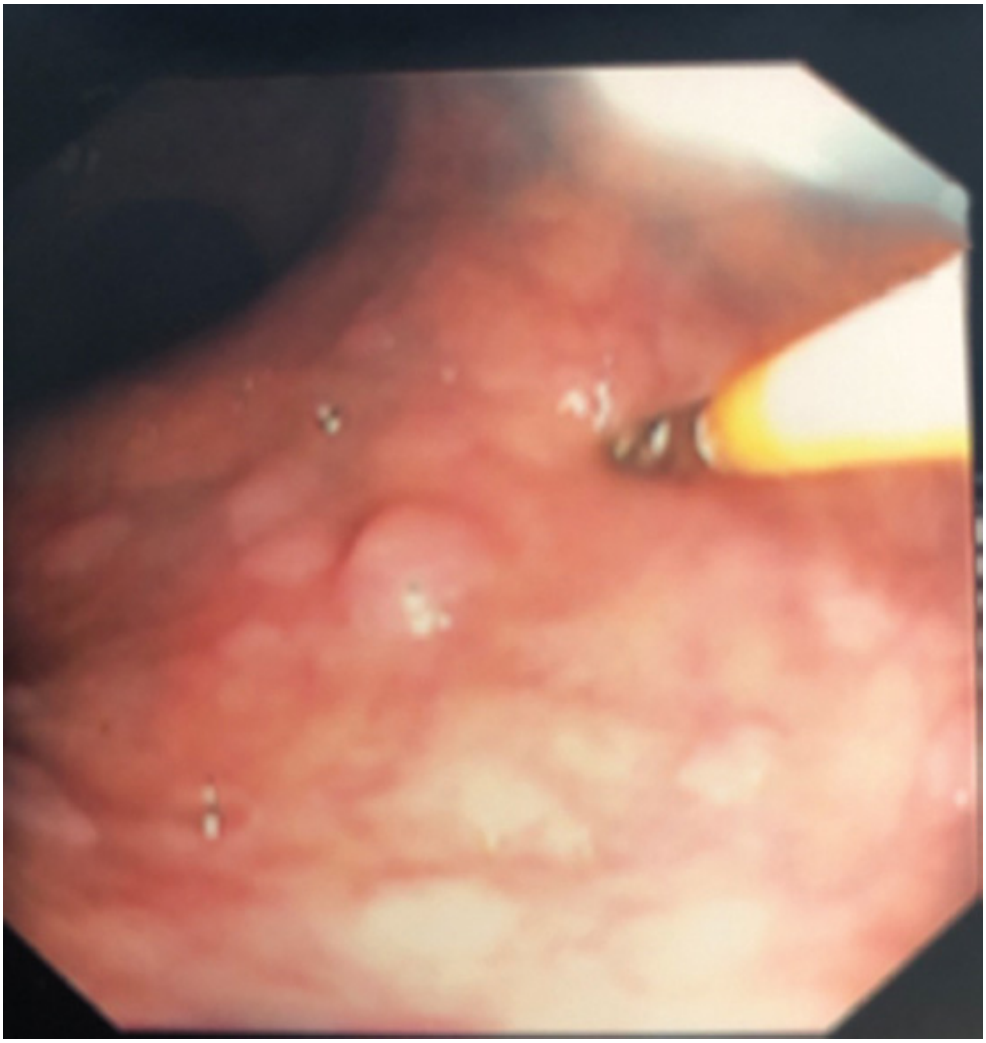

Figure 67.7 Colonoscopic appearance of hyperplastic polyp.

Hyperplasic Polyps

HPs appear as pale, broadly based, flat, smooth nodules. Usually, they are less than 5 mm in size. Most occur in the rectosigmoid and typically multiple are present (**Fig. 67.7**). They arise from faulty epithelial maturation and a failure of apoptosis.

Incidence

HPs are found in more than 30% of individuals over age 50. They may coexist with other types of polyps. There is no evidence of malignant potential once they have been distinguished from adenomas and serrated lesions. The presence of HPs on colonoscopy does not change future

screening recommendations unless they are thought to be part of a polyposis syndrome.

Histology

While HPs are the most common type of serrated polyp, they do not have malignant potential. Histologically, they are characterized by elongated, nonbranching mucosal crypts and hyperplasia without atypia. The main component is mature goblet cells. HPs are generally considered to be nonmalignant, though adenomatous changes can occur. HPs are distinct from SSAs.

"Mixed" hyperplastic and adenomatous or serrated polyps can also occur. When HPs occur as part of a polyposis syndrome, they are associated with an increased risk of malignancy.

Hamartomatous Polyps

Hamartomatous polyps are localized overgrowths of mature intestinal epithelial cells. They appear as smooth, pedunculated lesions with intact-appearing mucosa on endoscopy (**Fig. 67.8**).

They are usually lined with normal epithelium over a submucosal core that does not involve the muscularis mucosa. The pathogenesis is thought to be a mucosal ulceration or inflammation that blocks colonic glands. This leads to proliferation and dilation of the glands, followed by the growth of granulation and connective tissue in the area. Histologic examination demonstrates vascularity, cystica dilation, and a prominent fibrous stroma. Sporadic hamartomatous polyps do not have malignant potential unless they contain adenomatous components.

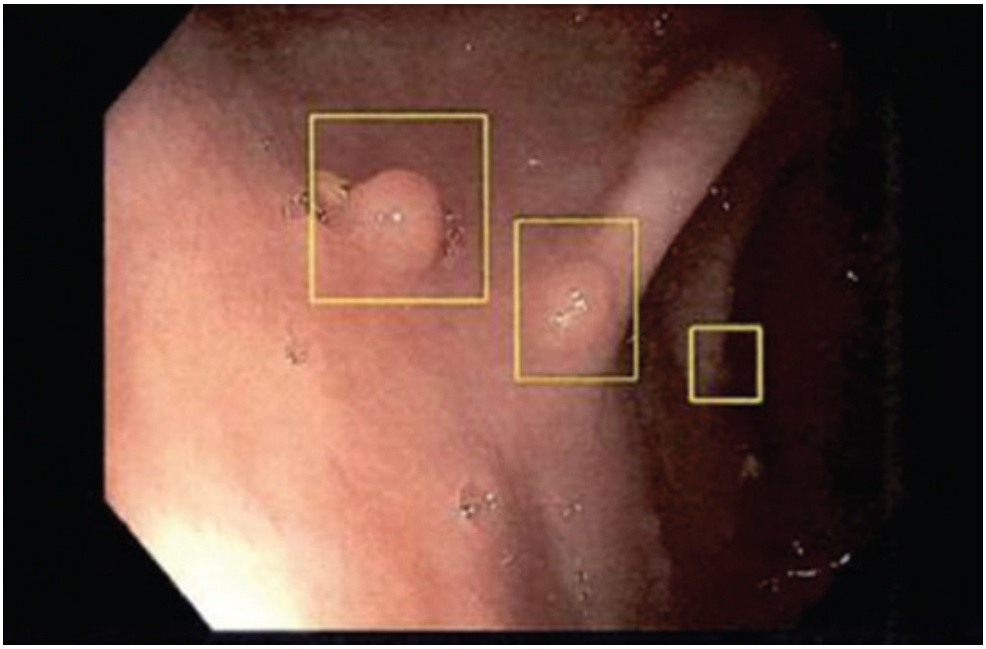

Figure 67.8 Colonoscopic appearance of hamartomatous polyps from a patient with a PTEN mutation.

However, hamartomatous polyps can cause symptoms such as abdominal pain, bleeding from ulceration, diarrhea, intussusception, or prolapse in the case of rectal polyps. When more than three hamartomatous polyps are found in a single patient, a polyposis syndrome should be considered.

Juvenile polyps can occur sporadically or as part of a syndrome. They are made up of dilated mucous-filled glands with abundant lamina propria. Unlike other polyps, these typically occur in children under age 10. Most frequently, a child will have a single pedunculated polyp with a smooth surface. They are thought to occur in about 2% of children. They often present with hematochezia due to their vascular nature. If they occur distally, they may prolapse (**Fig. 67.9**). More proximal lesions can cause intussusception. They have no malignant potential and are removed when symptomatic.

Inflammatory Polyps

Inflammatory polyps are sometimes referred to as pseudopolyps, occurring in areas of mucosal damage and repair. They are most frequently found in patients with ulcerative colitis, but may be found in other types of colitis as

well. Inflammatory polyps are uniform in width from the base to the head and consist of islands of inflamed regenerating mucosa surrounded by ulceration. Since they arise in areas of inflammation, multiple inflammatory polyps may develop in the affected area. The polyps themselves require no specific treatment and do not need to be removed unless there is uncertainty about the diagnosis.

Figure 67.9 Prolapsed hamartomatous polyp protruding through the anus.

SCREENING AND SURVEILLANCE MODALITIES FOR COLONIC POLYPS

3 A number of strategies to screen average- and high-risk individuals are available. Screening can be based on examination of the colonic mucosa, or stool-based tests looking for blood or genetic changes suggestive of advanced adenomas or cancers.

Flexible Sigmoidoscopy

Flexible sigmoidoscopy visualizes the rectum and parts of the sigmoid and descending colon. In general, it does not require a full bowel preparation and polypectomy may be completed at the time of the procedure; if precancerous polyps are identified, full colonoscopy is typically recommended. Though flexible sigmoidoscopy does not visualize all at-risk mucosa, it has been demonstrated to reduce mortality from CRC approximately 26% to 31% compared to no screening.[7] Even when performed once at age 60, a 33% reduction in CRC has been observed.[8] However, with the rightward migration of adenomas and cancer over recent decades, the applicability of this data derived from earlier decades may be limited.

Colonoscopy

Colonoscopy involves direct visualization of the entire colorectal mucosa while facilitating synchronous removal of polyps, biopsies of larger polyps/masses, and has been demonstrated to reduce CRC mortality. Colonoscopic polypectomy is associated with a 53% reduction in CRC mortality.[9] A SEER-Medicare database study also confirmed via case-control study that colonoscopy is associated with a significant reduction in CRC-related death; interestingly, the association was stronger with left-sided cancers, which is consistent with other European and Canadian studies.[10] These findings suggest that right-sided lesions are not detected as frequently and/or that they grow at different rates. Colonoscopy remains the gold standard test for detecting adenomas and CRC. Colonoscopy requires patients to complete a bowel preparation with cathartics and sedation and carries risks such as bleeding or perforation.

CT Colonography

CT colonography, also referred to as "virtual colonoscopy," involves high-resolution cross-sectional images of the abdomen and pelvis. It is a rapid and safe method of evaluating the colon. The National CT Colonography Trial, a multicenter study that compared CT colonography with same day colonoscopy in 2,600 patients, found that the sensitivity of CT colonography for polyps >10 mm was 90% and the negative predictive value was 99%. However, patients still require mechanical bowel preparation for the test and

those with abnormal findings then typically need to undergo colonoscopy for biopsy or polypectomy. One area of concern is the ability to detect serrated lesions, which are typically flat and more likely to be located in the right colon. Additionally, extracolonic findings are not infrequent; this may result in early diagnosis of occult disease but often leads to unnecessary additional testing for incidental findings.

Stool-Based Tests

Stool-based tests are noninvasive screening modalities that detect blood or shed cellular debris from polyps or cancer. Patients can often complete these tests at home and avoid the risks of sedation, and the potential discomfort or risks of an invasive procedure. While they do not require mechanical bowel preparation, some dietary changes in days leading up to the test may be necessary for optimal results.

Fecal occult blood test (FOBT) assesses for the presence of peroxidase in stool. It is a qualitative test that can be altered by the presence of peroxidase from red meat, certain fruits and vegetables, or inactivated by high doses of vitamin C. Patients must comply with dietary restrictions for several days prior to testing to improve the accuracy of the results and typically three samples are utilized to complete the test with appropriate sensitivity and specificity. Importantly, only 15% of polyps <1 cm are detected with this modality, while 80% of polyps >2 cm result in a positive FOBT. Annual or biannual testing reduces CRC-related deaths by 15% to 30%.[7]

Fecal immunohistochemical test (FIT) is an immunohistochemical, semi-quantitative test that measures hemoglobin in a stool sample. The premise is that adenomas and cancers are prone to minor bleeding and therefore the presence of blood in the stool may suggest their presence. Compared to FOBT, FIT test is quantitative. It has improved sensitivity and specificity compared to FOBT. However, FIT tests are less effective at detecting adenomas as compared to carcinomas. FIT testing is intended to be repeated every year. If the test is positive, colonoscopy is recommended. The sensitivity of FIT is estimated at 79%, with a specificity of 94%, though depending on the threshold for a positive test, these numbers can vary.[1] There is no high-quality evidence evaluating the impact of FIT testing on CRC mortality in the United States.

Stool DNA testing (multitarget stool DNA, MT-sDNA, Cologuard®) has also been introduced as a noninvasive screening test. The sensitivity for CRC is 92.3% and 42.4% for adenomas. Stool DNA testing generally has higher sensitivity but lower specificity compared to FIT.

While colonoscopy remains the gold standard for screening and surveillance for CRC, many patients do not wish to undergo this procedure, and the best screening test is the one that the patient will have. A number of societies offer evidence-based guidelines that are updated regularly to enable practitioners to counsel patients about the appropriate age to screen for CRC and the suggested interval depending on the patient and modality utilized.

POLYPOSIS SYNDROMES

There are a number of syndromes associated with colonic polyps and an increased risk of CRC (**Table 67.1**). Importantly, nearly all patients with a hereditary polyposis syndrome are at risk of extracolonic manifestations and require heightened screening and surveillance. The adenomatous polyposis syndromes include familial adenomatous polyposis (FAP) as well as the attenuated form, aFAP; LS; *MUTYH*-associated polyposis (MAP), familial colorectal cancer type X (FCC-X); as well as a number of newly described syndromes that have been found in a small number of families. HP syndrome is characterized by hyperplastic, and sometimes serrated and adenomatous polyps. Hamartomatous polyposis syndromes are characterized by gastrointestinal hamartomas, and include juvenile polyposis syndrome (JPS), Peutz–Jeghers syndrome (PJS), and *PTEN* hamartoma syndromes (Cowden disease and Bannayan–Riley–Ruvalcaba syndrome [BRRS]). Hereditary mixed polyposis syndrome is characterized by both hamartomatous and adenomatous polyps of the gastrointestinal tract.

4 Patients who are suspected of having a hereditary syndrome should be referred to a medical geneticist, genetic counselor, or another healthcare professional with specialized expertise and experience in cancer genetics for consideration of genetic testing. If there is a family history of a CRC syndrome, the decision to refer is straightforward. In addition, patients with ten or more adenomas, two or more hamartomas, and five or more serrated

polyps proximal to the sigmoid should also be considered for further evaluation. The reason for referral prior to testing is to take a more detailed family history, to provide risk counseling, psychosocial assessment and support, education, and a detailed discussion about genetic testing prior to obtaining informed consent.

Table 67.1 Genetic Syndromes

	Gene/Chromosome		Colon Phenotype	Extracolonic Features
Familial adenomatous polyposis (FAP)	*APC* 5q21	Autosomal Dominant	Dozens to hundreds of polyps Early age of onset CRC	Upper GI neoplasia, hepatoblastoma, thyroid cancer, desmoid tumors, supranumerary teeth, osteomas, fibromas, cysts
Lynch syndrome	*MLH1, MSH2, MSH6, PMSH2*	Autosomal dominant	Increased risk CRC, early age of onset CRC	Small bowel cancer, urothelial cancer, endometrial and ovarian cancer, breast cancer, gastric cancer
MUTYH-associated polyposis (MAP)	*MUTYH* 1p35	Autosomal recessive	Dozens to hundreds of polyps Early age of onset CRC	Same as FAP
Peutz–Jeghers syndrome	*LKB1/STK11* 19p13.3	Autosomal dominant	Hamartomatous polyps Higher than average risk CRC	Small bowel polyps, mucocutaneous pigmentation; cancers of bowel, pancreatic cancer, ovarian cancer, cervical cancer, breast cancer
Juvenile polyposis	*SMAD4/MADH4, BMPR1A, ENG* 10q21.1, 10q22.3, 9134.11	Autosomal dominant	Hamartomatous polyps; few to hundreds 10–50% risk of CRC	15% with malrotation, heart or brain abnormalities, cleft palate, polydactyly, genitourinary tract abnormalities
Bannayan–Riley–Ruvalcaba	*PTEN* (60% of cases) 10q23 Unknown	Autosomal dominant	Hamartomas, increased risk of CRC	Macrocephaly, macrosomia at birth, genital freckling in males, developmental delay/intellectual disability, hemangiomas, hypotonia
Cowden syndrome	*PTEN* 10q23 Unknown	Autosomal dominant	Hamartomas, increased risk of CRC	Hamartomas of mucous membranes, breast cancer, thyroid cancer, endometrial cancer, renal cancer, melanoma (all early onset)
Serrated polyposis syndrome/Hyperplastic polyposis syndrome	*RNF43* Unknown	Unknown	Few to hundreds of hyperplastic and serrated polyps; increased risk CRC	Multiple other cancers reported; not enough data to conclusively determine
Hereditary mixed polyposis	*GREM1* 15q13.3	Autosomal dominant	Adenomas, hyperplastic polyps, hamartomas, serrated polyps	Unknown

Adenomatous Polyposis Syndromes

Lynch Syndrome

LS is defined by germline mutation in one of the MMR genes: *MLH1, MLH2, MSH6,* and *PMS2*. Patients with LS are at increased risk for a number of cancers including CRC, endometrial, urothelial, and small bowel; the risk varies based on which gene is mutated.

Incidence

LS accounts for approximately 3% to 5% of all CRCs, though the frequency may be higher in younger patient groups. It is estimated to occur in 1:370 to 1:2,000 individuals.

Genetics/Molecular Pathways

LS is an autosomal dominant syndrome with varying penetrance. It is caused by a mutation in an MMR gene. LS-associated CRC develops via the MSI pathway. Additionally, deletions in the *EPCAM* gene cause hypermethylation of the *MSH2* promoter, which leads to silencing of the gene and causes LS. Rarely, if two parents carry mutations to the same MMR gene, their offspring will be at risk of constitutional MMR deficiency (CMMRD); in this situation, the cancer risk is extremely elevated and occur at even earlier ages.

Diagnosis

Previously, LS patients were identified by family history utilizing the Amsterdam Criteria, and subsequently, the Bethesda criteria. More recent studies have shown that family history is neither sensitive nor specific and germline testing is required; tumor-based testing can be suggestive of LS but is not diagnostic. Identification of LS is important because of the high risk of metachronous cancers, and because it enables affected family members to benefit from potentially lifesaving early detection or prevention of the characteristic cancers.

Although not necessarily sufficient for diagnosis, patient or family history may suggest that further evaluation is necessary. A family history that meets either the Amsterdam II criteria or Bethesda criteria should prompt further evaluation. Amsterdam criteria include an individual with one or more first-degree relative diagnosed with CRC or endometrial cancer under age 50, more than one first-degree relative with CRC or endometrial cancer plus another LS-related cancer, more than two first- or second-degree relatives

with LS-related cancers including more than one diagnosed before age 50, or more than three first- or second-degree relatives with LS-related cancers regardless of age. The Bethesda criteria include: colorectal or endometrial cancer prior to age 50, or at any age in an individual with another LS-related cancer, with more than one first- or second-degree relative who has an LS-associated cancer under age 50, or more than two first- or second-degree relatives with LS-related cancers regardless of age.

There are several models available online that predict risk for LS including PREMM5, MMRpro, and MMRpredict, which are based on individual and family history. If an individual has a greater than 5% risk of having a pathogenic mutation based on a predictive model, genetic testing is generally recommended.

There are also certain histologic findings in CRC that may prompt genetic testing: MSI-H histology, absence of staining for one or more MMR proteins, the presence of tumor-infiltrating lymphocytes, Crohn's like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern are all suggestive of LS (**Fig. 67.10**).

There are two options for tumor-based testing for LS; immunohistochemistry (IHC) and MSI testing. IHC uses antibodies to stain for the four most common MMR proteins; their absence is suggestive of LS. MSI testing uses PCR to assess for five microsatellites. If three or more are unstable, the tumor is considered MSI-high and suggestive of LS. There is high concordance between the two techniques. However, 10% to 15% of CRCs will display MSI-H and absence of staining for *MLH1* due to hypermethylation of the promoter region of *MLH1*; these represent the sporadic CRCs that develop along the MSI pathway. Absence of *MLH1* on staining should trigger assessment for the *BRAF* V600E variant that accounts for nearly all of these sporadic cases; if it is mutated, the cancer is likely sporadic rather than suggestive of LS. Neither IHC nor MSI is sufficient to diagnose LS and germline testing is necessary for definitive diagnosis.

While adenomas can be evaluated via IHC, sensitivity is decreased compared to CRC, especially with smaller-sized lesions. Therefore, while positive results may be useful, a negative result does not rule out LS. Another important caveat is that neoadjuvant therapy in rectal cancer may lead to falsely positive IHC staining on subsequent biopsy. Whenever possible, biopsy specimens prior to treatment should be obtained. Because tumor-

based testing is not definitive, it should not be used alone to guide surgical decision making. In most cases, germline testing can be expedited to enable informed decision making about the extent of surgery.

Colon Cancer Risks

Not all patients with LS will develop CRC; the overall lifetime risk is between 52% and 82%, but varies by mutation. Individuals with *MSH6* and *PMS2* mutations have a risk of 10% to 22% while those with *MLH1* and *MSH2* mutations represent the higher end of the spectrum, with a 40% to 80% lifetime risk as noted in consensus guidelines.

CRC Surveillance

Patients with LS are at high risk for a large number of malignancies and therefore may require complex surveillance regimens. Colonoscopy should begin at age 20 to 25 (or 2 to 5 years younger than the earliest family member with CRC), with surveillance intervals of 1 to 2 years. This approach has been demonstrated to decrease the risk of CRC in LS patients.

It appears that aspirin may decrease the risk of CRC in patients with LS; the benefit may also extend to other LS-associated cancers.[11] The optimal dose and duration of treatment are not yet clear.

Extracolonic Cancers and Surveillance

5 Patients with LS are at high risk for extracolonic malignancies. The risk by gene mutation compared to the general population and the average age at diagnosis is found in **Table 67.2**.

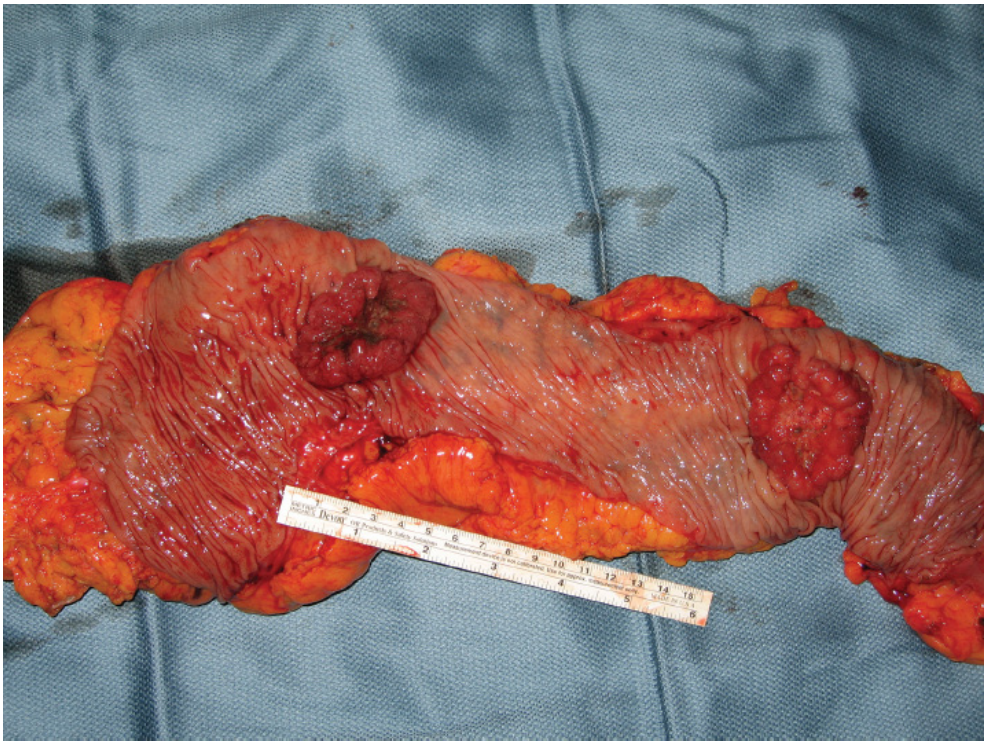

Figure 67.10 Colon resection from a patient with Lynch syndrome demonstrates synchronous cancers.

Table 67.2 Summary of Surveillance Guidelines for Lynch Syndrome Patients

Organ System	Surveillance Test	Frequency
Skin	Skin Exam	Annually
Gynecologic	Endometrial Biopsy Consider TVUS, CA-125	Annually
Small bowel	Capsule endoscopy	No recommendation
Stomach	EGD	1–3 yrs
Hepatobiliary/Pancreas	Consider ultrasound	No recommendation
Urologic	Urinalysis/Cytology	Annually
Breast cancer	Mammogram	Per general population guidelines

Gynecologic Cancers. The lifetime risk of endometrial cancer may be even higher than CRC in some cases. While the risk of endometrial cancer in the general population is about 3%, for women with LS it is approximately 18% to 60% for those with an *MLH1* mutation, 21% to 60% for *MSH2* mutation, 16% to 71% with mutations in *MSH6*, and 13% to 24% for those with *PMS2* mutations. The mean age at endometrial cancer diagnosis in women with LS is 46 to 54 years, compared with a mean age of 60 years otherwise. Up to 20% of Lynch-associated endometrial cancers are diagnosed before age 40. Similar to sporadic cases, endometrial cancer in LS tends to be diagnosed early and have a good prognosis. Women with LS who have atypical bleeding should be evaluated promptly. In addition, endometrial biopsy should be performed every 1 to 2 years for surveillance as it is highly sensitive and specific. Transvaginal ultrasound in postmenopausal women may also be used, although supportive evidence is generally lacking.

The lifetime risk of ovarian cancer for women with LS is 7% to 24%, again varying by mutation. The mean age at diagnosis is 43 to 50 years compared to 60 years in the general population. It is not clear that screening for ovarian cancer reduces the morbidity or mortality of ovarian cancer in women with LS, as also observed with sporadic cases.

Based on the high risk of gynecologic malignancies, hysterectomy with or without salpingoophorectomy should be considered in women who have completed childbearing and are fit for surgery.

Small Bowel Cancer. The risk of small bowel carcinoma in LS is highest in those with *MSH2* and *MSH6* mutations, who have a lifetime risk between 0.6% and 7%. Tumors are found throughout the small intestine at a median age of 39 to 53 years.[12] There are no specific guidelines for routine screening. The use of enteroscopy as well as video capsule endoscopy have not been demonstrated to decrease rates of small bowel cancer in LS patients. While there are no clear data to support screening for small bowel cancer, EGD with visualization at the duodenum at the time of colonoscopy every 3 to 5 years starting at age 40 is suggested by consensus guidelines.

Gastric Cancer Some studies have estimated the lifetime risk of gastric cancer in LS to be as high as 13% in Asian populations. But the lifetime risk in North America and Western Europe is likely closer to 5%; the mutation

with the highest frequency is *MSH2*. A carefully conducted time-trend study of gastric cancer found an 8.0% and 5.3% lifetime risk of this malignancy in males and females with MMR gene mutation, respectively, and a lack of familial clustering.[13] There are no studies that have evaluated the effectiveness of screening and surveillance for gastric cancer in LS patients, but EGD with gastric antrum biopsy every 3 to 5 years starting at age 40 is considered reasonable. If *Helicobacter pylori* is detected, it should be treated.

Hepatobiliary and Pancreatic Cancer Compared to other cancers, hepatobiliary cancer and pancreatic cancer are rare in LS. The lifetime risk of each is estimated at 0.2% to 4%, respectively. Median age at diagnosis is 62 years. The benefit of screening for these cancers in LS has not been evaluated. An international pancreas consensus panel recommended that MMR gene mutation carriers with one affected first-degree relative (FDR) should be considered for annual PC surveillance with magnetic resonance imaging (MRI) and/or endoscopic ultrasound based on early data in other cohorts with comparable risk.[14]

Urothelial Cancer Patients with LS, particularly *MSH2* and *MSH6* mutations are at increased risk of urothelial cell cancer at a rate of 20 times the general population, or a lifetime risk of 0.4% to 20%. The median age at diagnosis is 56 years. The current recommendation is for annual urinalysis and cytology starting at age 30 to 35 though some also recommend cystoscopy or CT urogram, particularly in those with a prominent family history of urothelial cancer in the context of LS.

Prostate Cancer The relative risk of prostate cancer is 3.6 times the general population, but there are no specific screening guidelines or evidence to suggest earlier onset or higher stage at diagnosis compared to average-risk populations.

Breast Cancer While there is an increased risk of breast cancer in LS patients, there is insufficient evidence to support increased screening above the recommendations for average-risk individuals.

CNS Cancer Other than annual physical examination and neurologic examination beginning at 25 to 30 years, no additional testing is recommended.

Surgical Treatment of CRC in LS

When LS is suspected preoperatively, testing should be considered to diagnose or rule out LS unless there are compelling reasons for more urgent surgery. There is clear evidence that patients with LS who have colon cancer should be offered total abdominal colectomy with ileorectal anastomosis; in rectal cancer, decisions are individualized, based on patient and tumor factors.[15] After segmental resection, the rates of metachronous adenomas and carcinomas are 33% and 25% even with excellent follow-up, compared to 11% and 8% after total abdominal colectomy.[16] There is a clear benefit in terms of cost effectiveness, probability of being alive and cancer free, and quality-of-life years with more extensive surgery in many circumstances.[17]

In women with LS, it is recommended that they undergo prophylactic hysterectomy and bilateral salpingoophorectomy by age 40. When women have completed childbearing earlier than age 40, it is reasonable to contemplate prophylactic surgery. In addition, when women with LS who still have their uterus, tubes, and ovaries undergo surgery for CRC, synchronous prophylactic hysterectomy and salpingoophorectomy are recommended.

Familial Adenomatous Polyposis/Attenuated FAP

Incidence

FAP is an autosomal dominantly inherited syndrome that occurs in 1 in 10,000 births. The penetrance and presentation can vary even within the same family who share a mutation. It accounts for less than 1% of all CRC. Importantly, up to one-third of cases of FAP are de novo mutations, meaning that there is no family history of the syndrome. It is the second most common inherited CRC syndrome. FAP is characterized by hundreds to thousands of polyps throughout the colon as well as a variety of extracolonic manifestations (**Fig. 67.11**). The median age for adenoma development in patients with classical FAP is 17 years. Untreated patients develop CRC at a median age of 40, with death at a mean age of 44.

Figure 67.11 Colon resection from a patient with FAP with thousands of polyps throughout the colon.

Genetics/Molecular Pathways

The *APC* gene is located on chromosome 5q21. Its most well-described function is in the Wnt signaling pathway, in which the APC protein forms a complex with c-myc, GSK3, axin, and casein that allows the degradation of β-catenin. When it is nonfunctional, β-catenin accumulates and enters the nucleus where it induces transcription of cellular growth factors. Cell proliferation, enhanced cell-to-cell adhesion, and cell migration result. The APC protein also stabilizes microtubules and help organize cell migration; it also binds cytoskeletal regulators and when not present, mis-segregation of chromosomes during mitosis can occur.

A number of different mutations in the *APC* gene can lead to FAP; there are truncating mutations that lead to a dysfunctional protein as well as missense mutations. When there is a germline mutation in one copy of the *APC* gene, it creates a situation where there is loss of heterozygosity in which a so-called "second-hit" leads to the classical adenoma to carcinoma sequence. While there are correlations between specific genetic mutations and phenotypic features, the phenotype can still vary between individuals with the same

mutation, even within the same family (**Fig. 67.12**). These differences may be a result of other genes, environmental influences, or other factors. When the *APC* gene mutation occurs in the "mutation cluster" region of exon 15, it predicts a more virulent form of FAP with thousands of colonic polyps and an earlier age of onset of CRC. Mutations at the 3′ end of the gene, in contrast, tend to have a milder phenotype.

Diagnosis

Many patients are diagnosed based on screening or genetic testing, prompted by a family history of FAP. Up to one-third of FAP patients represent de novo mutations; they do not have a parent with FAP. However, each child of an affected patient with FAP has a 50% chance that they will inherit the mutation and therefore develop the manifestations of disease.

Some patients without a family may also be referred for testing based on extracolonic findings such as supranumerary teeth, osteomas, or congenital hypertrophy of the retinal pigment epithelium (CHRPE). Others present with symptoms from polyposis that may include bleeding, change in bowel habits, and abdominal pain. FAP can be diagnosed on a clinical basis when more than 100 colonic adenomas are identified. However, genetic testing should always be performed to confirm the diagnosis. Up to 90% of individuals with a suggestive clinical phenotype will have a mutation identified.

Genetic counseling is an important part of genetic testing for FAP and other hereditary syndromes. Screening panels can sometimes identify one or more mutations of uncertain significance that must be interpreted. Patients may also misunderstand their results and subsequent cancer risk, as well as the implications for family members. There are frequently psychosocial implications with testing both of affected and unaffected family members that should be considered and addressed. With the frequent availability of panel-based testing, more than one gene alteration may be identified. Therefore, informed counseling is critical and should be performed by an experienced genetic counselor.

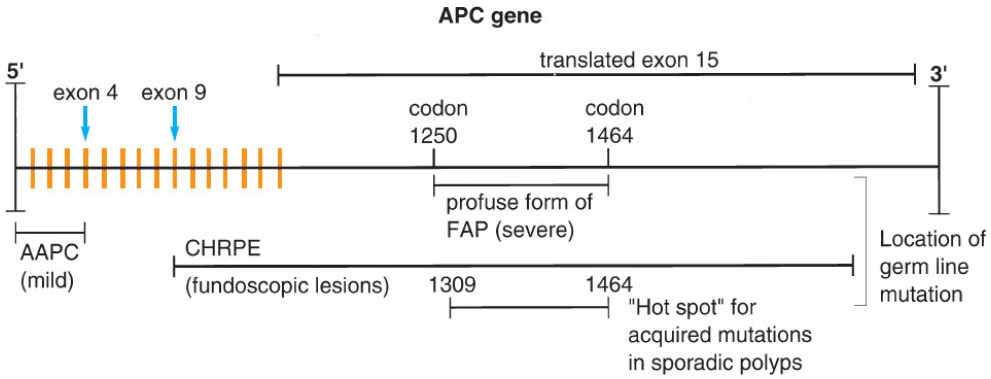

Figure 67.12 This scheme of the APC (adenomatous polyposis coli) gene illustrates the genotype–phenotype correlations. Most mutations of APC result in premature stop codons; therefore, the site of the mutation usually indicates the relative length of the mutant protein product. Mutations at the 5′ end of the gene produce "attenuated" FAP, a milder form of the disease. The retinal lesions (congenital hypertrophy of retinal pigmented epithelium [CHRPE]) occur when the mutations are between exons 9 and 15. The portion of the *APC* gene that binds to other cytoskeletal elements in the cell is represented at the 3′ end of the 15th exon. Mutations in a hot spot immediately downstream from the β-catenin–binding site (between codons 1250 and 1464) result in a more virulent, profuse form of familial adenomatous polyposis. This site is also the location of most of the acquired mutations in sporadic colorectal neoplasms.

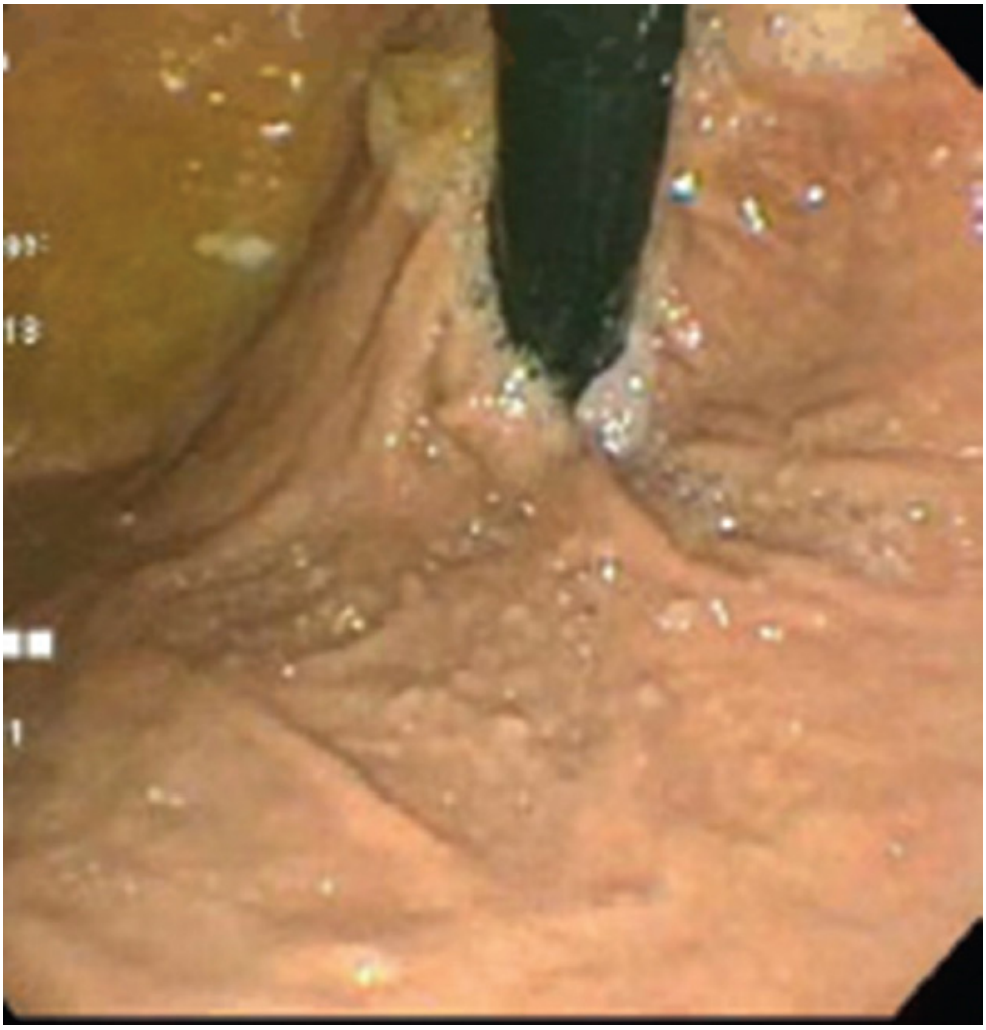

Figure 67.13 Endoscopic appearance of fundic gland polyps from a patient with FAP.

Colon Cancer Risks and Surveillance

Virtually all patients with classical FAP will develop CRC if untreated. The incidence of CRC rises dramatically after age 30. Typically, risk-reducing surgery is recommended once an individual reaches physical and emotional maturity in their late teens or early 20s. However, polyp burden or symptoms may necessitate earlier intervention. Patients with fewer than 20 polyps, and none larger than 10 mm may continue to be surveyed with colonoscopy and polypectomy.

Patients with known or suspected FAP, or those in families with a known *APC* mutation who have not undergone genetic testing should undergo annual colonoscopy at age 10 to 15 years. Most patients with FAP will develop

polyps by their early 20s. Flexible sigmoidoscopy may be an option, but would miss the onset of polyps in the right side of the colon, where they are more likely to occur in attenuated cases.[15]

Extracolonic Features

Gastroduodenal polyps. More than 90% of FAP patients will have upper GI lesions. The most frequent finding is fundic gland polyps, which are benign and have no malignant potential (**Fig. 67.13**). Histologically, they are hamartomatous. However, gastric adenomas and carcinomas may be found, particularly in Japanese and Korean patients. In Western populations, the risk of gastric cancer is less than 1%. Factors associated with an increased risk include carpeting of the stomach, larger polyp size (>20 mm), polypoid appearing mounds, and adenomas. Duodenal and periampullary polyps and carcinoma are also a common feature in FAP patients; the lifetime risk of duodenal cancer is 3% to 5% and half of all duodenal polyps occur in the periampullary location. The duodenal polyps tend to occur later than the colonic lesions and there tend to be fewer polyps compared to the more diffuse colonic polyposis. Duodenal polyps are classified by the Spigelman system (**Table 67.3**) which estimates the risk of carcinoma and determines the appropriate surveillance protocol.[18] It is based on the number, size, and histologic features of the polyps.

CHRPE is a common and completely benign feature present in some FAP patients. The lesions are well demarcated and gray-brown or oval; they are sometimes described as "bear claws." While small, isolated lesions occur in the retinal epithelium of nonaffected patients, the presence of multiple or bilateral lesions is highly suggestive of FAP. CHRPE lesions can be seen on slit lamp examination but are otherwise not seen on routine ophthalmologic examinations. Mutations between codons 543 and 1309 of the *APC* gene are associated with a higher incidence of CHRPE. In some families, the presence of CHRPE can be used to identify affected family members.

Osteomas and fibromas are benign, slow-growing neoplasms of the bone. The classical description in FAP is in the jaw or skull, but they can be present in any bone. They may be detected on physical examination if they are large, or on x-rays, particularly those done for dental indications. Osteomas are associated with a subtype of FAP known as Gardner syndrome and they may precede the development of gastrointestinal polyposis. Other

manifestations of Gardner syndrome include epidermoid cysts, supernumerary teeth, and desmoids. In addition, other benign lesions such as epidermoid cysts, fibromas, and lipomas occur much more frequently in the FAP population. Epidermoid cysts occur in mid to late adolescence and often occur in atypical locations such as the face, scalp, and extremities. Supernumerary teeth, dentigerous cysts, and secondary retention of teeth are all associated with FAP. Supernumerary teeth are usually present before age 10, and should be removed only if they impede the development of normal dentition. Dentigerous cysts develop from the epithelium of the enamel organ and develop before teeth erupt from the jaw. They can grow and occupy a significant portion of the jaw.

Table 67.3 Spigelman Classification for Duodenal Adenomas in FAP

Points	1	2	3
Polyp number	1–4	5–20	>20
Polyp size (mm)	1–4	5–20	>20
Histology	Tubular adenoma	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe
Interval to next EGD			
Stage 0 (0 points)	5 yrs		
Stage I (1–4 points)	5 yrs		
Stage II (5–6 points)	3 yrs		
Stage III (7–8 points)	1–2 yrs		
Stage IV (9–12 points)	EUS or surgery		

Thyroid cancer has been recognized at increased rates in FAP patients. The rates range from 1% to 12% and more frequently affects female patients.

Thyroid cancer is diagnosed at a mean age of 27 years. In most cases, the histology is papillary but the cribriform-morular variant is closely associated with FAP. Multicentric thyroid cancer is more frequent in FAP patients compared to sporadic cases. As with sporadic thyroid cancer, outcomes are excellent and treatment is similar. Screening for thyroid cancer is now typical for FAP patients.

Hepatoblastoma. Unlike other FAP-associated cancers which typically occur in adulthood, hepatoblastoma tends to occur in young children. The incidence in FAP patients is 1.6% and is more common in males. Screening can be performed using ultrasound as well as alpha-fetoprotein levels every 3 to 6 months from birth until 5 or 10 years of age. However, genetic testing is usually deferred until adolescence in individuals from FAP families; in order to decide about screening for hepatoblastoma, genetic testing must be performed in infancy to determine if the child is at risk.

Desmoids are slow-growing mesenchymal tumors made of well-differentiated fibroblasts and myofibroblasts with abundant collagen. Up to one-third of FAP patients develop desmoids; however, the rate is more than 1,000 times the rate in nonaffected populations. While the tumors are technically benign and do not metastasize, they do tend to be locally aggressive and infiltrate surrounding tissues. Additionally, recurrence rates are high after removal. Desmoids may occur in any part of the body, but the intra-abdominal desmoids tend to be most clinically significant; up to 80% of FAP-related desmoids are found in the mesentery with the remainder occurring primarily in the abdominal wall (**Fig. 67.14**). In addition to mass-like desmoids, flat-white desmoplastic plaques may also be found. They can affect the mesentery and lead to ischemic bands or obstructions.

Desmoid tumors are a major source of both morbidity and mortality following risk-reducing colectomy. Though these tumors are not technically malignant, complications including obstruction, necrosis, and fistulization can be extremely problematic. They represent one of the more common reasons for FAP-related mortality in patients who have undergone risk-reducing colectomy and therefore are unlikely to get CRC. Typically these lethal desmoids occur in the mesentery and this can make resection extremely treacherous. High recurrence rates are observed after attempted excision. Previously, some authors had suggested that ileorectal anastomosis (IRA) was better than ileal-pouch anal anastomosis (IPAA) to avoid desmoids but

this does not necessarily appear to be the case. In particular, this management strategy has been proposed for women who are concerned about desmoids affecting fertility but will ultimately require completion proctectomy.

The clinical presentation of desmoids ranges from asymptomatic plaques or masses discovered incidentally on imaging or during prophylactic surgery, or with nonspecific symptoms. Large or locally aggressive desmoids may lead to abdominal pain, bowel obstruction, ischemia, venous thrombosis via compression, motor or sensory deficits from nerve compression, ureteric obstruction, sepsis from enteric fistula, and gastrointestinal hemorrhage.

One of the major risk factors for desmoid development is surgical trauma. Desmoids are identified at the time of initial surgical intervention in <5% of patients. Other risk factors for desmoid disease include female gender, the presence of other extraintestinal manifestations of FAP, and a family history of desmoids.[19] Mutations toward the 3′ end of the *APC* gene are associated with the development of desmoid tumors, but family history is a risk factor for the development of disease, independent of genotype.

Intra-abdominal desmoid staging takes into account tumor size, symptoms, behavior, and the presence of complications.[20] This can help in evaluating desmoids over time and determining treatment options. Stage I desmoids are asymptomatic and not growing. They are usually found incidentally at the time of surgery or CT scan performed for other reasons. Stage II tumors are symptomatic and 10 cm or less, but not growing. These tumors may require treatment because of symptoms. Stage III desmoids are symptomatic tumors that are 11 to 20 cm in size, or asymptomatic and slow growing. Treatment may also be recommended for these large desmoid tumors. Finally, Stage IV desmoids are symptomatic and more than 20 cm in size, display rapid growth, or cause significant complications. Tumors that cause life-threatening complications such as sepsis, free bowel perforation, or massive bleeding require urgent treatment. Other features of desmoids that are taken into account include their shape (mass, nodular, or flat), the number of tumors present, the location, whether they occur before or after operative intervention, and hormone receptor status. These can all help guide management.

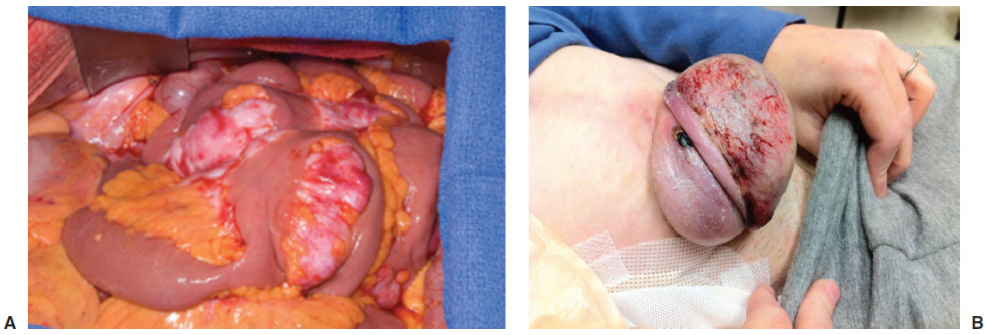

Figure 67.14 **A:** Mesenteric desmoids may limit the ability to perform colon resection or to create a pouch that reaches the pelvis for a restorative procedure. **B:** Abdominal wall desmoid in a young woman with FAP. This is a source of significant morbidity for the patients despite the nonmalignant nature of the desmoid tumor.

There are both nonsurgical and surgical treatments for desmoids. Nonsteroidal anti-inflammatory drugs (NSAIDs) such as sulindac and indomethacin are considered first-line therapy for desmoids. Antiestrogens, primarily tamoxifen and raloxifene may be similarly effective to NSAIDs, and the two may be used together. Chemotherapy typically aimed at sarcoma may also be utilized, as well as tyrosine-kinase inhibitors. Radiation therapy is another option for local control, particularly after surgery or when the tumor is unresectable; but there are substantial risks as the small bowel is likely to be present in the field of radiation in these cases.

Surgery for intra-abdominal desmoids may not be feasible when they are in their common location in the root of the mesentery. In addition, high recurrence rates following resection limit the utility of surgery to carefully selected cases. Often, the characteristic infiltrating growth pattern makes complete resection impossible without extensive small bowel resection. Major complications have been reported in up to 50% of patients with intra-abdominal desmoids treated with surgical resection. In addition, extensive resection may lead to short bowel syndrome and its attendant management challenges. Abdominal wall desmoids may be treated with surgical resection, including 2-cm margins. Reconstruction with prosthetic mesh or a myocutaneous flap may be required for larger tumors.

Surveillance Protocols

Patients with FAP should undergo annual colonoscopy starting at age 10 to 12. Upper endoscopy with a side-viewing endoscope to optimize

visualization of the ampulla is performed by age 20 to 25. Subsequent intervals depend on findings and are typically based on the Spigelman classification. Annual thyroid examination should be performed; many experts recommend that FAP patients undergo thyroid ultrasound in the late teenage years, and that the examination be repeated potentially up to every 3 years, particularly for women. The surveillance for desmoids may include annual abdominal examination or routine imaging with either CT, MRI, or ultrasound if dictated by personal or family history after colectomy; this should begin within 1 to 3 years of colectomy and be repeated every 5 to 10 years. There is no specific protocol for evaluating the small bowel beyond the duodenum in FAP. There is no evidence supporting routine enterography or video capsule endoscopy. In cases where screening for hepatoblastoma is desired, AFP levels can be measured every 3 to 6 months for the first 5 years of life and along with abdominal ultrasound and palpation (**Table 67.4**).

Table 67.4 Summary of Surveillance Guidelines for FAP Patients

Organ System	Surveillance Test	Frequency
Stomach/duodenum	EGD	At least every 3 yrs depending on findings
Thyroid	Ultrasound	Annually
Liver (hepatoblastoma) *controversial	Ultrasound and alpha-fetoprotein	Every 6 mo until 5–10 yrs of age
Adrenal	Ultrasound	Not recommended

*This is to note that surveillance of the liver is a controversial recommendation.

Surgical Treatment of FAP

6 Patients with classical FAP are destined to develop CRC unless they undergo risk-reducing colectomy. Surgical options depend on the number and distribution of polyps; timing also depends on the number and size of polyps, symptoms, patient age, and maturity. Ideally, surgery should occur when

patients have reached physical maturity as well as the ability to cope psychologically with their diagnosis and consequences of surgical treatment.

Total proctocolectomy is appropriate for patients with diffuse polyposis involving the colon and rectum, as well as those with primary colonic disease who prefer a more definitive operation. Patients may choose to have a permanent ileostomy, but restorative proctocolectomy with IPAA is typically performed in suitable candidates. Continent ileostomy, or Kock pouch, may also be an option in selected individuals with FAP.

In the setting of restorative proctocolectomy, the role of mucosectomy is debated in FAP. The idea behind mucosectomy is that by removing all at-risk mucosa, the chance of polyps and cancer developing is eliminated. However, even with a mucosectomy, it is possible to leave behind microscopic islands of mucosa that are at risk for neoplasia. Adenomas occur in the anal transition zone at a rate of 28% to 51% after stapled anastomosis and 10% to 22% after mucosectomy with hand-sewn anastomosis. Cancer is rare, but does occur at a rate of 1% to 2% following either approach, so continued surveillance is necessary.

When polyp distribution is primarily colonic and there are less than 20 to 30 polyps in the rectum that can be managed endoscopically, patients can be considered for colectomy with IRA. With appropriate patient selection, the risk of subsequent proctectomy is less than 2%.

Patients must have regular surveillance of either their IRA or ileal pouch following risk-reducing surgery. It is generally recommended than an IRA be evaluated with flexible endoscopy every 6 to 12 months, depending on the rectal polyp burden. Pouchoscopy should be performed every 1 to 3 years.

Attenuated FAP

Attenuated FAP (aFAP) is a milder phenotype of FAP; it is characterized by fewer colonic polyps with a later age of onset and a lower risk of CRC. The typical range of polyps in aFAP is 10 to 100 adenomas. The distribution is more likely to be right sided than pan-colonic compared to FAP. The onset of CRC tends to occur later in life compared to classic FAP but the risk of cancer may be up to 80% by age 70. Routine colonoscopy and polypectomy may decrease the risk. The extracolonic tumor spectrum is similar to FAP and therefore screening and surveillance regimens are also similar.

Some patients with mild, attenuated FAP may be managed endoscopically and avoid colectomy. If their colon and rectum can be endoscopically cleared of polyps and they are willing to submit to frequent follow-up, they may be able to forego surgery. Most patients with aFAP are well suited to colectomy with IRA.

MUTYH-Associated Polyposis (MAP)

MAP is an autosomal recessive polyposis syndrome caused by mutations in the base-excision repair gene, *MUTYH*. Patients tend to have a milder form of colonic polyposis compared to FAP. Most patients have fewer than 100 adenomas. Other polyp types such as hyperplastic or serrated lesions may also be present. Because of the autosomal recessive inheritance pattern, the family history may not be as obvious as in FAP. Polyps typically develop in the third to sixth decades of life.

Incidence

Between 1% and 2% of the Caucasian population carry a single-mutated copy of the *MUTYH* allele; the most frequent alterations are Y179C, G396D, and E480X. The Y179C variant is less active than G396 and therefore represents the most severe phenotype. For non-European descent individuals, the genetic alterations may be different and occur at different frequencies but this has not yet been well described.

Genetics/Molecular Pathways

Germline mutations in *MUTYH* permit excess number of acquired mutations in the *APC* gene, which is why MAP is phenotypically similar to FAP. The *MUTYH* gene encodes a specific DNA glycosylase excision repair protein that is responsible for excising adenine nucleotides that are mismatched with 8-oxo-guanine, which is a product of oxidative damage to DNA. The mutations are typically G:C → T:A transversions. MAP is an autosomal recessive syndrome, so the individual must inherit two mutated alleles of the gene.

Extracolonic Features

The spectrum of extracolonic features and cancers in MAP is similar to FAP. However, they occur less frequently and are not as well characterized in this

syndrome. Consequently, the surveillance protocols are similar in the two syndromes.

Cancer Risks

The estimated lifetime risk of CRC for patients with MAP is approximately 60%. The typical age of onset is between ages 45 to 59, slightly older than in FAP. Monoallelic carries of *MUTYH* gene mutations may be at increased risk of CRC. The estimated risk is two to three times higher than the general population.[21]

Surveillance Protocols and Management

Patients with MAP should undergo colonoscopy every 1 to 2 years with polypectomy as indicated. Surveillance should be initiated by age 25 to 30. Those with unresectable polyps or a large polyp burden should be referred for surgical consideration. Similar to those patients with FAP, the extent of surgery (total abdominal colectomy with IRA vs. total proctocolectomy) depends on the polyp burden in the rectum. In a patient with an IRA, the rectum should be surveyed with flexible sigmoidoscopy every 6 to 12 months. Monoallelic carriers of *MUTYH* mutations should also have colonoscopies every 5 years beginning at age 40, or 10 years prior the earliest diagnosis of CRC in the family.

Because of the risk of upper GI neoplasia, baseline upper endoscopy including visualization of the ampulla of Vater should be performed by age 30 to 35. Surveillance examination interval is determined by the Spigelman stage in the same way it is used for FAP. The overall risk of duodenal cancer in MAP is approximately 5%.

Novel Genes or Syndromes (NTHL1, CRAC1)

With advances in genetic testing, a number of newer syndromes have been described. Polymerase proofreading-associated polyposis is an autosomal dominant syndrome characterized by mutations in the polymerase proofreading genes *POLE* and *POLD1*, which results in a highly penetrant syndrome of tens to hundreds of polyps and a high risk of CRC. The carcinomas are microsatellite stable, follow the chromosomal instability or classical pathway to development from adenomas, and are a result of unrepaired DNA replication errors. Patients may have family histories suggestive of LS. Female patients may be at increased risk for endometrial,

breast, and ovarian cancers. There are also descriptions of small bowel cancer and brain tumors associated with this syndrome.

The *NTLH1* gene, which encodes for a base excision repair protein, has been implicated in an autosomal recessive syndrome that is similar to MAP. It has been described in a cluster of Dutch families with a single founder mutation. The suspected carrier frequency in that population is 1 in 75,000. In a different individual with two separate mutations in the gene, the constellation of CRC, carcinoma of the bladder, meningioma, breast carcinoma, intradermal nevi, and basal cell carcinoma has been described. This suggests that the range of DNA lesions affected by this protein is broader than in MAP. The phenotype in affected families is consistent with an attenuated colorectal polyposis.

A mixed polyposis syndrome is described in patients with mutations to the *CRAC1* gene. Polyps may be serrated, hamartomatous, and adenomatous. CRC risk appears to be elevated. This gene is described in the Ashkenazi Jewish population. The gene was identified via linkage analysis and appears to be a single, founder mutation.

Because these syndromes are just being defined in small groups and clusters of families, the spectrum of the phenotype is not well known. There is insufficient evidence for specific screening, surveillance, or surgical treatment. As in cases without an identifiable genetic mutation, the individual and family phenotype should guide treatment decisions.

Familial CRC Type X and Undefined Syndromes

Families that meet the Amsterdam II criteria but do not have a pathogenic variant in an MMR gene identified are referred to familial CRC Type X. Compared to LS, it appears that the risk of extracolonic cancers are decreased. However, surveillance at short intervals is still recommended.

There are patients who phenotypically meet criteria for a polyposis syndrome and/or have a family history that is extremely suggestive of a polyposis syndrome, but do not have an identifiable genetic mutation. Management, therefore, is based on phenotype. Those individuals with dozens to hundreds of polyps should be managed in the same way as FAP patients, though their risk of extracolonic features may be less. The more common scenario, however, is a patient with 11 to 20 polyps; these patients

are managed individually based on specifics of the phenotype and clinical judgment. The patient must be willing to undergo frequent surveillance at 1- to 3-year intervals and polypectomy should be performed to clear the colon. If it becomes impossible to safely survey the colon endoscopically or advanced lesions are found, colectomy is appropriate.

Serrated Polyposis Syndrome

Serrated polyposis syndrome (SPS) was previously referred to as HP syndrome. It is rare, even compared to other hereditary CRC syndromes, and less well understood. It does appear to have an autosomal dominant inheritance pattern; 40% of first-degree relatives of SPS patients also have serrated polyps.

Genetics

Some patients who meet the clinical criteria for SPS have pathogenic variants in the *RNF43* gene but the majority of patients do not have an identifiable genetic mutation. The *RNF43* gene regulates *AMTIATR* (ataxia-telangiectasia mutated/ataxia-telangiectasia and Rad3-related protein) response to DNA damage.

Diagnosis

The clinical diagnosis for SPS includes at least five serrated polyps proximal to the sigmoid colon with at least two greater than 1 mm in size, any number of serrated polyps in an individual with a first-degree relative with SPS, or 20 or more serrated polyps anywhere in the colon. While small HPs are frequently found in the distal sigmoid and rectum of normal individuals, SPS represents a distinct phenotype.

Cancer Risk

Individuals with SPS are at higher than average risk for CRC, with a range of 16% to 35% reported in the limited literature that addresses the topic.[22,23]

Surveillance

If endoscopic management is feasible, all polyps 5 mm or greater in size should be removed. Subsequently, patients should undergo surveillance colonoscopies at 1- to 3-year intervals. If the number and/or size of polyps

renders endoscopic management impossible, or if there are advanced lesions, patients should be referred for surgery.

Because most patients do not have an identifiable genetic mutation, management of their relatives presents a challenge. It appears that first-degree relatives, even those without an SPS phenotype, have an increased risk of CRC.[24] Consensus guidelines recommend that first-degree relatives should be screened at the youngest age of onset of SPS in the family, 10 years earlier than the diagnosis of CRC, or by age 40—whichever is earliest in the case of an individual family. Colonoscopy should be repeated at least every 5 years and more frequently if indicated by findings.

Hamartomatous Polyposis Syndromes

Peutz–Jeghers Syndrome

PJS is an autosomal dominant syndrome associated with GI polyps and characteristic skin pigmentation. There are two genetic alterations associated with PJS, *LKB1,* and *STK11*, both of which encode serine/threonine kinase.

The GI polyps in PJS are hamartomatous. They are nonneoplastic but histologically distinct from other hamartomatous polyps such as juvenile polyps. They may be found in the stomach, small intestine, or colon. Polyps may cause bleeding, intussusception, or obstruction.

PJS is also characterized by distinctive cutaneous manifestations. The dark, macular lesions on the mouth and buccal mucosa as well as on the nose, lips, hand, feet, genitals, and anus tend to be more prominent early in life and then less obvious by puberty (**Fig. 67.15**). They are different than typical freckles in that they are present at birth and the buccal mucosa may be involved in PJS; the lesions also extend within the vermilion border of the lips.

Patients with PJS are at increased risk of cancers within and outside the GI tract. At-risk organs include the stomach, small intestine, colorectum, breast, pancreas, and biliary tree. Ovarian cysts, sex cord tumors, and sertoli cell testicular tumors may also be present. Small bowel cancer and CRC are relatively rare in PJS.

Management of PJS is aimed toward removal of polyps in the GI tract. Traditional upper and lower endoscopy are utilized, but more advanced

techniques such as double balloon or push enteroscopy may also be required. Surgery is utilized in cases where endoscopic management is not feasible. Combined laparoscopy and endoscopy may also be useful to enable treatment of the entire small bowel. There is no prophylactic surgery recommended for PJS.

Figure 67.15 Perioral hyperpigmentation associated with PJS.

Juvenile Polyposis Syndrome

JPS has been described with three distinct phenotypes: JPS limited to the colon, JPS limited to the stomach, and JPS throughout the GI tract. There are two genetic alterations associated with the syndrome, involving the *SMAD4* and *BMPR1A* genes. Each are thought to account for 20% of JPS cases; the remainder of cases have an unknown genetic etiology. When JPS occurs in conjunction with hereditary hemorrhagic telangiectasia, it is typically associated with *SMAD4*. In addition, some *PTEN* mutations have also been linked to JPS, but this is rare.

Clinical manifestations include bleeding, intussusception, obstruction, and autoamputation of polyps that then pass through the GI tract. Rarely, protein-losing enteropathy may develop. Approximately 15% of patients with JPS

have other abnormalities such as malrotation, heart or brain abnormalities, cleft palate, polydactyly, or genitourinary tract abnormalities.

Cowden Syndrome

Cowden Syndrome, also known as PTEN hamartoma tumor syndrome, is associated with a mutation on chromosome 10q23.3. Mutations are found in about 85% of patients diagnosed with Cowden syndrome. The PTEN gene is a tumor suppressor gene that acts as a negative regulator of the Akt/PKB signaling pathway, which in turn regulates levels of phosphoinositol triphosphate. It is also involved in regulating cell cycle, apoptosis, and angiogenesis. While intestinal polyps are important features, the extracolonic manifestations are more prominent. Though hamartomatous intestinal polyps occur in 30% to 85% of cases, there is no strong evidence of an increased risk for CRC from the hamartomatous polyps related to this syndrome. Patients may also have benign hamartomas and malignant tumors of the breast, thyroid, uterus, brain, and mucocutaneous tissue.

Diagnosis is based on meeting pathognomonic major and minor criteria developed in consensus guidelines. Testing should be offered to patients who have a family history of the syndrome if they meet the diagnostic criteria or if they have Lhermitte–Duclos disease. Major criteria include breast cancer, endometrial cancer, follicular thyroid cancer, multiple GI hamartomas or ganglioneuromas, macrocephaly, macular pigmentation of the glans penis, or mucocutaneous lesions including trichilemmoma, palmoplantar keratoses, multifocal or extensive oral mucosal papillomatosis, or multiple cutaneous facial papules. Minor criteria include autism spectrum disorder, CRC, more than three esophageal acanthoses, lipomas, intellectual disability, certain forms of thyroid cancers or benign lesions, renal cell carcinoma, single GI hamartoma or ganglioneuroma, testicular lipomatosis, or vascular malformation. In an individual with a relative who meets the clinical diagnosis criteria but who has not been tested, testing is appropriate if they meet any “major” or two “minor” criteria.

Breast cancer rates in women with Cowden syndrome are between 30% and 50%; men are also at risk. Benign breast conditions are also common in Cowden syndrome. Thyroid abnormalities including goiter, thyroglossal duct

cysts, and thyroid cancer are an important feature of Cowden syndrome. Renal cell cancer has also been described.

Because of the broad spectrum of tumors, patients with Cowden syndrome are recommended to undergo surveillance of their breast, endometrium, kidney, and thyroid. In terms of CRC risk, it is recommended that colonoscopy be started at age 35 or 5 to 10 years prior to the first known CRC in the family. Patients should undergo colonoscopy at least every 5 years for surveillance.

Bannayan–Riley–Ruvalcaba Syndrome

BRRS is a hamartomatous polyposis syndrome that also includes a constellation of macrocephaly, hypotonia, developmental delays in about half of all cases, pigmented speckling of the penis in men, hypermobile joints, and lipomas and hemangiomas in addition to the hamartomas of the intestine. More than two-thirds of patients with BRRS have a mutation in the PTEN gene. It is a rare disorder with dozens of cases reported in the literature but it may be underdiagnosed in milder phenotypes The incidence of gastrointestinal polyps is 45%.[25] The cancer risks associated with this syndrome are not well defined but many authors consider it analogous to Cowden syndrome. Most authors suggest considering individuals with BRRS at higher than average risk for malignancy, similar to Cowden syndrome.[26]

CONCLUSIONS

Polyps are an extremely common finding on colonoscopy, particularly as individuals age. Screening and surveillance with polypectomy has the potential to decrease both the risk and the mortality related to CRC. Polyposis syndromes are complex clinical problems that require coordinated care from multiple specialists; patients are often at higher risk for cancer in multiple organ systems. Optimal care is given in the context of a registry or organized program to ensure that all screening and surveillance guidelines are followed.

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68

Colorectal Cancer

Julio Garcia-Aguilar and Emmanouil P. Pappou

Key Points

1. Incidence and overall mortality for colorectal cancer (CRC) are declining, especially among those aged 65 years or older, likely due to increased screening and improvement in treatment modalities. However, a surge in incidence among young adults, particularly those younger than 50 years has been recently noted. The cause of increase in young-onset CRC is currently unknown.
2. Our greater understanding of the molecular biology of CRC and the identification of disease biomarkers has allowed the introduction of targeted therapies, including immunotherapy into clinical practice.
3. Advances in imaging techniques have improved risk stratification via more accurate baseline tumor staging and treatment selection.
4. Improved risk stratification and neoadjuvant therapy have enabled physicians to tailor therapeutic components of treatment.
5. Use of laparoscopic and robotic surgical techniques in combination with enhanced recovery programs has accelerated patient recovery, reduced length of hospital stay, and reduced postoperative complications.
6. While long-term survival for patients with stage IV disease remains low, median survival for these patients has improved significantly in recent years, probably due to more effective chemotherapy and more aggressive surgery.
7. Multidisciplinary treatment involving surgical oncologists, medical oncologists, radiation oncologists, as well as liver surgeons, gastroenterologists, and stoma therapists improves outcomes and quality of life in patients with CRC.

INTRODUCTION

Colorectal cancer (CRC) kills more than 50,000 people every year in the United States. If diagnosed at an early stage, however, it is one of the most curable malignancies. Identification of populations at risk and screening of asymptomatic patients are therefore crucial imperatives. This chapter provides

a comprehensive overview of the disease, including epidemiology, risk factors, molecular characteristics, progression, staging, screening, diagnosis, and treatment.

EPIDEMIOLOGY

CRC is the third most common malignancy and the second most common cause of cancer death in the United States. It is estimated that in 2020, a total of 147,950 people will be diagnosed with CRC in the United States, and 53,200 will die from the disease.[1] Approximately 1 in 20 Americans will be diagnosed with CRC in their lifetime. Death from CRC could be reduced significantly by implementing screening for cancer prevention and early diagnosis, as well as adherence to standards of cancer care. The incidence and mortality rates for CRC have been decreasing for the last three decades, with a large drop in the late 2000s thought to be reflective of the nationwide adoption of CRC screening with colonoscopy. Most recently, however, there has been a deceleration in the decline of CRC incidence and mortality (**Fig. 68.1**).[2]

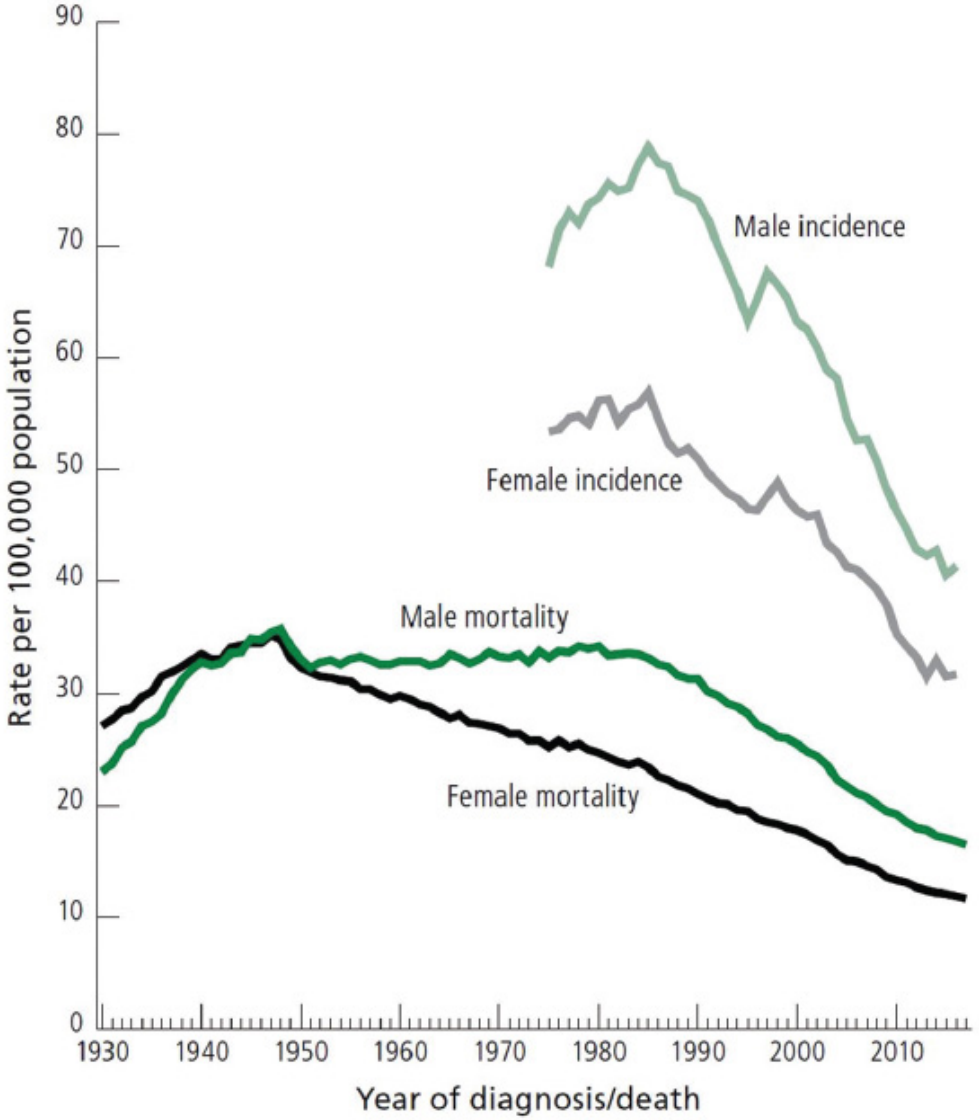

Figure 68.1 Trends in Colorectal Cancer Incidence and Death Rates by Sex, USA, 1930–2017. (Reproduced with permission from The American Cancer Society, Colorectal Cancer Facts and Figures 2020–2022. Atlanta: American Cancer Society, Inc.)

The incidence and mortality rates for CRC vary with age. The median age at colon cancer diagnosis is 67 years in men, and 71 years in women; for rectal cancer, 62 years in men and 63 years in women.[2] While the incidence and mortality for CRC have decreased in older adults (50+ years old), they have 1 increased in younger adults (<50 years old) (**Fig. 68.2**). This change in trend is especially worrisome, as the incidence is occurring in patients younger than the recommended screening age.[2] Both, the incidence and mortality for CRC are 30% to 40% higher in men than in women. The reasons for these differences are

not completely understood but probably reflect an interaction between risk factors and hormonal differences. There are also gender differences in the distribution of CRC, with a higher proportion of proximal tumors in women.

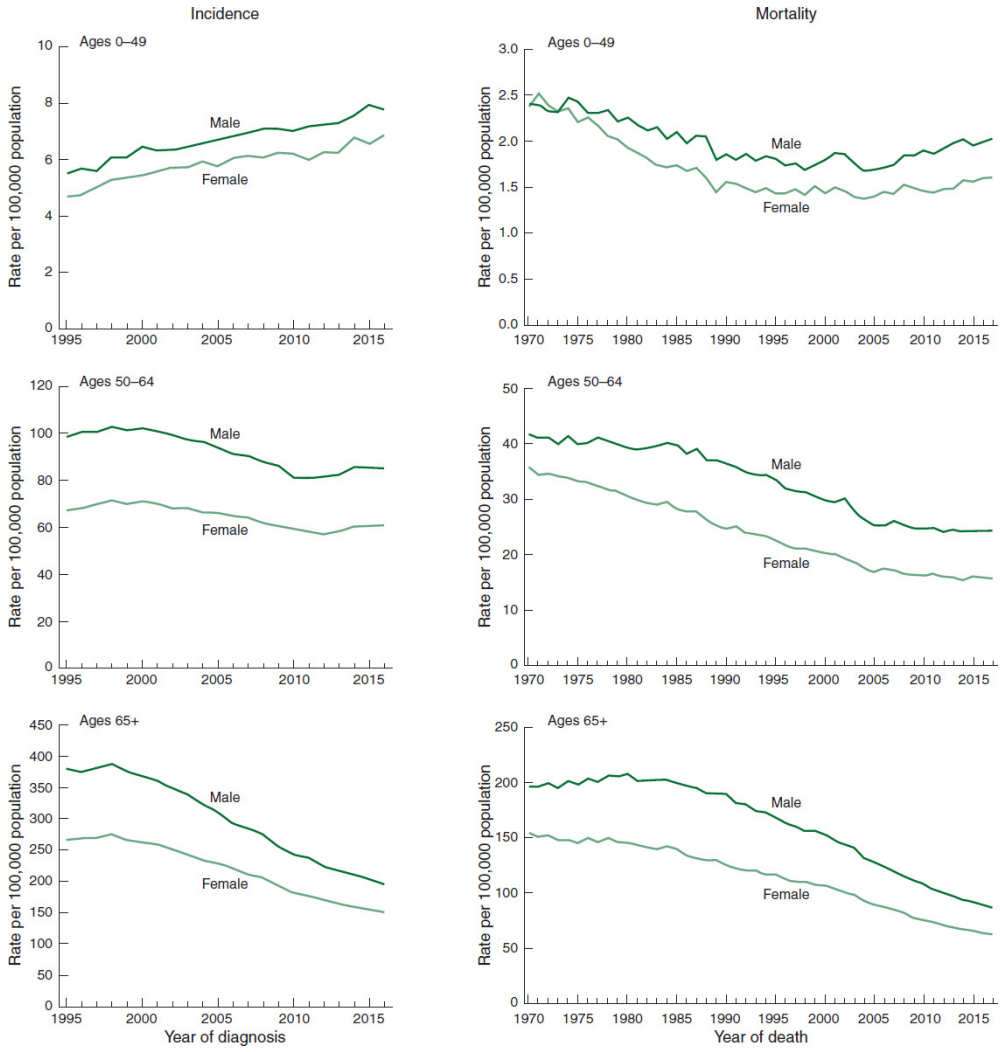

Figure 68.2 During the most recent five data years (2012–2016), incidence rates of CRC increased by 2.2% annually in individuals younger than 50 years and by 1% annually in those ages 50 to 64 years, a sharp contrast to declines of 3.3% per year in adults ages 65 and older. Reasons for the increasing CRC trend in younger age groups are unknown. (Reproduced with permission from The American Cancer Society, Colorectal Cancer Facts and Figures 2020–2022. Atlanta: American Cancer Society, Inc.)

There are great disparities in CRC incidence and mortality between ethnic and racial groups. Both are highest for African Americans and lowest for Asians/Pacific Islanders, but the differences in mortality are proportionally larger compared to the differences in incidence. The decline in mortality for

CRC that began in the 1980s did not start affecting African Americans until the 1990s. Since the mid-2000s, CRC incidence rates decreased by 1% to 3% per year in all racial groups.[2]

CRC is the third most common cancer in men and the second most common cancer in women worldwide, with an estimated 1.8 million new cases diagnosed in 2019.[3] It is responsible for 9% of cancer deaths worldwide. The age-standardized incidence of CRC varies significantly by country. It is decreasing in developed countries that have implemented screening programs (U.S., Israel, and Japan) or have modified factors known to be associated with increased risk of CRC (Australia and New Zealand). However, the incidence rates are increasing in both developed and developing countries with changes in unfavorable risk factors such as adoption of a western diet, obesity, and smoking. Despite the increase in incidence, mortality for CRC is decreasing in many countries, most likely because of improvements in both screening and treatment.[3]

RISK FACTORS

There are numerous factors associated with the risk of CRC (**Table 68.1**). Some are behavioral, and potentially modifiable. Others are genetic or hereditary, and therefore nonmodifiable. Information about individual risk factors can be used to reduce incidence and mortality through behavior modification and screening programs.[4] Except for the relatively uncommon hereditary syndromes with known patterns of inheritance, the relative contribution of inherited and environmental factors to the development of CRC is controversial. Analysis of cohorts of twins from Scandinavian countries suggests a significant but relatively minor contribution of hereditary factors to the development of sporadic CRC; the environment seems to play a larger role in the development of sporadic cancers.[5]

Table 68.1 Relative Risks for Established Colorectal Cancer Risk Factors

Factors that Increase Risk:	Relative Risk[a]
Behavioral, Modifiable	
Heavy alcohol use (daily average >3 drinks)	1.3
Obesity (body mass index ≥30 kg/m^2)	1.3
Colon, male	1.5
Colon, female	1.1
Rectum, male	1.3
Rectum, female	1.0
Red meat (100 g/day)	1.1
Processed meat (50 g/day)	1.2
Smoking	
Current vs. never	1.5
Former vs. never	1.2
Hereditary, Nonmodifiable	
Family History	
Family history of CRC	
1 or more first-degree relatives	2.2
1 or more first-degree relatives diagnosed before age 50	3.6
2 or more first-degree relatives	4.0
1 or more second-degree relatives	1.7
Family history of adenoma	
1 or more first-degree relatives	2.0
Medical History	
Inflammatory bowel disease (Crohn disease, ulcerative colitis)	1.7
Type 2 diabetes mellitus	
Male	1.4
Female	1.2
Factors that Decrease Risk:	
Physical activity	0.7

Dairy (400 g/day)	0.9

[a]Relative risk for dietary factors compares the highest with the lowest consumption. If the relative risk is more than 1.0, then risk is higher among exposed than unexposed persons. Relative risks less than 1.0 indicate a protective effect.

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The list of behavioral or modifiable factors that increase CRC risk includes obesity, smoking, diet, and alcohol intake. More than half (55%) of CRCs in the United States are attributable to potentially modifiable risk factors.[3] Physical activity and dairy products reduce CRC risk.[2] Obesity is associated with increased risk of developing CRC in both men and women.[6] Abdominal obesity, measured as waist size, seems to be more important than excess weight, particularly in men. Being overweight increases the risk of CRC, independent of the level of physical activity. The most physically active people have a 25% lower risk of developing CRC, compared to the least active people. Both recreational and occupational physical activity reduces CRC risk, and sedentary people who become physically active later in life do reduce their CRC risk.[7] An increased risk of CRC has been associated with high consumption of red or processed meats.[8] On the other hand, the risk of CRC is inversely correlated with the intake of fiber and whole grains, fruits and vegetables, dairy products and calcium, vitamin D, and folates.[8] Heavy alcohol consumption (more than 3 drinks/day) is associated with the development of CRC, and the effect seems to be dose dependent. The risk seems to be higher for men than for women. There is no difference in the effect with regard to the type of alcohol.[9] Smoking increases the incidence and mortality from CRC, and in particular, rectal cancer.[10,11]

Three-quarters of CRCs occur in people who do not have any particular predisposing factors, and are therefore considered to be at average risk. The remaining 25% of patients have hereditary risk factors that predispose them to the development of CRC: either a well-defined hereditary CRC syndrome (5%) or a close relative who has been diagnosed with the disease (20%). People with one or more first-degree relatives with CRC have between a 1.9 and 4.4 relative risk of developing CRC, compared to the average population. The risk is higher when the affected relative was diagnosed at an early age, or when several relatives have been affected.[12,13] Recent population-based studies have found a greater familial aggregation of early-onset CRC among first-degree

relatives diagnosed before the age of 40, compared to patients diagnosed after the age of 41. This age-of-onset effect could not be attributed solely to known hereditary CRC syndromes.[14] CRC survivors have four times the lifetime risk of developing a new (metachronous) CRC, compared with people at average risk. The estimated mean annual incidence of metachronous CRC is 0.3%, with a cumulative incidence of 3.1% at 10 years.[15] A personal history of adenomatous colorectal polyps also increases the risk of CRC, in particular for patients with larger or multiple polyps and an early age at diagnosis.[16]

Patients with chronic inflammatory bowel disease, both ulcerative colitis and Crohn disease, are at increased risk of developing CRC.[17] The risk increases with the duration of the disease. It is estimated that, after 10 years of disease, the risk of developing CRC increases by around 1% each year. Thus, it is estimated that patients with 30 years of inflammatory bowel disease have an 18% risk of developing CRC. The risk is higher for patients diagnosed with inflammatory bowel disease at an early age and with disease extending proximal to the splenic flexure. A high cumulative burden of inflammation, that takes into consideration the intensity and the duration of inflammation, has been associated with a higher risk of colorectal neoplasia.[18] However, the incidence of CRC in patients with ulcerative colitis seems to be decreasing. A recent meta-analysis of population-based cohort studies reported a 1.7 increased risk of CRC among inflammatory bowel disease patients, compared to the general population, after adjusting for age, gender, and duration of disease.[19] These changes are probably due to more effective treatments and the efficacy of surveillance programs.[20]

Patients with type II diabetes have a higher risk of developing CRC compared to the nondiabetic individual, even when adjusting for factors such as obesity and sedentary lifestyle.[21] In addition, CRC survival rates are lower for diabetic patients compared to nondiabetic patients.[22] The relationship between diabetes and CRC seems to be stronger for men than for women.

MOLECULAR CHARACTERISTICS

The traditional model of CRC tumor development is often represented as a linear and sequential progression from normal epithelium to small adenoma, to large adenoma, to invasive carcinoma, and finally to metastatic disease.[23] This so-called adenoma–carcinoma sequence has been deemed the result of the

progressive accumulation of alterations in the genome. This model has shaped our understanding of key genetic alterations that result in colorectal tumorigenesis and has had an enormous clinical impact by highlighting the importance of screening and surveillance. Whole genome analysis with high-throughput technologies has added new information that is broadening our understanding of colorectal carcinogenesis. Every CRC has a multitude of distinct genetic alterations that perturb a number of molecular pathways. This genetic heterogeneity ultimately has a bearing on the speed of growth, local invasiveness, metastatic potential, and response to therapy. As our understanding of these molecular changes improves, we anticipate 2 that we will be able to provide better screening and prognostic tools and discover new tumor-specific therapies.

The most comprehensive molecular analysis of CRC to date has been conducted by The Cancer Genome Atlas (TCGA) Consortium.[24] They have used state of the art technology to elucidate the mutational spectrum, the chromosomal and subchromosomal changes, the epigenetic regulation and transcriptional alterations in a large number of CRCs. A key finding that has helped frame our molecular understanding of CRC is the wide variation in the number of somatic mutations present in most tumors. According to the number of mutations, CRC can be effectively classified as hypermutated, harboring a median of 728 nonsilent mutations per tumor, and nonhypermutated, with a median of 58 nonsilent mutations (**Fig. 68.3**). Nonhypermutated tumors comprise 84% of CRCs, and are characterized by chromosomal instability (CIN). CIN is the result of missegregation of chromatids in tumor cells, resulting in gains and losses of entire chromosomes or chromosomal segments; manifesting as aneuploidy and copy number alterations (CNAs).[25] Common patterns of aneuploidy and CNAs in nonhypermutated CRC include amplifications in chromosome arms 1q, 7p and q, 8q, 13q, 17q, and 20p/q, and deletions in 8p, 14q, 15q, 17p, and 18p/q. Some of these CNAs could account for the loss of important tumor suppressors such as TP53 (on 17p), DCC, and SMAD4 (on 18q), and the amplification of oncogenes such as ERBB2 (on 17q). In short, CIN in nonhypermutated tumors can activate critical oncogenes, and inactivate tumor suppressors that contribute to the acquisition of tumorigenic traits.

The hypermutated tumors, representing 16% of all CRCs, are deficient in the mismatch-repair (MMR) mechanisms controlling the correction of errors that occur during DNA replication. The end result of MMR deficiency (dMMR) is a

form of genetic instability characterized by the accumulation of mutations throughout the genome, primarily in repetitive sequences known as microsatellites; this is known as microsatellite instability (MSI).[26] The mutational burden ultimately provides these MSI tumors with their malignant potential. Unlike CIN tumors, also known as microsatellite stable or MSS, MSI tumors generally remain diploid or near-diploid. They are less likely to have KRAS, TP53, SMAD4 mutations, and more likely to have BRAF and TGFBR2 mutations. MSI can arise from either the germline inactivating mutations or the epigenetic silencing of one of several MMR genes (MLH1, MLH3, MSH2, MSH3, and MSH6). Research into the mechanisms of epigenetic silencing of MSI tumors has helped elucidate the CpG Island Methylator Phenotype (CIMP), whereby the methylation of CpG sequences in the promoter region of MMR genes (most commonly MLH1) leads to their transcriptional silencing.

The classification of CRC according to the type of genomic instability is clinically relevant.[27] MSI tumors tend to be preferentially right sided, have a solid or cribriform histologic pattern, and contain a large number of tumor-infiltrating lymphocytes.[28] Nonmetastatic MSI tumors have a better prognosis, compared to MSS tumors.[29] However, in a metastatic setting, MSI tumors are associated with a worse survival compared to MSS tumors.[30] MSI tumors are less responsive to fluoropyrimidines, but most responsive to immune checkpoint inhibitors (ICIs), compared to MSS tumors.[31]

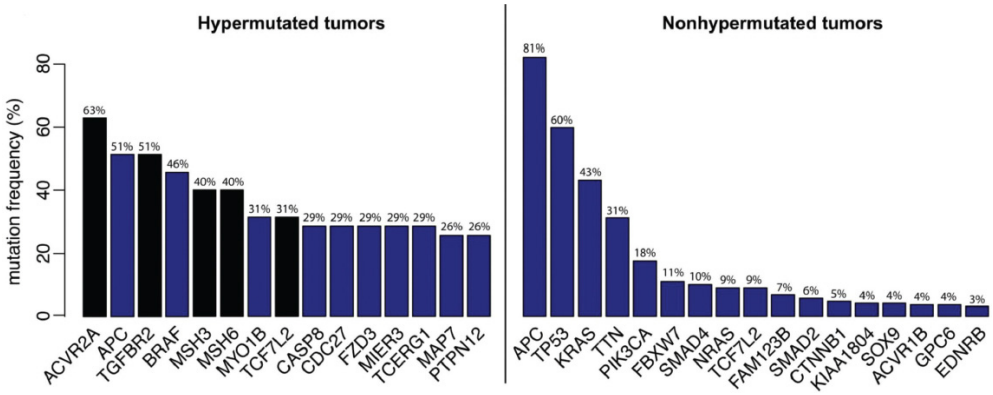


Figure 68.3 Mutation frequencies in hypermutated and nonhypermutated tumors in CRC. *Blue bars* represent genes identified by MutSig and genes in *black bars* are identified by manual examination of sequence data. (Reproduced with permission from Comprehensive molecular characterization of human colon and rectal cancer. The cancer genome atlas network. *Nature* 2012;487(7407):330–337.)

The genomic instability that characterizes CRC is associated with alterations in a number of key pathways; among others, the WNT, MAPK, PI3K, TGF-β, and p53 pathways.[24] The WNT signaling pathway contributes to the tightly regulated homeostasis of intestinal epithelial crypts, and its alteration is considered an initiating event in colorectal carcinogenesis. It is altered in more than 90% of both hypermutated and nonhypermutated CRCs. The most prevalent alteration leading to dysregulation of the WNT pathway occurs through biallelic inactivation of the tumor suppressor adenomatous polyposis coli (APC) gene.[32] Patients with familial adenomatous polyposis (FAP) have a germline mutation in one allele of the APC gene, and their risk of developing CRC is virtually 100%. The WNT pathway is also commonly altered as a result of stabilizing mutations of the CTNNB1 gene coding for β-catenin, a protein normally targeted for degradation by APC. The accumulation of β-catenin as a result of APC loss or stabilizing CTNNB1 mutations leads to its translocation to the nucleus, where it interacts with transcription factors of the TCF/LCF family, turning them into transcriptional activators. The end result is an increase in the transcription of genes that are normally important for stem cell renewal and differentiation but, when inappropriately expressed at high levels, can cause cancer.

Mutational inactivation of the TGF-β pathway, important in regulating cell growth arrest and apoptosis, is a common event in CRC.[33] Downstream effectors of this pathway such as the transcription factor SMAD4, and associated proteins SMAD2 and SMAD3, are also inactivated by mutation or homozygous deletion of chromosomal segment 18q. Another member of this pathway, deleted in CRC (DCC), is also commonly inactivated by deletion of chromosome 18q.

A common theme of the WNT and TGF-β signaling pathways is the increased activity of c-Myc, a regulator gene that codes for a multifunctional transcription factor which plays a role in cell cycle progression, apoptosis, and cellular transformation. c-Myc seems to play a central role in colorectal carcinogenesis.[34]

The TP53 gene is a member of a pathway of regulators of cell cycle arrest and cell death in response to a variety of genotoxic stresses. Mutations in the TP53 tumor suppressor gene occur in more than half of nonhypermutated CRCs. In most tumors, both alleles of the gene are inactivated by a combination of a mutation in one allele, and loss of the second allele by deletion of the chromosomal segment 17p. Loss of the TP53 tumor suppressor gene is

generally considered an early event that plays a role in the transition from adenoma to invasive carcinoma.[35] In hypermutated tumors, the TP53 pathway may be attenuated by mutations in other genes, such as the proapoptotic BAX.

The MAPK pathway consists of a cascade of tightly coordinate kinases that work together to regulate cell division and proliferation. KRAS, a protooncogene that becomes constitutively activated by mutation, resulting in uncontrolled cell proliferation, is mutated in 37% of CRC. Interestingly, a number of studies from model organisms reveal that KRAS mutation by itself is not sufficient to initiate tumorigenesis; in order to have oncogenic potential it requires a previous APC mutation. The MAPK pathway is the molecular pathway that has successfully been therapeutically targeted in CRC. Inhibition of this pathway using antibodies against the epidermal growth factor receptor (EGFR) reduces progression in wild-type KRAS/NRAS metastatic CRC.[36] Activating mutations of BRAF, also an effector member of the MAPK pathway downstream of KRAS, are seen in 13% of CRC. The BRAF mutation is associated with poor prognosis, specifically in MSI tumors.[37]

The PI3K/AKT/mTOR signaling pathway, with important roles in cell proliferation and apoptosis, is abnormally activated in nearly half of all CRCs. Moreover, in the TCGA cohort, PI3K and RAS pathways are simultaneously affected by mutations in one-third of all CRCs, suggesting that simultaneous inhibition of both pathways may be required to achieve a therapeutic effect.[38]

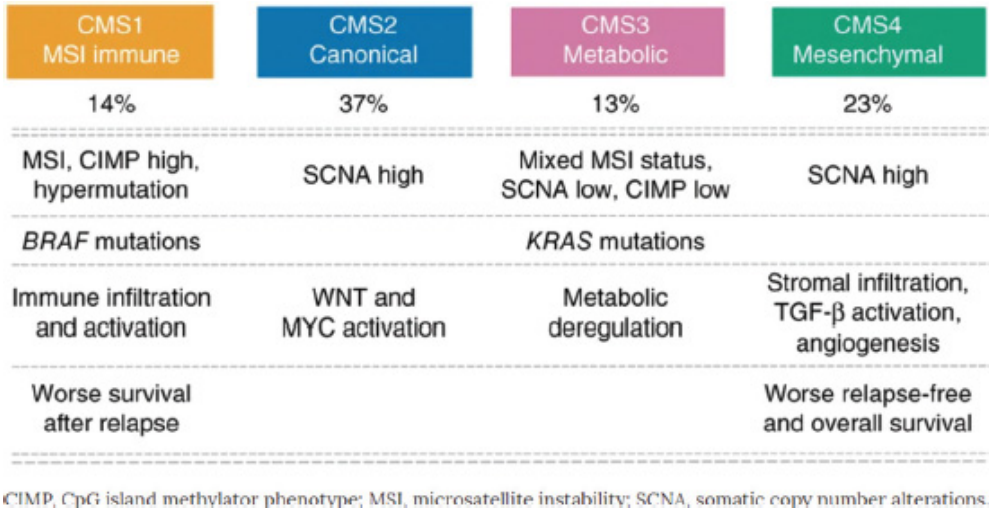


Figure 68.4 The consensus molecular subtypes. CMS1 displays subtype clusters that involve hypermutation and microsatellite instability along with increased immune cell infiltrates consisting of Th1 lymphocyte, cytotoxic T cell, NK cell infiltration, and upregulated immune checkpoints such as PD-1. CMS2 clustering involves the upregulation of canonical pathways including WNT and MYC downstream targets. CMS3 clustering is defined by dysregulation of metabolic pathways including carbohydrate and fatty acid oxidation and the loss of TH17 cells. CMS4 clustering is referred to as a mesenchymal subtype that involves the upregulation of EMT pathways. CMS4 clustering also shows elevated TGF-β signaling, matrix remodeling, angiogenesis, complement activation as well as integrin-β3 upregulation, stromal infiltration, immune upregulation, and platelet signatures. (Reproduced with permission from Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015;21(11):1350–1356.)

Gene expression has been linked to tumor phenotype and biologic behavior in CRC. Recently, an international consortium of six groups that examined shared, large-scale high-throughput gene expression data was able to create a transcriptomic-based molecular classification of CRC. This novel classification distinguishes four consensus molecular subtypes (CMS) of CRC, with distinct genomic and clinical features (**Fig. 68.4**).[39] The CMS group classification is currently considered the most robust molecular system connected to distinct biologic and clinical characteristics, and serves as a framework for molecularly targetable interventions. CMS2 was named the canonical subtype that made up 37% of all clusters observed and exhibited epithelial characteristics with marked WNT and MYC activated pathway signaling. CMS1 made up 14% of the categorized molecular clustering and displayed MSI along with significant immune activation and hypermutated features. The CMS3 subtype made up 13% of the molecular clustering and showed features of epithelial and metabolic dysregulation. The CMS4 subtype

was found in 23% of the molecular clusters with epithelial mesenchymal transformation (EMT) characteristics accompanied by prominent stromal invasion and angiogenesis, hallmarked by transforming growth factor-β (TGF-β) activation. The remaining 13% of tumors had molecular features that were mixed and are thought to reflect a transition phenotype or intratumoral heterogeneity, typically with characteristics of multiple CMS.[40] The identification of molecularly distinct subtypes can provide distinct subsets of patients on which to test new treatments, and may provide insight into specific biologic pathways to target for these subgroups.

HISTOPATHOLOGY AND PROGRESSION

CRC is an adenocarcinoma arising from the epithelial lining of the large bowel. Some CRCs may develop de novo, but most result from malignant transformation of adenomatous polyps. In the past, only tubular and villous adenomas were considered to develop into invasive adenocarcinomas. However, recent evidence suggests that serrated polyps can also develop into CRCs. Polyps arise from normal mucosa, and gradually increase in size. Some polyp characteristics—size larger than 1 cm, tubulovillous or villous histology, multiple occurrences—are associated with a high risk of malignant transformation. Most screening programs are designed to recognize the presence of polyps, or early malignant change in polyps or the surrounding mucosa.

Table 68.2 Histopathologic Types of Colorectal Cancer

Carcinomas
Adenocarcinoma
Medullary carcinoma
Mucinous adenocarcinoma (greater than 50% mucinous content)
Signet ring cell carcinoma (greater than 50% signet ring cells)
Neuroendocrine adenocarcinoma
Squamous cell carcinoma
Adenosquamous carcinoma
Small cell carcinoma
Undifferentiated carcinoma
Other Tumors
Carcinoid
Lymphoma
Sarcomas

The majority of CRCs are typically adenocarcinomas that form glandular structures resembling the normal colonic epithelium. However, there are several histologic types of adenocarcinoma (**Table 68.2**). Colorectal adenocarcinomas are assigned to one of four histologic grades according to their histologic resemblance to the normal colonic epithelium. The histologic grade is associated with oncologic outcome independent of other risk factors, including tumor staging.

CRC is locally invasive, potentially spreading through the full thickness of the bowel wall into adjacent tissues. From the primary site, CRC often extends to the regional lymph nodes and to other organs. CRC can metastasize to almost any organ, but the most common sites are the liver and lungs. Approximately 20% to 34% of patients have metastases at the time of diagnosis, and another 30% of those initially treated with curative intent will subsequently develop distant metastases. Other sites of distant metastasis are the brain and bones, but these are unusual in the absence of liver metastases. Patients may also develop peritoneal spread, with the formation of malignant ascites. The risk of nodal metastasis increases with the depth of tumor invasion into the bowel wall, and the risk of distant metastasis is higher for patients with nodal metastasis.

STAGING AND PROGNOSIS

The anatomical extent or stage of the tumor at the time of diagnosis is a key factor in deciding upon treatment and defining prognosis in patients with CRC. The tumor–node–metastasis (TNM) classification developed by the UICC/AJCC is firmly established as the preferred staging system (**Table 68.3**).[41] It classifies CRC according to the extent of the primary tumor (T), the involvement of the regional lymph nodes (N), and the presence or absence of distant metastasis (M). The TNM classification is important for both clinical and pathologic staging. Most colon cancers, and many rectal cancers, are staged after surgery and pathologic examination of the surgical specimen (pTNM). Many rectal cancer patients, and a small but growing number of colon cancer patients, do not receive surgery as the initial therapy, which makes clinical TNM (cTNM) staging based on medical history, physical examination, endoscopy, and imaging, increasingly important. As tumors experience a variable degree of regression with preoperative chemotherapy and/or radiation, it is important that patients receiving neoadjuvant therapy are assigned an accurate cTNM stage before starting treatment. For patients who have received neoadjuvant therapy, a modified pathologic staging is generated after surgical resection, annotated by the prefix y (ypTNM). The 8th edition of the AJCC Cancer Staging Manual incorporates a four-tier tumor regression grading (TRG) system for patients receiving neoadjuvant therapy. In this grading system TRG 0 represents Complete Response, no viable tumor cells or complete pathologic response (pCR); TRG 1, Near-complete Response; TRG 2, Partial Response; and TRG 3, Poor Response. Tumor regression seems to correlate closely with prognosis and long-term oncologic outcome.[41]

The AJCC staging system is updated periodically in response to newly acquired clinical data and understanding of the biology of the tumor. The 8th edition of the AJCC Cancer Staging Manual, for all cancers diagnosed after January 1, 2018, was updated based on observed survival outcomes obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. Relative survival in CRC patients decreases according to the depth of tumor penetration into the bowel wall and number of lymph nodes involved, but the presence of distant metastasis is the single most important predictor of survival in these patients (**Table 68.3**). Other tumor and treatment-related prognostic factors, in addition to the TNM stage, are listed in **Table 68.4**.

Quantitative parameters of lymph node evaluation—number of positive lymph nodes, total number of lymph nodes examined, and lymph node ratio—have prognostic implications in CRC. The number of nodes involved by tumor is included in the N category of the TNM system. The current staging system recommends examining a minimum of 12 lymph nodes for adequate staging.[41] The total number of lymph nodes retrieved is lower in rectal cancer patients treated with preoperative chemotherapy and radiation, but the minimal number of nodes required for adequate staging in these patients is unknown. The total number of nodes examined has an important impact on outcome in patients with colon and rectal cancer; in patients with all T and N combinations, the probability of survival increases linearly with the number of lymph nodes examined. The lymph node ratio, defined as the number of positive lymph nodes divided by the total number of retrieved nodes, has also been considered an independent predictor of survival.[42] However, the results have not been extensively validated and the lymph node ratio is not currently included in staging. Irregular tumor deposits in the mesocolon or mesorectum without surrounding lymph node tissue, are considered peritumoral tumor deposits; they are not counted as lymph nodes but are classified as N1c, and contribute to stage III.[41] These are considered to represent large vessel or perineural invasion. The significance of micrometastasis detected by immunohistochemistry (usually with anticytokeratin antibodies) in H&E negative nodes of patients with stage II disease is controversial. Although some studies have reported an association between micrometastasis, increased recurrence and reduced survival, the detection of micrometastasis has not been incorporated into clinical practice, and at the present time should be considered investigational.[43]

Tumor sidedness has prognostic implications that are probably related to epidemiologic, clinical and biologic factors. In general, patients with right-sided tumors tend to be older, more frequently women, have more advanced histologic grade and more advanced disease stage at diagnosis. Right-sided tumors are more likely to be MSI and have more BRAF mutations. Stage I and II right-sided cancers have better cancer-specific survival compared to left-sided tumors, but stage III and specially stage IV right-sided tumors have worse specific survival compared to left-sided tumors.[44] In patients with rectal cancer, tumors located in the distal rectum have worse prognosis compared to tumors located in the upper rectum.

Table 68.3 American Joint Committee on Cancer (AJCC) TNM Staging Classification for Colorectal Cancer 8th ed., 2017

Definitions for T, N, M

T Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosae but not into the muscularis propria)
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into the pericolorectal tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to adjacent organs or structures
N Regional Lymph Nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	1–3 regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	1 regional lymph node is positive
N1b	2–3 regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic or perirectal/mesorectal tissues

N2	4 or more regional lymph nodes are positive
N2a	4–6 regional lymph nodes are positive
N2b	7 or more regional lymph nodes are positive

M Distant Metastasis	
M0	No distant metastasis by imaging etc.; no evidence of tumor in distant sites or organs
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one organ or site (e.g., liver, lung, ovary, nonregional lymph node) is identified without peritoneal metastasis
M1b	Metastases to two or more sites or organs or metastasis to one organ or site (e.g., liver, lung, ovary, nonregional lymph node) is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Prognostic Groups

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1–T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3–T4a	N1/N1c	M0
	T2–T3	N2a	M0
	T1–T2	N2b	M0
IIIC	T4a	N2a	M0
	T3–T4a	N2b	M0

	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b
IVC	Any T	Any N	M1c

Note: cTNM is the clinical classification, pTNM is the pathologic classification. The y prefix is used for those cancers that are classified after neoadjuvant pretreatment (e.g., ypTNM). Pathologic complete response ypT0N0cM0 may be similar to Stage 0 or I. The prefix r is to be used for those cancers that have recurred after disease-free interval (rTNM).

Used with permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.

Table 68.4 Colorectal Cancer Prognostic Factors

Pathologic Features
TNM stage
Total number of nodes examined
Extramural non-nodal tumor deposits
Tumor location
Circumferential resection margin
Local residual disease (R status)
Tumor regression after neoadjuvant therapy
Lymphovascular invasion
Perineural invasion
Histologic type, grade, and presence of mucin
Host immune response (presence of tumor-infiltrating lymphocytes within tumor)
Clinical Features
Preoperative serum CEA levels
Bowel obstruction and/or perforation
Molecular Features
Microsatellite instability
KRAS mutation
BRAF mutation

The quality of the surgery and the completeness of tumor resection also provide important prognostic information. The distance of tumor to the

circumferential resection margin (CRM)—defined as the surgically dissected nonperitonealized surface of the specimen—provides important prognostic information in both colon and rectal cancers.[45,46] The CRM is considered positive if tumor is found within 1 mm of the resection margin (rather than 0 mm). In rectal cancer patients, involvement of the CRM (i.e., the margin created by the surgeon around the rectum and mesorectal fat) occurs most frequently anteriorly, where the mesorectum is at its thinnest. The presence of tumor at the CRM, because of advanced stage or inadequate resection, is associated with a high rate of recurrence and decreased probability of survival.[47]

The AJCC has established codes for completeness of the resection, which should be reported for each procedure.[41] A resection is defined as R0 when the entire tumor is resected and the margins are histologically negative; R1 when the margins are grossly uninvolved but histologically positive; and R2 when the tumor is not completely resected, and there is gross residual tumor at the primary site, regional lymph nodes, or metastatic sites.

Other factors associated with worse outcomes include elevated CEA levels before surgery, high histologic grade, signet ring cell and small cell histopathologic type, lymphatic and blood vessel invasion, and perineural invasion.[41] Vascular invasion is considered a sign of aggressive behavior in CRC, and has been associated with a higher risk of disease progression and poor prognosis. Capillary invasion is often associated with lymphatic invasion, and these are commonly designated as lymphovascular invasion. Large vessel invasion, detectable on magnetic resonance imaging (MRI), has been shown to be an adverse risk factor in rectal cancer.[48]

While the TNM staging system provides important prognostic information, it is inadequate for individual prognostication. Outcomes for individual patients within each tumor stage are variable. Recently, nomograms using a number of clinical and pathologic characteristics have been designed to improve prediction and survival beyond TNM staging in patients with colon or rectal cancer, particularly in the setting of stage II tumors (**Fig. 68.5**).[49] In addition to providing prognostic information, nomograms may potentially guide clinical decisions, such as the use of adjuvant chemotherapy or the regularity of surveillance. However, nomograms have not been routine part of clinical decision making.

A number of molecular markers such as MSI, 18q loss of heterozygosity, KRAS, and BRAF, among others, have been associated with prognosis in CRC patients. In addition, some of these markers are now used to make treatment

decisions, particularly in metastatic CRC. For example, MSI tumors are likely to respond to PD-1 blockade, KRAS wild-type tumors are likely to respond to anti-EGFR therapy, and BRAF V600E mutant tumors are likely to respond to a combination of BRAF, MEK, and EGFR inhibitors.[50–53]

Increasing evidence demonstrates that the evolution of cancer is strongly dependent on the complex tumor microenvironment in which it develops, comprised of a variety of elements including fibroblasts, lymph vessels, and cells of the immune system. The presence of tumor infiltrating lymphocytes (TILs), usually seen in MMRd patients, is associated with good prognosis in patients with CRC, regardless of mismatch repair (MMR) status.[54] Quantification of lymphocyte populations, in particular CD3- and CD8-positive T cells, has led to the development of a score referred to as Immunoscore, a score highly reproducible across institutions, with increasing score correlating with longer patient survival.[55]

Based on recent advances in the molecular characterization of CRC, a number of multigene molecular signatures (Oncotype DX, Coloprint, and ColDx) have been designed as prognosticators of recurrence and outcomes. While these molecular signatures seem to determine risk of recurrence independent of other well-established risk factors, they have not been fully incorporated into clinical practice.[56–58]

SCREENING AND PREVENTION

The slow development of CRC from a benign polyp to an invasive cancer provides a window of opportunity for the detection and removal of premalignant adenomatous polyps and early-stage cancers. Removal of adenomatous polyps reduces the incidence of cancer, and the diagnosis of CRC at earlier stages reduces mortality.[59,60] A number of prospective studies have proven that screening for colorectal polyps and cancer using a variety of methods reduces CRC mortality, and the reduction in mortality persists long-term after screening.[61–64] There is good evidence that screening has contributed significantly to the drop in CRC mortality rates from a peak a few decades ago. Screening for CRC is cost-effective, in terms of the quality-adjusted life-years gained, compared to nonscreening. In the United States, screening for CRC is recommended for men and women over age 50, although the guidelines are currently changing due to the recent rise in young onset CRC. While overall

uptake of CRC screening is improving, it remains relatively low among individuals with lower socioeconomical status and without a usual source of health care.[65]

Screening Tests

Numerous screening methods for CRC have been used over the years (**Tables 68.5** and **68.6**). These fall into one of two categories: stool tests, which detect the presence of blood or altered DNA in the stool; and structural tests, which identify polyps and cancers. Efficacy in detecting CRC, cost-effectiveness as a screening tool, supporting evidence, and patient acceptability vary for each of these tests.[66]

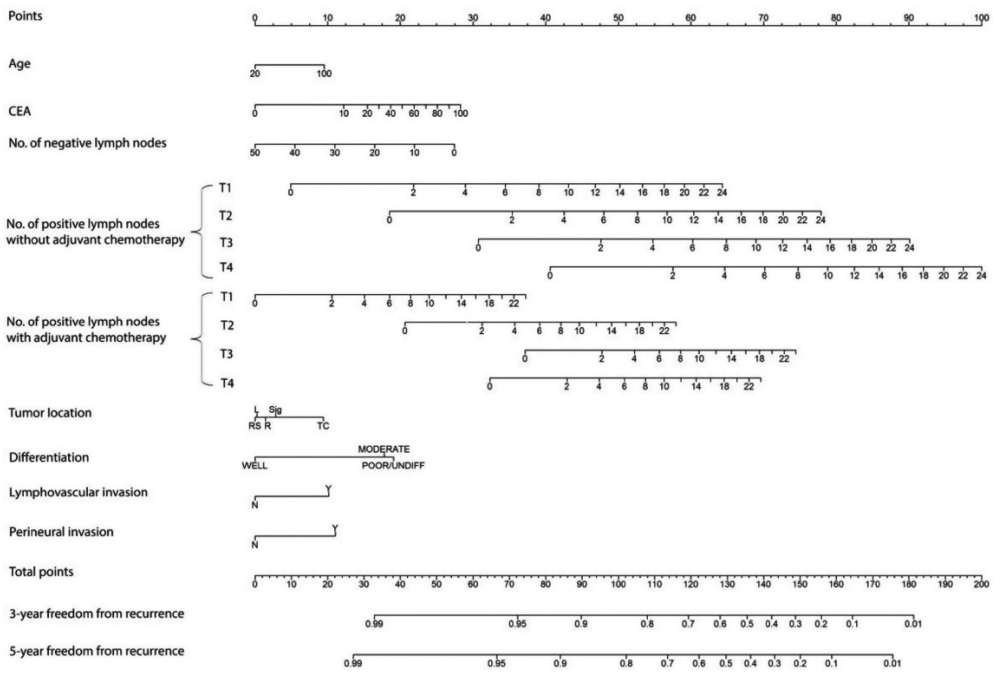


Figure 68.5 Colon cancer nomogram for freedom from recurrence. Locate the patient's preoperative level of carcinoembryonic antigen (in nanograms per milliliter) on the CEA axis. Draw a straight line up to the Points axis to determine how many points toward recurrence the patient should receive. Repeat this process for each of the remaining axes, drawing a straight line each time to the Points axis. Sum the points received from each prognostic variable and locate this number on the Total points axis. Draw a straight line from the total points down to the 3- or 5-year freedom from recurrence axis to ascertain the patient's specific risk of remaining free from recurrence for either 3 or 5 years. CEA, carcinoembryonic antigen; L, left colon; R, right colon; RS, rectosigmoid colon; Sig, sigmoid colon; TC, transverse colon. (Reproduced with permission from Konishi T, Shimada Y, Hsu M, et al. Contemporary validation of a nomogram predicting colon cancer recurrence, revealing all-stage improved outcomes. *JNCI Cancer Spectr* 2019;3(2):pkz015.)

Stool Tests

CRCs and polyps bleed more than the normal mucosa and detecting occult blood in the stool is the basis of the most widely used screening tests. Blood is detected by searching the stool for hemoglobin using chemical or immunologic methods; patients found to have blood in the stool should then undergo colonoscopy. The original fecal occult blood tests (FOBTs) relied on guaiac-based detection of the pseudoperoxidase activity of hemoglobin. However, as pseudoperoxidase activity is not specific to human hemoglobin, foods such as red meat can produce false positives. Additionally, medications, such as aspirin and nonsteroidal anti-inflammatory drugs, and foods, such as those rich in vitamin C, should be avoided due to the risk of an inaccurate test. These drugs

and foods should be avoided 2 to 3 days prior to the FOBT. As most tumors bleed slowly and intermittently, the sensitivity of this test remains low. Rehydration of the test cards increases sensitivity, at the cost of reducing specificity. The sensitivity of the test increases with the number of samples tested; testing two samples per stool on three consecutive bowel movements is recommended. Several prospective, randomized trials have demonstrated that screening by FOBT, followed by total colonic evaluation with colonoscopy in individuals with a positive test, reduces mortality from CRC.[67–70]

Table 68.5 Tools for Colorectal Cancer Screening

a. Fecal tests—detect primarily cancer
   Guaiac-based fecal occult blood test (gFOBT)
   Fecal immunochemical test (FIT)
   Stool DNA test (sDNA)
b. Structural examinations—detect polyps and colorectal cancer
   Flexible sigmoidoscopy (FSIG)
   Optical-colonoscopy (OC)
   Double–contrast barium enema (DCBE)
   Computed tomography colonoscopy (CTC)

Fecal immunochemical tests (FITs) rely on antibodies that are specific to human hemoglobin, and the analysis of samples by automated quantification methods. FITs are as sensitive as the guaiac-based tests, but more specific in detecting human hemoglobin in stool. As this avoids the false-negative results in the presence of vitamin C and false-positive results in the presence of red meat, the test does not require any dietary modification prior. As with any fecal test, a positive result with FIT requires a complete colonoscopic examination. FIT has better screening performance, compared to FOBT.[71–75] As an additional consideration, FIT may be more easily implemented as a screening regimen, compared with sole usage of colonoscopy.[76] Based on this evidence, a number of countries have introduced screening programs utilizing these tools.

Table 68.6 Screening and Surveillance for Colorectal Cancer According to Risk[a]

Risk Category	Age to Begin	Recommendation	Comment
Average Risk			
	45–50	Annual gFOBT/FIT/ FIT-DNA every 1–3 yrs OR flexible sigmoidoscopy every 5 yrs OR flexible sigmoidoscopy with FIT every 10 and 1 yrs OR Colonoscopy every 10 yrs OR CTC every 5 yrs	If positive, colonoscopy is indicated. Screening is recommended up to 75 yrs of age (with individual risk assessment up to 85 yrs old)
Increased Risk—Patients with History of Polyps at Prior Colonoscopy			
Patients with small rectal hyperplastic polyps	—	Colonoscopy or other screening options at intervals recommended for average-risk individuals	An exception is patients with a hyperplastic polyposis syndrome. They are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow-up

Patients with 1 or 2 small tubular adenomas with low-grade dysplasia	5–10 yrs after the initial polypectomy	Colonoscopy	The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician)
Patients with 3–10 adenomas, 1 adenoma ≥1 cm, or any adenoma with villous features or high-grade dysplasia	3 yrs after the initial polypectomy	Colonoscopy	Adenomas must have been completely removed. If the follow-up colonoscopy is normal or shows only 1 or 2 small tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 yrs (7–10 yrs

			for 3–4 small adenomas)
Patients with ≥10 adenomas on a single examination	1 yr after the initial polypectomy	Colonoscopy	Consider the possibility of an underlying familial syndrome
Patients with adenomas (≥20 mm) that are removed piecemeal	2–6 mos to verify complete removal	Colonoscopy	Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment. Completeness of removal should be based on both endoscopic and pathologic assessments
Increased Risk—Patients with Colorectal Cancer			
Patients with colon and rectal cancer should undergo high-quality perioperative clearing	3–6 mos after cancer resection, if no previous colonoscopy, and if no unresectable metastases are	Colonoscopy	In the case of nonobstructing tumors, this can be done by preoperative colonoscopy. In the case of

	found during surgery; alternatively, colonoscopy can be performed intraoperatively		obstructing colon cancers, CTC with intravenous contrast or DCBE can be used to detect neoplasms in the proximal colon
Patients undergoing curative resection for colon or rectal cancer	1 yr after the resection (or 1 yr following the performance of the colonoscopy that was performed to clear the colon of synchronous disease)	Colonoscopy	This colonoscopy at 1 yr is in addition to the perioperative colonoscopy for synchronous tumors. If the examination performed at 1 yr is normal, then the interval before the next subsequent examination should be 3 yrs. If that colonoscopy is normal, then the interval before the next

		subsequent examination should be 5 yrs. Following the examination at 1 yr, the intervals before subsequent examinations may be shortened if there is evidence of HNPCC or if adenoma findings warrant earlier colonoscopy. Periodic examination of the rectum for the purpose of identifying local recurrence, usually performed at 3–6-mo intervals for the first 2 or 3 yrs, may be considered after low

			anterior resection of rectal cancer
Increased Risk—Patients with a Family History			
Either colorectal cancer or adenomatous polyps in a first-degree relative before age 60 yrs or in 2 or more first-degree relatives at any age	Age 40 yrs, or 10 yrs before the youngest case in the immediate family	Colonoscopy	Every 5 yrs
Either colorectal cancer or adenomatous polyps in a first-degree relative age 60 or older or in 2 second-degree relatives with colorectal cancer	Age 40 yrs. Screening options at intervals recommended for average-risk individuals	Screening options at intervals recommended for average-risk individuals	Screening should be at an earlier age, but individuals may choose to be screened with any recommended form of testing
High Risk			
Genetic	Age 10–12 yrs	Annual FSIG to	If the genetic test

diagnosis of FAP or suspected FAP without genetic testing evidence		determine if the individual is expressing the genetic abnormality and counseling to consider genetic testing	is positive, colectomy should be considered
Genetic or clinical diagnosis of HNPCC or individuals at increased risk of HNPCC	Age 20–25 yrs, or 10 yrs before the youngest case in the immediate family	Colonoscopy every 1–2 yrs and counseling to consider genetic testing	Genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited MMR gene mutation. It should also be offered when the family mutation is not already known, but one of the first three of the modified Bethesda criteria is present
Inflammatory bowel disease, chronic ulcerative	Cancer risk begins to be significant 8 yrs after the onset of pancolitis or	Colonoscopy with biopsies for dysplasia	Every 1–2 yrs; these patients are best referred to a center with

colitis, and Crohn colitis	12–15 yrs after the onset of left-sided colitis	experience in the surveillance and management of inflammatory bowel disease

[a]Summary estimation of published guidelines.

gFOBT, guaiac-based fecal occult blood test; FIT, fecal immunochemical test; FIT-DNA, multi targeted stool DNA test; CRC, colorectal cancer; CTC, computed tomographic colonography; DCBE, double-contrast barium enema; FAP, familial adenomatous polyposis; FSIG, flexible sigmoidoscopy; HNPCC, hereditary nonpolyposis colon cancer; MMR, mismatch repair.

Detection of altered DNA from exfoliated tumor cells has been investigated as a screening test for CRC for years. Similar to the detection of hemoglobin, detection of altered DNA triggers patient referral for colonoscopy. Large, prospective studies of this test show fair sensitivity in detecting CRC and low sensitivity in detecting large adenomas, compared with colonoscopy.[77,78] Two recent studies found stool DNA testing sensitivity to be at the high end of the reported FIT range, but at the low end of the typical FIT range for specificity in detecting CRC and advanced precancerous lesions.[79,80] The most recent United States Preventive Task Force (USPTF) guidelines have included stool DNA testing as a screening option; however, they caution about the potential for overly intensive surveillance due to clinician and patient concerns in patients with a negative colonoscopy after an abnormal stool DNA test.[81]

Structural Tests

Two-thirds of CRCs and polyps are located in the sigmoid colon and rectum and can be reached with a 60-cm flexible sigmoidoscope. Flexible sigmoidoscopy is safe, fast, does not require sedation, and allows biopsying suspicious lesions. It has a minimal risk of perforation (approximately 1 in 20,000). The effectiveness of flexible sigmoidoscopy as a screening modality requires examination to at least 40 cm from the anal verge. The main limitations of flexible sigmoidoscopy are discomfort which can deter some patients from undergoing future examinations and that it is does not examine the entire colon. However, the presence of distal adenomatous polyps increases the probability

of finding additional polyps or cancers in more proximal segments of the large bowel. If an adenomatous polyp is found during flexible sigmoidoscopy, the patient should undergo complete colonoscopy. Due to differences in the distribution of colorectal neoplasia in patients of different age, gender, and racial groups, the efficacy of flexible sigmoidoscopy may vary. Several case-control studies have demonstrated that screening by sigmoidoscopy reduces mortality from CRC by two-thirds in the setting of tumors located within reach of the sigmoidoscope.[82,83] More recently, several prospective studies have demonstrated that screening with flexible sigmoidoscopy reduced CRC incidence and mortality by approximately 25%.[84–86] Furthermore, at least two prospective trials demonstrated a reduction in CRC incidence and mortality with only one flexible sigmoidoscopy screening between 55 and 64 years of age.[86,87] The long-term follow-up of these trials (15 to 17 years) demonstrated sustained reduction in CRC mortality.[88–90] The optimal testing frequency is still controversial. The USPTF currently recommends repeating surveillance every 5 years.[81]

The evidence for combining stool tests (FIT or FOBT) and flexible sigmoidoscopy is mixed. Some studies have shown that the combination of these two screening methods is more effective in detecting colorectal neoplasia than each method used individually, whereas one prospective study looking at flexible sigmoidoscopy with and without FOBT found no benefit in detection, but improvement in CRC mortality.[85,91] This screening strategy may be of benefit to patients who desire direct endoscopic visualization but wish to avoid a full colonoscopy.[81]

Colonoscopy is considered the most accurate test for the early diagnosis and prevention of CRC. It allows direct visualization of the mucosa of the entire colon and rectum, simultaneously allowing the biopsy or removal of suspicious lesions. Colonoscopy is also used to evaluate patients who have tested positive on other screening tests. However, colonoscopy is inconvenient, requires dietary modification and bowel preparation beforehand, is usually performed under conscious sedation, and carries a risk of complications of 1–2 per 1,000. Colonoscopy is also more expensive compared to other screening methods. Overall, patient acceptability of colonoscopy seems to be higher compared to other invasive screening methods, and it is now the most commonly used screening method in the United States. There is evidence to suggest that colonoscopy reduces CRC mortality.[91–95] Comparative studies show that colonoscopy is more effective in detecting advanced colonic neoplasia, in both

men and women, than a single FOBT combined with sigmoidoscopy. Colonoscopy is more likely to detect preneoplastic polyps, but just as likely to detect invasive CRC as FITs. In addition, colonoscopy provides the protective benefit of screening the proximal colon.[96] Several randomized control trials to assess long-term outcomes of CRC site-specific incidence and mortality for colonoscopy are currently underway.

Computed tomography colonography (CTC), also referred to as virtual colonoscopy, involves thin-section, multidetector, helical CT, and three-dimensional viewing for interpretation.[97] It has largely replaced double-contrast barium enema as it has been shown to be superior.[98,99] A meta-analysis of studies looking at CTC compared to colonoscopy found CTC to have a high sensitivity for adenomas ≥10 mm with somewhat lower sensitivity for adenomas ≥6 mm.[100] Besides the challenge of identifying small lesions, CTC has been shown to be less accurate with flat lesions and sessile serrated polyps.[101,102] CTC obviates some of the drawbacks of colonoscopy, such as the need for sedation and recovery time. However, it still requires standard bowel preparation and gaseous distension of the colon. New methods of tagging and subtracting residual stool are trying to obviate the need for bowel preparation. Furthermore, patients found to have lesions on CTC still require full visualization of the colon with colonoscopy. CTC has downstream consequences including radiation exposure and detection of incidental extracolonic findings that may trigger expensive and, sometimes, unnecessary diagnostic tests.

Risk Categories

Patients with symptoms of CRC should undergo the appropriate diagnostic studies; they are not candidates for screening. Screening recommendations for the general population are based on individual risk assessment. Based on the past medical history and family history of CRC or polyps, individuals are assigned to one of three risk categories, with different screening recommendations (**Table 68.6**).[103] Several different groups provide guidelines for CRC screening including the USPTF, American Cancer Society, and United States Multi-Society Task Force.[81,99,104]

Average Risk

Most guidelines define average risk as asymptomatic, without family history of CRC or familial CRC syndromes, without personal history of CRC or adenomatous polyps or IBD, and at the age of 50. However, in response to the increase in young onset CRC, the American Cancer Society has recently changed the age to start screening to 45. Furthermore, most recommend cessation of screening at 75 years old, with the option of screening up to 85 years based on comorbidities, life expectancy, and individualized discussion with each patient, as the benefit of early detection of and intervention declines after age 75 years. Acceptable forms of screening include FIT, FOBT, stool DNA testing, flexible sigmoidoscopy, CTC, or colonoscopy. The most recent American Cancer Society and USPTF guidelines do not offer a preferred or ranked order of screening strategies, but rather offer various choices, with the goal to maximize overall screening uptake. Digital rectal examination (DRE) should be performed at the time of sigmoidoscopy or colonoscopy in all individuals. People found to be positive on stool testing, CTC, or flexible sigmoidoscopy should undergo entire colon and rectum examination by colonoscopy.

Increased Risk

Family History

Individuals with a first-degree relative (parent, sibling, or child) with CRC or adenomatous polyps diagnosed before 60 years of age or two first-degree relatives diagnosed at any age should start screening with colonoscopy at 40 years of age or 10 years younger than the earliest diagnosis in their family, whichever comes first. The test should be repeated every 5 years. Individuals with one first-degree relative with CRC or adenomatous polyp diagnosed at 60 years of age or older, or with two or more second-degree relatives (grandparent, grandchild, aunt, uncle, niece, nephew, half-sibling) with CRC or adenomatous polyps at any age, should undergo screening as average-risk individuals—but starting at 40 years of age. Patients with one second-degree relative or one or more third-degree relatives (first cousin) affected are considered to be at average risk.

History of Polyps at Previous Colonoscopy

Patients undergoing endoscopic excision of 1–2 small (<1 cm) adenomatous polyps should have the entire colon examined at the time of the polypectomy.

Colonoscopy should be repeated 7 to 10 years later. If the test is negative, they should then follow the screening recommendations for average risk.[106]

Patients with more than three small adenomas (<10 mm), adenomas with villous features or high-grade dysplasia, or a large adenomatous polyp (>1 cm) who have the entire colon examined at the time of polypectomy, should undergo complete colonoscopy 3 years later—and, if normal, every 5 years thereafter (except in patients with more than three small adenomas—they can go back to 10 years).

A complete colonic examination should be carried out before surgery in any patient undergoing a planned curative resection for CRC. The colonoscopy should be repeated at 1 year to exclude metachronous lesions. If the examination at 1 year is normal, it should be repeated after 3 years, and every 5 years thereafter if the previous one was normal.

Patients with Colorectal Cancer

Patients with colon and rectal cancer should undergo high-quality perioperative clearing of polyps with colonoscopy 3 to 6 months after resection, if not performed before surgery. Surveillance after curative resection is described in detail in Surveillance after Curative Resection for Colon and Rectal Cancer section.

High Risk

This category includes individuals from families diagnosed with hereditary forms of CRC as noted in consensus guidelines. At-risk members of families with hereditary cancer syndromes should be informed about the benefits and limitations of genetic counseling and genetic testing.

Familial Adenomatous Polyposis

Once the diagnosis of FAP is established, the patient should undergo colectomy, or a yearly colonoscopy until colectomy. Upper gastrointestinal endoscopy should be performed regularly at intervals of 6 months to 4 years based on the extent of the duodenal polyposis. Siblings and children of a patient with FAP should start surveillance by flexible sigmoidoscopy at puberty.

MYH-Associated Polyposis

Depending on the individual, age of presentation, and number and size of polyps, the patient may be advised to undergo a prophylactic colectomy or yearly colonoscopy beginning at 25 years of age. Upper gastrointestinal

surveillance should be performed following the guidelines for patients with FAP.

Lynch Syndrome

Individuals from families fitting the Amsterdam criteria for HNPCC should have a colonoscopy at 21 years of age, then every 2 years until 40 years of age, and yearly thereafter. Genetic counseling and testing should be considered.

Consequences of Screening

The full spectrum of clinical consequences of screening, other than the prevention of deaths from CRC, is difficult to predict because every screening strategy initiates a cascade of events, each one with uncertain probability. The rate of false-positive tests, the number of colonoscopies performed, the complications of the screening and diagnostic tests, and the number of patients who may require surveillance as a consequence of screening, are complex factors that arise at different times over several decades. However, cost-effectiveness analysis in the United States has demonstrated that screening for CRC in average-risk patients, according to the strategies outlined above, compares favorably with other healthcare interventions such as mammography or treatment of mild hypertension.[108,109] It is important to understand that screening does not completely eliminate the risk of CRC. Up to 9% of CRCs are diagnosed within 6 to 36 months after a screening colonoscopy.[110,111] These interval cancers tend to be preferentially located in the proximal colon. This may be related to failure to reach the proximal colon, residual stool obscuring the view in the proximal colon, or different characteristics of the proximal lesions that makes them more difficult to detect or remove.

Implementation of Guidelines

The general population has limited awareness of the risks of CRC or its symptoms; as a result the number of individuals participating in screening programs has been low. The dissemination of information to patients is an essential part of the screening program. Primary care physicians have a responsibility to inform their patients about their risk of CRC, the benefits of screening and different screening strategies, and to set up a system for implementing these guidelines.[109,112,113] Through such efforts, the proportion of

adults 50 to 75 years of age having colonoscopy has increased steadily over the past decades: from 19.1% in 2000 to 55% in 2010, and to 68.8% in 2018.[114]

DIAGNOSIS

While the proportion of CRCs diagnosed through screening is increasing, most are still diagnosed after patients become symptomatic. CRC can cause a myriad of symptoms, many of which are nonspecific and highly prevalent among healthy individuals. Therefore, the diagnosis of colorectal carcinoma often requires a high index of suspicion.

Symptoms and Signs

The most common symptoms in patients with CRC are abdominal pain, change in bowel habits, rectal bleeding, anemia, anorexia, and weight loss. The clinical manifestations of CRC differ depending on the location and stage of the tumor.

Abdominal pain is nonspecific; it may be localized to any quadrant of the abdomen, or may be diffuse. When the pain is persistent and colicky, it is more likely to represent obstructive symptoms resulting from a left-sided lesion. More localized tenderness with signs of localized peritonitis indicates local invasion of the adjacent peritoneum or perforation. It can be difficult to distinguish the pain associated with diverticular disease from that due to a carcinoma in the sigmoid or descending colon. Patients with diverticular disease may also have an underlying carcinoma. Abdominal pain may occasionally be related to extensive metastatic disease in the liver or retroperitoneal lymph nodes. Rectal cancer can also cause perineal discomfort and is often associated with tenesmus, the sensation of incomplete defecation. A locally advanced rectal cancer can also cause sacral or sciatic pain.

An unexplained change in bowel habits lasting more than 2 weeks requires investigation for CRC. Constipation associated with colicky abdominal pain is a common manifestation of partially obstructing tumors. Abdominal pain, constipation, and abdominal distension suggest a complete colonic obstruction, which is more common in tumors located in the sigmoid colon and rectum. Some patients with sigmoid or rectal cancer may also complain of diarrhea, which may sometimes be bloody.

Bleeding from tumors in the sigmoid colon and rectum is often wrongly attributed to hemorrhoids or other benign anal conditions. However, blood from hemorrhoids is usually bright red and is accompanied by anal discomfort; the bleeding is intermittent and splashes the toilet pan. Anal fissure is also a common cause of rectal bleeding; the blood is often bright, occurring after defecation, and is typically associated with sharp anal pain triggered by defecation. Painless defecation with rectal blood that is darker in color and mixed in with stool is more likely to be secondary to an underlying carcinoma. Rectal bleeding, particularly when associated with tenesmus, requires a thorough diagnostic investigation to exclude an underlying rectal tumor.

The development of nonspecific anemia of unknown origin is a common manifestation in patients with a carcinoma in the proximal colon. Patients with unexplained microcytic anemia should be examined initially with colonoscopy. Anorexia and weight loss frequently accompany CRC, and are often associated with advanced disease. The differential diagnosis in these patients is a gastric carcinoma, but when investigations are negative it is important to exclude a large-bowel malignancy. As the bowel lumen is larger and the stools overall looser in the proximal colon, obstructive symptoms are uncommon; therefore, patients with tumors proximal to the splenic flexure often present with advanced disease.

It should be remembered that the presence of colon cancer can also be identified incidentally during investigations for other pathologies such as gallstones, gynecologic, or urinary conditions. A complete family history, with emphasis on past history of CRC or polyps, is essential to diagnose some hereditary cancer syndromes. A family history of endometrial, gastric, urologic, or other HNPCC-associated cancers is also important because it may help in diagnosing Lynch II syndrome.

The evaluation of patients suspected of CRC requires a complete physical examination. Features that should arouse suspicion of malignancy include pallor, palpable abdominal mass, and a palpable mass on DRE. Hepatomegaly indicates advanced disease with extensive liver metastases, and consequently a very poor prognosis. A hard mass in the pouch of Douglas felt on DRE may indicate peritoneal carcinomatosis. Other signs of an underlying CRC include pneumaturia, ischiorectal or perineal abscesses, or even deep venous thrombosis.

The differential diagnosis of CRC includes diverticulitis, irritable bowel syndrome, inflammatory bowel disease, ischemic colitis, and benign anorectal

conditions such as hemorrhoids or rectal mucosal prolapse.

Diagnostic Evaluation

Patients with symptoms suggesting CRC should have a colonoscopy to evaluate the entire colon (**Fig. 68.6**). The examination should be complete, as up to 4% of patients with CRC have synchronous cancers and many more have colorectal polyps.[115,116] Up to one-third of these synchronous cancers are in locations requiring a different surgical resection, further emphasizing the importance of complete colonoscopy. As many patients undergo minimally invasive surgery, the endoscopist should mark the vicinity of the tumor with India ink to help locate the lesion intraoperatively. CT colonography and DCBE are less effective in investigating patients with symptoms suggestive of CRC, but they are useful in patients with partially obstructive tumors, in whom colonoscopy cannot be completed. In patients with obstructive lesions, the proximal colon can be examined either by preoperative imaging studies such as PET-CT, or intraoperatively by direct palpation of the colon. In any case, patients with a complete colonoscopy before surgery should have a surveillance colonoscopy 6 months after surgery.

Assessment of the extent of disease at the time of diagnosis is important because clinical stage, particularly in rectal cancer, dictates treatment decisions. A CT scan of the chest, abdomen, and pelvis with intravenous and oral contrast is important in order to locate the tumor, detect mesenteric nodes, 3 and exclude liver metastasis and gross peritoneal carcinomatosis (**Fig. 68.6**). In addition, preoperative imaging helps the surgeon plan the resection. In patients with iodine allergy, and in patients with undetermined lesions on CT, a PET-CT or an abdominopelvic MRI may provide additional information.

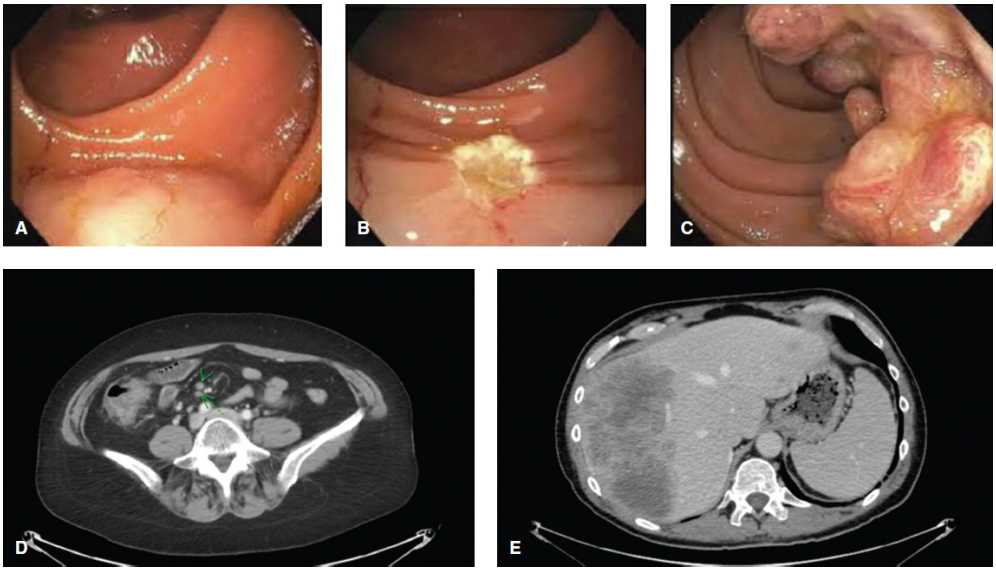


Figure 68.6 Staging modalities for colorectal cancer. **A:** Sessile polyp. **B:** Polyp removed at colonoscopy with hot snare technique. **C:** Sigmoid colon cancer at colonoscopy. **D:** Circumferential ascending colon tumor with regional lymphadenopathy (*arrowheads*). **E:** Liver metastases of colorectal origin.

Laboratory evaluation includes complete blood cell count, coagulation parameters, and chemistry panel. Preoperative CEA should be measured because it provides prognostic information, and can be useful during patient surveillance.

TREATMENT

Surgery is the primary treatment for CRC, but for many patients surgery is not the initial form of treatment and some do not require surgery at all. Treatment is different for colon than for rectal cancer, and depends also on the clinical stage of the tumor. Treatment decisions must also take into account the patient's performance status, comorbidities, hereditary CRC predisposition, as well as desires and expectations.

Preoperative Preparation

All patients undergoing surgery for colon and rectal cancer require similar preoperative preparation aimed at optimizing the technical success of the procedure and avoiding perioperative complications. Surgical site infection

(SSI) is the most common complication after colon and rectal cancer resection, occurring in 4% to 26% of cases.[117,118] In addition to causing patient suffering, SSIs lengthen hospital stay and increase costs.[119] The institutional rate of SSI after colorectal surgery is now an important quality metric for several benchmarking programs. A number of federal and state-wide initiatives aimed at improving surgical care recommend implementing measures to reduce the rate of SSI and other complications in patients undergoing elective colorectal surgery.[120,121]

The colon has the largest concentration of bacteria in the human body. A gram of feces contains 10^{11} polymicrobial bacteria, mostly gram negatives and anaerobes.[122] Oral mechanical bowel preparation using polyethylene glycol to reduce the bacterial load and risk of intraoperative fecal spillage has been considered an axiom in colon and rectal surgery. However, a number of prospective trials have failed to demonstrate benefit from mechanical bowel cleansing in preventing SSIs.[123,124] Combination of mechanical bowel preparation with oral antibiotics, usually neomycin and erythromycin, may be more effective than mechanical bowel preparation alone. A large retrospective study of more than 27,000 patients undergoing elective colorectal resection compared the use mechanical bowel preparation with and without oral antibiotics, oral antibiotics alone, or no preparation. Dual preparation was associated with lower rates of SSI, organ space infection, wound dehiscence and anastomotic leak compared to no preparation, and lower rates of SSI than antibiotic bowel preparation alone. Dual preparation was not associated with an increased risk of *Clostridium difficile* infection.[125]

High-quality evidence indicates that antibiotics covering aerobic and anaerobic bacteria, delivered orally or intravenously (or both) prior to elective colorectal surgery, reduce the risk of postoperative surgical wound infection by as much as 66%.[126] For patients without penicillin allergy, a second-generation cephalosporin (cefotetan, or cefoxitin) is often administered intravenously within 30 minutes of the surgical incision, with redosing during the procedure as required according to the half-life of the drug and the duration of surgery. For penicillin-allergic patients, metronidazole or clindamycin combined with either ciprofloxacin or gentamicin is acceptable, as are aztreonam and fluoroquinolones.[127] Ertapenem, a long-acting carbapenem active against gram negatives and anaerobes, is an accepted alternative to second-generation cephalosporins for prophylaxis in CRC. Ertapenem has a long life and does not require redosing in prolonged procedures, but has been associated with

increasing risk of *C. difficile* infection.[128] Other measures that prevent SSI include tight glucose control in diabetic patients, smoking cessation, clipping rather than shaving the skin of the abdominal wall, and maintaining normothermia and adequate oxygenation during anesthesia.[129]

Patients undergoing surgery for CRC are also at risk of venous thromboembolism (VTE), and should have thromboembolic prophylaxis with unfractionated heparin or low–molecular-weight heparin during the peri- and postoperative periods.[130] The American Society of Clinical Oncology (ASCO) has published evidence-based clinical practice guidelines which include the recommendation for prophylaxis starting before surgery and continuing for at least 7 to 10 days following surgery. Extended prophylaxis for up to 4 weeks following surgery should be given to patients undergoing major abdominal and pelvic surgery.[131]

As the incidence of CRC increases with age, many patients have cardiovascular or respiratory conditions requiring medical clearance before surgery. While technical advances have made CRC operations safer, optimal outcomes require special effort to ensure that the patient's overall health is optimal at the time of surgery. Many CRC patients have other comorbid conditions such as diabetes, hypertension, and coronary artery disease requiring medical evaluation before undergoing surgery. Comorbidities can impact decision-making and affect short- and long-term outcomes. Patient clinical and performance status should be optimized to reduce the risk of perioperative complications. Fertility options should be discussed with all individuals of child-bearing potential.

Patients who may require a stoma should be seen before surgery by an enterostomal therapist. Adequate marking of the site improves outcomes for patients requiring a stoma. Preoperative teaching shortens the time patients require to become proficient managing the stoma, and reduces hospital stay.[132]

The Enhanced Recovery After Surgery (ERAS) protocols were introduced in open colorectal surgery in the 1990s, with the aim of speeding patient recovery, improving patient outcomes and satisfaction, shortening hospitalization, and reducing healthcare costs.[133] ERAS protocols span the entire perioperative period, and attempt to minimize surgical stress and postoperative ileus through patient education, preoperative hydration and carbohydrate loading, goal-directed intraoperative fluid management, narcotic sparing for intraoperative and postoperative pain control, and early mobilization and oral feeding in the postoperative period. A number of prospective trials have indicated that the

implementation of ERAS protocols reduces length of hospital stay, compared to conventional recovery in patients undergoing open or minimally invasive surgery for CRC.[134,135] A recent systematic review and a meta-analysis confirmed that ERAS protocols resulted in a shorter length of stay and a reduction in overall complications, with no difference in mortality and surgical complications.[136,137] Similar results have recently been reported from an international registry.[138]

Principles of Surgical Treatment

The goal for any curative-intent surgery is to remove the tumor-bearing segment of the bowel with adequate margins, along with en bloc excision of the mesentery containing the feeding vessels and regional lymph nodes. The location of the primary tumor determines lymphatic drainage and dictates the extent of the resection. Lymphatic capillaries are primarily located in the submucosal and subserosal layers of the bowel wall. The lymphatic flow in the colon is primarily circumferential, with longitudinal spread along the bowel wall thought to be less than 1 cm in each direction. Therefore, a 5-cm margin of normal bowel on either side of the primary tumor is considered sufficient to avoid anastomotic recurrence. The length of the terminal ileum resected in patients with right colon cancer does not influence the risk of anastomotic recurrence. In the rectum, where the longitudinal lymphatic flow is primarily upward, cancer cells rarely spread distally along the bowel wall farther than 1 cm from the macroscopic distal end of the tumor. Consequently, a 2-cm margin of normal bowel distal to the tumor, or even less in patients treated with neoadjuvant therapy, is considered appropriate to an oncologically safe resection.[139]

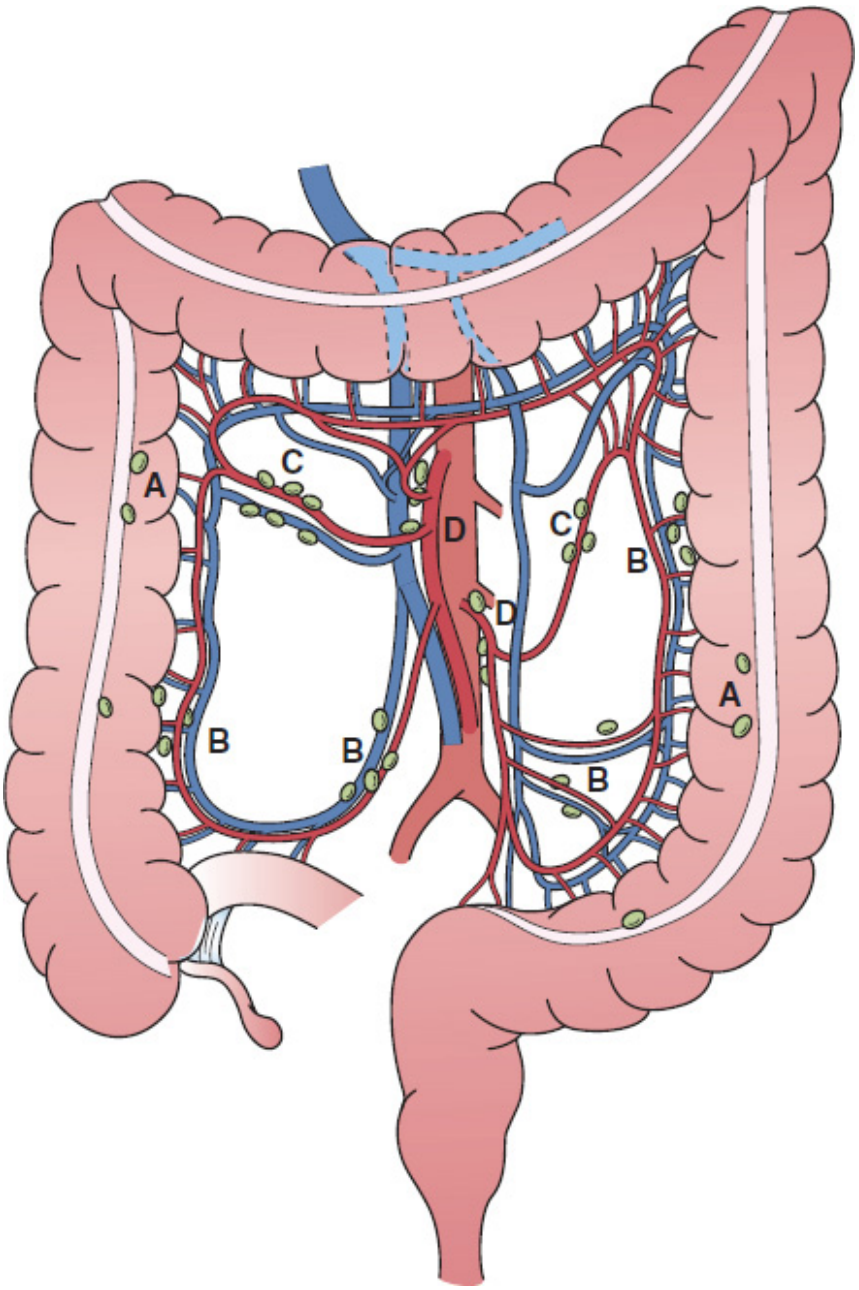


Figure 68.7 Anatomy of the colon. ***A***, Epicolic lymph nodes. ***B***, Paracolic lymph nodes. ***C***, Intermediate lymph nodes. ***D***, Apical-central lymph nodes.

The lymphatic channels in the bowel wall drain to the regional nodes, which are classified in different groups according to their proximity to the bowel and its blood supply (**Fig. 68.7**). The "epicolic" nodes are located in the bowel wall under the peritoneum, usually close to the epiploic appendices. The "paracolic" lymph nodes are located along the marginal vessels. Next, the "intermediate" nodes are positioned in the middle of the mesentery. Finally, the

"central" or "apical" lymph nodes are located close to the root of the mesentery, near the origin of the named vessels. While CRC generally spreads sequentially from the paracolic to the central or apical lymph nodes, nodal metastases skipping one of the groups are common.[140]

The extent of the mesenteric resection is determined by the need to remove all the lymph nodes draining the corresponding segment of bowel, including the central lymph nodes located at the origin of the named feeding blood vessels. As most tumors are located between two named vascular pedicles, both of these should be resected at their origin. When suspected of being involved by tumor, the central nodes should be marked on the specimen, as they have negative prognostic information. Other lymph nodes located away from the feeding vessels and suspected of tumor involvement during surgery, should be removed and analyzed, because in some patients the lymphatic drainage does not follow an orderly pattern.[141,142] If residual metastatic lymph nodes remain after sampling, the resection should be considered incomplete.

While achieving safe oncologic margins and adequate lymphadenectomy are the main considerations when performing a surgical resection for CRC, ensuring an adequate blood supply to the bowel ends, and maintaining tension-free anastomosis, are also important in order to avoid anastomotic complications.

Locally advanced tumors attached to other organs should be removed en bloc with contiguously involved structures. As it is impossible to distinguish clinically or radiographically between inflammatory adhesions and tumor infiltration, it is preferable to perform an en bloc resection of any organ attached to the primary tumor, rather than spilling cancer cells by separating structures infiltrated by tumor. Intraoperative tumor perforation has negative prognostic implications. It is important to report the completeness of the resection (R0, R1, or R2), combining clinical and pathologic information, to determine risk of locoregional recurrence and long-term prognosis.

The concept of the no-touch technique, with initial control of the vascular supply before manipulation of the tumor to avoid releasing cancer cells into the blood stream, has not been shown to be associated with improved outcomes.[143] However, early vascular control with medial-to-lateral dissection of the mesentery, before mobilization of the colon, is the preferred approach during minimally invasive colorectal surgery, because it helps identify all vascular and retroperitoneal structures.

Proper surgical technique is crucial in achieving optimal results in CRC patients. The removal of the rectum along with its mesorectal envelope, using sharp dissection along normal anatomical planes—an operation called total mesorectal excision, or TME—is associated with a reduced risk of local tumor recurrence.[144,145] Conversely, application of the same surgical principles to colon cancer, including the removal of all the lymph node-bearing mesentery to the origin of the named blood vessels—an operation called complete mesocolic excision or CME——has not been universally adopted due to conflicting evidence of the association of CME with improved survival and concern for higher complication rates in CME.[146–148] Published studies on CME are difficult to evaluate and compare because of inconsistent definitions, unclear description of the extent of dissection, and absence of randomization.[149] Often, the radicality of resection is self-reported by the surgeons. Confirmation of correct extent of resection should be validated by pathologists.[150] Prospective clinical trials should provide more conclusive evidence to the efficacy of CME.

TREATMENT OF LOCALIZED COLON CANCER

Malignant Colonic Polyps

The identification of a focus of invasive carcinoma in a polyp removed by snare excision during colonoscopy represents a surgical dilemma. These types of polyps are often referred to as “malignant polyps,” to distinguish them from lesions that are almost exclusively invasive adenocarcinoma with exophytic or polypoid morphology. Malignant polyps are now encountered more often because tumors are diagnosed at an earlier stage, as a result of screening programs. Although there are some lymphatic channels in the lamina propria, tumors superficial to the muscularis mucosa (also known as intramucosal carcinoma, carcinoma in situ, or Tis) are considered to carry no risk of lymph node metastasis. When the malignant cells penetrate beyond the muscularis mucosa they can access the lymphatic channels of the submucosa and metastasize to the regional lymph nodes. This risk of nodal metastasis depends on the morphology of the polyp, the depth of the invasive component, the presence of unfavorable histologic features (grade 3 or 4, lymphovascular invasion, perineural invasion) and the margin of resection.[151] Imaging studies are usually of no help in these patients, except to exclude distant metastases

(which are uncommon). In pedunculated polyps with focus of invasive cancer located in the head, neck, or stalk of the polyp, with favorable histologic features, resected with negative margins, the risk of nodal metastasis is small (**Fig. 68.8**). In these circumstances additional surgery is considered unnecessary, as the risk of surgery may outweigh the risk of residual tumor in the bowel wall or nodal metastasis. On the other hand, patients with pedunculated polyps with focus of invasive adenocarcinoma reaching the base of the polyp, sessile polyps with focus of invasive adenocarcinoma, the presence of adenocarcinoma at the resection margin, and malignant polyps with unfavorable histologic features, are at risk of regional nodal metastasis, and should be offered surgical resection.[152,153] Other factors such as the location of the polyp in the colon or rectum, the patient's comorbidities and performance status, and the patient's desires, should be taken into consideration.[154] Therefore, a final decision should only be made after full review of the pathology reports, and disclosure to the patient of the risks and benefits of each approach.

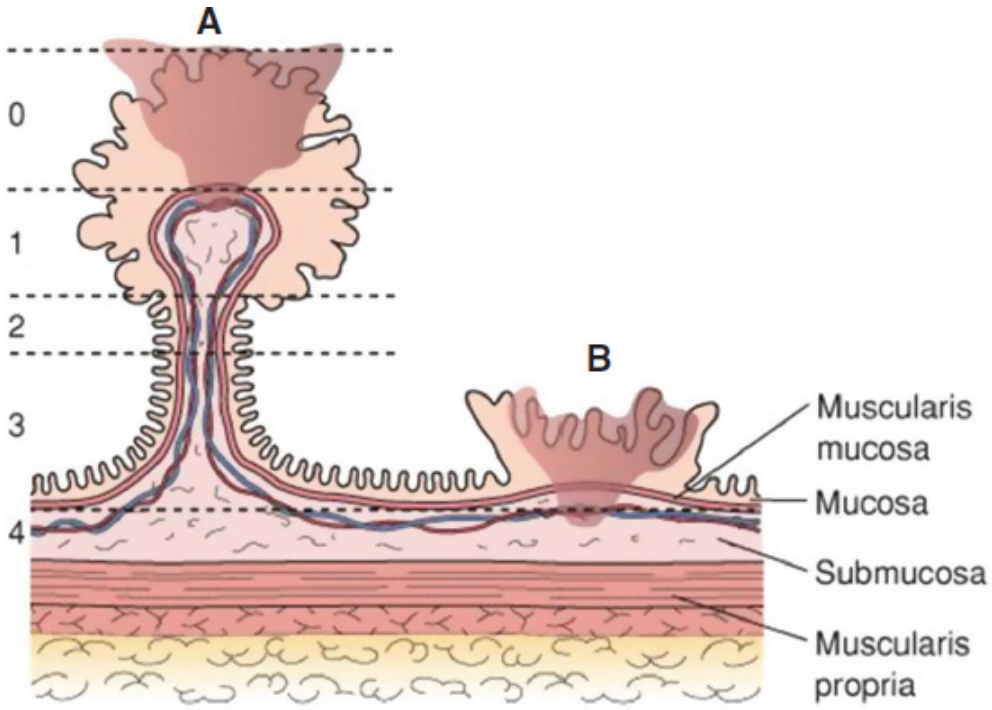


Figure 68.8 Malignant polyp. Haggitt levels of invasion. Level 0, Noninvasive, severe dysplasia; Level 1, Invading through muscularis mucosa but limited to the head of pedunculated polyp; Level 2, Invading the neck of pedunculated polyp; Level 3, Invading the stalk of pedunculated polyp; Level 4, Invading into submucosa of the bowel wall below the stalk of a pedunculated polyp and all sessile polyps.

Surgery for Localized Colon Cancer

Patients with biopsy-proven adenocarcinoma of the colon without evidence of distant metastasis, and without contraindications to major surgery, should be treated with surgical resection. The extent of a colon cancer resection is dictated by the location of the primary tumor. Tumors in the cecum and ascending colon require a right hemicolectomy that implies division of the ileocolic, right colic (if present), and the right branch of the middle colic vessels (**Fig. 68.9**). The portion of the omentum attached to the removed segment of colon should be resected en bloc with the colon and mesentery. Tumors located at the hepatic flexure and in the right side of the transverse colon require an extended right colectomy that, in addition to the ileocolic and right colic vessels, requires division of the middle colic vessels at their origin (**Fig. 68.9**). Tumors in the mid portion of the transverse colon can be treated with an extended right colectomy, or a transverse colectomy. A transverse colectomy involves division of the middle colic vessels only, but often requires mobilization of both the hepatic and splenic flexure to ensure a tension-free anastomosis (**Fig. 68.9**). Tumors located in the distal transverse colon, splenic flexure, and proximal descending colon can be treated with a left hemicolectomy, which requires division of the left branch of the middle colic and left colic artery at its branch point from the inferior mesenteric artery (**Fig. 68.9**). Locally advanced tumors located in the transverse colon can metastasize to the regional lymph nodes located along the greater omentum and gastroepiploic arcades, leading some surgeons to recommend removal of the omentum with the gastroepiploic arcade. In these patients, an omentectomy with division of the gastroepiploic vessels at their origin may be necessary for complete nodal control.[155] However, the benefit of such an extended lymphadenectomy is debated. Sigmoid tumors require sigmoid colectomy, which includes the superior rectal artery and its takeoff from the inferior mesenteric artery (**Fig. 68.9**).

Patients with synchronous tumors, which occur in up to 5.3% of patients with CRC, should be investigated for hereditary CRC syndromes or other predisposing conditions. Patients with sporadic synchronous cancers can be treated with separate resections, or an extended resection incorporating both lesions, depending on the location of the primaries.[156] When performing a segmental resection, it is important to preserve the blood supply to the intermediate segment of colon in order to avoid ischemia, which can lead to

perioperative complications. Synchronous tumors in patients with HNPCC, or other risk factors such as inflammatory bowel disease, are indications for a subtotal or total colectomy.

A number of well-conducted prospective trials have proved that laparoscopic colectomy for cancer is associated with short-term benefits and equivalent long-term oncologic outcomes, compared with the traditional open surgical approach. Patients treated laparoscopically have less postoperative pain, earlier return of bowel function, shorter hospital stay, and a decreased rate of complications. However, laparoscopic surgery is technically challenging and has a long learning curve. Laparoscopy may be particularly difficult in patients with multiple adhesions from previous surgery, in obese patients, and in patients with locally advanced disease. Late conversion from laparoscopic to open surgery (also known as reactive conversion) is associated with higher complication rates compared to open surgery, while early or preemptive conversion is associated with complication rates similar to open surgery.[157]

Laparoscopic colectomy is typically performed using a number of ports, usually 3 to 5, and a specimen extraction site. A single port laparoscopic approach that uses a small incision to insert all instruments and extract the specimen, increases the technical difficulty without reducing complications or expediting recovery compared to conventional laparoscopic surgery.[158]

The introduction of robotic platforms, which enhance the visualization and dexterity of the surgeon, has added a new dimension to minimally invasive colon cancer surgery. The evidence accumulated so far indicates that robotic colon resection is associated with lower conversion rates, similar complication rates, and higher costs, compared to conventional laparoscopic colon resection.[159]

Postoperative Adjuvant Therapy for Localized Colon Cancer

Many patients with what appears to be localized colon cancer at the time of diagnosis develop recurrence after a curative-intent surgery. These recurrences are attributed to micrometastases that are already present, but clinically undetectable, at the time of diagnosis. Postoperative adjuvant chemotherapy aims to improve survival by eradicating micrometastatic disease. Numerous chemotherapeutic agents are now considered for adjuvant therapy, mostly based

on their efficacy as observed in the setting of metastatic colon cancer. However, the mainstays of adjuvant therapy following resection of localized colon cancer remain fluoropyrimidines (5-fluorouracil [5-FU] and capecitabine) and oxaliplatin.

5-FU, a member of the family of antimetabolites, is a pyrimidine analog that works by irreversible inhibition of thymidylate synthase (TS), the rate-limiting enzyme in pyrimidine nucleotide synthesis, and by incorporation of its metabolites into RNA and DNA. 5-FU can only be delivered intravenously and is commonly administered with leucovorin, a reduced folate that is thought to stabilize fluorouracil's interaction with the enzyme TS. Capecitabine is an oral prodrug of fluorouracil that is absorbed intact through the gastrointestinal mucosa and undergoes enzymatic conversion to fluorouracil. Response rates to fluoropyrimidine, as first-line therapy alone for metastatic CRC, are only around 10% to 20%. Neutropenia, stomatitis, and diarrhea are the most common side effects of 5-FU. The toxicity profile for capecitabine is similar to 5-FU, with hand-foot syndrome being more frequent. Oxaliplatin produces cytotoxic effects by forming both inter- and intrastrand cross links leading to disruption of DNA replication and apoptosis. As a single agent, oxaliplatin has limited effect in CRC; but in combination it enhances the cytotoxic effect of fluoropyrimidines, possibly through downregulation of TS. The most relevant side effect of oxaliplatin is a progressive and often irreversible peripheral neuropathy. Other chemotherapy agents commonly used in patients with metastatic CRC have not shown proven benefit in the adjuvant setting.

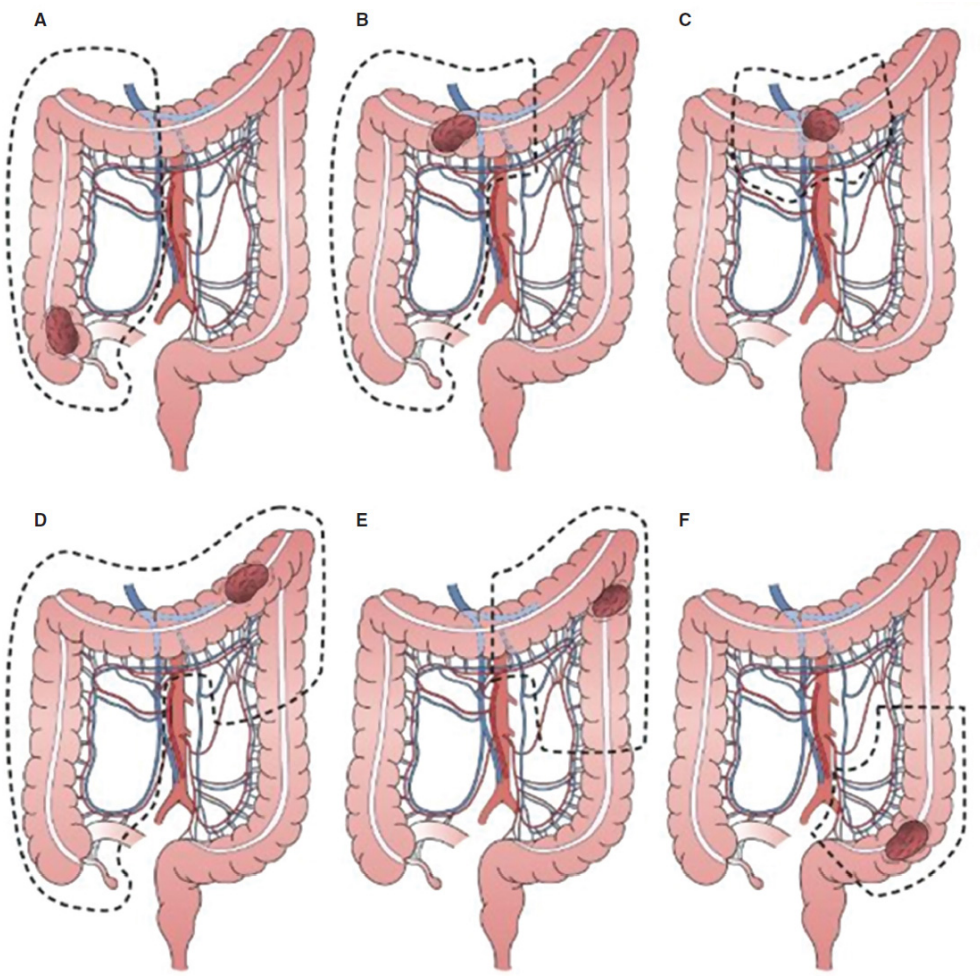


Figure 68.9 Segmental colonic resections. **A:** Right colectomy. **B:** Extended right colectomy to transverse colon. **C:** Transversectomy. **D:** Right colectomy extended to splenic flexure. **E:** Left colectomy. **F:** Sigmoidectomy.

The use of adjuvant therapy for stage III colon cancer was first shown to provide measurable benefit in the National Cancer Institute (NCI) Cooperative Intergroup trial INT-0035. Patients who received 5-FU and levamisole for 1 year after surgical resection had a 33% risk reduction in death or recurrence, compared to those who underwent surgery alone.[160,161] Since then, we have come to recognize that levamisole is overall an inactive agent; therapeutic combinations have evolved and have been tested rigorously.[162] A number of multi-institutional prospective, randomized trials have demonstrated a survival advantage with postoperative chemotherapy in selected patients after curative-intent surgery, compared to surgery alone. Pooled analyses of these trials have reported an approximately 30% reduction in recurrence, and 26% improvement in survival, in patients with stage III colon cancers treated with 6 months of

postoperative fluoropyrimidine-based chemotherapy.[163,164] More recently, the landmark MOSAIC (Multicenter International Study of oxaliplatin, fluorouracil, and leucovorin in the Adjuvant Treatment of Colon Cancer) trial, which randomized 2,246 stage II/III colon cancer patients to 5-FU/leucovorin with or without oxaliplatin, reported an additional 20% reduction in recurrence and 5% improvement in 5-year disease-free survival (73.3% vs. 67.4%; $p = 0.003$) in patients treated with 5-FU/leucovorin plus oxaliplatin, compared to 5-FU/leucovorin alone.[165,166] Based on these results, the current recommendation for patients with stage III colon cancer following curative-intent surgery consists of 6 months of 5-FU/leucovorin and oxaliplatin (FOLFOX), or capecitabine and oxaliplatin (CAPEOX).

Recently, the largest investigation into adjuvant therapy for stage III colon cancer was conducted in the scope of the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration; it included six different prospective trials conducted in different countries, and randomized patients after curative resection to either 6 months, or 3 months of postoperative fluoropyrimidine- and oxaliplatin-based adjuvant chemotherapy. An expert panel interpretation of the results recommends 6 months of postoperative adjuvant chemotherapy for patients at high risk of recurrence (T4 or N2). For low-risk patients (T1–3/N1), 3 or 6 months of adjuvant chemotherapy is considered equivalent. Based on these results, a shared decision-making approach between the patient and the provider is recommended when deciding duration of adjuvant chemotherapy in patients with resected stage III colon cancer, taking into consideration the patient's comorbidities and performance status, the completeness of the surgical resection, the number of lymph node retrieved, and the histopathologic characteristics of the tumor.[167]

Several studies have proven that the addition of irinotecan—a topoisomerase I inhibitor that is effective in metastatic CRC—to standard fluoropyrimidines is not superior to fluorouracil/leucovorin combinations alone in stage III colon cancers.[168] Similarly, bevacizumab (anti–VEGF-A) and cetuximab (anti-EGFR), two biologic agents that have shown efficacy in metastatic disease, do not improve survival, compared to FOLFOX alone.[169–171] Therefore, at the present time irinotecan, bevacizumab, and cetuximab are not recommended in the adjuvant treatment of nonmetastatic CRC.

The use of adjuvant chemotherapy after curative resection for stage II CRC has been controversial for more than a decade. Three prospective, randomized trials have addressed the subject using 5-FU–based regimens, all of them

failing to show a clear benefit of adjuvant treatment over observation alone.[161,172,173] The addition of oxaliplatin to the adjuvant regimen does not seem to improve the results of pyrimidine-based regimens for stage II. Most of the evidence for adjuvant treatment in stage II CRC comes from pooled analyses, in which stage II and III CRC patients, undergoing different chemotherapy regimens and controls, are analyzed. The most influential study, including 37 trials and 11 meta-analyses, found a significant improvement in DFS for 5% to 10%, favoring adjuvant chemotherapy; nevertheless, no difference in OS was observed.[174] Therefore, postoperative adjuvant chemotherapy is still not routinely recommended after curative resection for stage II CRC. However, there is evidence that some node-negative patients at high risk for recurrence may benefit from postoperative adjuvant chemotherapy. Determining which patients are at high risk has most commonly included consideration of features such as tumor perforation, T4 category tumors, poorly differentiated histology, lymphovascular or perineural invasion, and patients with fewer than 12 nodes in the surgical specimen (who are considered inadequately staged).[175] At the present time, the use of adjuvant therapy for stage II disease ought to be weighed carefully by a multidisciplinary team, with adequate counseling of the patient. As mentioned earlier, some predictive nomograms may help stratify risk in patients with stage II disease, enabling us to more effectively select those more likely to benefit from adjuvant therapy; however, these tools have not been widely incorporated into clinical practice.

The search for molecular prognosticators aimed at stratifying stage II patients according to the risk of relapse, is an active area of research. MMR deficiency has been associated with an improved prognosis, but a decreased benefit from fluoropyrimidine-based adjuvant therapies, in patients with stage II disease.[31] Because of this, MMR/MSI testing is recommended for patients with stage II disease. Current guidelines recommend no use of single-agent fluoropyrimidine treatment for patients with stage II tumors exhibiting MSI or MMR deficiency. The discovery that ICIs are effective in MMRd CRC has revolutionized the treatment of locally recurrent and metastatic MMRd CRC.[176,177] Immune checkpoint blockade is currently not recommended in nonmetastatic MMRd CRC, but clinical trials are investigating the efficacy of ICI in nonmetastatic dMMR/MSI CRC.[178] The multigene molecular signatures discussed previously were developed, in large part, to stratify risk in patients with stage II CRC, and to identify those most likely to benefit from adjuvant chemotherapy.[56–58] While

initial results are promising, there is insufficient evidence to recommend their use in selecting adjuvant therapy for patients with stage II CRC.

TREATMENT OF LOCALIZED RECTAL CANCER

The treatment of rectal cancer presents different challenges, but also different opportunities, compared to colon cancer. Given the location of the rectum within the narrow bony pelvis surrounded by the urogenital organs, large blood vessels, and autonomic nerves, and its proximity to the anal sphincters, rectal cancer surgery is technically challenging, potentially associated with perioperative complications, and often followed by loss of urinary, sexual, and bowel function that permanently impairs quality of life. In addition, rectal cancer has been associated with a higher rate of local recurrence after curative-intent surgery, compared to colon cancer. But the extraperitoneal location of most of the rectum and its proximity to the anal orifice make it accessible to explorations (DRE, endorectal ultrasound [ERUS]) and interventions (external-beam radiation therapy, brachytherapy, and local excision [LE]) not currently available for colon cancer.

The selection of the best treatment option for each rectal cancer patient is a complex process and requires consideration of the clinical tumor stage, location of the tumor within the rectum, the impact of treatment upon anorectal and genitourinary function, and the consequences for the patient in terms of prognosis and quality of life. Some rectal cancers can be treated with LE. Others require a TME, with or without sphincter preservation. Finally, many rectal cancer patients require chemotherapy and radiation to reduce the risk of local recurrence and distant metastasis.

Anatomy of the Rectum

The rectum represents the distal portion of the large bowel, extending from the rectosigmoid junction—the area where the tenia coli (characteristic of the sigmoid colon) splay and become the longitudinal muscular layer of the rectum—to the anorectal ring, a palpable anatomical landmark that corresponds to the imprint of the puborectalis muscle on the bowel wall. The anal canal extends from the anorectal ring to the anal verge, the palpable groove between the distal edge of the internal sphincter and the subcutaneous portion of the external sphincter (**Fig. 68.10**). For practical purposes and standardization, the rectum is

defined in terms of distance in centimeters from the anal verge. The distance of a tumor from the anal verge is best measured using a rigid proctoscope, which allows the simultaneous visualization of the anal verge and the centimeter marks on the outside of the scope. In European countries, tumors with the distal edge located within the last 15 cm of the large bowel are considered rectal cancers; in the United States, the limit is 12 cm. The location of tumor in relation to the peritoneal reflection and the sacral promontory, and its distance from the anal verge, can also be determined by MRI, particularly in sagittal views.

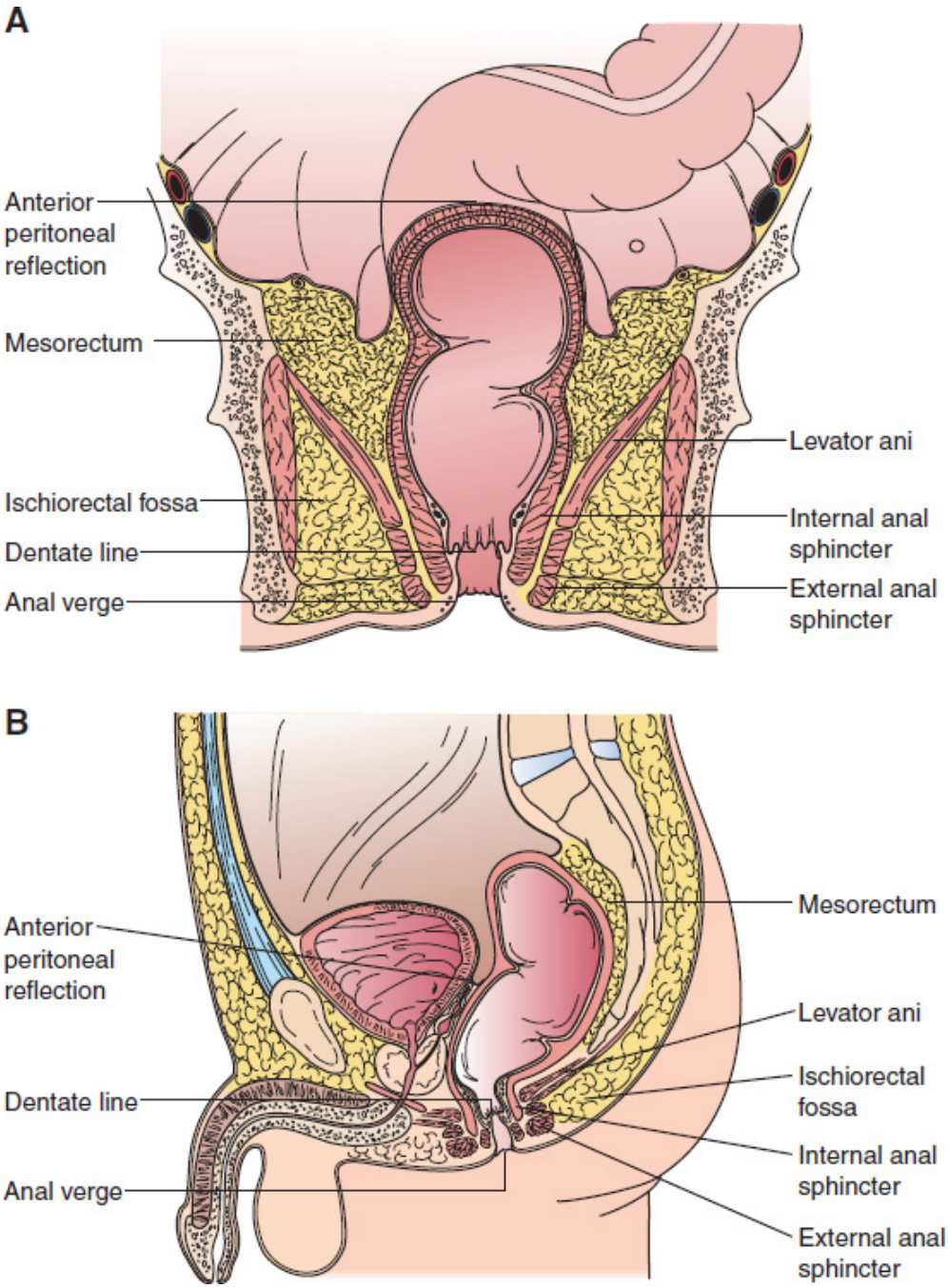


Figure 68.10 Anatomy of the rectum. **A:** Coronal pelvis. **B:** Sagittal pelvis.

The mesorectum is the visceral mesentery of the rectum containing the terminal branches of the superior rectal vessels and the rectum's lymphatic drainage. The upper portion of the rectum, located above the anterior peritoneal reflection, is covered with peritoneum in the front and on both sides. In this upper portion of the rectum, the mesorectum which is a continuation of the mesentery of the sigmoid colon, covers the rectum only posteriorly and is

attached to the concavity of the sacrum. Below the peritoneal reflection the rectum is completely extraperitoneal and fully surrounded by the mesorectum. The mesorectum is covered by a thin, glistening membrane called the mesorectal fascia (MRF). Posteriorly, the mesorectum is separated from the presacral fascia by an avascular plane of loose areolar tissue that is the natural plane of dissection during a radical proctectomy. Anteriorly, the mesorectum is separated from the urogenital organs by a remnant of the fusion of two layers of the embryologic peritoneal cul-de-sac known as Denonvilliers fascia——an important anatomical landmark in rectal cancer surgery. Below the peritoneal reflection, the lateral rectal ligaments or "lateral stalks" connect the mesorectum to the pelvic sidewall. The mesorectum tapers off distally as the rectum funnels toward the anorectal ring, where the longitudinal layer of the muscularis propria becomes the internal anal sphincter.

The blood supply of the rectum comes primarily from the superior rectal artery, which is the terminal branch of the inferior mesenteric artery after it gives off the left colic artery. The superior rectal vein has a parallel course to its homonymous artery, and joins the left colic vein to form the inferior mesenteric vein draining into the splenic vein. The lower portion of the rectum and the anal canal also receive blood supply from the internal iliac vessels through the middle rectal artery, an inconsistent branch of the inferior vesical artery. The inferior rectal artery is a branch of the pudendal artery. The middle and inferior rectal vessels anastomose with the upper rectal vessels, supplying enough blood to the entire rectum. As in other locations, the middle and inferior rectal veins follow the course of the homonymous arteries, draining into systemic circulation through the internal iliac veins.

The anatomy of the autonomic pelvic nerve system is very important when operating in the rectum, because of its proximity to the plane of dissection during different parts of the operation. Damage to these nerves can result in urinary and/or sexual dysfunction. The hypogastric plexus, located in front of the aorta, contains predominantly preganglionic sympathetic fibers originating from the lumbar sympathetic trunk. The fibers of the hypogastric plexus converge at the level of the aortic bifurcation into well-defined hypogastric nerves, which course laterally and anteriorly over the internal iliac vessels toward the lateral pelvic sidewall. There they join the splanchnic pelvic nerves, containing primarily postganglionic parasympathetic fibers from the anterior rami of S2, S3, and S4, to form the pelvic plexus. Branches of the pelvic plexus provide innervation to the distal ureter, the vas deferens, the

seminal vesicles, urinary bladder, and prostate. Branches of the pelvic plexus also provide innervation to the distal rectum, passing through the lateral stalks. Finally, distal to the lateral stalks, the distal pelvic plexus forms the urogenital neurovascular bundles that pass close to the posterolateral aspect of the seminal vesicles or the vagina, extending toward the apex of the prostate and the neck of the bladder.

Clinical Staging of Rectal Cancer

The preoperative evaluation of the rectal cancer patient follows the same principles as that of the colon cancer patient, but the wider spectrum of therapeutic options for rectal cancer patients requires accurate information about the location and stage of the tumor. The clinical stage is important in making treatment decisions, such as the intent of the treatment (palliative or curative), the need for neoadjuvant therapy, or even the extent of the surgery (LE vs. TME).

Patients with rectal cancer should undergo a complete colonoscopy because synchronous polyps are present in up to 30% of patients, and synchronous cancers in up to 5.3% of patients. They also require a CT scan of the chest, abdomen, and pelvis to exclude distant metastasis, which is present in 20% of patients at the time of diagnosis.

The preoperative locoregional staging of rectal cancer follows the clinical TNM system, based on depth of tumor penetration in the rectal wall and the presence of regional lymph nodes. However, the preoperative assessment of rectal cancer goes beyond determination of clinical tumor stage; it includes the distance of tumor from the anal verge, its relationship to the sphincter complex and the levator muscles, the proximity of tumor to the MRF, and the presence of extramural venous invasion (EMVI). This information is essential in planning treatment and surgery. Gross morphologic features such as size, morphology, and ulceration have been associated with prognosis. However, when stratified by stage, these characteristics have not appeared to contribute independently to oncologic outcomes, and therefore they are not incorporated into treatment decisions.

DRE and proctoscopy provide the surgeon with the first direct impression of the tumor. Tumor mobility on DRE provides a gross estimation of the tumor depth of invasion. There is a four-category clinical classification of rectal tumors, based on mobility on DRE, which supposedly corresponds to the four T

categories of the TNM system. However, the correlation between the clinical and pathologic T classifications is not very accurate, and varies significantly with the experience of the examiner. In general, DRE is able to distinguish between mobile tumors, most likely limited to the bowel wall, and tethered or fixed tumors, likely penetrating beyond the bowel wall. However, DRE fails to identify more than 50% of pathologically proven involved nodes. Finally, only very distal tumors are within reach of the examining finger. Therefore, pretreatment clinical staging requires imaging studies including ERUS, high-quality rectal MRI, as well as CT scan of the chest, abdomen, and pelvis with intravenous contrast.

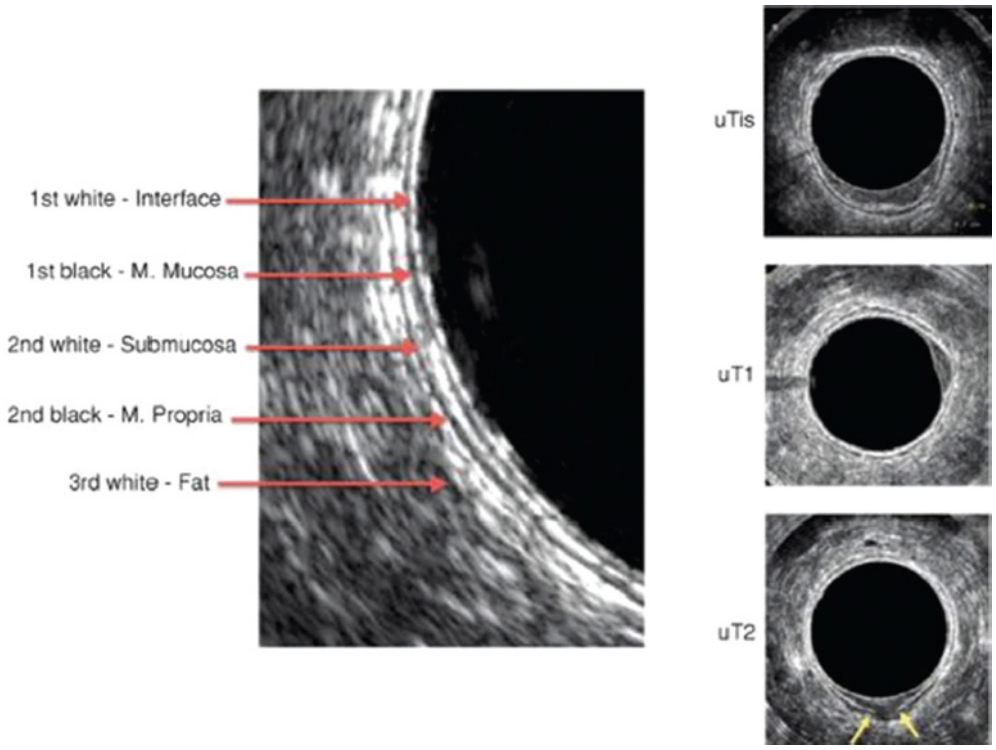


Figure 68.11 Endorectal ultrasound in rectal cancer staging. The sonographic five-layer structure of the rectal wall consists of three hyperechoic layers (interface, submucosa, perirectal fat and serosa) separated by two hypoechoic layers (muscularis mucosa and muscularis propria). Lesions are T staged as uT0/uTis when the mass is within the hypoechoic M. mucosa layer. Tumors staged as uT1 are invading the hyperechoic submucosal layer. Lesions with a distinct break of the submucosal layer and invasion into the hypoechoic muscularis propria layer are staged as uT2 (*yellow arrows*).

Ultrasound with an endorectal rotating probe is the imaging modality that best depicts the different layers of the bowel wall, and is most useful for staging early rectal cancer (**Fig. 68.11**).[179] But ERUS has a relatively short

focal range, and cannot depict important anatomical structures such as the MRF. CT scans provide accurate images of the rectum, adjacent pelvic structures, and even the MRF, but have lower tissue resolution compared to MRI. A CT scan of the chest, abdomen, and pelvis should be performed in every rectal cancer patient to exclude distant metastases. MRI with a surface phased-array coil has become the preferred imaging modality for locoregional staging of rectal cancer. Using various sequences and multiple planes, MRI provides high-tissue resolution and excellent anatomical depiction of the rectum, the mesorectum, the MRF, the levator muscles, and other pelvic structures, relative to tumor location (**Fig. 68.12**).[180] The addition of new contrast agents and advanced functional sequences such as diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE) permit the quantification of tumor biologic processes such as microcirculation, vascular permeability, and tissue cellularity. DWI images in particular are useful for assessment of rectal cancer response to neoadjuvant therapy.[181,182]

Tumor distance from the MRF—the CRM when performing TME surgery—has prognostic implications for local recurrence and patient survival, and has become one of the most important parameters in the preoperative evaluation of rectal cancer patients.[47] MRI is the most accurate imaging modality in determining the distance of the tumor to the MRF, and predicting CRM involvement. The MERCURY trial, a prospective observational study assessing the accuracy of MRI in predicting a curative resection in rectal cancer, reported 92% specificity in predicting a negative CRM.[183] Other important tumor features accurately assessed by MRI, and associated with patient outcomes, are extramural spread, EMVI, involvement of the peritoneal reflection, and distance of tumor from the levator muscle and sphincter complex.[184,185] Using information on these parameters for patients registered to the MERCURY trial, clinicians are able to stratify rectal cancer patients with good prognosis (e.g., clear CRM, no evidence of EMVI, T2 or T3 <5 mm and not involving the intersphincteric plane) with a 3% LR rate and an 85% 5-year DFS after treatment with surgery alone.[186] In European and Scandinavian countries, the information gained from imaging, rather than clinical TNM staging, is used to determine treatment in patients with rectal cancer.[187]

Tumor response to neoadjuvant therapy has prognostic value, 4 and restaging after neoadjuvant therapy is becoming increasingly important in reassessing treatment options and planning the surgical procedure. Some patients with a clinical complete response, a subjective assessment that no

viable tumor remains based on DRE, endoscopy with or without biopsy, and MRI, are now offered alternatives to rectal resection, such as "watch and wait," in the context of clinical trials.[188–190] In the investigation of the accuracies of DRE, endoscopy, and MRI in predicting complete response, endoscopy is the most accurate.[191] This is true despite the fact that MRI can provide both morphologic and functional information regarding the tumor that can be seen in T2-weighted and diffusion-weighted sequences, respectively. When all three modalities (DRE, endoscopy, and MRI) are consistent with absence of residual tumor, the accuracy of predicting complete response can be as high as 98%. Clinical and radiologic modalities underestimate response to neoadjuvant treatment. DRE underestimates response in 78% of patients, relative to response in pathologic specimens.[192] Nearly three-quarters of patients with pCR have a residual mucosal abnormality that would have led to their being categorized as having had an incomplete clinical response.[193] Of patients for whom DRE, endoscopy, and MRI all indicate the possible presence of residual tumor, 15% still experience a complete response.[191]

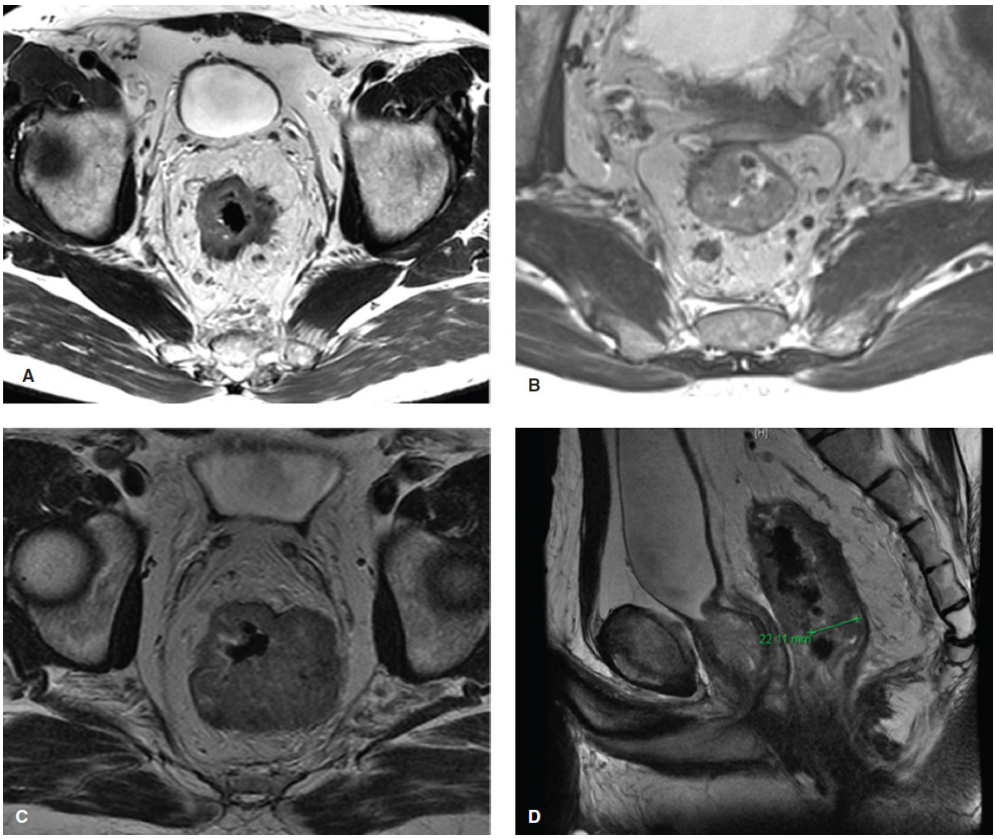


Figure 68.12 Magnetic resonance imaging in rectal cancer staging. Routine use of rectal MRI in the context of a multidisciplinary assessment of rectal cancer has been used to plan neoadjuvant therapy and surgery, and has been shown to reduce the incidence of positive circumferential margins. **A:** Rectal tumor with mesorectal lymph nodes suspicious for metastatic disease. **B:** Locally advanced rectal cancer threatening the mesorectum anteriorly. **C:** Rectal cancer invading the mesorectum in left lateral position. **D:** Sagittal view of a bulky locally advanced rectal cancer.

Local Excision for Early-Stage Rectal Cancer

Selected patients with stage I rectal cancer, those with tumors localized to the bowel wall (T1 or T2) and without involvement of the mesorectal nodes (N0), can be hypothetically cured with an LE of the portion of the rectal wall containing the tumor. This operation spares most of the mortality, morbidity, and bowel, urinary and sexual dysfunction associated with TME. However, the success of LE requires meticulous patient selection. With LE, the mesorectum is not inspected for pathologic nodal staging. Therefore, LE should only be offered to patients with a low risk of nodal metastasis. The selection criteria for LE include: tumor size smaller than 3 cm, involving less than 30% of the circumference of the rectum, mobile on DRE, localized to the submucosa on

ERUS, without evidence of metastatic lymph nodes on ERUS and CT or MRI, and no high-risk histologic features (i.e., grade 3 or 4, lymphovascular or perineural invasion) as noted in consensus guidelines.

In the past, only tumors located in the distal rectum could be treated with LE using conventional transanal techniques. Therefore, LE was only recommended for tumors located within 8 cm from the anal verge. With the use of endoscopic instrumentation and large operating proctoscopes (TEM, Richard Wolf Medical Instruments Corp., Vernon Hills, IL; TEO, Karl Storz Corp., El Segundo, CA) or single-port devices (TAMIS, Trans-Anal Minimally Invasive Surgery), LE can now be easily performed for tumors located in the mid and upper rectum. However, the benefit of LE is more significant for very distal tumors that otherwise would require a low anastomosis or a permanent stoma. The real benefit of LE for tumors located in the upper rectum is a matter of debate.

Independent of the approach, a full-thickness excision of the portion of the bowel wall involved by tumor, with a 1-cm negative margin is required to avoid local recurrence. The final decision regarding the suitability of LE is made after the pathologic evaluation of the surgical specimen. If the resection margins are positive, depth of invasion is beyond the submucosa (T stage ≥2), or the histology reveals high-risk features (grade 3 or 4, lymphovascular or perineural invasion), the patient should be offered immediate salvage TME.

Even in patients with tumors meeting all selection criteria, LE is associated with a higher rate of LR compared to TME. The recurrence rates for T1 tumors treated with LE have been described as up to 23%.[195–197] While some patients who develop LR after a failed LE are candidates for salvage TME, only half of these patients are ultimately cured of their tumors. Recurrences after LE generally present as more advanced tumors, often requiring extended pelvic dissection.[198,199] The oncologic outcome for these patients is worse than those treated originally with TME; this reinforces the importance of patient selection for this strategy.

A recent systematic review of one small randomized trial and 12 observational studies, including a total of 2,855 patients with T1N0M0 rectal cancer treated by LE (TAE/TEM-TEO) versus TME, showed that LE was associated with lower perioperative mortality (relative risk 0.31, 95% CI 0.14–0.71), major postoperative complications (relative risk 0.20, 95% CI 0.10–0.41), and need for a permanent stoma (relative risk 0.17, 95% 0.09–0.30). The LR rate was higher for patients treated with LE, and overall survival significantly lower, compared to patients treated with TME. The relative risk of

dying after LE was 1.46 (95% CI 1.19–1.77), which corresponds to 72 more deaths per 1,000 patients at 5 years. Meta-regression showed that the difference in overall survival observed between groups could be explained by the higher use of LE for tumors located in the lower third of the rectum, which is associated with worse prognosis. Survival was similar between groups when only tumors located in the distal rectum were included in the analysis.[200]

A number of studies have compared the outcomes of different techniques—conventional transanal excision, TEMS, TEO, and TAMIS—for LE of rectal cancer, with most comparisons limited to conventional TAE and TEMS. A recent meta-analysis of 6 retrospective case series including 927 procedures, reported that TEMS was associated with less specimen fragmentation, less positive resection margins, and lower LR rates. No difference was observed in complication rate.[201]

In summary, the literature suggests that LE may be an alternative to TME for patients with small, distal T1N0 rectal cancers, without high-risk histologic features, that would otherwise require a CAA or an APE. Transanal endoscopic techniques may be superior to conventional transanal excision. Patients considering LE should be informed about the potential gains in improved quality of life, but also about the higher risk of LR and the need for salvage surgery.

Patients with T2N0 tumors are not candidates for treatment by LE alone, independent of tumor histologic features. The rate of LR for these patients when treated with LE alone ranges from 13% to 47%, significantly higher compared to similar stage tumors treated with TME. Five-year overall survival is also significantly lower for patients with T2N0 tumors treated with LE (65% to 67.6%) compared to TME (76.7% to 81%).[202] A recent survey of the NCDB found that patients with T2N0 tumors treated with LE alone had a higher hazard ratio for death compared to similar patients treated with TME (1.535, 95% CI 1.283–1.835).[203] Similar results have been reported in an independent cohort from the SEER database.[204] Based on this evidence, LE alone cannot be recommended as an alternative to RS for patients with T2N0 tumor treated with curative intent.

Radiation therapy has been used to reduce the rate of LR in patients with T2N0 rectal cancer treated with LE. A number of retrospective case series have reported 15% to 21% LR rates and 66% to 76.1% 5-year survival rates with LE followed by radiation or chemoradiation for T2N0 tumors.[205–207] The CALGB 8984 trial investigated the role of LE followed by 5-FU–based

adjuvant chemoradiation for patients with T2N0 cancers, reporting a 66% (95% CI, 51% to 84%) overall survival and 64% (95% CI, 51% to 80%) DFS.[208] The trial compared the survival curves of patients with similar stage tumors treated with TME, concluding that LE and postoperative chemoradiation may be an alternative for patients with T2N0 tumors. However, 32% of the patients initially accrued for this trial were ultimately excluded from analysis due to tumor size, inaccurate staging, surgical specimen fragmentation, high-grade histologic features, or involved resection margins. Therefore, the conclusion is applicable only for properly staged early rectal cancers penetrating only into the muscularis propria (pT2), with full-thickness excision negative resection margins, and no high-risk histologic features.

The results of several retrospective studies have suggested that chemoradiation before LE reduces the risk of recurrence to rates similar to those observed in similar stage patients treated with TME alone.[209,210] However, these studies are limited by small sample size, variable clinical staging criteria and imaging modalities, and the use of different CRT regimens. A retrospective study using the SEER database showed that patients who had undergone neoadjuvant CRT and LE had equivalent oncologic outcomes compared to patients who had a radical resection/TME.[204] One prospective trial found that patients with ERUS-staged T2N0 rectal cancer treated with neoadjuvant CRT had similar recurrence and survival rates when randomized to LE or TME. More than one in four patients in the TME arm required a permanent colostomy, and a similar number required a temporary ileostomy.[211] Two single-arm prospective studies have shown that CRT followed by LE for early-stage distal rectal cancers is associated with local recurrence and disease-free survival rate equivalent to similar tumors treated with TME.[212,213] However, this treatment approach is associated with bowel dysfunction and impairment in quality of life, particularly in patients with very distal tumors.[212,214] The GRECCAR-2 trial randomized patients with T2 or T3 distal rectal cancer that responded to CRT to either LE or TME. Local recurrence rates, disease-free survival, and fecal incontinence were similar for patients treated in both treatment arms.[215] In summary, the standard treatment of T2N0 rectal cancer is TME. Neoadjuvant CRT followed by LE may be an alternative for patients with very distal T2N0 tumors interested in organ preservation, who otherwise would require a permanent colostomy.

LE and other forms of local therapy, such as endocavitary radiation, brachytherapy, or electrofulguration, have been used for palliation in patients

who have more advanced tumors or are unfit for a major surgical procedure.

Transabdominal Resection for Rectal Cancer

Patient preparation for rectal cancer surgery is similar to that for colon cancer surgery. Stoma marking is particularly important in these patients, as many will require a temporary or permanent stoma. In addition to discussing fertility options with all individuals of child-bearing potential, female patients receiving neoadjuvant radiation who are interested in preserving fertility should consult their gynecologist regarding the possibility of ovarian transposition. Mechanical bowel preparation, antibiotic and thromboembolic prophylaxis are similar to those described for colon cancer patients. Many surgeons recommend a rectal washout immediately before surgery to eliminate exfoliated cancer cells that could potentially implant in the anastomosis and cause LR. In fact, a recent meta-analysis with 5,012 patients found that this practice is associated with a lower incidence of LR.[216] On the operative table, the patient should be placed in lithotomy with the legs in stirrups to provide the surgeon with simultaneous access to the abdomen and perineum. It is important to avoid pressure on the bony prominences, which might cause peroneal nerve compression. Patients requiring prolonged Trendelenburg position during surgery are at risk of compartment syndrome, in particular obese patients and those with peripheral vascular disease. These patients require monitoring of the peripheral pulses, and position changes, to prevent compartment ischemia.

Principles of Total Mesorectal Excision

The principle of rectal cancer treatment is the eradication of the primary tumor and its lymphatic drainage by en bloc removal of the rectum and the mesorectum, following well-defined anatomical planes. This operation, known as total mesorectal excision, or TME, requires dissection under direct vision along the areolar tissue plane situated between the MRF and the presacral fascia. A sharp dissection along this plane is associated with a higher probability of achieving a negative CRM, lower risk of bleeding from inadvertent tearing of the presacral veins, and reduced risk of injuring the hypogastric nerves.

Adequate lymphadenectomy requires division of the lymphovascular pedicle at the origin of the superior rectal vessels, caudal to the branching of the left colic artery from the inferior mesenteric artery. In patients with clinically

suspicious nodes at the origin of the inferior mesenteric artery, the lymphovascular control should be extended proximally by dividing the inferior mesenteric artery close to the origin (high tie). In both cases the sigmoidal branches are included in the surgical specimen; therefore, the proximal division of the bowel should ideally be performed at the junction of the descending and the sigmoid colon, incorporating most of the sigmoid colon in the surgical specimen.[217] As distal tumor extension along the rectal wall is limited, a distal margin of 2 cm of normal bowel wall is considered adequate for most tumors. However, distal spread in the mesorectum may extend farther than intramural spread. Not infrequently, mesorectal deposits are found 3 to 4 cm distal to the lower edge of the tumor. Therefore, for tumors of the upper rectum, the mesorectal excision should be extended to 5 cm distal to the lower edge of the tumor. In these patients the mesorectum should be divided perpendicular to the axis of the rectum. As some of the distal mesorectum is left in the pelvis along with the distal rectal stump, this operation is known as tumor-specific TME (TSME), to distinguish it from the TME performed with dissection carried to the pelvic floor, the rectum divided distal to the end of the mesorectum, and the entire mesorectum included in the surgical specimen.

Sphincter Saving Procedures

A TSME or a TME is compatible with sphincter preservation by anastomosing the divided end of the descending or the sigmoid colon to the rectal stump. This operation is known as a low anterior resection or LAR (**Fig. 68.13**). In this operation the rectum is divided distal to the tumor using a stapling device that simultaneously staples and divides the rectum, leaving a short rectal stump. The anastomosis is completed with a circular stapler that brings together the end of the colon to the rectal stump. The reestablishment of the large bowel's continuity by suturing the colon to the anal canal, working through the anus, is known as coloanal anastomosis or CAA (**Fig. 68.13**). The connection of the colon to the rectum or anal canal can be performed by an end-to-end or a side-to-end connection, or with the creation of a J-pouch reservoir. A tension-free, well-vascularized low colorectal or coloanal anastomosis requires a complete mobilization of the entire left colon with take-down of the splenic flexure, including division of the inferior mesenteric vein close to the ligament of Treitz. Following ligation of the IMA, the blood supply to the entire left colon is based on the left branch of the middle colic vessels through the marginal artery.

Many patients undergoing a sphincter-saving procedure report high bowel frequency, urgency, soiling, and inability to defer defecation for 15 minutes.[218] This constellation of symptoms is commonly known as low anterior resection syndrome (LARS).[219] The frequency and severity of these symptoms is variable and depends, to some degree, on the location of the tumor and the anastomosis, the patient's prior bowel function, and the use of neoadjuvant or adjuvant therapy.[220] Pelvic irradiation, before or after surgery, increases significantly the risk of bowel dysfunction.[221,222] The anatomical and physiologic factors that contribute to LARS are not completely understood. Anal sphincter pressures are not different in patients with or without LARS. What appears to be different is an exaggerated anal sphincter relaxation to even small volumes of stool within the neorectum.[223] Surgeons have tried to overcome this low capacitance of the neorectum—which results from an end-to-end anastomosis—by creating a colonic reservoir: either a colonic J-pouch, or a side-to-end anastomosis. A number of studies have compared the functional outcomes after straight end-to-end anastomosis and a colonic J-pouch. A systematic review of reconstructive techniques after LAR identified 9 trials that randomized a total of 473 rectal cancer patients to either colonic J-pouch or straight end-to-end anastomosis, reporting that short-term bowel function was better for J-pouch compared to straight anastomosis.[224] Frequency and urgency were less prevalent in patients with a colonic J-pouch, but the rate of fecal incontinence was similar in both groups. The only two trials that followed patients for more than 118 months found minimal or no long-term differences between groups. Although the methodology of these studies was very heterogeneous, they do indicate that a colonic J-pouch is associated with a short-term improvement in frequency and urgency, but no apparent long-term benefit, compared to end-to-end anastomosis. The same systematic review found no differences in anastomotic leak rate, or other complications, between groups. Of note, almost one-third of patients with colonic J-pouches often complained of long-term difficulty emptying the rectum, requiring use of laxatives or suppositories.[225,226] These symptoms are more prevalent when larger pouches are created; therefore, pouch size should be limited to 5 to 6 cm.[227,228]

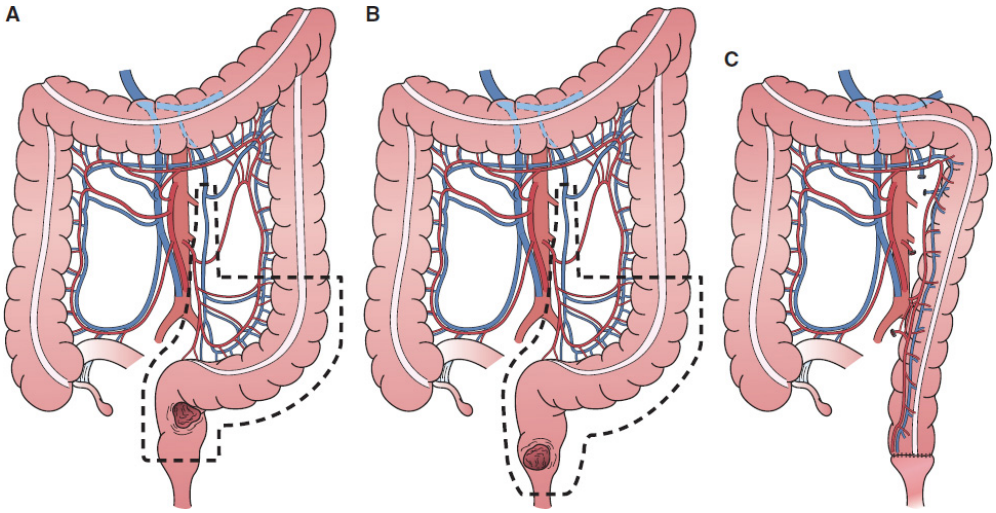


Figure 68.13 **A:** Low anterior resection, section in the distal third of the rectum, candidate for colorectal anastomosis. **B:** Low anterior resection, section above the sphincteric complex, candidate for coloanal anastomosis. **C:** Colorectal anastomosis.

The side-to-end anastomosis (created by inserting the anvil of a circular stapler 3 to 4 cm from the end of the mobilized descending colon) can also potentially increase the reservoir capacity of the anastomosis. It has similar functional results, but is easier to construct than the colonic J-pouch; although it, too, is associated with defecatory problems.[229] The creation of a transverse coloplasty proximal to an end-to-end anastomosis is another option used to increase the capacity of the neorectum, but is associated with a higher anastomotic leak rate.[224]

In summary, colonic reservoirs are associated with a temporary improvement in bowel frequency and urgency, but have the risk of long-term defecatory problems. In general, the authors prefer an end-to-end anastomosis using the larger descending colon, rather than the sigmoid colon, for creation of the neorectum.

The integrity of the anastomosis should be tested intraoperatively with a pneumatic test, or by endoscopy, with distension of the bowel while submerging the anastomosis in water. Air leaks thus detected may be treated with suture repair, redo of the anastomosis, and/or the creation of a proximal diverting stoma. Testing the integrity of the anastomosis during surgery has been associated with a lower risk of clinical postoperative anastomotic leak.[230]

Low colorectal and coloanal anastomoses have a risk of leakage ranging from 3% to 34%, depending on the patient population, the use of neoadjuvant radiation, the distance of the anastomosis from the anal verge, and the surgical

technique.[231,232] An anastomotic leak can cause pelvic sepsis, which may not only preclude sphincter preservation, but may also be associated with an increased risk of local recurrence and poorer survival, although more recent data have questioned this association.[233–235] To prevent these possible complications, a diverting stoma is recommended for patients having a TME, and for patients receiving neoadjuvant radiation.[236] Diverting stomas do not prevent complications, but mitigate the consequences of a leak and reduce the need for urgent reoperation in patients developing a leak.[237,238] A loop ileostomy is preferred over a transverse loop colostomy because it is easier to create and close.[239] However, loop ileostomies are associated with postoperative dehydration and electrolyte abnormalities requiring hospital readmission.[240,241] Prevention of these complications requires adequate patient education and training about stoma management.

Abdominoperineal Excision

For many cancers located in the distal rectum, particularly those infiltrating the levator muscles or the anal sphincter, an oncologically safe circumferential and/or distal resection margin is not compatible with sphincter preservation. In these patients an R0 resection requires a TME with en bloc excision of the levator muscles and the anal canal, and the creation of a permanent end colostomy. This operation is known as abdominoperineal excision of the rectum or APE (**Fig. 68.14**). As the name indicates, the APE has two parts: an abdominal part and a perineal part. During the abdominal part, the proximal lymphovascular control, division of the colon, and dissection along the mesorectal plane are similar to those in LAR, except that the mesorectal dissection should stop at the upper level of the levators, to avoid disturbing the portion of the rectum resting on the levator muscles. During the perineal part, the anal canal with the sphincter complex and the levator muscles are dissected off the ischiorectal fat, all the way to the apex of the ischiorectal fossa. The levators are divided close to their insertion in the white line near the obturator internus and coccygeus muscles. The levator muscles are left attached to the rectum, and the resulting surgical specimen has a cylindrical appearance; therefore, this procedure is called cylindrical APE or extralevator APE (ELAPE) (**Fig. 68.14**).[242] However, some surgeons question the need to entirely remove both levator muscles in every rectal cancer patient, and recommend removing only the portion of the levators required to clear the tumor. This

operation has been called the standard APE (SAPE).[243] The choice between an ELAPE and SAPE is controversial. The potential oncologic benefit of larger tissue removal needs to be weighed against the increased morbidity potentially associated with a larger perineal defect, particularly in patients treated with neoadjuvant therapy.[244] A recent meta-analysis with 949 patients from 1 randomized trial, 1 prospective case-control study, and 6 retrospective case series, indicated that ELAPE is associated with lower intraoperative rectal perforation, lower positive CRM, and lower risk of local recurrence, but with similar complication rates, compared to SAPE.[245] At the present time, the hypothetical benefit of the ELAPE over the SAPE has not been proven conclusively. It is possible that both techniques—the total or the tumor-specific excision of the levator muscles—may be equivalent as long as an R0 resection, with an intact rectal specimen, is achieved.

Many surgeons will perform both parts of the APE operation with the patient in modified lithotomy, also known as the Lloyd–Davis position. It provides relatively good access to the perineum and allows two teams to work simultaneously—one in the abdomen, and one in the perineum. Others perform the abdominal part in the supine position, and the perineal part with the patient prone over a hip roll and padding of the bony prominences. The prone position, also known as jackknife position, provides better exposure of the perineum, and facilitates assistance and teaching. It requires turning the patient, which takes time, and does not allow a two-team approach. Results seem to be similar with both approaches, and the selection is based on surgeon preference.[246]

Minimally Invasive Surgery for Rectal Cancer

Open surgery for rectal cancer requires long abdominal incisions. An APE can be performed though a midline infraumbilical or low transverse incision. Most sphincter-preserving procedures (SSPs) require a long midline incision, extending from the epigastrium to the symphysis of the pubis, in order to permit access to the entire left side of the large bowel from the splenic flexure to the lower rectum. These abdominal incisions are a source of patient discomfort, and short- and long-term morbidity. The goal of minimally invasive surgery in rectal cancer is to reduce the size of the abdominal incision, thus expediting recovery, without compromising the completeness of the mesorectal excision or the oncologic outcomes. However, the adoption of minimally invasive surgery for rectal cancer has been slow due to the difficulty of working in the relatively

deep and narrow pelvic space using long, rigid, nonarticulated laparoscopic instruments. According to a number of retrospective case series and small randomized controlled trials, laparoscopic TME is associated with less postoperative 5 pain, less surgical morbidity, and shorter length of hospital stay, but equivalent completion of the mesorectal excision, CRM positivity, and even LR, compared to open TME.[247–249] While these studies have shown that laparoscopic TME is feasible, less than 25% of all rectal cancer operations are performed laparoscopically in the United States.[250]

Five large multi-institutional prospective, randomized trials have compared open and laparoscopic TME for rectal cancer (**Table 68.7**).[251–255] The combined experience of these trials indicates that laparoscopic TME results in longer operative time, less blood loss, faster bowel recovery, and shorter hospital stay compared to open TME. Operative mortality and intraoperative and postoperative complications were not different between groups. When investigating successful oncologic resection comprised of positive distal margin, positive circumferential margin and completeness of TME, ALACART and Z6051 both failed to demonstrate noninferiority of laparoscopic resection. In addition, although not all of them powered to demonstrate differences in oncologic outcomes, these five studies have shown that LR, distant metastasis (DM), and survival were not different between groups. The combined experience of these studies suggests that with the noninferiority margin for the quality of the surgical resection in some studies, the long-term oncologic outcomes are equivalent for patients treated with open or robotic TME. However, patients in these trials were treated at high-volume centers and operated by surgeons experienced in minimally invasive techniques. Whether similar results can be achievable in the community is still debatable.

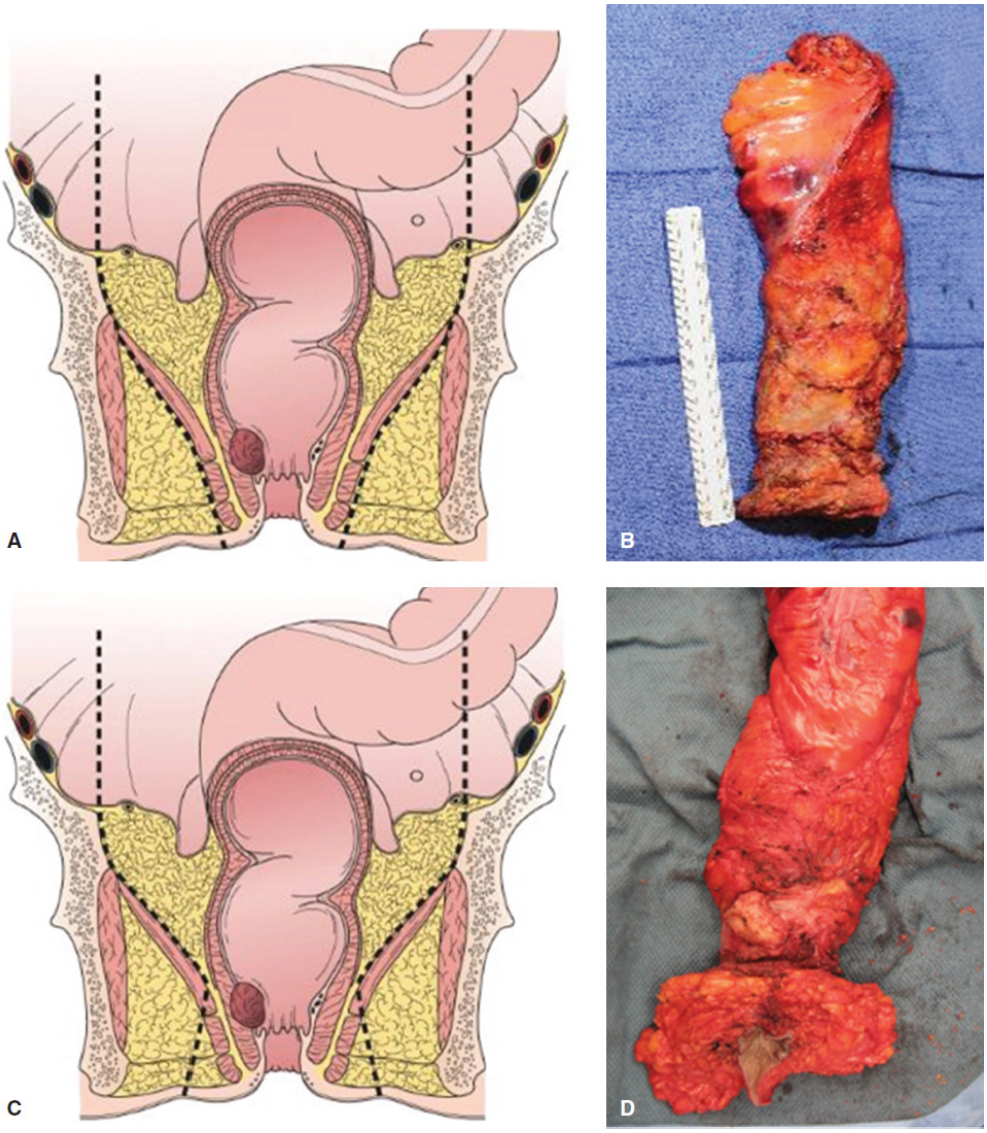


Figure 68.14 Total mesorectal excision. Following correct anatomical planes and avoiding entry into the mesorectum or sphincter muscles (extralevator approach) results in a surgical specimen that has a cylindrical appearance with no mesenteric "waist" or narrowing. **A:** Planes of dissection for ELAPE. **B:** ELAPE specimen. **C:** Planes of dissection for SAPE. **D:** SAPE specimen with mesenteric "waist."

Many surgeons currently perform a hybrid approach consisting of the laparoscopic lymphovascular control and colon mobilization, and the open mesorectal dissection and anastomosis through a lower abdominal transverse incision. The hybrid approach is aimed at facilitating the most technically challenging portion of the operation: the dissection of the distal rectum and the creation of the anastomosis. With this approach the size of the abdominal wall incision is smaller compared with a totally open procedure, but larger than with

a totally laparoscopic procedure. Although there is some evidence of short-term advantages to this approach compared to open surgery, long-term benefits compared to the totally open or laparoscopic approaches are unknown.[256]

The robotic platform (da Vinci) was introduced to the surgical armamentarium to facilitate the minimally invasive approach to procedures such as prostatectomy, hysterectomy, and TME, which require optimal visualization and dexterity in the narrow pelvic space. The experience accumulated thus far—based on retrospective institutional case series—suggests that robotic TME is equivalent to laparoscopic TME in terms of completeness of the mesorectal excision, CRM positivity, and short-term oncologic outcomes. Conversion rates appear to be lower compared to laparoscopic TME, but hospital charges are higher.[257] A prospective, randomized study comparing laparoscopic and robotic TME—the Robotic Versus Laparoscopic Resection for Rectal Cancer (ROLARR) trial—demonstrated no difference in conversion or circumferential margin positivity between the two surgical approaches.[258] However, as laparoscopy has not become standard in locally advanced rectal cancer (LARC), it is likely that the controversy regarding the benefit of robotic TME will continue for years.

Table 68.7 Open versus Laparoscopic Rectal Resections: Results of the Most Representative Series

Open/ Laparoscopic	CLASICC (2005–2007–2010–2013)	COLOR II (2013)	COREAN (2010–2014)	ALaCaRT (2015–2019)	ACOSOG-Z6051 (2015–2019)
n	381	1,103	340	473	462
Rectal cancers included	All	T1–3 (>2 mm from endopelvic fascia) Upper-mid-low	Mid-low cT3NX	T1–3 (>2 mm from endopelvic fascia) Upper-mid-low	Stage II and III, Upper-mid-low
Neoadjuvant CRT (%)	0	34/32	100/100	48/50	91.2/95
Operative time (min)	135/180[a]	188/240 $p < 0.001$	197/224.9 $p < 0.001$	190/210 $p = 0.007$	221/266 $p < 0.001$
Blood loss (mL)	NR	400/200 $p < 0.001$	217.5/200 $p < 0.006$	150/100 $p = 0.002$	318/256 $p = 0.004$
TME (%)	67/79	67/60 $p = 0.120$	100/100	92/87	90.5/84.6 $p = 0.05$
APR (%)	27/25	23/29	14.1/11.2 $p = 0.708$	10/11	23.8/22.7
Conversion (%)	34	17	1.2	9	11
Positive CRM (%)	14/16 $p = 0.8$	10/10 $p = 0.850$	4.1/2.9 $p = 0.770$	3/7 $p = 0.06$	7.7/12.1 <1 mm
Lymph nodes (*n*)	13.5/12	14/13 $p = 0.085$	18/17 $p = 0.085$	NR	16.5/17.9
First bowel movement (days)	6/5	3/2 $p < 0.001$	5.12/4.02 $p < 0.001$	2/2	3/2 $p = 0.04$
Hospital stay (days)	13/10	9/8 $p = 0.036$	9/8 0.056	8/8	7/7.3
Morbidity (%)	13/14	37/40 $p = 0.42$	23.5/21.1 $p = 0.603$	25/20	54.1/53.8
Local recurrence (%)	10.1/9.7 $p = 0.96$	5/5[a,c]	4.9/2.6 $p = 0.42$	3.1/5.4	4.5/4.6
Systemic recurrence (%)	18.6/16.4 $p = 0.74$	20.1/19.1[a,c]	17/15 $p = 0.42$	17.3/19.6	16.7/14.6
DFS (%)	52.1/53.2 $p = 0.953$[a]	70.8/74.8[a,c]	72.5/79.2[b]	82/80	83.2/79.5
OS (%)	52.9/60.3 $p = 0.132$[a]	83.6/86.7[a,c]	90.4/91.7[b]	93/94	86.5/85

[a]3-yr survival.
[b]5-yr survival.
[c]Difference <5% calculated for noninferiority.

The transanal–total mesorectal excision (TaTME), or down-to-up TME, is a transanal, minimally invasive approach for the dissection of the distal rectum in patients with a narrow pelvis.[259,260] With this approach, lymphovascular control, the entire colonic mobilization, and dissection of the upper rectum are performed using conventional transabdominal laparoscopy. The dissection of

the distal rectum is performed through the anus, using either conventional transanal equipment for very distal tumors, or endoscopic equipment (TEMS, TEO, TAMIS) for higher tumors. The rectal wall is incised circumferentially, distal to the tumor, and the MRF is identified. The lumen of the colon is closed with a purse-string suture to avoid contamination. The dissection is carried cephalad in the proper plane until the abdominal field is reached. The specimen is then removed, and the anastomosis performed through the anus. This approach is particularly useful for patients with very distal rectal cancers treated with chemoradiation therapy, in which the surgeon has no anatomical cues about where to transect the rectum in order to achieve a negative distal margin. The transanal approach allows the surgeon to choose precisely the point for transecting the rectum while visualizing the distal edge of the tumor. The benefit of the down-to-up approach for higher rectal cancers that could be treated with a conventional transabdominal dissection and a double-stapled anastomosis are uncertain. A multicenter matched comparison of robotic resection and TaTME of 730 patients with mid to distal rectal cancer did not show differences in specimen quality or conversion rate between these surgical approaches.[261] Outcomes of all patients that underwent TaTME in Norway were compared to outcomes of patients that underwent TME in a national database. TaTME patients experienced more local recurrences and anastomotic leaks. These reports were alarming enough to halt all TaTME in Norway.[262] TaTME is technically challenging, has a long learning curve and should be considered a treatment option for rectal cancer only in very experienced hands.

Adjuvant and Neoadjuvant Radiation and Chemotherapy for Locally Advanced Rectal Cancer

Several randomized, controlled trials conducted in the pre-TME era demonstrated that radiation therapy (RT) given before or after surgery reduced the rate of LR, compared to surgery alone.[263–265] However, the relevance of these trials was later questioned, because surgery was not standardized and the LR rates reported in the control arms—approximately 25%—were considered too high compared to that of patients treated in later years with surgery alone according to TME principles. The efficacy of RT in the setting of quality TME surgical resection was investigated in the Dutch Colorectal Cancer Group trial, which randomized 1,861 patients with resectable disease to TME alone or

short-course RT (SCRT) (5 Gy a day × 5 days, for a total dose of 25 Gy), followed by TME within 2 to 7 days. The study showed that SCRT reduced the rate of LR in resectable rectal cancer treated by TME, compared to TME alone; however, SCRT did not provide a significant survival benefit.[266] This trial proved that preoperative RT decreases the rate of LR in LARC patients treated with TME surgery.

The benefit of combining chemotherapy with RT was proven by several randomized trials that compared postoperative RT combined with 5-FU, administered as a bolus or as continuous venous infusion (CVI), to postoperative RT alone, in patients with pathologic stage II and III rectal cancers.[267,268] The results proved that combined 5-FU and radiation was more effective than radiation alone in reducing the risk of LR, and that CVI 5-FU was associated with lower toxicity compared to bolus 5-FU.

The European Organization for Research and Treatment of Cancer (EORTC) protocol 22921 was developed to assess the effect of adding chemotherapy to preoperative RT, and the subsequent value of postoperative chemotherapy in rectal cancer patients.[269] At the 5-year mark, LR was significantly lower in all three arms receiving any chemotherapy (pre- or postoperative) compared to preoperative RT alone, indicating a benefit of chemotherapy in reducing the risk of LR, regardless of when it was administered. The addition of chemotherapy to RT did not impact survival. Additional work by the Federation Francophone de la Cancerologie Digestive corroborated these findings.[270] These studies showed that, similar to what was found using postoperative radiation, adding chemotherapy to preoperative RT also reduced the rate of LR, compared to preoperative RT alone.

The German Rectal Cancer Group (CAO/ARO/AIO 94) compared preoperative versus postoperative CRT in 823 patients with clinical T3–4/N+ rectal cancer.[271] RT in this trial consisted of 50.4 Gy in 25 fractions with bolus 5-FU as a radiosensitizer. In the preoperative treatment group, surgery was performed 6 weeks after completion of CRT. Both groups had surgery according to TME principles, and received postoperative adjuvant chemotherapy. The preoperative CRT group had less toxicity and lower 5-year LR rates compared to the postoperative CRT group (6% vs. 13%). This study found no differences in the rates of DR, DSS, or OS. The NSABP R-03 study also compared the use of preoperative versus postoperative 5-FU/LV, using 45 Gy in 25 fractions in T3/4, N+ patients, to evaluate differences in DFS, LR, or OS.[272] Despite stopping the study early due to limited accrual, the R-03 study

reported better DFS in the preoperative CRT group, compared to the postoperative group, with a near-significant difference ($p = 0.065$) in OS and no difference in LR. The results of these two trials established preoperative CRT as the preferred treatment for LARC in both Europe and the United States.

More recently, it has been shown that capecitabine is noninferior to infusional 5-FU as a radiosensitizer for LARC, in both the NSABP R-04 trial and the German Cancer Research Center multi-center trial.[273,274] Several large, prospective trials have failed to prove that the addition of oxaliplatin to a fluoropyrimidine (5-FU or capecitabine) is superior to fluoropyrimidine alone as a radiosensitizer in patients with LARC.[274–277] Therefore, based on the current evidence, oxaliplatin is not recommended as a radiosensitizer added to a fluoropyrimidine in patients with LARC.

Alternatively to the standard hypofractionation (180 to 200 cGy a fraction) commonly delivered during the standard long-course CRT over a 6-week period, radiation therapy may be delivered as short course (SCRT) using fewer, larger fractions (5 Gy daily fractions for 5 consecutive days and a total dose of 25 Gy). In these patients, surgery is performed within 7 days of completion of the radiation. Both schemes are biologically equivalent in eradicating cancer cells, but SCRT has the potential benefits of shorter duration of treatment, more efficient utilization of resources, and reduced cost compared to CRT. However, higher dose per fraction increases the risk of delayed toxicity, and tumor regression is lower with SCRT. Two prospective, randomized trials comparing SCRT with CRT have reported equivalent local tumor control with both regimens, and the selection between CRT and SCRT is based on doctor and patient preferences.[278,279] In general, tumor regression is lower with SCRT when surgery is performed within 7 days of the last dose of radiation. For that reason, CRT has been the preferred radiation modality in the setting of large tumors that may benefit from maximal tumor regression before surgery. However, recent data suggest that the tumor response rate increases if surgery is delayed for 6 to 8 weeks after SCRT.[280]

Current guidelines recommend CRT or SCRT with the aim of reducing the risk of LR for all patients with stage II and III rectal cancers. However, the risk of LR depends on the distance of the tumor from the anal verge, the risk being lower for tumors located in the upper rectum compared to those in the lower rectum. It is possible that some patients with high rectal cancers, specifically those with T3N0 tumors and a clear CRM, may not actually benefit from preoperative radiation but may simply be exposed to radiation-associated

toxicity. A current trial in the United States seeks to address this question by comparing the outcomes of rectal cancer patients treated with neoadjuvant chemotherapy, with or without radiation, before TME.[281]

Chemotherapy for Locally Advanced Rectal Cancer

In the past, LR was the dominant problem in patients with LARC, but in the modern era more patients develop distant metastasis than LR. Consequently, patients with LARC treated with neoadjuvant CRT and TME are recommended for postoperative adjuvant chemotherapy, with the aim of reducing distant metastasis and improving survival. However, the data supporting this recommendation are limited, and based heavily on experience using adjuvant therapy for resected colon cancers. A meta-analysis of 21 controlled trials in patients receiving potentially curative surgery, including a total of 4,854 patients randomized to surgery plus fluoropyrimidine-based postoperative chemotherapy, and 4,367 patients to surgery and observation, has shown a significant reduction in the risk of death (17%) (HR = 0.83, CI: 0.76–0.91) and a reduction in the risk of DR (25%) (HR = 0.75, CI: 0.68–0.83) among patients undergoing adjuvant chemotherapy, compared to those undergoing observation.[282] A review of the experience of a large national database suggests that there is a survival benefit for rectal cancer patients receiving chemotherapy after CRT and TME.[283] On the other hand, a pooled analysis of four prospective randomized trials suggests a minimal improvement in DFS from postoperative 5-FU–based adjuvant chemotherapy in patients with rectal cancer treated with preoperative chemoradiation.[284] Despite these conflicting results, current guidelines recommend 4 months of postoperative adjuvant chemotherapy (5-FU or capecitabine plus oxaliplatin) for patients with locally advanced rectal cancer treated with neoadjuvant chemoradiation and TME surgery.

Postoperative adjuvant chemotherapy is often cancelled or delayed in many rectal cancer patients due to surgical complications or slow recovery from surgery. This is particularly relevant, as the delay in the initiation of adjuvant chemotherapy reduces the probability of survival.[285] Delivering systemic chemotherapy before surgery has the potential advantages of increasing treatment compliance, treating micrometastatic disease early, enhancing the response of the primary tumor, and shortening the time to temporary ileostomy

reversal. In this new treatment approach, in which all radiation and chemotherapy is delivered before surgery, known as total neoadjuvant therapy (TNT), systemic chemotherapy can be given before chemoradiation or after chemoradiation, but in both cases before surgery. Patients treated with TNT experience a greater grade of primary tumor response compared to patients treated with chemoradiation and surgery, but a beneficial effect in terms of survival has not been proven yet.[286–289]

Outcomes of Multimodality Treatment in Patients with Locally Advanced Rectal Cancer

Perioperative mortality in patients undergoing multimodality therapy, including total mesorectal excision for LARC, ranges from 1% to 3.5%, and between 23% and 48% of patients develop perioperative complications.[290] Sepsis is the most common complication after rectal cancer surgery. A recent systematic review of the literature, including 53 prospective cohort studies and 45 randomized trials, found a 2% postoperative death rate, 7% rate of surgical wound infection, 11% rate of anastomotic leakage, and a 12% rate of pelvic sepsis.[291] In addition to pelvic sepsis, perineal wound dehiscence is the most common complication after APE. In a large systematic review of 45 studies, the rate of perineal wound complication after SAPE was 15.3% for patients treated with surgery alone, and 32% in those treated with surgery and RT.[292] Many of these patients also had pelvic sepsis. The proportion of patients with perineal complications was similar for those who had ELAPE: 14.8% for surgery alone and 37.6% for surgery and radiation. The rate of perineal hernia was also similar for patients treated with SAPE and ELAPE: 1.8% versus 2%. Other common postoperative complications include urinary retention, pneumonia, and thromboembolic disease.

Surgery for rectal cancer, particularly when combined with CRT or SCRT, has iatrogenic long-term consequences including urinary, sexual, and bowel dysfunction. Up to 39% of patients develop urinary complications, 45% sexual dysfunction, and even a larger proportion, bowel dysfunction.[293,294] A recent population-based study found a 26% rate of moderate bowel problems, 17% urinary dysfunction, and 25% severe problems with sexual function among patients treated for rectal cancer. Patients with a stoma were more likely to have difficulty with body image and sexual activity compared to patients with no stoma. Less than 30% of rectal cancer patients reported perfect health; rectal

cancer patients were more likely to report problems, compared to patients with colon cancer. A follow-up study of the Dutch TME trial recently reported that these treatment-related symptoms persist 14 years after treatment; they reported increased sexual dysfunction, and a small decrease in overall functioning, as measured by a variety of quality-of-life questionnaires distributed to the general population.[295]

Contemporary cohorts of stage II and III rectal cancers treated with neoadjuvant CRT, TME, and postoperative chemotherapy have mostly reported 5-year LR rates between 5% and 10%, 5-year DFS of around 60%, and 5-year OS around 70%.

Treatment Selection in Patients with Localized Rectal Cancer

Unlike patients with localized colon cancer, who all require oncologic resection as the initial form of therapy, patients with rectal cancer have multiple treatment options. The selection among different options depends primarily on the clinical stage of the tumor, as determined by DRE, proctoscopy, and imaging studies, on the distance of tumor from the anal verge, and on patient performance status and expectations.

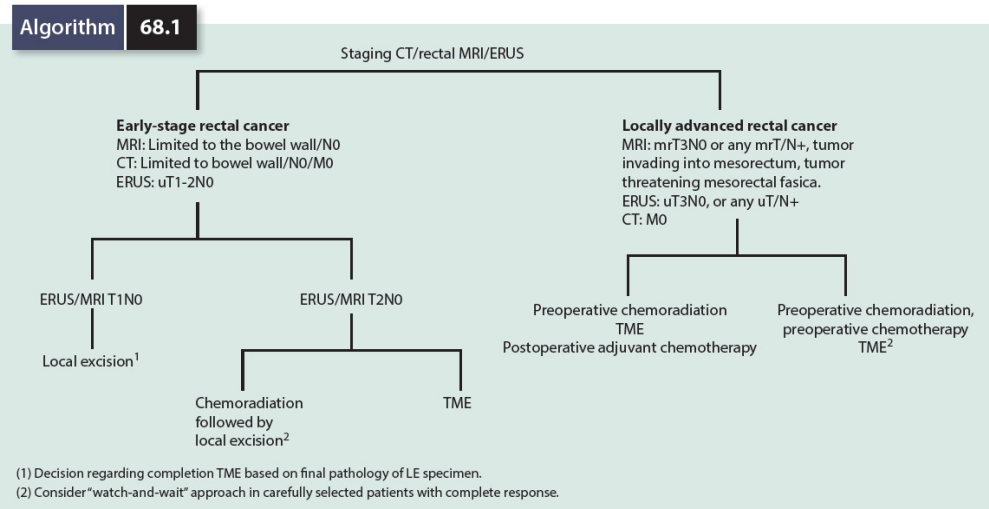
The standard treatment for patients with stage I rectal cancer (T1N0 or T2N0) is TME, but LE has increasingly been chosen as a reasonable and acceptable alternative for patients with distal T1N0 tumors. CRT and LE may also be considered as an alternative to TME in patients with T2N0 tumors interested in sphincter preservation, in whom a TME would require a permanent colostomy.

More advanced tumors—those penetrating beyond the muscularis propria (T3–4, any N) and/or involving the regional lymph nodes (any T, N+), and without evidence of distant metastasis—have several treatment options. In the United States and many other countries, where decisions regarding the treatment of rectal cancer are based on clinical TNM staging, patients with locally advanced disease are treated with 5-FU or capecitabine-based CRT, followed by TME, with consideration given to FOLFOX prior to CRT as an acceptable option (**Algorithm 68.1**).

In Europe and Scandinavia, where rectal cancer patients are stratified into different risk categories based on MRI features, patients are recommended for different treatment approaches according to their individual risk category

(**Algorithm 68.2**). The MRI-based risk stratification system uses a number of features, such as the proximity of the primary tumor to the MRF, the depth of tumor penetration into the mesorectum, the presence of large venous invasion, and the presence of metastatic lymph nodes. Based on these features, they have developed a three-tier classification scheme that includes low risk (the good), intermediate risk (the bad), and high risk (the ugly); each group has a different risk of relapse, and therefore requires different treatment strategies.[187,296] The low-risk group is recommended TME alone. The intermediate group is recommended SCRT followed by TME, while the high-risk group is recommended neoadjuvant CRT followed by TME. This treatment approach, guided by MRI risk categorization, is based mainly on results of prospective observational studies conducted in institutions with significant expertise in rectal cancer, but has not yet been tested in prospective, randomized trials.

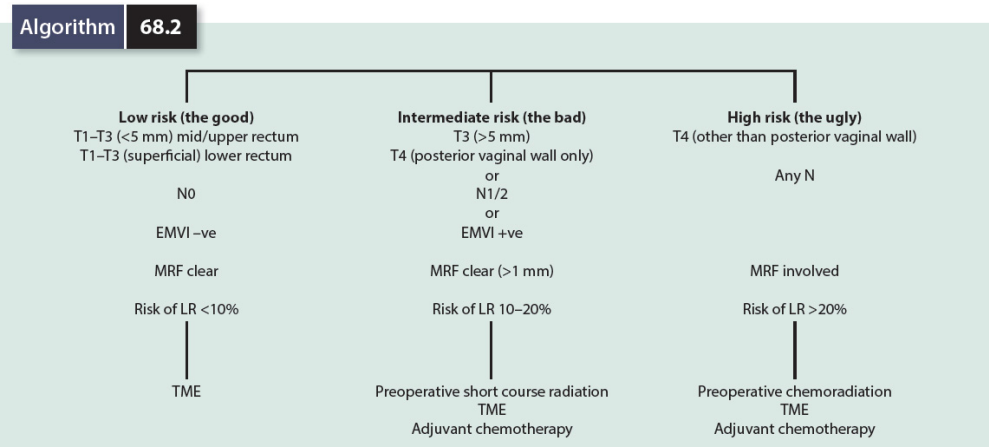
For patients requiring a TME, the decision between an APE and a sphincter-preserving low anterior resection depends on the relationship of the tumor with the anal sphincter and the levator muscle. In general, an APE is required when the tumor directly involves these structures, or is so close to the sphincter that resection with a negative resection margin will result in a loss of sphincter function. In borderline cases, baseline anal sphincter and bowel function, as well as patient wishes and desires should be taken into consideration. The patient should be counseled about LR rates and expected long-term surgical outcomes.



Algorithm 68.1 Approach to rectal cancer according to clinical staging.

Watch and Wait

Rectal adenocarcinomas display a variable degree of response to radiation and chemotherapy. A significant proportion of patients undergoing neoadjuvant chemotherapy and radiation have no viable cancer cells in the rectal specimens after TME surgery. Patients with such a pathologic complete response, have a low risk of tumor recurrence and excellent long-term survival.[297] Based on this observation, surgeons are now questioning the need for TME surgery in patients without apparent residual viable tumor based on DRE, endoscopy, and MRI.[298] Patients with such a clinical complete response are now followed in a close surveillance protocol known as watch and wait (**Fig. 68.15**). While some patients have developed local tumor regrowth requiring TME surgery, some have achieved long-term organ preservation. This approach is particularly appealing to patients with distal rectal cancer who otherwise will require an abdominoperineal excision of the rectum and an end colostomy. The evidence supporting the watch-and-wait strategy for patients with a clinical complete response to neoadjuvant CRT is limited to retrospective institutional case series.[299] While the combined experience of those studies suggests that watch and wait may be safe, at the present time, it should be considered an experimental approach deserving further investigation.[190]



Algorithm 68.2 Approach to locally advanced rectal cancer based on a three-tier risk stratification system ("the good, the bad, and the ugly").

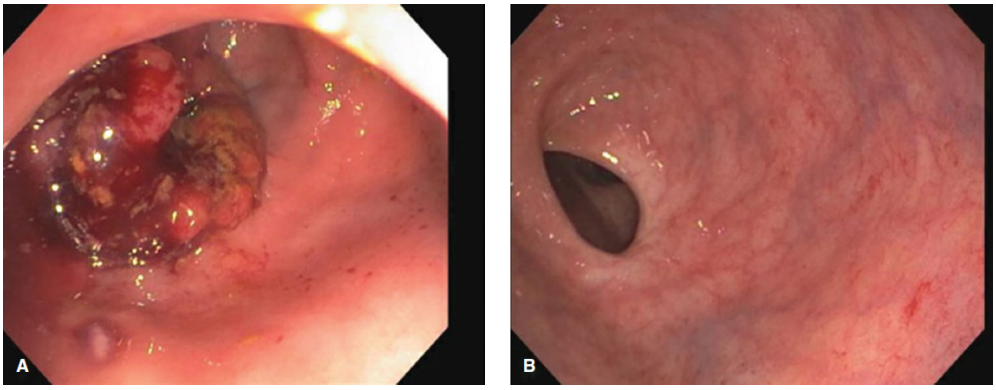


Figure 68.15 Neoadjuvant treatment including chemoradiation and chemotherapy in rectal cancer can lead to a complete response, and selected patients with such response can potentially avoid surgery. This nonoperative management strategy is referred to as the "watch-and-wait" approach. Recent data suggest that watch-and-wait can be a reasonable option in carefully selected and closely followed patients. **A:** Low rectal cancer invading sphincter muscles, proctectomy would require a permanent stoma. **B:** No evidence of tumor regrowth, 3 years after completion of neoadjuvant therapy the patient remains cancer free with a rectum-preserving watch-and-wait approach.

TUMOR-RELATED EMERGENCIES

Between 15% and 30% of all CRC patients present as surgical emergencies, obstruction (78%) being the most common presentation, followed by perforation (10%) and bleeding (4%).[300–302] Chronic bleeding leading to severe anemia is common, particularly in right-sided tumors; but acute hemorrhage requiring surgical or endovascular intervention is infrequent. Obstruction is the presenting symptom in more than 15% of patients diagnosed with CRC, and CRC is responsible for more than 50% of all cases of acute colonic obstruction.[303] Rectal cancers seldom present as an emergency (5.9%); this is much more likely with colon cancers (21.7%), most of which are in the left colon where the feces are solid, the lumen is smaller, and tumors are more likely to be annular.[301] Large-bowel obstruction may be secondary to other conditions such as diverticular disease and volvulus, which are the differential diagnosis of CRC.

The obstructed bowel undergoes significant changes in motility, secretion, and blood flow, which are responsible for the clinical manifestations. Proximal to the obstructed segment, particularly in left-sided obstructions, the colon develops mass action contractions, which cause colic pain. Persistent

obstruction and progressive distension lead to colonic hypomotility. Colonic obstruction causes progressive abdominal distension as a result of the accumulation of gas (mostly nitrogen from swallowed air), increased fluid secretion, and hyperproliferation of anaerobic bacteria. The accumulation of fluid in the distended colon can lead to dehydration. Progressive distension in the presence of a competent ileocecal valve results in a closed-loop obstruction. The increase in intraluminal pressure can compromise the mucosal blood flow and lead to irreversible ischemia. Tension in the wall of the distended bowel increases in proportion to the fourth power of the radius; the risk of ischemia and subsequent perforation is therefore high, particularly in the cecum, the segment of colon with the largest diameter.[304] The risk of perforation is related not only to the caliber of the colon, but also to the onset of obstruction (higher risk when acute) and the duration of the obstruction. Mucosal ischemia has been implicated as the cause of a nonspecific form of colitis that, in some patients, develops proximal to the site of obstruction. The presence of ischemia, which can only be diagnosed at the time of surgery, should influence the extent of resection.

Acute colonic obstruction manifests as abdominal discomfort or frank pain (depending on the onset of the obstruction), reduction or complete cessation of the passage of flatus and feces, and progressive abdominal distension. Abdominal tenderness, particularly if associated with fever and leukocytosis, requires immediate evaluation to exclude perforation or ischemia. DRE reveals an empty rectum in most patients with large-bowel obstruction.

Colonic obstruction must be distinguished from pseudo-obstruction. While the symptoms are similar, colonic pseudo-obstruction often presents in a specific clinical setting (patient immobilization, use of opioids, electrolyte imbalance), is still associated with passage of small amounts of stool and flatus, and is not associated with tenderness.[305] However, definitive diagnosis often requires specific radiologic tests, such as CT or water-soluble contrast enema.

A plain abdominal film demonstrates colonic distension, with air-fluid levels, and a cut-off at the site of obstruction. The absence of small-bowel distension indicates a competent ileocecal valve, with an increased risk of cecal perforation. The presence of gas in the small bowel and rectum raises the possibility of ileus or colonic pseudo-obstruction, but radiologic findings can be misleading. The presence of intramural gas indicates advanced ischemia. A

chest radiograph should always be obtained to exclude the presence of pneumoperitoneum.

A water-soluble contrast enema may help to determine the degree and level of obstruction. The flow of contrast to the cecum and the absence of mucosal abnormalities suggest pseudo-obstruction. The osmotic effect of the water-soluble contrast material may have a therapeutic effect in decompressing the colon in these patients.[306] The mucosal detail at the site of obstruction may help to define the cause of obstruction. However, endoscopy is a better alternative to contrast enema when confirming the presence of cancer. CT of the chest, abdomen, and pelvis often locates the transition point between the distended bowel above the obstruction and the collapsed bowel distal to that point. It also helps define the cause of the obstruction and, if malignant obstruction is confirmed, it is useful in staging the tumor.[307]

When compared with elective surgery, patients requiring emergency surgery tend to have more advanced disease. Even when stratified by stage, however, survival is worse for patients undergoing emergency surgery.[301,308] Also, an R1 or R2 resection is 10 times more likely for patients receiving emergency surgery.[309]

Patients presenting with obstructing CRC have higher operative mortality and morbidity and a poorer long-term prognosis than patients undergoing elective resection.[302,310] Perioperative mortality is three times higher in surgery performed for obstruction, compared with elective surgery.[302] Cardiopulmonary complications and abdominal sepsis are the major causes of in-hospital mortality and morbidity. The aim of surgery is therefore to minimize morbidity while obtaining functional results similar to those obtained for patients undergoing elective resection.

Patients with colonic obstruction are often dehydrated, and require preoperative fluid resuscitation and correction of electrolyte imbalances before surgery. A urinary catheter facilitates fluid management. Unstable patients should be monitored appropriately in the intensive care unit. A nasogastric tube prevents accumulation of swallowed air. Given the large fecal load proximal to the point of obstruction, antibiotic prophylaxis with a second-generation cephalosporin or a combination of an aminoglycoside and metronidazole should be given at the time of surgery.

The surgical management depends on the location of the obstruction. Lesions proximal to the splenic flexure are commonly treated by an extended right hemicolectomy, with primary anastomosis between the terminal ileum and the

nonobstructed colon distal to the lesion. This is a single procedure that removes the entire segment of distended and potentially ischemic bowel, and eliminates the risk of leaving a synchronous tumor in the obstructed colon. Some of these patients develop mild diarrhea, which is usually temporary.

The management of a lesion located distal to the splenic flexure is more controversial. The earlier described three-stage procedure (1—Diverting colostomy, 2—Tumor resection and anastomosis, 3—Colostomy closure) is rarely used today. A safe choice is the two-stage procedure, with initial resection of the segment containing the tumor, closure of the rectal stump as a Hartmann pouch, and construction of an end colostomy, followed by bowel anastomosis at a later date. However, the cumulative mortality and morbidity of both procedures is significant, and at least 30% of patients are left with a permanent colostomy.[311] In most tertiary centers, this operation is now limited to situations in which a primary anastomosis is contraindicated (e.g., extensive peritoneal contamination and/or severe sepsis).

The goal of surgery today is to relieve the obstruction and treat the cancer in a single operative procedure. Options include: (1) self-expanding metallic stents (SEMS) as a bridge to elective segmental colon resection, (2) subtotal colectomy and ileorectal anastomosis, (3) segmental colon resection, intraoperative colonic lavage, and primary anastomosis.

The rationale for the use of SEMS is temporary relief of the obstruction, avoiding the morbidity associated with an emergency operation, allowing medical stabilization, full staging work-up, one-stage surgery with primary anastomosis, and a minimally invasive approach. Most of the experience with this method comes from retrospective case-series studies; the success in relieving the obstruction ranges from 40% to 100%.[312] SEMS also has associated complications, such as reobstruction (12%), migration (11%), and perforation (4.5%).[312]

Several randomized, controlled trials comparing SEMS with emergency surgery have been published, with conflicting results.[313–317] Overall, the clinical success rate of relieving obstruction with SEMS ranges from 40% to 97%. It is important to recognize that the overall complication rate across these trials is variable (8.3% to 35%) and a recent prospective trial conducted in the Netherlands was stopped prematurely, due to an increased number of colonic perforations in the SEMS arm.[317] Perforation from the use of stents may result in a shorter DFS.[318] A Dutch population-based cohort study compared decompressing stoma and SEMS as a bridge to surgery for left-sided

obstructive colon cancer and found no difference in intermediate-term oncologic outcomes and similar complication rate.[319]

A subtotal colectomy with ileorectal anastomosis is a quick operation in which nondistended bowel is used for the anastomosis. This procedure minimizes the risk of fecal spillage, eliminates the risk of missing a synchronous tumor in the obstructed portion of the colon, and facilitates surveillance. The disadvantages, however, include a higher incidence of bowel obstruction after ileorectal anastomosis and the development of postoperative diarrhea, which may become incapacitating in elderly patients.[320]

A segmental resection with intraoperative colonic lavage and primary anastomosis avoids the risk of postoperative diarrhea, but carries a risk of fecal spillage and missing synchronous tumor. In addition, it requires using previously obstructed bowel for the construction of the anastomosis. Surgical tradition has condemned the performance of an anastomosis in an unprepared colon. Experience accumulated from the management of patients with civilian colon trauma has demonstrated that, under specific circumstances, a primary anastomosis can be performed safely in an unprepared colon, provided the bowel appears healthy and there is no extensive soiling in the peritoneal cavity. This experience has been transferred to the treatment of malignant colonic obstruction. Therefore, a segmental resection with colonic lavage and primary anastomosis is a viable option, as long as the colon is not ischemic and there is in no spillage during the operation. The use of a temporary diverting ileostomy may be necessary, but when the safety of a primary anastomosis is questionable, a staged procedure with a segmental resection, a Hartmann pouch, and an end colostomy, may be preferable.[321]

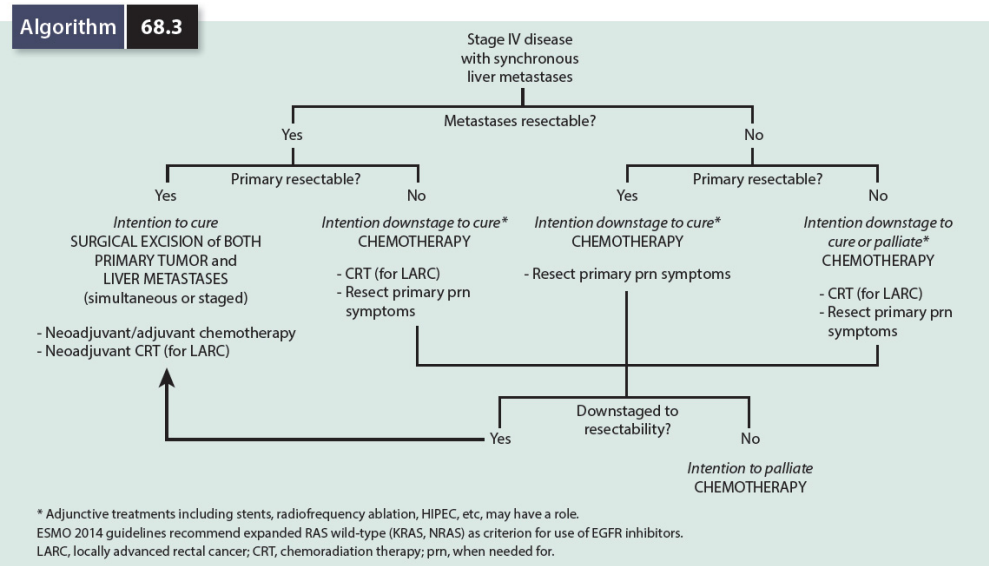
SURVEILLANCE AFTER CURATIVE RESECTION FOR COLON AND RECTAL CANCER

Of the almost 1 million patients diagnosed with CRC worldwide every year, two-thirds have curative intent surgery, but ultimately one-third of them will develop recurrence of disease or a second colorectal primary. Most recurrences arise within 3 years of the initial treatment, and almost all arise within 5 years. Recurrences are usually diagnosed at an advanced stage and

have an ominous prognosis. Surveillance regimens aim to identify recurrences before they become symptomatic, and while they are still potentially resectable.[322,323] Several meta-analyses of prospective, randomized trials comparing intensive or minimal surveillance after curative resection in patients with stage I to III CRC suggest that recurrences were diagnosed earlier and surgical salvage was more likely in patients undergoing intensive surveillance.[324] The survival benefit can only be partly attributed to the improved ability to resect recurrences; other elements such as increased psychological support, behavior modifications, and better treatment of comorbid conditions that accompany intensive surveillance regimens are also thought to contribute to improved survival. Based on this evidence, cancer organizations have established guidelines for surveillance after curative resection of CRC. All of them include a combination of regular history and physical examination, determination of CEA level, endoscopy, and imaging of the chest, abdomen, and pelvis. Some clinicians recommend surveillance for stage II and III diseases, while others also include stage I. In the future, surveillance will be risk adapted, targeting patients more likely to benefit from intensive surveillance based on clinical and molecular prognostic factors. Despite these recommendations, a recent population-based cohort study of 57 patients concluded that 70% were diagnosed between scheduled examinations.[323]

TREATMENT OF STAGE IV COLON AND RECTAL CANCER

Between 20% and 34% of all CRC patients are metastatic at the time of diagnosis; these are known as synchronous metastases. Another one-third of patients will develop metastasis sometime after undergoing treatment of the primary disease; this is known as metachronous metastasis. Synchronous metastases are usually more extensive and, in general, carry a worse prognosis compared to metachronous metastases.



Algorithm 68.3 Stage IV rectal cancer treatment algorithm.

The liver is the most common site of CRC metastasis, and liver metastasis is the most common cause of cancer death in patients with CRC. Autopsy studies have revealed that 50% of patients dying from CRC have liver metastasis and, in one-third of them, the liver is the only site of metastatic disease.[325] Some patients with liver-only metastatic disease are resectable at the time of diagnosis. Others are not resectable, due to the involvement of critical structures by large volume of metastatic disease. The treatment of stage IV CRC patients is complex, and requires consideration of the number of organs involved, the number and size of the metastasis, the location, the symptoms related to the primary in the colon or rectum, whether the tumor is resectable or not, and the patient's performance status. Treatment decisions should be made after discussion in a multidisciplinary tumor board.[326] A simplified algorithm for the treatment of patients with stage IV CRC is presented in **Algorithm 68.3**. The discussion is centered on patients with liver metastases, but these principles are equally applicable to patients with lung metastasis. Surgery is the only curative treatment for patients with colorectal metastases. Other forms of local therapy, such as radiation therapy or ablation, may improve survival. Most patients with metastatic disease benefit from systemic chemotherapy, either as adjuvant treatment to surgery or as the sole form of treatment.

Treatment of the Primary Tumor in Stage IV CRC

In the past, all patients presenting with synchronous metastasis were recommended to have resection of the primary tumor, to avoid complications such as obstruction or perforation during treatment of the metastatic disease. However, recent data suggest that patients with unresectable metastasis and an asymptomatic primary are unlikely to develop complications related to the primary tumor that require surgical intervention while the patient is receiving systemic chemotherapy. Currently, primary tumor resection is recommended for patients undergoing curative-intent resection of all metastatic disease, or for patients with unresectable metastasis and a symptomatic primary tumor. The treatment of patients with unresectable metastasis and an asymptomatic primary tumor is controversial. The benefit of avoiding complications related to tumor progression should be balanced against the mortality and morbidity associated with a noncurative resection, and the delay in starting systemic chemotherapy.

Observational studies and secondary analysis of prospective trials have reported an association between primary tumor resection and improved survival. A recent meta-analysis found a difference of 6.4 months in survival in patients undergoing resection.[327] However, these studies are limited by strong patient selection bias and outdated chemotherapy regimens. Patients undergoing resection are more likely to have liver-only disease, single metastasis, and tumors located in the colon. Rectal cancer patients are less likely to undergo primary tumor resection compared to patients with colon cancer, probably due to the higher complexity of rectal surgery, the possibility of using palliative CRT, and the fear of a colostomy.

Resection of asymptomatic tumors in stage IV disease has not consistently shown improvements in survival, nor does it necessarily reduce the risk of complications.[328] A recent analysis of the SEER database revealed that the proportion of patients with stage IV CRC undergoing primary tumor resection has been progressively decreasing in the last decade.[329] Despite this decrease in primary tumor resection, relative survival has been increasing during the same period of time. The improvement in survival has coincided with the introduction of more effective chemotherapy agents. However, the relative contribution of the declining rate of primary resection and the more active chemotherapeutic agents is unknown. In this SEER data analysis, more than half of patients diagnosed with stage IV CRC in 2009 had resection of the primary tumor, suggesting that current treatment practice lags behind evidence-based treatment guidelines. These data lend support to current guidelines that do not

recommend primary tumor resection in asymptomatic patients with unresectable metastases as noted in consensus guidelines.

Surgical Treatment of Colorectal Metastases

Overall, only 6% of CRC patients with liver metastases survive beyond 5 years, but in patients with resectable liver metastases the reported 5-year survival rate ranges from 25% to 40%. Patients with a single, isolated liver metastasis have 5-year overall survival rates as high as 71%. Liver metastases are considered resectable with curative intent if all disease can be removed with negative resection margin while preserving adequate liver reserve. Incomplete resection or tumor debulking is not recommended because it is associated with morbidity without impacting survival. The size of the metastasis is not a contraindication for surgery. When a curative liver resection may potentially result in insufficient liver remnant, portal vein embolization of the involved liver lobe is recommended to induce hypertrophy of the contralateral lobe of the liver. Repeated resection of recurrent liver metastases is feasible, but the probability of survival decreases with each subsequent resection. Simultaneous liver and colon resection is safe and efficient in a selected group of patients. Overall complication rate and hospital stay are lower as a second laparotomy can be avoided.[331,332]

The role of nonsurgical liver-directed therapy for the treatment of liver-only or liver-dominant metastatic disease is controversial. Tumor ablation is indicated in patients who are amenable to local therapy but are not candidates for surgical resection due to comorbidities. It can also be combined with surgery in patients with mixed resectable and unresectable lesions due to their anatomical location or insufficient liver remnant.[333] Other liver-directed therapies for which there is no consensus regarding efficacy are transarterial hepatic chemoembolization/radioembolization, liver-directed radiation, and hepatic arterial infusion (HAI) therapy. HAI was first developed over 45 years ago and has shown to be appropriate adjuvant treatment for patients with liver-dominant metastatic disease.[334] Patients with liver metastases refractory to all standard lines of chemotherapy may respond to HAI with 5-Fluorodeoxyuridine (5-FUDR).[335] Additionally, selected patients with strictly defined unresectable CRLM can experience enough response after combination treatment with HAI and systemic therapy to become resectable.[336]

Colorectal lung metastases can also be surgically removed following the same principles outlined for liver metastasis. Resection must be complete, based on the anatomic location of the disease, and with maintenance of adequate respiratory function. Resection of both liver and lung metastases is feasible in selected cases, but resection in the presence of nonhepatic extrapulmonary disease should be reserved for carefully selected patients. Ablation and radiation are also options for patients with nonresectable lung metastases as noted in consensus guidelines.

Chemotherapy for Metastatic Disease

Principles of Chemotherapy

A number of antineoplastic agents such as 5-FU or capecitabine, oxaliplatin, and irinotecan, and new biologic agents, such as bevacizumab, ziv-aflibercept, cetuximab, panitumumab, and regorafenib, are currently used in combination or as single agents in patients with metastatic CRC. The putative mechanism of action and the toxicity profile of each drug are presented in **Table 68.8**. The choice of the treatment regimen is based on the goals of therapy, the type and time of previous therapy, and the toxicity profile of the constituent drugs as noted in consensus guidelines. The chemotherapy regimens commonly used as first-line therapy in patients appropriate for intensive therapy include: FOLFOX (5-FU/LV/oxaliplatin), FOLFIRI (5-FU/LV/irinotecan), CapeOx (capecitabine/oxaliplatin), infusional 5-FU/LV, capecitabine as a single agent, or FOLFIRINOX (5-FU/LV/oxaliplatin/irinotecan). Cetuximab or bevacizumab can be added to first-line therapy in patients with KRAS/NRAS wild-type CRC, and other combinations such as FOLFOXIRI with bevacizumab have shown promising results.[337,338] The role of maintenance therapy after first-line therapy, and treatment after progression of metastatic disease on first-line therapy, is beyond the scope of this chapter. Median survival of patients with unresectable metastatic CRC, which 6 previously rarely exceeded 12 months, now exceeds 30 months when these agents are used. Increasing evidence suggests that the selection of chemotherapeutic agents will continue to be guided by molecular and genomic characterizations. Early reports have indicated that combined therapy with BRAF and EGFR inhibitors may be effective in treating BRAF V600E metastatic CRC specifically.[339]

Adjuvant Chemotherapy in Resectable Disease

The majority of patients who undergo resection for CRC liver metastasis ultimately relapse in the liver. It is theorized that the addition of systemic therapy provides treatment of occult micrometastatic disease, reducing the risk of relapse. A number of randomized controlled trials have found a modest improvement in RFS, but not in OS, with chemotherapy delivered before or after liver resection, compared with resection alone. The optimal timing of chemotherapy remains unknown.[340] The potential advantages of preoperative therapy include earlier treatment of micrometastatic disease, evaluation of tumor responsiveness, and the possibility of avoiding resection in patients with tumor progression during therapy. The main disadvantages of preoperative chemotherapy are the progression of nonresponsive tumors that become unresectable during systemic chemotherapy, and the increase in perioperative morbidity due to chemotherapy-induced liver toxicity. The EORTC Intergroup Trial—the only randomized trial evaluating the role of perioperative FOLFOX (3 months before and 3 months after liver surgery) in the management of resectable liver metastases—demonstrated an absolute increase of 7.3% in 3-year progression-free survival in the combined treatment group, compared with the resection-alone group.[341,342] This trial demonstrated an increased rate of postoperative complications in the chemotherapy group (25%) compared with surgery alone (16%), specifically showing a doubling in biliary fistula and hepatic failure rates. The study concluded that perioperative chemotherapy may improve cancer-specific outcomes, but at the cost of increased rates of postoperative complications, including liver dysfunction. Long-term follow-up has revealed the same benefit in progression-free survival, but no difference in OS with the addition of perioperative chemotherapy. The chemotherapy regimens used in the adjuvant setting are the same as those used in first-line therapy. However, bevacizumab can be added as long as it is discontinued at least 6 to 8 weeks before surgery and not restarted for 8 weeks after surgery, because it interferes with wound healing.[343] Cetuximab and panitumumab have been added to first-line regimens in patients with KRAS/NRAS wild type, but the benefits have been inconsistent. In fact, recent data suggest these could even be detrimental; therefore, they are not recommended at this time.[344]

Table 68.8 Main Chemotherapeutic Agents

Agents	Mechanism	Common Side Effects
5-FU	Pyrimidine analog, thymidylate synthase (TS) inhibitor	Hematologic: thrombocytopenia. GI: mucositis. Hepatic steatosis (yellow liver). Photosensitivity
Folinic acid (leucovorin)	Enhances 5-FU effects and contributes to TS inhibition	—
Irinotecan	Topoisomerase I inhibitor	Hematologic: myelosuppression. GI: diarrhea. Hepatic steatosis
Capecitabine	Pro-drug of 5-FU	GI: mucositis
Oxaliplatin	Platinum-based agent, DNA cross-linking	Peripheral neuropathy GI: sinusoidal congestion (blue liver)
Cetuximab/Panitumumab	Anti-EGFR monoclonal antibody (for use with KRAS wild-type tumors only)	Acneiform skin rash
Bevacizumab	Anti-VEGF monoclonal antibody	Compromised wound healing

Chemotherapy in Borderline Resectable Disease

A few patients present with liver-only metastases that are not amenable to a complete resection, due to close proximity to essential anatomical structures.

Systemic chemotherapy in this setting aims to convert an unresectable patient to resectable status. The duration of treatment in these patients is important. There is a need to balance the minimum time required to achieve a response that will make the patient resectable, while avoiding hepatotoxicity from the chemotherapeutic agents. Both FOLFOX and FOLFIRI increase resectability in 12.5% to 40% of patients initially considered unresectable. A study has shown that adding irinotecan to FOLFOX (FOLFIRINOX) in patients with initially unresectable metastasis increased the resection rate compared to FOLFOX alone.[345] Adding EGFR inhibitors to FOLFOX or FOLFIRI increased the resectability rate in patients with wild-type KRAS/NRAS tumors and initially unresectable liver metastasis.[346,347] Angiogenesis inhibitors combined with FOLFIRI modestly increase resectability of initially unresectable liver metastasis compared to FOLFIRI alone, but have no effect when combined with oxaliplatin-containing regimens.[348,349] To limit FOLFOX- and FOLFIRI-associated toxicity, patients receiving systemic chemotherapy to increase resectability should be evaluated for response every 2 months, and undergo surgery as soon as they become resectable.

Treatment of Peritoneal Carcinomatosis

Most patients with peritoneal carcinomatosis have widespread metastatic disease and are treated with systemic chemotherapy. The treatment of patients with the peritoneum as the only site of metastasis is controversial.[350,351] Complete cytoreductive surgery (CRS), with removal of all visible abdominal and pelvic disease, and hyperthermic intraperitoneal chemotherapy (HIPEC) are now commonly used in patients with peritoneum-only metastatic CRC. The most commonly used drug for intraperitoneal chemotherapy is mitomycin C, which is minimally active against CRC. As experimental data do not support any biologic benefit from the hyperthermia component, the role of HIPEC has been questioned. Oxaliplatin, irinotecan, doxorubicin, paclitaxel, and carboplatin have also been tested. Comparative studies have not shown a conclusive advantage of mitomycin C over oxaliplatin.[352] This aggressive treatment is associated with significant mortality (0.9% to 5%) and morbidity (12% to 52%), with the most common complications being SSI, hematologic toxicity, and intestinal fistula. Many single-institution case series have reported improved survival in patients treated with CRS and HIPEC followed by systemic chemotherapy, compared to systemic chemotherapy alone. A recent

review of 19 studies conducted from 1999 to 2009 reported a median survival of 33 months for patients treated with CRS and HIPEC versus 12.5 months for patients undergoing palliative surgery and/or systemic chemotherapy.[353] These studies have been criticized because of strong patient selection bias favoring peritoneum-only disease in the CRS/HIPEC group, an undefined role for palliative treatment, and suboptimal chemotherapy in the nonsurgical group. The only prospective trial published so far randomized patients to 5-FU/LV with palliative surgery versus CRS, HIPEC, and postoperative 5-FU/LV. OS was 12.6 months in the standard arm versus 22.2 months in the HIPEC group.[354] This study has been criticized because it also included patients with pseudomyxoma peritonei of appendiceal origin, and because it was conducted before most of the drugs currently used in metastatic disease were available. In the French PRODIGE-7 randomized trial, CRS-HIPEC showed no overall survival benefit over CRS alone and suggests that HIPEC should be abandoned in patients with resectable peritoneal carcinomatosis.[355] However, this study has been criticized because of its small sample size and for using oxaliplatin as a HIPEC regimen. In spite of this criticism, CRS and HIPEC are commonly performed regimens for patients with peritoneum-only colorectal metastases.[356]

The selection criteria for this complex and potentially morbid treatment are not well defined. The most important prognostic factors in patients undergoing CRS and HIPEC are the Peritoneal Cancer Index (PCI), a grading of tumor burden at the time of surgery, and the completeness of cytoreduction (CC) score. Unfortunately, the determinants of these scores are only available at the time of abdominal exploration during surgery. Therefore, they have not been useful in selecting those patients more likely to benefit from CRS and HIPEC. Recently, a Peritoneal Surface Disease Severity Score (PSDSS) that includes patient symptoms, extent of peritoneal dissemination, and primary tumor histology has been developed to stratify patients at the time of diagnosis, without the need of an operation.[357] The PSDSS score system has been found to be an independent prognostic factor in multivariate analysis, not only for patients undergoing CRS and HIPEC, but also for patients treated with systemic chemotherapy. This score may help eliminate selection bias in future comparisons of different treatments, in patients with peritoneum-only metastatic CRC.

Immunotherapy for CRC

In the last few years immune checkpoint inhibition—targeting inhibitory signal that tumors use to scape immune recognition—has become new treatment modality for MMRd/MSI-H metastatic CRC.[358] Antibodies targeting PD1 (Pembrolizumab, Nivolumab), PDL1 (Atezolizumab), and CTL4 (Ipilimumab) are now used in clinical practice in patients with metastatic disease and are being tested in the adjuvant setting for nonmetastatic MMRd/MSI-H colon and rectal cancers, alone or in combination with other chemotherapy agents and radiation therapy.[177,359–363] While highly effective in achieving durable responses, immune checkpoint inhibition is also associated with specific toxicity such as diarrhea and colitis, skin rashes, elevation of liver enzymes and fatigue.

TREATMENT OF LOCALLY RECURRENT CRC

LR after curative-intent surgery is defined as a relapse of tumor in the surgical field of the initial procedure, including the anastomosis, regional nodes, surgical scars, and drain tracts.[361] While most patients with LR also have distant metastasis, a few have isolated LR. A complete surgical resection is the only curative option for patients with isolated locally recurrent CRC, but is associated with considerable morbidity and mortality.[364]

The risk of LR is higher for rectal cancer compared to colon cancer, for advanced stage tumors (T4), for tumors with high-risk histologic features (lymphovascular and perineural invasion, grade III or IV, signet ring cell histology), perforating or obstructing tumors, and patients with close or involved CRM. Most local recurrences present within 3 years after the primary surgery, but LR tends to occur later in patients treated with CRT and surgery, compared to those treated with surgery alone. In the Dutch TME trial, 10% of LRs occurred more than 3 years after surgery in patients treated with TME, versus 31% in patients treated with preoperative RT and TME.[365]

While some LRs are detected though surveillance, while asymptomatic, most are diagnosed after they become symptomatic. Symptoms of local recurrence include bowel obstruction, abdominal distension, rectal or vaginal bleeding, and urinary problems.[366] Pelvic pain is common, and is a predictor of reduced long-term survival.[367] A common manifestation of recurrence in patients who have had abdominoperineal resection (APR) is a nonhealing perineal wound. Whenever symptoms suggestive of recurrence arise, a detailed history and

complete physical examination must be done. This includes DRE in patients who have undergone sphincter-preserving surgery, and a pelvic examination in females. If recurrent tumor is identified, endoscopy and imaging studies will help assess extent of disease and surgical risk. A complete colonoscopy should be performed if possible. Intraluminal recurrences are easily diagnosed with endoscopy and biopsy. Cystoscopy is required for patients who present with urogenital symptoms, as these strongly indicate tumoral invasion of the ureters and bladder.[368] CEA is routinely measured during follow-up surveillance after primary rectal cancer resection. Elevation of this tumor marker is frequently the first sign of recurrence.[369] However, elevated CEA is present in only about 50% of patients. Patients with elevated CEA should undergo further work-up with imaging studies.

A CT scan of the chest, abdomen, and pelvis is the primary imaging modality used in these patients, and it is especially helpful in identifying metastases in the liver, lung, and peritoneum, and evaluating regional adenopathy.[370] MRI is more accurate than CT in detecting and staging pelvic LR[371]; although it has been ineffective when added to routine follow-up, ERUS may be useful in diagnosing LR after LE of distal rectal cancer.[372] Positron emission tomography (PET) using the glucose analog fluorodeoxyglucose (FDG), particularly when combined with a CT scan, is helpful in distinguishing between postsurgical changes and tumor recurrence. In a recent meta-analysis comparing FDG-PET, FDG-PET/CT, CT, and MRI in the detection of recurrent CRC in patients with high suspicion of recurrent disease, based on symptoms or elevated CEA, FDG-PET and FDG-PET/CT performed more accurately than CT scan.[373] PET/CT also demonstrated greater accuracy than MRI in identification of lymph node recurrence in a lesion levels analysis.[374] Overall accuracy of FDG-PET/CT is slightly higher than FDG-PET: 92.3% (94% sensitivity, 77.2% specificity) versus 89% (90.3% sensitivity, 80% specificity).[375] However, lesions measuring less than 1 cm in diameter are more difficult to detect with PET scanning, as are mucinous tumors, due to poor FDG uptake. Finally, FDG-PET cannot be used to detect or evaluate LR if there is residual inflammation of the tumor bed secondary to chronic leaks. Regardless of the imaging studies used to help diagnose LR, histologic confirmation is imperative. Anastomotic recurrences should be biopsied endoscopically; extraluminal recurrences can usually be biopsied percutaneously, under radiologic (CT) guidance.

The treatment of locally recurrent CRC should be discussed in a multidisciplinary setting, since it often involves colorectal surgical

oncologists, radiation oncologists, medical oncologists, and other specialists. Patients with multifocal LR should be treated with systemic chemotherapy, as in metastatic disease. Only patients with localized LR and good performance status are candidates for surgical resection. Even these patients may benefit from additional systemic chemotherapy or chemoradiation, if they did not receive it at the time of treatment of the primary tumor.[376] Some patients with recurrent rectal cancer treated initially with standard doses of radiation (50.4 Gy in 180 cGy fractions, or biologically equivalent total dose) can be reirradiated to the gross tumor volume using small fractions (180 to 200 cGy), with or without sensitizing chemotherapy.[376] Reirradiation seems to increase the possibility of an R0 resection in patients with resectable disease, or provides good palliation in unresectable patients. Following preoperative chemotherapy and/or radiotherapy, restaging should be done to exclude interim development of distant metastasis and to ascertain the extent of the LR.

Surgery is the only curative option for patients with locally recurrent rectal cancer. Without treatment, median survival is typically 6 to 7 months[377]; systemic chemotherapy can prolong survival, similar to patients with systemic recurrence. Only patients with good performance status, with recurrences that, based on anatomical location, are amenable to an R0 resection, should be considered surgical candidates. A resection with gross positive margins (R2) should not be attempted, because it provides no oncologic advantage to the patient and is associated with significant morbidity. Patients found to have microscopic positive margins (R1) may benefit from intraoperative radiation. However, this modality is only available at some institutions, and requires preoperative planning. Therefore, the treatment of locally recurrent CRC should be limited to institutions with appropriate expertise and equipment.

Only about one-third of patients with isolated locally recurrent CRC are candidates for surgical salvage with curative intent. In the Intergroup Study 0114, which investigated several chemotherapy regimens in patients with locally advanced rectal cancer, only 159 (35%) of the 448 patients with single-site first recurrences in the liver, lung, or pelvis had curative-intent surgery.[366] The proportion of patients undergoing resection was similar for liver, lung, or local recurrences. OS differed significantly between the resected and nonresected groups, with 5-year OS of 27% and 6%, respectively ($p < 0.001$). The 5-year DFS was in the range of 30% for patients undergoing resection of tumors in solitary sites of the liver or lung, and 20% for those undergoing resection of LRs. Retrospective case series from institutions with experience in

the treatment of locally recurrent CRC report 5-year survival rates close to 35% for patients with R0 resections, compared to 21% for patients with R1 resections.

Palliation is an important aspect of the treatment of patients with unresectable LR. Bowel obstruction often requires palliative surgery, stomas, endoluminal stents, or percutaneous gastrostomy tubes. Urinary obstruction is common, requiring stents or percutaneous nephrostomies. Pain is a common symptom in these patients, often requiring the assistance of pain specialists and specialists in palliative care. Carefully selected rectal cancer patients who are unable to or unwilling to undergo palliative resection due to extensive comorbidity, can be treated with aggressive palliative radiation.[378]

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69

Diverticular Disease

Lillias H. Maguire

Key Points

1. Although a minority of patients become symptomatic, the high prevalence of diverticulosis leads to a large and increasing burden of disease including diverticulitis, perforation, stenosis, fistula, and hemorrhage.
2. The prevalence of diverticulosis varies greatly across global populations. It is ubiquitous in older adults in North America and Europe.
3. The etiology of diverticulitis is incompletely understood, but includes both inherent and environmental risk factors.
4. Diverticulitis can be effectively diagnosed and its severity classified with cross-sectional imaging.
5. Acute uncomplicated diverticulitis may often be treated in the outpatient settings. Antibiotics may be omitted.
6. Acute complicated diverticulitis may be successfully treated with percutaneous abscess drainage or require urgent laparotomy and colectomy depending on disease severity.
7. Clinical guidelines for treatment of diverticulitis have changed meaningfully over a relatively short period of time reflecting improved understanding of the natural history of the disease.
8. The decision to operate electively for secondary prevention of diverticulitis should be individualized based on patient and disease-specific factors.

INTRODUCTION

Diverticular disease is one of the most common colorectal conditions evaluated and treated in the United States. The precursor 1 lesion, diverticulosis, is ubiquitous and its most common resultant pathology, diverticulitis, causes millions of outpatient visits, tens of thousands of surgeries, and results in billions of dollars in expense every year. Patient

presentations vary, including mild, self-limited disease, life-threatening abdominal sepsis, chronic complications, and recurrent disease. Recently, improved understanding of diverticulitis has meaningfully changed clinical guidelines over a short period of time. Traditional dogmas have fallen under increased scientific scrutiny. Today, diverticulitis patients may avoid antibiotics, are less likely to require inpatient admission or emergency surgery, less likely to undergo elective colectomy, and more likely to have percutaneous procedures and minimally invasive surgery. However, despite this progress, fundamental questions and clear opportunities for discovery remain.

TERMINOLOGY AND ANATOMY

Diverticulosis coli describes the presence of colonic pseudodiverticula, discrete sacs of mucosa and submucosa penetrating through the muscular layers of the colon wall (**Fig. 69.1**). Diverticula herniate through colonic circular muscle adjacent to penetrating mesenteric vessels, emerging between the tenia coli on the antimesenteric aspect of the colon.[1] With rare exception, diverticulosis is an acquired condition of adults that increases in frequency with advancing age.[2] Incidental diagnosis of this asymptomatic lesion can be made at the time of colonoscopy (**Fig. 69.2**), barium enema, or cross-sectional imaging. In Europe and North America, diverticulosis is most prominent in the sigmoid colon, effected in 95% of patients with diverticulosis.[3] Isolated sigmoid diverticulosis is present in 60% of cases and the pattern of involvement progresses proximally. Total colonic diverticulosis is present in up to 10% of cases. Much less common than colonic diverticulosis, small bowel and rectal diverticula are not included in this text.

The term "diverticular disease" encompasses pathology due to diverticula. The two most common diverticular diseases are diverticular hemorrhage and diverticulitis (inflammation of the diverticula) and its many sequelae. Two less common manifestations include segmental colitis associated with diverticulosis (SCAD) and symptomatic uncomplicated diverticular disease (SUDD). These entities have clinical overlap with inflammatory bowel disease (IBD) and irritable bowel syndrome, respectively.[4,5] Diagnosis is

controversial and the role of surgery even more so. For the purposes of this chapter they will not be considered further.

EPIDEMIOLOGY

North America and Europe

2 Diverticulosis is ubiquitous in older adults in Western Europe and North America. Endoscopic studies indicate that >50% of individuals over age 60 have diverticula.[3] Incidence increases with age, demonstrates a male predominance under age 60 and a female predominance thereafter.[6] Although only 4% of patients with incidentally discovered diverticulosis develop diverticular disease,[2] the high prevalence of diverticulosis leads to a substantial burden of disease. Nearly 200,000 inpatient admissions, 340,000 emergency room visits, and 1.9 million clinic visits a year are attributed to diverticulitis, resulting in billions of dollars in expense.[7] Diverticulitis is considered a disease of older adults in industrialized societies, but even within the modern era incidence continues to increase rapidly, particularly among young adults; between 1980 and 2007, diverticulitis increased 132% in Americans under age 50.[6] Within the United States, hospitalization for diverticulitis is more common in Northern latitudes and in urban areas.[8] Incidence is highest in the white population (62/100,000), lower in blacks and Hispanics (32/100,000), and lowest among Asians (10/100,000).[9]

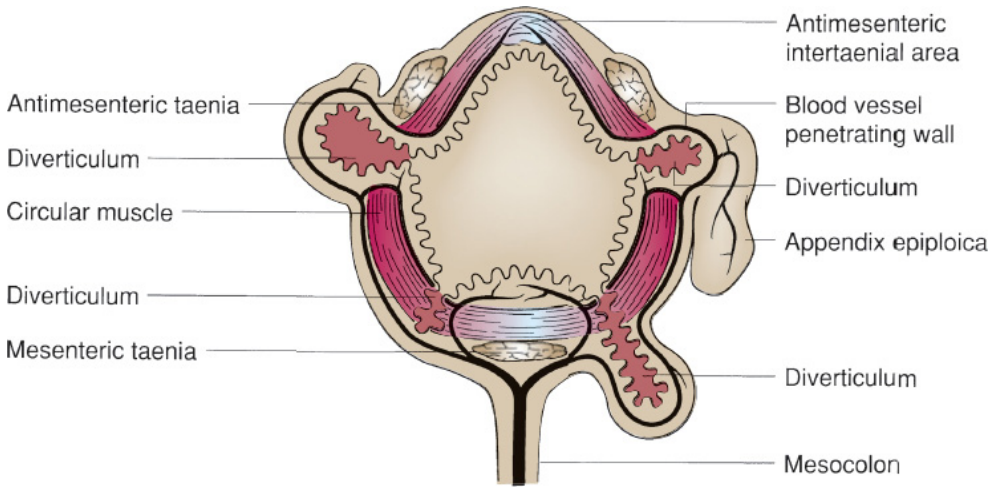

Figure 69.1 Cross section of the colon illustrating the relation of diverticula to the blood vessels penetrating the circular muscle layer, the taeniae, and the appendices epiploicae.

Africa

The observed low incidence of diverticular disease in Africa in the 1960s led to lasting etiologic theories.[10] In Sub-Saharan Africa, lack of routine screening endoscopy makes the true rate of asymptomatic diverticulosis impossible to know. However, in small endoscopic series of patients with hematochezia, presumably enriched for pathology, incidence of colonic diverticulosis is <5%.[11] Despite this low incidence, diverticular disease is reported with increasing frequency in some African hospitals.[12]

Asia

Incidence of diverticulosis in Asia is lower than in Europe and the United States. Reported incidence ranges from <5% in mainland China,[13] 12% to 14% in Korea and Taiwan,[14,15] 28% in Thailand,[16] and 32% in older adults in India.[17] Diverticulosis in Asia is anatomically distinct. Unlike European-ancestry populations, diverticulosis in Asians is right sided in up to 80% of cases.[13] The reason for this anatomic variation is unknown.

ETIOLOGY

3 The causes of diverticulosis and the triggers that produce diverticulitis are incompletely understood, but compelling associations between inherent and environmental risk factors have been observed (**Table 69.1**). The ubiquity of diverticulosis, difficulty in separating diverticulosis-risk from diverticulitis-risk, and the lack of model organisms are challenges for testing the causal relationships of these observations.

Figure 69.2 Endoscopic image of diverticulosis coli. Multiple diverticula are visible without evidence of inflammation of bleeding.

Inherent Risk Factors: Genetic Background

Traditionally considered a purely environmental condition, recent evidence indicates that an individual's genetic background also influences the development of diverticular disease. Two twin studies performed in Scandinavian populations identified increased disease concordance between monozygotic twins as compared to dizygotic twins and siblings. These

studies estimated that 40% to 53% of individual risk for diverticular disease is due to heritable factors.[18,19] Disease concordance was higher for more severe disease. Additionally, family history has been recognized as an independent risk factors for recurrence and complications.[20] Three recent genome-wide association studies[21–23] performed in European-ancestry populations have begun to define the genetic architecture of the disease, identifying associations with genes with known roles in immunity, connective tissue, and intestinal motility, among others. These data suggest that like most common diseases, diverticulitis is a complex trait with both environmental and genetic risk factors.

Table 69.1 Inherent and Environmental Risk Factors Associated with Diverticular Disease

Risk Factors Associated with Diverticular Disease	
Inherent	**Environmental**
▪ Age ▪ Sex ▪ Genetic background *Family history, ethnicity* ▪ Mendelian syndromes *Ehler–Danlos syndrome, Marfan syndrome, polycystic kidney disease, Williams syndrome* ▪ Acquired connective tissue disorders *Aneurysm, rectal prolapse, hernia, senescent collagen cross-linking* ▪ Altered colonic motility	▪ Geography *Country of birth, country of residence, Northern latitude, urban environment* ▪ Diet *Low fiber, high red meat intake* ▪ Lifestyle factors *Obesity, smoking, low physical activity* ▪ Microbiome ▪ Other *Medication use, UV light exposure, vitamin D*

Inherent Risk Factors: Changes in Colonic Structure and Function

The acquired, age-related nature of diverticulosis has led to the theory that connective tissue generation is involved in its pathophysiology. Observed associations with rare connective tissue disorders such as Ehlers–Danlos syndrome, Marfan syndrome, and Williams syndrome support this theory,[24,25] as does the association of diverticular disease with more common acquired connective tissue traits such as hernia, rectal prolapse, and aneurysm.[26] At the histologic level, natural connective tissue senescence is increased in patients with diverticulosis, as noted by cross-linking of collagen fibrils.[27] Increased elastin deposition is observed in the tenia coli, leading to the thick walls and foreshortened haustral folds frequently appreciated in diverticulitis patients.[28]

The Western predominance of diverticulosis in the relatively narrow noncompliant sigmoid colon led to the theory of diverticula being secondary to increased intraluminal pressure. Motility studies have overall demonstrated increased contractility in patients with diverticulosis compared to controls.[29] Histopathologic studies comparing patients with diverticular disease to controls have noted alterations in enteric and somatic innervation and disruption of signaling molecules including serotonin, vasoactive intestinal peptide, and acetyl choline,[30,31] but it is unknown if these alterations are causal, correlated, or reactive to the disease state.

Environmental Risk Factors: Diet and Lifestyle

Multiple modifiable lifestyle risk factors have been associated with diverticular disease. Dietary fiber was first identified in the 1960s. Working in Uganda, Painter and Burkitt observed the high-fiber diets and low disease prevalence among Africans compared to their British counterparts.[32] Modern work confirms that prudent diets low in red meat and high in vegetable and whole grain intake are associated with significantly lower risk of incident diverticulitis.[33] Obesity, smoking, and low physical activity are associated with incident diverticulitis.[15,34,35] Assuming these associations are causal, widespread adoption of a healthy lifestyle including <4 servings of red meat a week, 23 g of daily fiber, vigorous physical activity, body mass index <25, and abstaining from smoking could prevent 50% of diverticulitis cases.[36]

Other associations including vitamin D level, UV light exposure, seasonality, medication use, and others have been observed, but whether these relationships are causal or correlative is unknown.

Environmental Risk Factors: Microbiome

Multiple lines of reasoning suggest a role for the microbiome in diverticular disease. The colonic microbiome may link diet and disease through the bacteria that process dietary fiber into the short chain fatty acids (SCFAs) critical for intestinal epithelial proliferation and barrier function.[37] Western diet is associated with both decreased diversity of the gut microbiome and diverticular disease. However, the data are to date less compelling than the theory. Studies of the microbiome in diverticulitis have been limited to date by clinical reluctance to perform colonoscopy (and harvest samples) during acute diverticulitis, pretreatment with antibiotics, and a preponderance of studies in the controversial clinical entity SUDD. Despite these limitations, changes in the microbiome have been observed in patients with a history of diverticulitis, but it is unknown whether these changes predate or follow diverticulitis.[38,39] Nonetheless, the microbiome remains a compelling area of diverticulitis research.

ACUTE DIVERTICULITIS

Presentation and Differential Diagnosis

Acute diverticulitis presents with local inflammatory symptoms and systemic septic physiology depending on the severity of disease. 4 The modified Hinchey classification (**Table 69.2**) provides ordinal categorization to the severity of acute inflammatory diverticulitis correlated with associated CT findings.[40,41] Initial treatment strategy is guided by Hinchey stage. Stage 0–I disease typically presents with local inflammatory symptoms and signs alone. Patients complain of left lower quadrant pain, fever, altered bowel habit, malaise, and may have nausea and vomiting or urinary symptoms. Duration of symptoms on presentation is typically 12 to 48 hours. When taking a history, patients should be asked about prior surgeries and

endoscopies, family history of colorectal cancer, bowel habit, and continence. Review of systems should ascertain the presence or absence of fecaluria, pneumaturia, frequent urinary tract infections, foul vaginal discharge, and stool per vagina which suggest the presence of a fistula.

Table 69.2 Modified Hinchey Classification, Expected CT Imaging Findings, and Likely Initial Treatment Strategy for Increasingly Severe Presentations of Diverticulitis

Modified Hinchey Classification	CT Findings	Initial Treatment
0 Mild clinical diverticulitis	Diverticuli, colonic wall thickening	Supportive care or antibiotic treatment
Ia Pericolic inflammation	Diverticuli, wall thickening, pericolic soft tissue changes, small extraluminal gas locules	Supportive care or antibiotic treatment
Ib Pericolic or mesocolic abscess	Ia Changes with local fluid collection(s)	<3 cm abscess—antibiotics >3 cm abscess—antibiotics and percutaneous drainage
II Pelvic, retroperitoneal, distant abscess	Ia Changes with remote fluid collection(s)	<3 cm abscess—antibiotics >3 cm abscess—antibiotics and percutaneous drainage
III Purulent peritonitis	Pneumoperitoneum, ascites, peritoneal thickening, possible extravasation of oral contrast	Operative exploration, antibiotics, potential need for critical care
IV Feculent peritonitis	Same as III	Same as III

Modified from Klarenbeek BR, de Korte N, van der Peet DL, et al. Review of current classifications for diverticular disease and a translation into clinical practice. *Int J Colorectal Dis* 2012;27(2):207–

History should also seek evidence of other etiologies. Profuse diarrhea and history of travel, sick contacts, or suggestive food exposures should prompt consideration and evaluation of gastroenteritis. Chronic abdominal pain, weight loss, subacute change in bowel habit, and history of melena or hematochezia are not typical of acute diverticulitis and should arouse suspicion for an alternative diagnosis such as IBD or colorectal cancer. Because diverticular hemorrhage is typically painless, acute diverticulitis with hematochezia is unusual. Other causes such as IBD, malignancy, or ischemic colitis should be suspected and interrogated with sigmoidoscopy in this setting.

Physical examination in stage 0–II disease reveals focal tenderness or local peritonitis in the left lower quadrant. Rectal examination may demonstrate pelvic tenderness. Fever may be present but hypotension, tachycardia, and signs of septic physiology are typically absent. At these stages, differential diagnosis includes colitis, constipation, and genitourinary pathology. Stage III and stage IV diverticulitis presents with peritonitis and attendant septic physiology, which may range from fever and tachycardia to septic shock with multiple organ failure. Patients demonstrate diffuse peritonitis on examination. Differential diagnosis at this stage includes pancreatitis, perforated peptic ulcer disease, perforated appendicitis, perforated colon cancer, acute ischemic colitis, and flare of IBD among others.

Diagnosis

Standard laboratory investigations of abdominal pain including complete blood count, basic serum chemistries, amylase, lipase, pregnancy testing, and urinalysis should be performed. Nonspecific inflammatory markers including C-reactive protein (CRP), fecal calprotectin, and procalcitonin are frequently elevated in diverticulitis, more so in severe disease. Studies have demonstrated the potential of these tests to discriminate between complicated and uncomplicated diverticulitis,[42–44] but this has yet to be incorporated into routine diagnostic algorithms.

CT scan is the most common and useful radiologic test for acute diverticulitis. Ideally performed with intravenous and oral contrast, CT sensitivity and specificity for diverticulitis are greater than 95% even without contrast media.[45] CT scan findings can be used to stratify patients into Hinchey stages and exclude mimicking pathology. Typical findings in stage 0–I disease include the presence of diverticula, colonic wall thickening, pericolic inflammatory changes and abscesses, and even small pericolic locules of gas consistent with "microperforation." Stage II disease includes the same findings with the addition of pelvic or remote abscesses and stages III and IV are marked by free air, free fluid, peritoneal thickening, and potentially extravasation of enteric contrast. Aside from confirming and categorizing the diagnosis of diverticulitis, CT scan has other uses. CT evaluation of diverticular abscesses can predict the likelihood of antibiotic failure based on size and location, guide percutaneous abscess drainage, and predict recurrent abscess formation. Air in the bladder or vagina may suggest an occult fistula. For the surgeon, CT scan can also be useful for operative planning in evaluating the degree of inflammation, particularly adjacent to pelvic sidewall structures, and gauging the colon redundancy and height of the splenic flexure. However, a notable limitation of CT scan is its inability to distinguish inflammatory from malignant pathology. In patients who cannot undergo CT, MRI is similarly useful. In the setting of peritonitis, abdominal x-ray demonstrating pneumoperitoneum may appropriately prompt operative exploration without further diagnostic testing. Endoscopy is not a routine component of the acute diagnostic algorithm but should be used judiciously when other diagnoses, such as malignancy, IBD, and ischemia are seriously considered.

TREATMENT

Acute Uncomplicated Diverticulitis

Although less formal than the Hinchey classification, uncomplicated diverticulitis refers to inflammation limited to the colon and pericolic tissues without pelvic abscess or peritonitis. Traditional treatments of acute diverticulitis are inpatient admission, bowel rest, and antibiotics, but all of

these therapies lack an evidence base and have come under scrutiny. It is clear that patients with uncomplicated diverticulitis can be managed as outpatients with a failure rate <5%.[6] Acceptance of outpatient treatment is clear from national trends. Between 2006 and 2013, rates of hospital admission after emergency room 5 visits for diverticulitis fell from 58% to 46%.[46] Outpatient treatment is most prudently applied to otherwise healthy, reliable individuals with relatively mild local symptoms and no systemic systems.

Antibiotics have long been standard of care medical therapy for acute diverticulitis. However, randomized controlled trials and systematic reviews have failed to demonstrate a benefit. The Swedish AVOD trial randomized 623 patients to inpatient antibiotics or inpatient IV hydration alone. Short-term follow-up revealed no differences in complications, recurrence, or time to recovery. At a median follow-up of 11 years, the two groups remained equivalent in terms of recurrence and GI-specific quality of life.[47] The Dutch DIABOLO trial is more relevant to current clinical management. Participants with first episode, uncomplicated sigmoid diverticulitis were randomized to 10 days of outpatient antibiotics or observation alone. Time to recovery was equivalent between groups and no differences in recurrence or complications were observed, other than an 8% rate of antibiotic-related adverse events.[48] Systematic reviews of these and other studies have supported the findings. In 2020, the American Society of Colon and Rectal Surgeons incorporated these data into its clinical practice guidelines, including omission of antibiotics as a strong treatment recommendation in otherwise healthy patients with early diverticulitis.[49]

Following resolution of a first episode of diverticulitis, 10% to 30% of patients will recur.[2] Physicians commonly recommend adoption of lifestyle modifications associated with reduced incident diverticulitis: weight loss, high fiber diet, and smoking cessation, although it is unknown if these measures prevent recurrence. It is unclear whether patients with uncomplicated diverticulitis harbor increased risk for occult colorectal neoplasia, but colonoscopy is generally recommended[49] after resolution of a first episode and should be strongly considered if CT imaging demonstrates lymphadenopathy or colonic wall “shouldering,” symptoms are suggestive of malignancy, or complete recovery is not achieved.

Acute Complicated Diverticulitis

Intra-Abdominal Abscess

Diverticular abscess is present in 10% to 25% of hospitalized diverticulitis patients. Abscesses may be intramural, pelvic, pericolic, hepatic, or retroperitoneal (**Fig. 69.3**). The underlying etiology is assumed to be contained diverticular perforation and associated flora are enteric in nature. Small abscesses <3 cm may often be treated successfully with antibiotics alone, but larger collections fail medical management up to 34% of the time.[50] Image-guided percutaneous drainage is the mainstay 6 of therapy. Drainage is most likely to be successful in the hands of a skilled interventional radiologist approaching a unilocular collection via a transabdominal route. Multifocal or loculated abscesses are less likely to be well drained percutaneously and transgluteal drainage routes are painful and poorly tolerated. Overall, nonoperative therapy is successful in 80% of cases,[51,52] but urgent surgical intervention is indicated if septic symptoms worsen or fail to improve.

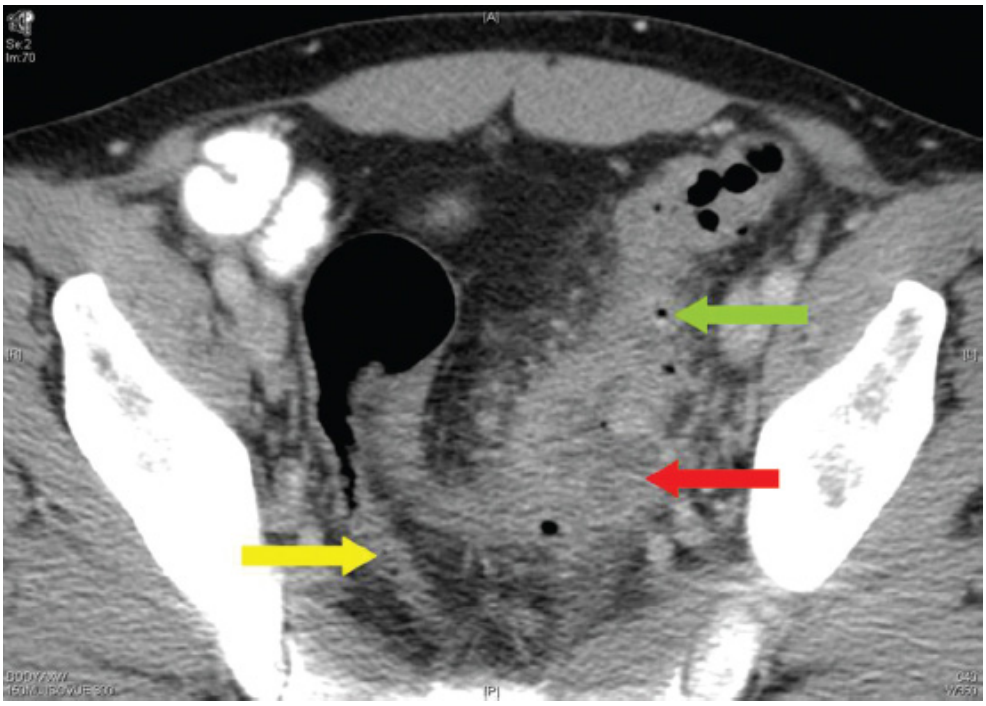

Figure 69.3 Sigmoid diverticulitis with pericolic abscess (*arrows*).

Following an episode of complicated diverticulitis, patients should undergo colonoscopy. Reported rates of occult malignancy range from 7.9% to 11%.[53,54] Until recently, surgical guidelines advised elective colectomy after an episode of complicated diverticulitis, but mandate is relaxing somewhat. Prior to widespread use of percutaneous drainage, the rate of recurrent abscess was considered unacceptably high and approached 40%. However, after percutaneous drainage, reported rates of recurrent complicated disease are lower, ranging from 15% to 25%.[55–59] Data are varied, in some series, all recurrent episodes were managed percutaneously without surgery[57] and in others, substantial minorities required urgent operation.[58] These data are heterogeneous, retrospective, and limited, speaking to the challenge of studying relatively rare events prospectively. Additionally, varied conclusions drawn from the same data reveal that surgeons do not agree on an acceptable rate 7 of abscess recurrence. However, the observation that recurrence and surgery are not inevitable consequences of diverticular abscess has led to a relaxation of guidelines from advising colectomy to advising consideration of colectomy.[49] Patients should be seen in consultation with a surgeon and the risks of recurrence balanced against patient preferences and anticipated surgical morbidity. When counseling patients on risk of recurrence, it should be noted that large abscesses (>5 cm) and pelvic abscesses are more likely to recur.

Perforated Diverticulitis with Peritonitis

Emergency surgery is required in 1% of diverticulitis patients overall, but may be required in 15% to 32%[52] of hospitalized patients. Hinchey III and IV disease presents with peritonitis and requires urgent operative intervention. Patients should be given broad-spectrum antibiotics, rapidly hemodynamically stabilized as needed, and explored. The goal of the operation is to achieve infectious source control by resecting the affected bowel and evacuating intraperitoneal pus and feces. Emergency colectomy for diverticulitis is morbid, potentially fatal, and care of unstable, elderly, or frail patients should be rapid and meticulous. Overall 30-day mortality is 5.1%. Patients >80 years of age, with serum creatinine >1.2 mg/dL, ASA class 4/5, or albumin <2.5 g/dL are increased risk of mortality and patients with four of these predictors have a 30-day mortality rate >50%.[60]

The most common approach to Hinchey III and IV diverticulitis is a Hartmann procedure: resection of the diseased bowel to soft compliant proximal colon, stapled or suture closure of the distal stump, and creation of an end colostomy. The major downside of this approach is the need for a second major operation to restore intestinal continuity. Hartmann reversal most often requires repeat laparotomy, can entail a challenging lysis of adhesions and pelvic dissection to "dig out" the rectal stump, and is associated with significant operative morbidity. Because of this, at least one-third of "temporary" urgent colostomies are permanent.[61] Therefore, creation of a primary anastomosis with diverting loop ileostomy (DLI) is an attractive alternative. Three randomized controlled trials, ColonPerfRCT (n = 62), DIVERTI (n = 102), and the DIVA arm of the LADIES trial (n = 133) randomized Hinchey III or IV patients to Hartmann procedure or sigmoid colectomy with DLI.[62–64] The three trials reached similar conclusions: morbidity and mortality of the primary operation were the same between the two approaches, but stoma-free survival was higher with primary anastomosis. Hartmann procedure at the initial operation led to greater morbidity at the time of ostomy takedown. Although compelling, these results have not changed clinical practice. In the United States >90% of urgent colectomies for diverticulitis are performed with end colostomy. In contrast to the results of randomized controlled trials, observed inhospital morbidity (32% vs. 23%) and mortality (16% vs. 6.4%) seem to be significantly higher for patients undergoing primary anastomosis than patients undergoing Hartmann procedure, respectively.[65] In clinical practice, the surgeon should decide to perform a colostomy or an anastomosis on an individual basis, evaluating the acute and chronic condition of the patient, the quality of the tissues, and the degree of contamination. Other considerations include baseline renal insufficiency, which could worsen with an ileostomy and continence, which is likely to be impaired after sigmoid colectomy.

An alternative approach to Hinchey III diverticulitis, laparoscopic lavage garnered serious clinical and academic interest as a potential alternative to resection. In laparoscopic lavage, the patient undergoes laparoscopic irrigation and drainage of intraperitoneal pus without mobilization or resection of the colon. Three heterogeneous randomized trials of laparoscopic lavage versus sigmoid resection did demonstrate some advantages of laparoscopic lavage including shorter operative times,

reduced superficial wound infections, and decreased stoma creation rates.[66–68] However, higher than expected rates of deep space infection and urgent reintervention occurred, forcing the early closure of one trial. Additionally, the occurrence of some unusual complications such as conversion of purulent to fecal peritonitis, fecal fistula, and missed adenocarcinomas dimmed enthusiasm for laparoscopic lavage. Colectomy remains the preferred approach to Hinchey III and IV diverticulitis.[49]

Surgical Technique—Urgent Operation for Perforated Diverticulitis

Preoperatively, the patient should be marked bilaterally for a potential ostomy while sitting up if possible, avoiding skin folds and creases. Operative approach may be open or minimally invasive considering the condition of the patient, anticipated severity of contamination, and skill of the operating surgeon. The patient should be placed in the lithotomy position to allow creation of circular stapled anastomosis if possible, perform colonoscopy if necessary, and assist in identification of structures in the inflamed pelvis. After clearing stool and pus from the operative field, the small bowel is swept free of the pelvis. Purulent rinds and adhesions may be broken up bluntly. Areas of perforation may be quickly oversewn to control contamination. The colon is divided just proximally to the diseased area and dissection carried to the sacral promontory. Sidewall structures are identified (**Fig. 69.4**) and dissection is kept close to the inflamed colon. The distal noninflamed sigmoid or upper rectum is transected and the specimen passed from the field. Any remaining contamination is irrigated to clear. If the patient is in shock after contamination is controlled, it is reasonable to stop at this point, leave the abdomen open, the bowel in discontinuity and proceed to the intensive care unit for resuscitation. However, if the patient is stable, the colon is mobilized for either creation of a colostomy or anastomosis. Due to inflammatory foreshortening of the mesentery, either approach may require takedown of the splenic flexure (**Fig. 69.5**), division of the inferior mesenteric artery (IMA), and possibly division of the inferior mesenteric vein (IMV) to achieve adequate colonic reach for a tension-free anastomosis or appropriately spouted colostomy. If the patient and bowel are judged by the surgeon to be suitable for an anastomosis, full mobilization and

careful assessment should be employed to assure that the anastomosis is tension-free, straight, and viable.

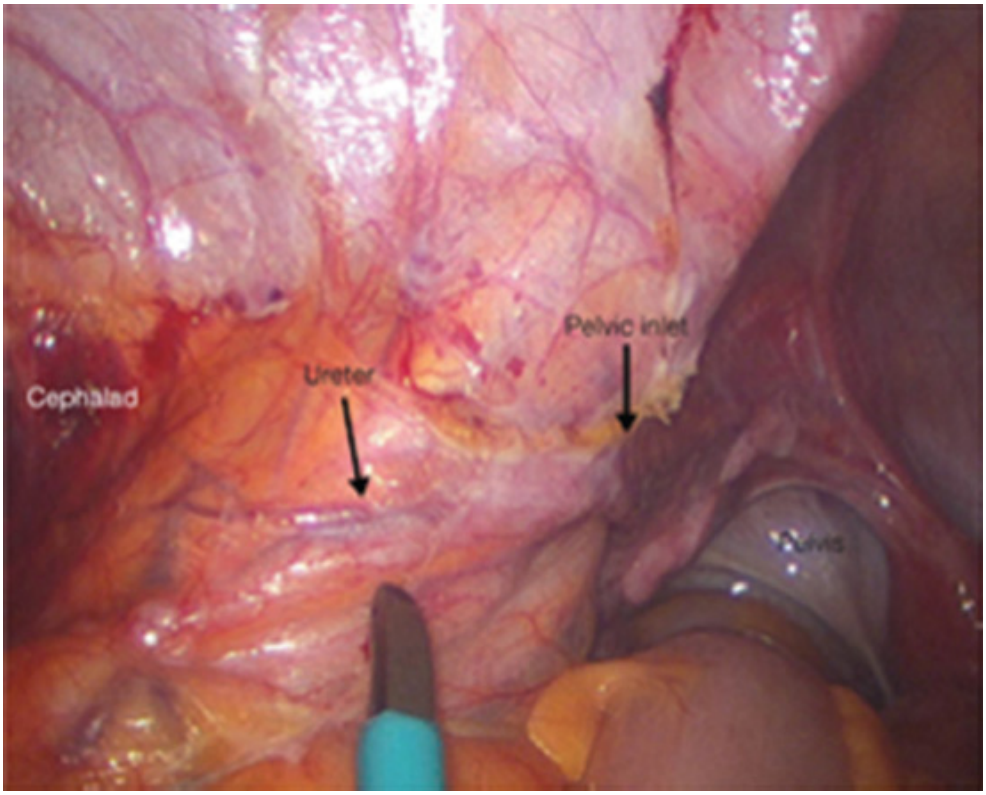

Figure 69.4 Surgical view of the left-sided pelvic sidewall structures demonstrating the ureter and iliac vessels.

If a Hartmann procedure is performed and a reversal is desired, the patient should be allowed to recover for at least 3 to 6 months. Colostomy reversal is elective and time should be taken to recover the patient from their acute perforation and optimize functional status through management of comorbid conditions, increased physical activity, smoking cessation, nutritional support, and weight loss as necessary. Thorough review of the operative note is key to understand the handling of the rectal stump and mesenteric vasculature. Colonoscopic screening should be updated if necessary. Preoperative continence should be queried and can be evaluated formally by manometry and defecography, or informally by examination and asking the patient to hold an enema in the rectum. Hartmann reversal can be undertaken by an open or minimally invasive approach. The rectal stump should be freshened to healthy compliant rectum and any residual sigmoid removed.

The stump can be foreshortened and shrunken with disuse, placement of an EEA sizer per anus may assist in identification.

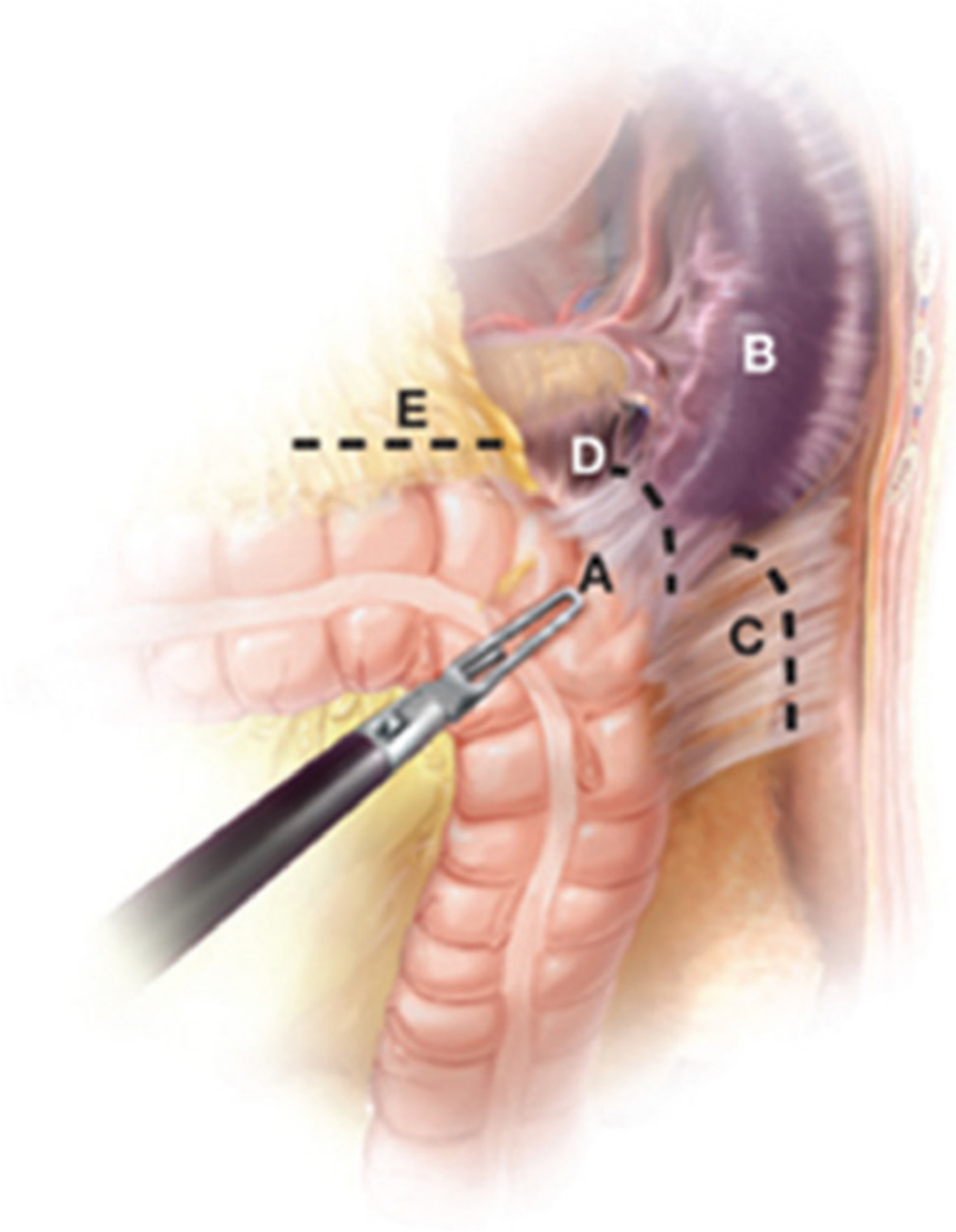

Figure 69.5 Illustration of the relationship of the splenic flexure of the colon (**A**) to the spleen (**B**). Full mobilization requires division of the abdominal (**C**), lienocolic (**D**), and omental (**E**) attachments.

If, at the index operation, a primary anastomosis is performed with a DLI, the patient should typically be allowed to recover for 3 months, the

anastomosis evaluated with barium enema and/or sigmoidoscopy, and the ileostomy reversed electively.

DIVERTICULITIS—RECURRENT AND CHRONIC INFLAMMATORY PRESENTATIONS

Recurrent Diverticulitis

After recovering from acute, uncomplicated diverticulitis 13% to 33% of patients will have recurrent attacks.[2] After one inpatient admission, the chance of a second admission is 9% and the risk of a subsequent attack increases thereafter. After two admissions, 23% have a third admission and 36% a fourth.[69] Physicians cannot predict or prevent recurrent attacks. For decades, the mechanistic assumption that every uncomplicated diverticulitis attack added up incrementally to an individual's risk of free perforation led the recommendation for routine, elective sigmoid colectomy for secondary prevention after two hospitalizations. However, improved understanding of the natural history of the disease has demonstrated that 80% to 90% of emergency colectomies happen on index admission.[70,71] Therefore, colectomy should not be routinely performed to prevent free perforation and colostomy after uncomplicated diverticulitis. Current practice guidelines recommend a case-by-case 8 decision for each recurrent diverticulitis patient, balancing the burden of disease, patient preferences, and surgical morbidity.[49] Patient factors influencing the decision might include frequency and severity of episodes, missed work and activities, health care expense, persistent symptoms between attacks, and antibiotic intolerance. These should be balanced against surgical candidacy, likelihood of operative morbidity, and predicted postoperative functional outcome using a framework of shared decision making.

Sufficient equipoise exists in recurrent diverticulitis that a randomized clinical trial of colectomy versus observation was performed. The DIRECT trial randomized a total of 108 recurrent diverticulitis patients to elective sigmoid colectomy versus observation. A total of 46% of conservatively treated patients crossed over to the surgical arm over 5 years of follow-up. Despite early termination due to high rates of stoma creation and anastomotic

leak, surgical patients still had higher gastrointestinal quality of life at 5-year follow-up.[72] The results of this trial suggest that although most surgeons focus on ostomy and operative morbidity, other factors may be more important to patient quality of life. There has been little research on patient-reported outcomes in diverticulitis compared to other common diseases. Further study could assist in improving shared decision making and patient counseling.

Surgical Technique—Elective Sigmoid Colectomy for Recurrent Diverticulitis

Sigmoid colectomy may be performed open or in a minimally invasive fashion using "straight stick" laparoscopy, hand assist technique, or robotics. When surgical expertise allows, a minimally invasive approach has several advantages and is preferred. As with other abdominal operations, minimally invasive surgery, particularly when coupled with enhanced recovery pathways, can shorten length of stay, decrease pain, and minimize wound complications.[73] Surgery for diverticulitis, including for complicated disease, urgent indications, and ostomy reversal is increasingly performed laparoscopically.[74] National trends indicate use of laparoscopy for elective diverticulitis surgery increased from 48% to 70% between 2006 and 2013.[75] Laparoscopic conversion rates are reported between 4% and 26% of cases and are higher with complicated disease.[76,77] Robotic surgery demonstrates equivalent outcomes with respect to length of stay and patient outcomes, with the exception of a decreased conversion rate compared to laparoscopy and increased overall hospital charges.[78,79]

Regardless of approach, the goal of the operation is not to remove all diverticula but all affected bowel. Proximal margin should be soft, pliable, and healthy left colon. Distal margin of resection is at the upper rectum, identified by its partially extraperitoneal location, splaying of the tenia, and loss of haustral folds. Transection in the distal sigmoid can be associated with recurrent diverticulitis postsurgically. Dissection may proceed from medial to lateral or vice versa. The ureter should be clearly seen and protected. The lateral attachments and mesentery of the colon should be divided and mobilized until a tension-free anastomosis is created. Typically, this requires high ligation of the IMA and mobilization of the splenic flexure.

Occasionally, division of the IMV and complete release of the greater omentum may be required. The anastomosis is created in a hand-sewn or stapled fashion according to the principles of a tension-free, straight, viable, and patent anastomosis and the surgeon's preference.

Fistula, Stenosis, and Obstruction

Fistula is a rare complication of diverticular disease and presumably occurs when a contained diverticular perforation erodes into an adjacent viscera or the abdominal wall. Some patients have a provocative presentation of building abdominal pressure followed by relief and discharge of gas and pus via the bladder, vagina, or skin. Although the fibrotic inflammation found at operation speaks to chronic inflammation, presentation of a fistula is not necessarily preceded by recurrent attacks of diverticulitis.

Colovesical fistulas are the most common type of diverticular fistula (65%) and are more common in men than women.[80] They present with pneumaturia, fecaluria, frequent urinary tract infections, renal impairment, or urosepsis. "Dirty" urinalysis and gas in the urinary bladder are appreciated on imaging and suggest the diagnosis. Differential diagnostic concerns include emphysematous cystitis and rectourethral fistulas, particularly in patients who have had prostate surgery or radiation. Cystoscopy and colonoscopy should be performed to exclude a locally advanced colonic or bladder malignancy.

Colovaginal fistulas are the next most common (25%) present with foul vaginal discharge and gas per vagina, typically in women who have had a hysterectomy. Many patients are referred from gynecologists and an area of inflammation and granulation tissue at the vaginal cuff is commonly seen on speculum examination. Colonoscopy should be performed to exclude malignancy. Differential diagnosis includes vaginal infection, anovaginal fistulas, and erosion of pelvic mesh in women with a history of proctopexy or sacrocolpopexy. Rare diverticular fistula types include colouterine, coloenteric, and colocutaneous. Principles of surgical repair for all fistulas broadly are resection of the diseased colon, repair of the attached normal organ, and separation of the two repairs with healthy tissue.

Colonic stenosis and large bowel obstruction can occur as sequelae of chronic diverticular inflammation. Patients may present urgently with a large

bowel obstruction or subacute symptoms including cramping pain, change in bowel habit, and bloating. Obstruction can be secondary to inflammatory phlegmon or abscess and therefore may respond to antibiotics, percutaneous drainage, and observation, obviating the need for emergent resection. However, completely obstructing fibrotic strictures risk perforation and require surgical intervention. Interval endoluminal stent placement as a bridge to surgery can be considered. Successful stent placement is less likely in diverticular disease than colorectal cancer and has a reported perforation rate up to 30%,[81] and can make subsequent colectomy more challenging. Endoluminal stent placement as definitive treatment should only be considered in very poor surgical candidates. Urgent presentation of large bowel obstruction may preclude endoscopic diagnosis and the fibrotic, thick inflammation can make differentiating diverticular strictures impossible to distinguish from malignancy on table. The cecum should always be assessed for viability as a first step in the operation. Inflammatory fibrotic strictures and tensely dilated colon may make for prohibitively challenging urgent pelvic operations. Surgical options include diversion with a loop or end-loop colostomy if inflammation precludes safe resection. Hartmann procedure or primary anastomosis with or without DLI are both options depending on the condition of the bowel and patient. Often completely obstructed patients are too deconditioned and bowel too dilated to permit consideration of an anastomosis. In the case of the tensely distended, obstructed colon, on table decompression may assist in safe handling of the bowel and decrease the chance of uncontrolled stool spillage. This can be performed using saline lavage delivered via the appendix and collected off the field. The author prefers to select a site for proximal transection, place a double purse string around a colotomy and carefully pass a 36-Fr Argyle chest tube proximally to evacuate stool and gas.

Surgical Technique—Operation for Diverticular Fistula

Chronic inflammation can alter anatomy and create challenging pelvic dissections in these patients. Patients should be placed in lithotomy and consideration given to use of ureteral stents. Minimally invasive approaches are appropriate if within the skill set of the surgeon. Minimally invasive mobilization of the splenic flexure in particular is useful as it reduces the

incision needed to appropriately mobilize the colon. Dissection can proceed in a lateral to medial or medial to lateral fashion and the IMA need only be taken high on the aorta to achieve appropriate colonic mobilization. Care should be taken to identify and preserve the ureters. In the area of the fistula, woody inflammation often makes laparoscopic dissection tedious, although use of hand-assisted technique, sponge sticks, or suction may mimic manual blunt dissection well. In the open technique, the colon can be bluntly pinched apart from the bladder or vagina. It is critical to exclude malignancy preoperatively in these patients to avoid "cracking through" a locally advanced malignancy that requires a multivisceral resection.

Colonic dissection is carried to the top of the rectum and sometimes lower, if necessary, to identify soft pliable bowel. The colon anastomosis is typically carried out with a circular stapling device. Colovesical fistulas are typically to the dome of the bladder, but urologic help may be advisable if they involve the trigone. Repair of the vaginal or bladder is typically unnecessary. It is the author's practice to fill the bladder and repair only if urine is leaking and place an EEA sizer in the vagina and repair only if the tissues are quite attenuated. A flat of viable omentum can be interposed between anastomosis and bladder or vagina. Alternatively, a peritoneal flap can be positioned in the space. Postoperatively after colovesical fistula repair, a urinary catheter is typically left in place for 7 to 10 days and a cystogram performed prior to removal.

Less Common Presentations of Diverticular Disease

Giant Diverticula

Giant diverticula are rare, commonly found in the sigmoid colon, and have been described to grow to 44 cm.[82] The etiology is unknown, but hypotheses include physical air trapping and gaseous overproduction by bacteria. Symptoms may cause mass effect, but asymptomatic presentation is common. Treatment is by sigmoid colectomy.

Right-Sided Diverticulitis

Right-sided diverticulitis is rare among European-ancestry populations, but more common in Asia and in Asian immigrants. Clinical presentation includes right-sided pain, fevers, chills, and gastrointestinal distress. Given the location, the differential diagnosis included terminal ileitis, cholecystitis, epiploic apendagitis, mesenteric adenitis, genitourinary pathology, and, of course, appendicitis, which may be clinically indistinguishable and radiologically confusing. Similar to sigmoid diverticulitis, patients with uncomplicated inflammation and a clear diagnosis can be managed with antibiotics. Recurrent disease, unclear diagnoses, and perforation should be treated with right hemicolectomy.[83,84]

Diverticular Hemorrhage

Diverticular hemorrhage is a noninflammatory diverticular pathology caused by erosion of the mesenteric vessels by an adjacent herniating diverticulum. Diverticular bleeding is the most common source of lower GI hemorrhage.[85] Hemorrhage is classically bright red, painless, and brisk. Differential diagnosis includes rapid upper gastrointestinal hemorrhage, arteriovenous malformations, neoplasms, colitis, and anorectal hemorrhage. Patients should be stabilized, blood made available, nasogastric lavage performed, and a thorough rectal examination performed to exclude pathology. Bleeding ceases spontaneously in 80% of cases.[86] Diagnosis is made via colonoscopy demonstrating sigmoid diverticulosis. In the absence of other pathology, the presumptive diagnosis of diverticular hemorrhage is made. When a bleeding lesion is seen, endoscopic treatments include epinephrine injection, cautery, and clips. Rebleeding occurs in a minority of patients and surgery is rarely required. In one large modern cohort of 14,925 patients with diverticular hemorrhage, 1,368 had a second episode, but only 64 required colectomy.[87] Segmental resection may be necessary in diverticular hemorrhage that is massive, recurrent, or fails endoscopic control.

SUMMARY

Diverticular disease is a common colorectal disease with a spectrum of presentations, treatments, and prognoses. Due to its high incidence, the practicing general, colorectal, or acute care surgeon is likely to see multiple manifestations throughout their career. Emerging basic research suggests that diverticulitis is a complex trait with both environmental and inherent risk factors, although its exact pathophysiology remains incompletely understood. Diagnosis is frequently suspected on the basis of symptoms and signs and confirmed with CT imaging. Treatment parallels the Hinchey severity classification system. Current treatment guidelines have changed with improving clinical understanding of the disease. Uncomplicated disease may be treated with or without antibiotics. Indications for elective surgery have changed and minimally invasive approaches adopted. Complex presentations including recurrence, free perforation, fistula, and obstruction remain challenges for the surgeon to pick the right operation for the right patient at the right time. Scientific understanding of the disease remains limited with many fundamental questions unanswered. For instance, global anatomic variation remains a mystery, the triggers of diverticulitis remain unknown, recurrence cannot be predicted or prevented, and the complex interplay between the individual and his environment that produces diverticular disease remains to be completely understood.

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70

Anorectal Disorders

Amy L. Halverson and Vitaliy Y. Poylin

Key Points

1 The most common manifestation of internal hemorrhoids is painless, bright red rectal bleeding associated with bowel movements. A high-fiber diet supplemented with bulk-forming agents may reduce symptoms of hemorrhoids and is ideal for first- and second-degree hemorrhoids.

2 Rubber band ligation is suitable for symptomatic first- and second- and some third-degree internal hemorrhoids that do not respond to bulk-forming agents. Hemorrhoidectomy is required in only a few patients with symptomatic hemorrhoids.

3 An anal fissure is an ischemic ulcer in the lower portion of the anal canal. Treatment, both medical and surgical, involves relaxing the internal anal sphincter.

4 The basic principles of anal fistula treatment are to limit the access of fecal contents into the tract while preserving the anal sphincter.

5 Pilonidal disease results from hair in the subcutaneous tissue as the nidus for a chronic foreign body reaction. Treatment aims to remove the offending tuft of hair.

6 Rectal prolapse results from intussusception that extends beyond the anal verge. Fit patients are best treated with transabdominal rectopexy. Patients with significant medical comorbidities are best treated using a perineal approach.

7 Anal condylomata acuminata are caused by human papillomavirus, as are anal intraepithelial neoplasia and anal cancers.

8 Palpable lesions of the anal canal are not hemorrhoids and might be cancers; examination under anesthesia and biopsy allow for correct diagnosis.

ANATOMY AND PHYSIOLOGY

The Rectum

The rectum begins at the level of the sacral promontory and measures approximately 15 cm in length. At the proximal colon, the tinea of the colon splays to form a uniform layer of muscle in the rectal wall. The rectum descends along the curvature of the sacrum and passes through the levator ani muscles, where it becomes the anal canal (**Fig. 70.1**). The mesentery of the rectum (mesorectum) is surrounded by a thin investing fascia that is distinct from the presacral fascia and serves as a dissection plane in rectal cancer surgery. The endopelvic fascia that covers the sacrum posterior to the rectum is referred to as Waldeyer fascia; anteriorly, Denonvilliers fascia lies between the rectum and the vagina in females and between the rectum and seminal vesicles in males.[1]

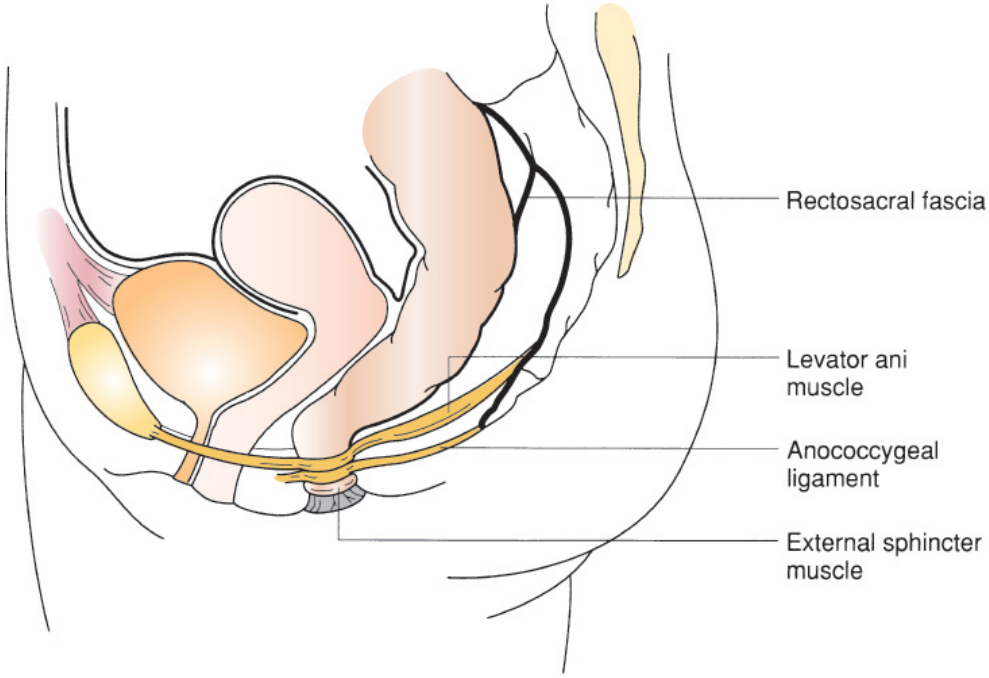


Figure 70.1 Pelvic anatomy.

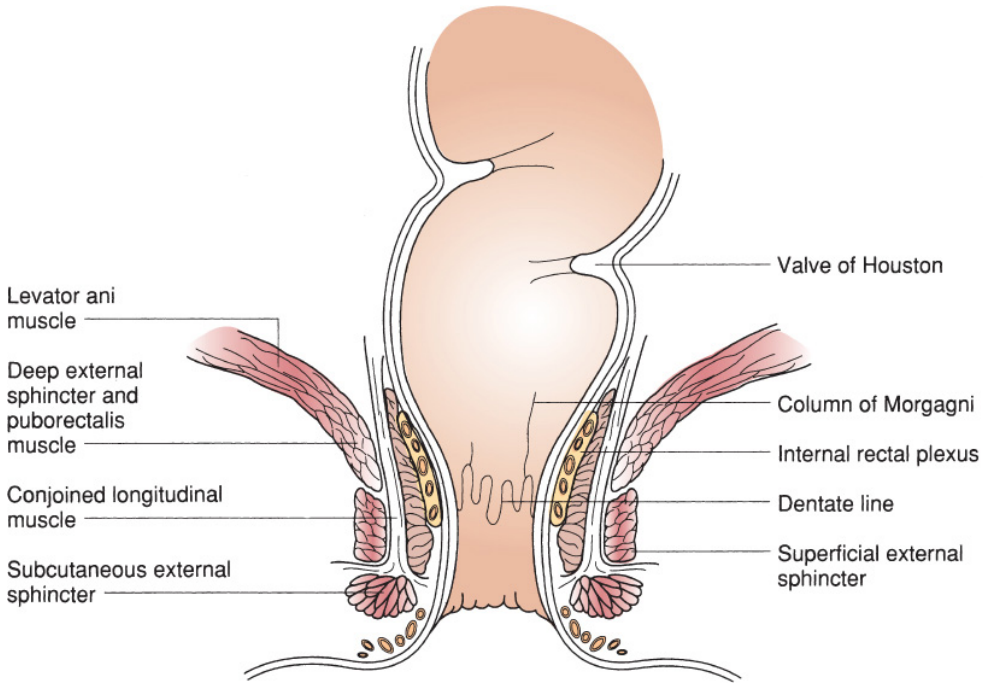


Figure 70.2 Anatomy of the anal canal.

The Anal Canal and Pelvic Floor

Anal Canal

The anal canal is the terminal portion of the intestinal tract. It continues from the rectum 4 to 5 cm through the pelvic floor musculature to the hair-bearing skin of the anal margin. Understanding the various types of anal epithelium helps to elucidate the diagnosis of both benign and malignant conditions. At the anal verge, skin becomes anoderm, a squamous epithelium without hair. The anoderm extends to the dentate line, which represents the division between embryonic endoderm and ectoderm (**Fig. 70.2**). Folds of tissue at the dentate line form anal papillae. Between the papillae lie the anal crypts, which house the anal glands. These glands are the structures from which anal abscesses and fistulae commonly originate. The endoderm in the first 1 to 2 cm proximal to the dentate line is called the transition zone and represents a gradual change from squamous epithelium to the columnar epithelium lining the rectum.

The muscularis propria of the rectum continues distally to form the internal anal sphincter. The pelvic floor is composed of the levator ani muscle (which has three parts, puborectalis, pubococcygeus, and Iliococcygeus) and

external anal sphincter. Together, these muscles and their connections are responsible for both continence and defecation. The puborectalis muscle forms a sling that extends from the posterior pubis around the rectum and maintains an acute angle at the anorectal junction, which contributes to the continence mechanism (**Fig. 70.3**). The external anal sphincter is a striated muscle that surrounds the internal anal sphincter. It is contiguous with the levator ani and attaches to the coccyx with the anococcygeal ligament. In addition to its role in maintaining continence, the anococcygeal ligament plays a role in the development of fistulas—posterior abscesses that cannot break through this tuft of connective tissue, can extend to both ischiorectal fossae, creating a horseshoe abscess.

Anorectal Spaces

There are several anorectal spaces created by myofascial relationships in the pelvis (**Fig. 70.4**). The perianal space contains external hemorrhoids, the subcutaneous component of the external sphincter, and the most distal portion of the internal sphincter. It communicates with the intersphincteric space located between the internal and external sphincters. It is the most common path for cryptoglandular infections, which include abscesses and fistulas. The ischioanal and ischiorectal spaces are the largest potential spaces, extending from the skin caudally to the levator ani and obturator fascia cranially. Horizontally these spaces lie between ischial tuberosities and the anus/rectum. These spaces communicate with the postanal/postrectal spaces and can be a common path by which infections spread. Posterior to the anus and rectum, the postanal and postrectal spaces are limited by the anococcygeal ligament and levator muscles. If an infection develops in this area, the above structures often limit the spread of the infection distally or proximally, forcing the infection to spread laterally to the ischioanal/ischiorectal space creating horseshoe abscesses.

Blood Supply and Innervation

The rectum and anus receive abundant blood supply from the superior, middle, and inferior rectal arteries (**Figs. 70.5** and **70.6**). The superior rectal (hemorrhoidal) artery starts as the terminal branch of the inferior mesenteric artery, descending posterior to the rectum where it bifurcates to supply the

rectum and upper anal canal. The middle rectal arteries (present as a distinct vessel in <15% of people) arise from the internal pudendal or inferior gluteal arteries (branches of the internal iliac artery). The inferior rectal arteries also arise from the internal pudendal arteries to supply the anal sphincters and anal canal. The venous drainage of the anus is via both the portal and systemic venous systems. The superior rectal vein drains the rectum and upper anal canal into the portal venous system through the inferior mesenteric vein. The middle and inferior rectal veins drain into the systemic venous system via the internal iliac veins. Because of the rich communication between these veins, patients with portal hypertension may develop portosystemic shunts resulting in bleeding rectal varices. Hemorrhoids are submucosal sinusoids that contain both arterial (typically terminal branches of the superior hemorrhoidal artery) and venous (usually superior, middle, and inferior hemorrhoidal veins) supply. Sinusoids differ from veins in that histologically, the walls of these vascular structures do not contain muscles.

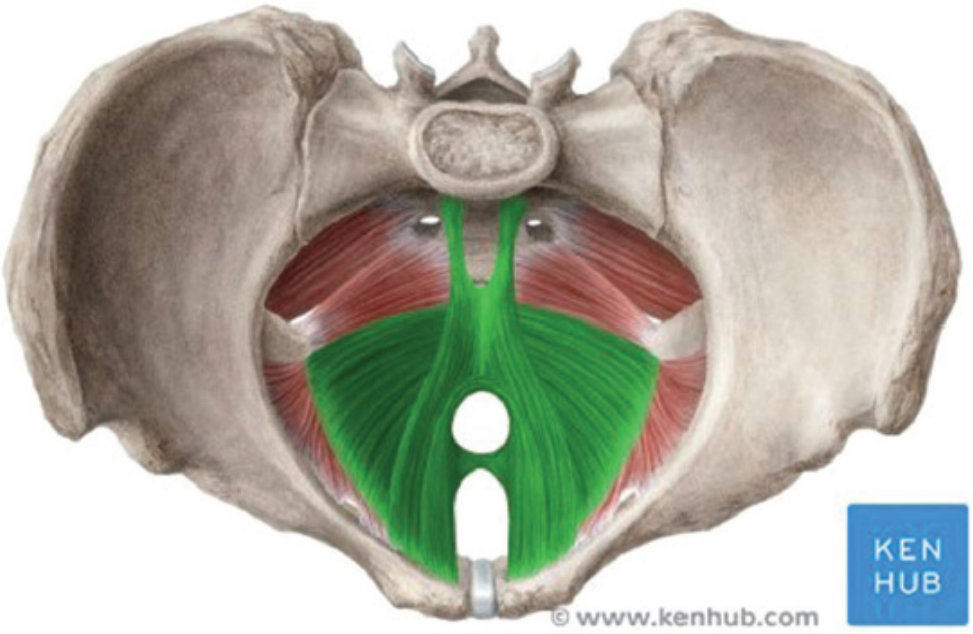


Figure 70.3 Muscles of the pelvic floor.

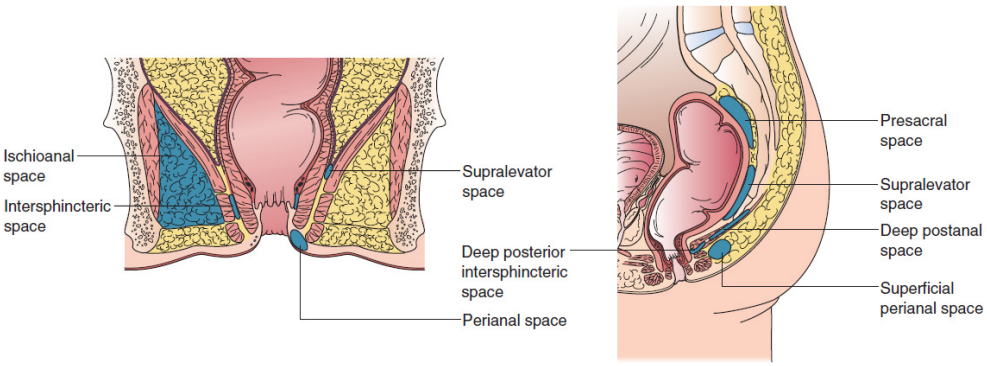


Figure 70.4 Anorectal spaces.

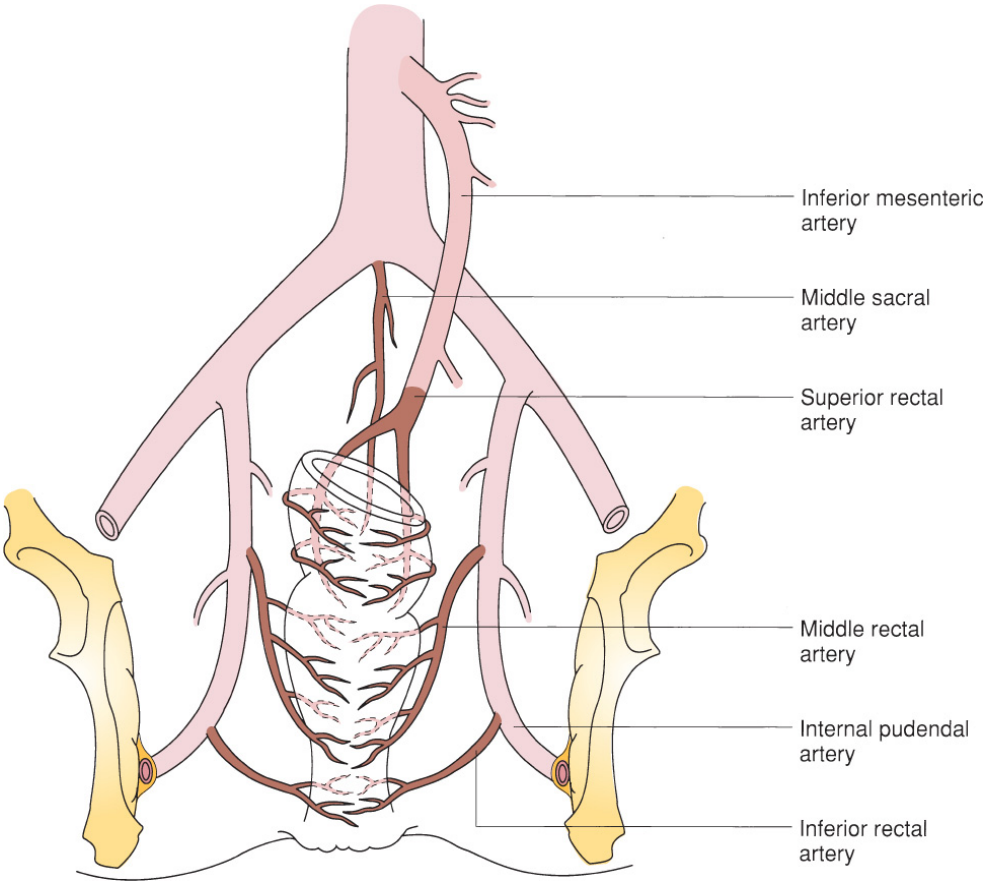


Figure 70.5 Arterial supply.

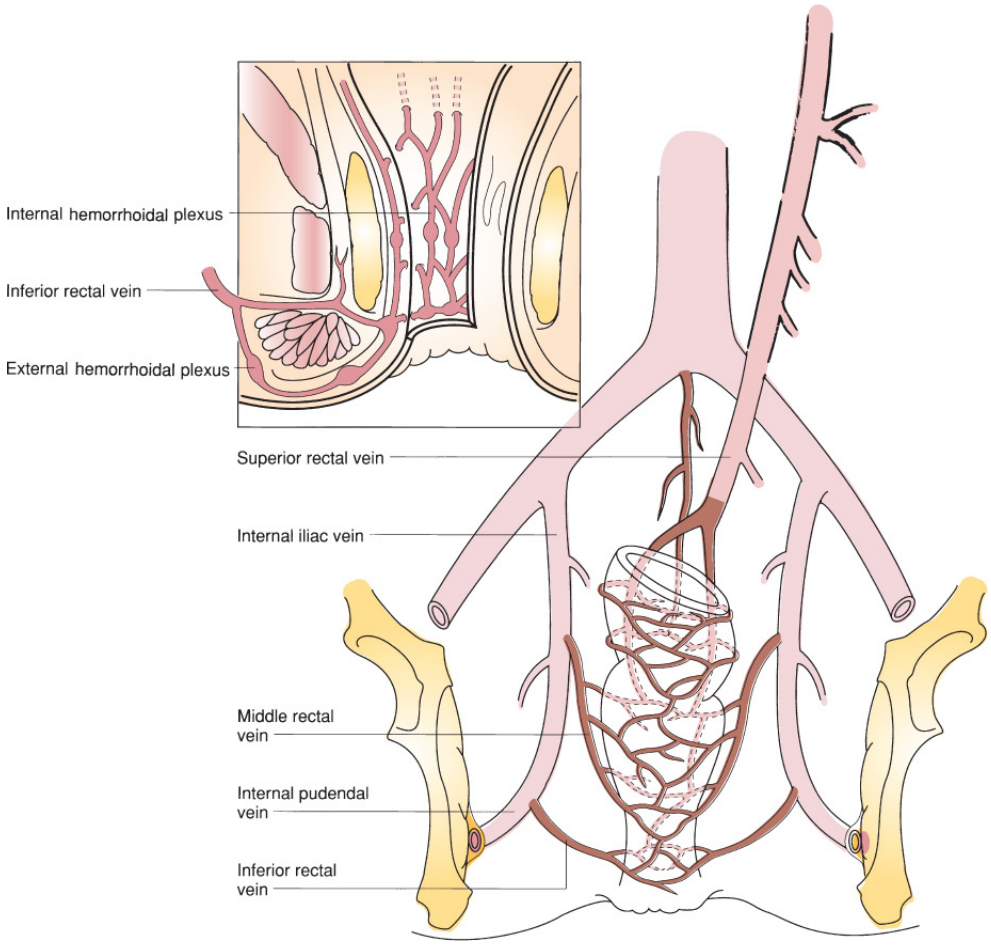


Figure 70.6 Venous supply.

Lymphatic drainage of the rectum and anus mirrors the arterial supply (**Figs. 70.7** and **70.8**). Drainage from the upper and middle rectum flows to the inferior mesenteric lymph nodes. The lower rectum and upper anal canal may drain to the inferior mesenteric nodes or may drain laterally to the internal iliac nodes. Lymph from the anus below the level of the dentate line typically drains to the inguinal lymph nodes. However, drainage may also occur to the inferior mesenteric and internal iliac nodes. Clinically this drainage pattern is relevant in cancer patients to identify the extent of their disease. For example, lymph node metastases from anal cancer often develop in the inguinal lymph nodes.

Sympathetic innervation of the rectum originates from the first three segments of the lumbar spinal cord and synapse at the preaortic plexus (**Fig. 70.9**). The nerves bifurcate to form the hypogastric plexus, which, during anterior resection, can be routinely observed overlying the top of the sacrum

before extending laterally and joining the pelvic plexus. Parasympathetic innervation (nervi erigenti) originates from the second, third, and fourth sacral nerve roots and eventually extends medially along Denonvilliers fascia. In men, nervi erigenti are responsible for erection, and damage to these nerves during rectal or prostate surgery would lead to impotence.[2] Sympathetic nerves are responsible for ejaculation, and damage to these structures during surgery (sigmoid colectomy or anterior resection) would lead to retrograde ejaculation. Injury to the pelvic nerves may also lead to bladder dysfunction. In women, dysfunction following nerve injury is less well understood. Some patients do report dyspareunia and decreased lubrication during intercourse following pelvic surgery.

The internal anal sphincter receives both sympathetic and parasympathetic innervation and maintains tonic contraction at rest. The inferior rectal branch of the pudendal nerve and perineal branch of the fourth sacral nerve innervate the external anal sphincter. The inferior rectal nerve also carries sensory information from the anal canal. The majority of sensory nerve endings within the anal canal are located distal to the dentate line. However, patients may sense painful stimuli up to 1.5 cm proximal to the dentate line. This pattern of innervation has clinical implications on planning, counseling, and establishing expectations for pain during and after anorectal procedures.

Physiology

The primary function of the rectum is to serve as a distensible reservoir for stool. The principal function of the anus and pelvic floor is the maintenance of continence and regulation of defecation. Continence and defecation involve a combination of voluntary and involuntary muscular activities. At baseline, both internal and external sphincters are closed and the puborectalis is tightened, pulling the rectum forward and providing extra support. Hemorrhoids are also thought to contribute to continence, especially of mucus and gas. Defecation starts with rectal distention that causes the internal anal sphincter to relax and external sphincter to tighten—the rectoanal inhibitory reflex. This process, which presents a small amount of stool into the anal canal, is called sampling. If the call for defecation is not answered, both sphincters and the puborectalis maintain control by further tightening and making the anorectal angle more acute.

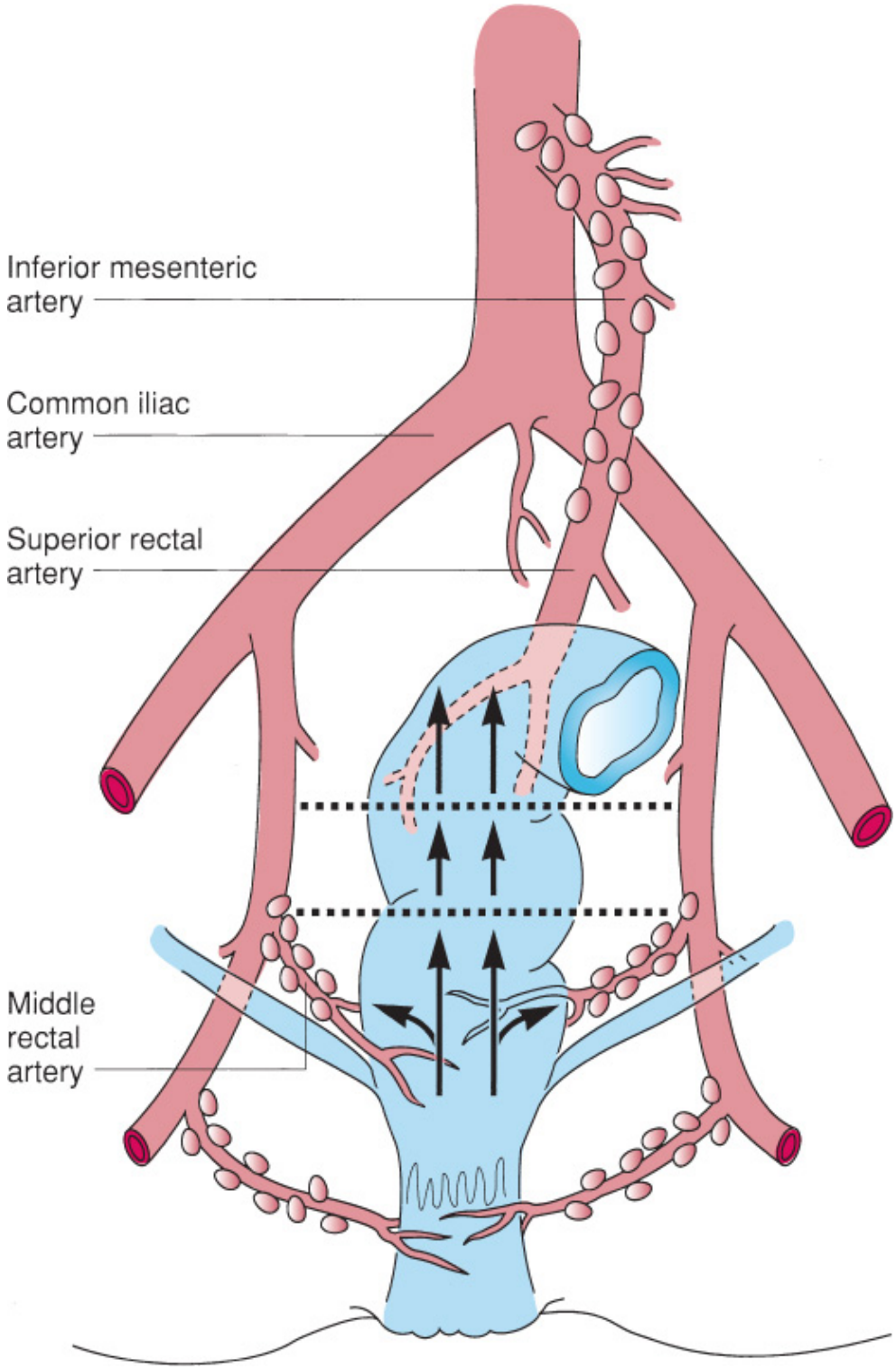


Figure 70.7 Lymphatic drainage of the rectum.

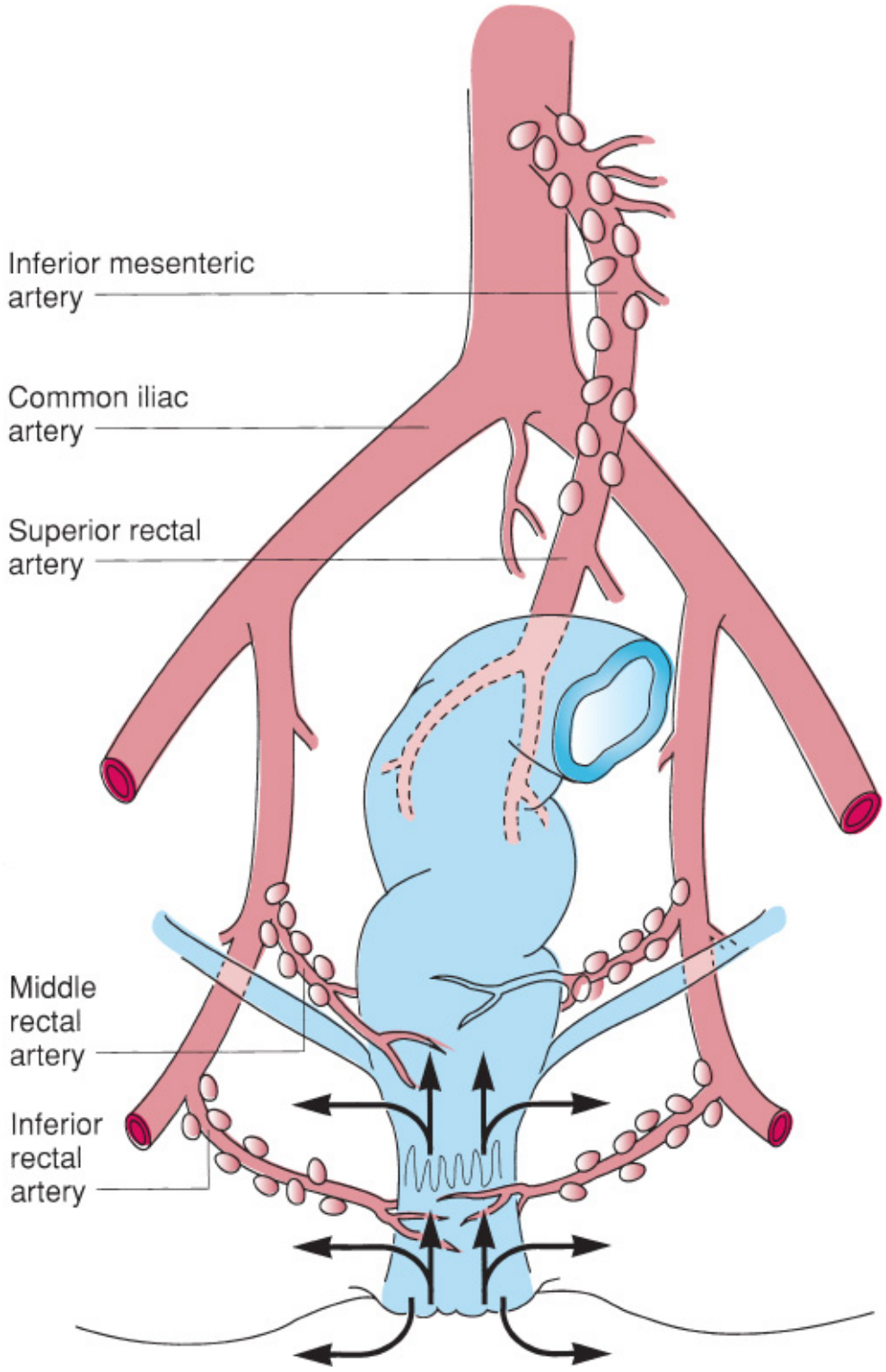


Figure 70.8 Anal canal.

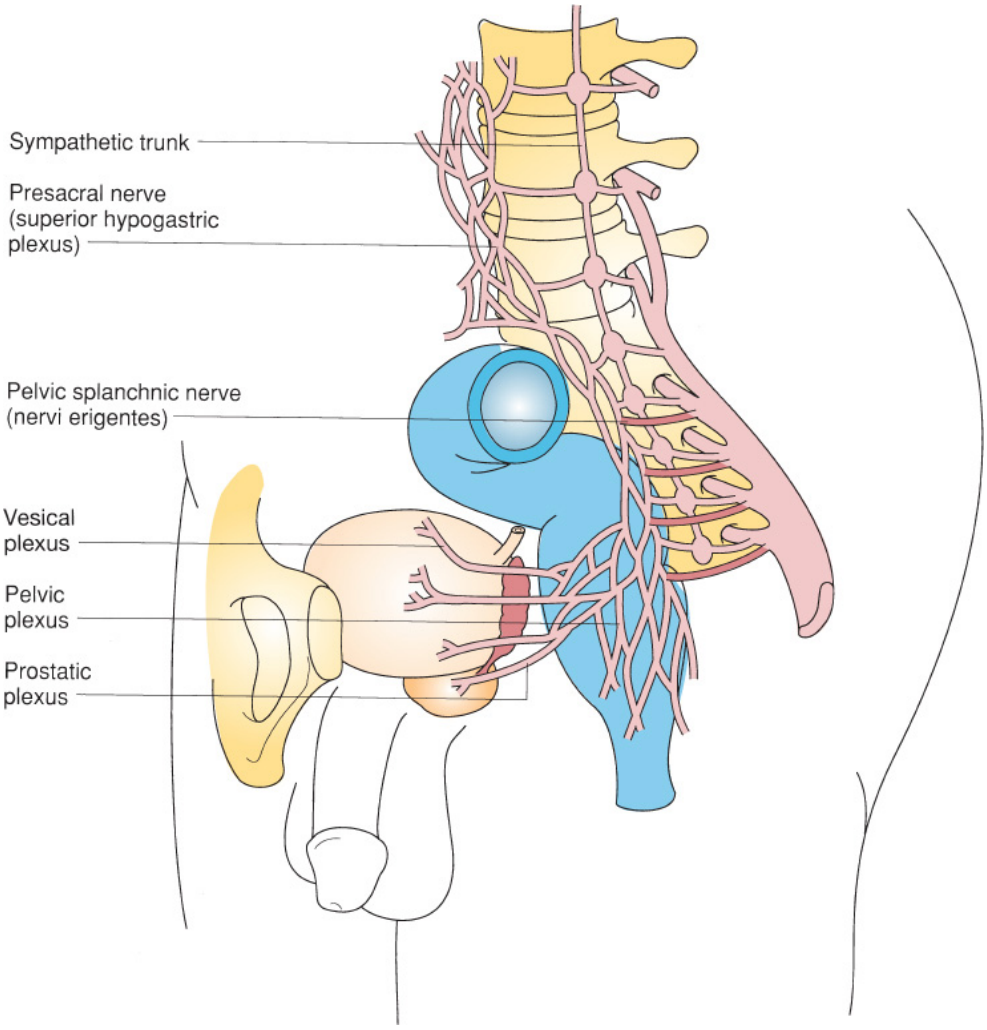


Figure 70.9 Innervation.

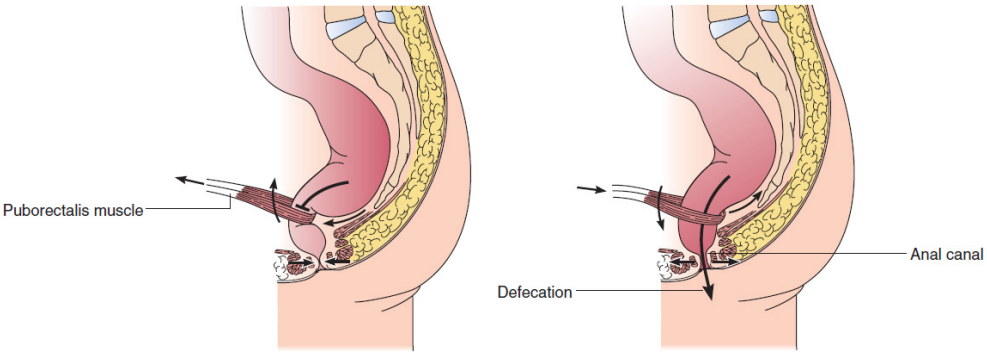


Figure 70.10 Mechanism of defecation.

Contraction of the external anal sphincter will often more than double the intra-anal pressure. This muscle can typically be contracted voluntarily for only 30- to 60-second periods. If the call to defecate is answered, either the

sitting or squatting position is assumed, thereby helping to straighten the anorectal angle. Defecation occurs through the coordinated effort of increasing the intra-abdominal pressure (Valsalva) and relaxing the puborectalis muscle, which further opens the anorectal angle and shortens the anal canal (**Fig. 70.10**). Subsequently, both the internal and external anal sphincters relax, the pelvic floor descends, and a funneling occurs, allowing the rectal contents to pass. After completion of rectal evacuation, a "closing reflex" occurs, where transient contraction of the external anal sphincter and puborectalis help to restore the tonic contracture of the internal anal sphincter.

DIAGNOSTIC EVALUATION OF THE ANUS

An accurate and detailed history is essential to diagnosing anorectal disorders. Common presenting symptoms of anorectal problems include pain, bleeding, and the presence of prolapse or a mass. Symptoms may be acute or chronic. Painless bleeding is characteristic of internal hemorrhoids. Pain is indicative of pathology distal to the dentate line. Common etiologies of pain include thrombosed external hemorrhoids, abscesses, and anal fissures. Anal fissures may cause bleeding, and fissure pain is typically worse with bowel movements rather than constant and often described by patients as, "it feels like I am passing glass." A perirectal abscess often has associated fever. Patients may also report itching and incontinence. Many diagnoses are evident by history alone and are confirmed with physical examination (**Table 70.1**).

Table 70.1 Symptoms of Common Benign Pathology

	Pain	
Bleeding	+	−
+	Fissure	Internal hemorrhoid
−	Thrombosed external hemorrhoid Abscess	Residual hemorrhoidal tag Condyloma

Alternations in bowel habits are often a contributing factor to anorectal pathology. Although there is a wide range of what is considered a normal frequency of bowel movements—between one bowel movement every 3 days and three times a day, patients with extremes in bowel movement frequency are more likely to develop symptoms. Frequency, consistency of stool, straining with evacuation, and time spent defecating should be assessed. Other relevant components of history include trauma (including injuries and episiotomies during childbirth in women), prior surgery, travel history, sexual history, and in women, a history of prior cervical dysplasia is helpful to assess the risk of anal dysplasia.

Physical examination of the anus should include a visual inspection of the perianal area as well as a digital examination (**Table 70.2**). Patients may be examined in either the left lateral decubitus or prone jack-knife position. Providing the patient with a simple explanation and reassurance regarding the planned examination helps to ensure cooperation and minimize anxiety. Inspection of the anus may demonstrate skin tags or external hemorrhoids, fissures, scars, or excoriation of the skin. Straining during inspection may help to demonstrate rectal mucosal or full-thickness prolapse and assess the degree of perineal descent. Digital examination with a gloved, well-lubricated index finger assesses for tenderness, the tone of the anal sphincters, and the presence of a rectal mass. A more detailed evaluation of the anus includes anoscopy and rigid or flexible proctosigmoidoscopy, which patients usually tolerate in the office setting.

BENIGN ANORECTAL DISEASE

1 Hemorrhoids

Hemorrhoids are cushions of vascular tissue and are a normal part of the anal canal. The number and location of hemorrhoids may vary, however. Most commonly, there are three pillars located in the left lateral, right anterior, and right posterior quadrants. Hemorrhoids are generally classified as internal (proximal to the dentate line), external (distal to the dentate line), and mixed (most commonly seen). Additionally, internal hemorrhoids are classified by the degree of prolapse (**Table 70.3**).

Clinical Manifestations

Internal Hemorrhoids

As there is no somatic innervation above the dentate line, internal hemorrhoids do not cause pain. The most common presenting symptom is painless bleeding with bowel movements, which can manifest as either blood on the toilet paper to blood dripping into the toilet bowl. Bleeding may be associated with firm bowel movements and may persist for a few days, followed by a period of no symptoms. Hemorrhoidal bleeding rarely leads to anemia, but may be of increased concern in chronically anticoagulated patients. Prolapsing tissue that retracts either spontaneously or with manual reduction may cause fecal soiling or itching.

Table 70.2 The Complete Digital Rectal Examination

Preparation
Enema
Left lateral decubitus position
Lighting, gloves, lubrication, anoscope

Visualization
Retract the buttocks
Inspect for:
- Soiling
- Excoriation or abrasion
- Scarring
- Patulous anus, deformity, or flattening of folds
- Fissure
- External fistula opening
- Anal wink reflex
- Prolapse through anus with strain
- External hemorrhoids

Palpation
Slow insertion of gloved, lubricated finger
Pain with examination
Palpable sphincter defect
Perineal body scarring
Anal stenosis
Relaxed or increased tone
Prostate abnormalities (men) or anterior rectocele (women)
Gross blood present
Muscle function: squeeze
- Adequate
- Accessory muscle use

Strain
- Adequate
- Puborectalis relaxation
- Prolapsing tissue
- Other organ prolapse

External Hemorrhoids

External hemorrhoids present with the acute onset of pain and swelling. The pain is highest in the first 48 hours after the onset of the thrombosis and gradually subsides over the next few days. The clot may resorb or erode through the epithelium, causing spotting of blood.

Table 70.3 Hemorrhoidal Classification

Degree	Description
First	Hemorrhoids bleed but do not prolapse
Second	Hemorrhoids prolapse on straining but reduce spontaneously
Third	Hemorrhoids prolapse and require manual reduction
Fourth	Prolapsed hemorrhoids cannot be manually reduced

Evaluation

On physical examination, hemorrhoids may present with prolapsed mucosa, as edematous external tags or soft, residual hemorrhoidal skin tags. Thrombosed external hemorrhoids appear as tender, firm, and often bluish masses. Having patients strain may be useful to demonstrate hemorrhoid prolapse. The digital examination allows for assessment of sphincter tone and the presence of a mass. Anoscopy is used to inspect internal hemorrhoids and assess the appropriateness of office-based treatment. Colonoscopy is indicated when patients have bleeding that is not consistent with physical examination findings, or when symptoms do not respond to initial treatment.

Treatment

Treatment should be tailored to the patient's symptoms, which do not always correlate with physical examination findings. One should clarify the patient's goals in seeking treatment. Patients may only want evaluation and reassurance that their condition is benign. Treatment of internal hemorrhoidal bleeding may not satisfy patients who are bothered by residual hemorrhoidal

tags. Treatment options include nonoperative measures alone, office-based procedures, or operative procedures.

Nonoperative Management

Excessive straining during defecation or prolonged sitting on the toilet, for example, while reading, contribute to hemorrhoidal problems. Symptoms can be reduced or eliminated in many patients by altering their dietary intake and lifestyle. Increasing fiber and fluid intake eliminates a large proportion of problems with grade I and II hemorrhoids and can significantly improve symptoms with higher-grade hemorrhoids. Fiber can be either dietary or supplemental and works by increasing bulk and moisture in the stool. Suppositories and topical ointments may provide temporary relief, but do not address the cause of the problem. Since most formulations include corticosteroids, long-term use can lead to issues with thinning of the skin and itching. Sitz baths soothe symptoms, but do not address the underlying cause of the problem. However, in patients with external hemorrhoid problems, using water for cleaning can be a useful adjunct to improving itching and avoiding overcleaning.

Office-Based Treatments

2 Rubber band ligation can be performed through an anoscope in the office without the use of anesthesia. It is essential to clarify expected outcomes with the patient, and that the office-based procedures might require repeat treatments. However, these procedures are quick and usually painless alternatives to surgery.

The band is placed around the hemorrhoid two to three cm above the dentate line, causing localized ischemia of the intervening tissue. Placement of the band too close to the dentate line will result in pain and is unlikely to help with symptoms (**Fig. 70.11**). Placing more than two bands at once may increase discomfort and is generally not recommended. Approximately 1 to 2 weeks after rubber band placement, the hemorrhoid tissue will slough, and the patient may experience spotting of blood. Rarely, significant bleeding requiring urgent intervention may occur. Fibrosis that occurs at the site of the banding causes fixation of the remaining hemorrhoidal tissue, which helps to prevent further prolapse and bleeding. Improvement or complete disappearance of symptoms may be achieved in more than 80% of grade I

and II hemorrhoids, but less than 30% of more advanced hemorrhoids.[3] Complications are rare and include pain and thrombosis, but a few cases of pelvic sepsis have been reported. Sclerotherapy involves the injection of a sclerosing agent (such as 5% phenol solution) into the submucosa that leads to fibrosis of the surrounding tissue. Injection is performed through an anoscope, and is an option for symptomatic hemorrhoids that are too small to band. It is important not to inject the sclerosant directly into the hemorrhoids, or thrombosis may ensue.

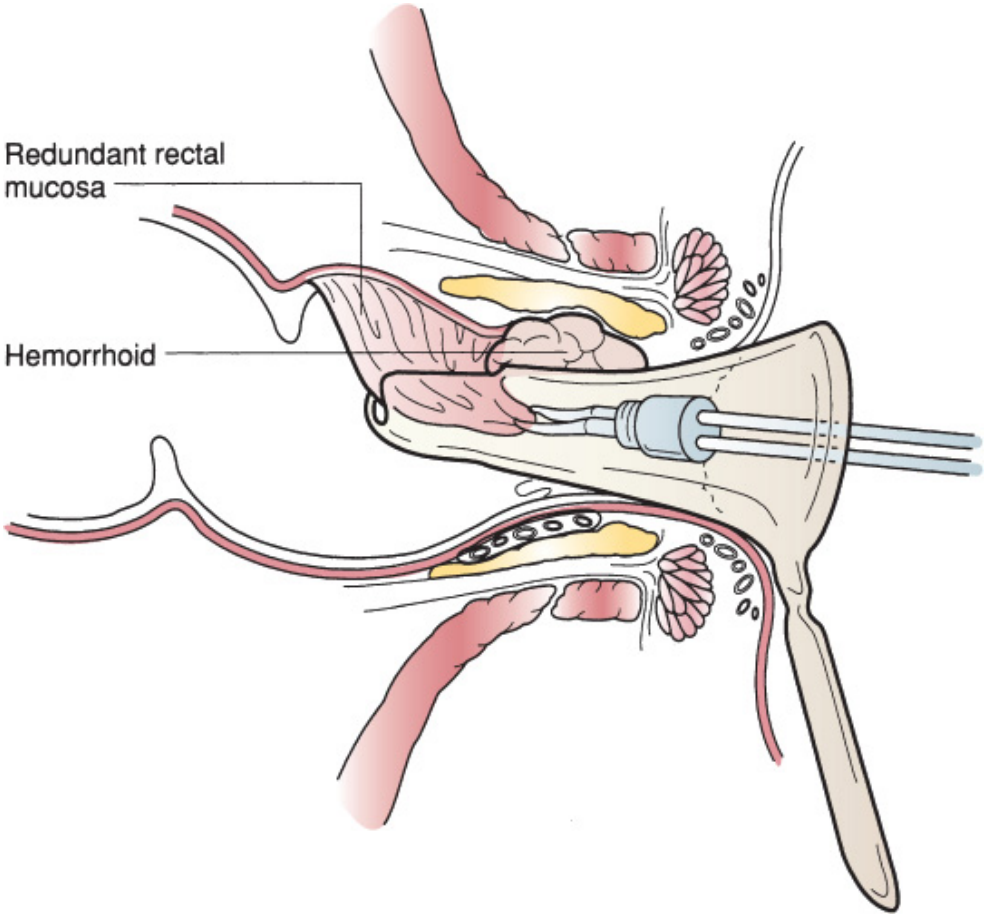


Figure 70.11 Rubber band ligation.

Operative Treatment

Excisional hemorrhoidectomy is the most definitive treatment for hemorrhoid-related symptoms and is indicated in patients who fail conservative or office-based procedures. Hemorrhoidectomy is typically an outpatient procedure, and in most cases performed under monitored

anesthesia care (MAC) and local or regional (spinal) anesthesia. The patient is placed in the prone jack-knife position with the buttocks taped apart. Initial ligation of the apex of the hemorrhoidal tissue helps to decrease bleeding during dissection. The skin is incised at the distal extent of the hemorrhoid and the hemorrhoidal tissue is carefully separated off of the underlying internal sphincter. The dissection may be undertaken with the use of a scalpel, scissors, electrocautery, or controlled electrical energy such as ultrasonic shears or a bipolar vessel-sealing device (**Fig. 70.12**). Vessel-sealing devices should be used with caution so as to not excise too much tissue. If more than one hemorrhoidal bundle is excised at once, it is also critical to ensure that at least 2 cm of normal anoderm is left between the excision sites to avoid postoperative anal stenosis. It is critical to preserve the underlying internal anal sphincter muscle. The wound may be left open or, more commonly, may be closed with absorbable suture. When closing the mucosa and anoderm, the dentate line should be reapproximated to avoid mucosal ectropion. Additionally, limiting intravenous fluids to <700 cc may help to decrease postoperative urinary retention, which occurs after approximately 15% of procedures.[4] Excisional hemorrhoidectomy is superior to office-based therapies in achieving complete remission. Surgery is associated with significant postoperative pain.[5] Multimodal analgesia including acetaminophen, NSAIDs, and minimal use of opioids is recommended. Gabapentin can also be added safely in most patients.

Stapled hemorrhoidopexy, known as procedure for prolapse and hemorrhoids (PPH), involves excision of a circumferential sleeve of mucosal and submucosa, thus interrupting hemorrhoidal vessels and pulling up the tissue. Enthusiasm for this procedure has waned due to rare but severe complications, including rectovaginal fistula, debilitating chronic pain, and pelvic sepsis. Long-term follow-up of hemorrhoidopexy compared to excisional hemorrhoidectomy show inconsistent results. Aytac et al. found similar rates of recurrent symptoms in both groups.[6,7]

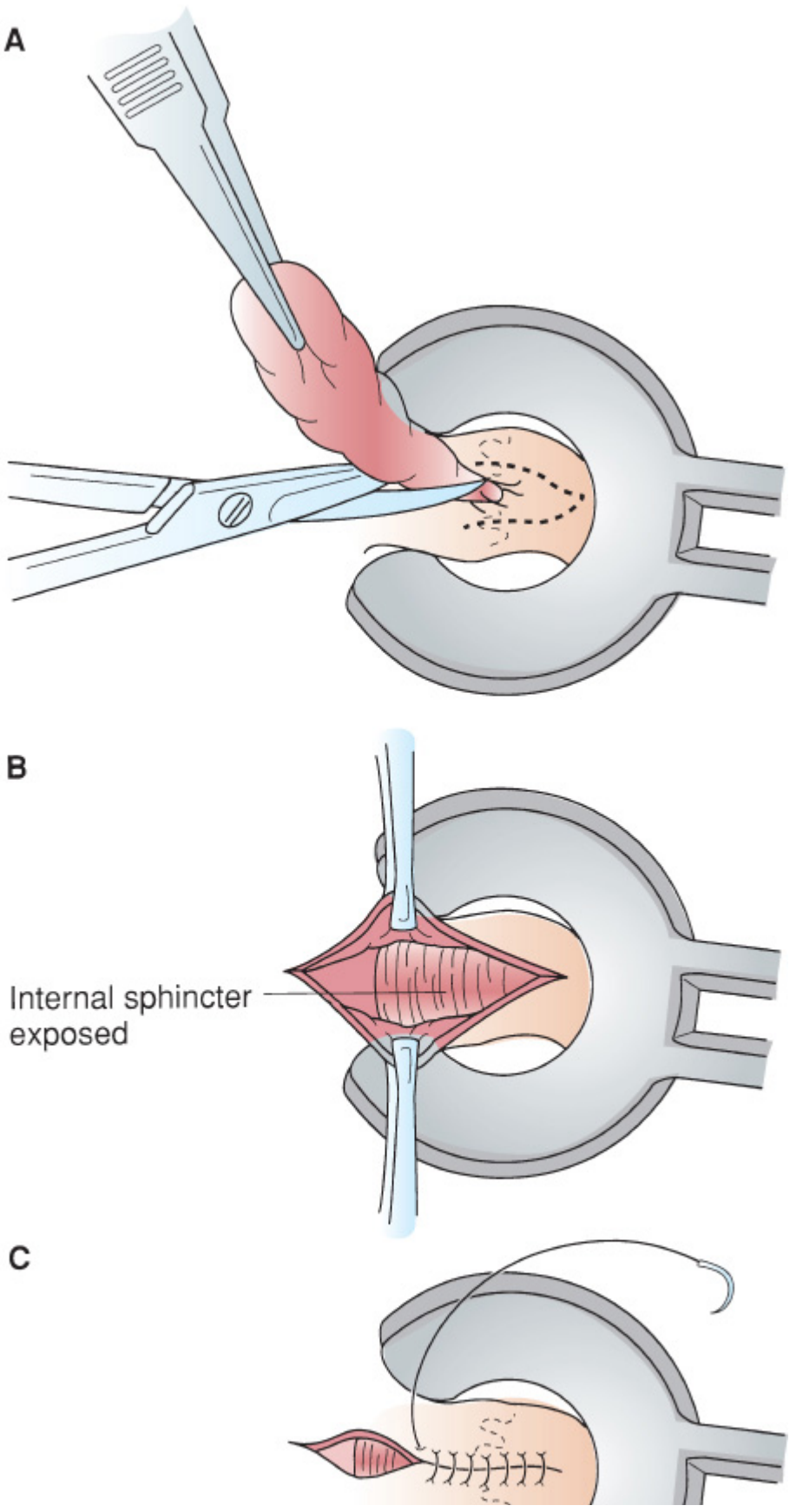

A
B
Internal sphincter
exposed
C

Figure 70.12 Technique of closed hemorrhoidectomy.

Doppler-guided transanal hemorrhoid devascularization involves suture ligation of each hemorrhoidal column without resection of the hemorrhoid. A specific anoscope that includes a Doppler probe is used to identify the signal of the vessel feeding each hemorrhoidal column, typically above or just at the top of the column. Once the vessel is identified, it is then ligated with a suture and the Doppler probe is again used to confirm the disappearance of the signal. Typically, the hemorrhoidal column is then also oversewn with this suture. The purported benefit of this procedure is that because the ligation occurs above the dentate line, postoperative pain should be significantly lower than with an excisional hemorrhoidectomy. This procedure requires the purchase of specific equipment and supplies and thus can have cost limitations.[8]

Special Hemorrhoid Situations

Thrombosed External Hemorrhoids

Thrombosed external hemorrhoids are a relatively common complication of hemorrhoidal disease. The exact etiology is unknown. Their occurrence is often associated with physical exertion or straining as well as severe diarrhea. Patients typically present with a painful, tender mass in the perianal area. Pain peaks at 48 to 72 hours and subsides over 3 to 5 days. This condition is self-limited and usually resolves on its own over a few weeks without any significant issues, although some patients are bothered by residual skin tags. Management is typically conservative and includes pain control with mild oral analgesia, warm sitz baths, and a bulk-producing agent. If a patient presents within 72 hours, when pain is still rising or at its peak, consider performing a thrombectomy. This procedure can usually be done in the office using local anesthesia and tends to decrease the intensity of pain, but not overall duration of symptoms. After administration of local

anesthetic (typically lidocaine with epinephrine) an incision is made in the anoderm overlying the thrombus and the clot evacuated with gentle pressure.[9]

Incarcerated Hemorrhoids

Rarely, patients present with prolapsed fourth-degree hemorrhoids that have become incarcerated. While internal hemorrhoids do not typically cause pain, patients with incarcerated hemorrhoids often have severe pain. On inspection, edematous prolapsed mucosa, with occasional thrombosis is seen. Although these hemorrhoids may look impressive, conservative management with analgesia, stool softeners, and sitz baths is preferred.

Gangrenous Hemorrhoids

Rarely, incarcerated hemorrhoids may necrose. This situation constitutes a surgical emergency, especially in high-risk patients with diabetes or immunosuppression. Precautions including leaving generous anoderm bridges between hemorrhoidectomy sites and avoiding injury to the sphincters should be undertaken to minimize the risk of the long-term complications.

Anal Fissure

An anal fissure is a tear in the mucosal lining of the distal anal canal. Although more commonly found in younger patients, fissures can occur at any age and equally afflict male and females. Fissures are classified as acute or chronic based on the duration of symptoms (with the 8-week mark distinguishing acute from chronic). The vast majority of the fissures (90%) are located in the anterior or posterior midline and are theoretically associated with a watershed area of blood supply.[10] Fissures may occur with trauma from passing hard stool or from diarrhea. Lateral fissures are less common and should alert the clinician to the possibility of infection, HIV, Crohn disease, or malignancy.

Clinical Manifestations

Anal fissure typically presents with sharp pain during defecation. Some individuals experience a persistent throbbing pain lasting from minutes to

hours after defecation. Rectal bleeding is typically minimal and limited to spotting on toilet paper.

Because most patients come in with severe pain, one should reassure the patient and limit the initial evaluation to avoid further pain and trauma. Gently spreading the buttocks apart to visualize anal verge and observing even part of the tear, often with an associated anal skin tag, is generally sufficient. Fibers of the internal anal sphincter are often visible at the base of the chronic fissure. Adding a digital examination or anoscopy exacerbates pain and is unlikely to provide additional information. If there is a concern for other issues, the patient should be taken to the operating room to be examined under anesthesia or return to the clinic within 6 to 8 weeks after treatment starts to allow for a more thorough examination. Some patients have superficial fissuring on the perianal skin, often accompanied by itching after a bowel movement, which is associated with perianal irritation/dermatitis. These fissures are more distal, superficial, and often multiple with associated skin irritation.

3 Management

Medical Management

Treatment of anal fissures concentrates on symptom relief. The presence of a fissure without any symptoms (once other causes are ruled out) is not an indication for treatment. Most patients experience improvement or complete disappearance of symptoms with a bowel management program consisting of increased dietary fiber, oral liquid intake, and stool softeners.[11] Topical application of 0.2% nitroglycerin ointment or a calcium channel blocker such as 2% nifedipine or diltiazem can also facilitate healing fissures. All formulations are applied superficially and have similar success rates of 50% to 60%. Nearly 30% of individuals treated with topical nitroglycerine report headaches.[12,13]

Botulinum Toxin Injection

Injection of endopeptidase blocks acetylcholine release, thus causing temporary paralysis of the muscle. Effects last for up to 3 months. The technique, dose, and success rate vary widely in the literature. Generally, 100 Units of botulinum toxin are injected directly into the internal sphincter in four to five aliquots. Recent studies show similar effectiveness between

Botox and topical nitrates.[14] Treatment with Botox may result in short-term incontinence to gas or rare infection from the injection itself. No significant long-term complications have been reported. Botox is an option for patients with continence problems, or when the use of a more definitive procedure is associated with a higher chance of complications. Although Botox can be injected in the office with local anesthesia, if the patient cannot tolerate anoscopy and diagnosis is uncertain, then anoscopy with sedation should be undertaken.

Surgical Management

Lateral internal sphincterotomy (LIS) is considered the gold standard for treating anal fissures and has a 98% success rate. LIS is an outpatient procedure associated with minimal postoperative discomfort. LIS is performed by incising anoderm overlying the internal sphincter and sharply dividing internal sphincter muscle extending cephalad with electrocautery under direct vision. Alternatively, using a closed technique, a scalpel is inserted in the intersphincteric groove, turned toward the anal canal and a portion of the muscle is divided toward, but not including mucosa. With both approaches, a divot in the internal sphincter should be easily palpated afterward. The defect in the anoderm is closed with absorbable suture (**Fig. 70.13**). The amount of sphincter muscle divided should be limited to the length of the fissure (tailored sphincterotomy) to decrease the chance of incontinence without significantly compromising the success rate. Sphincterotomy is associated with a 5% risk of incontinence and should not be offered to patients with baseline continence problems.[13] Sphincterotomy should not be performed in the anterior or posterior midline since this can result in a keyhole deformity leading to leakage of mucus and stool. If sphincterotomy is not successful, one may proceed with a repeat lateral sphincterotomy on the opposite side. In patients with resistant fissures or continence problems, advancement flaps such as house or V-Y flaps can be performed. Healing rates following fissurectomy and advancement flap are comparable to those following sphincterotomy.[15]

Anorectal Abscess

Anorectal abscesses typically result from infection of the glands that empty into the anal crypts within the anal canal. Anorectal abscesses may also occur following iatrogenic trauma or malignancy. Rarely, infections such as tuberculosis and actinomycosis may result in a perianal abscess. The glands lie within the intersphincteric space. Therefore, when the glands become infected, an abscess originates within the anal space and may extend to other perianal spaces (**Figs. 70.14** and **70.15**).

Clinical Manifestations

Abscesses present with acute onset of perianal pain, often accompanied by fever. Superficial perianal or ischiorectal abscesses may have associated external induration, fluctuance, or erythema, whereas deeper abscesses may lack external manifestations. Tenderness and fullness may be palpable on digital rectal examination. Associated symptoms may include tenesmus and difficulty voiding.

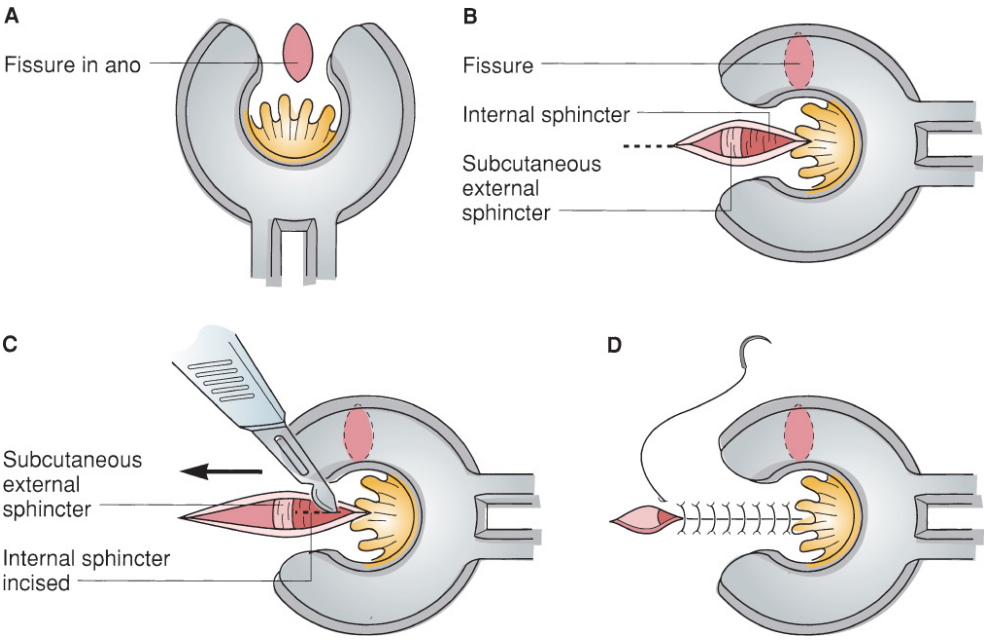


Figure 70.13 Lateral internal sphincterotomy.

Evaluation

When a perianal abscess is suspected, but physical examination findings are limited, a computed tomography (CT) scan or pelvic MRI is helpful to identify underlying pathology.

Management

The key to managing an anorectal abscess is adequate incision and drainage. Superficial abscesses may be amenable to drainage in the outpatient setting. One approach to draining an abscess is to make a 1-cm incision over the abscess cavity at the point of most tenderness or fluctuance. When choosing the site for incision, consider the potential for subsequent fistula formation. An external fistula opening may occur at the site of the incision site. Therefore, one should choose an incision site as close as possible to the anal verge that still allows for adequate drainage. A 10-F to 16-F drainage catheter (Pezzer or Malecot) is inserted through the incision into the abscess cavity (**Fig. 70.16**). Alternatively, a larger elliptical or cruciate incision may be made over the abscess cavity. If using a cruciate incision, excise the skin edges to allow for ongoing drainage. Patients should irrigate or soak the wound and cover it with dry gauze. Anoscopy with examination of the dentate line may reveal an internal fistula opening. Probing to identify a fistula tract at the time of abscess drainage should be done with caution as aggressive probing may create a false tract. A superficial fistula tract identified at the time of abscess drainage may be treated with primary fistulotomy. For deeper fistulas, a draining seton, consisting of a silastic band or nonabsorbable suture, should be placed in the fistula track.[16] Antibiotics are not used routinely after adequate drainage, but are indicated when there is extensive surrounding cellulitis or in patients with diabetes or who are immunocompromised.

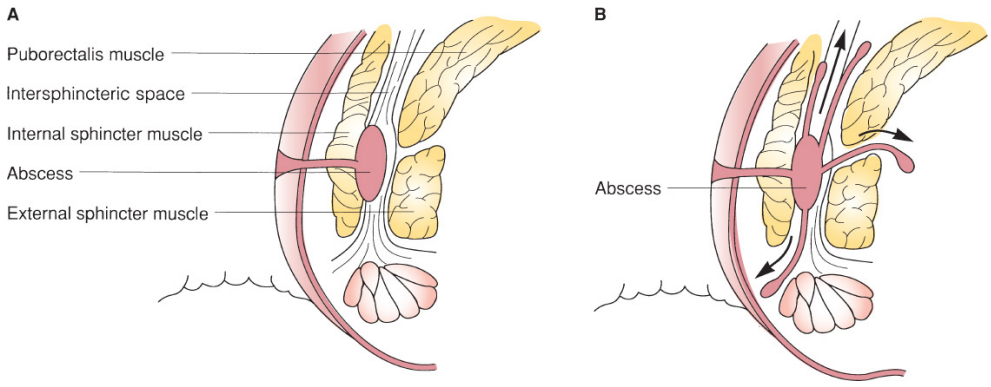


Figure 70.14 **A, B:** Pathways of infection.

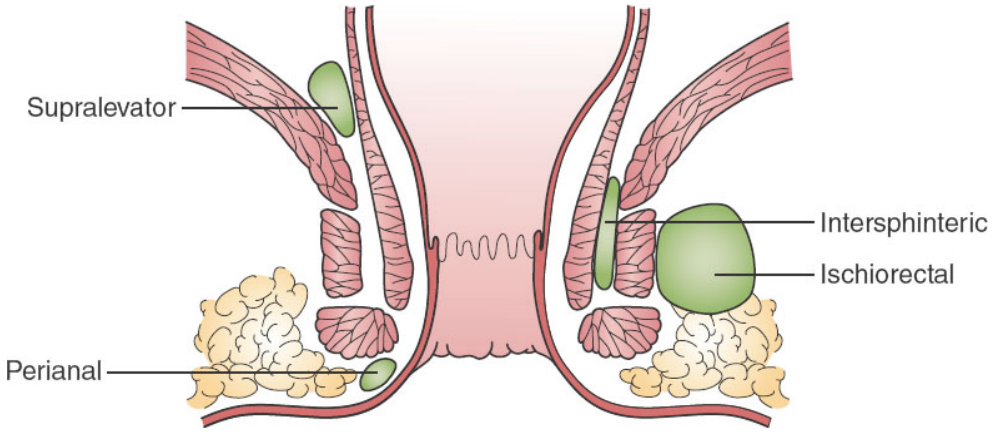


Figure 70.15 Classification of anorectal abscesses.

Deeper abscesses may require drainage in the operating room with sedation or general anesthesia. An abscess involving bilateral ischioanal spaces is referred to as a horseshoe abscess. These infections originate in the posterior midline and extend to both ischioanal spaces. Treatment may require bilateral incisions overlying the ischioanal areas. Supralevator abscesses are less common and can be difficult to diagnose. Because the location of the abscess is adjacent to the abdominal cavity, patients may present with abdominal or pelvic pain. Digital examination may demonstrate induration or a tender mass located in the distal rectum above the level of the anorectal ring. The etiology of a supralevator abscess dictates its management. These abscesses may result as an extension of an intersphincteric abscess, extension of an ischioanal abscess, or may result from an intra-abdominal abscess from perforated diverticulitis, appendicitis, or Crohn disease. A supralevator abscess secondary to extension from an ischioanal abscess should be drained through the ischioanal area. A supralevator abscess secondary to extension from an intersphincteric abscess should be drained into the rectum, as drainage through the ischioanal area may result in a complex suprasphincteric fistula. Percutaneous, image-guided, drainage may be an option in patients with a supralevator abscess secondary to an intra-abdominal source.

Rarely, anorectal abscesses can result in necrotizing infection and death, a condition referred to as Fournier gangrene. This situation may result from a delay in diagnosis and management of an anorectal abscess, infection with a highly virulent organism, or may be due to patient factors such as diabetes or compromised immune function. The infection superficially spreads around

the perineum, causing necrosis of the skin and underlying muscle and fascia. Treatment includes empiric broad-spectrum intravenous antibiotics and prompt surgical debridement of the necrotic tissue until healthy tissue is encountered.

After adequate drainage, approximately half of patients heal.[16] Alternatively, patients may experience a recurrent abscess or develop an anal fistula.

Anal Fistula

Clinical Manifestations

A recurrent abscess is usually indicative of a cryptoglandular fistula arising from the glands in the anal crypts. Fistulas may occur without a prior history of an abscess. Fistulas present as a perianal nodule, often with persistent or intermittent purulent drainage. On physical examination, there may be an external opening with granulation tissue. Sometimes the external opening closes over superficially, making the fistula challenging to identify.

The differential diagnoses of cryptoglandular fistulae include hydradenitis, which is inflammation of the apocrine sweat glands with resulting subcutaneous fistula tracts. In hydradenitis the fistulae are superficial and do not extend into the anal canal. A second differential is pilonidal disease. The origin of inflammation of pilonidal disease is a tuft of hair in the gluteal cleft creating a foreign body reaction.

Evaluation

A thorough history should include information about the duration of symptoms, a history of prior anorectal surgery, sphincter function, and associated urogenital symptoms. Additionally, one should inquire about a change in bowel habits or abdominal symptoms that may suggest Crohn disease.

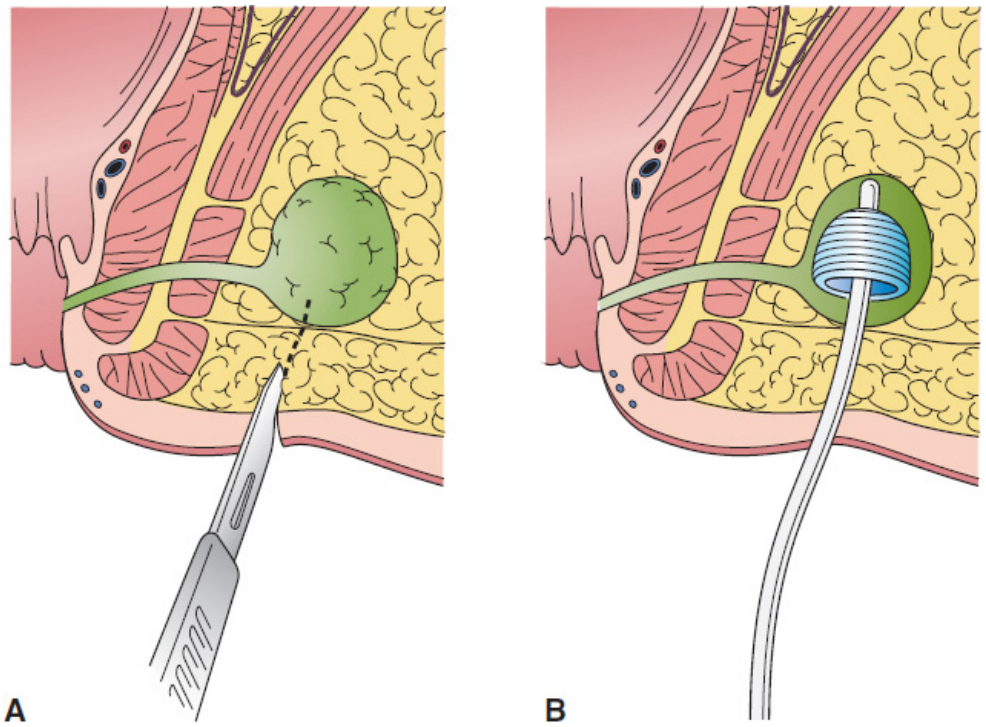


Figure 70.16 Abscess drainage with drain placement.

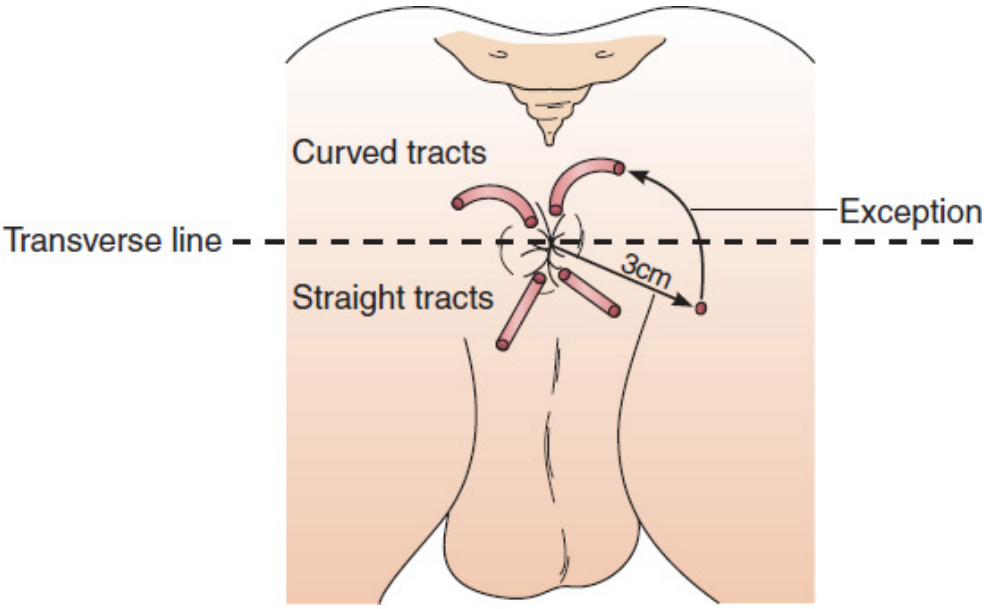


Figure 70.17 Goodsall rule.

Goodsall rule states that if an imaginary line is drawn transversely across the anus, an external fistula opening seen posterior to this line originates from an internal opening in the posterior midline, whereas an opening anterior to this line originates from the closest anal crypt (**Fig. 70.17**). Locating the

internal opening is not always possible with a fistula probe, and in this situation other diagnostic maneuvers may be necessary. Injection of the external opening with hydrogen peroxide, with or without the use of endoanal ultrasound, may help identify smaller fistulas. For patients with complex fistulas, including multiple fistulas, recurrent fistula, and fistulas associated with Crohn disease, ultrasound, MRI or fistulography with a water-soluble contrast and fluoroscopy may help to delineate a fistula tract.

Management

The first step in treating a fistula is to identify the entire length of the fistula tract. During an examination under anesthesia with the patient under MAC in the prone or lithotomy position, a probe is passed along the course of the fistula tract and assessed relative to the degree of sphincter muscle proximal and distal to the fistula tract. The fistulotomy, that is, unroofing of the fistula tract, is performed for the portion of the fistula peripheral to the anal sphincter. Simple, superficial fistulas may be treated with primary sphincterotomy. In general, involvement of less than 30% of the sphincter muscle is considered amenable to primary sphincterotomy. In women, the anterior anal canal is shorter, and one should be cautious about performing an anterior fistulotomy. Primary fistulotomy is associated with fistula healing rates as high as 90%.[16] For fistulas involving more sphincter muscle than is prudent to divide, place a seton and plan for a definitive interval procedure.

4 There are numerous options for treating fistulas. Regardless of technique, the goal is to obliterate the fistula tract while preserving sphincter function. Treatment options include primary fistulotomy, seton placement, advancement flaps, and ligation of intersphincteric fistula tract (LIFT). Instillation of fibrin glue and the use of a fistula plug are associated with high recurrence rates and are not recommended as primary treatment for fistulas.[16]

After initial placement, a seton may be sequentially tightened at 2- to 4-week intervals to form a “cutting” seton where the seton gradually erodes through the sphincter muscle. When the seton is deemed to be superficial enough, a second-stage fistulotomy is performed to remove the seton. The cutting seton is associated with success rates as high as 94%. The disadvantage of using a cutting seton is the risk of compromise of the

sphincter function. There is a wide range of rates of reported incontinence following the use of the cutting seton ranging between 23% and 22%.[17,18]

An endoanal advancement flap is commonly used for more complex fistulas. This procedure involves raising a flap of mucosa with the underlying internal sphincter muscle (**Fig. 70.18**). The fistula tract is curetted, and the internal fistula tract opening is sutured closed with absorbable suture. The raised flap of tissue is placed over the internal opening and sutured in place. The success rate of the advancement flap ranges from 66% to 87%.[16,19] In the case of a failed advancement flap, one may perform a repeat flap repair after an interval to allow for resolution of inflammation.

Another treatment for an anal fistula is the LIFT procedure (**Fig. 70.19**). After a seton has been in place long enough for fibrosis around the seton to form, the fistula tract is ligated and divided. An incision is made over the intersphincteric groove and deepened down to the fistula tract. Both ends of the exposed length of the fistula tract are ligated, and the tract is sharply divided. Reported success rates after the LIFT procedure range from 40% to 95%.[20,21]

Anal Fistula and Crohn Disease

Anal fistulas occur in 13% to 54% of individuals with Crohn disease.[22] Asymptomatic fistulas in the setting of Crohn disease do not need to be treated.[16] Crohn-related fistulas may be complex with more than one external opening. The first step in treating these fistulas is to unroof the branching tracts to create a single track at the internal opening. Patients may experience adequate symptomatic control with medical management using an anti-TNF medication.[23] Once a single fistula without inflammation is achieved, the techniques for treating fistulas described previously are applicable to patients with Crohn-related fistula. Before attempting a fistula repair procedure, examination should assess for anal canal fibrosis and acute mucosal inflammation. Crohn-related anal fistulae may be controlled with long-term seton placement and medical management. Temporary diversion may facilitate fistula healing, and proctectomy may be necessary for severe perianal disease (**Box 70.1**).[24]

Anovaginal and Rectovaginal Fistulae

Clinical Manifestations

A rectovaginal fistula is a communication between the anterior anus or rectal wall and the posterior vagina. Such fistulae can be debilitating due to the passage of gas or stool into the vagina resulting in incontinence and skin excoriation. An anovaginal fistula may occur as a complication from cryptoglandular disease with or without associated Crohn disease. Anovaginal fistulae may also result from obstetric injury, iatrogenic injury from stapled hemorrhoidopexy, low anterior resection, or other perineal trauma.

Box 70.1 Classification of Anal Fistulas

Intersphincteric Fistula. The tract of the fistula lies within the intersphincteric space and the external opening lies close to the anal verge. These fistulas are the most common, and typically result following a perianal abscess.

Transsphincteric Fistula. The fistula tract begins in the intersphincteric space and then traverses through a portion of the external sphincter muscle. The external opening typically lies over the ischioanal fossa.

Suprasphincteric Fistula. The fistula tract begins in the intersphincteric space and then passes upward above the external sphincter and then perforates the levator ani muscles to drain through the ischioanal fossa.

Extrasphincteric Fistula. The fistula tract begins in the distal rectum rather than the anal canal and perforates the levator ani muscles to drain through the ischioanal fossa. These fistulas are rare and develop typically from Crohn disease or rectal trauma.

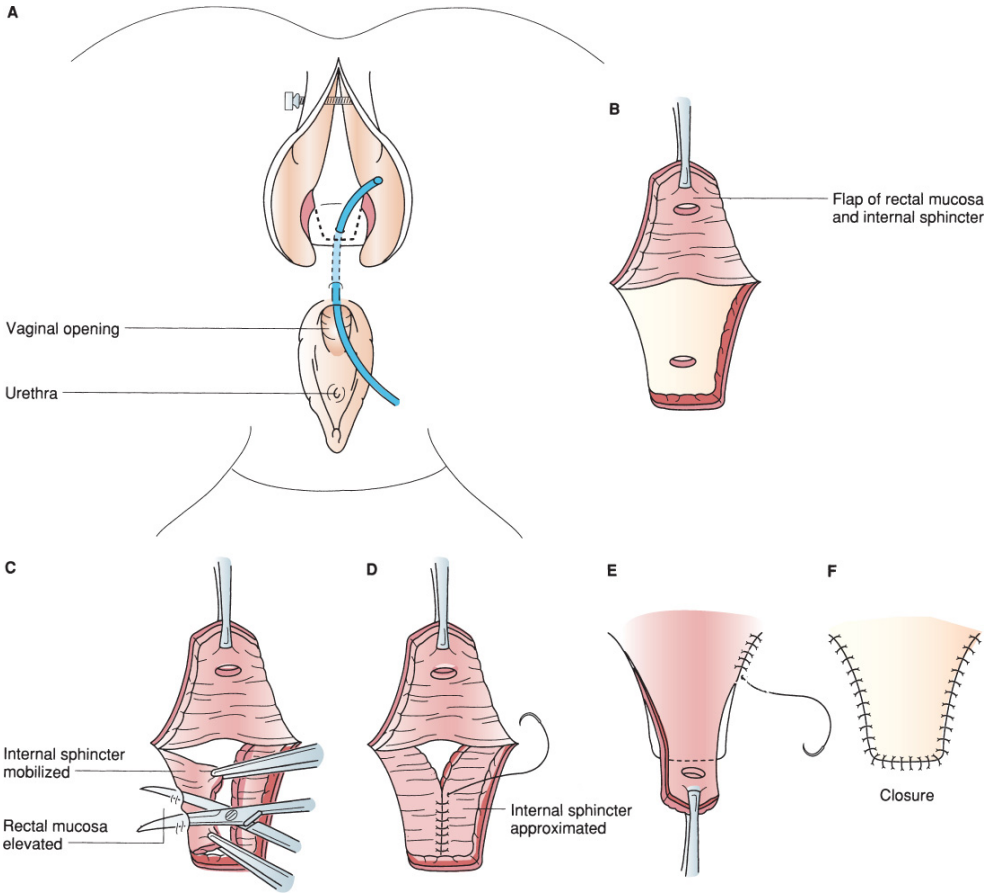


Figure 70.18 Mucosal advancement flap.

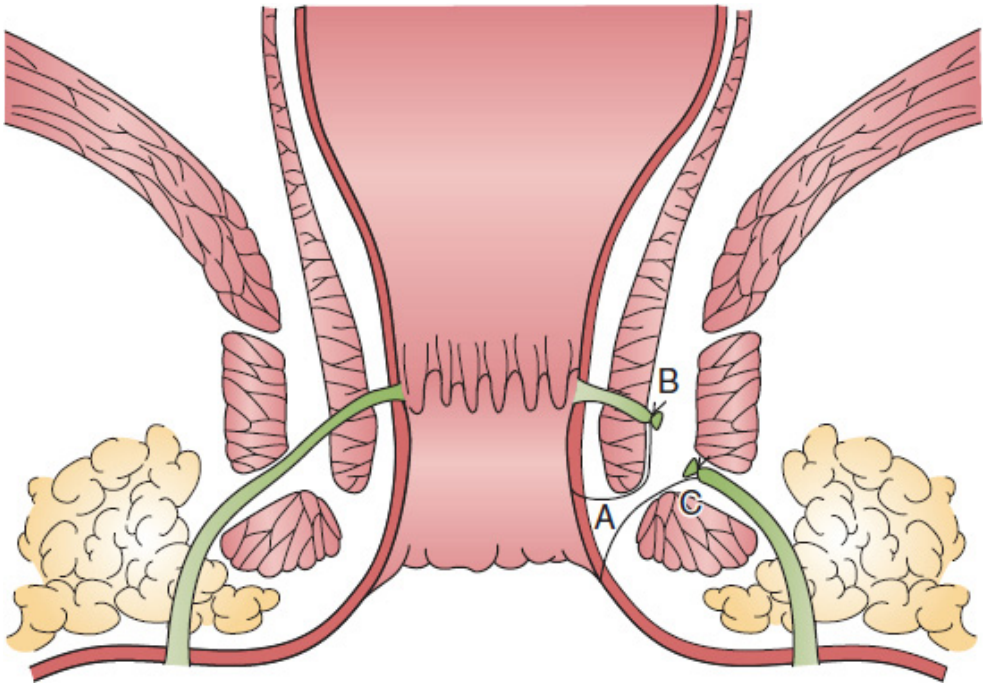


Figure 70.19 Anal fissure: ligation of intersphincteric fistula tract.

Evaluation

The clinician should ask about the patient's obstetric and surgical history. Obstetric injury may result in a fourth-degree (full thickness) tear of the rectovaginal septum. In addition to leakage of stool per the vagina, individuals may experience anal incontinence due to sphincter compromise. Physical examination should include inspection of the perianal skin and introitus. A digital rectal examination allows for assessment of sphincter tone, the thickness of the perineal body, and possible palpation of an anterior rectal wall defect. Anoscopy may help to visualize the opening in low fistulas, while proctoscopy or flexible sigmoidoscopy may be necessary to identify mid or high fistulas. If a rectovaginal fistula is suspected clinically, but no defect can is seen, a rectal enema of saline or water with methylene blue after vaginal tampon insertion can be useful. Staining on the tampon is indicative of a fistula. A contrast enema under fluoroscopy may be needed in complex cases to identify the fistula. In the setting of a low fistula occurring after obstetric injury, evaluation should include an assessment of the anal sphincter using ultrasound.

Management

In patients with small fistulas and minimal symptoms, medical treatment with bulking agents such as fiber may be sufficient in controlling symptoms. Fistula repair following an obstetric injury should be delayed 3 to 6 months to allow for resolution of inflammation. Similarly, repeat surgery after a prior failed repair should be delayed 3 to 6 months following the prior repair.[25]

Treatment of low rectovaginal or anovaginal fistulas with an intact sphincter may be accomplished by endorectal advancement flap or vaginal advancement flap. Most colorectal surgeons prefer to perform an advancement flap transanally rather than vaginally as the repair is to the high-pressure side. The opening in the vagina may be left open to drain. Success rates of endorectal advancement flaps for simple low rectovaginal fistulas range from 41% to 78%.[16]

If a low rectovaginal fistula is associated with incontinence secondary to a defect in the anal sphincter, repair with an overlapping sphincter repair has been shown to have good results. Episioproctotomy (perineoproctotomy) involves dividing the tissue distal to the fistula. The rectal mucosa is then repaired followed by an overlapping sphincter repair to form a buttress between the rectal and vaginal defects. Finally, the vaginal mucosa and anoderm are reapproximated. Hull et al. compared the outcomes of 50 women with rectovaginal fistulas treated with episioproctotomy and 37 who underwent rectal advancement flap for anovaginal fistulas. The success rates for fistula healing were similar for both procedures—78% for episioproctotomy and 62% for mucosal advancement flap. Episioproctotomy was associated with significantly better fecal continence ($P < 0.01$) and sexual ($P = .04$) function.[26]

High rectovaginal fistulas are treated with an abdominal procedure based on the etiology of the fistula and the condition of surrounding tissues. The principles of fistula repair include identifying healthy, well-vascularized tissue and utilizing interposition grafts such as omentum or rectus muscle to decrease the risk of recurrent fistulization.

Pilonidal Disease

Clinical Manifestations

Pilonidal disease is subcutaneous inflammation caused by embedded hair resulting in a foreign body reaction. Pilonidal disease may present as an acute abscess with pain, induration, erythema, or fluctuance adjacent to the gluteal cleft. Pilonidal disease may also manifest as a series of one or more chronic sinus tracts or "pits" in the gluteal cleft.

Evaluation

Physical examination is usually adequate for evaluating a pilonidal sinus tract. MRI may be helpful to differentiate a pilonidal sinus from a cryptoglandular fistula.

5 Management

An acute pilonidal abscess is managed by incision and drainage. Definitive treatment of chronic pilonidal disease involves excising the nidus of infection, commonly with excision of the skin and subcutaneous tissue to incorporate all of the residual pits. The wound can then be left open or closed. There are various described techniques for wound closure.

Midline closure is associated with a relatively high recurrence rate.[27] The alternative closure techniques involve incision placement lateral to the gluteal cleft and skin advancement or rotational flaps that result in an asymmetric closure off of the midline (**Fig. 70.20**). Less-invasive techniques, including pit excision alone using a punch biopsy and phenol instillation to obliterate the sinus tract, are associated with higher recurrence rates (**Table 70.4**).[28]

Fecal Incontinence

Clinical Presentation

Fecal incontinence is, "the uncontrolled passage of feces or gas over ≥1 month's duration, in an individual of ≥4 years of age, who had previously achieved control."[29] The severity of incontinence may range from minor soiling to complete incontinence of solid stool. Fecal incontinence affects up to 18% of the population.[30]

Anal continence depends on the reservoir function of the rectum, the individual's ability to sense the presence of stool in the rectum, and the

coordinated function of the anal sphincters and pelvic floor. (See section on Physiology.) Fecal incontinence is a symptom that may result from a variety of clinical conditions. Alterations in stool consistency or changes in rectal compliance due to inflammatory bowel disease or following pelvic radiation may overwhelm normal anal sphincter continence mechanisms. Neurologic disorders may affect both rectal sensation and muscle coordination. Iatrogenic injury to the sphincter can occur with anal surgery such as fistulotomy, sphincterotomy, or hemorrhoidectomy. In women, obstetric injury is a common cause of anal incontinence. Approximately 5% of vaginal deliveries result in sphincter injury. The effects of an obstetric sphincter injury may not manifest until decades following the injury. Risk factors for obstetric sphincter injury include nulliparity, increased birth weight, Asian race, use of instrumentation such as vacuum-assisted birth, and a prolonged second stage of labor.[31]

Evaluation

A thorough history should identify potential causes of incontinence and delineate the nature of the patient's symptoms, including frequency of bowel movements, the presence of tissue prolapse with bowel movements as well as the frequency of incontinence episodes, and whether the incontinence is to flatus, liquid stool, or solid stool. The initial evaluation should also assess the extent to which a patient's symptoms affect their quality of life.[29] When evaluating a patient with incontinence, differentiating between incontinence related to a compromised sphincter, soiling due to mucosal prolapse, or overflow incontinence related to underlying constipation is necessary. Fecal incontinence in the absence of urgency or incontinence to flatus is suggestive of soiling related to mucosal prolapse. Straining with bowel movements or a sensation of incomplete evacuation raises the suspicion of pelvic floor dysfunction.

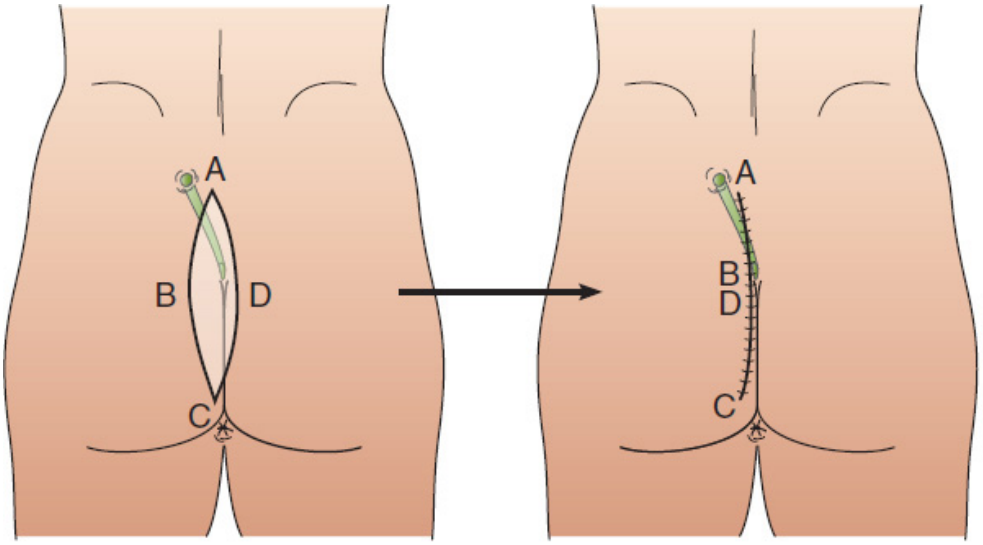
Physical examination should include inspection of the perianal skin for scars from previous surgery or obstetrical injury and excoriation from chronic soiling. Separation of the buttocks may demonstrate gaping of the anus in individuals with a compromised sphincter. Digital examination can provide a gross assessment of both resting tone and squeeze effort. Anoscopy may identify mucosal inflammation or enlarged internal hemorrhoids.

The structural integrity of the anal sphincters is commonly assessed using endoanal ultrasound. Transperineal ultrasound or MRI can also assess sphincter anatomy. Defecography, dynamic MRI, and anal manometry are useful to assess anal sphincter and pelvic floor muscle function. Manometry measures anal pressure using a transducer catheter placed in the anal canal. Pressures are recorded with the patient at rest, when squeezing, and during simulated defecation. Evaluation of rectal sensation is performed by placing a balloon catheter above the anorectal ring and then gradually inflating the balloon with air. There are wide ranges of manometric values in asymptomatic individuals and variability with age and sex (see **Table 70.5**).

Management

Bowel Management Program

Patients with loose stool may benefit from a bowel management program that includes increased dietary fiber to bulk the stool and absorb excess liquid, making the stool easier to sense and control. Medical management may include constipating agents such as loperamide or diphenoxylate atropine. Bile acid binders can also thicken the stool and decrease stool frequency. Taking an enema after a bowel movement helps to empty the rectum, thereby decreasing the leakage between bowel movements.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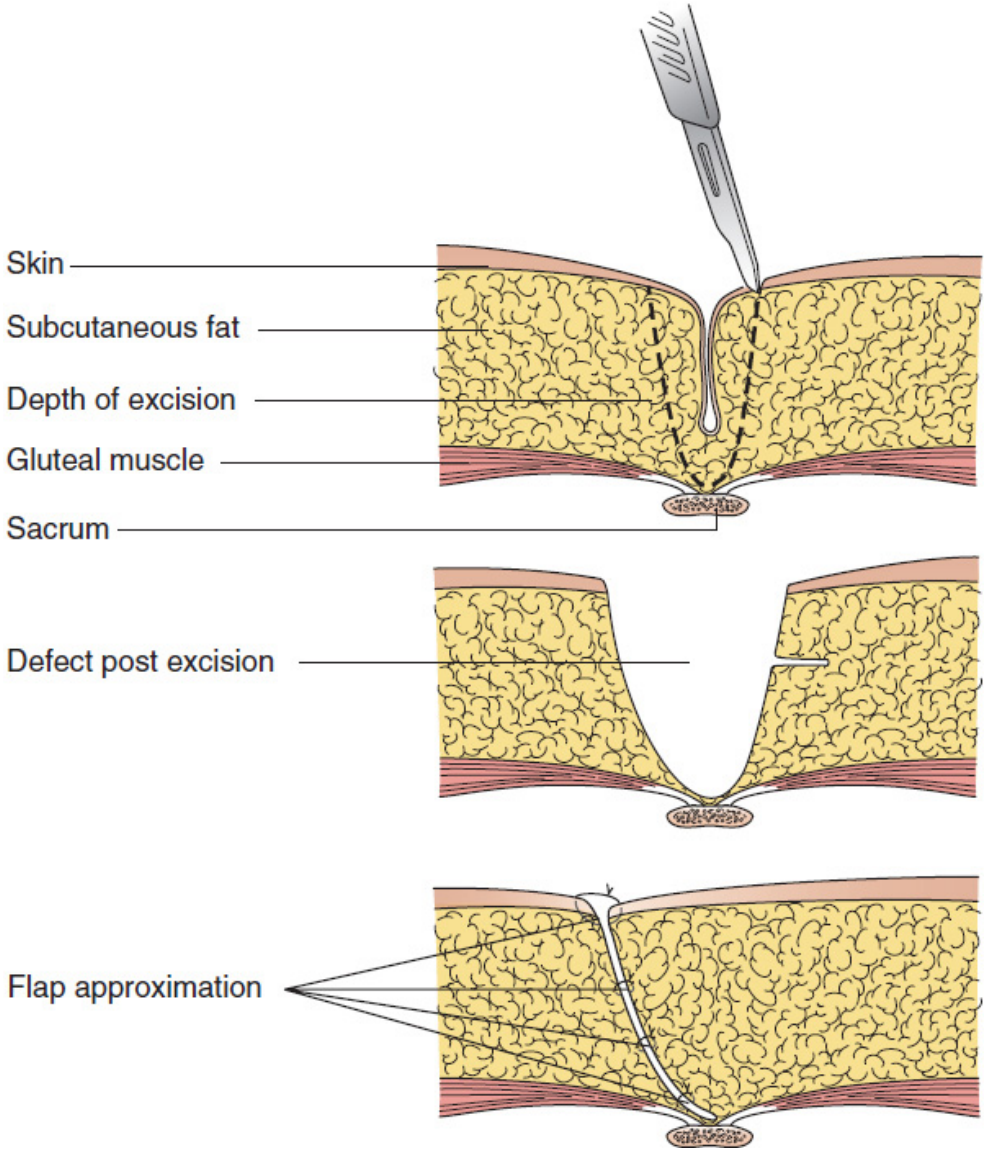
Skin
Subcutaneous fat
Depth of excision
Gluteal muscle
Sacrum
Defect post excision
Flap approximation

Figure 70.20 Pilonidal disease: excision of pilonidal disease.

Table 70.4 Treatment Options and Outcome for Chronic Pilonidal Sinus

Procedure	Recurrence Rate (Mo Follow-Up)		
	12	24	60
Incision and Drainage	10.4	25.9	40.2
Phenol	1.9	14.1	40.4
Pit Excision	2.7	6.5	15.6
Primary Excision and Open Wound	1.5	4.2	13.1
Midline Wound Closure	3.4	7.0	16.8
Asymmetric Closure +/− Flap	0.2–1.0	0.6–1.6	3.2–5.2

Stauffer VK, Luedi MM, Kauf P, et al. Common surgical procedures in pilonidal sinus disease: a meta-analysis, merged data analysis, and comprehensive study on recurrence. *Sci Rep* 2018;8(1):3058.

Pelvic Floor Physical Therapy

Pelvic floor physical therapy helps to optimize sphincter and pelvic floor function. Therapy is targeted to the patient's need and may include sphincter strengthening, coordination of pelvic floor relaxation during defecation, and improving rectal sensation. Biofeedback typically employs the use of a pressure-sensitive probe placed into the anal canal to measure the strength and coordination of the anal sphincter and pelvic floor musculature. Data is transmitted to a monitor, where the patient can watch the manometric tracings. Through a series of coached exercises and visual feedback, patients can improve abdominal wall and pelvic floor muscle coordination. Reported rates of improvement with biofeedback range from 50% to 90%.[32] Successful therapy depends on the knowledge and skills of the therapist and patient motivation.

Sacral Neuromodulation

Interventions to treat fecal incontinence consistent of neuromodulation and techniques of sphincter augmentation. Sacral neuromodulation involves stimulation of a sacral nerve with an implantable stimulator (**Fig. 70.21**). The exact mechanism of this technique is not known. Studies have demonstrated improvement in symptoms even with an existing sphincter defect. This technique involves placing an electrode into the foramen of the sacral vertebrae, most commonly S3. The electrode is initially connected to an external neurostimulator. If the patients experience improvement in function, a long-term neurostimulator is placed subcutaneously. Complications following neurostimulator implantation include infection, pain, either at the stimulator site or painful stimulation and loss of efficacy over time. Reoperation rates, including replacement of a lead, battery, or explant of the device range up to 39%.[33]

Table 70.5 Anal Manometric Parameters

Measurement	Definition	Normal Range
High-pressure zone	The length of the anal canal with resting pressures ≥30% higher than rectal pressure	3–5 cm
Resting pressure	The pressure in the high-pressure zone at rest after a period of stabilization	40–70 mm Hg
Maximum voluntary pressure	The highest pressure recorded above the baseline (0) at any level of the anal canal during maximum squeeze effort by the patient	>70 mm Hg
Squeeze pressure	Calculated difference between the maximum voluntary pressure and the resting pressure	>100 mm Hg
Sphincter endurance	The length of time that the patient can maintain a squeeze pressure above the resting pressure	>10 sec
Rectal pressure	Pressure generated by the rectum with rest, squeeze, and push	60–70 mm Hg
Sensory threshold	The minimum rectal volume perceived by the patient	20–40 mm Hg
Urge sensation	*Sensation* is the volume associated with the initial urge to defecate	80–140 mm Hg
Maximum tolerated volume	The volume at which the patient experiences discomfort and an intense desire to defecate	130–150 mm Hg

Balloon expulsion test	Evaluates the ability of the patient to expel a balloon inflated with 50–60 mL of water	Patients with normal anorectal function are expected to expel the balloon

Lee GC, Kunitake H, Milch H, et al. What Is the Risk of Anal Carcinoma in Patients With Anal Intraepithelial Neoplasia III? *Dis Colon Rectum* 2018;61:1350–1356.

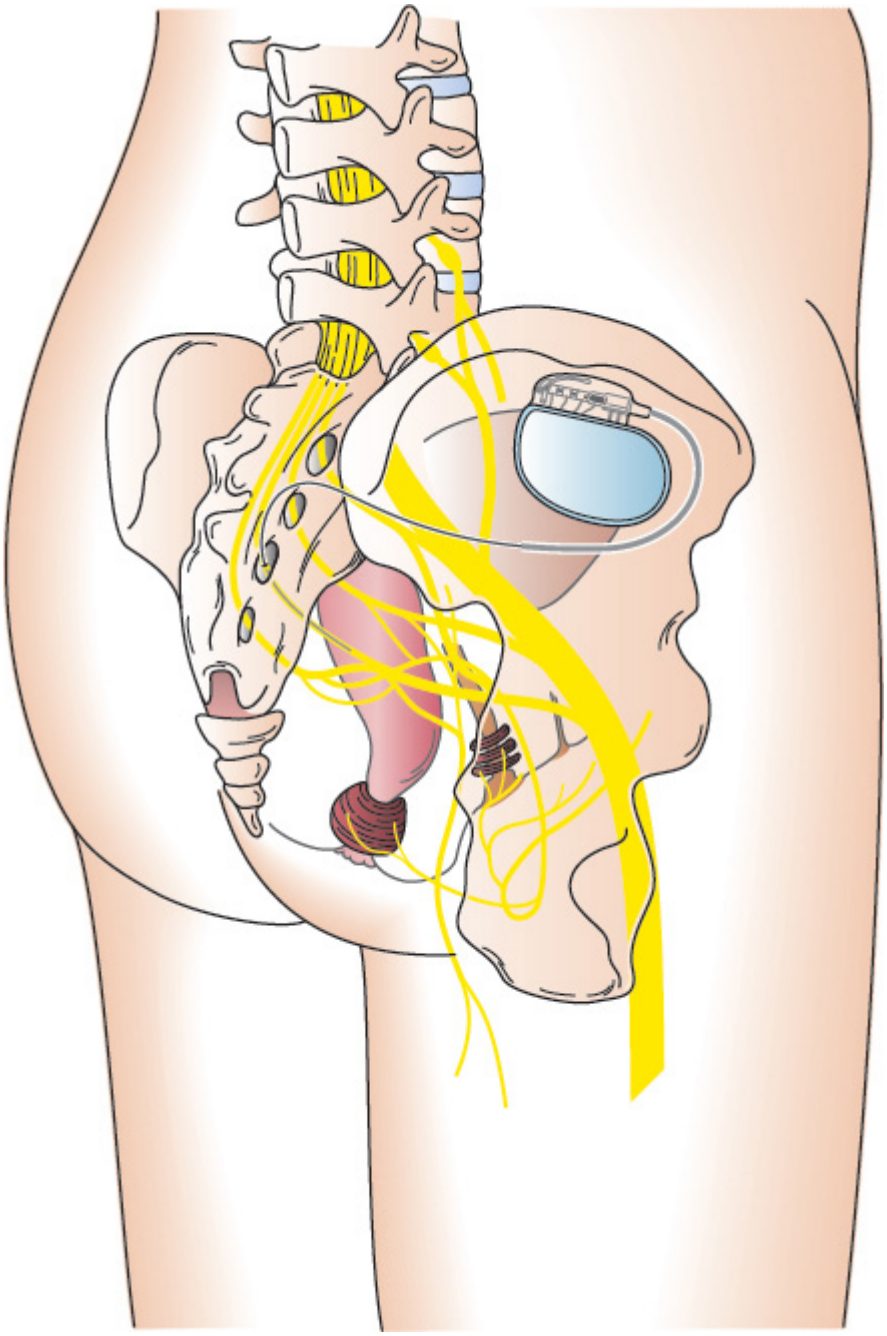

Figure 70.21 Fecal incontinence: sacral neuromodulation.

Sphincter Repair and Augmentation

An overlapping sphincter repair is an option for patients with significant external sphincter defects. The fibrotic scar tissue at the site of the defect is divided, and the two ends of the sphincter muscle are identified and are mobilized laterally. The ends of the muscle are sutured in an overlapping fashion (**Fig. 70.22**). While this procedure is associated with an initial success rate of greater than 80%, the durability of the repair is limited with nearly half of patients developing recurrent incontinence after long-term follow-up.[34] Less common treatments include the Secca procedure, which involves the use of radiofrequency delivered to the anal sphincter, results in tissue remodeling.[35] Several case series have demonstrated the short-term efficacy of this procedure, with more than half of patients treated reporting improvement in their symptoms. More recent studies show varied results regarding the long-term effectiveness of the Secca procedure.[36,37] Another option for treating mild incontinence is the injection of a bulking agent (silicone or carbon-coated microbeads) into the anal submucosal or intersphincteric space to increase resting pressures by augmenting the anal cushions or restoring anal canal symmetry.[38]

In rare instances, sphincter replacement with a prosthetic device may be considered (**Fig. 70.23**). Durable 5-year results have been reported, with 89% of patients reporting improvement and 36% reporting full continence.[39] In patients with severe incontinence for whom alternative methods have failed, the creation of a sigmoid colostomy may improve quality of life and allow them to resume normal daily activities.

Rectal Prolapse

Clinical Manifestation

Rectal prolapse is the full-thickness protrusion of the rectum through the anal canal. Rectal prolapse occurs in approximately 0.5% of the general population and is more common in women.[40] Although typically seen in women over age 50 years old, rectal prolapse may be seen in younger individuals with developmental delay or psychiatric comorbidities. Rectal prolapse may be associated with chronic constipation in up to 50% of

individuals.[40] The chronic traumatic stretch of the anal sphincter results in fecal incontinence in the majority of patients.

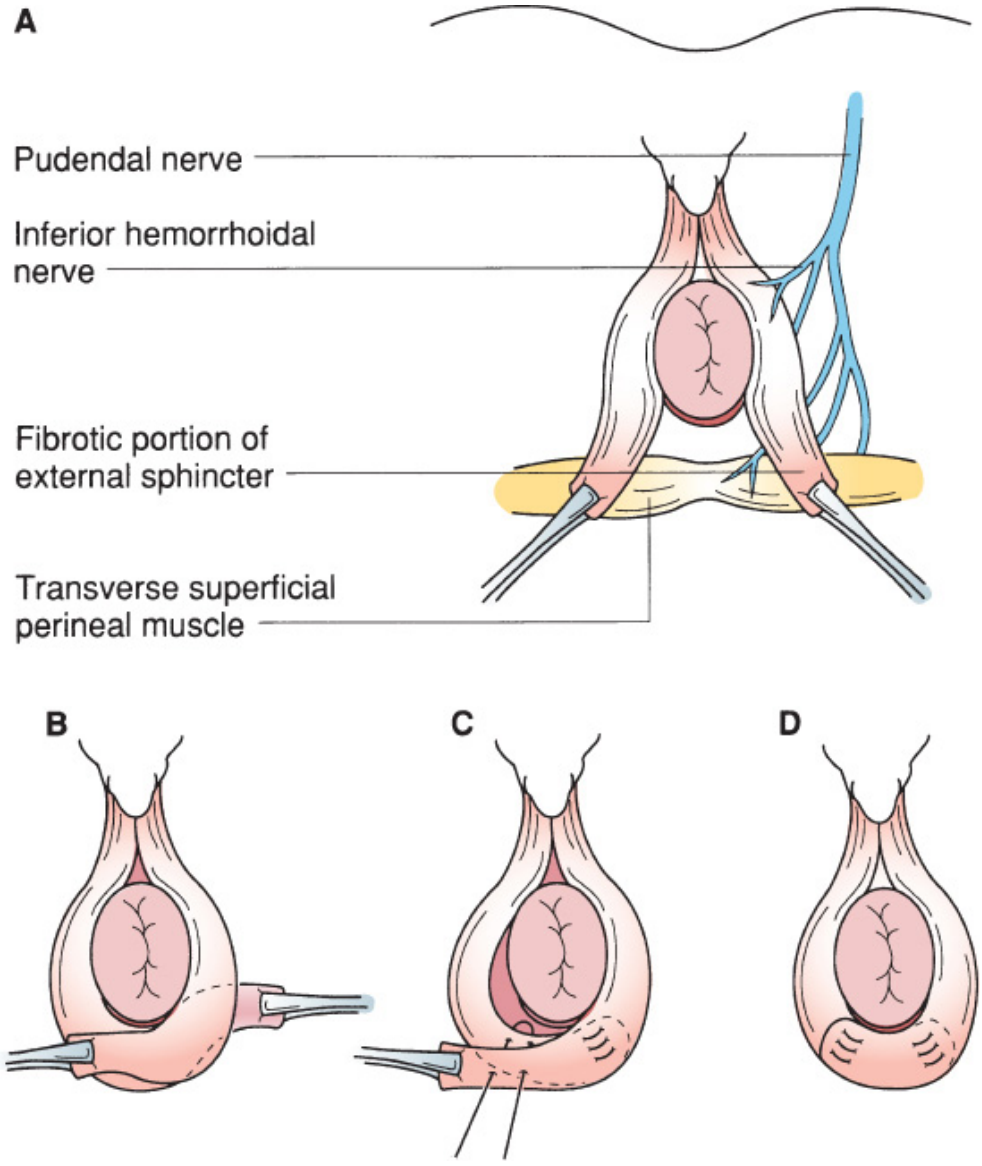

Figure 70.22 Overlapping sphincteroplasty.

Evaluation

Patients report protrusion of tissue that occurs with defecation or, in more advanced prolapse, may occur with moderate activity such as ambulating. The prolapse may reduce spontaneously or require manual reduction. Patients may experience fecal soiling and symptoms of incontinence. A complete history should include information about bowel habits and any

associated genitourinary dysfunction such as urinary incontinence or vaginal vault prolapse. On digital rectal examination, there may be decreased sphincter tone. An enterocele appears as smooth prolapse limited to the anterior rectal wall. It is crucial to differentiate full-thickness rectal prolapse, with concentric folds of tissue from mucosal prolapse, with radial folds of tissue (**Figs. 70.24** and **70.25**). Examination of the prolapsed tissue is facilitated by having the patient Valsalva while seated on a commode (**Fig. 70.26**). Endoscopy often shows edematous mucosa. Patients should be evaluated with colonoscopy to rule out a mass, which could serve as the lead point of intussusception. Ten percent to 15% of patients have an anterior ulcer identified on proctoscopy.[40] Defecography is helpful to clarify the diagnosis when prolapse is suspected, but cannot be demonstrated on examination. Additionally, defecography can reveal intussusception and concomitant pathology such as enterocele and pelvic floor dysfunction. Anorectal manometry may also be useful to evaluate for associated pelvic floor dyssynergia.

Patients may present with full-thickness rectal prolapse that is not reducible. If the prolapsed bowel appears viable, then the application of table sugar directly to the exposed mucosa may facilitate manual reduction. If the prolapsed tissue has advanced ischemia, then prompt, transperineal resection is indicated.

6 Management

Treatment of rectal prolapse requires surgical intervention. The choice of procedure depends on a history of previous procedures and the patient's overall medical condition.

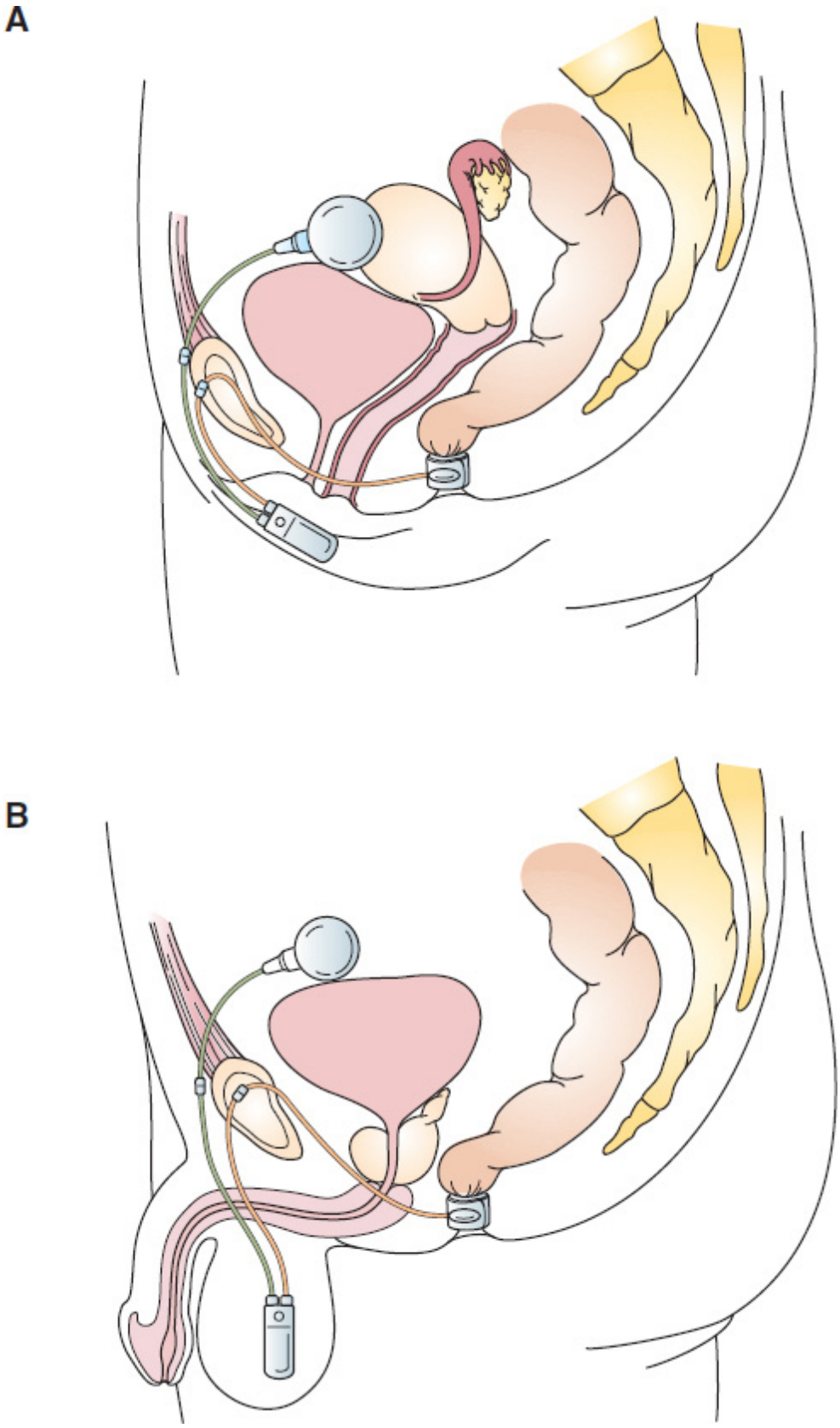

Figure 70.23 Implanted artificial sphincter.

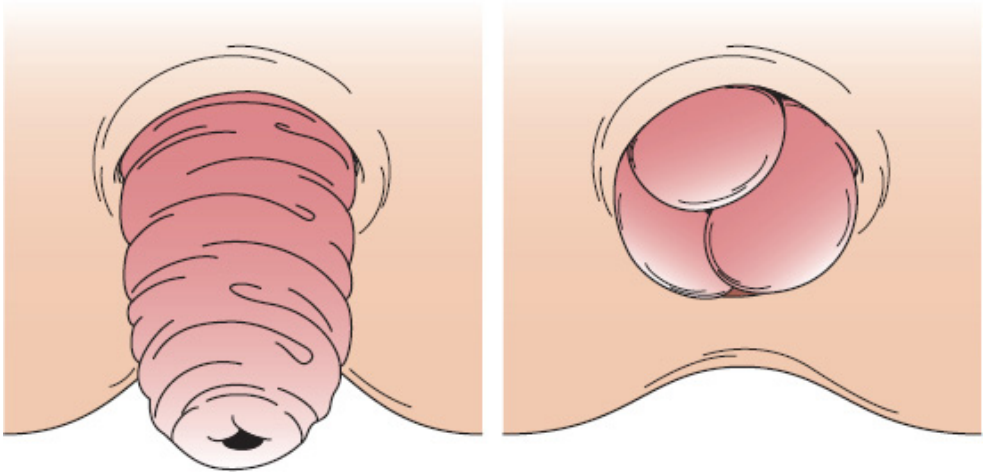

Figure 70.24 **A:** circumferential folds and **B:** radial folds.

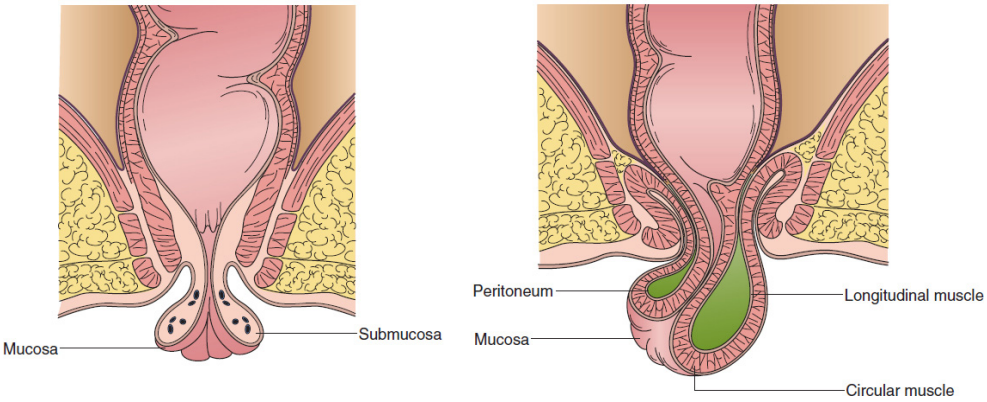

Figure 70.25 **A:** rectal mucosal prolapse and **B:** full thickness rectal prolapse.

Abdominal Operations for Rectal Prolapse

Transabdominal fixation of the rectum is the procedure of choice due to comparable or lower recurrence rates and better functional outcomes. A transabdominal repair involves mobilization and fixation of the rectum. Historically this involved posterior and anterior mobilization of the rectum and fixation of the rectum to the sacral promontory, with or without concomitant sigmoid colon resection. One problem with this approach is that posterior mobilization of the rectum may worsen constipation. In one report 50% of individuals with baseline constipation reported worsening constipation and 15% of patients reported de novo constipation.[41] In theory, the increased constipation could be related to disruption of rectal innervation. A newer technique involves only limited anterior mobilization

of the rectum and fixation of the rectum to the sacrum with synthetic or biologic mesh. Early reported outcomes of this anterior rectopexy technique indicated improvement in patients with preoperative constipation and no patients reporting new constipation (**Fig. 70.27**). Subsequent studies reported recurrence rates up to 14%, and de novo constipation was reported in 6%.[42,43]

Figure 70.26 Photo of full-thickness rectal prolapse.

Perineal Operations for Rectal Prolapse

A transperineal approach for rectal prolapse is indicated for ischemic, nonreducible prolapse. This approach has the advantage that it may be performed under regional anesthesia. The patient is positioned in the prone position. Excess rectum is excised, and the colon is anastomosed to the distal rectum, just proximal to the dentate line (**Fig. 70.28**). Levator muscle

imbrication prior to colonic anastomosis may ameliorate postoperative incontinence. The Delorme procedure is an alternative perineal approach that is appropriate for individuals with limited prolapse of 5 cm or less. This procedure involves stripping the mucosa of the prolapsed rectum from the muscularis propria, followed by plication of the muscularis propria and reanastomosis of the mucosa. This technique has a high recurrence rate but has very low associated morbidity, and may be appropriate for frail, older patients.

SEXUALLY TRANSMITTED DISEASES OF THE ANORECTUM

Gonorrhea

Gonorrhea is caused by the gram-negative intracellular diplococcus *Neisseria gonorrhoeae,* with an incubation period that ranges from 3 days to 2 weeks.

Clinical Manifestation

Symptomatic anorectal gonococcal infection results in pruritus or tenesmus, accompanied by a mucoid and sometimes bloody rectal discharge. Anorectal gonorrhea results in a thick yellow mucopurulent discharge from the anus.

Evaluation

Anoscopy or sigmoidoscopy may reveal a proctitis extending to no more than about 10 cm from the anal verge. Although these findings may be mistaken for ulcerative or nonspecific proctitis, abscesses, fistulae, and ulcers are not typical. Diagnosis is confirmed by culture on a Thayer–Martin medium plate incubated in a carbon dioxide environment.

Treatment

First-line treatment is a single intramuscular injection of 250 mg of ceftriaxone. Alternative treatments that have been proposed include single oral dose of 500 mg of cefixime or a single oral dose of a fluoroquinolone.

Because of the high rate of concomitant infection with Chlamydia, patients should be given appropriate treatment for Chlamydia as well. Sexual partners from the past 60 days should also be treated.

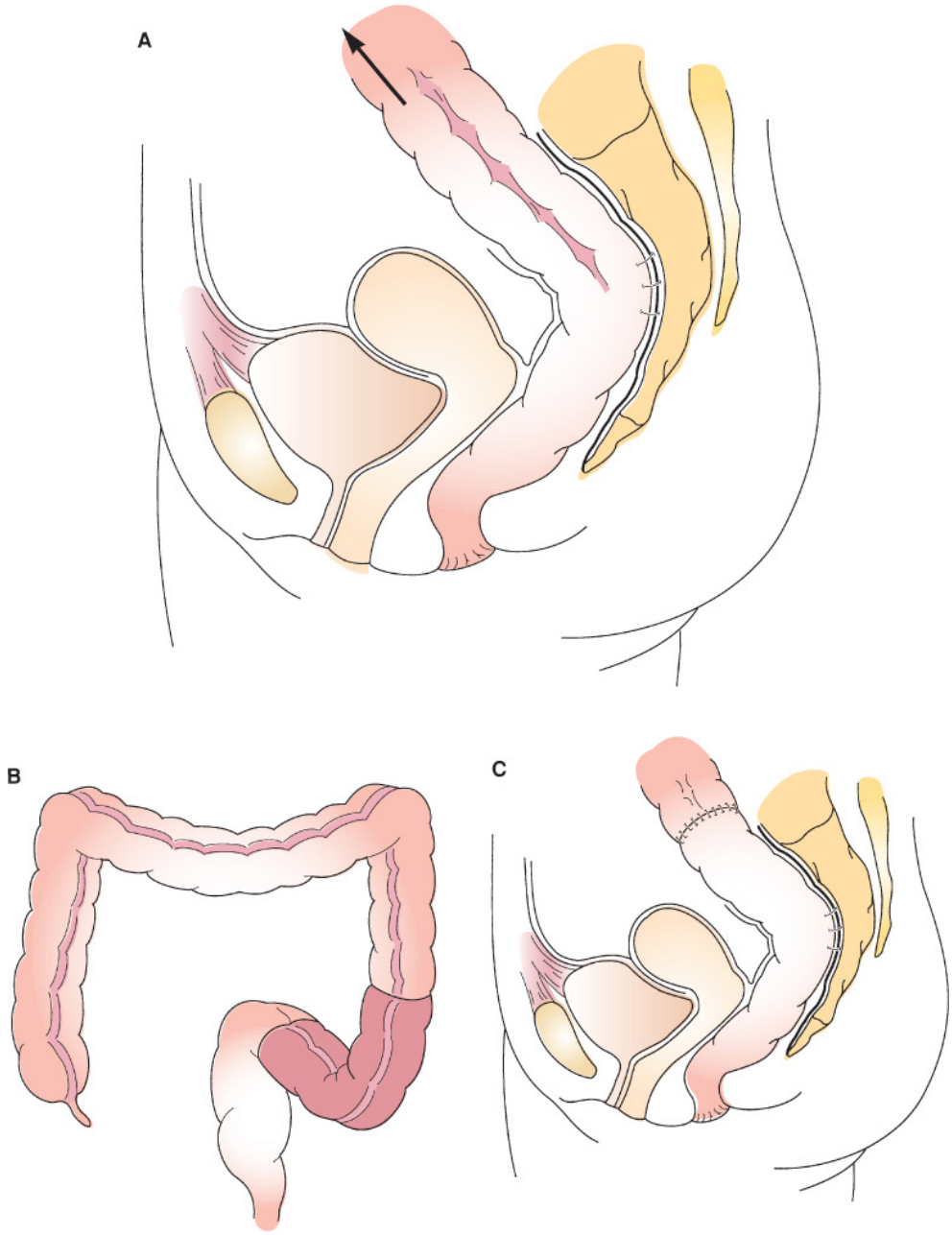

Figure 70.27 Ventral rectopexy. Mesh is sutured to the anterior rectum and sacral promontory.

Chlamydia/Lymphogranuloma Venereum

Chlamydia trachomatis is the most common sexually transmitted bacterial infection worldwide. With 15 known serotypes, anorectal Chlamydia infection can cause proctitis (serotypes D–K) or lymphogranuloma venereum (LGV) (serotypes L1–L3). Transmission of disease is through anoreceptive intercourse, with an incubation period ranging from 5 days to 2 weeks; secondary involvement can also occur as a late manifestation of genital infection.

Clinical Manifestations

Symptoms of non-LGV anorectal infection include rectal pain, tenesmus, and fever, although a substantial number of infected patients will be asymptomatic.

Evaluation

Examination reveals enlarged, matted inguinal lymph nodes, and proctosigmoidoscopy shows an erythematous rectal mucosa without frank ulcerations. Patients with LGV also complain of pain, fever, and tenesmus but often have a slight mucopurulent discharge and hematochezia. The inguinal lymph nodes in LGV are often more enlarged as they fuse into a large indurated mass with overlying erythema. Evaluation of the rectal mucosa reveals a more severe granular proctitis with mucosal friability and frank ulceration. If left untreated, the disease may progress to fistulae, abscesses, and late rectal strictures. In this setting, LGV may be confused for perianal Crohn disease. The marked inguinal lymphadenopathy may help distinguish LGV from Crohn.

Treatment

Chlamydia infection is treated with a single oral dose of azithromycin (1 g) or doxycycline (100 mg) twice a day for 7 days. Alternative therapy includes erythromycin or a fluoroquinolone. Treatment of LGV is a 21-day course of either erythromycin or doxycycline. Sexual partners also require treatment to prevent reinfection.

Herpes Simplex Virus

An estimated 20% of the general population are affected by herpes. The majority of anorectal herpes infections are caused by HSV-2 with only about 10% being caused by HSV-1. Transmission is through autoinoculation or direct contact with an infected individual who is shedding the virus. The clinical infection may begin 4 to 21 days following anoreceptive intercourse.

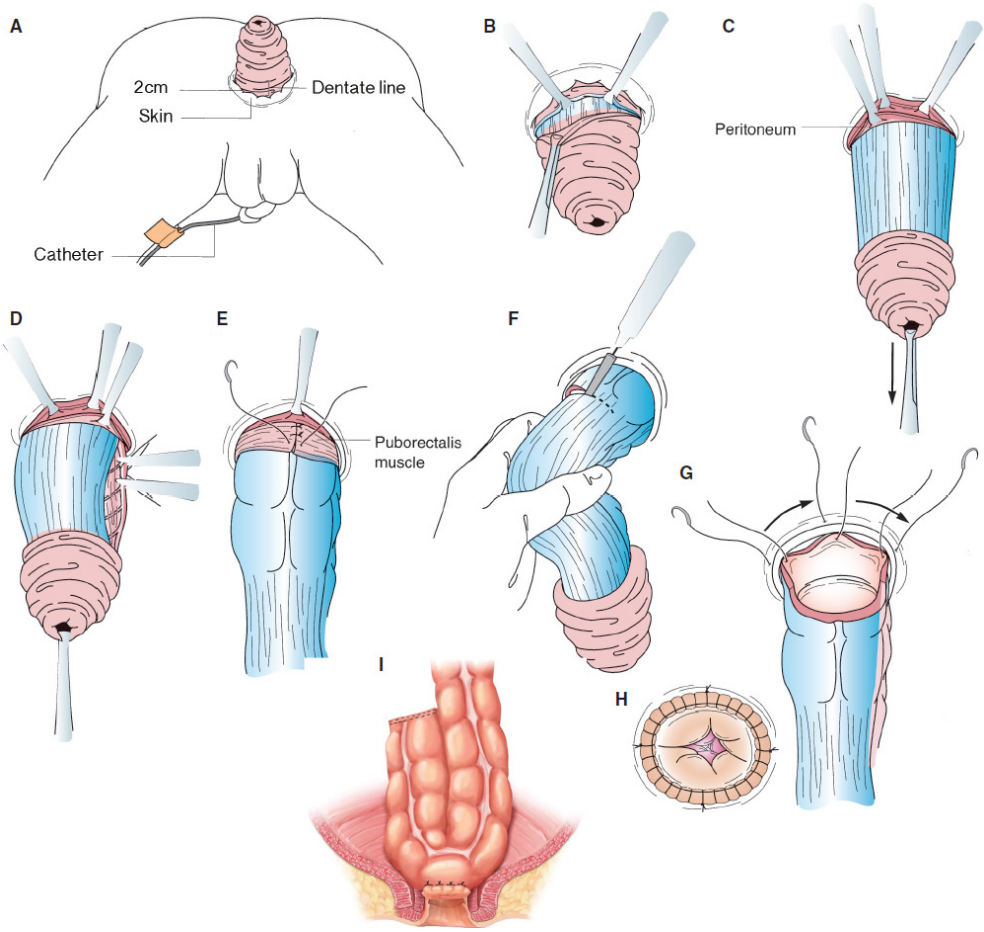

Figure 70.28 Perineal proctosigmoidectomy.

Clinical Manifestations

Patients present with small red vesicles, which may be clustered or scattered in the perianal skin, anal canal or perineum. These lesions are extremely painful to touch. Mucus discharge occurs in some patients with proctitis.

Evaluation

Proctoscopy reveals friable mucosa, ulceration, and mucopurulent discharge. These findings are limited to the distal 10 cm on proctoscopy. Tender

inguinal adenopathy occurs in up to 50% of patients with HSV proctitis. Diagnosis is made on clinical examination, finding multinucleated giant cells with intranuclear inclusion bodies on Pap smear, a positive Tzanck preparation or a positive culture.

Treatment

Acute infection is self-limited; treatment includes warm sitz baths and oral analgesics. The use of antiviral medications has been shown to shorten the length of symptoms but does not affect recurrence rates. Acyclovir (400 mg five times/day for 10 days) is most commonly used for initial infection. Recurrent attacks may be treated with acyclovir (200 mg five times/day) or valacyclovir (500 mg twice/day).

HIV and AIDS

Surgery for anorectal diseases is the most common indication for surgery in HIV infected. With significantly improved life expectancy for patients with HIV it is important to be cognizant of a number of conditions associated with this disease. Primary manifestations of HIV (anal ulcers) are rare and usually limited to patients with AIDS. However, these patients have high rates of other problems such as human papilloma virus (HPV), HSV, and anal fissures. Some of these problems are related to immunosuppression and concomitant infections, while others likely arise from treatment (HAART therapy) that can cause diarrhea. Treating these conditions is not significantly different when compared to other patients, but potential issues with healing, infection, and a higher chance of recurrence should be taken into consideration.

Condyloma 7 Acuminata and Squamous Intraepithelial Lesions

Anal condylomata acuminata or “warts” are caused by the HPV. HPV is a papovirus of which more than 130 subtypes of HPV have been identified. The prevalence of any genital HPV is estimated to be approximately 43%.[44] Inoculation of the anal epithelium allows entry of the HPV into the basal cell

layers. As these cells proliferate, viral replication occurs in the nucleus. The basal cells then migrate toward the surface, and infective particles are released in the form of visible warts.

HPV changes are classified into three grades of dysplasia: condyloma (no dysplasia), low-grade, and high-grade squamous intraepithelial lesions (LSILs and HSILs). Select serotypes are implicated in oncogenic cellular transformation; HPV serotype 16 is associated with 89% of anal squamous cell cancers (SCCs).[45] Individuals at increased risk for anal dysplasia include women with a history of cervical neoplasia, men who have sex with men (MSM), and individuals who are immunosuppressed. The mechanism for oncogenesis involves the inactivation of the P53 tumor suppressor gene by viral proteins.

Clinical Manifestations

Patients with anal dysplasia may experience pain, bleeding, or pruritis, although the majority of patients are asymptomatic.[46]

Evaluation

Condyloma acuminata are easily recognized as epithelialized cauliflower-like projections. They may be flat, raised, sessile or pedunculated, and range in size from millimeters to a large fungating lesions. They may be in clusters or grow to cover the perineum and anal canal in a "carpet-like" fashion. Anoscopy is used to identify lesions within the anal canal. Visualization of anal dysplasia is enhanced with the topical application of 4% acetic acid. Irregular and white blanching areas are suggestive of dysplasia. High-resolution anoscopy (HRA) can be used in high-risk patients and allows for better visualization and often simultaneous treatment of the lesions. It is not clear that HRA provides better screening then regular anoscopy. None of the above techniques have been clearly shown to be superior in preventing anal cancer.

Treatment

Treatment of a few easily accessible lesions can be done in the office by tangential excision, fulguration, cryotherapy, or chemical therapy (trichloroacetic acid). Larger or multiple lesions are treated in the operating

room by electrodesiccation, laser, or excision in the operating room. Topical agents such as podofilox, imiquimod, and fluorouracil applied by the patient on the perianal skin and in the anal canal may slow the progression of the disease and decrease the need for reintervention.[47] Vaccination against more virulent strains of condyloma (Gardasil) is currently available. The vaccine is effective in lowering rates of cancer when administered before initiation of sexual activity. The utility of giving this vaccine to adults after the diagnosis of condyloma is uncertain.

Since HPV and anal dysplasia are currently not curable and are often asymptomatic, individuals with anal dysplasia should be evaluated. Surveillance with anal cytology (anal Papanicolaou [Pap] test) smears every 1 to 2 years can be used, although sensitivity and specificity is low.[48] Recent studies found the 5-year incidence of progression from high-grade dysplasia to invasive SCC to be 6% to 9%.[49,50]

NEOPLASTIC ANORECTAL DISEASE

Neoplasms of the anal region are relatively rare, and include both benign and malignant tumors. Defining the location of the tumor is essential in the diagnosis and management of these conditions. The American Joint Commission on Cancer has developed standardized terminology and has recognizes the anal verge as the line dividing between the anal canal and anal margin. Practically, lesions that can be visualized by opening patient's buttocks are anal margin lesions. It may be sometimes challenging to determine primary location of large, bulky tumors, history of symptoms, examination, and histology can often serve as a guide.

Squamous Cell Carcinoma

Historically anal cancer was most common in women aged 50 to 70. Over the past three decades, the incidence of anal cancer has increased in women and at an even higher rate in MSM. Recent data shows that the rate per 100,000 is 1.6 for men and 2.2 for women.[51] Fewer than half of patients present with localized disease.[51]

8 Clinical Manifestations

Squamous cell carcinoma may occur on the perianal skin and in the anal canal. Patients often present with symptoms of pain and bleeding, similar to symptoms of hemorrhoids or an anal fissure. The gross appearance is typically a firm, ulcerated mass with rolled, everted edges.

Evaluation

While symptoms may mimic other conditions such as fistula, hemorrhoids, or chronic pruritus, any chronic unhealed or indurated ulceration in the perianal area should be biopsied. A digital examination and anoscopy should be performed to evaluate the location and size of an intra-anal tumor. Physical examination should include careful evaluation of inguinal lymph nodes as the most common sites of locoregional disease. Suspicious nodes may be evaluated further with fine-needle aspiration. A chest and abdominal CT scan along with CT or MRI of the pelvis are indicated for disease staging. Additional workup includes HIV testing and evaluation for cervical dysplasia in women. Also, one should discuss fertility preservation in appropriate patients per consensus guidelines.

Treatment

Anal Margin Tumors

T1 (<2 cm) and T2 (2 cm to 5 cm) well-differentiated lesions that do not invade the sphincter muscle may be treated with local excision with a 1-cm margin. More advanced lesions are best treated with a combination of 5-fluorouracil, mitomycin C, and radiation. Patients generally receive 50.4 Gr with an additional boost to inguinal lymph nodes if lymph node metastases are suspected. Abdominoperineal resection (APR) is indicated for persistent or recurrent disease and in the setting of significant functional issues related to tumor or consequences of treatment (incontinence). This surgery may require excision of a large portion of the perineum and flap closure.

Anal Canal Tumors

The standard treatment for anal canal lesions is chemotherapy and radiation per consensus guidelines. According to SEER data, overall 5-year survival is 68%, ranging from 82% for localized disease to 32% for distant disease.[51]

Recent studies have suggested that local excision alone may be considered for select T1 tumors.[53] The decision to proceed with local excision must consider the resectability of the lesion based on the potential for sphincter preservation and avoidance of anal canal stricture. APR (usually with omental or myocutaneous flap closure of the perineum) is reserved for patients with persistent or recurrent disease. Tumors may continue to regress for up to 6 months. Unless there is a clear growth of tumor at the end medical treatment, tumor response should be closely monitored up to 6 months before proceeding with APR.[54]

ADENOCARCINOMA

Paget Disease

Paget disease is an intraepithelial adenocarcinoma of the perianal skin. While this disease was initially described in the breast, it may also occur in the axilla and anogenital region. The exact origin of Paget cells is unknown. However, authors have hypothesized that they arise from apocrine or sweat glands, or are metastatic from an underlying adenocarcinoma. Perianal Paget disease begins as a benign in situ neoplasm but may eventually become invasive as an adenocarcinoma. Paget disease is a rare disease and occurs most commonly in elderly patients.

Clinical Manifestations

The typical appearance is an erythematous, sometimes sharply demarcated rash that may ooze or scale. Paget disease must be differentiated from other dermatologic conditions such as eczema, lichen sclerosis, and hyperkeratosis; these conditions tend to present in a circumferential pattern, whereas Paget disease tends to be unilateral.

Evaluation

The diagnosis is made by biopsy, which demonstrates the presence of periodic acid–Schiff positive Paget cells. Patients with Paget disease should also undergo a colonoscopy as perianal Paget disease may occur with synchronous colonic neoplasia.[55]

Treatment

The treatment of perianal Paget disease in the absence of invasive carcinoma is wide local excision. Because the disease may extend beyond the grossly visible margin, mapping biopsies at least 1 cm from the edge of the lesion in all four quadrants is recommended and consideration for flap closure for larger defects should be given. Patients with underlying cancer are generally treated based on the type of cancer they develop but often require radical resection after neoadjuvant treatment.

Anal Canal Adenocarcinoma

Anal canal adenocarcinomas are relatively rare, accounting for less than 10% of all anal carcinomas. Histologic studies show that these neoplasms arise from either the colonic mucosa or the anoderm and arise via HPV-dependent and independent pathways.[56]

Clinical Manifestations

The presentation of adenocarcinoma is similar to SCCs of the anal canal, with pain, bleeding, pruritus, and a palpable mass. These tumors tend to have a more aggressive natural history than SCC. Workup should include CT of the chest and abdomen as well as MRI pelvis with rectal cancer protocol and carcinoembryonic antigen (CEA). Colonoscopy should be performed if not recently done.

Treatment

These tumors are treated similar to rectal cancer, with chemoradiation followed by APR.

Basal Cell Carcinoma

Basal cell carcinomas of the perianal skin are rare. This condition is more common in men than women, and one-third of patients have basal cell cancers on other cutaneous sites.

Evaluation

Similar to basal cell cancers of the skin elsewhere on the body, these tumors typically appear as an ulcer with irregular and raised edges.

Treatment

These tumors are treated with local excision followed by close surveillance.

Melanoma

Melanoma occurs most commonly in the skin and eyes, but can also develop from the transitional epithelium within the anal canal or the anoderm at the anal verge. This tumor is more common in females than in males and is relatively rare, accounting for less than 4% of all anal malignancies.[57]

Clinical Manifestations

Symptoms include pain, pruritus, and bleeding. Some anal melanomas may not contain pigment and can be challenging to differentiate from SCC. Anal canal melanomas spread submucosally into the rectum, but do not typically invade other organs. Lymphatic spread to mesenteric lymph nodes is present in up to 32% and distant spread in 13% of patients at the time of diagnosis.[51]

Evaluation

The initial evaluation should include CT of the chest and abdomen and MRI of the pelvis. Careful evaluation of lymph node and anal sphincter involvement should be done by physical examination and imaging. Further genetic analysis of tumors can identify specific mutations in molecular pathways that can be targeted by systemic therapies.

Treatment

Melanomas of the anal canal do not respond to chemotherapy or radiation, making surgery the only chance for cure. Options include wide local excision or APR. With either option, the prognosis is poor, and recurrences are common. A recent review by Matsuda et al. found that APR provided better local control, but overall survival and relapse-free survival did not differ between local excision and APR.[57] Consideration should be given to palliation of symptoms and maintaining adequate function. If the presenting

lesion is not amenable to local excision without sacrificing function, then APR is warranted. Recent studies using targeted systemic therapy and immunomodulators have shown prolonged survival in patients with cutaneous melanoma; however, data on their effects on mucosal melanomas is still lacking.[58]

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71

Appendiceal Diseases

Arden M. Morris

Key Points

1. Recent data indicate an immune-related role for the appendix as a repository for beneficial bacteria of the microbiome.
2. Acute appendicitis, one of the most common urgent abdominal conditions in high income countries, is considered to be the result of a closed loop obstruction due to fecolith, inflammation of lymphoid aggregates, or other blockage at the appendiceal orifice.
3. Seasonal and geographic variation in the incidence of uncomplicated but not in the incidence of complicated or perforated appendicitis support potentially different etiologic mechanisms.
4. Signs and symptoms of appendicitis may be especially vague in the early stages, due to autonomic innervation, and become more pronounced with progressive inflammation of the somatically innervated parietal peritoneum.
5. An abdominal computed tomography scan is the imaging test of choice among patients with clinical signs of appendicitis.
6. Complicated appendicitis refers to the presence of abscess or perforation and occurs in about 10% of cases in the United States.
7. Controversy persists about the role for interval appendectomy among patients with complicated appendicitis. Adults with complicated appendicitis who do not undergo interval appendectomy should at least undergo a follow-up CT scan and/or colonoscopy to rule out other pathology.
8. Substantial randomized controlled trial data support using antibiotics first among patients with uncomplicated appendicitis, absence of fecolith, and the ability to follow up; still, about 27% of patients can expect to fail non-operative management in the first year after diagnosis.
9. Appendicitis is the most common non-obstetrical abdominal condition of pregnancy and should be treated by appendectomy due to high risk for premature delivery or fetal demise.

ANATOMY AND PHYSIOLOGY

The vermiform appendix is a finger-like, antimesenteric projection of bowel, approximately 6 mm in diameter and up to about 9 cm long, attached at the cecum as a closed tube. It sits adjacent to the ileocecal valve at the proximal convergence of the taeniae coli. Its free end is mobile and can extend in any direction. In a postmortem analysis of 10,000 cases in England,[1] Wakeley described its location primarily in relation to the cecum and ileum: retrocecal, 65.3%; pelvic, 31%; subcecal, 2.3%; preileal (anterior), 1%; and right paracolic gutter and postileal (posterior), 0.4%. As with the small intestine and colon, the wall of the appendix consists of mucosa, submucosa, muscularis externa, and serosa. The appendix is innervated by the autonomic nervous system and thus lacks somatic pain fibers. The appendiceal artery, a branch of the ileocolic artery, provides the blood supply, and is encased in the mesoappendix, a short extension of ileal mesentery. Similar to the terminal ileum, the submucosa harbors numerous lymphoid follicles.

Most nonhuman mammals have no appendix, which was considered support for the long-standing theory that it was a vestigial organ that may have assisted with cellulose digestion but 1 had no current function. More recently, however, investigators have proposed an immune-related role as a repository for beneficial bacteria of the microbiome and a site of defense against pathogens.[2] The gut microbial biofilm is an extracellular matrix of mucin and immunoglobulins, produced by mucous cells and abundant lymphoid tissue of the appendix, containing densely packed bacterial communities that line the gut lumen.[3] The microbiome is thought to aid in digestion, provide a barrier, elaborate immune responses to pathogens, interact with hormones such as insulin, and to play a role in obesity and cardiovascular health.[4,5] Theoretically, if an enteric pathogen were to destroy the colonic microbiome, the size and shape of the appendix would facilitate a protected space for normal flora that could then repopulate the colon.

APPENDICITIS

Etiology and Pathophysiology

At more than 270,000 cases annually, acute appendicitis is one of the most common urgent abdominal conditions in the United States with a lifetime risk of 6% to 9%.[6] Due to its 2 unique structure, inflammation of the appendix or acute appendicitis generally is considered the result of a closed loop obstruction, either by a foreign body such as a fecolith or alternatively by inflammation of lymphoid aggregates, effectively blocking the appendiceal orifice. The ensuing bacterial entrapment causes further activation of lymphoid cells, cytokines, and edema; all the while, mucus accumulates contributing to luminal pressure. The resultant dilation leads to increased mural pressure, venous congestion, ischemia, and ultimately necrosis and perforation. This convenient etiologic explanation is likely accurate in many cases. The common finding of a fecolith could explain the higher prevalence of appendicitis among persons who consume a Western diet.[7] The finding of lymphoid hyperplasia could explain the higher prevalence of appendicitis among persons between the ages of 10 and 20, who have substantially more lymphoid tissue in the appendiceal submucosa.

There is also evidence, however, that appendicitis occurs in the absence of luminal obstruction.[8] Several hypotheses have been advanced to explain this phenomenon but most remain speculative. The "hygiene hypothesis"[9] proposed that adaptive immunity after early pathogen exposure conveys a protective effect, reducing the risk of lymphoid hyperplasia in the appendix. With progressively better living conditions in the early 20th century, young children were exposed to fewer enteric pathogens and therefore presumably became more prone to aberrant immune responses (nonobstructing lymphoid hyperplasia) with concomitant increased incidence of appendicitis. Recent evidence that acute appendicitis is actually less common among those with higher socioeconomic status[10] contradicts the hygiene hypothesis, but the study authors did not address the difference in antigen exposures among those of low socioeconomic status in the early 20th century versus the early 21st century. Although there is little evidence to support the hygiene hypothesis in appendicitis, allergists and immunologists are actively investigating variations of it related to inflammatory bowel disease and other autoimmune diseases. Another hypothesis to explain appendicitis in the absence of obstruction is that specific bacterial or viral pathogens induce ulceration of the appendiceal mucosa, permitting bacterial invasion of the wall and inciting an inflammatory cascade.[8] While a number of bacterial pathogens

have been identified and associated viral agents include Coxsackie, adenovirus, measles, and cytomegalovirus, most study sample sizes are too small to draw reliable conclusions.

3 Although appendicitis traditionally was thought to progress steadily until perforation, a more recent theory posits that complicated (perforated) and uncomplicated appendicitis may have different etiologies, suggesting that they should be treated as different entities. An analysis of the National Hospital Discharge Survey between 1975 and 2006 described outbreaks and seasonal variation in the diagnosis of uncomplicated appendicitis,[11] supporting an infectious etiology, and noted epidemiologic similarities between uncomplicated appendicitis and influenza that were not identified for *perforating* appendicitis.[12] A more recent study identified geographic clustering of uncomplicated appendicitis cases that was not present for cases of complicated, or perforating, appendicitis.[10] Still others[8,13] have identified specific bacteria that may play a role in perforating versus nonperforating appendicitis but these studies are subject to serious sample size limitations and require confirmation through larger studies. One such study, the Microbiology APPendicitis ACuta (MAPPAC) trial, is currently accruing patients with CT-confirmed perforated and nonperforated appendicitis to study microbiologic and immunologic characteristics at the time of diagnosis and 12 months after treatment.[14] While the MAPPAC trial study design is complex, drawing from multiple existing clinical trials, it may shed light on high-risk versus protective bacteria within the gut lumen and may clarify the unintended outcomes of treatment on the microbiome.

Diagnosis

History and Physical Examination

4 Vague periumbilical pain, the most common symptom of early appendicitis, can be attributed to the embryologic origin of autonomic fibers in the midgut. As the appendix becomes increasingly inflamed, it activates somatic pain fibers in the parietal peritoneum. Most often, this will be at McBurney point, one-third of the distance from the anterior superior iliac spine to the umbilicus. The numerous potential locations of the middle and tip of the appendix can result in a confusing array of possible symptoms, as

reflected by the variety of signs associated with different anatomic sites (**Table 71.1**). Additional symptoms can include nausea, vomiting, diarrhea, constipation, and even burning with urination, although all are unlikely to be as severe or as progressive as pain.

Table 71.1 Signs of Acute Appendicitis on Physical Examination

Name	Description	Implication
McBurney Sign	Pain with pressure to McBurney point	Right lower quadrant inflammation
Dunphy Sign	Right lower quadrant abdominal pain with abdominal wall flexion, for example, cough	Inflammation of the parietal peritoneum
Rovsing Sign	Referred pain at the right lower quadrant after pressure to the left lower quadrant abdomen	Right lower quadrant inflammation
Psoas Sign	Right lower quadrant abdominal pain upon tapping the right heel	Retrocecal inflammation
Obturator Sign	Pain with internal and external rotation of the right hip	Pelvic inflammation

Physical examination signs can be just as ambiguous as the clinical history. Patients may have a low-grade fever that is rarely higher than 102°F and may or may not have mild tachycardia. Although tenderness to pressure at McBurney point is highly suggestive, it is not entirely reliable, especially among women who may be experiencing ovarian torsion or cystic disease. Conversely, cervical motion tenderness during a pelvic examination may indicate an inflamed pelvic appendix rather than a gynecologic condition.

Rebound tenderness and involuntary guarding, or contraction of the abdominal wall in response to pressure, can help to clarify peritoneal irritation. To establish retrocecal appendicitis, stimulating the iliopsoas muscle by tapping the heel or extending the right hip may be helpful.

Laboratory and Imaging Studies

The white blood count and a urine analysis are the most important laboratory values in the diagnosis of appendicitis, although obtaining C-reactive protein is becoming more common. While the white blood count may be normal, it is more likely to be in the slightly high range from 10 to 14,000 white blood cells per mL. Urine analysis may show increased leukocytes or microscopic hematuria. In the setting of a suspicious history and physical examination, a C-reactive protein level >10 mg/mL is suggestive of acute appendicitis and >50 mg/mL suggests complicated appendicitis.

Given the imprecision of clinical history, physical examination, and laboratory signs, several authors have proposed grading schemes to assist with diagnosis (**Table 71.2**). The rationale for a scoring system rather than simply relying on imaging is based on concerns for radiation associated with CT scan, especially among children, the inaccuracy and operator dependency of ultrasound, and the absence of a role for plain radiographic imaging. In a retrospective study of 747 consecutive children who presented to a Dutch hospital with symptoms concerning for appendicitis, a head-to-head comparison of the three grading schemes was performed. Thirty-six percent of patients overall were diagnosed with acute appendicitis. The area under the receiver-operator curve of the appendicitis inflammatory response (AIR) score was 0.90, the Alvarado score was 0.87, and the pediatric appendicitis score was 0.82. In a study of adult patients, the AIR continued to outperform the Alvarado score.[15]

Table 71.2 Grading Schemes to Assess Risk of Acute Appendicitis

Scoring System	Symptoms (Points)	Signs (Points)	Laboratory Values (Points)	Score (Sum of Points)	Recommendation
Alvarado Score	Migration of pain (1) Anorexia (1) Nausea/ vomiting (1)	Right lower quadrant tenderness (2) Rebound pain (1) Elevated temperature ≥37.3°C or 99°F (1)	Leukocytes ≥10,000 (2) Differential ≥75% polymorphonuclear cells (1)	5–6 7–8 9–10	Compatible with appendicitis; observation Probable appendicitis; surgery High probability of appendicitis; surgery
Pediatric Appendicitis Score (PAS)	Migration of pain (1) Anorexia (1) Nausea/ vomiting (1)	Right lower quadrant tenderness (2) Cough/hopping/ percussion/tenderness in the right lower quadrant (2) Elevated temperature ≥37.3°C or 99°F (1)	Leukocytes ≥10,000 (2) Differential ≥75% polymorphonuclear cells (1)	≤5 ≥6	Not appendicitis; observation Appendicitis; surgery
Appendicitis Inflammatory Response Score (AIR)	Nausea/ vomiting (1)	Right lower quadrant tenderness (1) Rebound tenderness (1, 2, 3) Elevated temperature ≥38.5°C	Leukocytes 10,000–15,000 (1); ≥15, 000 (2) Differential polymorphonuclear cells 70–84% (1); ≥85% (2) C-reactive protein 10–49 mg/ mL (1); ≥50 mg/mL (2)	0–4 5–8 9–12	Low probability of appendicitis Indeterminate group; inhospital observation with additional imaging or diagnostic laparoscopy High probability of appendicitis; surgery

Adapted from Macco S, Vrouenraets BC, de Castro SMM. Evaluation of scoring systems in predicting acute appendicitis in children. *Surgery* 2016;160(6):1599–1604.

The diagnostic utility of imaging studies was previously subject to some debate. Ideally, imaging studies should be sufficiently accurate to help the clinician to balance timeliness of treatment with a reduction in unnecessary operations. As noted, ultrasound is operator dependent and not reliably accurate but may still be favored among children as a means to spare radiation exposure. Signs of appendicitis by ultrasound include a target lesion (thick-walled, noncompressible lumen), peritoneal fluid, or abscess.

Arguments against the use of CT were based on the now-refuted belief that appendicitis inexorably progressed to perforation and therefore mandated a rapid operation; CT scans were seen as time consuming and unnecessary since a negative appendectomy rate of 15% to 20% was acceptable. Although early CT scans did not have the precision necessary to reduce 5 the rate of negative appendectomies,[16] technologic advances and a paradigm shift in surgical culture over the past 15 years have led to standard use of helical CT with thin-cut slices and intravenous contrast for suspected appendicitis in adult patients.[17] Oral and rectal opacification are now

believed to improve neither sensitivity nor specificity. Signs of appendicitis on CT scan include appendicolith, mesenteric fat stranding, diameter >10 to 13 mm, appendiceal wall thickening >3 mm, and phlegmon (**Fig. 71.1**); complicated or perforated appendicitis can be identified through periappendiceal gas or abscess. Because radiation exposure is an increasing concern with CT scan, a single-institution randomized controlled trial powered for noninferiority compared low-dose and standard-dose CT scans among 891 adults with suspected appendicitis.[18] The study demonstrated similar rates of negative appendectomy (3.2% and 3.5%) and similar rates of perforation (26.5% and 23.3%), concluding that low-dose CT is not inferior to standard-dose CT for the diagnosis of appendicitis in young adults. Although uptake of a low-dose protocol has been slow, additional randomized controlled trials have supported these findings.[19] While magnetic resonance imaging (MRI) has high sensitivity and specificity, it is currently an expensive and uncommon approach for diagnosing appendicitis.

Differential Diagnosis

The differential diagnosis must be considered during the preliminary workup and should include enteritis, pyelonephritis, nephrolithiasis, gynecologic issues such as ovarian torsion or cyst, tubo-ovarian abscess or tubal pregnancy, small bowel or cecal obstruction or perforation, Meckel diverticulitis, and cecal diverticulitis or cancer. Clinical examination, laboratory studies, and CT scan can help to distinguish most but not all of these conditions as demonstrated by a low but ongoing negative appendectomy rate.

Management

Complicated Appendicitis

Traditional management of appendicitis has focused on performance of surgical resection as rapidly as possible after diagnosis, and appendectomy remains the most common urgent abdominal operation in the United States. As noted above, much of the rationale for urgent surgery was related to a perceived risk of impending perforation and a desire to avoid sepsis. 6 Complicated appendicitis refers to appendicitis accompanied by gangrene,

abscess, or phlegmon, indicating an extant micro- and macroperforation, and occurs in up to 10% of acute appendicitis cases.

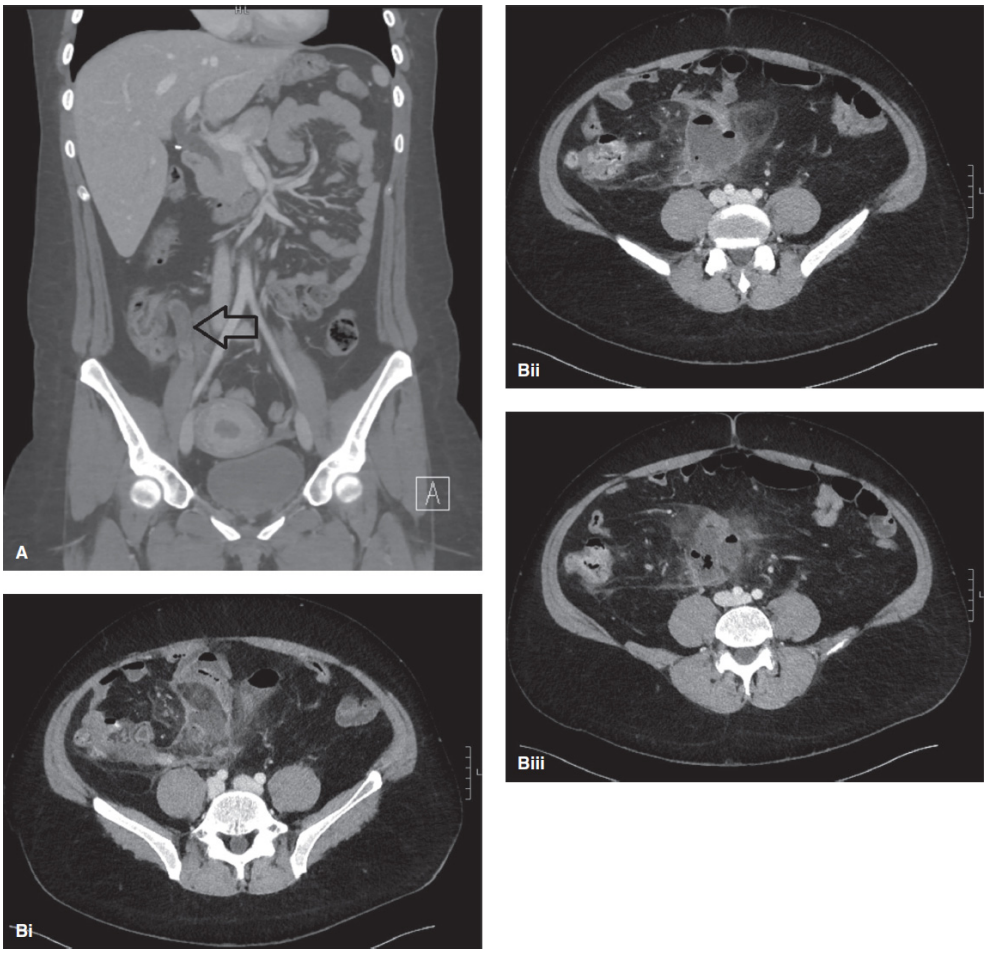

Figure 71.1 Computed tomography displaying (**A**) nonperforated appendicitis with a distended, thick-walled appendix; (**B**) perforated appendicitis with an adjacent abscess.

In the setting of complicated appendicitis, there are essentially three management options. First, an operation to remove the appendix can be performed urgently either open or laparoscopically. The second management option entails controlling infection and reducing inflammation using antibiotics, percutaneous drainage if possible, and supportive measures such as bowel rest and intravenous hydration. After a 6- to 12-week interval, laparoscopic or open appendectomy is performed. The rationale for interval appendectomy rather than urgent appendectomy is that nearby structures are less likely to be injured when inflammation has subsided. Interval

appendectomy was first described in the mid-20th century and gained traction in the early 2000s as preoperative CT scans became common practice, enabling preoperative identification of appendiceal abscesses.

As interval appendectomy became an accepted management strategy, surgeons began to question the need for any appendectomy thereby giving rise to the third treatment option for complicated appendicitis: antibiotics, drainage if possible, and supportive measures followed by no appendectomy. Proponents of no further treatment cite a low rate of previously unrecognized pathology, low rate of recurrent appendicitis, and a high operative complication rate. By contrast, advocates of interval appendectomy for complicated appendicitis cite the concern for possible cystadenoma or malignancy, early recurrence, and low complication rate. To be fair, the complication rate is generally less than 10% and complications are often limited to wound infection or abdominal abscess; the sheer volume of appendectomies, however, makes the absolute complication rate higher than many other types of operations.[20] Surgeon investigators on each side of the debate support their positions with single-institution case series for the most part,[21] and indeed practicing general surgeons have been shown to make clinical decisions based on heuristic-based concern for adverse outcomes more than deliberative evaluation of the data.[22] Regardless, 7 adult patients with perforated appendicitis who do not undergo an immediate or interval appendectomy must be evaluated with a follow-up CT and/or colonoscopy in order to ascertain the absence of other pathology such as Crohn disease or cancer.

Surgical Approaches

The classic open appendectomy operation starts over McBurney point with an oblique incision of the skin in Langerhans lines, incision of the external oblique aponeurosis, and a muscle-splitting incision before opening the peritoneum. If the appendix is not immediately apparent, the terminal ileum is grasped and followed to the cecum. At times, depending on the location of the appendix and the patient's body habitus, it may be necessary to mobilize the cecum laterally to locate the appendiceal base. If the base is obscured by substantial inflammation, following the teniae proximally can be helpful. The appendiceal artery is divided and the appendiceal base is ligated usually

with a stapler or suture. The appendix is amputated just distal to ligation and removed. Previously, the appendiceal stump was inverted with suture to prevent mucocele formation or fistula but there are no data to support this step. The peritoneum and pelvis then should be irrigated and the abdominal wall is closed in layers. Recent data indicate no benefit of leaving a drain or of delayed skin closure.[23]

Laparoscopic appendectomy, first described in 1983,[24] is essentially the same operation as open appendectomy, usually performed through three laparoscopic ports instead of an open incision. With the exception of the laparoscopic specific procedures such as insufflation of the abdomen, each step is the same and the major potential risk categories (bleeding, abscess, wound infection, damage to nearby structures) are also the same. Compared with open appendectomy, the laparoscopic approach leads to fewer wound infections, reduced hospital stay, and reduced pain, and is an advantageous approach in the setting of uncertainty or unexpected operative findings with a normal appendix.[25] Both randomized trials and case series have demonstrated that the laparoscopic approach confers about 35% higher odds of organ space surgical site infection than the open approach, but the risk remains well under 10%. A 2010 cohort study[26] that included over 32,000 patients from 222 U.S. hospitals demonstrated that, in spite of these benefits, open appendectomies are still performed in about 20% of cases, largely among elderly patients or those who were at higher risk due to comorbid disease.

Single-incision laparoscopic surgery (SILS), in which a single port site scar is hidden in the umbilicus, has garnered interest for it is a cosmetic advantage over conventional laparoscopic appendectomy. Although case duration and expense can be much higher, the single-incision approach in pediatric surgery is increasingly accepted. A large single-institution cohort study found that the need for conversion to conventional laparoscopy was associated with obesity, male sex, or complicated appendicitis.[27] Another study of 970 pediatric patients with appendicitis found that an adaptive approach utilizing one, two, or three ports depending on operative difficulty was associated with substantial cost savings.[28]

In the event that an open or laparoscopic operation is performed and a normal appendix is identified, a search for other pathology should be conducted. Specifically, the surgeon should examine the terminal ileum for

evidence of Crohn disease or more proximally a Meckel diverticulum, the cecum for diverticulitis, Crohn disease, or neoplasm, the sigmoid colon (if redundant) for evidence of diverticulitis, Crohn disease, or neoplasm, and in a woman, the adnexal structures for evidence of cysts, inflammation, infection, neoplasm, or other mass. A major advantage of the laparoscopic approach is the ease of examination of and potentially intervention on nonappendiceal structures.

Nonoperative Management of Uncomplicated Appendicitis

Traditional management of appendicitis has been based on the poorly supported hypothesis that appendicitis is a progressive disease—that is, a disease that will culminate in appendiceal perforation and pelvic abscess if untreated surgically. This hypothesis was so widely accepted that, throughout the 20th century, an unnecessary or negative appendectomy (i.e., no histologic evidence of appendicitis) rate of 15% was considered acceptable within the surgical community.[16] Even in the best case scenario, an appendectomy is painful and requires several weeks of recovery (3 to 4 weeks for laparoscopic and 4 to 6 weeks for open surgery) before return to usual activity. Recovery time is especially pertinent because appendicitis is more common among active young adults[29] who are more likely than their older counterparts to hold physically demanding jobs, to have a high deductible health insurance plan, and to lack paid sick leave. Appendectomy also has a complication rate from 3% to 21%[20,29,30] and is costly at a median charge per case of $33,000 in 2012.[31]

Noting circumstances in which delayed or omitted appendectomy has *not* resulted in peritonitis, or even in progression of disease, many surgical investigators have proposed that nonoperative management is a viable option among selected patients.[32] Thus far, five randomized trials suggest that use of broad-spectrum antibiotics may change what was perceived as the natural history of acute appendicitis and that many adult patients can be treated with antibiotics only[30,33–36] and one U.S. study 8 is currently underway.[37] The largest and most recent, the APPendicitis ACuta (APPAC) trial,[30] compared antibiotic therapy with appendectomy and found that among 257 adults with computed tomography (CT) confirmed uncomplicated appendicitis who were

treated with antibiotics, 73% did not require appendectomy within 1 year of initial presentation. Among the 27% in the nonoperative management arm who had appendectomy following failure of antibiotics alone, the surgical complication rate was no higher than among patients who underwent appendectomy initially. The trial was designed as a noninferiority trial, meaning that it was powered to detect whether nonoperative management with antibiotics was inferior to the gold standard, that is, appendectomy. The study team assigned the minimal clinically important difference (MCID) to be less than or equal to 24% "failure." That is, if nonoperative management failed in less than or equal to 24% of cases, it would be deemed noninferior to appendectomy. Based on the assigned MCID, the authors had to conclude that nonoperative management with antibiotics had not been shown to be noninferior.

Critics of the study pointed out that patients were highly selected (nonpregnant adults aged 19 to 60 with CT-demonstrated uncomplicated appendicitis and no evidence of an appendicolith), were treated with 3 days of a selected antibiotic not commonly used in the United States, and underwent open appendectomy which is also increasingly uncommon; others questioned the assignation of MCID.[38] The implications were that the patient cohort and the treatment delivered was not representative of U.S. practice. Another Finnish study, the Peri-Appendicitis Acuta (peri-APPAC) trial,[39] in which patients with complicated appendicitis who had been treated with antibiotics and drainage if necessary were randomized 3 months later to appendectomy versus MRI. This study was terminated prematurely on ethical grounds due to 20% rate of malignancy, about tenfold higher than expected from a meta-analysis of 61 studies.[40] Finally, recently published 5-year results of the APPAC study[41] indicated that another 12% of patients eventually underwent appendectomy more than 1 year after the initial presentation.

Taken together, these findings added fuel to the hot debate in the surgical community about the safety of nonoperative management[42]—and lent credence to the criticism that patients and surgeons in Finland may differ in fundamental ways from those in the United States and other countries. There is one aspect of nonoperative management upon which all agree, however: no studies to date support a nonoperative approach for every patient who presents with signs and symptoms of acute appendicitis. Identifying

appropriate patients for nonoperative management—and importantly those for whom such an approach is likely to fail—is an area of keen interest among surgical researchers. Among the currently open questions are how to compare the relative benefits, harms, and costs of each treatment option and under what circumstances they differ. The risk of postoperative complications, for example, varies widely by patient age, comorbid disease, and clinical presentation. Moreover, the potential harms of broad-spectrum antibiotics, radiation exposure, and appendicitis recurrence are not easily quantified. The COVID pandemic may provide a natural experiment that will clarify clinical features or baseline patient characteristics to better guide nonoperative management.[43]

Special Populations

Pregnancy

Appendicitis is the most common nonobstetrical urgent abdominal condition among pregnant women, followed closely by cholecystitis. Both can be difficult to diagnose, especially in late pregnancy, due to common pregnancy symptoms of general nausea, mild leukocytosis, and compression or relocation 9 of structures by the enlarging uterus. Consequently, appendicitis in pregnancy is associated with late presentation, maternal morbidity, and fetal mortality. In a cohort analysis of 3,133 pregnant women who underwent appendectomy,[44] fetal loss and preterm delivery occurred in 6% and 11% of those with complicated appendicitis compared with 2% and 4% of those with uncomplicated appendicitis. Given the risk, nonoperative management is not considered an acceptable option among pregnant women. While there has been some debate about the safety of a laparoscopic versus open approach, several systematic reviews[45–48] indicate that in experienced hands, there is no elevated risk of fetal loss or preterm labor based on surgical approach.

Elderly Patients

The diagnosis of appendicitis in frail or elderly patients may be challenging and is often delayed. Elderly patients are much more likely to present with complicated and specifically perforated appendicitis. In contrast to younger

patients, a precipitous leukopenia may be identified rather than leukocytosis. In addition to perforation, the rate of unexpected malignancy is substantially higher as patient age increases. In the Peri-APPAC trial noted above,[39] all cases of malignancy occurred in patients aged >40 years. Among elderly patients with apparently perforated appendicitis, antibiotic treatment alone is inadequate and a planned resection should follow. In the setting of suspected cancer, a very conservative approach traditionally would include open appendectomy through a midline incision. A recent meta-analysis compared morbidity and mortality among 12 observational studies of 126,000 elderly patients who had undergone laparoscopic and open approaches.[49] Although the meta-analysis was limited by selection bias within studies and heterogeneity between them, it persuasively reported only one-third of the mortality and two-thirds the morbidity using laparoscopy compared with open surgery.

Low- and Middle-Income Countries

Population based studies of disease in low- and middle-income countries present a particular challenge, partly due to lack of reliably recorded health data that can be compared with high-income countries. Nonetheless, appendicitis typically has been considered a phenomenon of industrialized countries. A systematic review[7] of 120 population-based studies over the last 100 years found that in Western industrialized countries rates of both uncomplicated and complicated or perforated appendicitis have stabilized, while rates of surgery are in decline. The authors surmise that nonoperative management is increasingly accepted and being deployed. They note as well that, among currently industrializing countries in Asia, the Middle East, South America, and Africa, the incidence of acute appendicitis has been increasing, much as the United States did in the mid-20th century. The authors concluded based on these data that early industrialization contributes to increased incidence which later can be expected to plateau. A multicenter international cohort study[50] by the National Institute for Health Research's Global Health Research Unit in the United Kingdom tracked outcomes of surgery prospectively over 6 months with 30-day follow-up. Although the availability of laparoscopy was related to the Human Development Index (HDI), even among low-HDI countries, a laparoscopic approach was

associated with about three- to fourfold reduction in 30-day perioperative complications and surgical site infections.

APPENDICEAL NEOPLASMS

Neuroendocrine Tumors

About two-thirds of all appendiceal neoplasms originate from neuroendocrine tissue and about half of all neuroendocrine neoplasms in the gut are located within the appendix. Neuroendocrine tumors of the appendix are usually diagnosed incidentally after appendectomy. Most are low grade, confined to the appendix, and small at the time of diagnosis. Appendiceal neuroendocrine tumors <2 cm in size and without the advanced features of high mitotic index, mesoappendiceal invasion, or positive margin can be managed by appendectomy alone.[51,52] Follow-up right colectomy is recommended for neuroendocrine tumors with advanced features or size ≥2 cm due to concern for lymphatic spread. Hematogenous metastasis to the liver is also possible but extremely rare. So-called goblet cell carcinoid tumors have been reclassified as adenocarcinoma as they are not of neuroendocrine origin.[53]

Appendiceal Mucinous Neoplasms

Low-grade appendiceal mucinous neoplasms (LAMNs) and high-grade appendiceal mucinous neoplasms (HAMNs) are characterized by a dilated, mucus-filled appendiceal lumen. The term mucocele is no longer considered a pathologic diagnosis. LAMN and HAMN do not metastasize hematogenously or lymphatically and rarely invade structures; instead, in a phenomenon known as "pushing invasion," the wall of the appendix is dissected by acellular mucin which can then spread over surfaces.[53] An appendix in which LAMN is entirely contained without spillage into the peritoneal cavity can be safely followed with imaging. In the presence of intraperitoneal spillage, however, pseudomyxoma peritonei, a condition in which mucin inexorably accumulates within the abdominal cavity is a real concern. Pseudomyxoma peritonei, while not invasive, entraps structures and

fills the paracolic gutters, diaphragmatic peritoneum, pelvic peritoneum, and omentum. In the setting of perforated mucinous neoplasm, peritoneal stripping and potentially hyperthermic intraperitoneal chemotherapy (HIPEC) should be strongly considered. HAMN contains high-grade dysplasia but no infiltrative features. As a newly characterized diagnosis, its behavior is not well understood but it is believed to be more likely to contribute to aggressive pseudomyxoma peritonei than LAMN. Mucinous adenocarcinomas are similar to HAMN but also infiltrate surrounding structures and histologically display tumor budding surrounded by desmoplastic stroma. If the patient can tolerate it and disease is not too far advanced, HIPEC is appropriate in these cases.

Adenocarcinomas

Adenocarcinomas of the appendix are extremely rare and are characterized essentially identically to those of the colon. Identification of a nonmucinous adenocarcinoma should be followed by a right colectomy. Goblet cell adenocarcinomas have been recently reclassified, as noted above, and can exhibit a range of tumor biology including transmural spread. These tumors can be hard to distinguish pathologically from signet cell carcinoma. In both cases, aggressive treatment with right colectomy and a search for transmural, lymphatic, and hematogenous spread is warranted.

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Section J: HERNIA AND SPLEEN

72

Abdominal Wall Hernias

Benjamin K. Poulose, Jeremy A. Warren, and Robert J. Fitzgibbons Jr

Key Points

1 The concept of the “abdominal core” aims to capture the complex relationships of the circumferential soft tissues of the diaphragm superiorly, abdominal wall and flanks anterolaterally, and pelvic floor inferiorly. Maintenance of abdominal core health may include surgical (e.g., hernia repair) and nonsurgical interventions (e.g., physical therapy) with an emphasis on maximizing core stability and function.

2 Major risk factors for the development of abdominal wall hernias include chronic obstructive pulmonary disease, smoking, high intra-abdominal pressure, collagen vascular disease, thoracic or abdominal aortic aneurysm, peritoneal dialysis, abnormalities in the regulators of collagen homeostasis matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) in association with local cytokine induction, and an increased type I: type III collagen ratio.

3 Inguinal hernias constitute approximately 75% of abdominal wall hernias, with femoral hernia accounting for 5%. Femoral hernias are more common in women, but a woman with a groin hernia is still five times more likely to have an inguinal hernia (usually indirect) than a femoral. Incisional, umbilical, and epigastric hernias account for 15%, and miscellaneous hernias make up the other 5%.

4 Watchful waiting is an acceptable alternative to routine repair for male inguinal hernia patients with minimal symptoms. This does not apply to females because of the higher risk of a hernia accident. Patients in the watchful waiting group should be aware of the likelihood of long-term crossover into treatment group.

5 The performance of a “tension-free” inguinal hernia repair reduces the risk of recurrent hernia to a rate generally reported to be less than 2%.

6 The literature dealing with groin hernia in women is insufficient making management decisions difficult. In general, a laparoscopic approach is recommended if expertise is available.

7 The frequency of at least some long-term groin pain after inguinal herniorrhaphy is approximately 10% at 1 year with moderate to severe pain in 1% to 2%.

8 Abdominal wall dynamics are better addressed with muscles reapproximated, contributing to improved quality of life and patient satisfaction.

9 Abdominal wall reconstruction and myofascial release (separation of an abdominal wall fascial layer from a muscular layer) are useful tools in the armamentarium of the hernia surgeon.

INTRODUCTION

One of the most frequently performed operations by general surgeons worldwide is the repair of an abdominal wall hernia. According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in the years 2009–2010, abdominal wall hernias were responsible for 3.6 million ambulatory care visits, 380,000 hospitalizations, and 1,322 deaths in the United States.[1] In the past, most training programs relegated the repair of abdominal hernias to the junior members of the surgical team with little regard for results.[2] However, as we being to understand the complexities and relationships of the abdominal wall to other components of the abdominal core and its overall function, this is changing rapidly. Interest by the academic community in the science behind hernia repair as well as an explosion in device development by industry has resulted in significant changes to many surgeons' practices. In this chapter, we have provided a detailed description of the abdominal wall anatomy, an understanding of which is key to successful hernia repair.[3] We have then described the different treatment options with their available evidence and have included some of the newer developments in the field of hernia surgery.

ANATOMY OF THE ABDOMINAL CORE

The concept of the "abdominal core" aims to capture the complex relationships of the circumferential soft tissues of the diaphragm superiorly, abdominal wall and flanks anterolaterally, and pelvic floor inferiorly. Maintenance of abdominal core health includes exercise, physical therapy, medical therapy (including compression garment/truss use), alternative medical therapies, surgical intervention (e.g., hernia repair), and measures to prevent disease (e.g., hernia prophylaxis). Disease processes 1 involving abdominal core health include intrinsic diseases of the abdominal wall (e.g., hernia, diastasis, athletic pubalgia or core muscle injury, benign and malignant tumors) and extrinsic diseases of the abdominal wall (e.g., prosthetic and intervention-associated complications, benign and malignant tumors).[4] Most pertinent to abdominal core surgeons, the anatomy of the abdominal wall and the inguinal region are presented, first from the viewpoint of the surgeon using open techniques and subsequently from the perspective of the surgeon utilizing a minimally invasive approach. Anatomic terms for which synonyms and eponyms are commonly used are listed in **Table 72.1**. Specific anatomic nomenclature can now be found in *Terminologia Anatomica,* the successor to *Nomina Anatomica.*

Table 72.1 Anatomic Terms with Common Synonyms and Eponyms

Fascial Structures/Spaces
Fatty layer of superficial fascia; panniculus adiposus; Camper fascia
Investing fascia of external abdominal oblique; fascia innominata
Membranous layer of superficial fascia; Scarpa fascia
Retroinguinal space; space of Bogros
Retropubic space; space of Retzius
Ligamentous Structures
Iliopectineal ligament; iliopectineal arch
Iliopubic tract; Thompson ligament (band)
Inguinal ligament; Poupart ligament
Lacunar ligament; Gimbernat ligament
Pectineal ligament; Cooper ligament
Aponeurosis-Derived Structures
Arcuate line; semicircular line; linea semicirculars; line of Douglas
Falx inguinalis (often incorrectly referred to as *conjoined tendon*)
Reflected inguinal ligament; reflex ligament; Colles ligament
Semilunar line; linea semilunaris

The sheets of relatively thin muscles and aponeuroses that make up the abdominal wall would, individually, seem to predispose to visceral eventration. However, the laminar layout of these sheets over most of the wall precludes this in most cases. The most common sites of hernia formation are found between laminations, where only peritoneum and fascia are found between the viscera and skin. These weak areas are most important to the hernia surgeon and are described in detail in the subsequent sections dealing with the anterior and posterolateral abdominal wall and the inguinal region.

Diaphragm

The diaphragm forms the cranial "ceiling" of the abdominal core and separates the thoracic cavity from the abdominal cavity. The skeletal muscle of the diaphragm originates from the caudal aspect of the sternum, lower ribs,

and vertebrae forming a dome-shaped structure with a central membranous tendon. Unlike most other skeletal muscles, several vital structures pass through openings within the diaphragm including the esophagus, aorta, and inferior vena cava. The main arterial supply to the diaphragm include the musculophrenic and inferior phrenic arteries; venous drainage is obtained via the superior and inferior phrenic veins. Generally, vasculature of the diaphragm projects radially from the hiatal openings. The right and left phrenic nerves, originating from cervical roots C3–C5, enter the diaphragm mostly medially and branch radially outward. The esophageal hiatus has particular significance as it is a common site of herniation of intra-abdominal contents into the mediastinal space. The muscular right crus of the diaphragm, a critical landmark in hiatal hernia repair, has two components: a right and left pillar that form the esophageal hiatus itself. The left crus of the diaphragm itself typically does not encircle the esophagus. Functionally, the diaphragm is critical to breathing. As the diaphragm contracts, the thoracic cavity increases in volume, enabling inspiration. As the diaphragm relaxes, the recoil of the lungs and thorax allows for expiration. The diaphragm is also critical to forced expiratory functions such as coughing and sneezing.

Anterior Abdominal Wall and Flanks

Superficial Fascia, Vessels, and Nerves

The anterior abdominal wall does not consist solely of muscle and aponeurosis; it can also be the repository for copious amounts of adipose tissue (panniculus adiposus) in its superficial fascial layer, often called *Camper fascia.* This layer, which is continuous inferiorly with the outer layer of fascia covering the perineum and genitalia, also contains the dartos muscle fibers of the scrotum. The major blood vessels of the superficial fatty layer are the superficial epigastric vessels and superficial circumflex iliac vessels, which are tributaries of the femoral vessels. The superficial fascia is also replete with lymphatic vessels that drain into the inguinal lymph nodes inferior to the umbilicus. The lymphatic structures cross the inguinal ligament, so that they are potentially placed in the surgical field during open herniorrhaphy.

A second fascial layer in the superficial abdominal wall is the deep fascia of Scarpa. Although most commonly considered a distinct anatomic layer, Scarpa fascia actually consists of compressed fibrous components of the superficial fascia.[5] The deeper fibrous tissue of the superficial fascia forms the fundiform ligament of the penis (suspensory ligament of the female clitoris), continues onto the penis and scrotum, and ultimately fuses with the superficial fascia of the perineum.

The superficial fascia also fuses with the layer of fascia (fascia innominata) investing the external abdominal oblique muscle. This fascia is bound inferiorly to the inguinal ligament and pubis before continuing onto the thigh, where it blends with the fascia lata to seal the space beneath and inferior to the inguinal ligament, which is the inferior portion of the myopectineal orifice (**Fig. 72.1**). This portion of the inguinal region includes Hesselbach (inguinal) triangle superiorly and therefore constitutes the weakest aspect of the groin.

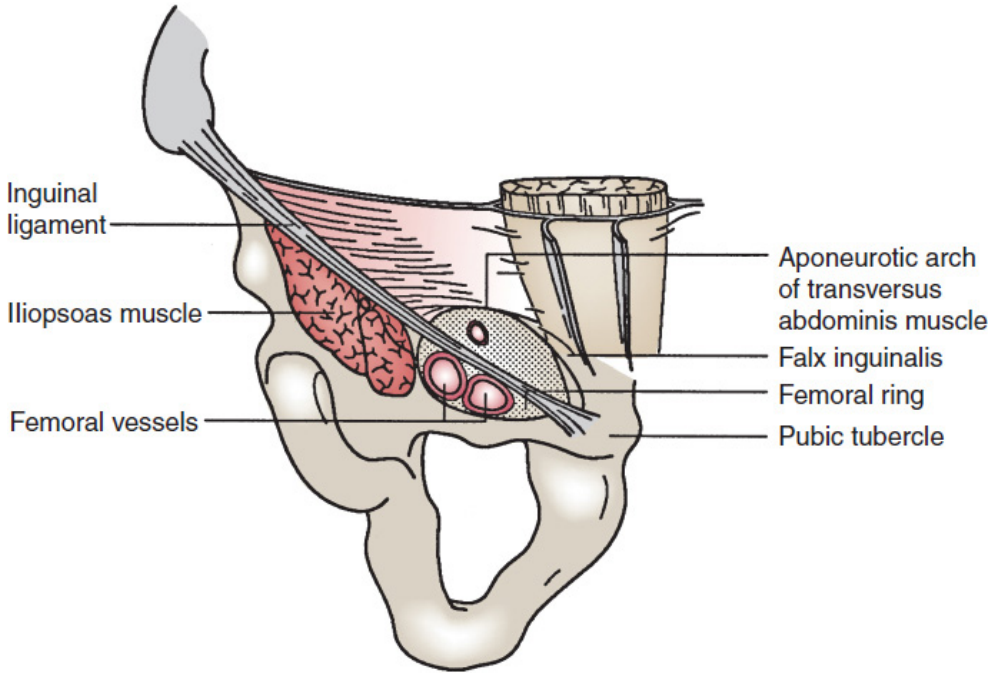


Figure 72.1 The myopectineal orifice. Superior to the inguinal ligament, this area includes the inguinal (Hesselbach) triangle. Inferior to the ligament, the orifice transmits the iliopsoas muscle, the femoral nerve and vessels, and the femoral canal and sheath. (Reproduced with permission from Wantz GE. *Atlas of Hernia Surgery*. New York: Raven Press; 1991:4.)

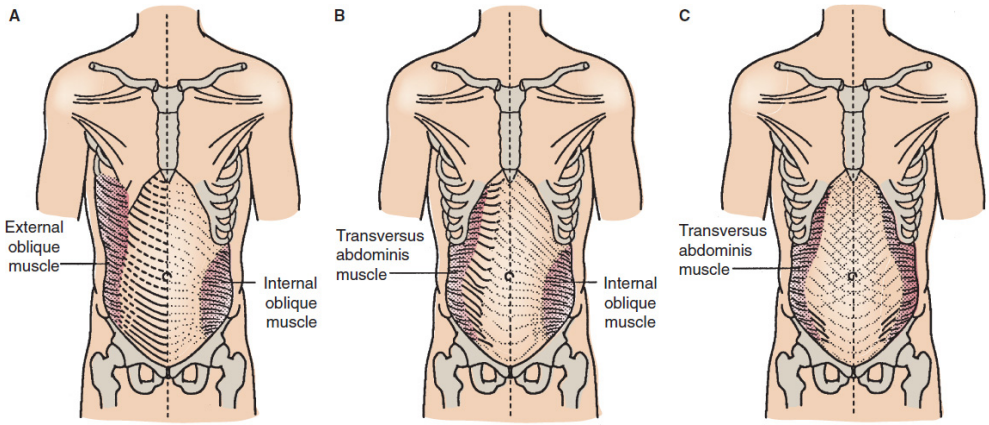


Figure 72.2 Pattern of crossing of the aponeurotic fascicles of the abdominal wall musculature. **A:** Fascicles from the right external oblique and anterior lamina of the left internal oblique. **B:** Fascicles from the right transversus abdominis and posterior lamina of the left internal oblique. **C:** Fascicles between the right and left transversus abdominis muscles.

The skin of the anterior abdominal wall is segmentally innervated in the familiar dermatome pattern. The nerve branches to this area are derived from the anterior and lateral cutaneous branches of the ventral rami of the 7th to 12th intercostal nerves and from the ventral rami of the first and second lumbar nerves. Disruption of one of these nerves is rarely noted by the postoperative patient because the dermatome fields overlap significantly. The anterior and lateral cutaneous branches reach the subcutaneous layer by coursing between the flat lateral muscles and by piercing the sheath of the rectus abdominis.

Anterior Musculature and Ligaments

The division of the wall into anterior and posterior segments is somewhat artificial because the anterior muscles, with the exception of the rectus abdominis, arise posteriorly and also form part of the posterior wall.

The three muscles of the lateral aspect of the anterior abdominal wall (**Fig. 72.2**) are composed of a variable amount of muscle with a large aponeurosis. The aponeurosis is the tendon of insertion for the lateral muscles, and it also forms the sheath of the rectus abdominis. The midline decussation of the three aponeuroses forms the linea alba. Fibrous tissue layers are of great importance to the hernia surgeon because of their ability to support sutures. *Fascia* and *aponeurosis* are terms commonly used to describe these fibrous

structures, but are often confused and used interchangeably. In this chapter, an aponeurosis is defined as the non–muscle-fiber-containing portion of a muscle usually present at insertion points. Muscle fibers are said to "give way" to the corresponding aponeurosis. Fascia, on the other hand, is the fibrous tissue that lines or envelops muscles.

External Abdominal Oblique Muscle and Associated Ligaments

The external abdominal oblique muscle (**Figs. 72.2** and **72.3A,B**) is the most superficial of the three lateral abdominal muscles. The external abdominal oblique arises from the posterior aspects of the lower eight ribs and interdigitates with both the serratus anterior and the latissimus dorsi at its origin. The direction of the muscle fibers varies from nearly horizontal in its upper portion to oblique in the middle and lower portions. The mostly horizontal fibers, which originate posteriorly, insert onto the anterior portion of the iliac crest. The obliquely arranged anteroinferior fibers of insertion fold on themselves to form the inguinal ligament. The remaining portion of the aponeurosis inserts into the linea alba after contributing to the anterior portion of the rectus abdominis sheath. Some fibers cross the linea alba to reinforce further the anterior rectus sheath of the opposite side.

The more medial fibers of the aponeurosis of the external oblique divide into a medial and a lateral crus to form the external or superficial inguinal ring. The spermatic cord (or round ligament) and branches of the ilioinguinal and genitofemoral nerves pass through this opening. The *inguinal ligament* (**Fig. 72.4**) is worthy of special consideration because of its important role as both a landmark and an integral component of many groin hernia repairs. The inguinal ligament is formed by obliquely oriented anteroinferior aponeurotic fibers of the external abdominal oblique. The ligament is formed when the aponeurosis folds beneath itself. Its lateral attachment is to the anterior superior iliac crest; its medial insertion is primarily on the pubic tubercle.

The medial insertion of the inguinal ligament in most persons is dual. One portion runs along the superior surface of the pubic tubercle and symphysis to form (or at least reinforce) the superior pubic ligament. The other portion is fan shaped and spans the distance between the inguinal ligament proper and

the pectineal line of the pubis. This fan-shaped portion of the ligament is called the *lacunar ligament* (**Fig. 72.4**). It blends laterally with the pectineal (Cooper) ligament.

Internal Abdominal Oblique Muscle and Aponeurosis

The middle layer of the lateral abdominal group is the internal abdominal oblique muscle (**Figs. 72.2** and **72.3B,C**). This muscle primarily arises from the iliac fascia along the iliac crest and forms a band of iliac fascia fused with the inguinal ligament. The uppermost fibers course obliquely toward the distal ends of the lower three or four ("floating") ribs. The muscle fibers of the internal oblique fan out following the shape of the iliac crest so that the lowermost fibers are directed inferiorly. These fibers arch over the round ligament, or spermatic cord. Some of the lower muscle bundles in the male join fibers of the transversus abdominis to form the cremaster muscle. The aponeurosis of the internal oblique (**Fig. 72.5A**) above the level of the umbilicus splits to envelop the rectus abdominis, reforming in the midline to join and interweave with the fibers of the linea alba. Below the level of the umbilicus (**Fig. 72.5B**), the aponeurosis does not split but rather runs anterior to the rectus muscle, continues medially as a single sheet, joins the anterior rectus sheath, and finally contributes to the linea alba. The aponeurotic portion of the internal oblique is widest at the level of the umbilicus.

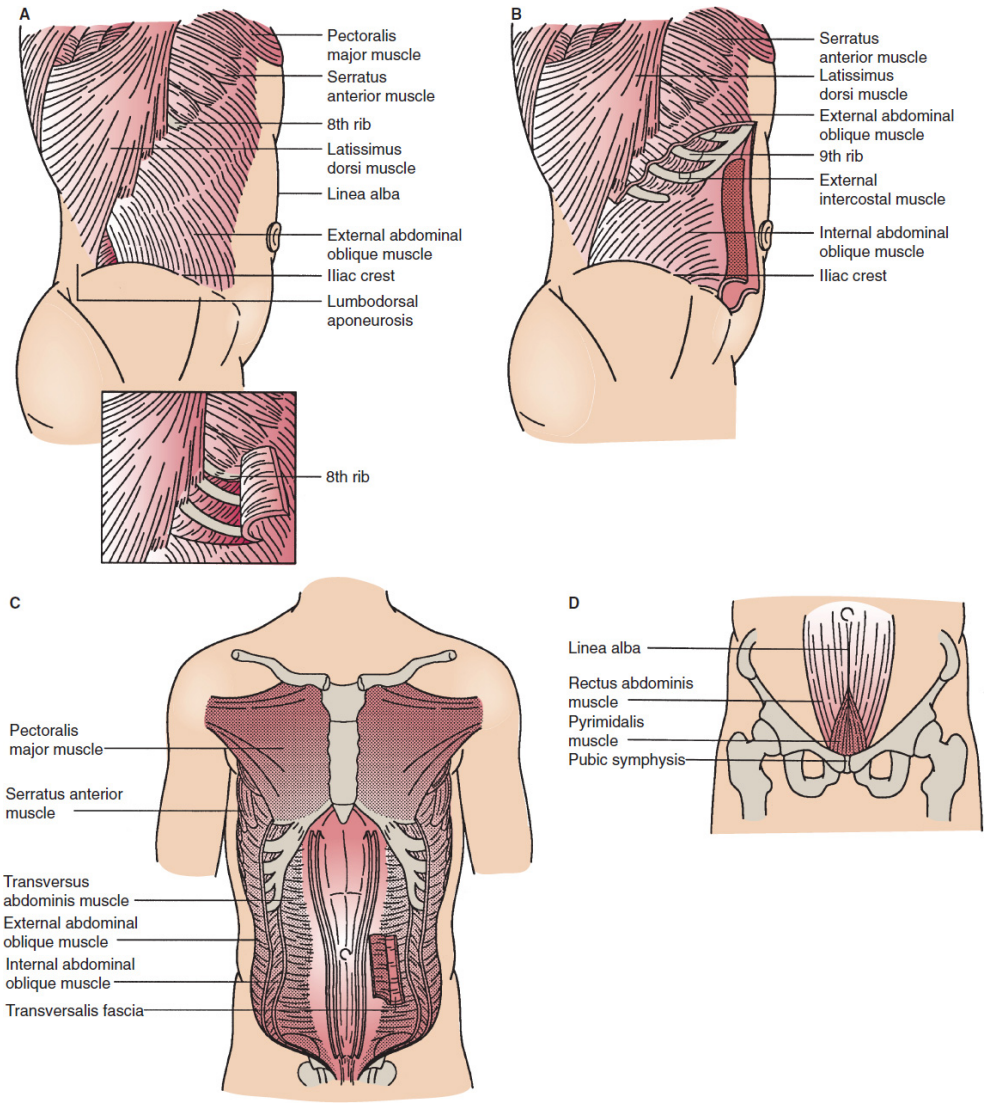


Figure 72.3 **A:** External oblique muscle and aponeurosis. **B:** Internal oblique muscle and aponeurosis. **C:** Transversus abdominis muscle and aponeurosis. **D:** Lower rectus abdominis and pyramidalis muscle. The linea alba is formed by the intermeshed fibers of the aponeuroses of the lateral muscle layers; it is tensed by the pyramidalis, which inserts into it.

Transversus Abdominis Muscle and Aponeurosis

The transversus abdominis muscle (**Figs. 72.2** and **72.3C**) arises from the fascia along the iliac crest and inguinal ligament and from the lower six costal cartilages and ribs, where it interdigitates with the lateral diaphragmatic fibers. The muscle bundles of the transversus abdominis for the most part run horizontally. The lower medial fibers, however, may

continue in a more inferomedial course toward the site of insertion on the crest and pecten of the pubis.

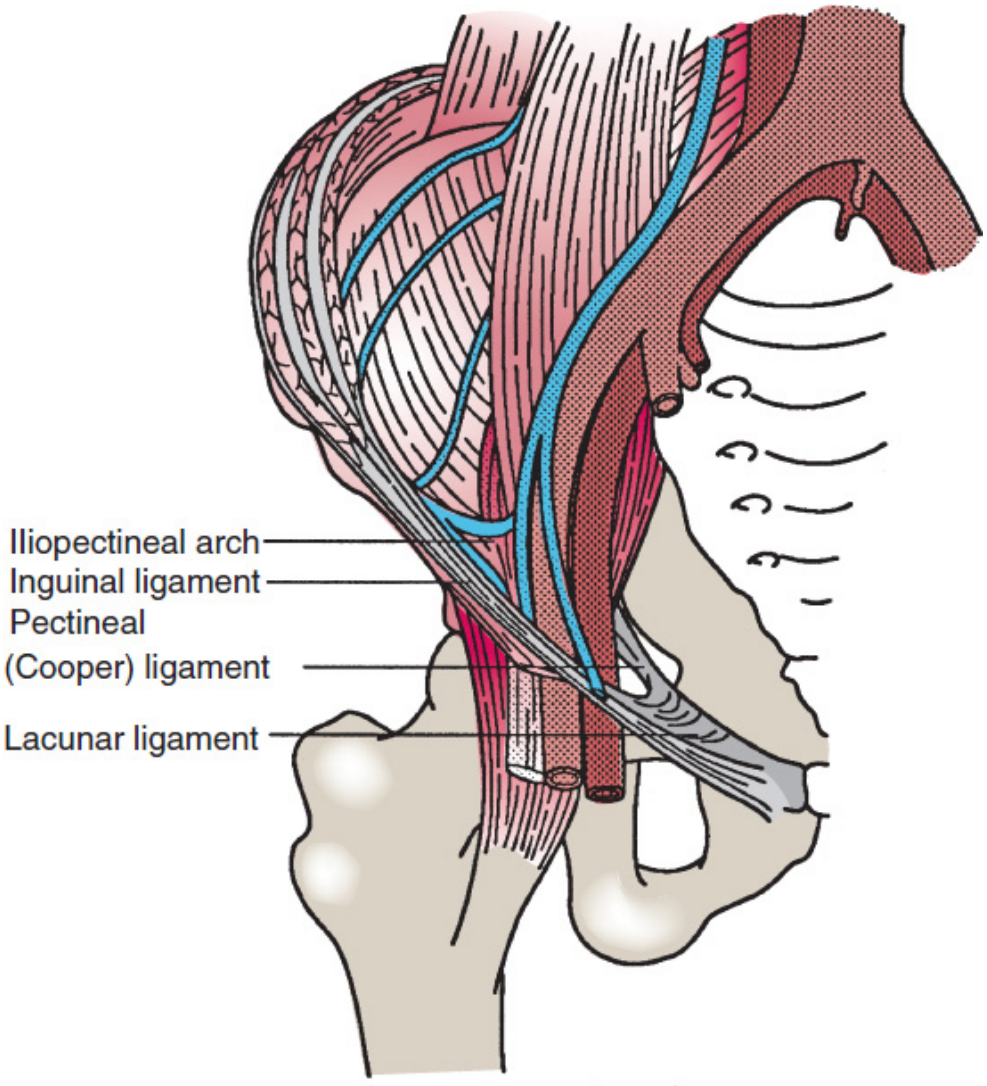


Figure 72.4 Ligamentous structures of the inguinal region. The iliopubic tract is not seen in this view because it is obscured by the inguinal ligament. The lacunar ligament is the expanded medial end of the inguinal ligament; on the pecten pubis, it blends with the inguinal (Cooper) ligament.

The aponeurosis of the transversus abdominis joins the posterior lamina of the internal abdominal oblique, forming above the umbilicus a portion of the posterior rectus sheath. Below the umbilicus, the transversus abdominis aponeurosis is a component of the anterior rectus sheath. The gradual termination of aponeurotic tissue on the posterior aspect of the rectus abdominis forms the arcuate line (of Douglas) (**Fig. 72.6**). The transversus

abdominis muscle and aponeurosis extend medial to the semilunar line. The medial aponeurotic fibers of the transversus abdominis insert on the pecten pubis and the crest of the pubis to form the falx inguinalis. These fibers infrequently are joined by a portion of the internal oblique aponeurosis; only then is a true conjoined tendon formed.[6]

The arch formed by the termination of the aponeurotic fibers of the transversus abdominis is called the *aponeurotic arch* (**Fig. 72.6**). The area beneath the arch varies. A high arch may be a predisposing factor in direct inguinal hernia. Contraction of the transversus abdominis causes the arch to move down toward the inguinal ligament in a kind of shutter mechanism, which reinforces the weakest area of the groin when intra-abdominal pressure is raised.

Rectus Abdominis

The rectus abdominis (**Figs. 72.3D** to **72.5**) forms the central and anchoring muscle mass of the anterior abdomen. The rectus muscle arises from the fifth to the seventh costal cartilages and inserts on the pubic symphysis and pubic crest. Each rectus muscle is segmented by tendinous intersections at the levels of the xiphoid process and the umbilicus and at a point midway between these two. The principal blood supply reaches the muscle from the superior and inferior epigastric arteries (**Fig. 72.5**), which anastomose just superior to the umbilicus. Other vessels are anterior branches of the intercostal arteries; these reach the muscle by entering the lateral aspect of the rectus sheath. The innervation of the muscle is from the 7th to the 12th intercostal nerves, which laterally pierce the aponeurotic sheath of the muscle. The lateral edge of the muscle is demarcated by a slight depression in the aponeurotic fibers coursing toward the muscle; this depression is the *semilunar line.*

The small pyramidalis muscle (**Fig. 72.3D**) accompanies the rectus abdominis at its origin in a minority of people. The pyramidalis arises from the pubic symphysis. It lies within the rectus sheath and tapers to attach to the linea alba, the conjunction of the two rectus sheaths and the major site of insertion of three aponeuroses from all three lateral muscle layers.

Rectus Sheath

Although the components of the rectus sheath individually have been discussed in relation to the three lateral abdominal muscles, it should also be considered as a distinct entity. Three features of the rectus muscle and its sheath can be observed even topographically in well-muscled or very thin subjects:

1. The semilunar line is a slight depression in the aponeurotic fibers corresponding to the lateral edge of the rectus muscle. It marks the site of initial lateral insertion of the aponeurotic tendons of the lateral abdominal muscles.
2. The tendinous inscriptions divide each muscle into three parts.[7] These are the basis of the expression "six pack," popularized by bodybuilders.
3. The linea alba is the midline confluence of the aponeuroses of the rectus muscles and also the internal and external oblique muscles.

The composition of the rectus sheath varies depending on the level sampled. The anterior sheath superior to the umbilicus is composed of the aponeurosis of the external abdominal oblique and the anterior lamina of the internal abdominal oblique. The transversus abdominis aponeurosis does not participate in the formation of the anterior sheath at this level. At a variable level inferior to the umbilicus, the anterior sheath is a composite of all the aponeurotic layers.

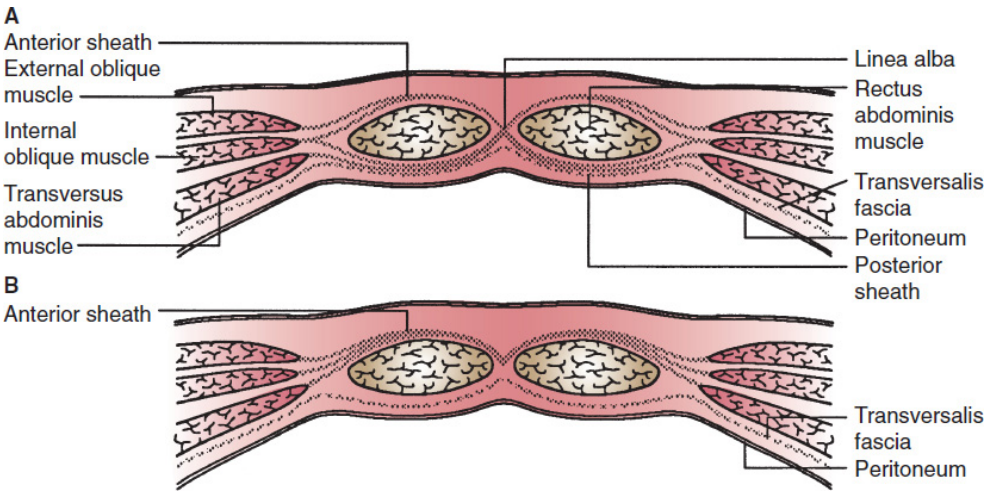


Figure 72.5 **A:** Immediately superior to the umbilicus, the rectus sheath consists of anterior and posterior components. The anterior sheath is composed of the aponeuroses of the external and internal abdominal oblique muscles, and the posterior sheath consists of the posterior aponeurotic lamina of the internal oblique and the aponeurosis of the transversus abdominis muscle. **B:** The rectus sheath inferior to the arcuate line (of Douglas) consists of an anterior portion made up of fibers from all aponeurotic layers; the posterior portion at this point comprises only transversalis fascia covered internally by peritoneum.

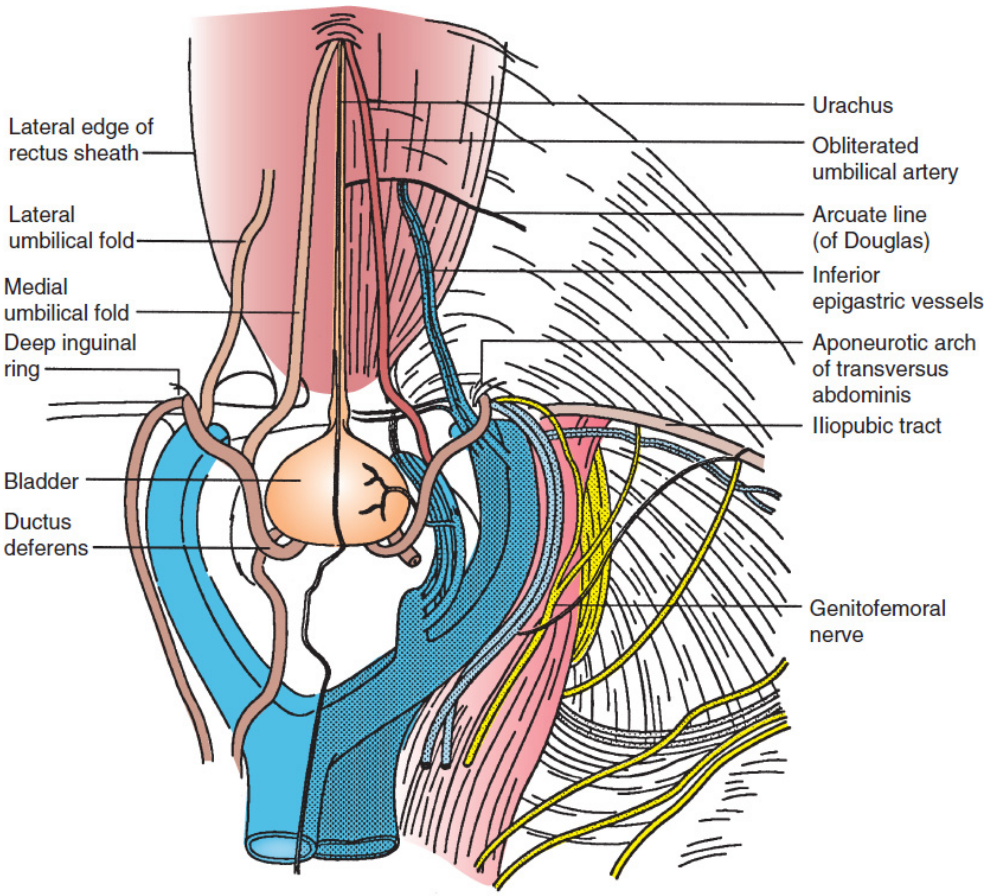


Figure 72.6 The deep inguinal region, pelvis, and anterior abdominal wall from the viewpoint of a surgeon using a laparoscopic technique. The anterior wall folds upward approximately at the iliopubic tract in this illustration.

The posterior sheath of the rectus muscle superior to the umbilicus is a lamination of the posterior lamina of the aponeurosis of the internal abdominal oblique and the transversus abdominis aponeurosis, while the transversalis fascia and peritoneum underly the aponeurotic layers. The external abdominal oblique does not participate in the formation of the posterior portion of the rectus sheath. At a highly variable site inferior to the umbilicus, all the aponeurotic tendons pass anteriorly to form the anterior rectus sheath. The fibers of the posterior sheath are seen to attenuate gradually. The aponeurotic fibers do not end abruptly at the arcuate line. This transfer of connective tissue away from the posterior rectus sheath causes the arcuate line (of Douglas) to form on the posterior surface of the muscle (**Fig. 72.6**). The tissue covering the deep surface of the rectus muscle inferior to the arcuate line is primarily the transversalis fascia and peritoneum.

Some have questioned this traditional scheme of rectus sheath composition, contending that each of the aponeurotic layers superior to the umbilicus is actually bifid, with both contributing to the anterior and posterior sheaths.[8] The fibers of the posterior sheath are seen to attenuate gradually. The concept of rectus sheath composition favored by most is shown in **Figure 72.7**.[9]

Innervation and Blood Supply of the Anterior Abdominal Wall

The innervation of the anterior wall muscles is multiple. The lower intercostal and upper lumbar nerves (T7 to T12, L1, L2) contribute most of the innervation to the lateral muscles, the rectus abdominis, and the overlying skin. The nerves pass anteriorly in a plane between the internal abdominal oblique and the transversus abdominis, eventually piercing the lateral aspect of the rectus sheath to innervate the muscle therein. The external oblique muscle receives branches of the intercostal nerves, which penetrate the internal oblique. The anterior ends of the nerves form part of the cutaneous innervation of the abdominal wall. The first lumbar nerve divides into the ilioinguinal and iliohypogastric nerves. These may divide within the psoas major muscle or between the internal oblique and transversus abdominis muscles. The ilioinguinal nerve may communicate with the iliohypogastric nerve before innervating the internal oblique. The ilioinguinal nerve then passes through the external inguinal ring to run with the spermatic cord, whereas the iliohypogastric nerve pierces the external oblique to innervate the skin above the pubis. The cremaster muscle fibers, which are derived from the internal oblique muscle, are innervated by the genitofemoral nerve (L1, L2).

The blood supply of the lateral muscles of the anterior wall is primarily from the lower three or four intercostal arteries, the deep circumflex iliac artery, and the lumbar arteries. The rectus abdominis has a complicated blood supply derived from the superior epigastric artery (a terminal branch of the internal thoracic, or internal mammary, artery), the inferior epigastric artery (a branch of the external iliac artery), and the lower intercostal arteries. The latter arteries enter the sides of the muscle after traveling

between the oblique muscles. The superior and inferior epigastric arteries enter the rectus sheath and anastomose near the umbilicus.

Posterolateral (Lumbar) Abdominal Wall

The posterolateral or lumbar portion of the abdominal wall (**Fig. 72.8**) is often overlooked in discussions of abdominal hernia, perhaps because of the much more common occurrence of groin and femoral hernias. The configuration of the muscle layers in the lumbar area also predisposes to hernia formation. For the purposes of this discussion, the lumbar portion of the abdominal wall is defined as the area bounded superiorly by the 12th rib, inferiorly by the iliac crest, and medially by the erector spinae group. Eight muscles arrayed in three layers constitute the posterolateral or lumbar portion of the abdominal wall.

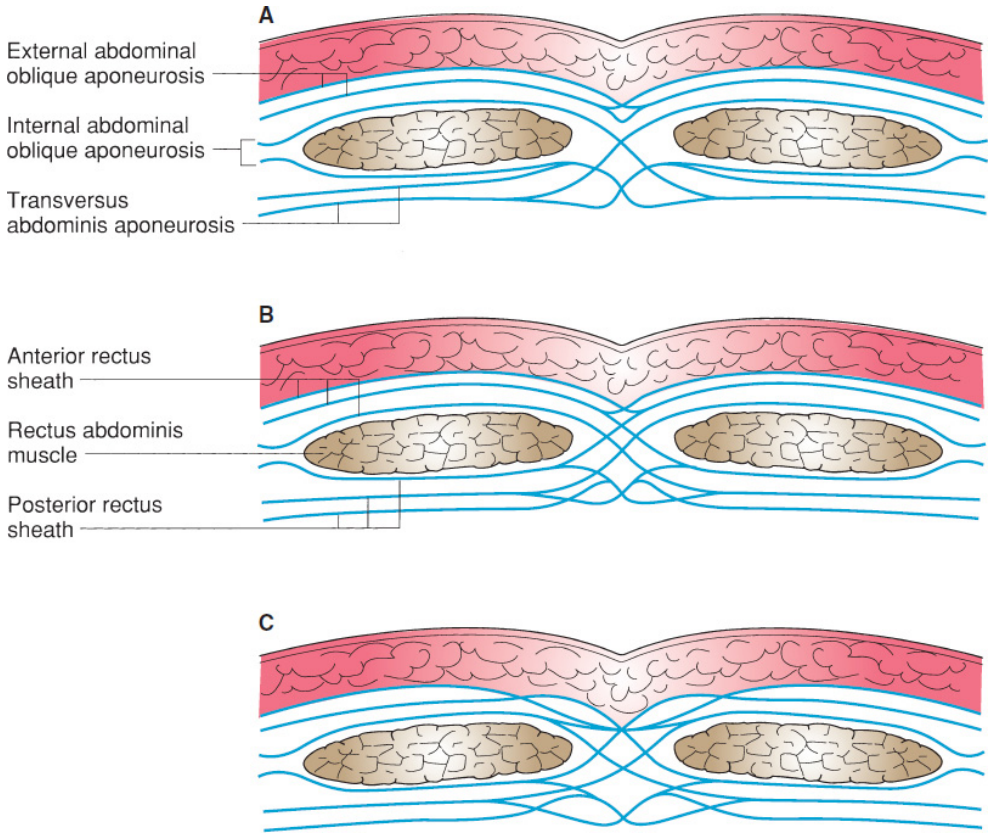


Figure 72.7 Patterns of midline decussation of the aponeuroses. **A:** Single anterior and posterior lines of decussation. **B:** Single anterior and triple posterior lines of decussation. **C:** Triple anterior and posterior lines of decussation.

The most superficial layer is composed of the external abdominal oblique muscle, which arises from the posteroinferior portion of the lower ribs and inserts in part along the posterior iliac crest. Closely associated with the external oblique in this area is the latissimus dorsi, which arises from the posterior iliac crest, the spinous processes of the sacrum and lumbar vertebrae, and the lumbodorsal fascia. The muscle courses obliquely toward its insertion on the medial aspect of the intertubercular groove of the humerus. The triangular space formed by the two muscles just described and the iliac crest is called the *inferior lumbar (Petit) triangle* (**Fig. 72.8A**).

The middle layer of lumbar abdominal muscles consists of the erector spinae, the internal abdominal oblique, and the extremely thin insignificant serratus posterior inferior. The erector spinae forms a significant portion of the abdominal wall in the lumbar region, with fibers extending nearly the length of the spinal column. The internal abdominal oblique muscle forms the remainder of the layer. The serratus posterior inferior arises from the lumbodorsal fascia and inserts on the lower four ribs. The middle layer of lumbar muscle is associated with the superior lumbar triangle, a more common site of hernia than the inferior lumbar triangle described previously. The superior triangle (**Fig. 72.8B**) is formed superiorly by the 12th rib, the serratus posterior inferior, and the superior lumbocostal ligament; inferiorly by the upper border of the internal abdominal oblique; and medially by the erector spinae.

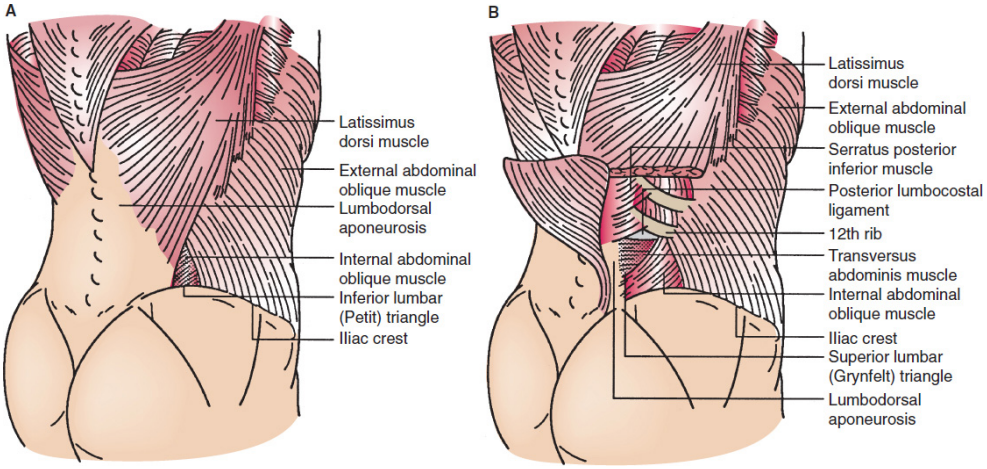


Figure 72.8 The lumbar abdominal wall with the inferior lumbar triangle (**A**) and the superior lumbar triangle (**B**).

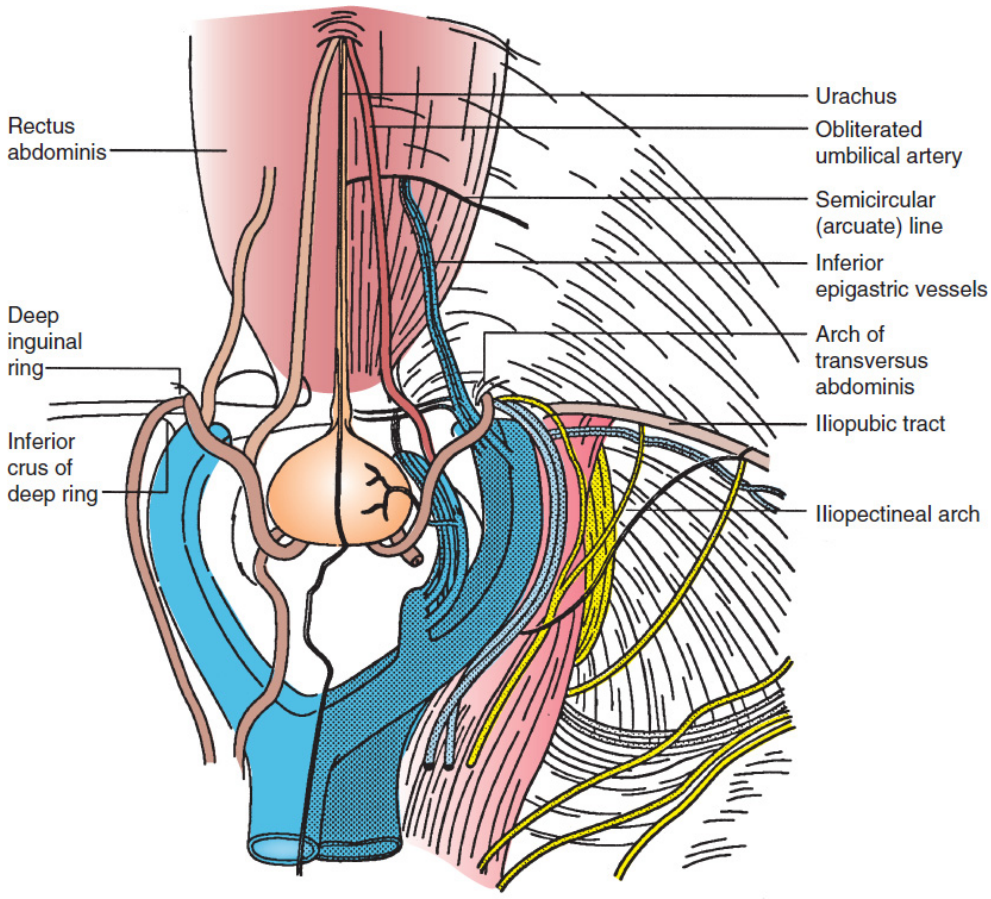


Figure 72.9 The deep inguinal region and the anterior abdominal wall seen from within the abdomen. The urachus, the obliterated portion of the umbilical artery, and the inferior epigastric vessels are covered by peritoneal folds, respectively called the median, medial, and lateral umbilical folds.

The deep layer of the lumbar abdominal wall includes three muscles: the quadratus lumborum, the psoas major, and the transversus abdominis. The quadratus lumborum primarily arises from the posterior iliac crest and inserts on the 12th rib. The psoas major arises from vertebrae T12 through L5 and passes beneath the inguinal ligament to insert on the lesser trochanter of the femur.

Deep Inguinal Region

Minimally Invasive View

Deep Aspect of the Anterior Abdominal Wall, Peritoneal Folds, and Associated Structures If one creates a space in the abdominal cavity by distending it with gas, an excellent view of the anterior wall can be obtained.

The umbilical peritoneal folds (**Fig. 72.9**) in most subjects are very prominent and provide easily identified landmarks. The folds (ligaments) primarily exist because the peritoneum covers underlying structures.

The single median umbilical fold extends from the umbilicus to the urinary bladder and covers the urachus, the fibrous remnant of the fetal allantois. The urachus may be patent for a short distance in adults or may open into the umbilical scar in newborns. The medial umbilical fold is formed by the underlying obliterated portion of the fetal umbilical artery. This normally cordlike structure, like the urachus, may be patent for a portion of its length. Indeed, the proximal, patent portion of the artery normally supplies the superior vesicular arteries to the bladder. The lateral fold covers the inferior epigastric arteries as they course toward the posterior rectus sheath, which they enter approximately at the level of the arcuate line.

Between the median and the medial ligaments, a depression is usually found that is called the *supravesical fossa.* This is the site of hernias of the same name. The fossa formed between the medial and lateral ligaments is the medial fossa; this is the site of direct inguinal hernias. The lateral fossa is less well delineated than the others. The medial border of the fossa is formed by the lateral umbilical ligament and the rectus abdominis. This fossa does not have a lateral border; rather, the concavity slowly attenuates. The deep inguinal ring is located in the lateral fossa and therefore is the site of the congenital or indirect inguinal hernia.

Transversalis Fascia

The transversalis fascia (endoabdominal fascia) is perhaps the most commonly misunderstood structure in the literature devoted to groin hernia. Confusion results because surgeons may actually be referring to very different anatomic structures when discussing various hernia repairs; however, each may use the same anatomic term or eponym. Indeed, perhaps the biggest reservation among surgeons intent on performing a Shouldice repair is a precise definition of what is being sewn to what.

The transversalis fascia proper is a continuous sheet that extends throughout the extraperitoneal space. The term *transversalis fascia* is generally defined as the deep or endoabdominal fascia covering the internal surface of the transversus abdominis, the iliacus, the psoas muscles, and the

obturator internus and portions of the periosteum. One variant of this convention is the use of terms specific to the muscle covered by the fascia (e.g., iliac fascia).

Most authors feel that only one layer of transversalis fascia exists, whereas others maintain that the transversalis fascia comprises two layers, or laminae.[10] The posterior lamina is a layer of fibrous connective tissue that widely varies in density and continuity and is interspersed with adipose tissue, as seen in **Figure 72.10**. This layer is often referred to simply as the *preperitoneal fascia.* The anterior lamina is more uniform and is adherent to the deep surface of the transversus abdominis and the rectus abdominis. The posterior lamina is contained within the preperitoneal space, which is defined as the space between the peritoneum and the anterior lamina of the transversalis fascia. The inferior epigastric vessels are enclosed by, or interspersed with, the adipose tissue and the fibrous tissue of the posterior lamina of the transversalis fascia. The vessels are in contact anteriorly with the anterior lamina of the transversalis fascia as they course upward to enter the rectus abdominis sheath.

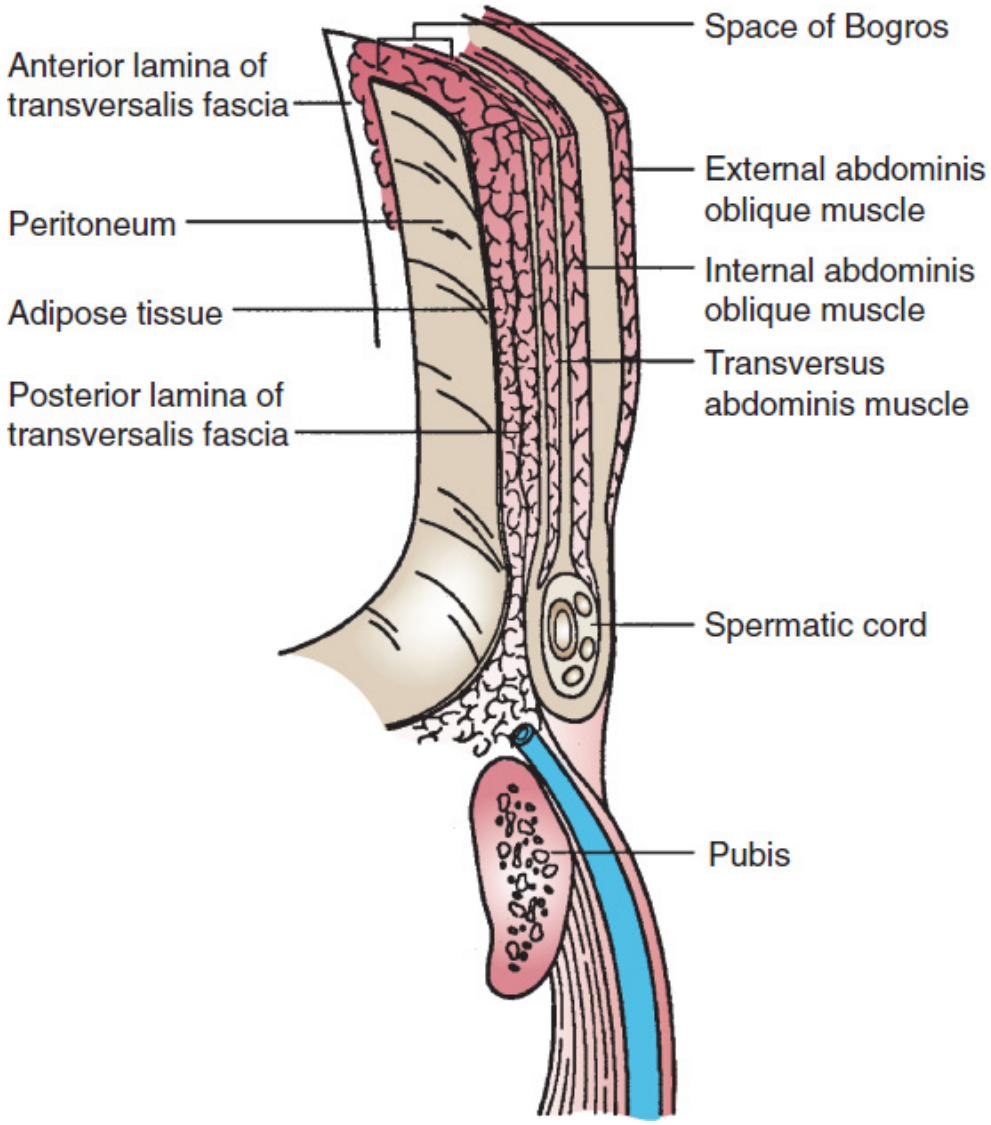


Figure 72.10 A parasagittal section through the layers of the anterior abdominal wall and groin. Observe that the transversalis fascia is depicted as a bilaminar structure.

Transversalis Fascia Derivatives

The transversalis fascia analogs or derivatives are the iliopectineal arch, iliopubic tract, and crura of the deep inguinal ring. The superior and inferior crura form a transversalis fascia sling, a structure shaped like a "monk's hood," around the deep inguinal ring (Fig. 72.9). The transversalis fascia also contributes the internal spermatic fascia to the spermatic cord at this point. This "sling" has functional significance; when the transversus abdominis contracts, the crura of the ring are pulled upward and laterally,

which results in a valvular action that helps to prevent the indirect formation of a hernia.

The iliopubic tract (**Figs. 72.9** to **72.11**) has become an increasingly important landmark for surgeons as the use of laparoscopic technology has increased.[11,12] The iliopubic tract is the thickened band of transversalis fascia formed at the zone of transition between the deep surfaces of the iliac and transversus abdominis muscles. The structure courses parallel to the more superficially located inguinal ligament, is attached to the iliac crest laterally, and inserts on the pubic tubercle medially. The tract forms along its course a portion of the inferior crus of the deep inguinal ring and then contributes to the anterior and medial walls of the femoral sheath. The tract fuses with the inguinal ligament to form a component of the inferior wall of the inguinal canal. At its insertion on the pubic tubercle, it curves backward slightly to blend with Cooper's pectineal ligament. The pectineal ligament is actually a condensation of periosteum and is not a true analog of the transversalis fascia, but it is reinforced by fibers from the iliopubic tract and inguinal ligament.

The iliopubic tract contains not only fibrous connective tissue but also some elastic fibers.[13] In one series, the iliopubic tract was a substantial structure, suitable for use in hernia repairs, in 42% of the specimens examined. The tract, whether substantial or not, can be used as a readily identified landmark.

The iliopubic tract has particular significance because of its importance as a landmark to the laparoscopic surgeon. Many of the branches of the lumbar plexus run inferior to the tract, and damage to these nerves may be the result of aggressive dissection or the placement of tacks or staples to affix a prosthesis below this structure. The tract is not obviously visible in every patient from a laparoscopic view, but its location should always be immediately known to the surgeon because of its constant relationship to the other landmarks in this area.

The iliopectineal arch (**Fig. 72.9**) is also a condensation of the transversalis fascia. The iliopectineal arch commences at the medial border of the iliacus muscle, where it is continuous with the iliac fascia, itself a portion of the transversalis (endoabdominal) fascia. The arch separates the vascular compartment containing the femoral vessels from the neuromuscular compartment containing the iliopsoas muscle, femoral nerve, and lateral

femoral cutaneous nerve. The iliopectineal arch also contributes to the proximal portion of the femoral sheath, thereby joining the iliopubic tract in the formation of the femoral sheath.

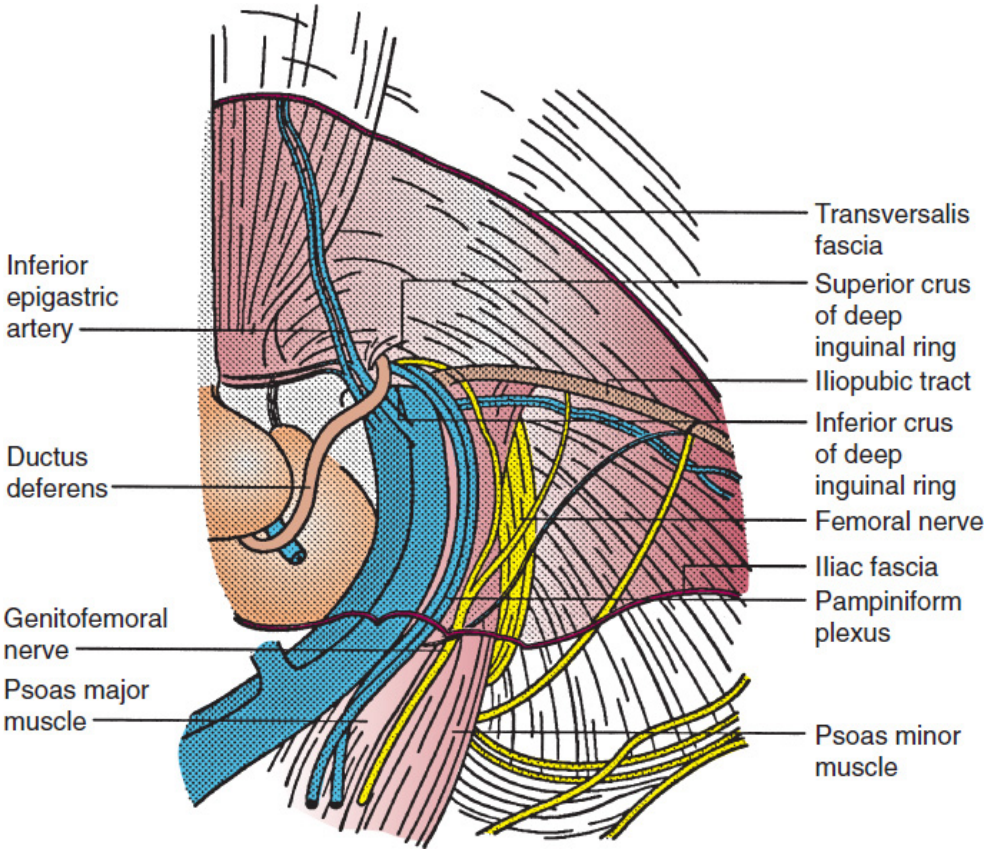


Figure 72.11 A schematic representation of the deep inguinal region. The iliopubic tract is shown as a thickening of the transversalis fascia, inferior to which many of the branches of the lumbar plexus exit the pelvis.

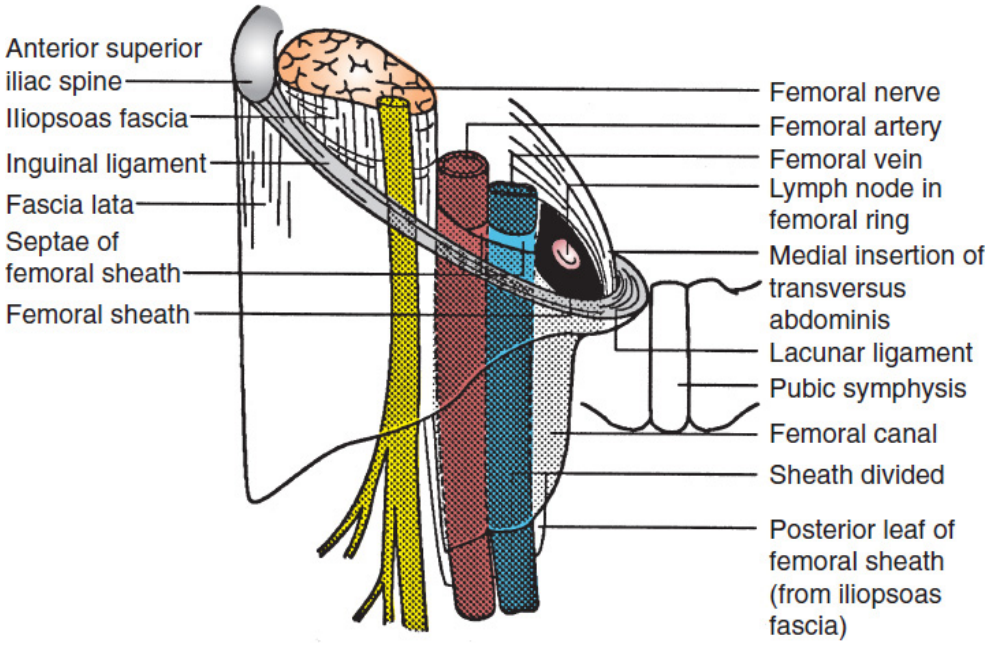


Figure 72.12 Schematic view of the femoral sheath, ring, and canal. The transversalis fascia forms the anterior portion of the sheath, and the iliopsoas fascia forms the posterior portion. Septae separate the vessels from each other and the vein from the femoral canal. The femoral ring contains a lymph node. The ring is formed medially by the aponeurosis of the transversus abdominis aponeurosis, anteriorly by the inguinal ligament, posteriorly by the pubic bone, and laterally by the femoral sheath.

Femoral Sheath, Canal, and Ring

The femoral sheath (**Fig. 72.12**) is primarily composed of extensions of the transversalis fascia. The sheath is best understood in terms of the structures contained within. As the external iliac artery and vein pass beneath the inguinal ligament to become the femoral vessels, they are covered anteriorly by the transversalis fascia proper. This fascial layer is posteriorly and laterally joined by portions of the iliopsoas fascia, which themselves are continuations of the transversalis fascia. At the inguinal ligament, the iliopsoas fascia forms the iliopectineal arch. This arch divides the vascular compartment (lacuna vasorum), containing the femoral vessels, from the muscular portion (lacuna musculorum), which contains the iliopsoas muscle, femoral nerve, and lateral femoral cutaneous nerve. The vascular lacuna is further divided by septa into compartments for the vessels and the femoral branch of the genitofemoral nerve.

The medial border of the femoral sheath follows the transversus abdominis aponeurosis to its insertion just lateral to that of the lacunar ligament and extends inferiorly to fuse eventually with the medial septum and adventitia of the femoral vein. The resultant cone-shaped cul-de-sac is the femoral canal. The canal normally contains only wisps of connective tissue and small lymphatic nodes. The wider proximal part of the canal, the femoral ring, contains a large node, which is often referred to as *Cloquet node.*

The femoral ring is the extraperitoneal opening of the canal. The boundaries of the ring are formed medially by the curved edge of the transversus abdominis aponeurosis, not the lacunar ligament, which inserts more medially.[14] Laterally, the ring is bounded by the connective tissue septum and the adventitia that is interposed between it and the femoral vein. The anterior boundary is the inguinal ligament; posteriorly, the ring is reinforced by the iliopubic tract and iliopectineal ligament. The canal is not in direct communication with the pelvic cavity. The transversalis fascia is not a component of the roof of the canal because it is diverted at this point to form the femoral sheath. This weakened area is therefore quite prone to hernia formation, especially in female subjects.

Inguinal (Hesselbach's) Triangle

The inguinal triangle is the site of direct inguinal hernias. This triangle is most often described from the anterior aspect (**Fig. 72.13**), in which case the inguinal ligament forms the base of the triangle, the rectus abdominis forms the medial border, and the inferior epigastric vessels form the superolateral border. The triangle as originally described by Hesselbach had the pectineal ligament as its base. The latter description is quite useful to the surgeon viewing the abdomen from within because the inguinal ligament cannot be seen from this viewpoint. When the inguinal triangle is transilluminated, the thinness and translucency of the area of abdominal wall within the triangle underscores its importance in hernia development and repair. In the most translucent area, little or no muscle is present. Only the peritoneum and the transversalis fascia cover the triangle here. The aponeurotic arch of the transversus abdominis crosses the triangle just below the apex in most people. A high aponeurotic arch affords less reinforcement to the triangle and

may therefore predispose a person to the formation of a direct inguinal hernia.

Components of the Spermatic Cord

The spermatic cord (**Figs. 72.11** to **72.14**) is closely associated with the deep inguinal ring. The spermatic cord is most appropriately described at this point because the deep ring itself is formed by derivatives of transversalis fascia, as is the innermost covering layer of the spermatic cord, the internal spermatic fascia. The middle covering layer is called the *cremasteric fascia* and contains the cremasteric muscle bundles; both are derived from the internal abdominal oblique muscle and fascia. The outermost covering of the spermatic cord is the external spermatic fascia, which is continuous with the investing fascia of the external abdominal oblique muscle.

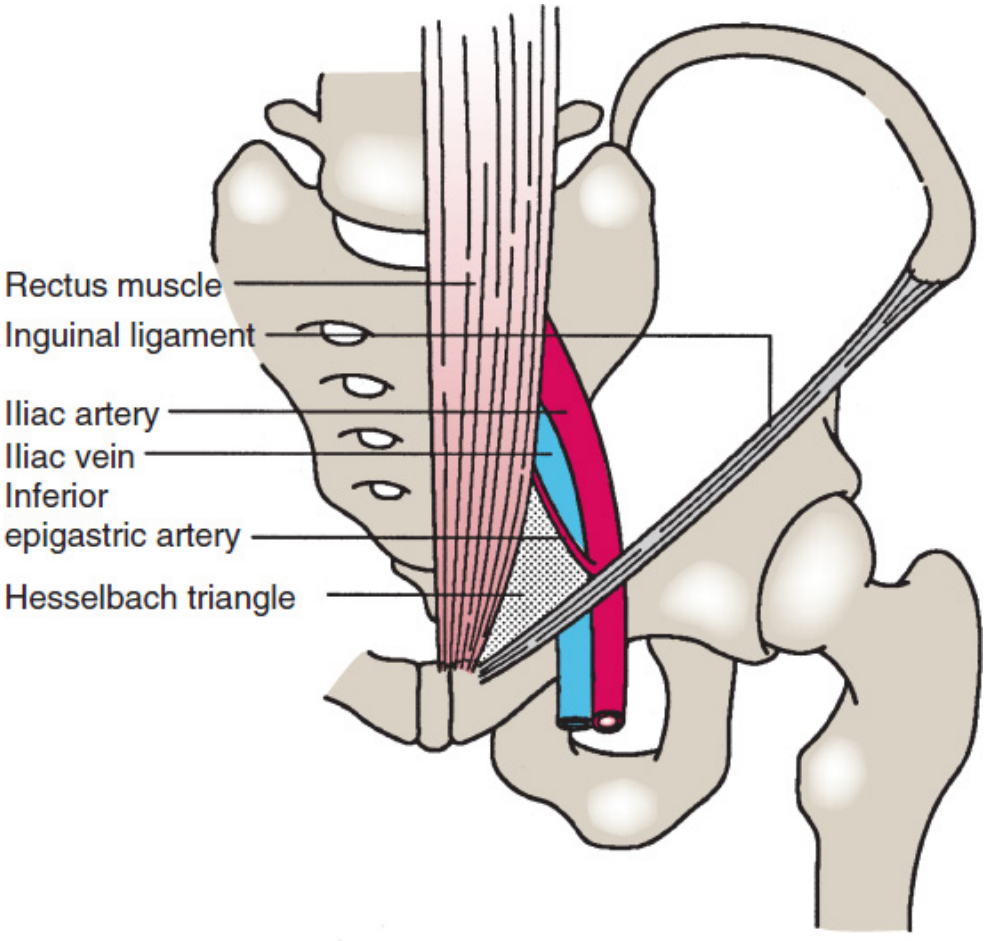


Figure 72.13 The inguinal (Hesselbach) triangle.

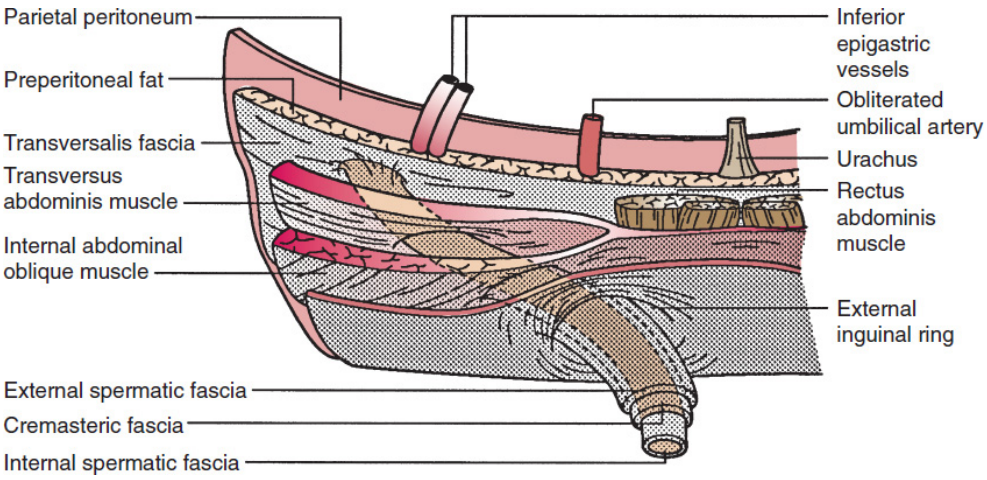


Figure 72.14 The component layers covering the contents of the spermatic cord.

The tunica vaginalis is initially a component of the cord, but normally it atrophies and closes early in neonatal life. This structure is an evagination of peritoneum. The testicle descends retroperitoneally in fetal life and is merely in contact with the posterior aspect of the tunica. An indirect congenital hernia enters the patent tunica vaginalis.

The cord structures enclosed by the coverings described earlier are the ductus (vas) deferens, the pampiniform venous plexus, the testicular artery, and the genital branch of the genitofemoral nerve, a branch of the lumbar plexus (**Figs. 72.9**, **72.11**, and **72.15**).

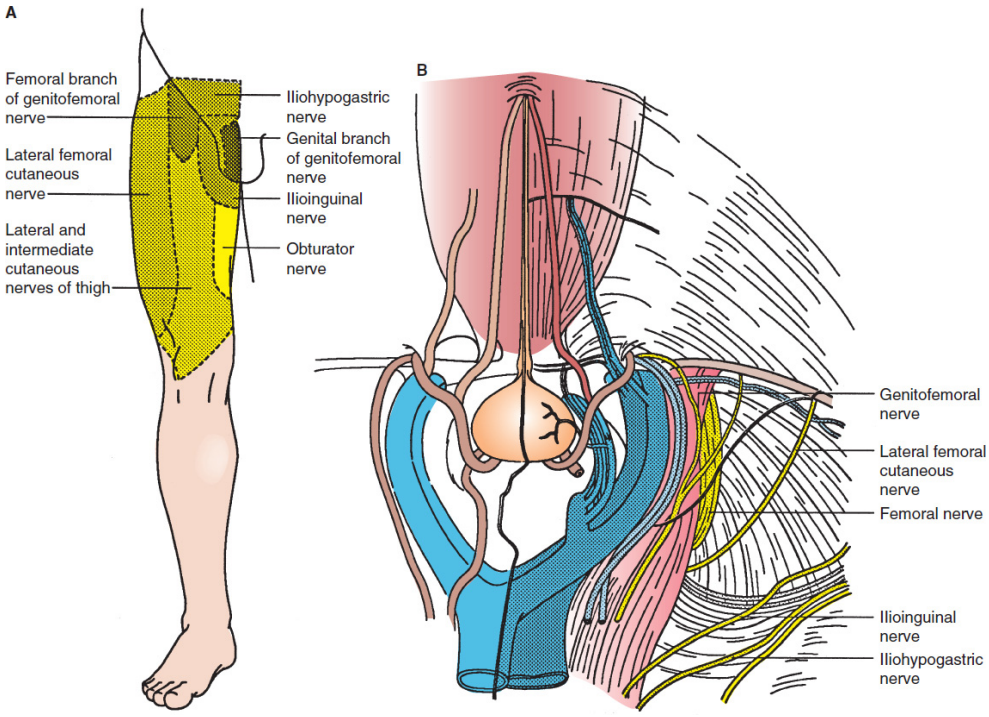


Figure 72.15 **A:** The cutaneous territories innervated by several branches of the lumbar plexus. **B:** Some of the branches of the lumbar plexus seen from within the abdomen.

Branches of the Lumbar Plexus

The nerves crossing the iliac fossa are some of the most variable in the body. This variability may be the cause of frequent intraoperative injury to the fragile nerves. The lumbar plexus is formed by roots from the 12th thoracic nerve and the first through fourth lumbar nerves. Cutaneous territories innervated by branches of the lumbar plexus are seen in **Figure 72.15A**. The five terminal branches commonly encountered in laparoscopic herniorrhaphy can be discerned in many people as they course across the iliacus muscle covered by peritoneum and the iliac fascia (a portion of the transversalis–endopelvic fascia). The nerves form within or deep to the psoas major muscle (**Fig. 72.15B**), often ramifying with other nerves within or close to the muscle. The nerve branches initially lie within the so-called triangle of pain,[15] bordered medially by the psoas muscle, anteriorly and inferiorly by the iliopubic tract, and laterally by the iliac crest. With the exception of the genital branch of the genitofemoral nerve, the branches of the lumbar plexus destined for the thigh run beneath the iliopubic tract.

The most anterior of the nerves encountered, the genitofemoral nerve, is also the most variable. This nerve may occur as a single trunk lying deep to the peritoneum and fascia on the anterior surface of the psoas muscle. The nerve may also divide into its component genital and femoral branches within the muscle. The genital branch travels with the spermatic cord, entering at the deep inguinal ring; it ultimately innervates the cremaster muscle and the lateral scrotum. The femoral branch of the nerve innervates the skin of the proximal mid-thigh.

The lumbar plexus branch encountered immediately deep to the lateral aspect of the psoas muscle is the large femoral nerve. Although not routinely encountered during laparoscopy, the femoral nerve has been injured in some cases.[16] The lateral femoral cutaneous nerve crosses the iliac fossa under the iliac fascia to run deep to the iliopubic tract and the inguinal ligament, which it pierces to enter the thigh.

The iliohypogastric nerve typically arises with the ilioinguinal by a common trunk from the first lumbar nerve. They may exchange fibers within the muscle, but they usually diverge immediately to form individual nerves. The iliohypogastric nerve crosses the iliac fossa just inferior to the kidney and pierces the transversus abdominis. The subsequent course of the nerve carries it between the transversus and the internal abdominal oblique until it pierces the aponeuroses of both obliques just above the external inguinal ring.

The ilioinguinal nerve normally crosses the iliac fossa just inferior to the iliohypogastric nerve. In its typical further course, the nerve pierces the transversus abdominis and internal abdominal oblique above the iliac crest and eventually enters the inguinal canal. The nerve may run more diagonally through the iliac fossa and then pierce the iliopubic tract to reach the inguinal canal.[17] This path "can obviously render the nerve more vulnerable to iatrogenic injury."

Vasculature of the Abdominal Wall and Deep Inguinal Region

The vasculature of the deep inguinal region and anterior abdominal wall has been analyzed by surgeons for well over 100 years. The importance and

variability of these vessels have been underscored by the ominous mnemonics used to refer to them—"crown of death" (*corona mortis*) and "triangle of doom." The primary blood supply to the deep anterior wall is from the inferior epigastric artery. This artery is a branch of the external iliac artery. In many cases, an artery called the "aberrant" obturator artery arises from the inferior epigastric, which joins the "normal" obturator artery and thereby forms a circle—the corona mortis—before entering the obturator foramen. Injury to the circle, usually sustained while the surgeon is working in the area of the Cooper ligament, causes copious bleeding. Recent studies have indicated that aberrant obturator vessels are present in between 60% and 90% of the whole pelves studied.[18,19]

The veins in this area are also prone to injury because many, especially the iliopubic veins and obturator veins and their tributaries, may be much larger than their accompanying arteries. One network of veins in the area is situated on the inferior deep surface of the rectus muscles. The veins of this network, which anastomose with the pubic branches discussed earlier, have been called the *rectusial veins*.[20]

The vessels in the vascular compartment of the deep inguinal region are the external iliac artery and vein. They arise within a triangular area bordered laterally by the gonadal vessels and medially by the ductus deferens. The primary continuations of the external iliac vessels are the femoral artery and vein. The inferior epigastric artery is a branch of the external iliac. The obturator artery may arise from either of these arteries as a replacement or accessory to the obturator branch of the internal iliac artery.

A final vessel to consider in this review is the deep circumflex iliac artery (**Fig. 72.10**). The origin of this artery is extremely variable, but its course is predictable along the iliopubic tract. It pierces the transversalis fascia and runs along the iliac fossa to anastomose eventually with a deep lumbar artery. Because the deep circumflex artery runs along the iliopubic tract, it can inadvertently be stapled or otherwise injured during laparoscopic herniorrhaphy.

Pelvic Floor and Obturator Muscles

The pelvic musculature normally affords remarkable support to the structures within the true pelvis and form the caudal most aspect of the abdominal core.

Although a myoaponeurotic hammock-like sheet forms the pelvic diaphragm, obturator muscles and membrane, and urogenital diaphragm, herniation of fat or viscera through or around any of these layers occurs. The potential for hernia formation is increased because of the openings through which many structures exit or enter the pelvis.

The Latin term *obturator* is translated as "stopper for a bottle." The aptly named obturator internus, along with its membrane and the obturator externus, closes off nearly all the large obturator foramen. The small superolateral aperture through which the obturator vessels and nerve pass is the site where obturator hernias form. The obturator internus arises from the deep surface of parts of all three pelvic bones. The muscle fibers converge on a tendon, which leaves the pelvis through the lesser sciatic foramen to insert on the greater trochanter. The dense internal obturator fascia covers the muscle and is thickened to form the arcuate ligament, from which the levator ani muscles (the pelvic diaphragm) are in part suspended. The obturator internus fascia splits to enclose the pudendal vessels in the pudendal canal. The external obturator muscle arises from the pelvic bones surrounding the obturator foramen and from the anterior portion of the obturator membrane. The external obturator muscle is supplied by the obturator nerve and vessels.

The component muscles of the bowl-shaped pelvic diaphragm, the pubococcygeus, iliococcygeus, and puborectalis, along with the coccygeus form the floor of the pelvis. The pubococcygeus arises from the posterior aspect of the pubis and the thickened portion of the internal obturator fascia, called the *tendinous arch* (**Fig. 72.16**), that spans the distance between the pubis and ischial spine. The puborectalis, the midportion of the diaphragm, arises from the pubis and loops around the rectum as the puborectal sling. The iliococcygeus is suspended at its origin from the tendinous arch and inserts on the coccyx. The coccygeus muscle completes the diaphragm posteriorly, arising from the ischial spine and inserting on the sides of the coccyx.

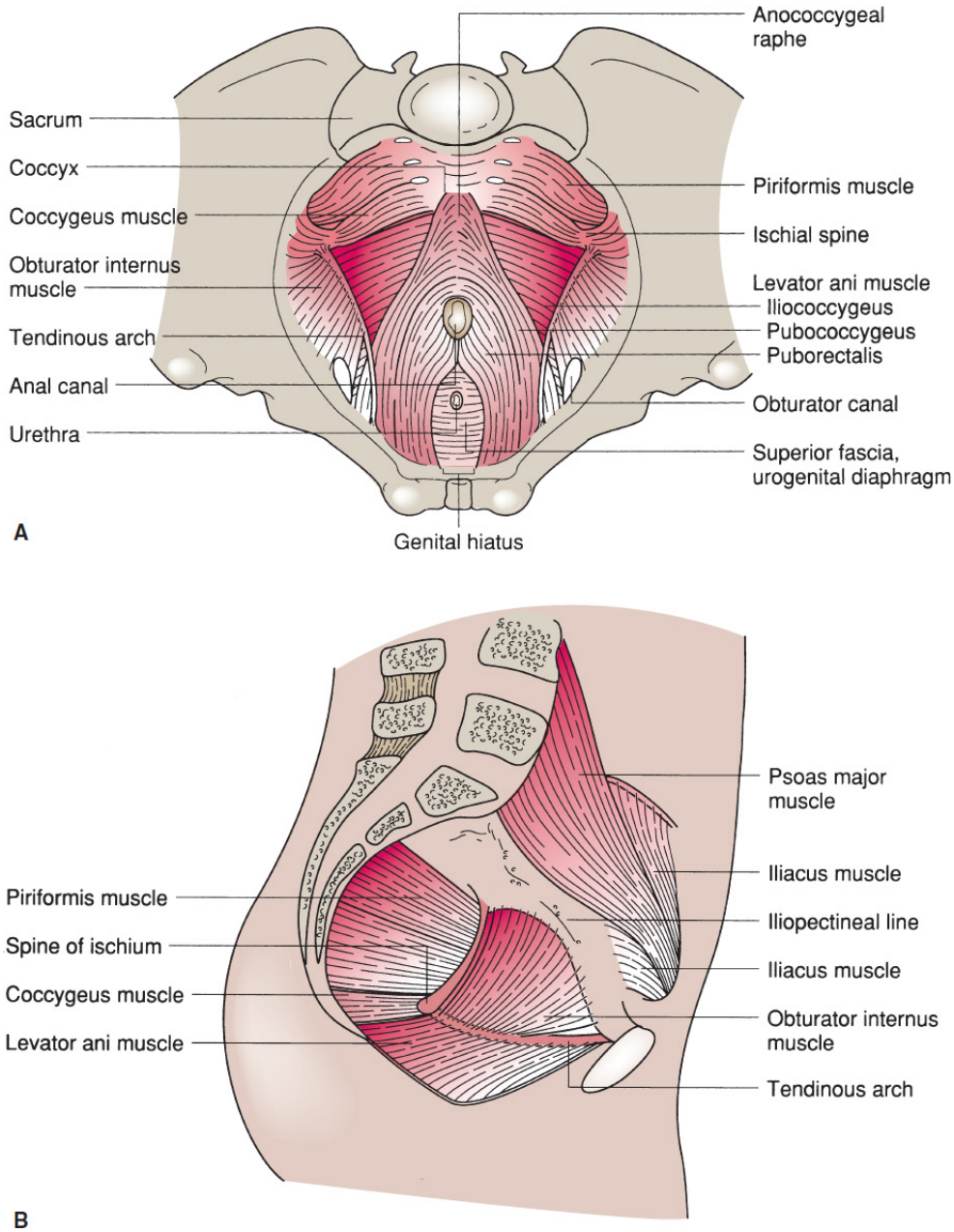


Figure 72.16 **A:** The pelvic diaphragm (levator ani and the piriformis) and the urogenital diaphragm viewed from within the pelvis. **B:** Hemisection of the pelvis revealing the levator ani, piriformis, obturator internus, and psoas muscles.

The area remaining between the sacrum and the greater sciatic foramen is filled for the most part by the piriformis muscle. The piriformis arises from the anterior surface of the second through fourth sacral vertebrae and the sacrotuberous ligament. This muscle exits the pelvis through the greater sciatic foramen, which is thereby divided into suprapiriform and infrapiriform portions (**Figs. 72.16** and **72.17**). The superior gluteal nerves

and vessels pass through the suprapiriform foramen, whereas the inferior gluteal nerves and vessels in company with the sciatic nerve pass through the infrapiriform foramen.

The most pronounced deficit in the pelvic diaphragm is situated anteriorly, where an aperture must allow the urogenital structures to pass out of the pelvis. This area is reinforced by the urogenital diaphragm, a structure primarily consisting of the superficial and deep transverse perineal muscles. The deep transverse perineal muscle is enclosed by a weak superior fascia and a sturdier inferior perineal fascia. The urogenital diaphragm recently has been shown to be more funnel shaped than sandwichlike, as previously depicted in many atlases. The urogenital diaphragm exists only in humans because the human pelvic outlet faces inferiorly, unlike that of quadrupeds.

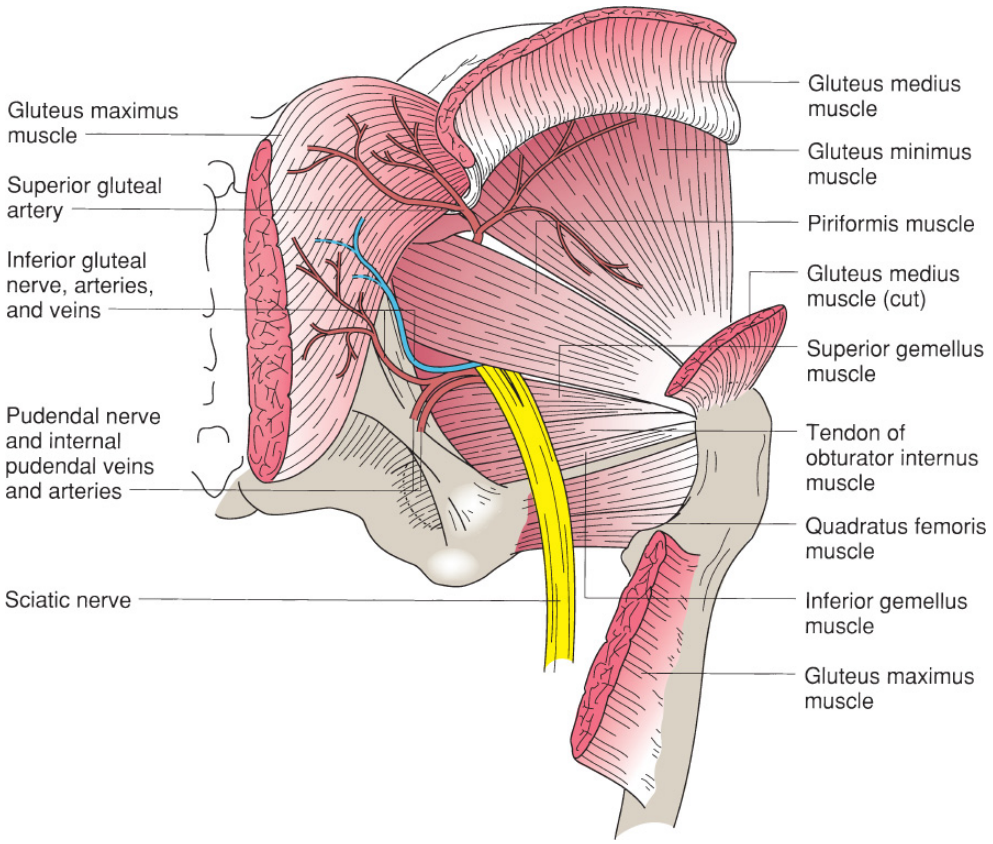


Figure 72.17 The gluteal muscles and lateral rotators of the hip. External relations of the sciatic foramen are also evident.

WHY DO HUMAN BEINGS DEVELOP ABDOMINAL WALL HERNIAS?

The most common hernias develop at sites where the abdominal wall has natural openings such as the internal inguinal ring, the umbilicus, and the esophageal hiatus. Previous surgical entry sites (incisional hernia) are also common areas where hernias develop. Factors that increase the pressure in the abdominal cavity, such as obesity, heavy lifting, coughing with chronic lung disease, straining during a bowel movement or urination (prostatism), chronic lung disease, and ascites, have traditionally been considered important in the etiology, especially at these natural openings. Developmental phenomena also play a role. For example, in the evolution from a quadruped to a biped, the unprotected groin is more vulnerable to changes 2 in intra-abdominal pressure, predisposing to inguinal herniation. Major risk factors for the development of an abdominal wall hernias include chronic obstructive pulmonary disease, smoking, high intra-abdominal pressure, collagen vascular disease, thoracic or abdominal aortic aneurysm, peritoneal dialysis, matrix metalloproteinase (MMP) abnormalities, and an increased type I: type III collagen ratio.

The role of heavy lifting, especially a single strenuous event, is an unsettled question and has considerable medical–legal ramifications. There is minimal evidence that vigorous abdominal wall activity is an independent risk factor for abdominal wall hernia development despite the overwhelming opinion to the contrary in the lay literature.[21–23] In a systematic review of existing evidence performed by Svendsen and colleagues, regarding the effects of occupational and mechanical exposures in relation to inguinal hernias, a causal relationship could not be established between specific mechanical insults and occurrence of inguinal hernia, hernia recurrence, and persistent pain after inguinal hernia repair.[24,25] According to the results of another register-based male cohort study in Denmark, increasing cumulative exposure to daily lifting activities and prolonged standing or walking at work was associated with an increased risk of having an indirect inguinal hernia repair.[24,25] The authors hypothesized that patent processus vaginalis may be more susceptible to changes in intra-abdominal pressures, whereas in a direct hernia, other mechanisms may be involved in connective tissue

degradation and weakening of the transversalis fascia. Still, the role of mechanical activity in the development of abdominal wall hernia is not completely clear, and further research is needed to determine if inguinal hernias can be prevented and if the postoperative prognosis can be improved by reducing occupational mechanical exposures.

Familial predisposition and the role of connective tissue diseases in hernia development have received considerable attention in recent years. Particularly important for inguinal hernia is a family history as it has been reported to increase the risk up to 8 times.[26,27] Various connective tissue disorders, such as osteogenesis imperfecta, Marfan syndrome, Ehlers–Danlos syndrome, and congenital hip dislocation, are associated with hernias. Imbalances in collagen, the basic building block of the abdominal wall, are believed to contribute to hernia disease. While type I collagen confers predominantly tensile strength, type III collagen consists of thinner fibers and is regarded as a temporary matrix during tissue remodeling. A decreased ratio of type I to type III collagens can be detected in fascial and skin specimens obtained from patients with hernias. A similar phenomenon was discovered by Cannon and Read in smokers when they performed biopsies of the rectus sheaths from adult smokers with inguinal hernias and coined the term "metastatic emphysema."[28] The investigators also demonstrated significantly greater levels of circulating serum elastolytic activity in patients who smoke.

Aside from primary defects in collagen synthesis, the imbalances in collagen in patients with hernia can be attributed to altered extracellular matrix (ECM) which is maintained in a dynamic balance of synthesis and degradation by a complex set of enzymes. MMPs,[29] which are a group of 23 structurally related zinc-dependent enzymes, protease with collagenolytic activity and have a pivotal role in the integrity and composition of the ECM.

The association between MMP overexpression and abdominal wall hernia was initially demonstrated by Bellon and colleagues, who studied the expression of MMP-1 and MMP-2 in the transversalis fascia of patients with direct and indirect inguinal hernia. Since then, several studies have been conducted, aiming at elucidating the role of MMPs in the development of primary and recurrent abdominal wall hernias. For this purpose, MMP levels in fascia, skin, hernia sac, and blood specimens of patients with inguinal, incisional, and recurrent abdominal wall hernias have been measured. The

expression of MMP mRNA in cultured fibroblasts has also been investigated to evaluate cell–cell and cell–matrix interactive mechanisms as causative factors for abnormal MMP production. In addition to this, in vitro studies have been performed to study the effect of different mesh materials on MMP expression on cultured fibroblasts; in one such study, polypropylene has been shown to induce less MMP2 expression than polygalactin. The function of MMPs is further regulated by a variety of endogenous regulators, the most important ones are known as tissue inhibitors of MMPs (TIMPs).[30–32] Studies have shown that an imbalance between MMP and TIMP activity may have a role pathogenesis of abdominal wall hernias.[33]

Despite the increasing knowledge regarding MMPs in incisional and inguinal hernia, the exact role of MMPs in the pathogenesis of hernia formation remains unclear. Most studies are small and not completely controlled; and there is a remarkable heterogeneity among studies concerning the characteristics of the study populations, the examined tissue specimens, and the biochemical assays used. In addition to MMP and TIMPs, factors that have been implicated in hernia development include deficiency of the elastic fiber system of the transversalis fascia, decreased tropoelastin and lysyl oxidase-like 1 synthesis, elastase overexpression and TGF-beta1 overexpression. It remains unclear whether these alterations in hernia patients are a part of the "cause-or-effect" phenomenon. Another interesting area of research are drug classes that can suppress MMP expression (e.g., tetracyclines, especially doxycycline, aspirin, statins, and thiazolidinediones) and understanding their role in hernia prevention and treatment.[34]

COMPLICATIONS OF HERNIAS

Hernia Accident

For years, surgeons have been taught that all hernias should be repaired at diagnosis to prevent a hernia accident, which is defined as a bowel obstruction or incarceration with strangulation, because of the perception that patients presenting with these complications have an unacceptable increase in mortality. This thinking, however, has not stood up when tested in

randomized controlled trials. For example, for men with asymptomatic inguinal hernias, randomized controlled trials have shown that a strategy of watchful waiting is safe.[35]

Incarceration

Incarcerated means "trapped" or "imprisoned." Clinically, an incarcerated hernia is an irreducible hernia. An incarceration is not in and of itself a surgical emergency. Many hernias are chronically incarcerated due to adhesions of contents (e.g., omentum, bowel, ovary, etc.) to the hernia sac. The hernia itself is not necessarily tense to palpation, and the overlying skin appears normal. Normal bowel sounds may be heard within the hernia. It is important to differentiate an incarcerated hernia from a hydrocele of the cord. One can get above the hydrocele with the examining fingers. One cannot get above a hernia, however, as it communicates with the abdominal cavity. Hydroceles will transilluminate clearly, but a hernia will not.

An acutely incarcerated, painful hernia must be managed carefully. An attempt at reduction is reasonable unless there are signs of strangulation, which is not always obvious by clinical examination. Immediate surgical exploration is the safest approach when the diagnosis is not clear. The advantage of reduction followed by elective repair is that edematous tissue associated with an acute incarceration can return to normal, which presumably will translate into a better repair with less chance of infection.[36] If an attempt at reduction seems reasonable, the patient is sedated and placed in bed. The Trendelenburg position should facilitate reduction of a groin hernia. An attempt should be made at the initial examination to reduce the hernia. The maneuver of taxis entails grasping the neck of the hernia with the fingers of one hand and then applying intermittent pressure on the most distal part of the hernia with the other hand. Taxis has the effect of elongating the neck of the hernia so that the contents of the hernia may be guided through this area back into the abdominal cavity with a rocking movement. Mere pressure on the most distal part of the hernia causes bulging of the hernia sac around the neck, which can occlude the neck and prevent it from being reduced (**Fig. 72.18**). The maneuver of taxis should not be performed with excessive pressure or too vigorously. If the hernia is strangulated, gangrenous bowel might be reduced into the abdomen or perforated in the process. One or two

gentle attempts should be made at taxis. If they are unsuccessful, this procedure should be abandoned. Rarely, the hernia together with its peritoneal sac and constricting neck may be reduced into the abdomen (reduction en masse). The patient would then have persistent obstruction after reduction of the hernia.

Intestinal Obstruction

One hundred years ago, the most common cause of intestinal obstruction was a hernia. At the present time, hernia is third, after adhesive obstructions and cancer. Hernia is an important cause of obstruction that is not infrequently missed on clinical examination. When a patient with an intestinal obstruction is examined, great emphasis should be placed on adequate exposure of the entire abdominal wall and groin area (from nipples to knees). Proper lighting is essential because previous scars can fade with time and become barely perceptible. The patient with intestinal obstruction as a result of a hernia will have a tense hernia that is irreducible. The abdomen itself will be distended, and high-pitched bowel sounds with frequent rushes will be heard. If the process continues to the complication of strangulation, these signs will disappear. Unlike adhesive small-bowel obstructions, partial small-bowel obstructions secondary to hernia are rare. Most patients will have had vomiting and obstipation.

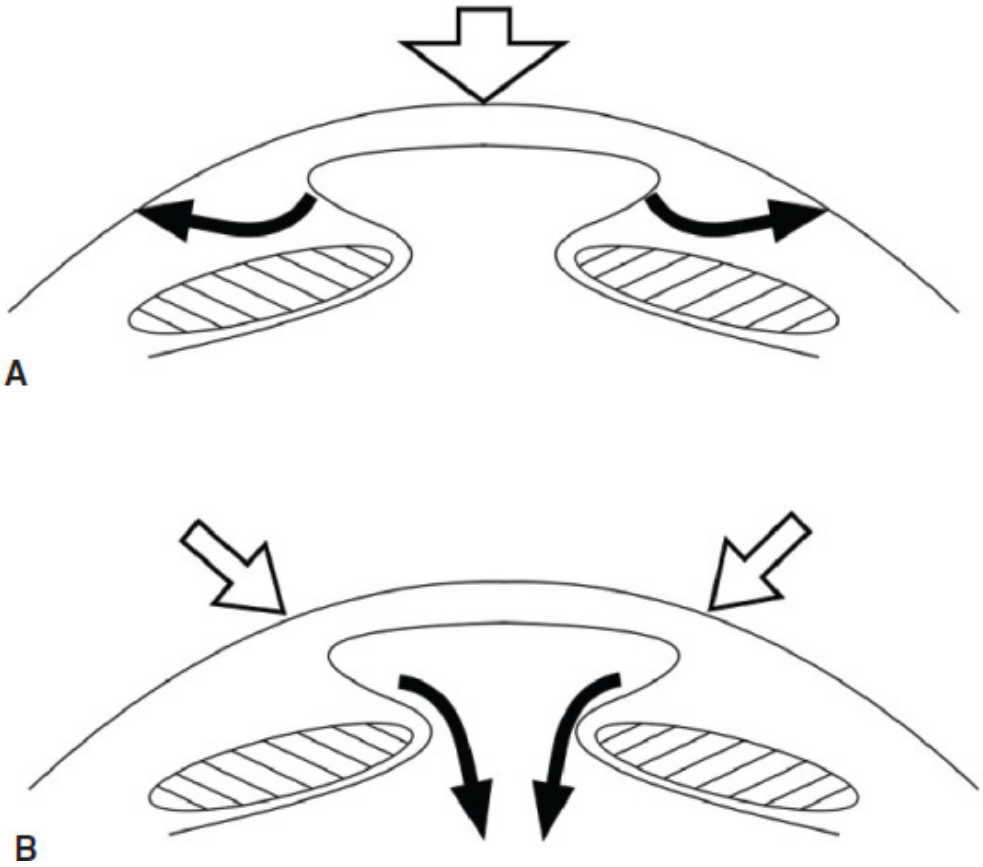


Figure 72.18 Reduction of a hernia by taxis. **A:** Applying pressure on the hernia directly occludes the neck. **B:** Elongating the neck of the hernia while applying pressure allows reduction.

Figure 72.19 Computed tomogram showing a left-sided inguinal hernia.

A plain roentgenogram of the abdomen will reveal the signs of an intestinal obstruction—dilated loops of bowel with air–fluid levels and no bowel gas distal to the obstruction. Frequently on a plain roentgenogram, one can see bowel shadows in the region of the hernia. A lateral view is often useful to demonstrate this feature more clearly. Contrast studies are not usually necessary in this instance. Computed tomography (CT) reliably demonstrates the hernia with characteristic features of obstruction and should be considered if the clinical diagnosis is not certain (**Fig. 72.19**) because a distal intestinal obstruction secondary to another cause (e.g., adhesions) may result in significant distention of a coincidental nonobstructing hernia of the abdominal wall. Should the examiner focus attention exclusively on the hernia, the real cause of the obstruction may be missed when the hernia is repaired.

The next steps in management include resuscitation followed by urgent surgery. At surgery, an approach directly over the hernia is used. In all patients, the entire gastrointestinal tract must be assessed to eliminate causes of obstruction other than the hernia itself. Diagnostic laparoscopy is a very useful adjunct to evaluate the bowel in these situations. This is done before the hernia is repaired. The bowel, if viable, is reduced into the abdomen. If

difficulty is encountered in reducing the hernia, the neck of the hernia can be widened. In the case of an inguinal hernia, division of the neck with or without ligation and division of the inferior epigastric vessels is safe, and the hernia contents can be reduced into the abdomen. In the case of a femoral hernia, the inguinal ligament can be split anteriorly and the hernia contents reduced into the abdomen. If the bowel is nonviable, then a bowel resection can be performed with anastomosis. The hernia is then repaired.

Strangulation

Strangulation of a hernia is a serious and life-threatening condition in which the hernia contents become ischemic and nonviable. The pathogenesis of this condition involves intra-abdominal contents within the hernia sac. Straining may push more contents into the sac, and the tense sac then causes pressure at the neck. This pressure initially produces venous congestion, resulting in edema. Eventually, the pressure is so great that the arterial supply is obstructed and the contents become gangrenous.

When intestine is involved, in addition to having an irreducible hernia and intestinal obstruction, the patient is toxic, dehydrated, and febrile. Examination of the abdomen reveals the signs of an intestinal obstruction, with distention and increased bowel sounds. Absolute constipation and vomiting are other manifestations. The hernia itself is tense, irreducible, and very tender, and the overlying skin may be discolored with a reddish or bluish tinge. No bowel sounds are heard within the hernia itself. The patient commonly manifests a leukocytosis with a predominance of polymorphonuclear leukocytes. Blood gases may reveal metabolic acidosis.

Management of these patients requires urgent attention to detail. No attempt should be made to reduce the hernia. Rapid resuscitation should commence immediately, with nasogastric suction and replacement of fluids and electrolytes. The patient should be given antibiotics. Once the patient is resuscitated, urgent surgery commences to expose the hernia, open the sac, and assess the viability of the bowel. More bowel can be pulled into the hernia so that viable bowel can be transected and the gangrenous portion removed. An anastomosis should be performed and the bowel then reduced into the abdominal cavity. The hernia is then repaired.

Richter Hernia

August Gottlieb Richter in 1785 described a hernia type that bears his name in which the antimesenteric border of the intestine protrudes into the hernia sac without involving the entire circumference of the intestine so that intestinal obstruction does not occur (**Fig. 72.20**). The most common site is the femoral ring (36% to 88%), followed by the inguinal canal (12% to 36%), and an abdominal wall incision (4% to 25%). Miscellaneous locations include umbilical, obturator, supravesical, Spigelian, triangle of Petit, sacral foramen, Morgagni, internal, and diaphragmatic.[37] The routine use of laparoscopy by general surgeons has resulted in an increased incidence at trocar sites such that most surgeons will repair the fascia for trocar sleeves greater than 5 mm. The surgical treatment is to expose the herniated bowel by opening the sac. The neck of the sac is enlarged to allow delivery of the bowel into the wound. Any areas of gangrene are excised and the bowel wall reconstituted. The hernia is then repaired.

Prosthetic Materials Used in Hernia Repair

The development of a wide variety of materials for inguinal and ventral hernia repair and abdominal core surgery makes it possible to individualize the selection of prostheses to a variety of clinical settings.[38,39] However, lack of clear data on optimal mesh selection, the sheer variety of options, and generally poor information and knowledge of specific mesh properties can make mesh selection quite daunting. It is important to note that there is little high-quality data regarding optimal mesh type for a given clinical scenario, and almost no direct comparative data between mesh types, let alone specific mesh brands or constructs. The choice of mesh is left largely to the judgment and experience of the operating surgeon. This section should serve as an overview to understanding mesh characteristics and some potential advantages or disadvantages of various mesh options in hernia repair. **Figure 72.21** summarizes mesh characteristics and key properties.

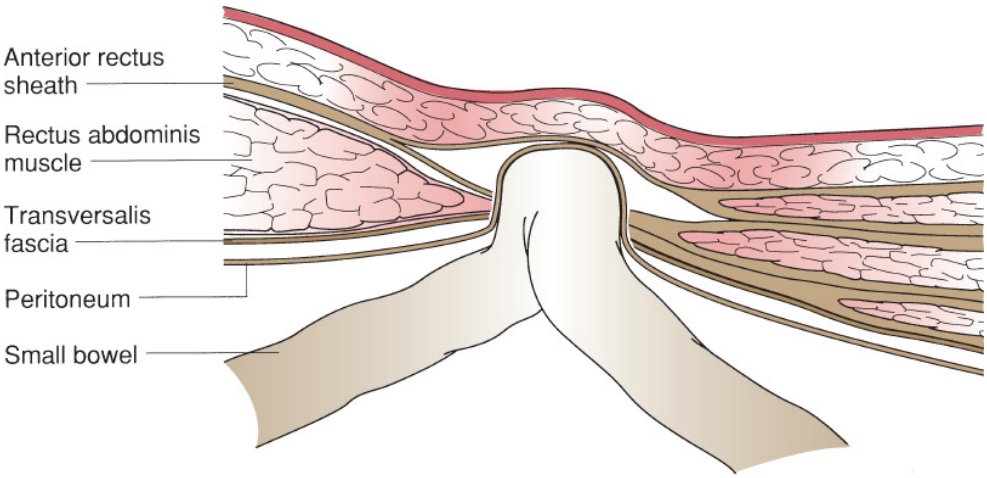


Figure 72.20 Richter hernia. Part of the bowel wall herniates through the defect in the abdominal wall.

Biologic Mesh

Broadly, mesh can be categorized as biologic, those meshes derived from some organic material, or synthetic. Biologic mesh comes from several possible sources including human, bovine, ovine, and porcine. Porcine is currently the most commonly used biologic mesh in hernia repair and has the largest volume of literature to support its use in various settings. In theory, all of these materials provide an acellular, biologically derived scaffold to allow nascent tissue ingrowth or remodeling that strengthens the abdominal wall repair. The actual behavior of these meshes is not entirely clear, however, and may behave quite differently from each other or in different clinical scenarios and in different patients.[40] The construct and processing of various biologic meshes, most of which are proprietary, vary greatly, and likely influences their behavior in vivo. Biologic mesh widely proliferated after their initial introduction, primarily for complex hernia repair and in the setting of contamination. No high-level clinical trials have yet demonstrated superiority of these materials in terms of infection, mesh removal, or hernia recurrence. In fact, many studies indicate a higher risk of hernia recurrence with biologic mesh repair compared to synthetic. Additionally, biologic mesh is quite expensive, as much as 200 times the cost of a comparable sized synthetic mesh. The very high cost and poor-quality data have led many away from routine use of biologic mesh in recent years.[41–44] However, the role for biologic meshes is yet to be determined as long-term catastrophic infection

rates associated with permanent synthetic meshes become better known and the cost-effectiveness tradeoff is better analyzed.[45]

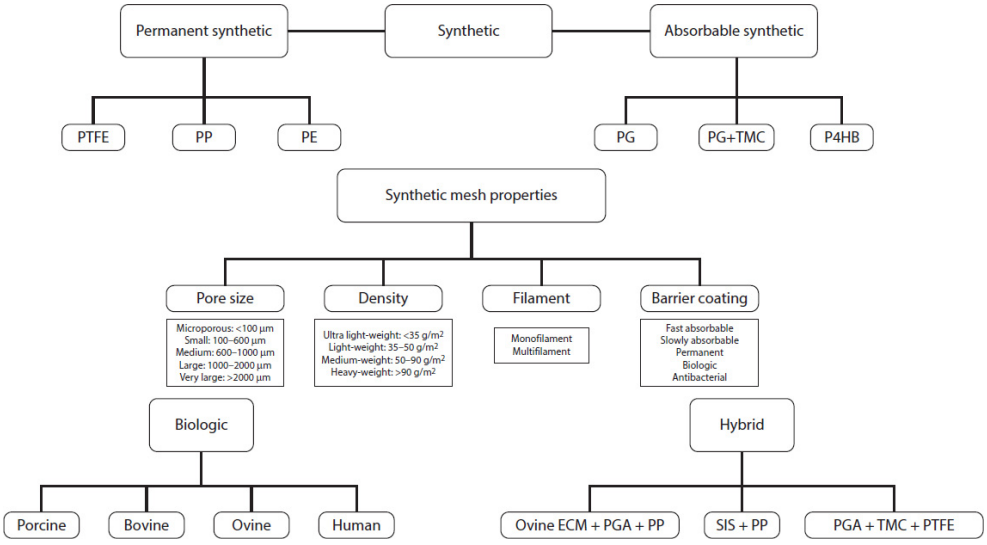


Figure 72.21 Classification of Materials Currently Available for Hernia Repair.

Absorbable Synthetic Mesh

Synthetic mesh can be further divided into absorbable and permanent synthetic mesh. Absorbable synthetic meshes, commonly referred to as biosynthetic, are recent additions to the available armamentarium. These are most often used in place of a biologic mesh in cases where there is a relative contraindication to the use of permanent synthetic mesh, as they are generally significantly cheaper. Early clinical data are conflicted, but seem to indicate acceptable clinical outcomes in terms of infection for absorbable synthetic meshes with a faster resorption profile. Longer-term resorption products tend to behave like heavyweight permanent synthetic meshes in the short term-appropriate caution should be employed when using these absorbable synthetic meshes in contaminated situations. No study has greater than 2-year follow-up to date, and there are scant comparative data of absorbable synthetic to biologic or permanent synthetic mesh for comparison.[46–48]

Permanent Synthetic Mesh

Permanent synthetic meshes are largely composed of one of three materials: polypropylene (PP), polyester (PE), or polytetrafluorethylene (PTFE). These can be further subdivided by their structural and physiomechanical properties. This is perhaps among the most misunderstood aspects of mesh,

while simultaneously being of the utmost importance in understanding how a mesh will perform in a given situation. While a comprehensive review of these characteristics is beyond the scope of this chapter, the key properties that appear to correlate with clinical performance are summarized here.

Mesh Properties

Pore Size Pore size, or the space between filaments of a mesh, is increasingly recognized as among the most important characteristics of a mesh, particularly in the setting of infection. This is characterized as microporous (<100 um), small-pore (100 to 600 um), medium-pore (600 to 1,000 um), large-pore (1,000 to 2,000 um), or very large pore (>2,000 um).[49] Smaller interstices and greater overall surface area may allow increased bacterial adherence and impede the ability of host immunity to fight infection should it occur. Conversely, large-pore mesh confers greater bacterial clearance and ability to avoid mesh explantation should infection occur.[50] Additionally, normal healing around a permanent mesh produces a granuloma around each fiber. In the case of microporous mesh, this can create a bridging fibrosis, increasing the overall stiffness of the mesh and potentially increasing the risk of chronic pain. Pore size of >1,000 um minimizes this possibility.[51]

Density Mesh density, defined as the material mass divided by area, is a function of fiber thickness and the construct (multifilament vs. monofilament, type of weave structure), and the pore size. Mesh density <35 g/m^2 is considered ultra light-weight, 35 to 50 g/m^2 light-weight, 50 to 90 g/m^2 mid-weight, and >90 g/m^2 heavy-weight.[49] Density has much to do with the strength of a mesh, but is not the sole determining factor. The strength of a mesh is measured by a few key metrics: suture retention strength, tear resistance testing, uniaxial tensile testing, ball-burst testing, and repetitive loading.[49,52] As density is partly determined by pore-size, these two parameters are intimately linked. Currently, all available heavy-weight meshes are also small-pore. Though quite strong, this has the potential disadvantage of creating bridging fibrosis and mesh contracture and poor tolerance of infection. Light-weight and ultra light-weight mesh, on the other hand, is more tolerant of infection, but has been shown in several studies to have a higher risk of hernia recurrence for ventral hernia repair.[53–55]

Structure Much of a mesh structure is determined by the material, but each material can be constructed differently, and this confers different properties. For example, PTFE has traditionally consisted of a laminar microporous structure. While this mesh provides probably the best available adhesion barrier, it cannot withstand infection and typically must be removed should mesh infection occur. A newer monofilament knitted PTFE hybrid mesh has recently become available as well, and while no clinical data are yet available, this appears to behave more like a monofilament polypropylene or polyester mesh. Similarly, multifilament mesh, common with polyester, is unable to withstand infection in most cases. Composite meshes, those composed of more than one distinct layer compressed into a single mesh, usually in order to provide and adhesion barrier, are similarly unable to withstand infection. Monofilament, large-pore material, however, generally tolerates infection without requiring mesh removal.

Barrier Coating A variety of substances and materials can be used to create barrier coated mesh, sometimes referred to as adhesive barrier or tissue-separating mesh, to make them suitable for intraperitoneal placement. Broadly, these barriers may be permanent or resorbable, synthetic or biologic, comprised of a second material layer or intrinsic to the mesh material itself, and may additionally have antimicrobial activity. No mesh is able to completely and consistently prevent adhesions to the viscera, and there are little clinical data to indicate the optimal barrier coating. In theory, a barrier should be present long-enough to allow neoperitonealization over the mesh, thus allowing native tissue to provide the ultimate barrier to adhesion. However, adhesion-related complications are a known, albeit uncommon, long-term risk of intraperitoneal mesh, including adhesive bowel obstruction, mesh-bowel fistula, or delayed infection, and the presence of intraperitoneal mesh can complicate subsequent abdominal operations, resulting in potentially high rates of enterotomy or secondary mesh infection.[50,55–57] As they are designed to prevent tissue ingrowth, barrier-coated meshes should not be used in extraperitoneal position.

Hybrid Mesh

A final category of mesh is the hybrid construct, comprised of a permanent synthetic and an absorbable synthetic or biologic component. There are

currently little data regarding the use of the meshes for various hernia repairs.

GROIN HERNIAS

Groin hernias are described as inguinal and femoral, the inguinal hernias being further subdivided into direct and indirect hernias (some authorities refer to these as medial and lateral hernias, respectively). Groin hernias may be primary or recurrent. An indirect hernia occurs as a protrusion of abdominal contents through the internal ring, lateral to the inferior epigastric vessels, into the inguinal canal. Indirect inguinal hernias (lateral hernias) are situated within the spermatic cord and therefore may extend into the scrotum. In female patients, the hernia follows the round ligament and may present as a swelling in the labium. A direct hernia (medial hernia) is a protrusion through the triangle of Hesselbach medial to the inferior epigastric vessels. These hernias develop through an area where the endoabdominal fascia is not protected by overlying muscle. Direct hernias do not usually involve the cord, as they tend to protrude forward. However, they occasionally track alongside the cord down the entire length of the inguinal canal and even enter the scrotum. For this reason, the only absolute distinction between a direct and an indirect hernia is the relationship to the inferior epigastric vessels. Inguinal hernias are more common in men (with a 15% lifetime risk among men aged >25 years) with a male to female age-adjusted ratio of 7.5:1.[58] A femoral hernia protrudes through the femoral canal, which is bordered by the inguinal ligament superiorly, the lacunar ligament medially, Cooper ligament inferiorly, and the femoral vein laterally. This hernia presents below the inguinal ligament (**Fig. 72.22**). In a sliding hernia, part of the sac is formed by the viscera, on the left side the sigmoid colon or bladder, and on the right side the cecum or bladder (**Fig. 72.23**).

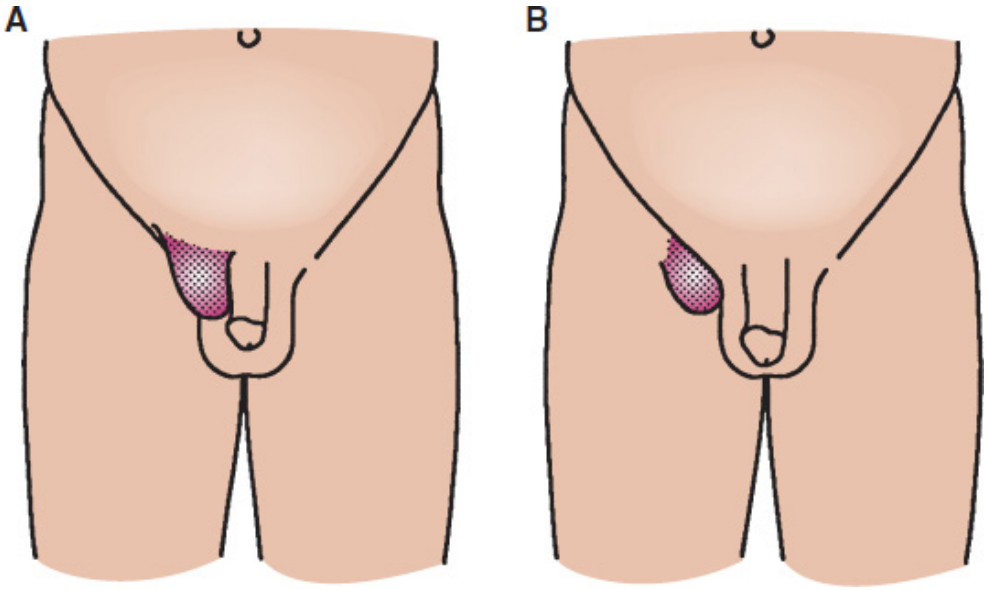


Figure 72.22 **A:** Inguinal hernia. This presents above the inguinal ligament and extends below it. **B:** Femoral hernia. This presents below the inguinal ligament.

Epidemiology

1. Inguinal 3 hernias occur in persons of all ages, from the neonate to the elderly. Inguinal hernias constitute approximately 75% of abdominal wall hernias, with femoral hernia accounting for 5%. Femoral hernias are more common in women, but a woman with a groin hernia is still five times more likely to have an inguinal hernia (usually indirect) than a femoral. Incisional, umbilical, and epigastric hernias account for 15% and miscellaneous hernias make up the other 5%. The lifetime risk of developing a groin hernia is approximately 25% in males and 5% in females. Inguinal hernias are more common on the right than the left and are 10 times more likely in males than in females.[59] Indirect inguinal hernias are twice as common as direct hernias. The reported prevalence of inguinal hernia in the general population varies widely in the literature primarily due to a lack of a consistent reporting mechanism; for example, questionnaire versus actual physical examination. The most reliable data use hernia repair as a surrogate for the prevalence.[60] For example, in a study using the Danish Hospital registry, the country's population of 5,639,885 people was studied. There were 46,717 groin hernia repairs

reported between 2005 and 2010 making it possible to estimate prevalence for various age groups as shown in **Figure 72.24**.

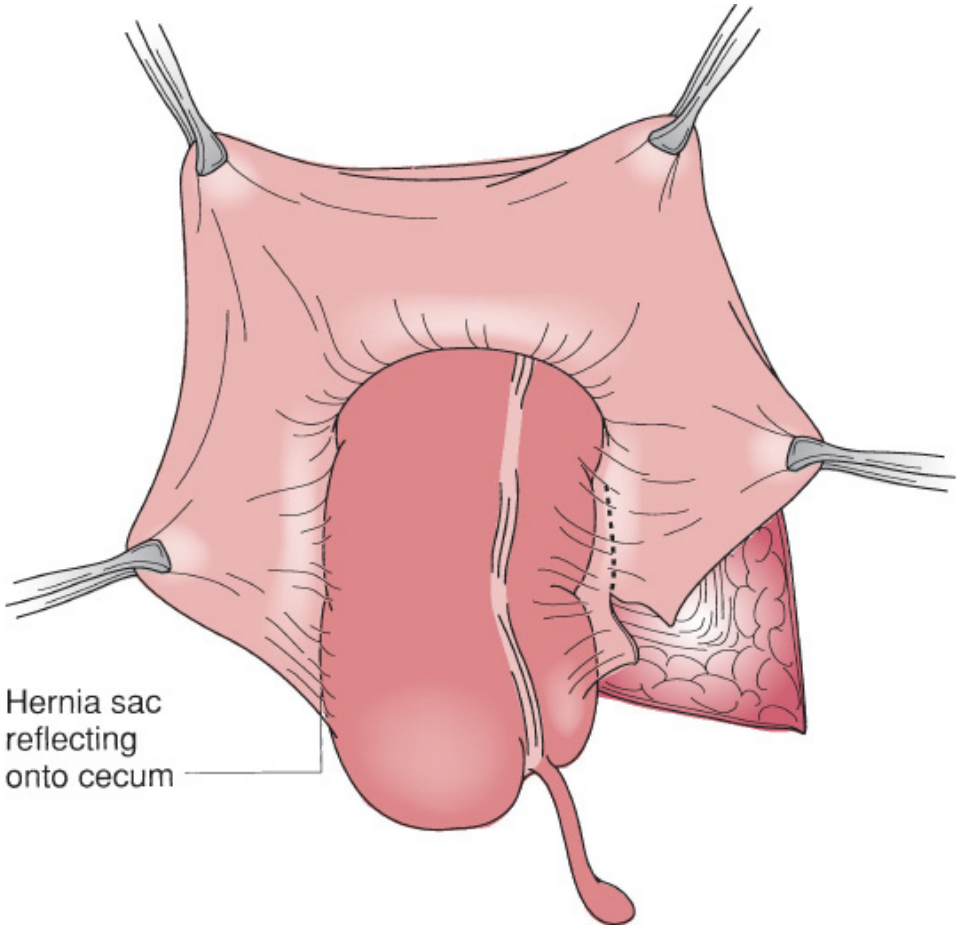


Figure 72.23 Sliding hernia (right indirect inguinal).

2. The figure confirms a bimodal incidence pattern peaking at the extremes of life with an initial peak at 0 to 5 years followed by a second peak at 70 to 80 years.[60] Right-sided inguinal hernias are more common than left. In men, indirect inguinal hernias outnumber direct by about 2:1, with femoral hernias making up a much smaller proportion. The literature dealing with groin hernia in women is insufficient making management decisions difficult. For females, indirect inguinal hernias are the most common which are five times more common than femoral hernias, with direct hernias occurring rarely. Overall, femoral hernias account for fewer than 10% of all groin hernias and the prevalence is higher in females than in males. Femoral hernias are especially dangerous as 40% of all femoral hernias

present as emergencies, with incarceration or strangulation and need emergency repair which is associated with high mortality. A study from the Swedish Hernia Registry analyzing 90,648 inguinal hernia operations (83,753 males, 6,895 females) between 1992 and 2003 revealed a higher percentage of emergency operations in women (16.9%) than in men (5%).[61] Femoral recurrences are particularly common in women in whom the diagnosis at the time of the primary repair was a direct inguinal hernia, strongly suggesting a missed femoral hernia at the original procedure since direct hernias are very rare in women. Femoral hernias are also more common in older patients and in those who have previously undergone inguinal hernia repair. Risk factors for the development of an inguinal hernia are listed in **Table 72.2**.

Classification

The primary purpose of a classification system for any disease is to stratify for severity so that reasonable comparisons can be made between various treatment strategies.[62] However, with the multiplicity of operative techniques and approaches for repair of groin hernias, no one classification system has been accepted by all practitioners. The reason why it is so difficult to develop a classification system that all surgeons can agree on is that in the final analysis, the physical examination represents an important component and no one has been able to eliminate its subjectivity. The European Hernia Society, Nyhus, Gilbert, Schumpelick, Harkins, Casten, Halverson and McVay, Lichtenstein, Bendavid, Stoppa, Alexandre, and Zollinger have developed groin hernia classification systems. The European Hernia Society classification is a simple system using three variables, location (M = medial, L = lateral, and F = femoral) and size of the defect (1 [≤1 finger], 2 [1 to 2 fingers], and 3 [≥3 fingers]) and status (P = primary, R = recurrent, and X = unknown) (**Table 72.3**).[63] The Nyhus system which is shown in **Table 72.4** remains popular among many surgeons in the Unites States.

Clinical Diagnosis

Groin hernias present with a swelling that has a cough impulse. With indirect hernias, the swelling may extend down into the scrotum. The swelling

typically reduces when the patient lies down, though sometimes requires manual reduction. Applying pressure over the mid-inguinal point (midway between the anterior superior iliac spine and the pubic tubercle and just above the inguinal ligament) with the fingertip will control an indirect hernia and prevent it from protruding when the patient strains. A direct hernia will not be controlled with this maneuver. Similarly, if the scrotum is invaginated with the index finger and the tip of the finger is placed through the external inguinal ring into the canal, and the patient is then asked to strain, an indirect hernia will push against the fingertip, whereas a direct hernia will push against the pulp of the finger. It should be noted that the accuracy of this clinical assessment is questioned by many authorities. A femoral hernia presents as a swelling below the inguinal ligament and just lateral to the pubic tubercle (**Fig. 72.22**).

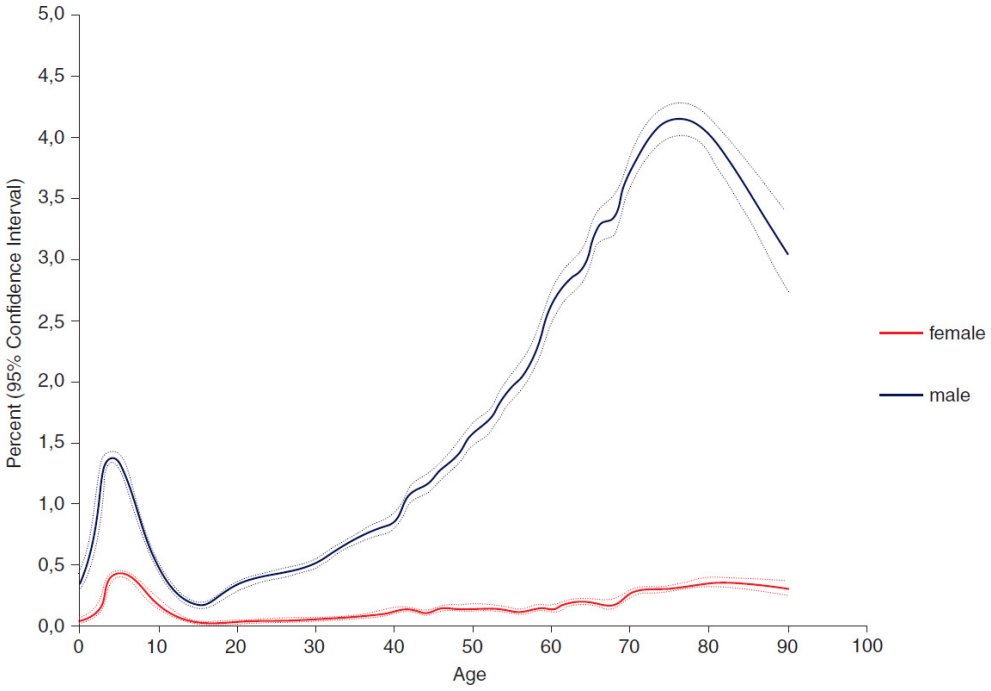


Figure 72.24 Prevalence of combined inguinal and femoral hernia repair (i.e., all groin hernias), stratified by age and gender. The results indicate the percentage of persons at a given age in the population who were operated for a groin hernia during the study period. Example: 4.19% CI 4.04% to 4.34% of all males aged 75 to 80 years in Denmark were operated for a groin hernia at least once during the study period. (From Burcharth J, Pedersen M, Bisgaard T, et al. Nationwide prevalence of groin hernia repair. *PLoS One* 2013;8(1):e54367, with permission.)

Table 72.2 Risk Factors for the Development of an Inguinal Hernia
Male sex
Increased age
COPD
Smoking
Low body mass index
High intra-abdominal pressure
Collagen vascular disease
History of abdominal aortic aneurysm
History of thoracic aortic aneurysm
Patent processus vaginalis
History of an open appendectomy
Peritoneal dialysis
Family history

Differential Diagnosis

The clinical presentation of a groin hernia, especially when large, is frequently obvious to the examiner. Smaller hernias and recurrent hernias can be confused with a number of different conditions that can be mistaken for a hernia (**Table 72.5**).

Table 72.3 EHS Classification of Groin Hernias

		Primary (P)		Recurrent (R)	
EHS Groin Hernia	0	1	2	3	x
Lateral (L)					
Medial (M)					
Femoral (F)					

Table 72.4 Nyhus Classification of Groin Hernias

Type	Description
I	Indirect hernia Normal-sized internal ring Typically in infants, children, small adults
II	Indirect hernia Dilated internal ring Posterior wall intact Inferior epigastric vessels not displaced Does not extend to the scrotum
III	Posterior wall defect
IIIA	Direct hernia Size not taken into account
IIIB	Indirect hernia Dilated internal ring encroaching on Hesselbach triangle (massive scrotal, sliding, or pantaloon type)
IIIC	Femoral hernia
IV	Recurrent hernia
IVA	Direct
IVB	Indirect
IVC	Femoral
IVD	Combined

A hydrocele extending into the scrotum or an encysted hydrocele of the cord can involve the groin area. The distinguishing features are that the examining hand can get above a hydrocele but not above a hernia and that a hydrocele transilluminates very clearly. A varicocele does not transilluminate, has the characteristic feel of a "bag of worms," and is more

tube-like in conformation. Lesions of the testicle may sometimes mimic a hernia, particularly in inflammatory conditions, such as epididymo-orchitis. The distinguishing features are intense pain extending down into the scrotum. The testicle itself is enlarged and tender, as is the epididymis. On rectal examination, the seminal vesicles are tender. This condition may be bilateral. Torsion of the testicle is distinguished by the fact that the testicle is absent from the scrotum and the swelling in the groin feels firm. A sonogram reveals a solid mass in the testicle, which has been pulled up because of the torsion. Testicular tumors, if large enough, may extend up to the groin area, but they have a solid feel and sonography can distinguish them. An aneurysm of the femoral artery may present as a groin swelling but with an expansile impulse and sometimes a bruit. If thrombosis develops in the aneurysm, pulsation may be lost. In this instance, the aneurysm becomes tender. Femoral aneurysms move from side to side but not up and down. A saphena varix usually presents below the inguinal ligament and represents a varicosity of one of the branches of the long saphenous vein as it emerges from the hiatus. It is particularly common in pregnancy. Like a hernia, the varix has a cough impulse and becomes more prominent when the patient is standing. Compression over the femoral hiatus obliterates this lesion. The varix is sometimes associated with varicose veins farther down the lower limb. The overlying skin has an associated bluish discoloration. A lipoma within the spermatic cord is a very common condition and, from anatomic studies and surgical dissection, is now regarded as a hernia of the extraperitoneal fat.[64] If found at surgery, the lipoma is removed to avoid a persistent bulge in the inguinal region despite a successful hernia repair.

Table 72.5 Differential Diagnosis of a Groin Hernia
Hydrocele
Encysted hydrocele of the cord
Varicocele
Epididymo-orchitis
Torsion of the testis
Undescended testis
Ectopic testis
Testicular tumor
Pseudohernia
Femoral artery aneurysm
Saphena varix
Lipoma of spermatic cord
Inguinal lymphadenopathy
Psoas abscess
Cutaneous lesions (e.g., sebaceous cyst and skin tumor)

Enlargement of inguinal lymph nodes may also be mistaken for herniation. Inflammatory nodes are usually tender; metastatic lymphadenopathy is usually not tender. If inguinal lymph nodes are replaced by metastasis, a primary lesion should be looked for in the skin in any part of the lower limb. The perineum and anal canal should also be examined. Lymphadenopathy can also be caused by lymphoma, and groin nodes may be the only site. Lymphadenopathy characteristically appears as a well-circumscribed mass below the inguinal ligament that one can get above with the examining hand.

Lymph nodes are solid on ultrasonography, and for this reason, it may be difficult to differentiate nodes from a femoral hernia containing omentum.

Surgical Indications

Historically, surgeons have recommended repair of inguinal hernias at diagnosis unless specific contraindications are present. This recommendation was based on the presumption that the morbidity and mortality associated with a bowel obstruction and/or strangulation was greater than the risks of operation. 4 This concept was challenged for asymptomatic or minimally symptomatic male patients based on several randomized controlled trials in the early part of this century which demonstrated that watchful waiting for minimally symptomatic inguinal hernias was safe.[35] However, long-term follow-up from these randomized controlled trials have demonstrated a crossover rate of up to 70% by 10 years for patients in the watchful waiting group, with crossover being much higher for patients older than 65 years of age. The most common reason for crossover is increasing pain. Patients who opt for this strategy should be informed that it is safe to delay surgery for several years, but increasing symptoms will more than likely make them choose to have their hernia repaired over the next 10 years.

An alternative to surgical repair is a mechanical device known as a truss which consists of a belt with a pad that is applied to the groin after spontaneous or manual reduction of a hernia and has been used for centuries. It serves to maintain reduction and possibly prevents enlargement of the hernia. There are insufficient studies to determine how effective trusses actually are and whether they are as good as surgery for the control of symptoms.[65] Most patients find them cumbersome to use and difficult to keep clean. With prolonged usage, atrophy of the spermatic cord has been reported and eventual surgical repair is made more difficult due to fibrosis of the tissues. However, some patients do achieve symptomatic relief. **Table 72.17** summarizes the International Guidelines for Groin Hernia Management.[66]

Preoperative Considerations

Most elective groin hernias can be repaired on outpatient basis. Local anesthesia is sufficient for most cases of open inguinal hernia repairs with or

without supplemental intravenous sedation. Its greatest advantage is the virtual elimination of urinary retention when compared to regional or general anesthesia.[67] Additionally, recovery can be quicker than techniques utilizing general anesthesia especially in the elderly population. General anesthesia is an acceptable alternative and is preferred by many surgeons in patients with acceptable perioperative anesthesic risk. Indeed, epidemiologic information from databases primarily in Europe discloses that local anesthesia is used in only about 10%.[68] Regional anesthesia has the highest incidence of cardiovascular complications and should be avoided.[68] Laparoscopic hernia repairs require general anesthesia and can only be performed in patients who can safely tolerate general anesthesia and a pneumoperitoneum. Antibiotic prophylaxis has not been shown to be of any value except in patients at high risk for infection.[66] Nevertheless, it is routinely used in the United States because of medicolegal considerations when placing a prosthesis.

Surgical Treatment of Groin Hernias

Four developments in the latter half of the 20th century significantly decreased morbidity and favorably influenced the recurrence rate to the currently accepted level of less than 2%: (a) the routine use of prosthetic materials, (b) the widespread acceptance of the "tension-free" concept, (c) the realization that the preperitoneal space can be used for hernia repair, and (d) therapeutic laparoscopy (**Algorithms 72.1** and **72.2**). These concepts are discussed in this section; the treatment strategies are divided between an open approach in the conventional anterior space and a preperitoneal approach, either open or laparoscopic.

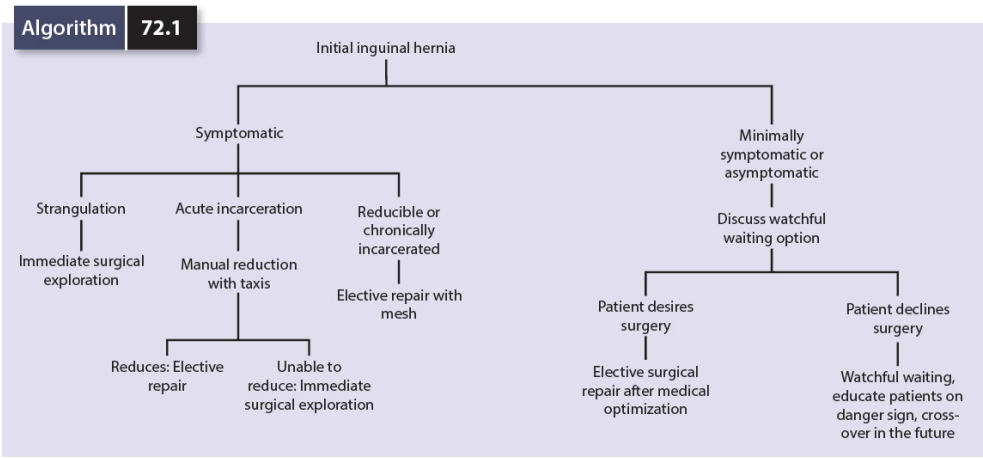
Open Approach

The simplest Nyhus type I indirect inguinal hernias, which include most inguinal hernias in children, are adequately treated by obliteration of the congenital patent processus vaginalis alone. Since the inguinal floor is otherwise normal, reconstruction is not required. Classically, the hernia sac is dissected from the cord structures, ligated, and removed at its origin at the internal ring, the so-called high ligation of the sac, thus the term *herniotomy.* The skin incision starts at the pubic tubercle and is extended laterally. The

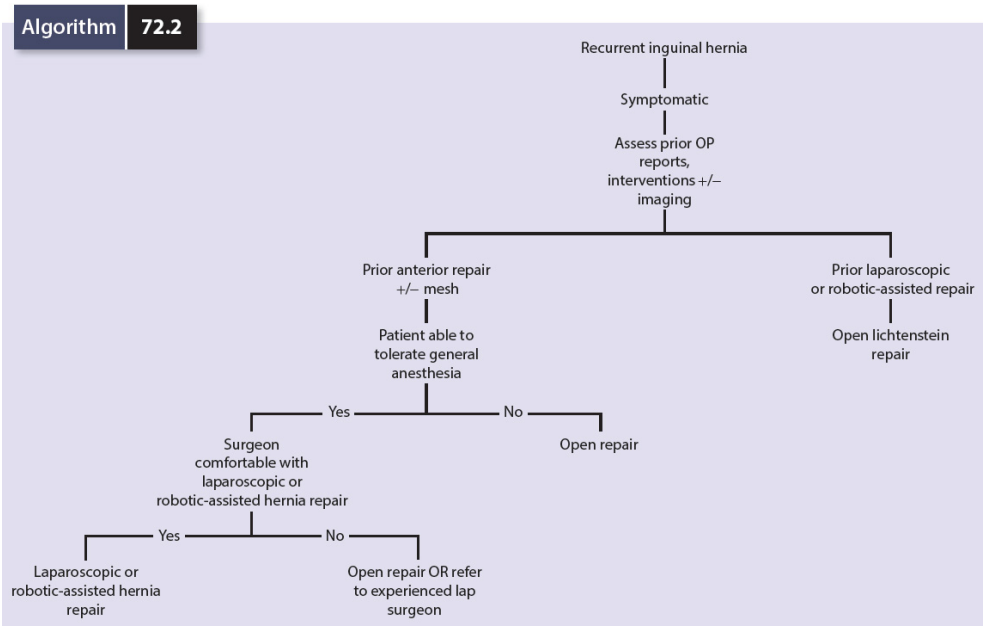
external oblique aponeurosis is opened in the line of its fibers through the external ring and the lower leaf is freed from the spermatic cord. The spermatic cord is freed from the floor of the inguinal canal and the pubic tubercle. Mobilization of the cord structures is completed by means of blunt dissection, and a Penrose drain is placed around them so that they can be retracted during the procedure.

The genital branch of the genitofemoral nerve and the spermatic vessels are included with the cord. The ilioinguinal and iliohypogastric nerves are usually preserved. The cremasteric fibers are separated, and the hernia sac is dissected from the cord structures to a point proximal to the internal ring. Ligation can be performed at this point (high ligation), followed by division of the neck of the sac. Prior to this, the sac can be opened to allow a digital examination of the abdominal cavity and femoral ring. Alternatively, the sac may be simply inverted. The proponents of not opening the sac feel that with this method the patient experiences less pain because the highly innervated peritoneum has not been violated. Notably, herniotomy is rarely utilized solely as a means of repair in adults.

The terms *herniorrhaphy* or *hernioplasty* are used when a procedure to reconstruct the inguinal floor is added. For indirect hernias, the sac is first dealt with in an identical manner as for a herniotomy. The only exception is large indirect inguinal scrotal hernias where complete removal of the sac might result in too high of an incidence of cord and testicular complications because of the extensive dissection required to completely separate them from the cord. Most authorities believe that these large sacs are best transected at the midpoint of the canal, and the distal sac is left in situ. Direct hernia sacs are almost never removed but instead are dissected from surrounding structures and reduced into the preperitoneal space. Dividing the transversalis fascia circumferentially at the neck (base) of the sac will aid in this reduction in some cases. The defect may be closed primarily at this point to maintain the reduction while a formal repair is being performed. The latter is considered a matter of convenience and adds nothing to the strength of the final outcome. The area of weakness in the posterior wall is then reinforced with the patient's own tissues or a mesh prosthesis.



Algorithm 72.1 Management of initial inguinal hernia.



Algorithm 72.2 Management of recurrent inguinal hernia.

The next step is to reconstruct the inguinal floor. There are two ways to do this. The first is a tissue repair, so named because only the patient's native tissue is used without foreign 5 prosthetic material. The second is the tension-free repair (TFR). This implies the use of a prosthesis to repair the weakened inguinal floor, eliminating the need to reapproximate tissues that were not in apposition naturally. Edoardo Bassini (1844–1924) is considered the father of modern inguinal hernia surgery because in the latter part of the 19th century he introduced the first tissue repair based on solid anatomic principles, which became the "gold standard" for inguinal hernia

repair for most of the 20th century. His scientific approach led to the development of several distinct steps essential for the procedure (**Table 72.6**). Before Bassini's achievements, elective herniorrhaphy was almost never recommended because the results were so bad.

Today, there are at least 70 named tissue repairs described in the literature.[69] Most are relatively minor modifications of the Bassini, Shouldice, and McVay repairs. In the Bassini repair, the transversus abdominis aponeurosis together with the transversalis fascia is sutured to the shelving edge of the inguinal ligament with nonabsorbable interrupted sutures (**Fig. 72.25**). In the Shouldice repair, the transversalis fascia is divided from the internal ring to the pubic tubercle. The musculofascial elements laterally are then sutured to different levels of the inferior flap of the external oblique aponeurosis with four rows of running sutures (**Fig. 72.26**). Although the suture material originally used for this repair was stainless steel wire, other nonabsorbable materials, such as Prolene, are now used. The McVay repair (**Fig. 72.27**) addresses both inguinal and femoral hernias. The central attenuated portion of the inguinal floor is excised. Cooper ligament must be clearly identified. The inguinal floor is then repaired by approximating the transversus abdominis aponeurosis and transversalis fascia to Cooper ligament between the pubic tubercle and the femoral vein. A so-called transition stitch is then necessary between the transversalis fascia, Cooper ligament, and inguinal ligament to bring the repair above the femoral vessels. The repair is then continued laterally along the inguinal ligament.

Table 72.6 Essential Steps for Open Inguinal Hernia Repair

1. Complete division of the external oblique aponeurosis and the transversalis fascia
2. Differentiation between indirect and direct defects
3. Isolation of the spermatic cord or round ligament
4. Ligation and removal of the sac at the deep inguinal ring flush with the peritoneum
5. Oblique reconstruction of the inguinal canal with an anterior and posterior wall and an internal and external ring

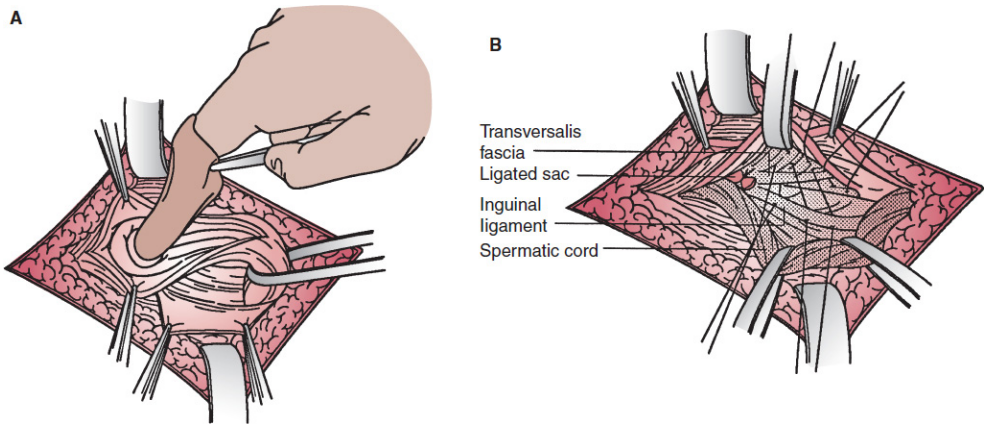


Figure 72.25 Bassini repair.

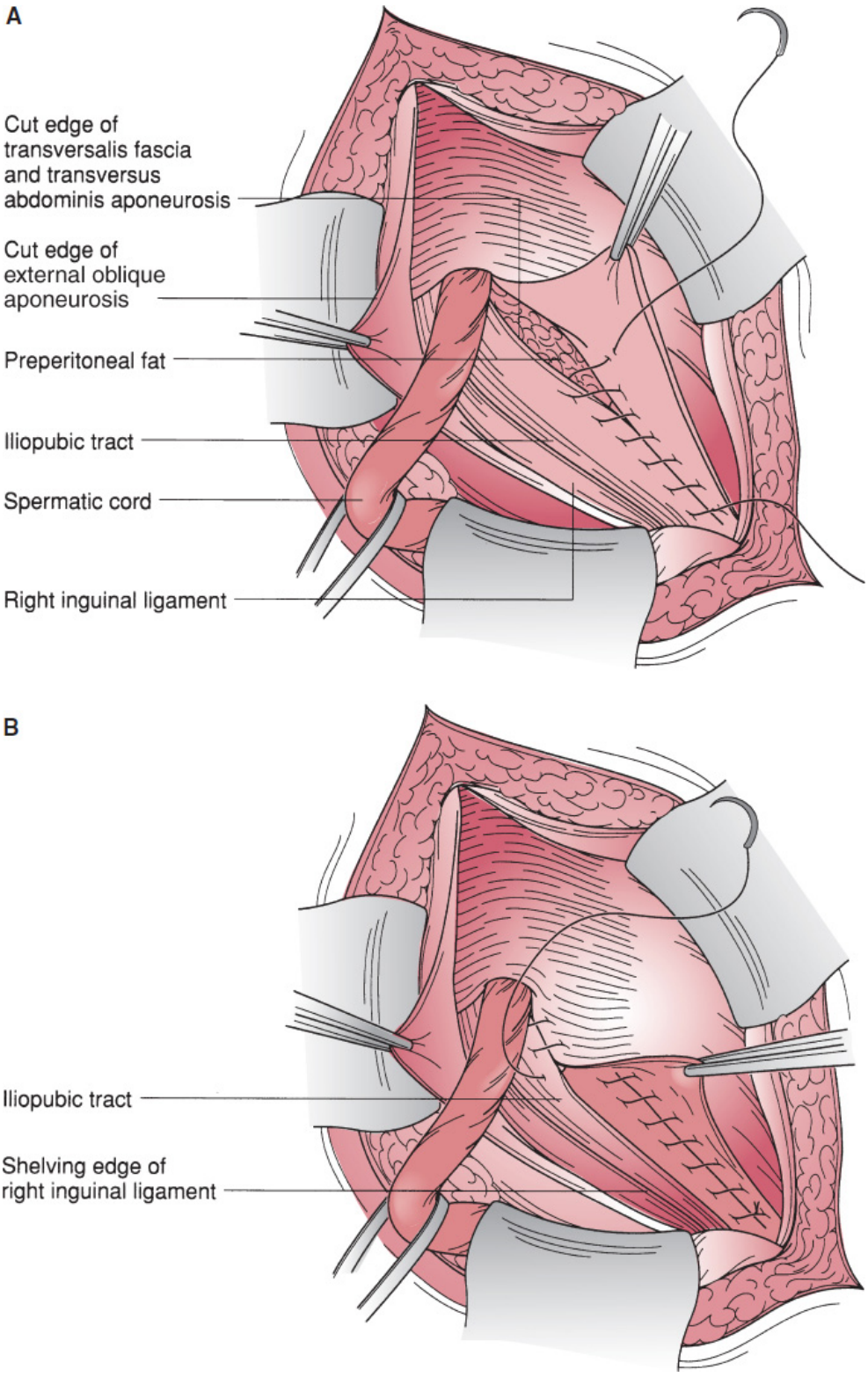


Figure 72.26 Shouldice repair.

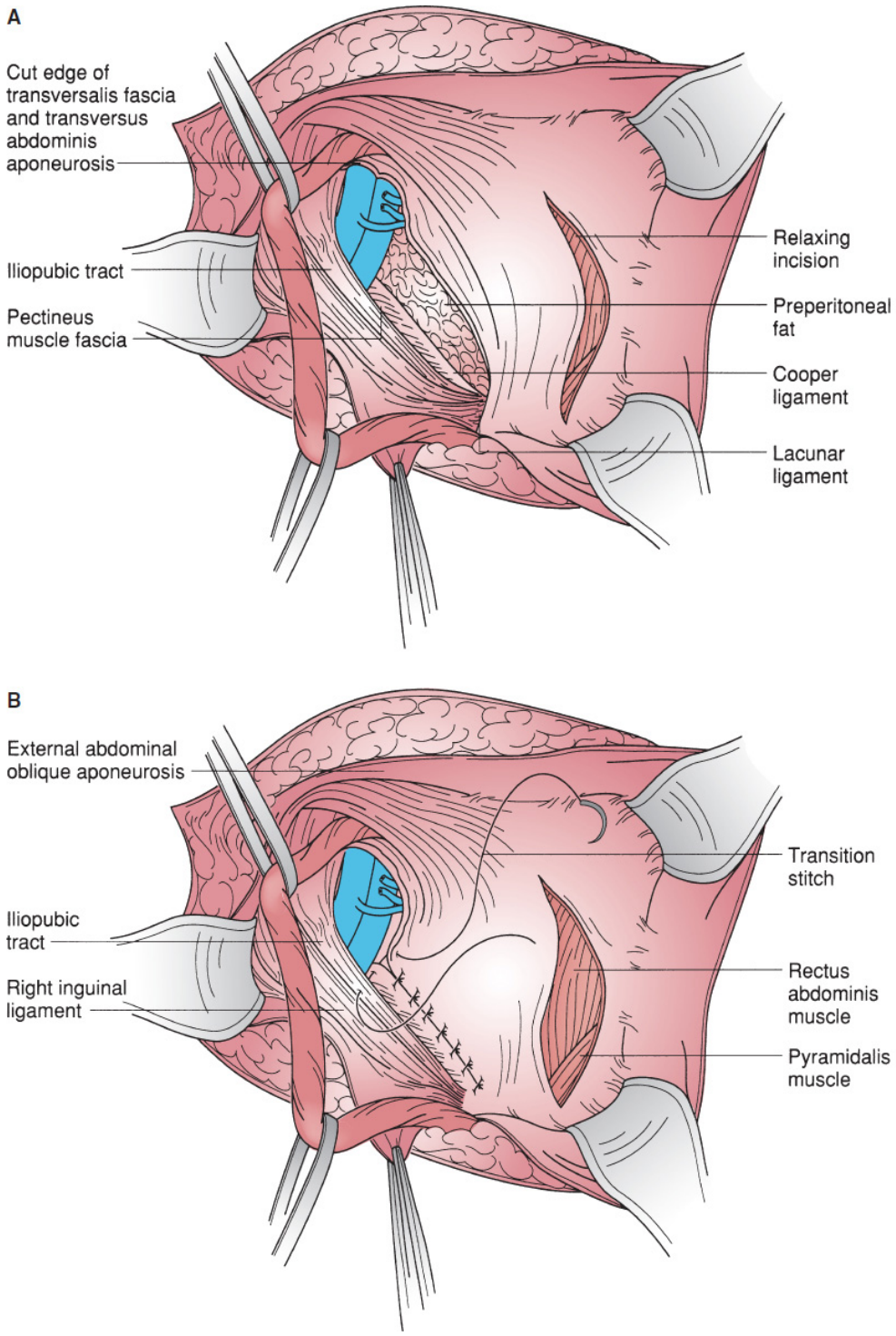


Figure 72.27 McVay (Cooper ligament) repair.

A relaxing incision is necessary for repairs of large indirect hernias and whenever the McVay repair is used. Failure to make a relaxing incision has been implicated in a greater incidence of recurrence. The relaxing incision is

made in the anterior rectus sheath in a vertical direction and is extended 3 to 4 cm above the pubis to a level opposite the internal ring (**Fig. 72.27**). The resulting defect in the sheath is protected posteriorly by the body of the rectus muscle, which prevents herniation at that site.

As population-based studies began to supplant personal series, it became obvious that the recurrence rate for tissue repairs with the exception of the Shouldice repair approached 10% to 15% in the general surgical practice.[70] In the 1990s, widespread adoption of the routine use of prosthesis (usually a mesh material) as popularized by Lichtenstein has resulted in the near elimination of the Bassini approach in the United States with recurrence rates decreasing by 50% to 75%.[71] The Lichtenstein operation or open mesh herniorrhaphy, which is considered the "gold standard" operation for inguinal hernias with a recurrence rate of 1% to 1.6% (**Fig. 72.28**).[72] The initial dissection is identical to the tissue repairs described. A useful adjunct to this approach is to separate the subcutaneous fat from the inguinal ligament exposing the femoral sheath. The femoral artery can usually be easily palpated and the typical space for femoral hernia palpated medial to the femoral vein. This allows assessment of the femoral space without division of the transversalis fascia. Care is taken to minimally disrupt the spermatic cord and its contents, dissecting only what is necessary to achieve each step of the operation. Attempts are made to identify and preserve in situ the ilioinguinal nerve, iliohypogastric nerve, and genital branch of the genitofemoral nerve. If a femoral hernia is present, the inguinal floor is incised, exposing the preperitoneal fat, femoral space, and Cooper ligament. Once the sac has been dealt with and any sizable cord lipoma resected, a 15- × 7-cm sheet of mid-weight polypropylene mesh is used, the medial end of which is rounded to the shape of the medial corner of the inguinal canal. This medial end is allowed to extend 2 cm medial to the pubic tubercle. The first running permanent suture approximates the inferior aspect of the mesh to the shelving edge of the inguinal ligament just adjacent to, but not through, the pubic tubercle. The periosteum of the bone is avoided to prevent osteitis pubis. This is continued just proximal to the internal ring and tied to itself. Next, superior absorbable sutures are placed in an interrupted fashion approximating the mesh to the conjoined tendon, taking care to avoid the iliohypogastric nerve. For a femoral hernia, a posterior "extension" of the mesh is added when shaping the mesh and approximated to Cooper ligament

after the inferior edge has been attached to the inguinal ligament. Alternatively, the inferior edge of the prosthesis is sewn directly to Cooper ligament medially and then transitioned to the inguinal ligament over the femoral vessels. Both techniques close the femoral canal. A slit is cut in the lateral end of the mesh to produce a narrow (one-third width) tail below and a wider (two-thirds width) tail above. The spermatic cord is positioned between the two tails. The wider tail is placed over the narrow one and a so-called shutter valve stitch placed just lateral to the cord including the inferior surface of the superior tail, the inferior surface of the inferior tail, and the inguinal ligament. The tails are then tucked under the external oblique aponeurosis to the level of the anterior superior iliac spine. The external oblique aponeurosis is closed to recreate the external ring. The wound is closed in layers.

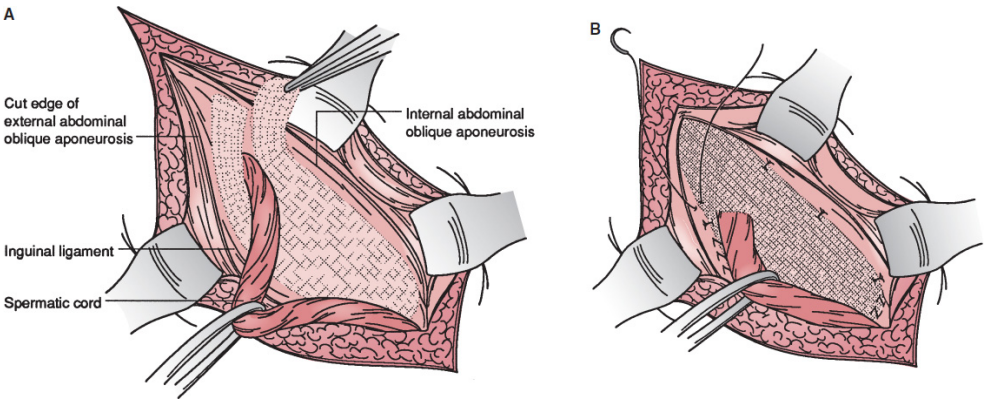


Figure 72.28 The Lichtenstein hernioplasty, showing placement of the mesh.

A popular modification of the Lichtenstein operation has been termed the plug-and-patch repair. As the name implies, a plug usually constructed from polypropylene is inserted in the defect and secured with interrupted sutures to either the internal ring (for an indirect hernia) or the neck of the defect (for a direct hernia). The patch is then placed over the plug to cover the inguinal floor as in the Lichtenstein. One might argue that this operation is nothing more than a Lichtenstein on top of a plug, and in fact the term "plugstenstein" has been used to describe it. However, the difference with a plug-and-patch repair is that only one or two sutures—or, sometimes, no sutures—are used to secure the flat prosthesis to the underlying inguinal floor. This results in an operation that is fast and very easy to teach. However, based on trials

comparing the plug and patch to the Lichtenstein technique, no benefit with respect to recurrence rate and/or chronic pain has been demonstrated.[66] The downside of this operation is the mesh burden placed in the inguinal region, including a dense plug that can migrate. In addition, plugs can make repairs for recurrence very challenging later in a patient's course.

A hybrid procedure described by Desarda combines elements of the Lichtenstein repair with a pure tissue repair avoiding the need for allogeneic material.[73] The initial steps are identical to Lichtenstein but then instead of using a synthetic prosthesis to reinforce the inguinal floor, the medial edge of the divided external oblique aponeurosis is approximated with a continuous suture to the inguinal ligament beginning at the pubic tubercle and extending to the internal ring. The external oblique aponeurosis is then divided again one to two CMs cranially parallel to the inguinal canal in effect creating a vascularized flap of external oblique which serve as an autologous patch to reinforce the inguinal floor. The cranial edge of this flap is then sutured to the internal oblique muscle from the pubic tubercle to the internal ring. The cord structures are returned to the inguinal canal and the two remaining cut edges of the external oblique aponeurosis are reapproximated to reconstruct the anterior surface of the inguinal canal and the external ring.

Preperitoneal Approach

The preperitoneal space is situated between the transversalis fascia and the peritoneum. The final common denominator in all groin hernias is failure of the transversalis fascia to retain the intra-abdominal contents. Repairs performed in this space make the distinction between direct, indirect, and femoral irrelevant because the repair is accomplished behind the defective transversalis fascia, addressing the entire myopectineal orifice.

For a conventional, open operation, the preperitoneal space can be entered via a lower midline incision or a transverse incision placed slightly higher than usual. The rectus muscle is retracted medially and the preperitoneal space entered. A large prosthesis is used that extends far beyond the margins of the myopectineal orifice and envelops the visceral sac. The mesh is held in place by intra-abdominal pressure, which pushes outward toward the undersurface of the transversalis fascia. If the hernia sac is large, it is amputated or inverted beneath a purse-string suture to smooth the external

surface of the visceral sac. The distal peritoneal sac is left in place, undissected, and attached to the cord. With a sliding indirect hernia, the sac is easily dissected away from the cord. For a bilateral repair, one large chevron-shaped mesh can be used for both sides as described by Stoppa. One disadvantage of this technique is the need for a larger incision and substantial amount of dissection and the associated pain. Laparoscopic hernia repairs avoid the disadvantages of a large incision while providing the advantages of preperitoneal repair.

Several newer, less invasive preperitoneal techniques have been developed to place a mesh in the preperitoneal space. For example, in the Kugel procedure, a small incision is made over the deep inguinal ring and the preperitoneal space is developed bluntly followed by the use of a prosthesis with an incorporated reinforcing ring. This ring can be deformed to allow the prosthesis to be introduced into the preperitoneal space and then the ring causes it to spring back to its original shape, providing wide overlap of the myopectineal orifice.[74] The procedure works well in experienced hands but because it is partially blind, considerable training is required. In addition, in earlier designs, the peripheral memory recoil ring was made of polyethylene terephthalate which had a tendency to fracture over time occasionally resulting in injury to nearby viscera.[75] In addition to the Stoppa and Kugel procedures, other preperitoneal repairs have been described including the Trans Rectus sheath Pre Peritoneal technique, the Trans Inguinal Pre Peritoneal, the Onstep technique and the Ugahary technique. A detailed description of each of these operations is beyond the scope of this chapter but a thorough discussion of them is provided in the reference.[76]

Another approach is to take advantage of both the preperitoneal space and the conventional anterior space using a bilayered prosthesis in which a cylinder of prosthetic material connects the two layers through the hernia defect or the internal ring.[77] One such prosthetic is the Prolene Hernia System (PHS) where both an onlay and sublay mesh is placed. Trials comparing PHS to the Lichtenstein technique have not shown any difference with respect to recurrence rate and chronic pain.[66] The objection to this system is that both the conventional anterior and the preperitoneal spaces are dissected making the repair of a recurrence more difficult.

Laparoscopic Approach

The terminology to describe a laparoscopic inguinal herniorrhaphy can be confusing. A laparoscopic preperitoneal hernia repair, in which a laparoscopy is performed and the preperitoneal space is entered with a second incision in the peritoneum, is called a *transabdominal preperitoneal repair,* or TAPP repair. An inguinal hernia repair in which prosthetic material is placed intraperitoneally over the defect under laparoscopic guidance is referred to as an *intraperitoneal onlay mesh repair,* or IPOM repair. The third general type of laparoscopic approach is the *totally extraperitoneal laparoscopic repair,* or TEP repair. Laparoscopy, by definition, implies that the peritoneal cavity has been entered. To refer to this technique as *extraperitoneal* therefore represents a contradiction in terms. However, because a laparoscope and related instruments are used, it is fitting to discuss the extraperitoneal approach along with the other laparoscopic inguinal herniorrhaphies.

The TAPP and the TEP laparoscopic inguinal herniorrhaphies are the most popular. Both are modeled after the conventional preperitoneal operations. The major difference is that the preperitoneal space is entered through three trocar sites rather than through a large conventional incision. The ensuing radical dissection of the preperitoneal space with placement of a large prosthesis is similar to the conventional preperitoneal operation.

Laparoscopic versus Conventional Herniorrhaphy; Mesh versus Non-Mesh

Randomized controlled trials as well as meta-analysis of pooled data from these trials have shown that on average, patients undergoing laparoscopic herniorrhaphy have less pain initially than open, tension-free herniorrhaphy and return to normal activities sooner with a lower incidence of wound infection and hematoma and less chronic pain/numbness.[66,78] These advantages of laparoscopic hernia repair must be interpreted in light of the disadvantages, which include longer operative time and complications related to the laparoscopy such as bowel perforation or major vascular injury, potential adhesive complications at sites where the peritoneum has been breached or prosthetic material has been placed, the need for a general anesthetic, and increased cost because of the expensive equipment. On the other hand, the conventional operation can be performed under local anesthesia on an outpatient basis, with minimal risk of intra-abdominal

injury, and the cost is less. The best indications are a recurrent hernia after an open conventional procedure or for bilateral hernias. The most important final determinate about the best procedure for an individual patient should be based on local factors such as surgeon expertise, size and degree of incarceration of the hernia and the patient's comorbid conditions. In general practice a mesh repair is recommended because of its dramatic decrease in recurrence rate when compared to tissue repair, realizing that there are specialty centers performing pure tissue repairs with results equaling a mesh repair.

Robotic-Assisted versus Laparoscopic Inguinal Herniorrhaphy

There have been several inconclusive evaluations comparing a robotic-assisted approach to inguinal hernia repair to a laparoscopic approach. Representative retrospective studies have not shown significant benefit.[79] The only prospective trial to date is the Transabdominal Laparoscopic Inguinal Repair (RIVAL) study.[75] In this randomized controlled clinical trial, 102 patients were randomized to either robotic-assisted or laparoscopic approach to inguinal hernia repair. No difference was noted for the primary outcomes of postoperative pain, quality of life, mobility, wound morbidity, or cosmesis. The robotic-assisted approach was associated with longer operative times (76 minutes vs. 41 minutes) and higher mean frustration levels as measured by the NASA Task Load Index Scale. No differences in ergonomics were noted between the groups. Higher median cost per case was noted for the robotic-assisted approach ($3,258 vs. $1,421) not accounting for capital equipment costs in either group.[80]

Patient and Procedure Selection

6 Assuming equivalence for recurrence and complication rates between laparoscopic and open tension-free hernia repair for a given surgeon, all adult patients with inguinal hernias who are candidates for general anesthesia can be considered candidates for laparoscopic inguinal hernia repair.[66] Certain hernia types, such as those that are recurrent, bilateral, or otherwise complicated, are particularly suited for the laparoscopic approach.[81,82] In addition, women may be better served with a laparoscopic operation because the femoral space is addressed, which should eliminate the excessive incidence of femoral recurrence observed with conventional

operations such as the Lichtenstein.[61] Contraindications to laparoscopic inguinal hernia repairs include intra-abdominal infection and coagulopathy. Relative contraindications for laparoscopic inguinal hernia repair include intra-abdominal adhesions from previous surgery, ascites, or previous retropubic space surgery, because of the increased risk for bladder injury. Severe underlying medical illness is also a relative contraindication because of the added risk of general anesthesia and these patients are better suited for a conventional operation under local anesthesia. An incarcerated sliding scrotal hernia is a relative contraindication, especially when it involves the sigmoid colon, because of the high risk for perforation during the dissection.

Operative Techniques

Transabdominal Preperitoneal Repair

The TAPP repair can be performed either via robotic-assisted or traditional laparoscopic approach. The procedure is begun with a thorough diagnostic laparoscopy done through an umbilical or periumbilical cannula to rule out unrelated pathology and carefully inspect both myopectineal orifices. Two additional cannulas are placed just lateral to the rectus sheath on either side of the umbilicus (**Fig. 72.29**). For a unilateral hernia, a transverse incision is begun at the lateral side of the medial umbilical ligament and extended to the anterior superior iliac spine. It is quite important to enter the true preperitoneal plane and not the retromuscular plane (anterior to the transversalis fascia) which leads to a bloodier dissection. Conversely, the retromuscular plane can be preferentially entered in situations where previous pelvic operations have been performed (i.e., prostatectomy, Pfannensteil incision, rectal surgery, open appendectomy). In these situations, the operation should be performed by surgeons with much experience with laparoscopic or robotic-assisted approaches. If the medial umbilical ligament appears to compromise exposure, it can be divided. Electrosurgical current is used to minimize bleeding from the remnants of the embryologic umbilical artery. A radical dissection of the preperitoneal space is then performed with mostly blunt dissection and generous use of electrosurgical current, as bleeding in this area is particularly troublesome if it interferes with illumination. The ipsilateral inferior epigastric vessels, Cooper ligament, and iliopubic tract are identified (**Fig. 72.30**). The cord structures

are mobilized, and the peritoneal flap is dissected well proximal to the bifurcation of the vas deferens and the internal spermatic vessels. Recurrences have been attributed to inadequate mobilization of the peritoneal flap, which does not allow the prosthesis to lie flat in this area. If small, an indirect sac is mobilized away from the cord structures and reduced. If large, the sac can be divided at a convenient point distal to the internal ring and only the proximal portion mobilized. A direct sac readily reduces during the preperitoneal dissection. An easily visible layer of fatty tissue separates the attenuated transversalis fascia lining the defect and the peritoneum.

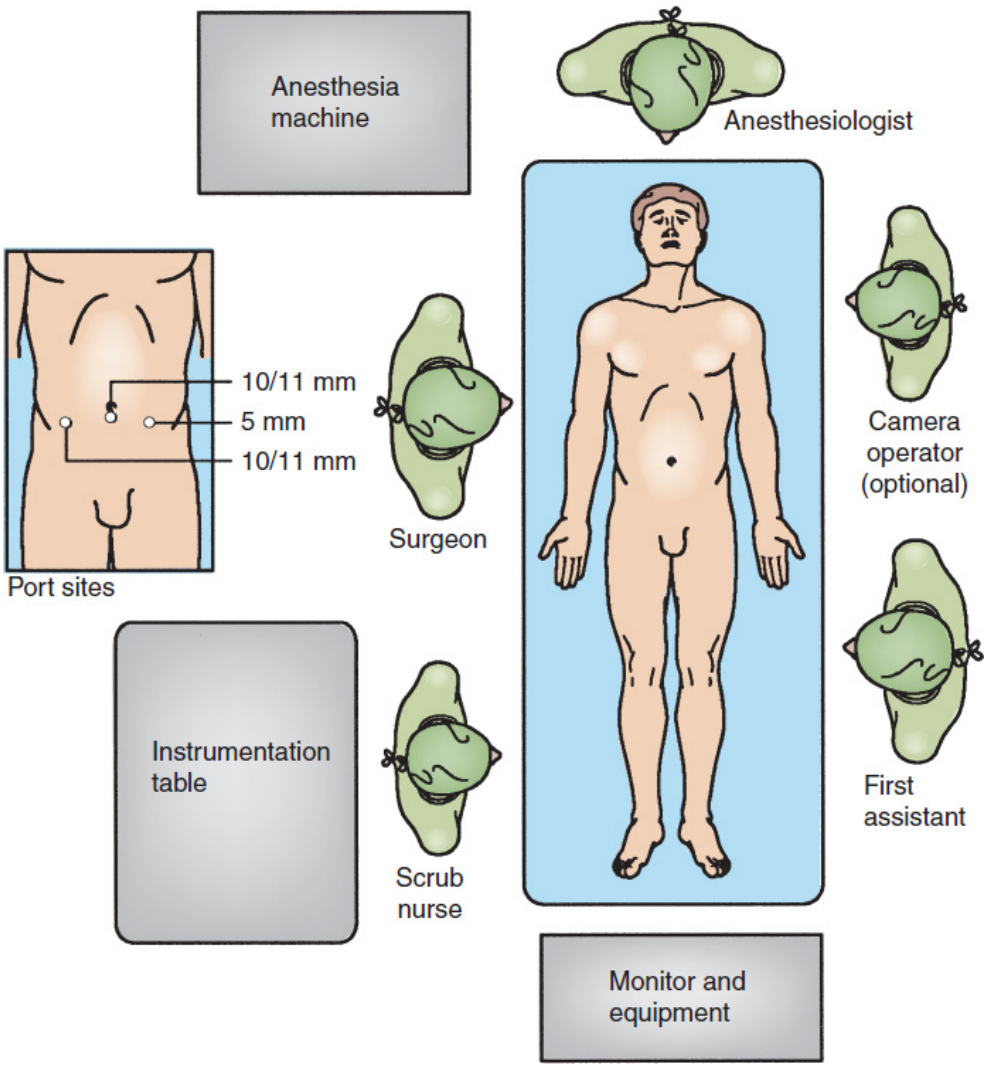


Figure 72.29 Typical operative setup and cannula site selection for a transabdominal preperitoneal (TAPP) laparoscopic inguinal herniorrhaphy.

A large piece of permanent mesh (at least 14 × 11 cm) is placed in the preperitoneal space to cover the entire myopectineal orifice and extending onto the anterior abdominal wall superiorly at least 2 cm above the hernia defect, to the anterior superior iliac spine laterally, and to Cooper ligament medially. Most surgeons prefer to fasten the prosthesis with staples, tacks, or glue, but there is increasing evidence that fixation is not necessary when a large prosthesis is used that widely overlaps the entire myopectineal orifice. Staples or tacks are never placed below the iliopubic tract when lateral to the internal spermatic vessel because of the danger of damage to the important nerves in this area. The last step is to cover the prosthesis by closing the peritoneum with sutures, tacks, staples, or glue.[66] The goal is to isolate the prosthesis from the abdominal viscera rather than to always achieve precise approximation of the peritoneal edges. This is because gaps can form if the peritoneum is closed under tension allowing bowel to migrate into the preperitoneal space. A better option is to secure the inferior peritoneal flap to the transversalis fascia above the prosthesis and leave the superior flap alone.

For bilateral inguinal hernias, two different approaches are commonly used. A separate peritoneal flap can be created similar to a unilateral approach. The advantage of this is easier handling of the peritoneal flap closure. Alternatively, the symphysis pubis is completely exposed so that both preperitoneal dissections communicate with each other. This exposure allows the placement of one large prosthesis (at least 25 × 11 cm) that essentially covers the entire lower pelvis.

Totally Extraperitoneal Repair

An incision is made at the umbilicus and the rectus sheath is opened on one side and the rectus muscle is retracted laterally. Blunt dissection is then begun in the space between the rectus muscle and the posterior rectus sheath. Once the space is large enough, two additional cannulas are placed in the midline, one approximately 5 cm above the symphysis pubis and the other midway between the umbilicus and the symphysis pubis. The dissection of the retrorectus and preperitoneal space immediately posteriorly is completed under direct vision. The rest of the operation is identical to the TAPP procedure described previously except that peritoneal closure is not necessary. Popular alternatives are to use a water- or air-filled balloon

dissector to perform the preperitoneal dissection and to place the two accessory cannulas on either side of the umbilicus, as in the TAPP procedure, instead of in the midline.

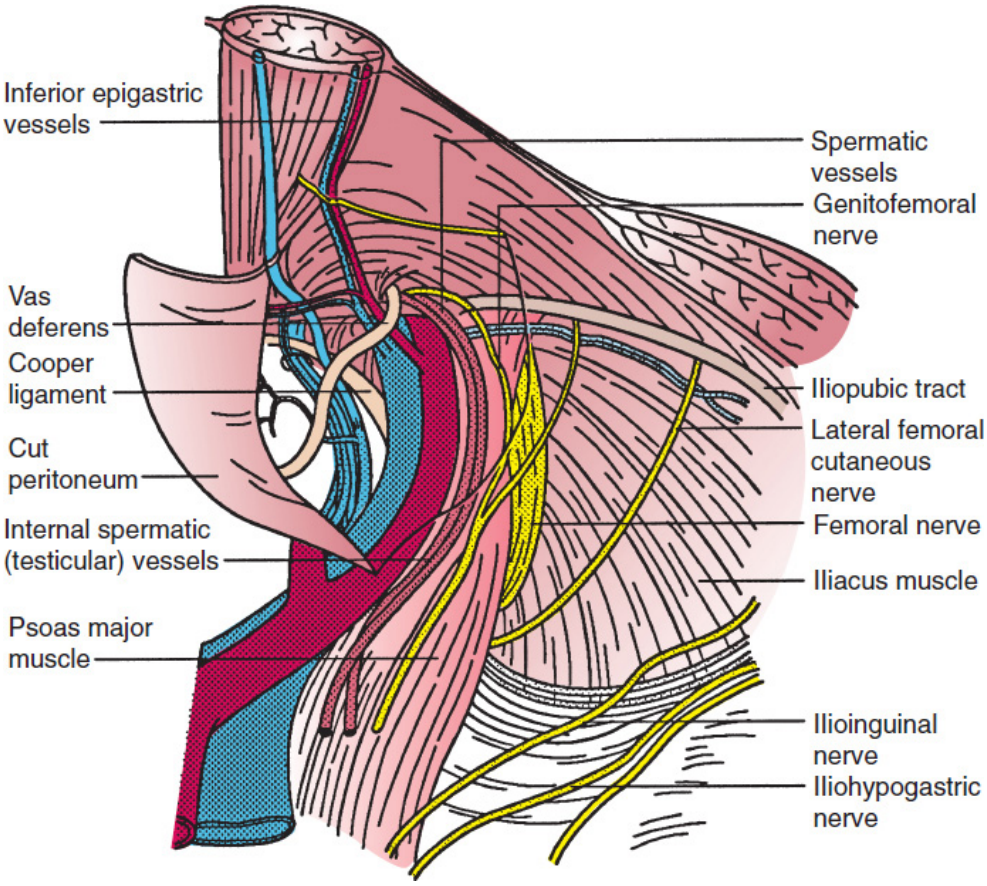


Figure 72.30 Important structures that must be identified after a preperitoneal dissection: inferior epigastric vessels, Cooper ligament, spermatic vessels, vas deferens, iliopubic tract, genitofemoral nerve, femoral nerve, lateral femoral cutaneous nerve, ilioinguinal nerve, iliacus muscle, and psoas major muscle.

The presumed advantages of the TEP procedure are that the inherent complications of entering the peritoneal cavity, such as intra-abdominal organ injury or postoperative bowel obstruction secondary to adhesions or trocar site herniation, are avoided. However, the operative space is limited, and considerable experience is required to become familiar with the anatomy from this perspective. Great care should be taken in reoperative fields or when prior mesh prosthesis is present. In addition, it is not yet clear whether inadvertent breaches in the peritoneal cavity that are difficult to visualize

because of the direction of the optics might negate the potential benefits of this approach.

Intraperitoneal Onlay Mesh Repair

The IPOM procedure which will be discussed in more detail in the incisional hernia section has never gained popularity for the treatment of an inguinal hernia. Nevertheless, it can be useful in patients with multiply recurrent inguinal hernias when dissection in both the conventional anterior space and the preperitoneal space has been made nearly impossible because of excessive scaring.[81] Often times in this situation, peritoneal closure is impossible and the adhesion barrier prosthetics developed for ventral hernia repair can be used.

Special Considerations: Pediatric Hernias

Given the high incidence of indirect inguinal hernias due to a patent processus vaginalis in pediatric patients, hernia repairs are completed using a high ligation technique. Concerns exist with the use of mesh in adolescents with respect to effect on fertility, long-term groin pain, and infection risk.[83,84] Postpubertal males have a similar anatomy to the adult population with a larger inguinal ring diameter and variations on transverse fascia defects. It is unclear as to which age/size does a child become an adult with respect to principles of hernia repair. Longitudinal studies comparing different hernia repair techniques in adolescents are needed before we can determine optimal treatment for adolescents especially those with weak inguinal floors and direct hernias.

Femoral Hernias

Femoral hernias are much more rare, accounting for 2% to 4% of groin hernia repairs, and can present a challenge to even the most experienced surgeon. Femoral hernias are more common in women and often present with an acute episode of incarceration, intestinal obstruction, or strangulation, so that emergency surgery is necessary. It can be difficult to reduce the hernia at surgery, and it is not uncommon to have to divide the inguinal ligament to obtain greater freedom to perform this reduction. Femoral hernias can be repaired from a lower “crural” approach, in which a transverse incision is

made over the femoral triangle in the upper thigh. The hernia is approached from below the inguinal ligament and reduced, and then the defect is closed by suturing the inguinal ligament to Cooper ligament from below. An alternative is to insert a small mesh plug into the defect and suture the periphery to the inguinal ligament and Cooper ligament.[72] If this technique is used, it is important to leave a layer of adventitial tissue between the femoral vein and the plug. The femoral vein should not be skeletonized. The repair can also be carried out from above via an inguinal approach, as in the McVay repair. The posterior floor of the inguinal canal is dissected out, and Cooper ligament is repaired after the hernia has been reduced. A third type of femoral hernia repair is the preperitoneal repair. Access to the preperitoneal space is gained through an abdominal incision or laparoscopy. A study based on the Swedish national register revealed that preperitoneal mesh techniques (both laparoscopic and open) are a better choice for women with femoral hernias.[85] For patient undergoing a Lichtenstein approach, modifications should be made to ensure evaluation of the femoral space and to address a femoral hernia if present. Prior to incising the external oblique aponeurosis, the subcutaneous tissue can be further separated from the inguinal ligament easily exposing the femoral canal. A femoral hernia from this approach will be palpated typically as a hard mass just medial to the femoral vein; reduction and repair can proceed as described above for the crural approach. Alternatively, the transversalis fascia can be incised exposing the preperitoneal fat and Cooper ligament. A femoral hernia can be reduced through this exposure and the flat sheet Lichtenstein prosthesis modified to include an inverted “triangle” that extends posteriorly overlapping Cooper ligament. This mesh extension is then suture to Cooper ligament covering the femoral space. Preperitoneal herniorrhaphies result in coverage of the entire myopectineal orifice and thus both femoral and inguinal hernias are treated. Indeed, in the Swedish study a much higher femoral recurrence rate was observed in women compared to men especially after the repair of a direct inguinal hernia. This is significant because direct hernias are rare in women providing strong evidence that the femoral hernia was actually missed at the index operation.[61]

SPORTS HERNIA/ATHLETIC PUBALGIA

The term *sports hernia* is confusing because, by definition, these patients do not actually have a hernia but rather a weakness of the posterior inguinal floor. This condition has received considerable attention in the lay press because of its prevalence in high-profile athletes involved in sports who require rapid changes in direction of the hip area such as soccer, football, basketball, track and field, tennis, and hockey. Alteration in the complex balance that must be maintained between the lower abdominal muscles and the leg adductor muscles and tendons, all revolving around the area of the pubic bone, is the final common denominator for many of the conditions that cause groin pain in up to 5% of athletes (**Fig. 72.31**).[86] The first step in approaching these patients is to make sure that one is not dealing with a cause outside of the groin with referred pain, such as lumbosacral radiculopathic pain, prostatitis, hip disease, and a gastrointestinal cause. The differential diagnosis is listed in **Table 72.7**.

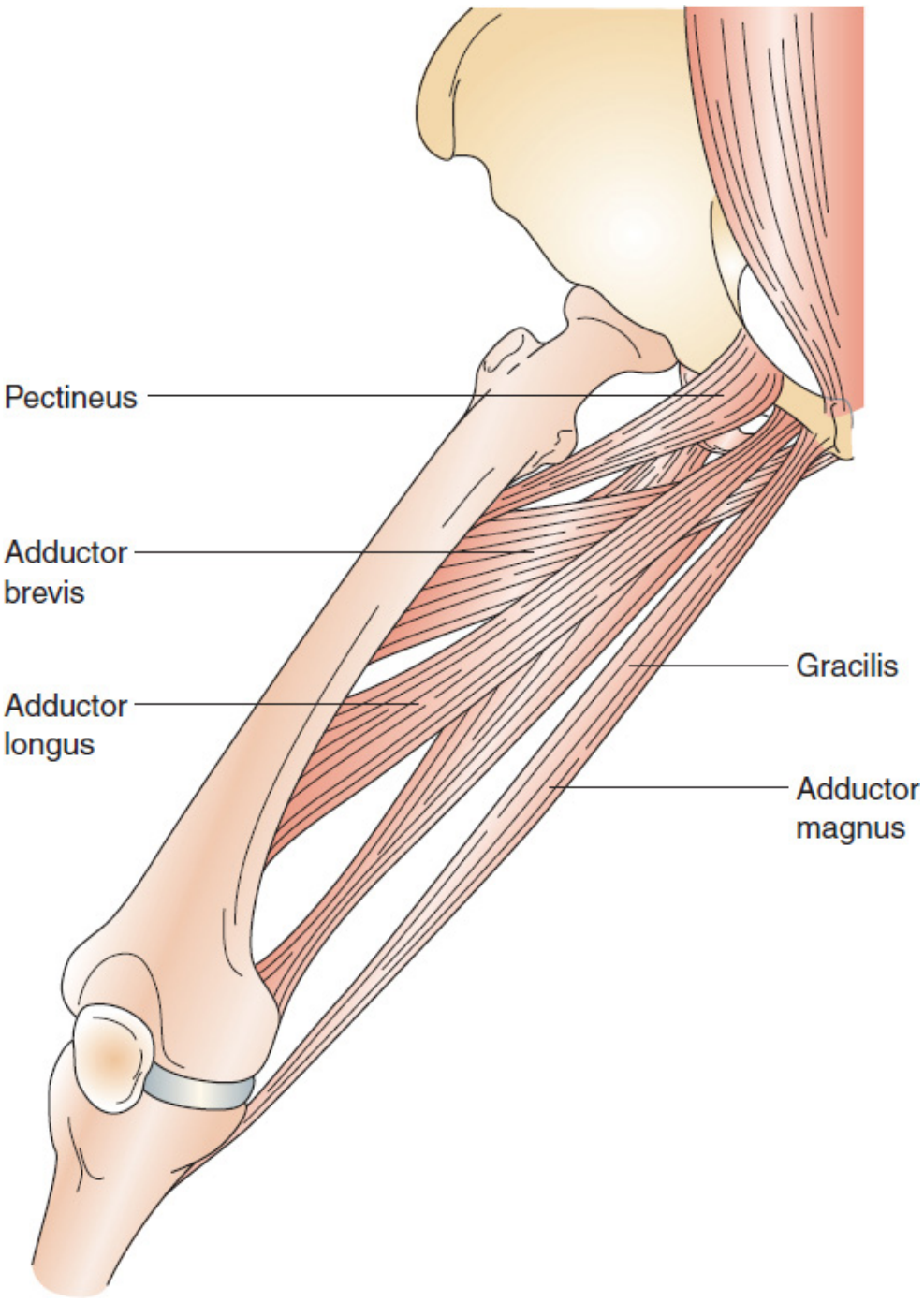


Figure 72.31 Complicated arrangement of muscle pulling in different directions that attach to the pubic bone.

Table 72.7 Conditions Other Than a Hernia Associated with Groin Pain

- Nerve entrapment
- Adductor tenoperiostitis
- Pelvic stress fractures
- Osteitis pubis
- Symphysis syndrome
- Gilmore groin (groin disruption)
- Iliopsoas bursitis
- Tendinopathies
- Posterior inguinal wall insufficiency or avulsion fractures
- Synovitis
- Osteoarthritis
- Legg–Calvé–Perthes disease
- Slipped femoral capital epiphysis
- Osteochondritis dissecans or avascular necrosis of the femoral head
- Acetabular labral tears
- Prostatitis
- Epididymitis
- Nephrolithiasis
- Urinary tract infection
- Lymphadenitis

Some authorities prefer to refer to this condition as "athletic pubalgia," as this conveys the concept that the physical examination is inconclusive and the cause of groin pain is unclear. Imaging may be performed by ultrasound, but cross-sectional imaging (CT or magnetic resonance imaging [MRI]) is the most useful diagnostic modality in the absence of a highly experienced ultrasonographer.[87] Compared to CT, MRI provides excellent overall anatomic detail especially with the development of fast imaging scanners that will allow dynamic imaging (i.e., performed during straining) with or without the addition of intraperitoneal contrast agents.

The initial treatment is conservative with mandatory inactivity, elastic immobilization bandages, ice/massage, nonsteroidal anti-inflammatory

analgesics, and occasional steroids (systemic and/or local). Physical therapy performed by a specialized practitioner can often improve symptoms. Surgery should be reserved after non-operative interventions have been performed. Although lacking clear-cut anatomic justification, a mesh hernia repair similar to either an anterior Lichtenstein or a TEP laparoscopic operation is the most popular procedure, sometimes combined with a variety of muscle reattachment procedures and tenotomies. The best results are obtained with a multidisciplinary approach including a surgeon, an orthopedist, a physical therapist, and a sports medicine physician. Not surprisingly, the results are variable given the lack of objective criteria to recommend operation but can be gratifying in some in this motivated group of patients.[88]

Complications of Inguinal Hernia Repair

Complications Related to the Patient

Urinary Retention

The most common predisposing factor for urinary retention after a hernia repair is the use of general or regional anesthesia.[67] Meta-analyses of randomized controlled trials comparing various hernia techniques performed under general anesthesia have not shown a difference in urinary retention rates.[89–92] Predisposing factors for urinary retention include overhydration with intravenous fluid during surgery, use of opioid analgesics, older age, prostatic symptoms, and prolonged operative time.[93,94] Intermittent catheterization or temporary placement of an indwelling urinary catheter is usually adequate therapy. Prophylactic and therapeutic use of alpha-adrenergic blockers including prazosin and tamsulosin has been shown in some studies as an effective strategy to prevent postoperative urinary retention.[95,96]

Ileus

Ileus can be seen with either the conventional or the laparoscopic procedure but is more common with the latter. Treatment is symptomatic, and spontaneous resolution is the rule. Nasogastric decompression is occasionally needed.

Complications Related to the Herniorrhaphy

Recurrence

The accuracy of reported recurrence rates after inguinal hernia repair comes in to question because recurrence can occur many years after the index operation (50 years or greater) making precise follow-up impossible.[97] A lower risk for recurrence with the use of prosthetic material for the repair of an inguinal hernia has been clearly proven by meta-analysis with relatively short-term follow-up.[66] Recurrence rates of 2% or less are now routinely reported from specialty centers performing either laparoscopic or conventional tension free repairs. Although the recurrence rate for hernia repairs is less than 1% at the Shouldice Clinic, others have not been able to duplicate this outstanding record with this or any of the other nonprosthetic repairs.[98] Complications during the first month after surgery; operation for recurrence; and sutured repairs without mesh, with either anterior or preperitoneal techniques, are associated with an increased recurrence rate. However, an increasing number of patients are seeking a tissue-based repair to avoid potential mesh-related complications even with higher recurrence. Formerly, a laparoscopic approach was thought to be associated with a higher chance of recurrence. This was felt to be the most likely reason for a higher recurrence rate at 2 years in a Veterans Affairs study for the laparoscopic approach (10%) compared to an open TFR (4% for the Lichtenstein repair).[99] Since that trial was performed, refinements and expertise in a laparoscopic approach to inguinal hernia repair have shown equivalent recurrence rates with possible decreased rates of chronic groin pain.[100]

A consistent definition of a recurrent hernia does not exist because of the difficulty in differentiating a lipoma of the cord, a seroma, or an expansile bulge of the internal oblique muscle from a true hernia recurrence. It may be that reoperation rates as a surrogate provides a reasonable estimate of recurrence.[101] From a clinical standpoint, a hernia should not be classified recurrent unless there is a visible bulge or there is unequivocal evidence of a hernia by an imaging modality such as ultrasound, CT, or MRI. This is especially important for patients who present with pain after their hernia repair because their pain is likely due to a preoperative condition other than the hernia or a postinguinal herniorrhaphy pain syndrome which might be

exacerbated by further groin surgery. Femoral recurrences are seen after a Lichtenstein repair because the femoral canal is not routinely closed with the classic technique.[61,97,102]

The general principle for managing recurrent hernias depends on the original repair.[103] The logical approach is to perform the herniorrhaphy in the space that has not been dissected. If the patient had a previous conventional repair, then a preperitoneal repair is best chosen. On the other hand, if the index operation was a preperitoneal one, then a repair that is performed in the conventional inguinal space is best. The dissection of the preperitoneal space after a failed herniorrhaphy has been performed is particularly challenging, with significant risk for vascular, neurologic, and bladder injury.

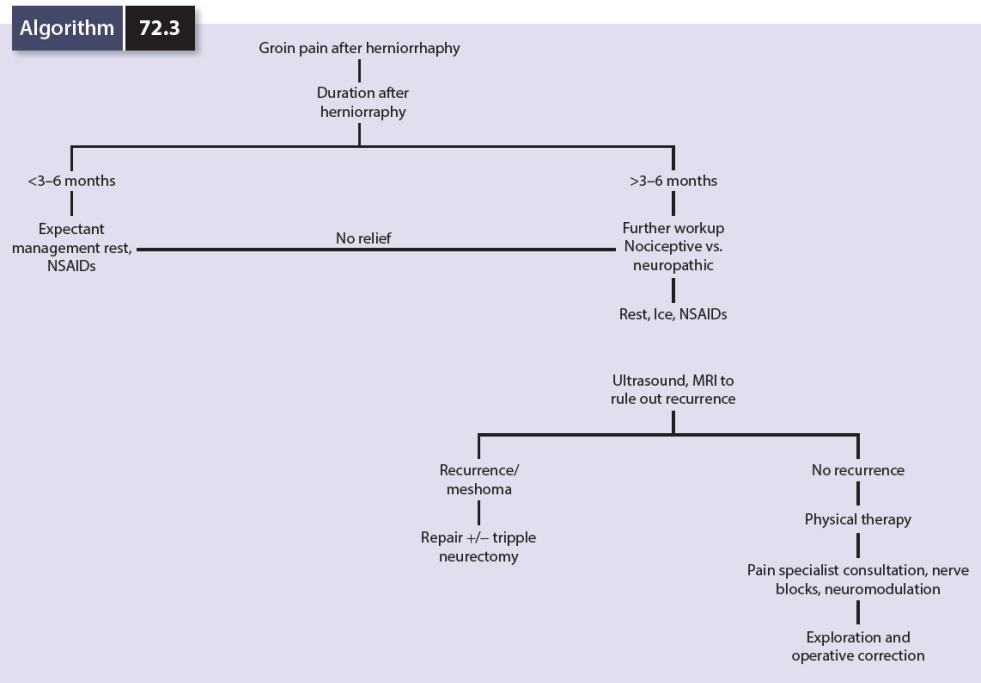
7 *Postherniorrhaphy Groin Pain*

Now that the recurrence rate has been brought down to a minimum using modern hernioplasty techniques, chronic postoperative groin pain syndromes (persisting >3 to 6 months post-surgery) have emerged as the biggest issue facing inguinal hernia surgeons (**Algorithm 72.3**). Poobalan and colleagues published a critical review of inguinal herniorrhaphy studies between 1987 and 2000.[104] The frequency of at least some long-term groin pain was as high as 53% at 1 year (range, 0% to 53%). On average, moderate or severe postherniorrhaphy groin pain probably occurs in about 10% of patients. Several factors have been suggested to be related to the development and intensity of postherniorrhaphy including psychological status, presence of preoperative pain at surgical site, nerve injury, intraoperative nerve handling, surgical technique (open vs. laparoscopic), and acute postoperative pain. Risk prediction model for persistent postoperative pain–based preoperative, intraoperative, and postoperative factors can be helpful in predicting which patients will be more likely to suffer from postherniorraphy pain.[83]

Perhaps the most important determination for patient's with chronic postherniorraphy pain is to determine if the pain is similar to that experienced before repair. There are a variety of conditions that cause groin pain (**Table 72.7**). CT, ultrasonography, herniography, laparoscopy, and MRI all have their place in the evaluation of these patients. MRI is perhaps the most beneficial because of its ability to differentiate between muscle tear,

osteitis pubis, bursitis, and stress fracture. Strain of the adductor muscle complex (adductor longus, brevis, magnus, and gracilis muscles) is commonly overlooked in this group.

True postherniorrhaphy groin pain should be divided into two types: (a) nociceptive pain, which is caused by tissue damage, is further subdivided into somatic and visceral pain, and (b) neuropathic pain due to direct nerve damage. Somatic pain is the most common and is usually caused by damage to ligaments, tendons, and muscles. Visceral pain refers to that which is related to a specific visceral function such as urination or ejaculation (see dysejaculation syndrome, later). Neuropathic pain is much less common but is important to recognize because surgical treatment is possible if the cause is incorporation of a nerve in staples or suture material. The nerves that are usually involved are the ilioinguinal nerve, the iliohypogastric nerve, both the genital and femoral branches of the genitofemoral nerve, and the lateral cutaneous nerve of the thigh. The former two are especially prone to injury during a conventional herniorrhaphy, whereas the latter are most likely damaged during laparoscopy. A femoral nerve injury is extremely rare and is usually the result of a gross technical misadventure. Pain and/or paraesthesia in their distribution characterize patients' symptoms for the more common nerves. There is significant overlap of these nerves, and therefore, it is commonly difficult to sort out exactly which nerve is damaged. Both nociceptive and neuropathic pain is best treated initially with reassurance and conservative treatment with anti-inflammatory medications and local nerve blocks because these will frequently resolve spontaneously. An exception is the patient who complains of severe pain immediately (i.e., in the recovery room). This patient may be best served by immediate reexploration before scar tissue develops. When groin exploration is required, triple neurectomy and neuroma excision, adhesiolysis, and foreign body removal (i.e., mesh or suture) are options for treatment. The patients reoperated for persistent pain after hernia surgery often experience a reduction in pain, but a small percentage of patients experience no relief or even worsening of their symptoms.[105] Given the heterogeneity of the problem, further well-designed studies are necessary to identify patient population that may benefit the most from surgical intervention. It cannot be overemphasized that these complex patients should be evaluated and treated at centers with specific multidisciplinary expertise in this area.



Algorithm 72.3 Management of groin pain after herniorraphy.

Cord and Testicles

Infertility

Infertility caused by inguinal hernia surgery is a recognized complication. The cause of infertility can be related to either the vas deferens or the testicle. The incidence of injury to the vas deferens during inguinal herniorrhaphy has been estimated at 0.3% for adults and between 0.8% and 2% for children.[106] Injury to the testicle, which eventually leads to atrophy, is estimated to occur in about 0.5% for primary hernia repairs but increases 10-fold to 5% for recurrent repairs. Injuries to the vas deferens that may present as an obstruction include division, ligation, clipping, stapling, electrocauterization, devascularization, and scarification. In addition, there is evidence that there is a small subset of patients whose inflammatory response to mesh is so severe that vasal obstruction results.[107] In addition to obstruction, traction injuries during normal cord mobilization may damage the muscular layer of the vas deferens, which then interferes with rapid sperm transfer during ejaculation.[108] Sperm antibodies may develop as a result of extravasation of sperm at an injury site, which is why a unilateral injury can also result in infertility. The role of mesh in the causation of infertility has been implicated by some small case series and case reports.

Ironically, one of the major arguments for the routine use of mesh in inguinal hernia surgery is to preserve fertility. The theory is that by decreasing the generally accepted recurrence rate in the general population from 10% to 15% seen with Bassini and its variants to less than 5% with the mesh tension-free approach, reoperative surgery, with its heavy toll of testicular loss, is avoided.[109]

Ischemic Orchitis

Damage to the blood supply of the testicle can cause ischemic orchitis and testicular atrophy.[108] Ischemic orchitis occurs in about 1% of primary hernioplasties but is much more common with operations performed for recurrent hernias.[110] It manifests as postoperative inflammation of the testicle developing within 1 to 2 days after surgery. The patient has a painfully enlarged testicle that is hard in consistency and associated with low-grade fever. Pain is severe and may last several weeks. Ischemic orchitis is caused by thrombosis of the veins draining the testicle after extensive dissection of the spermatic cord. It is generally accepted that the incidence can be decreased by division of large inguinal–scrotal sacs leaving the distal sac open in situ rather than excising it.[111] The majority of patients with testicular swelling as an immediate complication of herniorrhaphy recover without testicular atrophy. In one report, testicular atrophy developed in 19 patients among 52,583 primary inguinal hernia repairs (0.036%) and 33 patients among 7,169 recurrent inguinal hernia repairs (0.46%).[112] A substantial number of patients who develop testicular atrophy after inguinal herniorrhaphy have no history of a testicular problem at the time of the index operation. The management of a patient with ischemic orchitis is usually conservative with elevation and anti-inflammatory medication. Antibiotics and steroids have been used but their value is unproved.

Miscellaneous

Hydroceles occasionally develop after inguinal herniorrhaphy, but the cause is not known and therefore a preventative measure is not possible. The urologic literature suggests that the practice of leaving the distal aspect of an indirect inguinal sac in situ rather than removing it should be incriminated, but this is not accepted by most experienced hernia surgeons. The treatment is the same as for any other hydrocele. Testicular descent is a complication

felt to be related to complete division of the cremasteric muscle, but the occurrence is variable. The cord structures lose their tethering effect, allowing the testicle to descend into the most dependent portion of the scrotum. Due to the elasticity of the scrotum, with time, gravity causes the scrotum to elongate. Patients complain their testicle "drops into the toilet" and can be quite unhappy. Few hernia surgeons now routinely completely divide the cremasteric muscle, so it is hoped that this will become a rare phenomenon. The dysejaculation syndrome is characterized by searing, burning, painful sensations throughout the groin around the time of ejaculation. The incidence is approximately 0.04%.[111]

Wound Infection

This is a surprisingly rare complication of groin herniorrhaphy (<5%) and the reason for the "protected" status, especially when compared to prosthetic ventral herniorrhaphy, is not known.[111] Most cases of necrotizing fascitis following inguinal hernia repair have been associated with either strangulated bowel or appendicitis in the hernia sac. Necrotizing fasciitis has only previously been reported in a few cases following elective hernia repair. Other factors leading to infection are pre-existing infection or ulceration of the skin over the hernia, obesity, incarcerated or obstructed bowel within the hernia, and perforation of the bowel at the time of hernia repair. Untreated seromas can become secondarily infected. It is not always necessary to remove the mesh prosthesis in the presence of infection. A trial of local wound care after opening of the incision and debridement is warranted.

Seromas

Seromas are common with extensive flap dissection in large hernias and with the use of synthetic mesh in laparoscopic hernia repairs and are possibly related to the size of the mesh used. The fluid eventually resorbs spontaneously. Aspiration is performed for symptomatic relief only in rare instances of severe pain. Strategies to prevent and manage seromas are largely based on empiricism and personal opinion, as objective data are nearly absent.

Bleeding

Hemorrhage can occur from the cremasteric, internal spermatic, or inferior epigastric vessels. Conservative treatment with reassurance is preferred for a stable hematoma. Evacuation is rarely required. Injuries to the deep circumflex artery, the corona mortis, or the external iliac vessels may result in a large retroperitoneal hematoma.

Prosthetic Complications

Shrinkage of polypropylene and other meshes should be considered by surgeons when performing prosthetic repairs. The decrease in size is felt to be due to scarification of the recipient's tissue. Intestinal obstruction or fistulization is possible by erosion, especially if there is physical contact between intestine and the prosthesis. Rejection because of an allergic response is possible but extremely rare. What patients cite as "rejection" of the mesh is usually the result of infection. Local erosion into the cord structures has also been reported.[113]

Complications Related to Laparoscopy

Vascular Injury

These are for the most part related to access. The most serious injuries occur to vessels that reside in the retroperitoneum. For all laparoscopic procedures, the risk for major vascular injury that requires operative intervention is 0.9 per 1,000 cases.[114] The vessels most at risk are the distal aorta, common iliac arteries and veins, and inferior vena cava and the inferior epigastric vessels. Injuries to the renal vessels have also been reported. These vessels are fixed and may be penetrated even if the safety mechanisms of the needle or trocar are working properly. The mesenteric and omental vessels are also at risk, especially in the presence of adhesions. The epigastric arteries may be injured with secondary cannula placement.

The insufflation needle is the most common cause of vascular injury but may be self-limiting; on the other hand, injuries caused by a trocar are usually more obvious and catastrophic. The mortality associated with retroperitoneal injury secondary to trocar insertion ranges from 9% to 36%, even with rapid identification and repair. When retroperitoneal trocar injury is suspected, immediate conventional laparotomy is almost always indicated. Most abdominal wall vascular complications occur during the placement of secondary cannulas. Usually, pressure can be applied to bleeding at the

trocar site with the cannula. Occasionally, suture ligation is required, which has been simplified by the development of disposable "exit devices" designed to facilitate the placement of fascial sutures. Most of these complications can be avoided by placing the secondary trocars under direct vision.

Gas Embolism

This is caused by intravascular insufflation.[115] It is an uncommon complication, unique to the needle insufflation technique. Careful attention to tests confirming proper peritoneal needle placement will keep the incidence of this complication low.

Visceral Injury

Visceral injuries are uncommon, occurring in 1.8 per 1,000 cases of all laparoscopic procedures, but they have a mortality rate of 5%.[114] The most common means of injury is the insufflation needle. Simple repair laparoscopically is usually possible as most are self-limiting. If the injury is caused by a trocar, formal repair of the injury will be needed. The injury can be repaired laparoscopically if the skill of the laparoscopic surgeon is sufficient. Otherwise, laparotomy is mandatory. Quite often, these injuries go unnoticed at the time of insult, so that visceral injury is the most common cause of late morbidity and mortality associated with laparoscopic access. Patients typically present with peritonitis and sepsis 2 days to 1 week after surgery.

Bladder Injury

Bladder injury can be the result of a laparoscopic misadventure or can be directly related to the herniorrhaphy. Laparoscopic peritoneal access can result in a bladder perforation, usually the result of failure to decompress a distended bladder. Less commonly, injury is associated with a congenital bladder abnormality. Bladder injury has not been reported with the open access technique. Injury to the bladder can also occur during secondary suprapubic trocar placement during the course of an operation. When bladder injury occurs, it is usually obvious. After Veress needle insertion, urine is withdrawn into the syringe, or blood and gas are noticed in the urine if the patient is catheterized. In questionable cases, methylene blue dye may be instilled into the bladder to look for leakage. Bladder injury recognized

during laparoscopy should be repaired laparoscopically provided the experience of the surgeon is sufficient. This should be followed by bladder drainage for 7 to 10 days.

Bladder injury may present in a delayed fashion with hematuria and lower abdominal discomfort. A retrograde cystogram usually confirms the diagnosis. Small defects may be managed with postoperative decompression via an indwelling catheter for urinary drainage, while larger defects necessitate repair. The bladder is especially prone to injury during preperitoneal herniorrhaphies or when the preperitoneal space has previously been dissected (e.g., previous preperitoneal hernia repair or prostatectomy).[116]

Bowel Obstruction

This problem plagued the developmental stages of laparoscopic inguinal herniorrhaphy for two reasons. First, the importance of closing trocar sites at the fascial level if greater than 5 mm was not appreciated, resulting in the occasional patient with an incarcerated or strangulated ventral hernia at the trocar site, leading to the clinical presentation of a bowel obstruction. There are now several different types of reusable and disposable appliances designed to facilitate trocar site fascial closure, which should minimize the incidence of these hernias. The second is inadequate peritoneal closure over the prosthesis, which allows bowel to migrate into the preperitoneal space, also resulting in intestinal obstruction. Steps taken to avoid tension at the peritoneal closure site (see TAPP technique section) have decreased this problem. Theoretically, the TEP procedure eliminates the possibility of this complication because the abdomen is not entered. However, inadvertent breaches of the peritoneum during a TEP herniorrhaphy are common, especially in patients with thin peritoneum or those who have scar tissue associated with previous lower abdominal surgery. These peritoneal lacerations can be difficult to recognize because they are not in the visual field of the limited working space, and indeed, intestinal obstruction has been reported.[117]

Diaphragmatic Dysfunction

Phrenic nerve palsy has been reported with a variety of laparoscopic procedures; it is usually transient but has been known to require a short

period of mechanical ventilation. Stretching during the pneumoperitoneum probably causes this complication.

Hypercapnia

This is the result of inadequate compensatory ventilation given the fact that, in the vast majority of laparoscopic procedures, carbon dioxide is used as the insufflating agent.

VENTRAL ABDOMINAL WALL HERNIAS

Repair of ventral abdominal wall hernia is one of the most common procedures performed by a general surgeon. Ventral hernias comprise a diverse group of hernias and are best divided into their various subtypes when discussing surgical management because the natural history as well as results of operations varies depending on the specific hernia. Ventral hernia should be distinguished from pseudohernia which is a condition that occurs in patients with denervation of the abdominal wall musculature (e.g., after polio or flank incisions). The abdominal wall muscles bulge forward on straining and have the appearance of a hernia but no frank fascial defect can be discerned on physical examination or cross-sectional imaging. **Table 72.8** uses the common terminology familiar to all surgeons for classifying abdominal wall hernias. **Table 72.9** is a classification system published by Zollinger that expands upon **Table 72.8** by further subdividing ventral hernias based on etiology.[117] An expert panel of European Hernia Society proposed a grid classification system of incisional hernias based on localization, size, recurrences, and symptoms (**Table 72.10**)[118,119] and the Ventral Hernia Working Group (VHWG)[119] (**Table 72.11**) has proposed a grading system for ventral hernias based on risk of postoperative surgical site occurrences (SSOs).

Table 72.8 Classification of Ventral Abdominal Wall Hernias
Incisional
Umbilical and paraumbilical
Epigastric
Parastomal
Less common variations Spigelian hernias Interparietal hernia Richter hernia Miscellaneous

Table 72.9 Zollinger Classification of Ventral Abdominal Wall Hernias

Congenital Omphalocele Gastroschisis Umbilical (infant)
Acquired
Midline Diastasis recti Epigastric Umbilical Adult, acquired, paraumbilical
Median Supravesical Anterior, posterior lateral Paramedian Spigelian Interparietal
Incisional Midline Paramedian Transverse Special operative sites
Traumatic Penetrating, auto-penetrating Blunt Focal, minimal injury Moderate injury Extensive force or shear Destructive

Table 72.10 European Hernia Society (EHS) Classification of Incisional Hernia

Midline	Subxiphoid	M1
	Epigastric	M2
	Umbilical	M3
	Infraumbilical	M4
	Suprapubic	M5
Lateral	Subcostal	L1
	Flank	L2
	Iliac	L3
	Lumbar	L4
Recurrent incisional hernia	Yes	No
Length (cm)		Width (cm)
Width		W1
<4 cm		W2
4–10 cm		W3
>10 cm		

Table 72.11 Ventral Hernia Working Group (VHWG) Classification of Incisional Hernia

Grade 1	Grade 2 Comorbid	Grade 3 Potentially Contaminated	Grade 4 Infected
Low risk of complications	Smoker	Previous wound infection	Infected mesh
No history of wound infections	Obese	Stoma present	Septic dehiscence
	Diabetic	Violation of gastrointestinal tract	
	Immunosuppressed		
	COPD		

UMBILICAL AND PERIUMBILICAL HERNIAS

Umbilical and periumbilical hernias are usually congenital, caused by arrest of the normal spontaneous closure of the umbilical ring through which umbilical blood vessels pass in the developing fetus, which results in a defect in the fascia covered by skin. In infants, the fascial defect varies in size but is most commonly 1 to 2 cm. A large proportion of pediatric umbilical hernias heal spontaneously, and 80% of them close by the time the patient is 2 years old. This is the only abdominal wall defect genetically programmed to close. Persistent umbilical hernias require surgery. In older patients, the onset is often sudden and the defect is relatively small. There are several syndromes associated with umbilical hernias such as mucopolysaccharide storage diseases, Beckwith–Wiedemann syndrome, and Down syndrome. Predisposing factors for the development of umbilical hernias in adults are multiple pregnancies, obesity, cirrhosis with ascites, and large abdominal tumors, all of which cause an increase in intra-abdominal pressure.[120] Male gender is also a risk factor with the peak incidence of repair at about age 60 years.[121] The differential diagnosis includes the varicosities that extend radially from the umbilicus in persons with portal hypertension, the so-called caput medusae (**Fig. 72.32**). The varicosities have a bluish discoloration and fill when the patient is straining. A metastatic deposit of intra-abdominal cancer at the umbilicus may mimic umbilical herniation. Cancer cells reach this area via lymphatics in the falciform ligament. Metastasis presents as a hard nodule, and biopsy is diagnostic. Other periumbilical masses that can be confused with an umbilical hernia include umbilical granulomas, epidermal inclusion cysts, omphalomesenteric duct remnant cysts, and urachal cysts.

The management of umbilical hernias is nonoperative in children up to the age of 2 or 3 years because spontaneous closure is the rule. In those who require surgery, adults or children, several repair options are available. For open repairs, an infraumbilical semilunar incision is made and the hernia identified. There may or may not be a true peritoneal sac, as smaller hernias usually consist of preperitoneal fat only. If a sac is present, it can be opened and the contents reduced into the abdomen. Alternatively, the hernia can be dissected circumferentially to the fascial opening and reduced without entering the peritoneal cavity. The dissection can be continued beneath the

fascia creating a preperitoneal space for the placement of a prosthesis, if needed. Several techniques can be used to close the fascial defect. Simple suture repair with interrupted, running, or figure-8 sutures, either absorbable or permanent is commonplace, accounting for more than 50% of umbilical hernia repairs.[122] There is no clear evidence as to which of these suture techniques is optimal. There is evidence of lower recurrence rate with permanent suture repair compared to fast-absorbing suture.[123] Slow-absorbing suture is acceptable and has the benefit of no residual foreign body presence that can lead to subsequent infection/granuloma. In 1901, James Mayo described the classic overlapping, vest-over-pants (double-breasting or waistcoat) technique, which bears the name of his clinic, in which the upper edge of the linea alba overlaps the lower edge (**Fig. 72.33**).[124] The operation is losing popularity now because it is generally not consistent with the tension-free concept popular in hernia surgery today.[125] It requires more dissection than other procedures to create the flaps and is therefore more painful. Suture herniorrhaphy is the easiest procedure for repair, but has the highest recurrence rate. Factors known to increase recurrence include high body mass index (BMI), diabetes, smoking, and hernia size. Despite the higher recurrence rate for suture repair compared to mesh repair, the rate of recurrence is still relatively low; 10% for umbilical hernias smaller than 1 to 2 cm.[126] Conversely, 90% of patients do well with a suture repair long term without mesh prosthesis. Recurrence, if encountered, can usually be easily addressed at a subsequent operation typically using mesh.

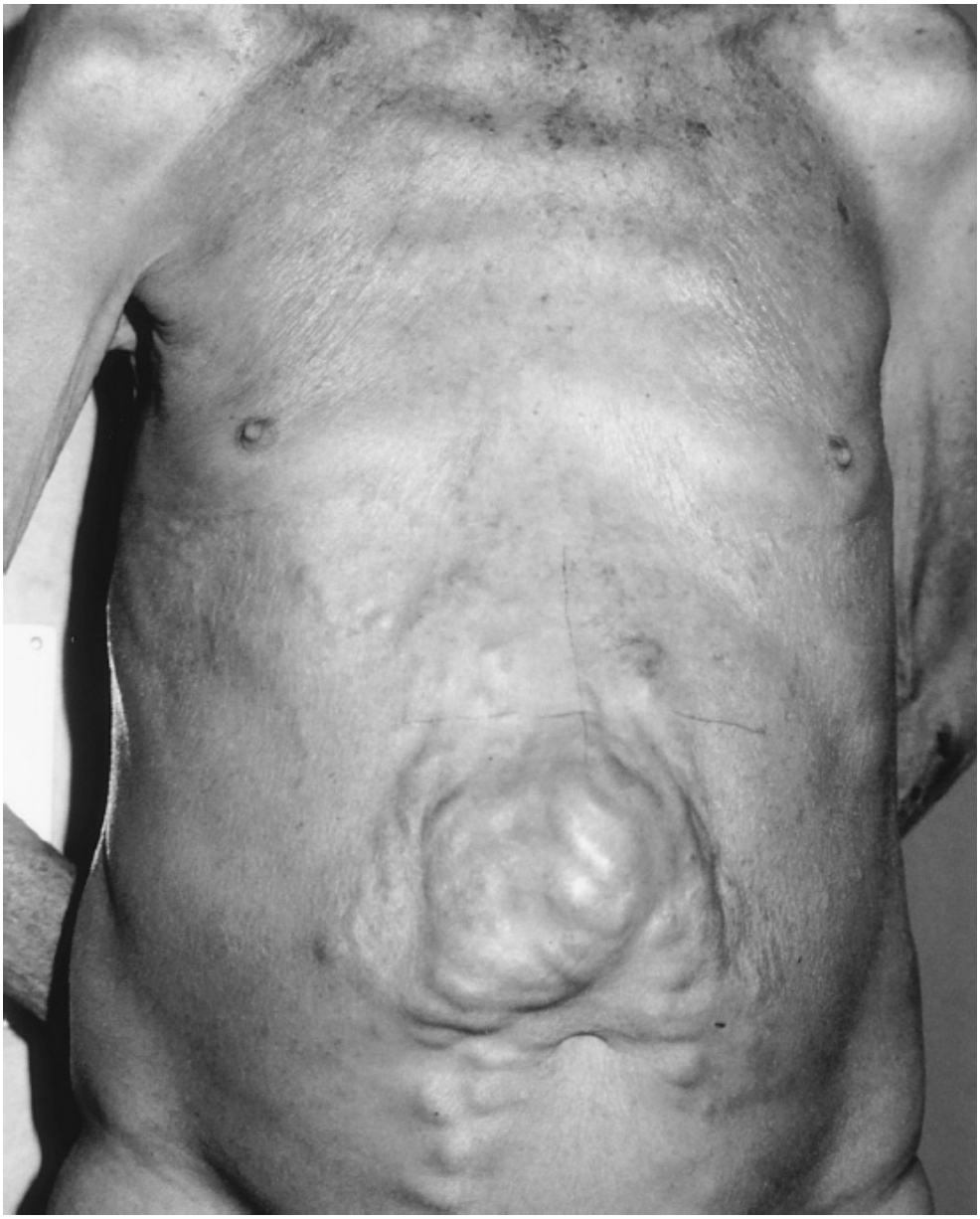


Figure 72.32 Caput medusae. Large periumbilical collaterals in a patient with portal hypertension.

For larger hernias, particularly in adults, the preperitoneal space can be exploited by bluntly dissecting the peritoneum from the undersurface of the posterior rectus sheath for enough distance to be able to place an appropriate prosthesis. A mesh prosthesis is placed in the preperitoneal space and then the fascial edges defect closed. Alternatively, intraperitoneal placement using a barrier-coated mesh (see prosthetic materials section) can be performed in the event of small defects through which preperitoneal

dissection is difficult, if the preperitoneal space plane cannot be maintained, or surgeon preference. It is still important to dissect the preperitoneal fat of the falciform ligament and median umbilical ligament to ensure proper seating of the mesh against the abdominal wall and prevent reherniation of the preperitoneal fat. Recent results from a multicenter randomized control trial suggest a higher complication rate for intraperitoneal versus preperitoneal mesh for umbilical hernia,[127] which has been seen in some other retrospective studies of intraperitoneal mesh as well.[55,57,128]

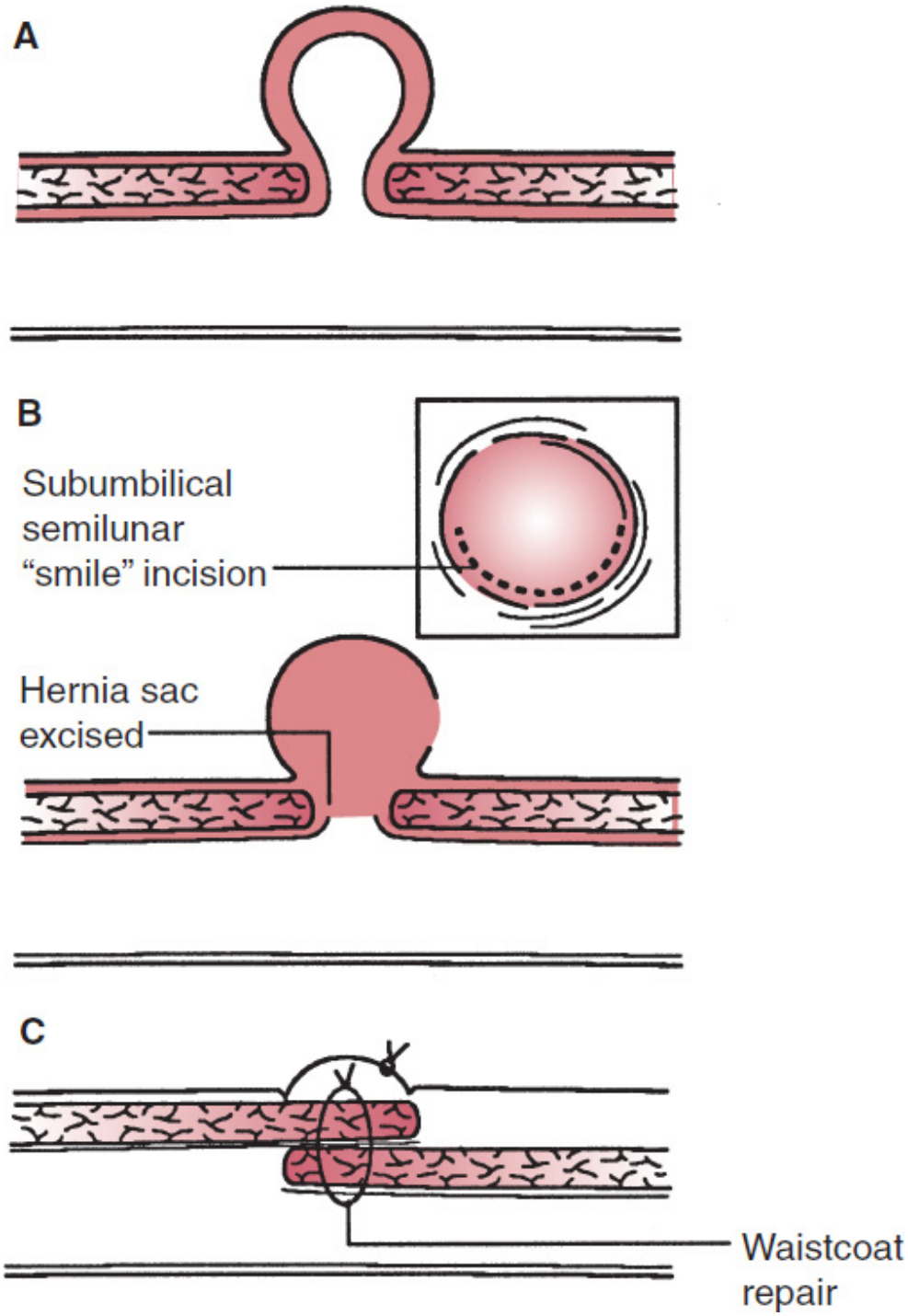


Figure 72.33 Mayo repair of an umbilical hernia. **A:** Diagram of longitudinal section through the hernia. **B:** Subumbilical "smile" incision. The hernia sac is excised. **C:** Waistcoat type of closure.

A laparoscopic or robotic approach for umbilical hernias is a good option as well, particularly for recurrent defects or hernias with larger than 3 cm.

There may be some benefit to this approach, including decreased operative time and faster return to normal activity. The technical details are similar to those of a laparoscopic incisional hernia repair (see incisional hernia section). With the advent of robotic-assisted surgery, a TAPP approach is increasingly popular, emulating the open preperitoneal repair in a minimally invasive fashion. While this can be performed either laparoscopically or robotically, a robotic-assisted repair may facilitate more reliable defect closure.[129–131]

EPIGASTRIC HERNIAS

Epigastric hernias occur through a defect in the linea alba. In the majority of these patients, only a single decussation of the fibers of the linea alba is present rather than the usual triple decussation (**Fig. 72.7**). The incidence of epigastric herniation reported varies from less than 1% to as high as 5%. Epigastric hernias are more common in woman than men with a peak incidence of repair around age 40 years.[121] About 50% of them are asymptomatic. Most are less than 1 cm and contain only incarcerated preperitoneal fat without a peritoneal sac. For this reason, epigastric hernias commonly cannot be visualized with laparoscopy. Patients complain of a painful nodule in the upper midline. Repair by reduction of the preperitoneal fat and simple closure of the defect is curative. These hernias are prone to recur, with rates as high as 10%, which has led many surgeons to routinely include a prosthetic underlay just as in umbilical or incisional hernias.

Left untreated, an epigastric hernia can become large enough for a peritoneal sac to form, into which the intra-abdominal contents can protrude. The sac is usually wide, and serious complications are not common. About 20% are multiple, and this needs to be ascertained prior to operation if all the defects are to be addressed, because after anesthesia induction, they can be difficult to identify.

In *diastasis recti,* the two rectus muscles are widely separated, with an intact, but stretched linea alba that protrudes like a fin. The condition rarely produces surgical complications and therefore surgical correction is not routinely recommended. However, many patients find the defect affects their self-image, abdominal core stability, and quality of life and request

treatment. They should be cautioned that many insurance companies consider this a cosmetic defect and will not reimburse. Surgery involves removal of a strip of the weakened linea alba and reapproximation, plication, of the widened linea alba, or mesh reinforcement in a sublay fashion, typically the retromuscular space. An alternative is a mesh repair performed laparoscopically. The management of diastasis, especially in our postpartum patients, needs additional research to gain information on appropriate therapies. These problems can greatly affect core stability similar to ventral hernia. Olsson et al. have demonstrated a link between surgical intervention for postpartum diastasis and improvement in pelvic floor function.[132] This is the first empiric evidence that elements of the abdominal core musculature function in an interdependent fashion as a cohesive unit. Importantly, this lends evidence that diastasis represents a diseased anterior abdominal wall with functional implications; it is not solely an issue of cosmesis.

INCISIONAL HERNIAS

Incisional hernias can complicate any type of abdominal surgery, regardless of the type of incision. The highest incidence is with midline laparotomy incisions when compared to, transverse incisions, paramedian incisions, pfannensteil incisions, and laparoscopic trocar sites.[133,134] Despite this fact, surgeons continue to prefer midline laparotomies because it provides better access to the entire abdomen.. More than 2 million laparotomies are performed yearly in the United States, with an estimated incidence of an associated IH on average felt to be between 10% and 20%, but higher incidence rates of up to 69% have been reported depending upon the patient population being studied.[135] The variability in the incidence rates is due to many contributing factors including patient-related comorbidities and technical factors during the surgery. Patients with certain diseases, such as diverticulitis and abdominal aortic aneurysm (AAA), are more prone to develop an incisional hernia when they require surgical intervention.[136,137]

The cumulative incidence of incisional hernias is linear, as they can present after considerable delay following the index operation. Poor surgical technique, rough handling of tissues, use of rapidly degraded absorbable suture materials, closure of the abdomen under tension, and infection of the

wound are technical causes of incisional hernias. Morbid obesity, cigarette smoking, pulmonary disease, debilitation from cancer, chemotherapy, the use of steroids, hypoalbuminemia, and other pre-existing comorbid conditions are patient factors that have been incriminated. Patients with a history of aortic aneurysm or a proven defect in collagen metabolism also exhibit an increased incidence of incisional hernias.[138] Read and Yoder in a retrospective review found that 17% of incisional hernias are incarcerated or strangulated at presentation.[139] The consequences of unrepaired enlarging symptomatic hernias include loss of abdominal domain; significant biomechanical alterations that affect posture; compromise of activities of daily living, including lifting and straining; and poor cosmetics. Most of the published literature on treatment options addresses midline defects. The management of nonmidline incisional hernias (i.e., subcostal, transverse, or gridiron incisions) to some extent must be extrapolated.[140]

At least some ventral hernias can be prevented by proper abdominal closure after a laparotomy. Slowly absorbable monofilament should be placed in the aponeurosis only 5 to 8 mm from the wound edge, not to include muscle, 4 to 5 mm apart in a single layer, creating at least a 4:1 suture length to wound length ratio. Two recent randomized control trials demonstrate the superiority of this small-bite technique compared to traditional large-bite technique in the prevention of incisional hernia.[141,142] Studies have shown that nonabsorbable sutures result in a lower incidence of incisional herniation but at the cost of increased wound pain and chronic suture sinuses when they become infected.[116] These suture sinuses tend to be multiple and take years to eradicate by probing the sinus tracks and removing deep sutures. The development of better monofilament absorbable sutures has caused most surgeons to use a slowly absorbable monofilament suture.[111] Using small needles is recommended to avoid including excessive amounts of tissue. By measuring the suture remnants in relationship to the total length of the suture, one can calculate a suture length to wound length ratio which should never be less than 4.[143] Several studies have also demonstrated the benefit of prophylactic mesh at the time of initial laparotomy, which can be placed in the retromuscular sublay or onlay position.[144–147] While this approach does significantly reduce the risk of incisional hernia, adoption is slow, likely due to concern for mesh-related complications, lack of reimbursement for the procedure, and medicolegal concerns.

Another common practice after laparotomy is to prescribe abdominal binders. Although most surgeons prescribe abdominal binders following laparotomy, there is no evidence that these devices decrease pain; improve respiratory function; or prevent incisional hernias, seroma formation, or wound complications. The use of a binder may provide some comfort in the immediate postoperative period to some patients and should be recommended for this purpose only.[148,149]

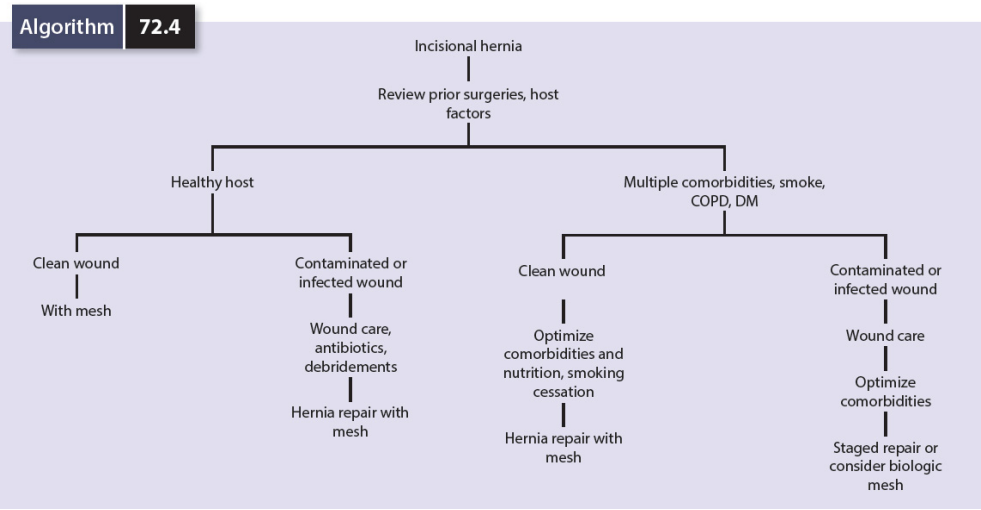
Treatment of Ventral Hernias

General Principles

As described above, the abdominal wall is a complex unit of the abdominal core and plays an important role in respiration, defecation, micturition, movement of the trunk, and protection of intra-abdominal organs (**Algorithm 72.4**). It has been shown that health-related quality of life improves after ventral incisional hernia repair, presumably related to improved abdominal 8 wall function.[150] Additionally, there is some risk of acute incarceration or strangulation, though this risk is likely fairly low and watchful waiting is appropriate for many patients. A variety of surgical techniques can be used to repair abdominal wall defects. There is considerable debate as to the gold standard for repair, in part due to the lack of prospective randomized trials comparing surgical techniques, but also due to the significant heterogeneity that is inherent to hernia repair. Considering the choice of surgical approach (open, laparoscopic, or robotic), the massive catalog of available mesh, the choice of position in the abdominal wall (onlay, retromuscular, preperitoneal, or intraperitoneal), and the number of mesh fixation options, combined with widely varied hernia morphology and patient comorbidities, it is no surprise the optimal repair has not yet been determined in the literature. Many experts believe that reapproximation of rectus muscles in the midline restores functional abdominal wall anatomy and is recommended if it can be performed without excessive tension.

Preoperative Preparation

Successful management of ventral hernias begins with appropriate preoperative evaluation and optimization. Many of these patients have had multiple prior surgeries, including previous attempts at hernia repair and it is important for the surgeon to obtain and review all the previous operative reports and evaluate the nature of previous surgeries, incision types, and closure techniques. Preoperative imaging may be necessary to delineate the extent of the hernia, the defect size, the morphology of the hernia and the abdominal wall musculature, or estimate the volumes of the hernia and the abdominal cavity in the case of loss of domain. Ultrasound and CT imaging is appropriate, though CT is generally preferred for more complex hernias.



Algorithm 72.4 Management of incisional hernia.

Patient factors, such as smoking, obesity, COPD, and diabetes are major contributors to failure of ventral hernia repair and perioperative complications. Smoking cessation is advocated by most surgeons for at least 4 weeks prior to complex ventral hernia repair. Obesity increases both the wound complications and risk of hernia recurrence, and many surgeons recommend against repair at BMI >40 kg/m^2.[151,152] Options include concurrent hernia repair with bariatric surgery, neoadjuvant bariatric surgery with delayed definitive repair of the abdominal wall, waiting for self-directed or medically supervised weight loss, or proceeding with a higher risk repair. The optimal strategy for these patients is difficult, as the surgeon must weigh the patients ability to lose weight, access to bariatric surgery, and the symptoms and risk of the hernia itself. Diabetes should be well

controlled, through there are currently no clear guidelines on optimal control before proceeding with hernia repair. Cardiopulmonary risk stratification is often needed in high-risk patients as well. Finally, there is increased attention given to preoperative nutritional optimization prior to hernia repair, with may improve perioperative morbidity, but evidence of improved hernia outcomes is lacking.

On the day of surgery, special attention must be paid to the administration of thromboembolism prophylaxis and preoperative antibiotics. An iodophor skin barrier may be used to decrease mesh contact with the skin. In the operating room, sharp debridement of devitalized or infected tissues is recommended and sometimes a staged approach for hernia repair is necessary. Prior to abdominal wall closure, attention should be paid to ventilator mechanics as rising peak and plateau pressures can be early signs of abdominal compartment syndrome.

Surgical Techniques

This section outlines several specific options for hernia repair. Detailing all possible manifestations and subtleties of each of these procedures, its complications, indications, and long-term outcomes is beyond the scope of this chapter, and much remains unsettled in the literature. As such, this should be considered a guide to the options available for repair. Complications specific to each surgical technique are discussed along with each section. Detailed definitions of these complications are discussed later in the chapter.

Nonprosthetic Repairs

Traditionally, the repair of an incisional hernia depended on the size of the hernia. If the defect was solitary and 3 cm or less, primary closure with nonabsorbable suture material was recommended. However, there is ample evidence, most notably the landmark prospective randomized trial by Luijendijk et al.,[153] and the 10-year completion of that study by Burger et al.,[154] that prosthetic mesh repair significantly decreases the risk of hernia recurrence compared to non-mesh repair, with rates of hernia recurrence after suture repair alone approaching 70%.[153,155] These investigators found a 50% reduction in the recurrence rate when a prosthesis was used, and this

even applied to small hernias (<10 cm^2). For this reason, a simple, nonprosthetic technique should be reserved for smaller hernias in patients with low-risk factors for further recurrence. With increasing recurrences observed over time regardless of mesh use, we are beginning to understand that ventral hernia is a chronic disease process. It may be simplistic to think of "recurrence rates" in the traditional sense with the implication that hernia recurrence is completely unanticipated. It may be more appropriate to think in terms of years of durability of a repair with an array of treatments needed for a particular patient over time. Some patients may be wish to undergo initial primary repair of even larger hernias without mesh especially considering the rate of long-term catastrophic complications with mesh use is largely unknown.

Prosthetic Repairs

The concept of prosthetic mesh repair of abdominal wall hernias was proposed by Usher and colleagues in 1958 using a polypropylene mesh.[156] Since that time, a massive proliferation of mesh products has occurred, particularly after the advent of laparoscopic repair. These are outlined above. The importance of understanding the physical properties of mesh and where it is positioned within the abdominal wall at the time of repair cannot be overstated (**Fig. 72.34**). The mesh material, fiber construct, pore size, fiber density and strength, barrier coating, and layer of the abdominal in which it is placed largely determine the risk of infection, mesh salvage in the event of infection, and the risk of hernia recurrence. Additional understanding of surgical technique, such as optimal mesh overlap beyond the borders of the hernia, appropriate mesh fixation, and choice of surgical approach are also critical. Details of mesh types and characteristics are discussed above. Here we focus on surgical technique and mesh utilization.

Onlay Prosthetic Technique

The onlay repair involves dissection of the subcutaneous fat away from the underlying anterior rectus fascia circumferentially around the hernia defect. The defect is closed, and mesh placed directly on the anterior rectus fascia. Typically a noncoated permanent synthetic mesh is used, and fixation techniques vary. Technically, this is probably the simplest repair, as the tissue planes are familiar and easy to identify, and has the potential

advantage of not requiring entry into the abdominal cavity. However, closure of larger defects with this approach may result in excessive tension, requiring some additional myofascial release for defect closure, increasing the complexity and risk of the operation. This technique has the highest rate of surgical site infection (SSI) and SSOs due to the subcutaneous dissection required. This space is inherently poorly vascularized, and dissection may further obliterate the periumbilical epigastric perforators, leading to increased risk of infection, seroma, or abdominal wall ischemia and necrosis. Patients should be well selected for this technique and have overall low preoperative wound risk. From a technical standpoint, care should be taken to preserve the vascular perforators in the subcutaneous space. Also, the thin layer of lymphatics immediately anterior to the fascial layer of the anterior abdominal wall should be preserved. Wound complications occur in up to 20% of traditional onlay repairs. With careful patient selection and using fibrin glue as an adjunct with midweight macroporous polypropylene, SSI and SSO rates are comparable to sublay placement of mesh.[157] Additionally, hernia recurrence appears to be higher after onlay repair. This may be explained by Pascal's law which states that pressure exerted on an enclosed fluid acts equally in all directions, and in the case of an onlay technique, this results in lifting forces against the mesh.[158] Further, SSI is a known risk factor for hernia recurrence. Though some advocate this technique, these factors should be considered.[159,160]

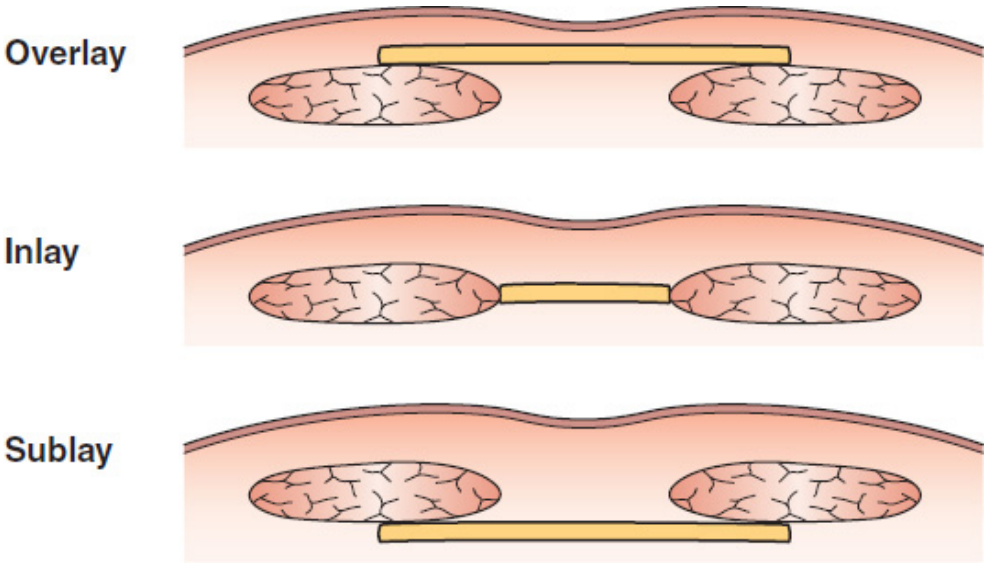


Figure 72.34 Potential spaces in the abdominal wall to place prosthetic material: onlay or on top of the anterior abdominal fascia; inlay placed within the defect at the level of the fascia; and sublay posterior to the fascia; three positions for sublay exist: retromuscular, preperitoneal, and intraperitoneal.

Prosthetic Bridging Technique

A bridged repair is one in which the hernia defect is left unclosed, instead placing mesh across the hernia defect with wide circumferential overlap, essentially replacing the defect with prosthetic and avoiding a high-tension closure. This became popular in the 1990s in keeping with the tension-free concept for inguinal herniorrhaphy and as laparoscopy became increasingly popular for ventral hernia repair. Laparoscopic repair is detailed below. Mesh selection depends on the approach. A barrier-coated, biologic, or absorbable synthetic mesh is required for intraperitoneal placement. If mesh is placed in an extraperitoneal position, a noncoated mesh may be used as long as there is some tissue layer between the mesh and viscera. Although this repair is theoretically attractive, it has not been as successful for incisional hernias as for inguinal hernias. The recurrence rate is especially high in obese patients and large hernia defects.

In the management of the open abdomen, a bridged mesh may be used to perform serial mesh excision. This is a technique whereby an open abdomen is closed by placement of a bridging ePTFE mesh, with serial visits to the operating room to tighten the mesh by serially excising a strip of the mid-portion of the mesh, thereby eventually bringing the native fascial edges into

apposition for closure. This approach allows for definitive abdominal wall closure after a mean of six visits to the operating room.[161]

Sublay Prosthetic Technique

The term sublay deserves specific definition. This can refer to any mesh position below the abdominal wall and includes intraperitoneal, preperitoneal, or retromuscular placement. As such, a thorough reading of the literature is necessary to determine the exact technique being discussed. Only recently has this term become more universally synonymous with the retromuscular repair, and will be used in this context here. First described by Rives, and commonly known as the Rives-Stoppa repair, this approach is characterized by the placement of a large prosthesis in the space between the abdominal muscles and the peritoneum (**Fig. 72.17**). It was popularized by Rives, Velamenta, Stoppa, and Wantz and is particularly suitable for large and multiply recurrent hernias when most of the abdominal wall must be reconstructed.[162–163] It is considered the most effective conventional incisional hernia repair and therefore the one against which other procedures must be measured.

The procedure is begun by excising the previous scar and dissecting the peritoneal sac of the hernia to the level of the fascia. Occasionally, the sac does not have to be opened and the procedure can be performed totally extraperitoneal. More commonly, the sac is thin and easily disrupted, making entrance into the peritoneal cavity inevitable. The myofascial release is begun by opening the posterior rectus sheath on each edge of the hernia defect just lateral to the linea alba and dissected away from the undersurface of the recti to the lateral edge of the rectus sheath, with care being taken to prevent damage to the perforating intercostal neurovascular bundles at the lateral side of the sheath (**Fig. 72.35**). Mobilization of the posterior sheath alone bilaterally has the effect of medializing the rectus-anterior sheath myofascial unit to facilitate primary fascial closure. The posterior rectus sheaths are then approximated to each other primarily (unless the peritoneum has not been opened). It is sometimes necessary to add additional myofascial release to further decrease the tension. In this case, a TAR is the preferred approach, though a posterior component separation or external oblique release may also be used. A large mesh prosthesis is then placed in this space outside the repaired posterior sheath but beneath the recti. The optimal

method of mesh fixation in this space has not been determined. Options include fixation to the costal margin or Cooper ligament, direct suture to the posterior rectus sheath, lateral percutaneous transfascial sutures, lateral tacks, adhesives, or no fixation at all. Suction drains are used by most surgeons which are typically removed prior to discharge in clean wound conditions.[164] The procedure is completed by reapproximating the anterior rectus sheaths, thus bringing the rectus muscles back to their normal configuration. The best long-term results are obtained when the anterior fascia can be closed bringing the muscles back together because of an improvement in abdominal wall mechanics. However, it is sometimes impossible to achieve this and the gap must be bridged with a prosthesis (**Fig. 72.36**).

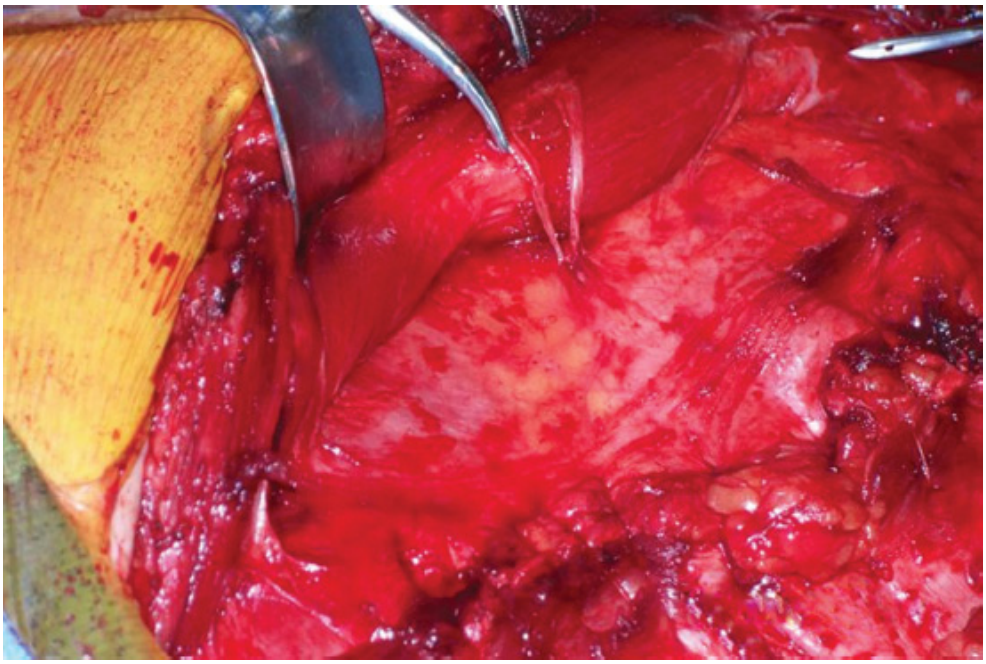


Figure 72.35 Neurovascular bundles in posterior rectus compartment supplying the rectus muscle.

Due to the well-vascularized compartment created for mesh placement during retromuscular repair, this approach has the lowest SSI and prosthetic-related complications of any open repair.[159,160] One unique complication deserves mention, however. Interparietal hernias may occur due to breakdown of the posterior rectus sheath closure. This can result in herniation of the viscera into the interparietal plane between the disrupted

posterior sheath and the intact mesh against the anterior abdominal wall. These often present acutely with small bowel obstruction. The surgeon must have a high-index of suspicious for this complication, as it will frequently be missed as the cause of SBO by radiology. This can be identified by typical signs of SBO along with visualization of the posterior rectus sheath below the herniated bowel. Repair is necessary, and the primary goal is obliteration of the potential space between the posterior sheath and mesh in which the bowel may be incarcerated.[165] This complication can occur with any procedure involving separation and closure of the posterior sheath, including a standard Rives-Stoppa repair, TAR, or posterior component separation.

Myofascial Release (i.e., Component Separation)

9 Abdominal wall reconstruction is defined as ventral hernia repair performed using a myofascial release technique. Myofascial release, in turn, is defined as separation of an abdominal wall fascial layer from a muscular layer, allowing medial advancement of the separated muscle layers in order to close the hernia defect and restore native abdominal wall anatomy. Previously this has been referred to as "component separation" which is a generic term describing a variety of myofascial release techniques. The main types of myofascial release techniques currently used are described below.

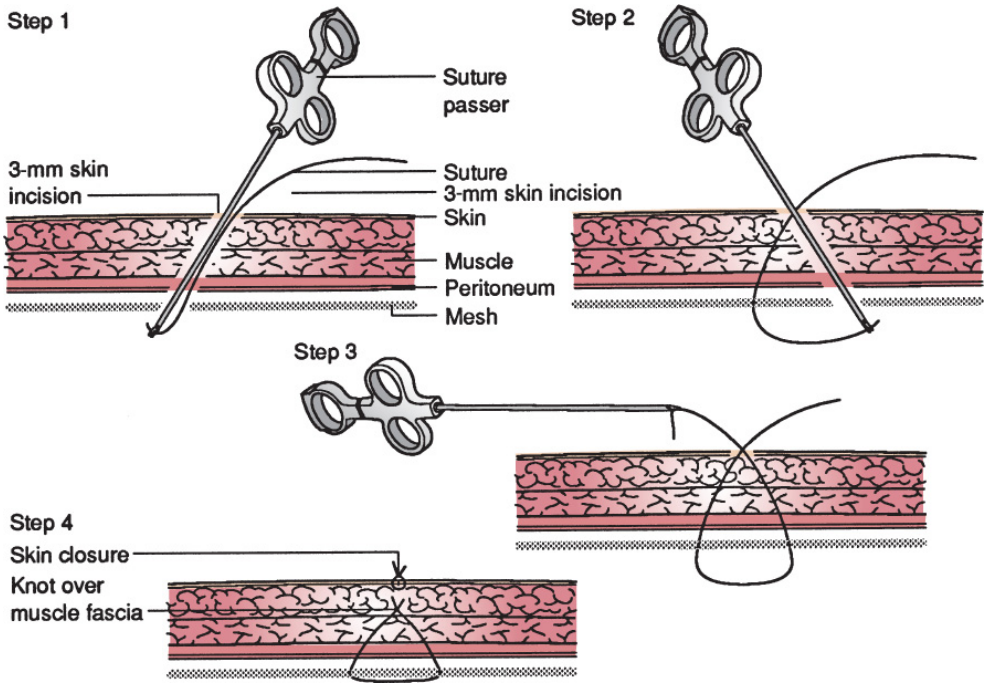


Figure 72.36 Fixation of prosthesis to the peritoneal surface of the abdominal wall with the use of a suture passer. **Step 1:** The suture passer device with a heavy nonabsorbable suture is passed through a 3-mm stab incision in the skin at an oblique angle. The device and suture traverse the entire abdominal wall and then the prosthesis. Once the peritoneal cavity is entered, the suture is released and the passer is withdrawn back into the subcutaneous tissue. **Step 2:** The device is redirected at a different angle through the abdominal wall and prosthesis and the suture is grasped. **Step 3:** The suture is pulled out of the abdominal cavity so that the two free ends are extracorporeal. **Step 4:** The suture is tied with the knot resting on the fascia. The skin is then closed.

Anterior Component Separation

The term component separation itself was initially used to describe a technique popularized in the early 1990s by Ramirez and colleagues which is based on lateral fasciotomies that allow sliding of the muscular fascia layers toward the midline providing coverage for large midline abdominal wall defects.[166] Originally, it was proposed as a tissue repair for patients with contaminated wounds to avoid use of prosthesis, but several modifications have been described since the original description. In this technique, the skin and subcutaneous fat are dissected free from the anterior sheath of the rectus abdominis muscle and the aponeurosis of the external oblique muscle. The aponeurosis and muscle belly of the external oblique muscle are transected longitudinally lateral to the semilunar line (**Fig. 72.37**). It is important to

extend the incision inferiorly to the inguinal ligament and superiorly onto the chest wall at least 5 to 7 cm cranial to the costal margin especially for defects close to the xiphoid. The external oblique muscle is separated from the internal oblique muscle, as far laterally as possible in a relatively avascular plane, beyond the area of skin undermining toward the midaxillary line. This step is safe because the neurovascular bundle (comprising the intercostal nerves and vessels) lies deep to the internal oblique muscle. Additionally, the rectus abdominis muscle is released from its encasing posterior fascia by incising the posterior rectus sheath and separating it from the overlying rectus muscle. The result of the combined posterior rectus release and the external oblique release is that the internal oblique-transversus abdominis muscle and the rectus abdominis complex slide medially for up to 10 cm in the mid-abdomen, allowing closure of defects up to 20 cm. In fact, release of the posterior rectus sheath alone results in mobilization of 5 cm in the mid-abdomen. Care must be taken not to damage the neurovascular bundles that runs between the internal oblique and transversus abdominis muscle to enter the rectus sheath posterolaterally. After advancement of the rectus complex toward the midline, the fascial closure is performed followed by layered closure of the subcutaneous tissues and skin with drains. Several modifications to the original technique have been described. The technique can also be used as an adjuvant to the prosthetic repairs described next.

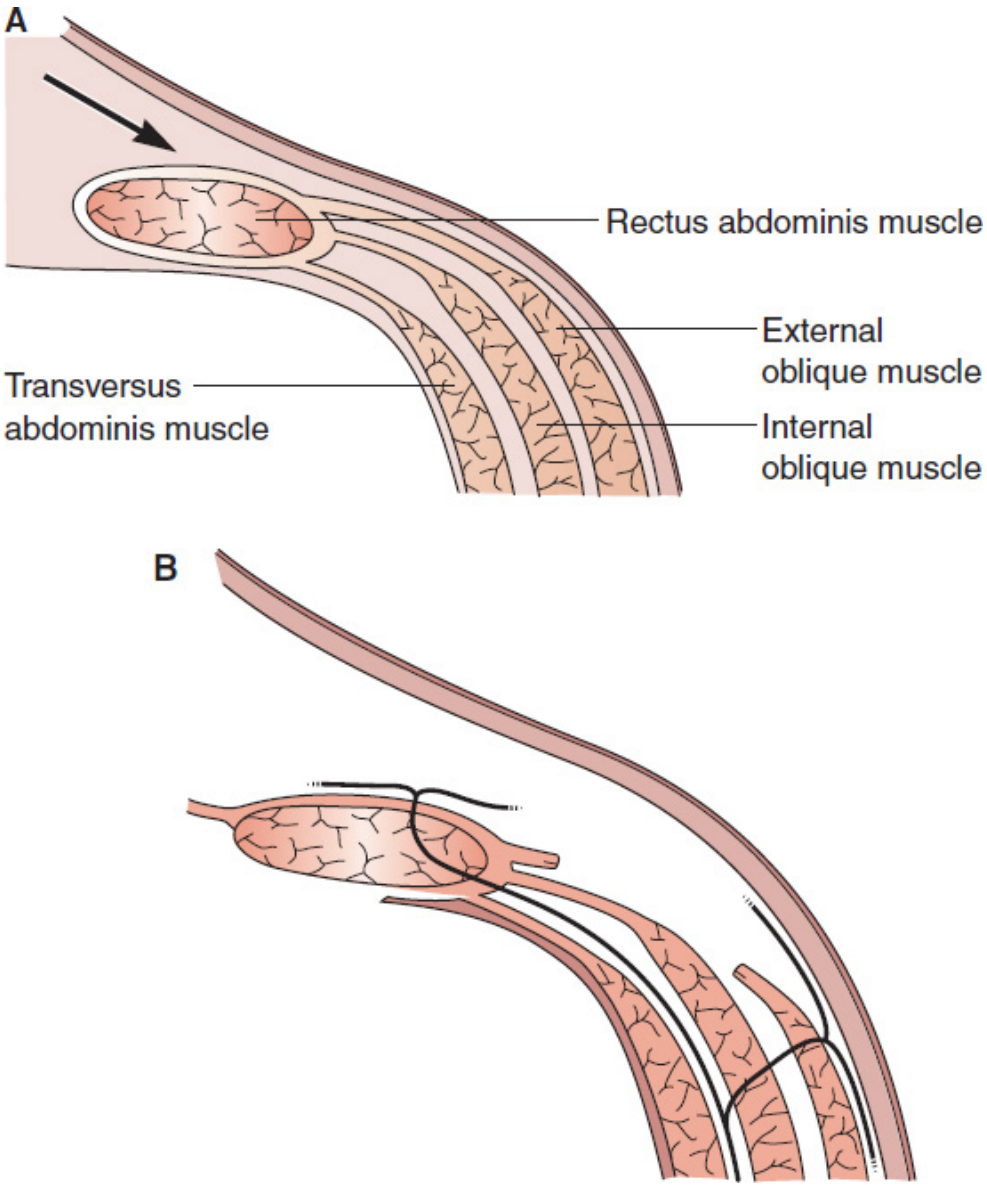


Figure 72.37 Component separation technique.

Unfortunately, SSO and SSI following anterior releases involving large subcutaneous dissections are significant, occurring in up to 50% of patients. This can range from simple seromas to full-thickness necrosis and loss of abdominal wall skin and soft tissue, creating potentially devastating chronic abdominal wall wounds. This results from division of the deep inferior epigastric perforators in the periumbilical region that are divided during the massive subcutaneous dissection required for this procedure, devascularizing the mid portion of the abdominal wall. Several modifications of the classic Ramirez component separation have been described to mitigate these

complications. The perforator preserving technique completes the subcutaneous dissection but identifies and preserves the periumbilical perforators, significantly reducing the risk of wound complications. Endoscopic component separation (discussed below) utilizes laparoscopy to dissect the interparietal plane between the external and internal obliques, thus eliminating the need for subcutaneous dissection and vascular disruption. The development of posterior approaches to lateral myofascial release (discussed below) offers an excellent alternative to the external oblique release with significantly lower wound complication rates while still gaining significant mobilization of the abdominal wall.

Endoscopic Component Separation This technique was developed to lessen the degree of abdominal dissection and potentially address the wound complications associated with open anterior component separation with the use of a balloon dissector and laparoscopic instruments. The technique involves making 2- to 4-cm incisions just below the costal margin in anterior axillary line (lateral to the attachment of the external oblique aponeurosis on the rectus sheath). The space between the external and internal oblique muscles is dissected and under camera guidance, dissector balloon is inflated which further aids blunt dissection in this layer. The external oblique aponeurosis is then divided. A Balloon dissector can be used in the subcutaneous space as well. This technique can be followed by either open, laparoscopic, or robotic-assisted hernia repair.[167–170] Potential limitation might be the adequacy of the myofascial advancements using this technique. Proponents of this technique claim reduction in postoperative stay by about 50% and a distinct advantage in the setting of stomas. The primary benefit, however, is the reduction in wound complications while still achieving significant myofascial advancement (**Fig. 72.33**). Care must be taken to ensure the proper interparietal plane is dissected, as disruption of more than just the external oblique may result in lateral bulging or hernia.

Transversus Abdominis Release/Posterior Component Separation

The transversus abdominis release (TAR) allows a posterior extension of the myofascial release after initial retrorectus dissection to achieve greater fascial mobilization and overlap of mesh placement.[171] This is done by incising the first layer of the posterior rectus sheath, which is the posterior

lamella of the internal oblique, just medial to the neurovascular bundles, followed by division of the transversus abdominis muscle (in the upper abdomen) or its aponeurosis (in the mid and lower abdomen) to enter either the "pretransversalis plane" or the preperitoneal plane. The pretransversalis plane is usually more robust and is readily entered superior to the arcuate line. Utilization of this plane near the costal margin minimizes extensive defects when mobilizing the preperitoneal space alone. Inferiorly, the preperitoneal space is typically entered and mobilized. This dissection continues laterally to at least the mid-axillary line, but can be carried as far posteriorly as the psoas muscle. Superiorly, this can extend under the diaphragm, dissecting the peritoneum away from the central tendon of the diaphragm. Inferiorly, this can extend into the Space of Retzius, exposing the symphysis pubis and Cooper ligament. This results in the disinsertion of the transversus abdominis from the rectus sheath and releases the circumferential tension it normally applies, allowing the medialization of the rectus abdominis across the midline defect (**Figs. 72.38** and **72.39**). After closure of the posterior elements, there remains a large retromuscular space for placement of prosthetic mesh to reinforce the anterior fascial closure.

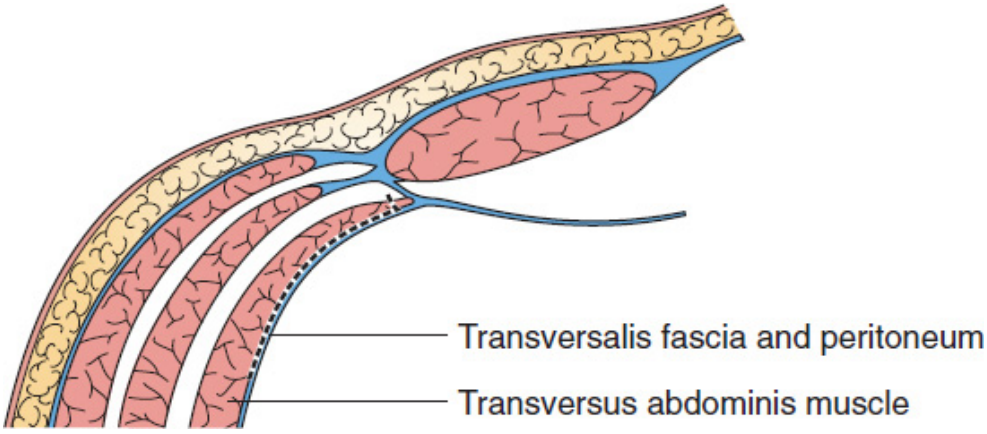


Figure 72.38 The posterior rectus sheath is incised about 0.5 to 1 cm medial to the anterior/posterior rectus sheath junction to expose the underlying transversus abdominis muscle. Note the perforator nerves that are preserved during retromuscular dissection and subsequent posterior component release.

As with the Ramirez external oblique release, significant myofascial advancement is possible with each incremental step of the retrorectus + TAR approach. In a cadaver study by Majumder et al., after midline laparotomy

and retrorectus dissection alone, the anterior fascia can be mobilized 4 to 7 cm, depending on the degree of tension. The addition of incision of the posterior lamella of the internal oblique, the first step in TAR, increased that release slightly, division of the transversus abdominis muscle by about 1 cm, and to a maximum of 5 to 10 cm after completion of the lateral preperitoneal dissection. Mobilization of the posterior sheath increased in similar fashion with each step of the procedure, but to an even greater degree, with maximal posterior medialization of 7 to 11 cm.[172]

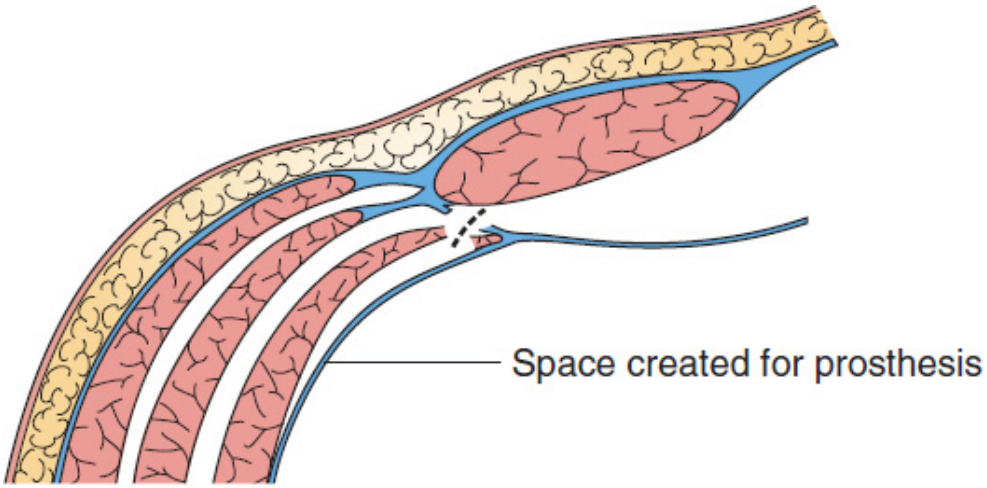


Figure 72.39 Division of the posterior rectus fascia just medial to the linea semilunaris and perforator nerves followed by division/release of the transversus abdominis muscle along its entire medial edge.

This technique is an important addition in the armamentarium of surgeons dealing with complex abdominal wall problems and has been shown to have favorable perioperative morbidity and acceptable recurrence rates compared to anterior component separation.[148] The technique is particularly suited for addressing recurrent hernias after a prior anterior component separation but probably should not be used simultaneously in combination with a concurrent anterior component separation. However, TAR is technically difficult because the transversalis fascia/peritoneum complex posteriorly can be extremely thin, tearing easily. In order to isolate the viscera from the prosthetic which will eventually be placed, these tears must be repaired. If this is not possible, an intervening fast absorbable mesh or biologic mesh can be used to separate the viscera from the retromuscular space. Alternatively, one of the adhesion barrier prostheses can be used.

Laparoscopic Ventral Hernia Repair

Laparoscopic ventral hernia repair was developed in the 1990s as a natural extension of the increasing application of this minimally invasive technology. The greatest value of laparoscopic surgery is the reduction in wound complications due to the small access incisions, and the ability to apply the "gold standard" sublay technique with mesh placed below the hernia defect in a tension-free manner, thus eliminating the need for the extensive abdominal wall dissection implicit in the conventional open operation.[62] Laparoscopic surgery provides several potential advantages including decreased blood loss, lower wound infection rates, decreased hospital stay, and patient preference.[173,174] Improvements in wound infection has been consistently demonstrated, though minor SSOs such as seromas are more commonly seen with laparoscopic repair. However, laparoscopic VHR has not clearly reduced hernia recurrence rate. As with any hernia repair technique, patient selection is key. This is most appropriate for patients at high risk for wound complications and small- to moderate-sized defects. Contraindications to laparoscopic VHR include patient intolerance of pneumoperitoneum or general anesthesia, and open abdominal wall wounds or other poor skin and soft tissue quality that requires resection. Relative contraindications include extensive intra-abdominal adhesions, COPD, heart failure, or large hernia defects >10 cm.

Entrance to the abdominal cavity followed by adhesiolysis can be problematic for a surgeon performing a laparoscopic ventral hernia repair and devastating complications resulting from visceral injury are possible. Typically, off-midline access is obtained via open cut-down (Hasson technique), Veress needle insufflation, or direct optical trocar entry into the abdominal cavity, typically at Palmer point in the left upper quadrant, or its corresponding point on the right side. This is left to the discretion and experience of the surgeon, as no one technique is clearly superior. Use of a Hasson open cut-down technique likely minimizes unrecognized enterotomies, especially in these complex settings. Once the abdomen has been safely entered, additional cannulae are placed according the size and location of the hernia, with at least one trocar typically placed on the contralateral side to assist in mesh fixation. Adhesiolysis is completed and the abdominal contents are reduced from the hernia defect. Once all the

hernia defects are identified, the operating surgeon must make a decision to either continue the procedure laparoscopically or convert to an open operation. Traditionally, laparoscopic VHR was a bridging repair, placing mesh with wide overlap around the hernia defect with no attempt to close the defect itself. In our opinion, multiple "swiss cheese defects" are the best indication for a laparoscopic repair. On the other hand, if there are only one or two defects with wide separation of the muscles, the laparoscopic repair is not as effective due to the risk of hernia recurrence for large bridged defects, and due to eventration or pseudorecurrence in which the mesh bellows out across the unclosed hernia defect, mimicking a hernia recurrence. This can be both painful and unsightly for patients.[175] Currently, most surgeons favor closure of the hernia defect during laparoscopic repair whenever possible, and the inability to do so is often a primary indication for conversion to an open procedure. Closure is typically performed using percutaneous transfascial sutures using a suture passer (**Fig. 72.36**). This closure can be aided by the addition of endoscopic component separation. More recently, robotic-assisted ventral hernia repair has grown in popularity due to the ability to suture reapproximate the fascial defect reliably. There is evidence that defect closure reduces seroma formation, but its effect on hernia recurrence and overall morbidity remains unclear.[176–178]

Mesh selection and placement is key to successful laparoscopic VHR. Mesh should have an antiadhesive barrier of some kind, often referred to as a tissue separating mesh, as it is in direct contact with the viscera. Several options exist as discussed above (**Figure 72.21**). The mesh should be sized after appropriately measuring the hernia defect and appropriate overlap. Ideal mesh overlap is 5 cm or greater, and likely increases with increasing defect size.[179,180] Measurements should be made intracorporeally in order to negate the effect of the insufflated abdominal wall.[181] Mesh should be placed through a trocar to avoid any potential contact with the skin, and unfurled against the abdominal wall. Fixation is a point of debate, with many surgeons increasingly avoiding transfascial sutures or any permanent fixation due to the concern for postoperative pain. While there is reliable evidence that tack fixation alone is adequate, absorbable fixation alone or the use of surgical adhesive alone appears to increase the risk of hernia recurrence. The International Endohernia Society published updated guidelines on laparoscopic ventral hernia repair in 2019 and is an invaluable resource into

surgical technique and the controversies in laparoscopic ventral hernia repair.[182]

Complications specific to laparoscopic VHR include those inherent to laparoscopy, such as inability to tolerate pneumoperitoneum or gas embolism. Of most concern is enterotomy. Though this is relatively low risk, typically reported around 1%, the limited field of view, off-screen instrument exchanges, and potential for thermal injury via direct contact or capacitive coupling increase the potential to miss these injuries. Additionally, because of the risk of mesh infection due to the mesh type and position in the abdominal cavity, an enterotomy during laparoscopic VHR typically requires a change of approach either to an open repair or aborting the case and delaying definitive repair. Long-term complications of intraperitoneal mesh are increasingly recognized and are inherent to the laparoscopic IPOM approach. Subsequent abdominal operations occur in up to 25% of patients, often for non–hernia-related pathology. Adhesions to intraperitoneal mesh can increase the risk of enterotomy, contamination, secondary mesh infection, or enterocutaneous fistula. Enteroprosthetic fistula may also occur due to erosion of mesh into the adjacent viscera.[56,57]

Robotic-Assisted Ventral Hernia Repair

In recent years, robotic technology has emerged as an alternative to traditional open and laparoscopic techniques in the repair of ventral hernias and its use is growing rapidly. Purported benefits of the robotic platform include enhanced three-dimensional visualization, articulating instruments, and improved surgeon ergonomics, particularly compared to traditional laparoscopic ventral hernia repair. This has also generated much controversy due to the high capital cost of the robotic system itself and few reported benefits in clinical outcomes. Robotic VHR can be divided into two broad categories. First is a simple extension of traditional laparoscopy, with standard transabdominal approach and intraperitoneal mesh placement. Second is conversion of traditional open techniques, such as preperitoneal or retromuscular repair, to the minimally invasive platform.

The majority of robotic VHR performed in a manner similar to traditional laparoscopy, consisting of transabdominal approach, lysis of adhesions, closure of the hernia defect, and placement of mesh in an intraperitoneal

position (IPOM). There are several potential benefits of the robot over traditional laparoscopy. First, the ability to achieve closure of the hernia defect is aided by the enhanced ability to suture the defect closed robotically. This is enabled by the articulating robotic needle drivers and avoids the often imprecise and painful transcutaneous methods of defect closure. Closure of the defect has been shown to decrease the risk of seroma formation and may decrease the risk of hernia recurrence, particularly for large hernias with a relatively lower area of mesh–tissue interface.[176,178–180] Secondly, the mesh is secured with intracorporeal suture rather than tacks or transfascial sutures, potentially reducing postoperative pain, though this benefit has little supportive clinical evidence to date.[183–185] There does seem to be a benefit in shortened length of hospital stay with robotic-assisted laparoscopic VHR, which has been consistently demonstrated in the published literature.[186,187] Finally, the ergonomic benefit to the surgeon has contributed to the proliferation of this approach. Laparoscopic VHR requires lateral trocar placement to work on the anterior abdominal wall, requiring downward external deflection of working instruments, often creating difficult and ergonomically unfavorable body position for the surgeon. Occupational injury involving the neck, back, and upper extremities is clearly associated with minimally invasive surgery, and this may be mitigated by robotic technology, preventing such injuries and potentially prolonging the operative career of the surgeon.[188–190]

The true benefit of robotic-assisted VHR may lie in its ability to convert traditional open VHR techniques, such as preperitoneal, retromuscular and component separation, to a minimally invasive platform. The robotic transabdominal preperitoneal repair (rTAPP) is a popular method for repair of small- to moderate-sized hernia defects. With this approach, intra-abdominal access is obtained similar to traditional laparoscopy, with lateral placement of trocars and instruments. Any necessary lysis of adhesions is completed, and the hernia reduced in standard fashion. A peritoneal flap is then created around the hernia defect, ideally to allow for at least 5 cm of mesh overlap. After completion of the peritoneal flap, the hernia defect is closed intracorporeally, mesh placed against the posterior rectus fascia, and the peritoneal flap closed below the mesh, completely excluding it from the visceral cavity. This approach is appealing, as it prevents the potential complications of intra-abdominal mesh and obviates the need for a barrier-

coated mesh and requires minimal mesh fixation, potentially reducing postoperative pain. There are currently limited published data on this approach, but it do appear to be safe and effective. Comparative data are lacking.[129,131]

For larger, more complex hernias, additional mobilization of the abdominal wall by way of myofascial release may be necessary to achieve fascial closure, limiting the applicability of the robotic IPOM or rTAPP techniques. However, using the robotic platform, release of the myofascial layers of the abdominal wall can be accomplished in order to medialize the rectus abdominis, close the hernia defect, and allow wide mesh reinforcement in the retromuscular plane. There are several variations in approach that can achieve this end result. The first description was a transabdominal approach. Trocars were placed in the lower abdomen, a transverse incision made in the posterior rectus sheath or peritoneum, and retromuscular dissection carried out in a cephalad direction. After adequate dissection, the defect is closed, mesh placed in the retromuscular position, and posterior layer closed. This approach works well for hernias in the upper abdomen via docking in the lower abdomen, or vice versa, but has limited applicability to infraumbilical hernias or longer defects.[181] Alternatively, incision of the lateral border of the ipsilateral rectus sheath can be performed, carrying the dissection medially to the linea alba, dropping down to the preperitoneal plane along the midline, and reentering the retromuscular plane on the contralateral side. This technique allows access to infraumbilical defects, but is limited by the width of the rectus sheath and the size of the hernia defect.[192]

The addition of a robotic TAR allows repair of large midline hernia defects. Trocars are placed transabdominally in the lateral abdominal wall. After necessary adhesiolysis and hernia reduction, the contralateral rectus sheath is opened. Retromuscular dissection is carried out along the length of the hernia, extending at least 5 cm above and below the defect, and continued laterally to the semilunar line. Of critical importance to this repair, as with the open approach, is the dissection of the midline above and below the hernia defect. The fascial elements coalesce to form the linea alba such that the retromuscular spaces are not continuous with each other. Thus, the midline peritoneum and preperitoneal fat must be dissected from the overlying linea alba, leaving it attached to the posterior sheath bilaterally

and with care taken to avoid damage to the intact linea alba, which may result in hernia recurrence. A TAR is then performed as described above by incising the posterior lamina of the internal oblique aponeurosis, dividing the transversus abdominis muscle and aponeurosis, and extending dissection laterally in the preperitoneal plane. This continues laterally to approximately the mid-axillary line, followed by placement of additional trocars in the contralateral abdomen directly into the dissected preperitoneal space. The robot is then docked from these new trocars ("double-dock" technique) and an identical retromuscular dissection and TAR performed on the opposite side, bringing the initial trocars into the dissected space. The posterior sheath is closed, along with any peritoneal defects, the anterior hernia defect is closed, and mesh placed in the retromuscular position. The bilateral myofascial release allows significant mobilization of the abdominal wall to accommodate defect closure, comparable to open repairs described above.[192–194]

This technique has one significant drawback in that it necessitates a bilateral TAR. Many patients with comparable hernias would likely not require this additional release if the repair was performed in an open fashion. The most recent iteration of robotic retromuscular repair is a modification of the totally extraperitoneal technique used for inguinal hernias, the extended totally extraperitoneal (eTEP) repair. It should be noted that this is not necessarily a new operation, but a modification of the above described techniques to allow a more tailored approach to ventral hernia repair. Using the eTEP approach, access to the retromuscular space is done directly, most often using an optical trocar, rather than first entering the abdominal cavity. After initial unilateral retrorectus dissection, a "crossover" is performed by which the rectus sheath in incised near the midline to enter the preperitoneal plane below the linea alba. This plane is dissected across the midline until the contralateral rectus sheath is identified, at which point it is incised to enter the contralateral retrorectus plane. Variations in this approach include placement of all trocars along the lateral aspect of one rectus sheath, performing crossover and ultimate repair from this lateral position, or placing the instruments in either the upper or lower rectus sheath bilaterally after the initial crossover is performed. In either case, bilateral retromuscular dissection is completed laterally to the semilunar line, and above and below the hernia defect at least 5 cm to allow

mesh overlap. The hernia defect is closed, as is any posterior sheath or hernia sac defects, and mesh is placed into the retromuscular plane. If needed, TAR can still be performed on one or both sides. Unlike the technique described above, however, this can be tailored to the need of the individual hernia defect, extending the dissection only as far as is necessary to achieve hernia closure.[195–197]

These robotic retromuscular techniques have demonstrated some clinical benefit, most notably shorter length of stay compared to both open retromuscular repair and standard laparoscopic IPOM VHR. There remains a fairly high rate of seroma, though typically clinically irrelevant. Though there seems to be a low rate of SSI with robotic retromuscular repair, this has not yet been clearly seen in the literature.[198,199] The double-dock procedures with bilateral TAR are limited to large defects, typically >10 cm, that are expected to require TAR even if performed open.

Massive Hernia with Loss of Domain

There is no consistent definition as to what constitutes a massive hernia. This term is often applied to large defects, >10 cm, or hernias with "loss of domain" in which the volume of herniated viscera exceeds the capacity of the abdominal cavity to accommodate its replacement into the visceral sac. Many of these hernias are recurrent and associated with morbid obesity, skin ulcerations, enterocutaneous fistulae, diverting stomas, and distortion of the abdominal wall from multiple prior repair attempts. Several physiologic changes such as alteration of ventilatory equilibrium and impairment of venous return results from long-standing massive hernias. Forced reduction of the hernia with replacement of contents into the abdominal cavity can increase intra-abdominal pressure considerably, resulting in respiratory insufficiency and cardiovascular compromise.[200] In extreme cases, it is impossible to return the contents to the abdomen and repair the hernia defect without resection of intra-abdominal contents, such as colectomy with omentectomy. Repair of massive ventral hernias with loss of domain is technically challenging and is associated with high morbidity, mortality, and recurrence rates. A good understanding of the abdominal wall anatomy and the nature of fascial defects is essential prior to repairing these ventral hernias. Complications of repair are common and include respiratory compromise, abdominal compartment syndrome, skin flap necrosis, and wound infection, in addition to the usual surgical complications. Therefore, repair should not be recommended unless there are overwhelming indications such as disabling symptoms, bowel obstruction or strangulation, or extensive skin ulceration caused by the hernia. These patients require complex abdominal wall reconstruction, and might best be seen in centers with special interest in this area where teams have been assembled to treat complex abdominal wall pathology.

Progressive Preoperative Pneumoperitoneum

Progressive preoperative pneumoperitoneum (PPP), which was first described by Goni Moreno for repair of massive incisional hernias, is a useful technique in patients with loss of domain, from incisional or massive

inguinal hernias, to expand the abdominal cavity by stretching the abdominal wall musculature and the diaphragm.[31,201–206] The maneuver involves injecting room air (or CO_2) via a needle or implantable catheter every 1 to 3 days for a prescribed period of time between 1 and 4 weeks. Volume of air injection varies but is most often administered to the degree the patient tolerates (development of shoulder pain, difficulty breathing, or subcutaneous emphysema). This can be performed by patients and families as outpatient, but is more often performed in a hospital setting. The effect of PPP is twofold. First, there is lengthening of the abdominal musculature and expansion of the abdominal cavity volume.[205,207] While the hernia sac expands as well, often more than the abdominal cavity, if the volume expansion of the abdominal cavity is equal or greater than the original hernia sac volume, the abdomen can typically accommodate the return of the herniated contents and allow fascial closure.[208] Second, the gradual expansion of the abdominal cavity seems to allow for physiologic adaptation that permits the massive abdominal wall reconstruction and increased abdominal pressure at the time of closure.[207]

Progressive preoperative pneumoperitoineum has been more commonly applied in Europe and South America with good results for large ventral hernias. Rate of fascial closure ranges from 50–100%, with reported recurrence rate of 3–37%.[206] Complications include extensive subcutaneous emphysema, surgical site infections, other non-infectious wound complications, abdominal wall soft tissue necrosis, venous thromboembolism (VTE), and cardiopulmonary complications. Complications tend to be higher than typical incisional hernia repairs owing to the more complex techniques usually required to achieve closure and the prolonged duration of hospitalization and/or abdominal insufflation. A variety of repair techniques are used in conjunction with PPP including external oblique release, retromuscular repair with or without additional posterior release, laparoscopic repair. Mesh reinforcement should be used due to excessively high recurrence rates with suture repair. Adjunctive measures such as chemical component separation (discussed below) may add benefit and improve the success rate of PPP.[209] Despite the relative success in reported series, this is a complex process reserved for only the most complex patients with large hernias and significant loss of abdominal domain

that have little chance of closure without some ability to expand abdominal volume.

Chemical Component Separation

A newer modality for expansion of the abdominal cavity utilizes chemical paralysis of the abdominal wall by botulinum toxin A (BTA) injection into the lateral abdominal wall musculature, often termed chemical component separation. The resultant flaccid paralysis of the oblique musculature, which peaks at approximately 3 weeks after injection, has been shown to elongate and decrease the thickness of the lateral abdominal muscles, which reduces the mean hernia defect size on subsequent imaging.[210,211] This potentially improves the ability to reapproximate the hernia defect or minimize the extent of other myofascial release techniques that may increase the operative risk. Indeed, all studies to date indicate the ability to close the hernia defect in all cases. In addition to the benefits of achieving fascial closure, BTA injection seems to provide significant postoperative pain control as well.[212]

There is significant heterogeneity in the literature on the use of BTA, however. The administered dose of BTA varies between studies, ranging from 200 to 500 units with dilutions between 2 and 100 units/mL, and injections sites vary from 3 to 5 per side. Additionally, the time between injection and attempted hernia repair varies from several weeks to intraoperative injection. Patient selection varies, with some studies done primarily in patients after open abdomen management,[213,214] which represents a significantly different pathology than typical incisional hernias. The complexity of incisional hernias ranges widely as well, making it difficult to discern the optimal patient that would benefit from BTA. Finally, surgical technique for hernia repair varies greatly in each study. These include simple suture repair, external oblique release (Ramirez component separation), retromuscular repair, laparoscopic repair, and concurrent progressive preoperative pneumoperitoneum. There is currently no comparative data of BTA versus other modalities of abdominal wall expansion, no randomized control trials, and no clear evidence that BTA injection ultimately effects the extend of myofascial release needed for closure. Despite these drawbacks in the current literature, BTA injection appears to be quite safe and warrants

further investigation to assess its efficacy in complex abdominal wall reconstruction.[210–217]

Tissue Expansion

Tissue expanders can also be used when either skin or the myofascial elements of the abdominal wall are deficient. They are implanted subcutaneously or subfascially and are gradually inflated until the desired amount of extra tissue is obtained. The limitation of the technique is the delay in definitive repair while the expansion is going on and the considerable amount of pain that patients complain of. The intra-abdominal placement of tissue expanders has also been described to address the issue of loss of domain, but this is primarily confined to the pediatric literature.

Visceral Reduction

The primary concern in hernias with loss of domain is the revisceration of the herniated contents back into the abdominal cavity. If the above measures to expand the abdominal cavity fail or are inadequate, consideration may be given to reducing the contents of the hernia itself by resection of the viscera. Options include omentectomy, colectomy, or small bowel resection. There are extremely limited data on this approach as a means to achieve fascial closure in complex hernia repair with loss of domain, and this should be considered only as a last resort in expert hands.[218,219]

Parastomal Hernias

Parastomal hernia is among the most common complications of permanent enterostomies and can have significant effects on the patients' quality of life, physical and psychological well-being, and health care resources.[220] The incidence of parastomal hernia varies with the type of the stoma (1.8% to 28% for ileostomy and 4% to 48% for colostomies).[221,222] Studies designed with very careful follow-up suggest that a paracolostomy hernia develops in more than 50% of patients followed for longer than 5 years with most occurring in the first 2 years. The true incidence of parastomal hernias has been difficult to quantify given the lack of uniform definition of what constitutes a hernia, variable follow-ups, and inadequacy of physical

examination to diagnose early occurrences.[223] Poor site selection or technical errors, such as making the fascial opening too large, excessive splitting and stretching of muscle fibers, epigastric nerve denervation, placing a stoma in an incision, or emergency rather than elective creation of stoma, account for some of these hernias. Placing a stoma lateral to the rectus sheath is widely touted as a cause, but this is now being challenged. Obesity, malnutrition, advanced age, collagen abnormalities, postoperative sepsis, abdominal distention, constipation, obstructive uropathy, steroid use, and chronic lung disease also contribute. Other techniques for stomal construction, such as extraperitoneal tunneling, stapled ostomy, and prophylactic mesh reinforcement for permanent colostomies especially in the posterior sublay position have been suggested. Currently, only prophylactic mesh reinforcement of permanent end colostomy has significant data to clearly warrant routine use.[224–226] A classification system for parastomal hernias has been recommended based on the size and presence of a concomitant incisional hernia by the European Hernia Society (**Table 72.12**) which will help standardize the definition of parastomal hernias for future studies.[227]

Most parastomal hernias are asymptomatic and therefore can be treated nonoperatively. Approximately one-third of patients will ultimately require repair, though life-threatening complications, such as bowel obstruction or strangulation, are rare. Routine repair is therefore not recommended. **Table 72.13** lists possible indications. The three general types of stomal hernia repair are fascial repair, stomal relocation, and prosthetic repair, which can be performed either laparoscopically, robotic-assisted, or open. Fascial repair involves a local exploration around the stoma site, with primary closure of the defect. This approach is associated with up to 75% recurrence rate[228] and should be considered of historical interest only. Stoma relocation[223] is usually indicated in patients with other stomal problems, such as skin excoriation or suboptimal stomal construction. Simple relocation, however, results in risk of parastomal hernia at the nascent site of 24% to 86%, as well as up to 50% hernia recurrence at the initial site, along with risk of midline incisional hernia if a laparotomy is required. The major drawbacks of stomal relocation are the fact that a laparotomy is required, which in and of itself causes more morbidity than some of the other techniques, and that it exposes the patient to the risk of three new incisional

hernias at (a) the old stoma site, (b) the laparotomy incision site, and (c) the new stoma site with reported recurrence rates ranging from 24% to 86%.

Table 72.12 European Hernia Society (EHS) Classification of Parastomal Hernias

EHS Classification Grid for Parastomal Hernia		Small <5 cm	Large >5 cm
Concomitant incisional hernia	No Yes	Primary	Recurrent

Table 72.13 Indications for Repair of a Parastomal Hernia

Absolute
Obstruction
Incarceration with strangulation
Relative
Incarceration
Prolapse
Stenosis
Intractable dermatitis
Difficulty with appliance management
Large size
Cosmesis
Pain

Whenever possible, a prosthetic repair should be considered as this appears to be the most effective. There are several potential options for repair.

1. Open onlay: Mesh is placed anterior to the anterior rectus aponeurosis. Incision may be midline or a curvilinear incision outside the boundaries of the patient's appliance (**Fig. 72.40**). The skin and subcutaneous tissue are then dissected from the underlying anterior fascia widely around the stoma and hernia defect. The defect is closed around the stoma, and a prosthetic

onlay placed around the stoma and fixed to the underlying fascia. The problem with this approach is that the undermining of subcutaneous tissue leads to wound complications due to the relative poor vascularity and potential disruption of perforating vessels during dissection. As with any onlay technique for ventral hernia repair, patients should be selected carefully to minimize wound risk. This approach is a reasonable one in patients with hostile abdomens and where intraperitoneal mesh is to be avoided. Recurrence rates of up to 26% have been reported with this technique with a mesh removal rate up to 23%.[229]

2. Open retromuscular or preperitoneal sublay: Mesh is placed posterior to the rectus muscle and anterior to the posterior rectus sheath (retromuscular repair) or mesh placement between posterior rectus sheath and peritoneum (preperitoneal repair) has been described in small case series. Posterior component separation with retromuscular mesh positioning is a technique that has been described in patients with complex parastomal hernias which uses mesh to reinforce all "at risk" areas for recurrence.[230,231] This approach allows any midline hernias to be easily addressed as well. Mesh may be cut as a keyhole, wrapping the mesh around the stoma left in situ and subsequent closure of slit cut in the mesh. If the stoma is revised or relocated, the stoma can be brought back through the mesh directly without requiring a long slit to be cut in the mesh. This can be also accomplished using a stapled technique, fixating the mesh to the posterior sheath with a circular stapler and bringing the stoma back through the mesh. An extraperitoneal Sugarbaker technique is also possible, lateralizing the stoma within the retromuscular space and placing an intact flat mesh below the stoma as described below.[232] This approach is feasible using a robotic approach, but is most often performed via midline laparotomy.

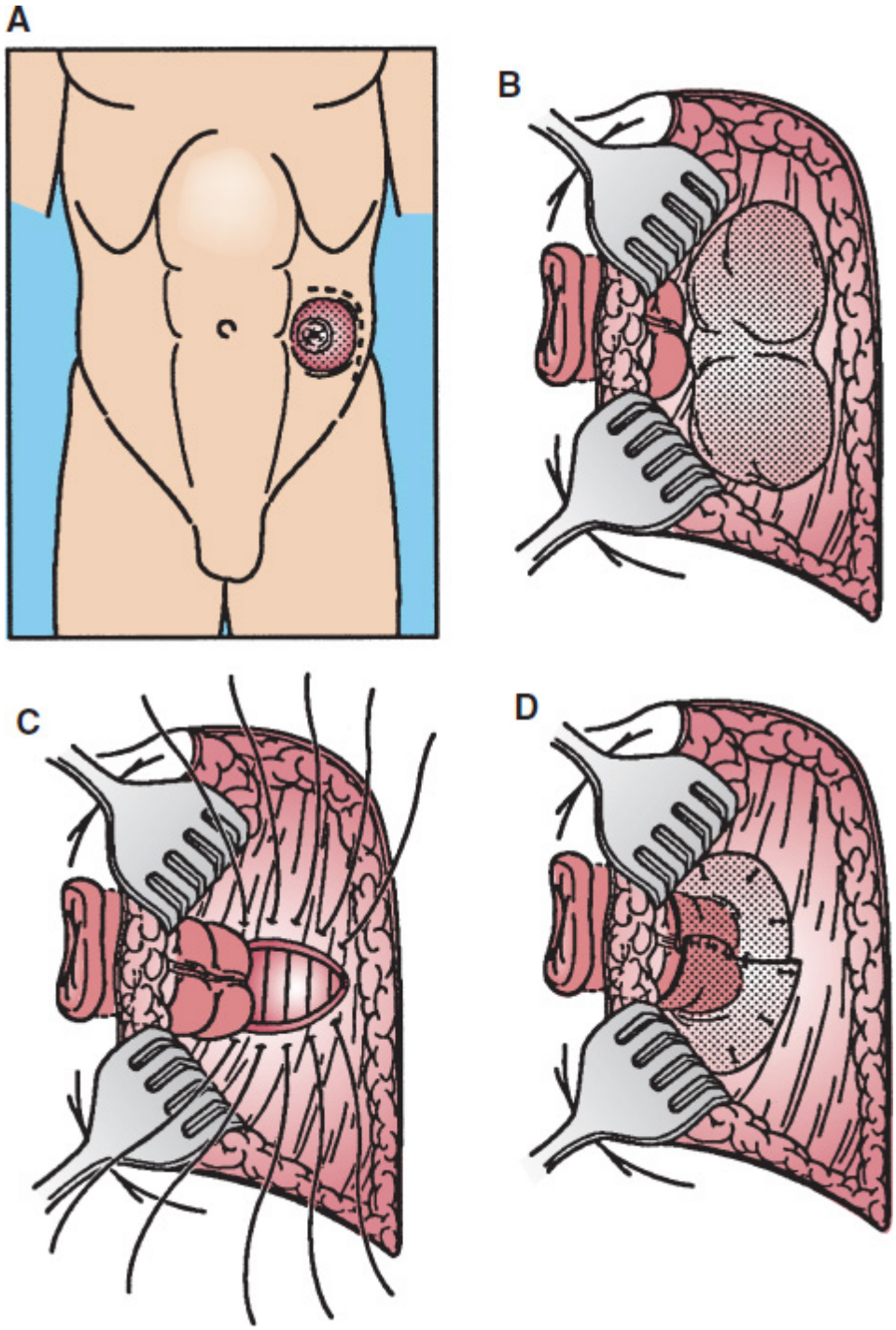


Figure 72.40 Repair of a parastomal hernia. **A:** Incision around hernia. **B:** Hernia sac is identified, the contents are reduced, and the peritoneum is closed. **C:** The edges of the fascial defect are reapproximated. **D:** The fascial repair is reinforced with polypropylene mesh, which is wrapped around the subcutaneous portion of the colon and sutured in place.

3. Open intraperitoneal sublay mesh (known colloquially as IPOM). An intra-abdominal prosthetic repair eliminates the need for the abdominal wall dissection. It also enlists the mechanical advantage of placing the prosthesis on the peritoneal side of the abdominal wall.[233] The intra-abdominal approach is particularly suited for laparoscopy or robotic surgery, which provide excellent visualization. Several techniques have been described.[234] This can be performed in two ways. (1) The Sugarbaker technique in which the bowel is first lateralized along the abdominal wall. The mesh is placed over the entire fascial defect and under the lateralized bowel, and fixated circumferentially except laterally where the bowel exits to create a mesh flap valve around the stoma. (2) The Keyhole technique requires a 2- to 3-cm cutout is made in the mesh for the ostomy while widely covering the defect. This can be tricky as too small of an opening can obstruct the enterostomy while too large of an opening can result in recurrence, the mesh must be slit, then reclosed, in order to place it circumferentially around the ostomy. Recurrence rate is lower with Sugarbaker repair compared to keyhole when mesh is placed intraperitoneally.
4. Laparoscopic repair of parastomal hernia. Laparoscopic repair of parastomal hernias has the advantage of avoiding a large incision while providing superior view of the defect and allowing for intraperitoneal mesh placement.[235] Currently descried techniques of laparoscopic repair include: (1) modified Sugarbaker technique, (2) Keyhole technique, and (3) Sandwich technique which combines both these approaches. Reported recurrence rates range from 0% to 47% with infection rates up to 16%, conversion rates range from 0% to 15% and 10% rate of mesh explantation. Optimal mesh for this approach has not been determined, but a barrier-coated mesh is necessary.
5. Robotic-assisted repair of parastomal hernias is an extension of both the laparoscopic and open approaches. Many surgeons prefer the enhanced three-dimensional visualization as well as the flexibility afforded by instrument articulation, which allows reliable hernia defect closure and mesh fixation using suture. Robotic parastomal hernia repair can follow the traditional laparoscopic approach identical to that described above. However, the potential benefit of the robotic platform is the ability to perform more complex operations, such as the retromuscular sublay repair,

in a minimally invasive fashion, which can be performed using a keyhole mesh or an extraperitoneal Sugarbaker approach.

Prophylactic Mesh Placement

Recent randomized controlled trials and a recent meta-analysis have shown that prophylactic implantation of both biologic and synthetic mesh in a preperitoneal or sublay position for both ileostomies and colostomies is safe and effective and may be associated with some of these studies showing a decreased incidence (15% vs. 52%) of parastomal herniation.[236,237] Synthetic meshes are cost effective without added morbidity or mortality. These studies have had limitations such as small sample size, heterogeneous population, and variable follow-up. Prospective multicenter randomized controlled study comparing standard stoma creation to reenforcement with porcine acellular dermal matrix showed similar incidence of parastomal hernia at 24 months in both groups. Early results of the Danish PREVENT-trial demonstrates significantly lower rate of parastomal hernia at 1 year when sublay light-weight polypropylene mesh is used.[226] Further large scale randomized controlled trials with long-term follow-up are necessary to identify specific group of patients in whom reenforcement is essential and cost effective, and to identify the optimal mesh type and location for prophylaxis.[237]

UNUSUAL HERNIAS

Spigelian Hernia

A Flemish anatomist, Adriaan van der Spieghel, first described the semilunar line, which is the lateral limit of the posterior rectus sheath. Also called the spontaneous lateral ventral hernia, a Spigelian hernia protrudes through an area of weakness just lateral to the rectus sheath most often below the arcuate line (**Fig. 72.41**). The hernia is usually interparietal, rarely penetrating the external oblique fascia, and therefore can be difficult to appreciate. This is an unusual hernia; only 744 cases have been described in the literature. The typical presentation is lower abdominal swelling or pain just lateral to the

border of the rectus muscle, and commonly occur in elderly female patients. They are usually small, about 1 to 2 cm in diameter, although large hernias up to 14 cm in diameter have been described. Omentum and small or large bowel may enter the sac. Incarceration and strangulation may occur. Because the hernia is deep to the external oblique fascia, the clinical presentation may not be obvious. Pain and tenderness may be the only signs. Plain roentgenograms may show a bowel shadow in this area, and CT can demonstrate the defect well. Treatment is operative repair. For open repair, a transverse incision is centered over the mass. The external oblique aponeurosis is split to reveal the protrusion. If a large sac is present, it is divided and sutured. The aponeurotic defect is triangular, with its base at or near the lateral border of the rectus muscle. The defect is closed by joining the separated transversus and internal oblique layers. As these hernias are often partial thickness, laparoscopy is probably the preferred choice for repair, as the defect is readily visualized. A preperitoneal mesh repair is preferred.

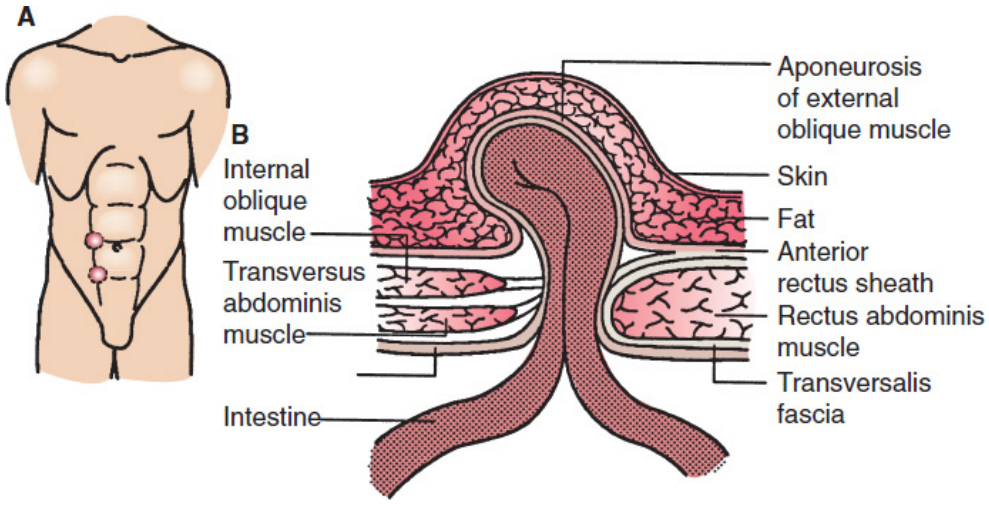


Figure 72.41 Spigelian hernia. **A:** Usual site of occurrence. **B:** Transverse section of abdominal wall showing site of defect.

Lumbar and Flank Hernias

The lumbar region is the area bounded inferiorly by the iliac crest and superiorly by the 12th rib, posteriorly by the erector spinae group of muscles, and anteriorly by the edge of the external oblique muscle as it extends from

the 12th rib to the iliac crest. The three varieties of primary lumbar hernia are described in **Table 72.14**. These hernias require repair if they are large or symptomatic, typically with mesh repair. A preperitoneal and retroperitoneal approach is most often used, and can be performed in an open, laparoscopic, or robotic fashion. For the inferior lumbar hernia, a rotation flap of fascia lata can be used (**Fig. 72.42**).[238,239]

Incisional hernias may also occur in the lateral abdominal wall when nonmidline incisions are required for various urologic, vascular, or neurosurgical procedures. This can lead both to true full-thickness incisional hernias, as well as partial-thickness defects or denervation and atrophy than appears clinically like a hernia, but without true anatomic defect. True incisional hernias are often larger than primary lumbar hernias and typically require repair. Options include a preperitoneal and retroperitoneal dissection to facilitate mesh reinforcement in this plane below the closed defect, and can be accomplished open, laparoscopically or robotically. For partial-thickness defects, a minimally invasive approach is sometimes helpful, as the external oblique layer is intact and the defect more difficult to identify from an open approach. For eventration in the absence of true hernia, nonoperative management is appropriate in most patients. If repair is desired due to significant size, abdominal wall and core instability, or patient young age, a similar approach with wide mesh reinforcement is appropriate, ideally in a sublay preperitoneal/retroperitoneal position, with plication of the redundant and atrophied overlying oblique musculature.[238,239]

Table 72.14 Types of Lumbar Hernia

Type	Description
Superior lumbar hernia of Grynfeltt	Occurs through a space between the latissimus dorsi, the serratus posterior inferior, and the posterior border of the internal oblique muscle
Inferior lumbar hernia of Petit	Occurs through a defect in the space bounded by the latissimus dorsi posteriorly, the iliac crest inferiorly, and the posterior border of the external oblique anteriorly
Secondary lumbar hernia	Develops as a result of trauma, mostly surgical (e.g., renal surgery), or infection; lumbar hernias were encountered relatively frequently in the past in cases of spinal tuberculosis with paraspinal abscesses

Obturator Hernia

This hernia is the result of abdominal contents protruding through the obturator canal in the pelvis. This canal is the opening in the superior part of the obturator membrane covering the foramen formed by the union of the pubic bone and ischium, through which the obturator nerve, artery, and vein pass from the pelvic cavity into the thigh. A recent history of profound asthenia and weight loss is not unusual, which is most likely due to the loss of the protective fat in the obturator canal.[240] This may account for the fact that women, more often than men, are afflicted with this hernia because their broader pelvis results in a larger obturator canal. The diagnosis of an obturator hernia is difficult because it is rare and physical examination is rarely helpful because the associated mass is concealed beneath the adductor muscles of the thigh. The main symptom is intermittent pain, however, this will classically present as bowel obstruction in the elderly patient in the absence of prior abdominal surgery. A helpful physical examination maneuver is the Howship-Romberg sign where inner thigh pain is experienced with internal rotation of the thigh. During repair, the defect is

approached transperitoneally; the hernia is reduced and mesh placed over the defect. Depending on the expertise of the responsible surgeon, either a conventional open or laparoscopic operation is reasonable, though laparoscopy offers the optimal visualization and ease of repair.

Sciatic Hernia

A sciatic hernia is a protrusion of a peritoneal sac through the major or minor sciatic foramen (**Fig. 72.43**). These very rare hernias present with a swelling on the buttock. The sciatic nerve may be involved. A ureter can become obstructed if it is included with the herniated tissues. The treatment of these hernias is surgical. Both transperitoneal and transgluteal approaches have been described. A combination of the two is sometimes used. The defect usually requires a prosthetic mesh repair.

Supravesical Hernia

This hernia is anterior to the urinary bladder and forms when the integrity of the transversus abdominis muscle and the transversalis fascia fail, both of which insert into Cooper ligament. The preperitoneal space is continuous with the retropubic space of Retzius, and the hernia sac protrudes into this area. The sac of the hernia is directed laterally, emerges at the lateral border of the rectus muscle, and presents in the inguinal, femoral, or obturator region. It can also be associated with an inguinal, femoral, or obturator hernia. Treatment of this hernia depends on recognizing it at the time of groin exploration and reinforcing the defect.

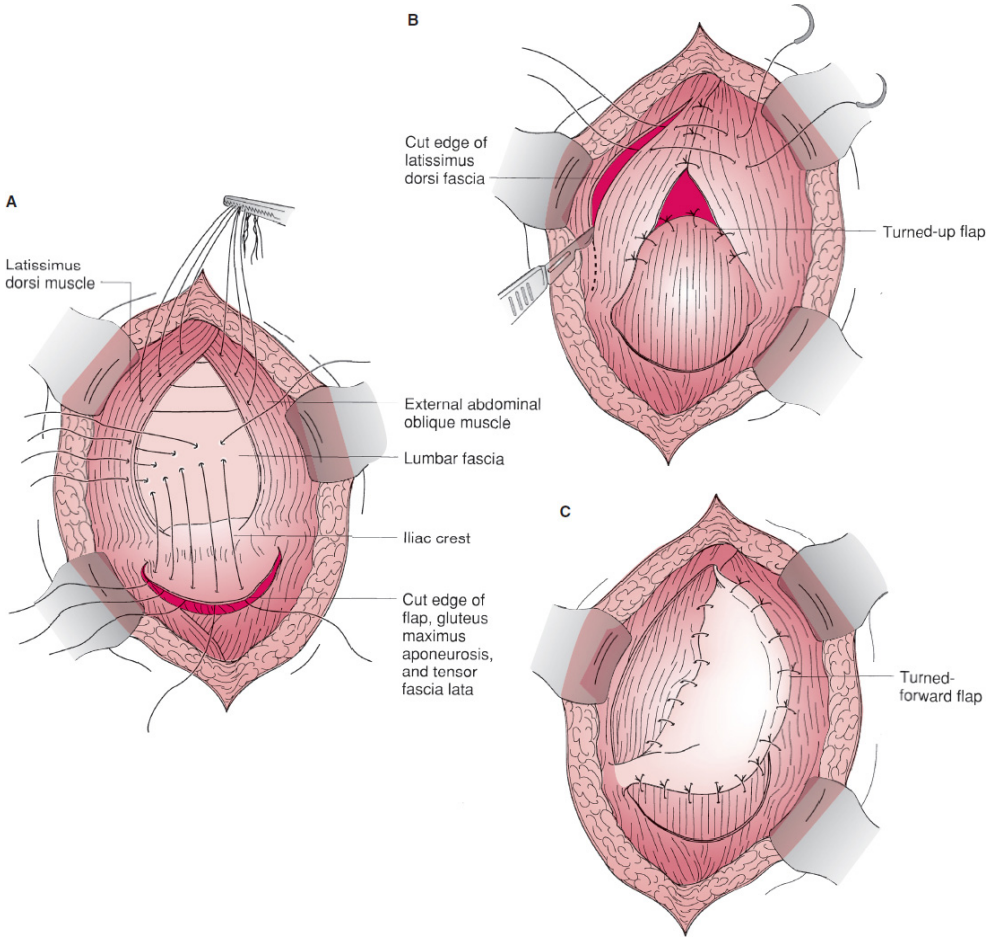


Figure 72.42 Technique of repair of inferior lumbar hernia.

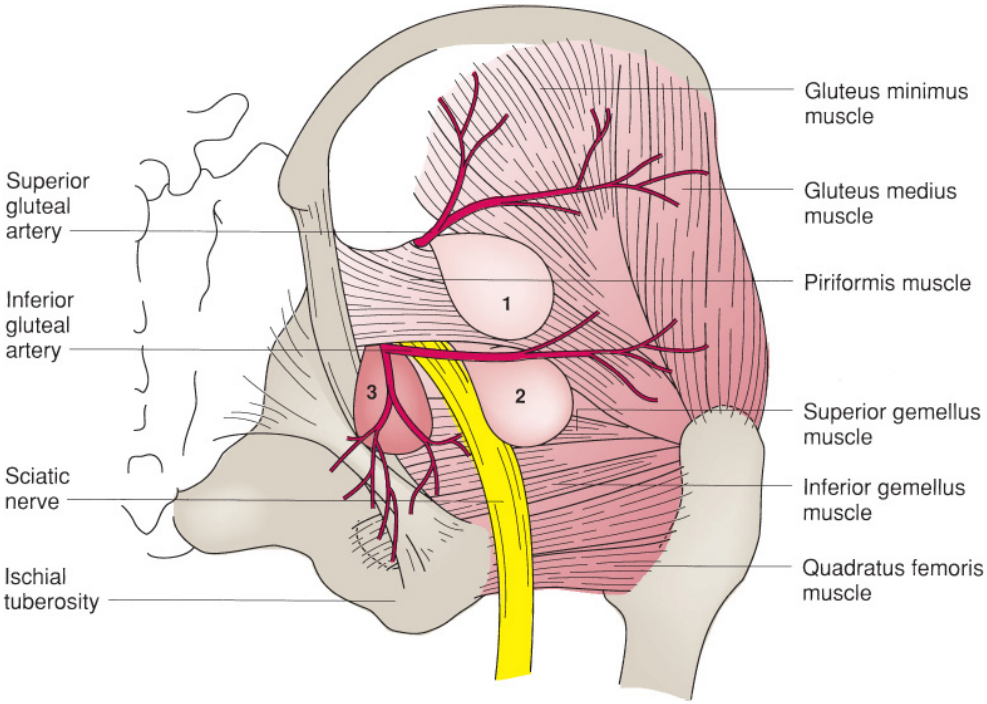


Figure 72.43 Sciatic hernia. **1:** Suprapiriform. **2:** Infrapiriform. **3:** Subspinous.

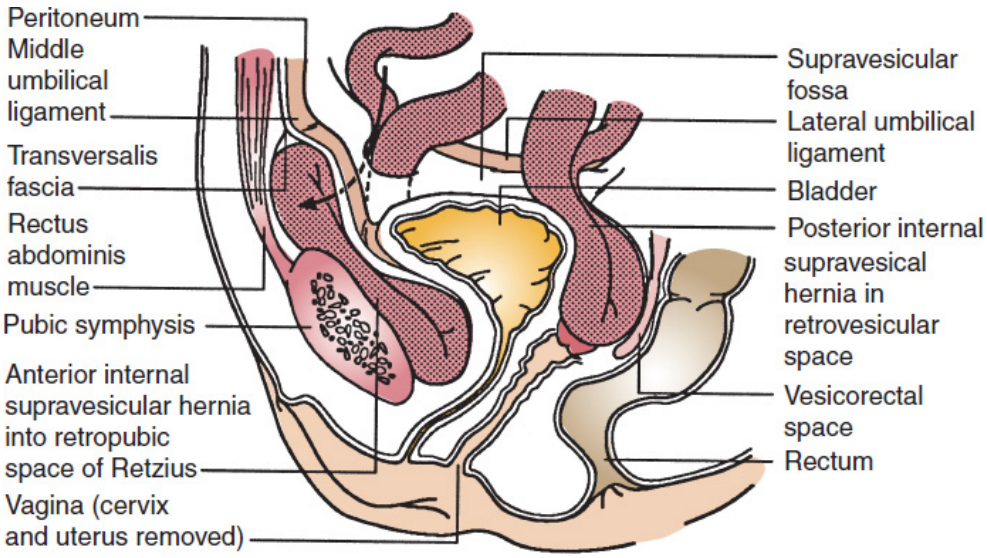


Figure 72.44 Internal supravesical hernias.

A second variety of these hernias is known as an internal supravesical hernia. They are classified according to whether they cross in front of, beside, or behind the bladder (**Fig. 72.44**). Bowel symptoms predominate in patients with these hernias, and urinary tract symptoms develop in up to 30%. The treatment is surgical, and a transperitoneal approach is used through a

low midline incision. The hernias can usually be reduced without difficulty. The neck of the sac should be divided and closed.

Interparietal Hernia

An interparietal, or interstitial hernia is a partial-thickness defect with herniation of visceral contents between layers of the abdominal wall. These may occur in the inguinal space, termed *inguinal interstitial* hernias. An *inguinal crural* hernia occurs when the sac passes behind the inguinal ligament in the region of the femoral ring. Spigelian hernias may be interparietal as well, as described above. The cause of these hernias appears to be related to congenital abnormalities; they have been associated with failure of the testis to descend, congenital pouches, and other abnormalities, such as absence of the cremaster and absence of the external abdominal ring. The diagnosis of these hernias is difficult because no swelling of the abdominal wall is obvious unless the hernia is large. Pain is commonly the only symptom, and it is not unusual for patients to present with intestinal obstruction secondary to incarceration. CT, ultrasonography, and laparoscopy can be helpful in making the diagnosis. Not infrequently, the correct diagnosis is made only at operation. The defect is repaired according to the principles described for inguinal and incisional hernias.

Acquired interparietal hernias are an uncommon but important complication of retromuscular hernia repairs, occurring after both open and robotic repairs. These occur due to disruption of the closed posterior rectus sheath or other defect in the peritoneum, allowing viscera to herniate through the posterior sheath, while the anterior fascia and mesh typically remain intact anteriorly. Incidence is approximately 1% and most often presents in the early post-operative period as a bowel obstruction. A high index of suspicion is needed to detect these defects, and CT is needed for diagnosis. Bowel can be seen against the abdominal wall with the disrupted posterior sheath angulated downward away from the abdominal wall, pinching the bowel at the neck of the hernia. Acute repair is needed and can be accomplished with laparoscopic exploration, reduction of the herniated contents, and obliteration of the potential space between the posterior sheath and anterior mesh. Tacks, transfascial sutures, or intraperitoneal mesh, either absorbable or barrier coated, are all viable options, the aim of which is to

prevent any subsequent herniation back into the retromuscular space. More chronic or subacute presentation does occur, and treatment is aimed at relief of presenting symptoms.[165,241]

Littre Hernia

Littre hernia is a groin hernia containing a Meckel diverticulum. These hernias sometimes also contain the appendix. If the diverticulum is symptomatic or strangulated, then it is mandatory to resect it at the time of the hernia repair.

Perineal Hernia

These hernias are more common in older female patients and are related to a lax pelvic floor. They are termed *anterior* or *posterior* according to their relationship to the transverse perineal muscle. The anterior hernias usually present as a swelling in the labium or lateral vaginal wall. The posterior hernias present between the rectum and the ischial tuberosity. Surgical repair requires a transperitoneal or posterior approach, and, if the opening is large, a prosthetic mesh repair is required.

Perivascular Hernia

These hernias present through defects between the inguinal ligament and the iliopubic bone. They are known by various eponyms according to their position. The hernia protruding through a defect in the lacunar ligament is *Laugier hernia.* The hernia protruding through the pectineal fascia is *Cloquet hernia.* The hernia extending anterior to the femoral vessels but behind the inguinal ligament is *Velpeau hernia.* The hernia behind the vessels is *Serafini hernia.* Lateral to the femoral artery are two hernias, the anterior one being *Hesselbach hernia* and the more posterior one *Partridge hernia* (**Fig. 72.45**).

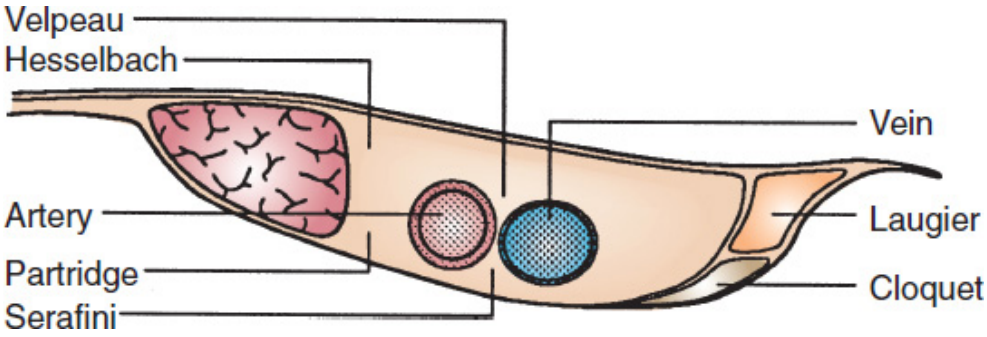


Figure 72.45 Perivascular hernias and their eponyms.

COMPLICATIONS OF VENTRAL HERNIA REPAIR

Ventral hernia repair and abdominal wall reconstruction is complex, and the incidence of complications depends on multiple factors including the complexity of the hernia repair, the technique used, mesh selection, and patient comorbidities. It is often difficult to parse and compare complications between different procedures and meshes in the literature due to the lack of comparative trials as well as nonstandardized nomenclature. The recently developed terminology of SSO, which includes both the commonly understood SSI as well as other noninfectious wound complications, provides a good framework for reporting and better comparison across hernia studies.[242] Several risk calculators are available to assist in optimizing patients for surgery, selection of the optimal surgical approach, and for informed consent. The American College of Surgeons National Surgical Quality Improvement Project (ACS NSQIP) risk calculator accounts for patient-related factors for morbidity and mortality. The Ventral Hernia Risk Score (VHRS), Hernia Wound Risk Assessment Tool (HWRAT), Ventral Hernia Working Group (VHWG), the Carolinas Equation for Determining Associated Risks (CeDAR), the Michigan Surgical Quality Collaborative (MSQC), and the Americas Hernia Society Quality Collaborative Outcomes Reporting App for Clinician and Patient Engagement (AHSQC ORACLE) are all available tools to assist the surgeon in predicting the risk of wound and general complications following VHR (**Fig. 72.46**, **Table 72.16**).[243,244] These scoring systems have been developed

using variable methodology, primarily based on retrospective or registry-based data, and none to date have been externally, independently validated.

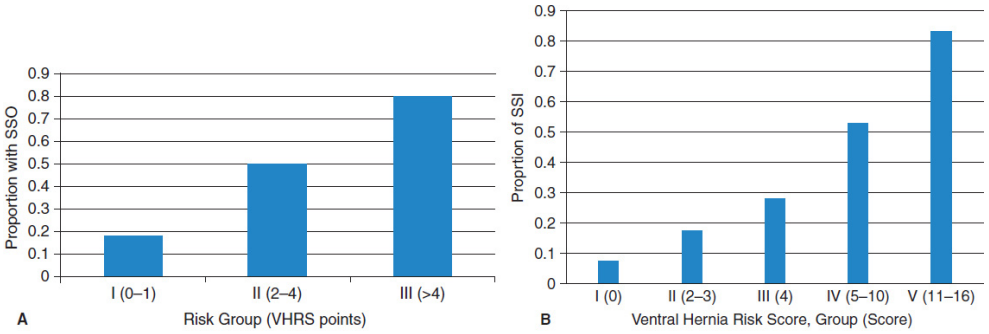
General Complications

There are many complications inherent to abdominal surgery, and VHR is no exception. Postoperative ileus, early SBO, cardiac, pulmonary, and renal complications can all occur following any VHR. These can be mitigated somewhat by choice of technique, with open repairs tending to have a higher risk of ileus, SBO, or wound complications. Cardiac arrhythmias may complicate pneumoperitoneum during laparoscopic or robotic repair. Urinary retention may occur in complex cases, particularly if dissection is required around the bladder. Pulmonary complications may be increased with some complex VHR, particularly large hernia defects and those with loss of domain. Attempting to reviscerate the herniated contents into the abdominal cavity and close the hernia defect may require significant tension, resulting in significant increase in intra-abdominal pressure. This may result in early postoperative respiratory insufficiency or failure, pneumonia, prevent initial extubation, or in the extreme result in abdominal compartment syndrome. Attention must be paid to airway pressures and other ventilatory parameters, along with intra-abdominal pressure, in such cases. All ventral hernia patients should be considered high risk for venous thromboembolic complications and be prophylaxed accordingly.

Surgical Site Infection

SSI is defined by the Center for Disease Control (CDC) and is divided into three types by the depth of the infection. Superficial SSI involves only the skin and subcutaneous tissue of the associated incision, presenting within 30 days with typical signs of infection including tenderness, swelling, erythema, or heat. Diagnosis requires one of these signs along with purulent drainage, positive culture, or deliberate opening of the surgical wound. This does not include cellulitis, stitch abscess/granuloma, or infection at stab incisions. This is the most common type of SSI with most hernia repairs. Deep SSI involves the fascia or muscle layers, also presenting with typical signs of infection. Also included in the criteria are fever, spontaneous wound

dehiscence, or abscess. Infection occurring in the retromuscular compartment or preperitoneal space after abdominal wall reconstruction would be considered a deep space infection. Organ-space SSI can have differing definitions depending on the procedure performed. For the purpose of hernia repair, these occur deep the abdominal wall musculature in the intra-abdominal compartment. Diagnostic criteria include purulent drainage from organ-space drains, percutaneously placed drains in fluid collection/abscess cavity with positive culture, or intra-abdominal sepsis.



	VHRS for SSO	VHRS for SSI
OR	Points	Points
Mesh implant	2	—
Concomitant hernia repair	2	2
Skin flaps created	2	2
ASA score ≥3	—	2
BMI ≥40	—	3
Wound class 4	9	7

Figure 72.46 **A, B:** Ventral Hernia Risk Score (VHRS) for surgical site occurrence and surgical site infection.

Table 72.15 Complications of Herniorrhaphy

Related to Laparoscopy
- Vascular injury
  - Intra-abdominal
  - Retroperitoneal
  - Abdominal wall
  - Gas embolism
- Visceral injury
  - Bowel perforation
  - Bladder perforation
- Trocar site complications
  - Hematoma
  - Hernia
  - Wound infection
  - Keloid
- Bowel obstruction
  - Trocar or peritoneal closure site hernia
  - Adhesions
  - Diaphragmatic dysfunction
  - Hypercapnia

Related to Patient
- Urinary infection
- Ileus
- Nausea and vomiting
- Aspiration pneumonia
- Cardiovascular and respiratory insufficiency

Related to Herniorrhaphy
- Recurrence
- Neurologic
  - Iliohypogastric
  - Ilioinguinal
  - Genitofemoral
  - Lateral cutaneous
- Cord and testicular problems
- Wound infection
- Seroma
- Hydrocele
- Hematoma
  - Wound
  - Scrotal
  - Retroperitoneal
- Osteitis pubis
- Prosthetic complications
  - Contraction
  - Erosion
  - Infection
  - Rejection
  - Pain

Table 72.16 HW RAT Breakdown of Risk Factors for Wound Complications

Risk Grouping	Risk Factors	Risk Score
Mild risk factors (+1)	Diabetes	1
	COPD	1
	Class I obesity	1
	45–64 yrs old	1
	Intra-abdominal procedure	1
Intermediate risk factors (+2)	Smoking	2
	ASA physical status >2	2
	Panniculectomy	2
	Clean-contaminated wound	2
	Partially dependent functional status	2
	Low albumin	2
	<45 yrs of age	2
	Operative time 43–71 (min)	2
Moderate risk factors (+3)	Totally dependent functional status	3
	Inpatient operation	3
	Class III obesity	3
	Component separation	3
Severe risk factors (+4 or more)	Contaminated wound	4
	Operative time (71–117 min)	4
	Dirty/infected	5

	wound		
	Operative time (>118 min)	6	
HW-RAT	**Risk Score**	**Number of Patients (%)**	**Incidence of SSO (%)**
1	0–10	16,097 (59.6%)	538 (3.3%)
2	11–13	5,784 (21.4%)	536 (9.3%)
3	14–16	2,861 (12.3%)	472 (14.2%)
4	17–19	998 (21.7%)	217 (21.7%)
5	>19	812 (3.0%)	215 (26.5%)

Table 72.17 Summarizes the International Guidelines for Groin Hernia Management

Grade 3/4

- Mesh-based repair is recommended for adult inguinal hernias.
- Flat mesh Lichtenstein technique is recommended over 3-dimensional implants.
- Laparo-endoscopic (TEP or TAPP) technique is suggested for male primary unilateral hernias.
- Shouldice technique is recommended in nonmesh repair.

Grade 4/4

- Antibiotic prophylaxis is not recommended in average-risk cases.
- Local anesthesia is recommended for reducible open repair.
- Timely repair, laparoendoscopic technique, and consideration of femoral hernias are recommended in female groin hernias.
- Minimizing spermatic cord trauma reduces orchialgia.
- Laparoendoscopic repair is recommended after failed anterior repair.
- Anterior repair is recommended after a failed posterior repair.
- Considering cost-effectiveness, day-case laparoendoscopic repair is recommended.

The risk of SSI increases with increasing level of contamination of the operation, with dirty or infected wounds having the highest risk of infection at around 40%. Other factors also contribute to this risk including smoking, COPD, diabetes, obesity, immune compromise, history of infection, and surgical technique. As discussed above, many of these risk factors are modifiable and should ideally be addressed prior to surgery. Most SSIs require treatment of some kind, referred to as an SSI requiring procedural intervention (SSOPI). This can include the use of antibiotics, wound opening, wound debridement, suture excision, or percutaneous drainage. If the infection involves the prosthetic mesh, partial or complete mesh removal may also be required. The risk of SSI can be mitigated with preoperative optimization of patient comorbidities, choice of surgical approach, and meticulous sterile technique. Minimally invasive approach has been clearly demonstrated to lower the risk of SSI, but is not appropriate for all patients

for a variety of reasons. Other strategies such as use of antimicrobial mesh, minimal handling of the mesh itself (the "no-touch technique"), use of iodine impregnated drapes, and antibiotic irrigation have some support in the literature as well, though no level 1 data currently support any of these practices.

Surgical Site Occurrence

There are a variety of wound complications that can occur as a result of hernia repair and AWR that do not meet the criteria for SSI. Current nomenclature refers to these as Surgical Site Occurrences (SSOs), though this term is sometimes used as a broader term under which SSI is included. Included under SSO are seroma or serous wound drainage hematomas, cellulitis, skin and soft tissue ischemia or necrosis, exposed prosthetic mesh, or enterocutaneous fistula. This also allows specific descriptors of the origins of some types of SSI, such as infected seroma or hematoma, infected or contaminated prosthetic mesh, or purulent wound drainage. As with SSI, intervention is sometimes necessary for treatment (SSOPI), though often simple SSOs, such as seroma, can be managed expectantly without intervention. Noninfectious SSOs can be reduced with the use of drains, though their use does not confer protection against SSI.[245]

Mesh-Related Complications

Among the most feared complications of VHR is a complication related to the implanted prosthetic mesh. This can include mesh infection or periprosthetic infection, exposed mesh, extrusion of mesh through the skin, or enterocutaneous fistula. Mesh infection is typically reported in <1% of laparoscopic or robotic cases and <5% for open repair. The risk of mesh erosion or fistula is unknown, with data limited primarily to case reports or small case series. The risk of any of these complications and the treatment required varies greatly by presentation, mesh type, and mesh location. Generally speaking, no particular mesh seems to be a higher risk of infection when used in clean cases. However, the properties of the mesh and location within the abdominal wall seem to have significant impact on the treatment needed. Intraperitoneal mesh typically requires removal, though there are

reports of salvage. Treatment of extraperitoneal mesh infection, those placed in the preperitoneal, retromuscular or onlay position, varies more by mesh type. Generally, microporous, multifilament, laminar, or composite mesh requires complete removal, whereas monofilament, large-pore mesh is salvage in the majority of cases. In the event of enterocutaneous fistula, mesh removal is generally required. Fistula can occur as an acute complication after hernia repair, typically as a result of unrecognized enterotomy, or can present late due to mesh erosion into the viscera or a subsequent abdominal operation. Mesh removal is universally required for intraperitoneal mesh in both the acute and late setting. For mesh in an extraperitoneal position, there are reports of spontaneous closure despite presence of the mesh, though partial or complete mesh removal are frequently required (**Table 72.15**).[50,192]

Complications Related to Laparoscopy

These complications have been described above and include gas embolism, visceral injury, bladder injury, bowel obstruction, diaphragmatic dysfunction, and hypercapnia.

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73

The Spleen

Oliver A. Varban and Anne P. Ehlers

Key Points

1. The spleen is a lymphatic organ with hematologic and immunologic function that is located in the left upper quadrant of the abdomen, relating to the diaphragm both superiorly and laterally and spans the 9th, 10th, and 11th ribs posteriorly.
2. Considered the second largest secondary lymphoid organ in the body, the normal size of the spleen is approximately 13 × 7 × 4 cm and the typical weight of a spleen is 150 to 200 g.
3. Accessory spleens are small nodules of splenic tissue that can be found in the tail of the pancreas, hilum of the spleen, gastrosplenic or splenorenal ligament, greater omentum, or in the pelvis.
4. The spleen removes senescent erythrocytes, remodels abnormal red blood cells (RBCs), recycles iron, and generates B- and T-lymphocytes in response to antigens.
5. The spleen facilitates opsonization and phagocytosis of encapsulated organisms including *Streptococcus pneumonia, Haemophilus influenzae, and Neisseria meningitidis*. Vaccines targeting encapsulated organisms can prevent overwhelming postsplenectomy infection.
6. Indications for splenectomy include trauma, hematologic and malignant disorders, cysts and infections and before allogenic hematopoietic stem cell transplant.
7. Physical enlargement of the spleen can occur as a result of neoplastic, infectious, inflammatory, congestive, infiltrative, and hematologic conditions.

INTRODUCTION

An understanding of splenic anatomy and physiology is important for both surgical decision making but also operative technique. Splenic diseases other than trauma have generally included hematologic or immunologic conditions. Historically, open total splenectomy was the only procedure applied for the

treatment of splenic disease, however current variations include a minimally invasive approach as well as spleen-preserving procedures. The surgical history of the spleen, its anatomy, physiology, indications for operative management, and techniques are reviewed.

HISTORY

The spleen has long been considered a mysterious organ with various descriptions of its function throughout history. Beginning in ancient Greece, Plato believed that the spleen's function was "to maintain the liver bright and pure."[1] Hippocrates described its role in producing one of the four vital humors—"black bile," which was later considered to be related to feelings of melancholy.[1] Terms such as "spleenful" and "spleenless" persisted even into the 17th century as a means to describe those with and without morose feelings, ill humor, malice, or spite.[2] The spleen has even been associated with the ability to run, with references to performing splenectomy in ancient literature as a means to allow men and horses to run faster. By the 14th century, descriptions of splenic anatomy improved and included Mondino De Liucci identification of short vessels from the stomach when studying splenic vascularization. In the early 16th century, Paracelsus rejected the black bile theory and began to question its physiologic function, reporting that the spleen was a superfluous organ that should be excised when diseased. During the same era, Versalius performed splenectomy in mice and other animals without adverse effects, supporting the theory that the spleen was not essential to life. It wasn't until 1911 when Micheli identified the spleen as the site of red cell destruction in autoimmune hemolytic anemia. In 1916, Paul Kaznelson, who was a Czech medical student, postulated that the removal of the spleen in patients with idiopathic thrombocytopenic purpura would be of benefit.

1 The first reported splenectomy was performed by Adriano Zaccaria in 1549, in Palermo Italy on a 24-year-old lady with malarial splenomegaly.[1] According to the report, the spleen weighed 1,340 g and the recovery from surgery was 24 days. Subsequent procedures were performed for a variety of indications. In 1826, Carl Frederick Quitterbaum performed a splenectomy for secondary hypersplenism due to cirrhosis. Meanwhile, Jules Pean

performed a splenectomy for a large cyst in France in 1865. By 1900, Bessel-Hagen reported on 360 splenectomies and noted a 40% mortality rate.[3] Conservative therapy for splenic disease was first explored during war-time periods, with Franciscus Roestti credited for performing the first successful partial splenectomy for trauma in 1590. By the 20th century, technical advances in hemostasis and blood transfusion as well as an understanding of the pathophysiology of splenic function led way to improved surgical outcomes.[4] The first laparoscopic resection was described in 1992 and has become well accepted, becoming the "gold standard" for surgical treatment for immune thrombocytopenia purpura.[5,6]

EMBRYOLOGY AND ANATOMY

The spleen develops as an outpouching from the mesogastrium during the 5th week of gestation.[4,7,8] The spleen's typical position in the left upper quadrant is the result of the natural rotation of the gut during development. In that location, the spleen relates to the diaphragm both superiorly and laterally, and it generally spans the 9th, 10th, and 11th ribs along the left mid to posterior axillary line (**Fig. 73.1**). The ventral surface of the spleen relates to the greater curvature of the stomach and the tail of the pancreas. The tail of the pancreas touches the splenic capsule in 30% of cases and is 1 cm away in 70% of cases. The inferior pole relates to the left kidney posteriorly and the splenic flexure of the colon anteriorly (**Fig. 73.3**).

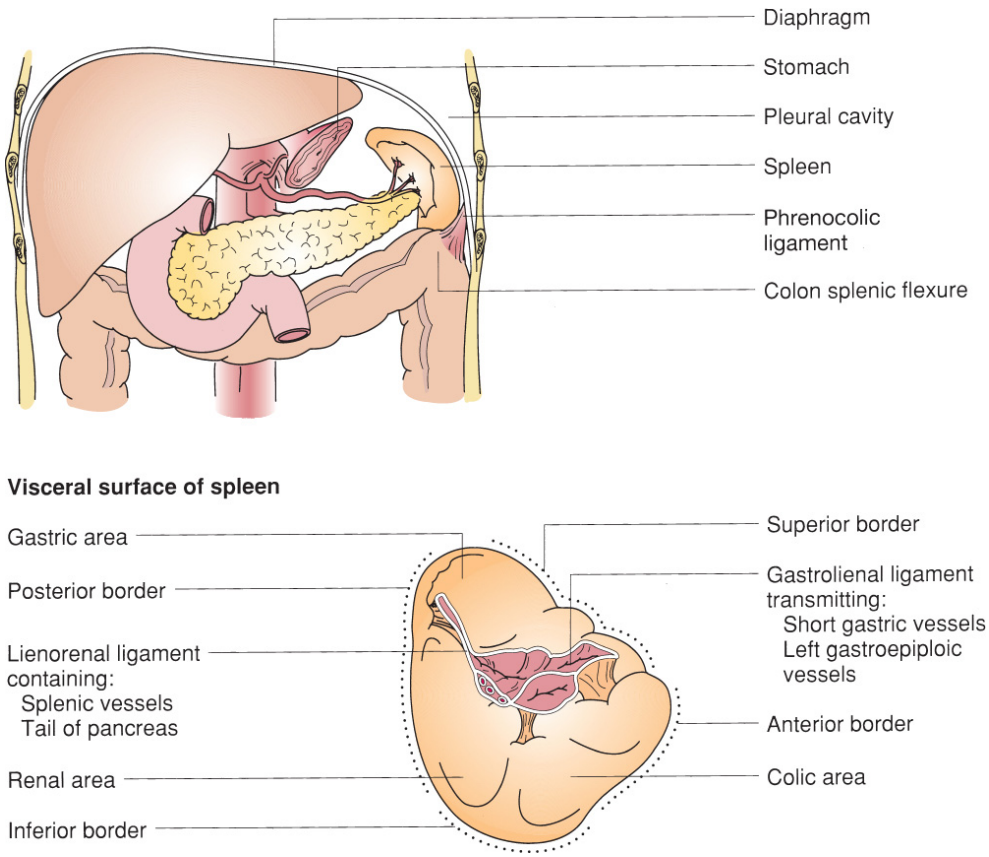


Figure 73.1 Anatomic relation of the spleen to the liver, diaphragm, pancreas, colon, and kidney. The stomach is sectioned to illustrate the anatomic relation in situ.

The typical spleen is 13 × 7 × 4 cm in size and weighs approximately 150 to 200 g.[7,8] In the elderly population the typical weight of a spleen decreases to approximately 100 g.[9] In general, the tip of the spleen can be palpated below the costal margin once it has doubled in size to range of 300 to 400 g.[10] The definition of massive splenomegaly has been arbitrarily set at 1,500 g or 10 times the average adult splenic weight. The spleen can also develop a significant cleft, which can be confused with splenic disruption on CT.

The vascular anatomy of the spleen includes the splenic artery, splenic vein, and short gastric vessels (**Fig. 73.2**).[11] The blood flow to the spleen in the typical adult is estimated to be 200 to 300 mL/min or approximately 5% of the cardiac output. The splenic artery is one of the major trunks branching off from the celiac axis and generally travels outside the parenchyma of the pancreas along the superior border. In some cases, the splenic artery is covered by the posterior surface of the pancreas and branches from splenic

artery are generally found in this location. The first major branch point along the splenic artery typically occurs between 2 and 3 cm from the hilum and it is called the superior polar artery. Subsequent branch points can vary from three and five segmental branches that enter along the trabeculae of the spleen. Additional blood supply from the short gastric vessels originates from the left gastroepiploic artery. The spleen is also capable of developing blood supply originating from the omentum, diaphragm, or the mesentery of the splenic flexure of the colon, particularly in the diseased state or when enlarged. Segmental venous branches that leave the trabeculae form the main splenic vein in the hilum of the spleen. The splenic vein is commonly associated with the posterior surface of the tail and body of the pancreas and forms a junction with the superior mesenteric vein prior to entering the portal vein. The inferior mesenteric vein may join the splenic vein directly at several areas along its course or may come together right at the junction of the superior mesenteric vein. In addition, there are again several pancreatic branches that directly enter this splenic vein. The lymph node drainage of the spleen follows the vasculature. Primary lymph nodes are located in the hilum of the spleen as well as along the splenic artery, typically located at the superior border of the pancreas and along the short gastric vessels.

The spleen remains fixed in position in the left upper quadrant primarily by the splenogastric, splenorenal, and splenocolic ligaments and mobilization of the spleen during splenectomy involves division of these ligaments (**Fig. 73.3**).[10] Ligaments are absent in the setting of "wandering spleen," in which the spleen may be found outside of the left upper quadrant and often in the pelvis.[12] The splenogastric ligament is a superior extension of the greater omentum along the proximal greater curvature of the stomach and the area includes short gastric vessels supplied by the left gastroepiploic vessels. The splenorenal ligament runs parallel to the posterolateral border of the spleen and attaches to the superior pole of Gerota fascia. The splenocolic ligament is short, associated with the splenic flexure of the colon and may be avascular or have small blood vessels that need to be controlled with ties or clips during mobilization of the splenic flexure. The splenoomental and splenophrenic ligaments are variably present and the greater omentum may be associated with the splenic capsule along the inferior pole. In order to avoid disruption of the inferior capsule of the spleen, it is imperative to investigate the extent of these attachments and divide them

prior to exerting vigorous traction along the omentum. Splenophrenic ligaments are more likely to be present when the spleen is enlarged or diseased and may be avascular or have branches of vessels that parasitized from the blood supply of the diaphragm.

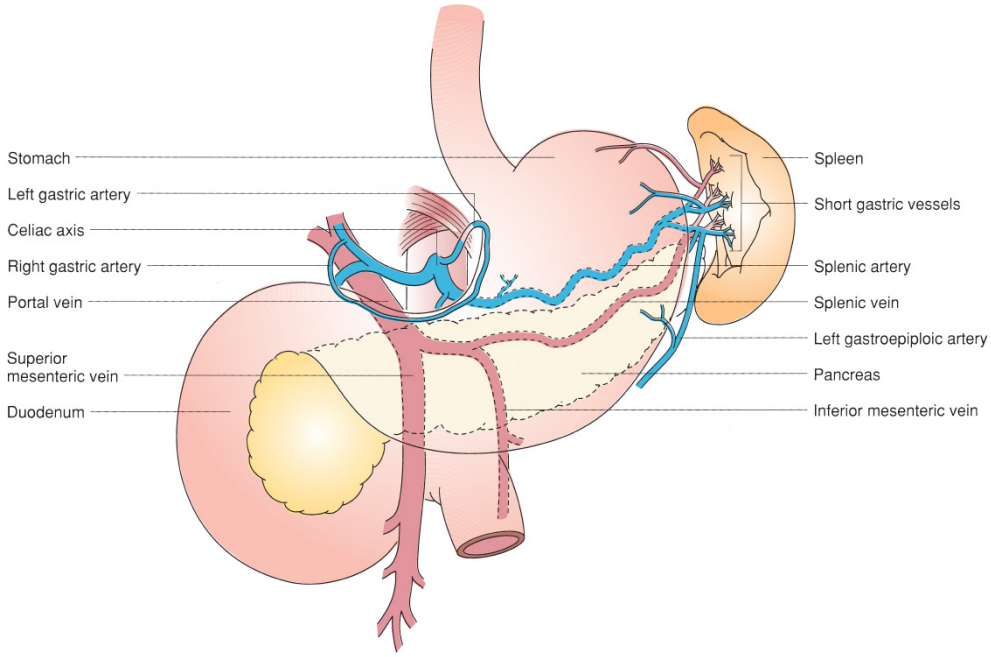


Figure 73.2 The arterial blood flow to the spleen is derived from the splenic artery, the left gastroepiploic artery, and the short gastric arteries (vasa brevia). The venous drainage into this portal vein is also shown.

2 The parenchyma of the spleen consists of white pulp, which surrounds the arteries, a marginal zone, and red pulp that comprises 75% of the spleen.[13,14] Arteries and veins feed the segmented anatomy of the spleen via trabecula, which are fibrous bands that attach to the splenic capsule.[11] The capsule of the spleen consists of a single layer of mesothelium and several layers of fibroelastic tissue. Trabecular arteries that enter the spleen are a continuation of the segmental arterial branches that form perpendicular branches and the central arteries (**Fig. 73.4**). Periarterial lymphatic sheath surround the central arteries and are composed of T lymphocytes and follicles with B cells at various stages of development. Secondary follicles form during antigenic stimulation. The marginal zone contains a mixture of lymphatics and macrophages, while the red pulp is made up of splenic cords, known as cords of Billroth as well as splenic sinuses. The splenic cords are a meshwork of fibroblasts and mature macrophages. The splenic sinuses are

an interconnective meshwork of thin-walled red cell spaces that are generally filled with erythrocytes.[14] Blood flow through the spleen can be both fast and slow.[15] Approximately 90% of the splenic blood flow is slow as erythrocytes travel through the fenestrated meshwork of the red pulp and relates to the role of clearing senescent erythrocytes. The fast flow pattern involves a greater volume of plasma and fewer erythrocytes allowing blood to flow through the splenic arteries and return rapidly to the splenic veins.

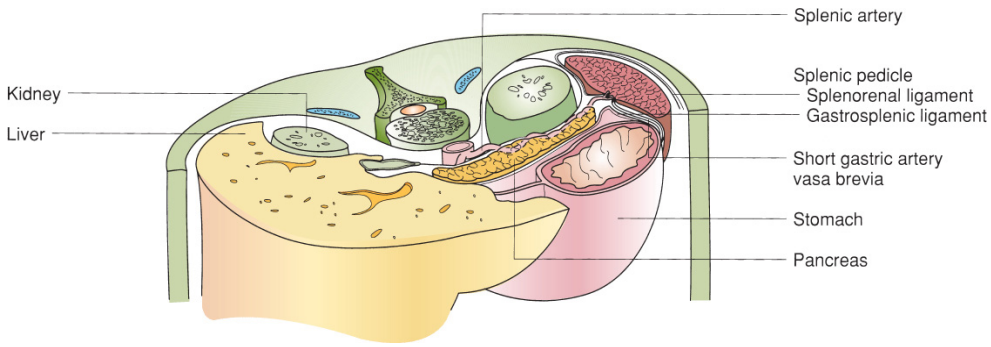


Figure 73.3 The relations of the spleen to the abdominal and retroperitoneal viscera are seen in a cross-section of the left-facing torso.

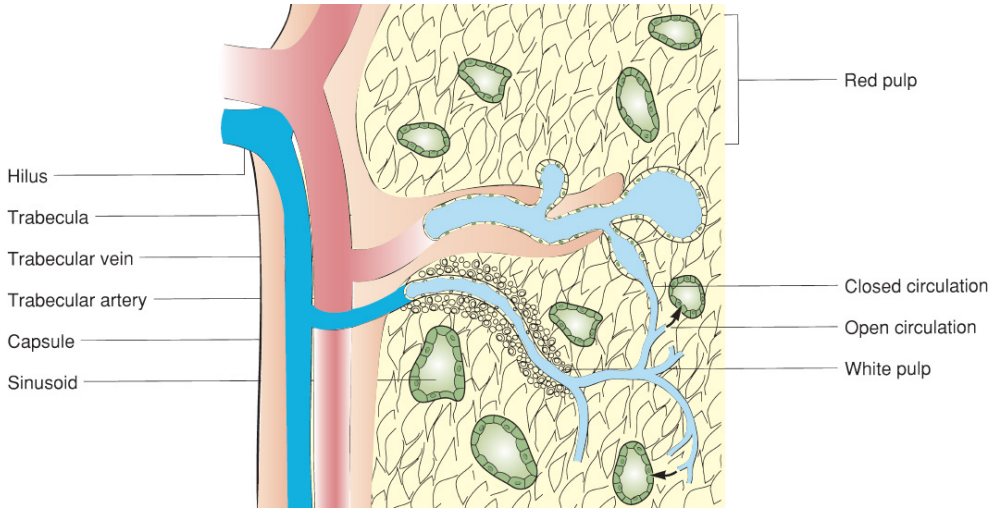


Figure 73.4 The splenic microanatomy is shown with depictions of both the open and closed circulations.

3 Accessory spleens are small nodules of splenic tissue (0.5 cm up to 3 to 4 cm) that are completely separate from the main body of the spleen and can be found in the splenic hilum, the omentum, small bowel mesentery, and less commonly in the retroperitoneum behind the spleen or in the pelvis. The

reported incidence of accessory spleens ranges between 10% and 20% and should be removed managing autoimmune disorders.[16] Nuclear scan of the spleen can be performed when trying to identify sources of residual splenic tissue and accessory spleens.[17]

PHYSIOLOGY

The spleen performs two major functions: hematologic and immunologic (**Table 73.1**).[14] The hematologic function involves destruction or clearance of the circulating blood cell elements as well hematopoiesis and storage of blood cells, consisting predominantly of platelets. In terms of the immunologic functions, the spleen generates cellular and humoral immune responses by producing specific antibodies, in particular to opsonized antigens and specific encapsulated microorganisms.

Hematologic Function of the Spleen

4 The hematologic function of the spleen includes removal of senescent erythrocytes, remodeling of abnormal red blood cells (RBCs), and recycling of iron by splenic macrophages (**Table 73.2**).[14] The average life span of a normal erythrocyte is estimated to be approximately 120 days.[18] Removal of erythrocytes occurs via phagocytosis performed by macrophages and is called culling. Hemoconcentrated erythrocyte-laden fluid enters the sinuses of the red pulp and flows slowly through a sinusoid network with adjacent cords filled with macrophages. The precise mechanism by which senescent red cells are identified for destruction in normal physiology is unclear. However, one hypothesis is that red cells become less compliant over time and are more prone to being trapped in the mesh of the sinusoids. Another hypothesis is that specific cell surface marker molecules are involved in identification of senescent cells targeted for destruction. Decreased pliability of erythrocytes occurs with conditions such as hereditary spherocytosis, elliptocytosis, and sickle cell anemia, resulting in destruction with clogging of the sinusoids and hypersplenism.

Erythrocytes can also undergo remodeling or pitting, which involves partial removal of the cell membrane typically associated with the

cytoplasmic inclusions, resulting in a larger size and thus will pass more slowly through the splenic red pulp.[14] Also, the nuclear remnant may be trapped passing through a small space in the spleen and pitting occurs when the solid particle that does not allow deformation gets pinched off. Intracytoplasmic inclusions include Howell–Jolly bodies that are nuclear remnants, Heinz bodies that are denatured hemoglobin, and Pappenheimer bodies that are iron granules.

Table 73.1 Normal Functions of the Spleen

Hematologic
Culling or destruction of senescent erythrocytes
Pitting or removal of cytoplasm inclusive in erythrocytes
Reservoir for platelets and granulocytes
Hematopoiesis—as fetus or in conditions with bone marrow destruction
Immunologic
Filtration and trapping of circulatory antigens
Lymphocyte stimulation and proliferation
Antibody production in germinal follicles
Production of opsonin: tuftsin and properdin
Opsonins: tuftsin and properdin

Table 73.2 Hematologic Changes Postsplenectomy/Hyposplenic Condition

1. Erythrocytes
    1. Howell–Jolly bodies (nuclear fragments)
    2. Heinz bodies (hemoglobin deposits)
    3. Pappenheimer bodies (iron deposits)
    4. Target cells
    5. Spur cells (acanthocytes)
2. Platelets
    1. Transient thrombocytosis
3. Leukocytes
    1. Transient leukocytosis
    2. Persistent lymphocytosis
    3. Persistent monocytosis

Destruction of circulating cellular elements in the blood (i.e., platelets and leukocytes) occurs in diseased states. If either platelets or white blood cells become coated with antibodies, the Fc portion of the immunoglobulin will interact with the Fc receptors on the macrophages in the splenic cords leading to phagocytosis of these cell types. Hypersplenism alone may also result in destruction of cells even without autoantibodies or defects in the cells.

During gestation, the spleen serves as a source for hematopoiesis of all cell types and in certain disease states, the spleen may develop the capacity for erythropoiesis and myelopoiesis. Germinal centers in the white pulp of the spleen produce reactive lymphocytes and the cords of the spleen are filled with macrophages. Finally, the spleen is also a reservoir of circulating cellular elements and it is estimated that 30% of all platelets resides in the spleen.[19]

Immunologic Function of the Spleen

The spleen is involved in generating an immune response to circulating opsonized antigens or specific encapsulated microorganisms so they may be

trapped by the spleen. Phagocytic cells, dendritic cells, T cells, and B cells can be found in the marginal zone of the white pulp in the spleen and can generate specific antibody responses. The cellular components and structure of the germinal follicles is anatomically similar lymphatic tissue and becomes enlarged in a similar fashion when simulated by antigens from microbes.

The spleen is also responsible for synthesizing opsonins, such as properdin and tuftsin. Tuftsin is a small peptide that binds to the surface of granulocytes and promotes phagocytic function by these cells.[20] Properdin can initiate the alternate pathway of complement activation, which results in destruction of abnormal cells or bacteria that are bound by antibodies. Since the spleen is not the only source of these nonspecific immune-enhancing proteins, splenectomy only leads to a modest alteration in this function.

PATHOPHYSIOLOGY

Hyposplenism and hypersplenism are broad categories that describe common pathophysiology of the spleen. These categories provide guidelines for deciding who should undergo splenectomy and also how to manage patients postoperatively.

Table 73.3 Causes/Disorders Associated with Hyposplenism
Splenectomy
Sickle cell anemia
Congenital asplenia (autosomal recessive disorder)
Autoimmune disorders (e.g., glomerulonephritis and SLE)
Celiac disease/inflammatory bowel disease
Tumor or cystic replacement of spleen
Amyloidosis
Splenic vascular accident
Radiation

SLE, systemic lupus erythematosus.

Hyposplenism

5 Causes for hyposplenism are listed in **Table 73.3**. While the most common cause is due to splenectomy,[21] congenital asplenia or autoimmune disorders resulting in the destruction of splenic tissue can be investigated by ^{99}Tc-labeled spleen scan or pitted RBC count.[17] Pathophysiologic consequences of hyposplenism includes an increase in Howell–Jolly bodies, Heinz bodies, and Pappenheimer bodies as well as an increase in circulating reticulocytes, platelets, and leukocytes. Platelet counts range between 500,000 and one million but may also be transient given the fact that the spleen may not be the primary area of platelet destruction and that platelets have a typical half-life of 10 days. The immediate increase of white cells reflects the storage of a large proportion of white cells in the spleen and as with thrombocytosis, the effect may also be transient. Given that the spleen is responsible for generating an immune response to circulating opsonized antigens, asplenic patients are also at risk for developing overwhelming sepsis by encapsulated microorganisms, which include *Streptococcus pneumonia, Haemophilus influenzae,* and *Neisseria meningitidis*.[21]

Hypersplenism

Hypersplenism is defined according to the following criteria: (1) documented anemia, thrombocytopenia, or leukopenia; (2) normal compensatory response by the bone marrow to correct the cytopenia; and (3) correction of this cytopenia by splenectomy.[22] Causes for hypersplenism are listed in **Table 73.4**, which are based on the primary disorder of the blood cells or of the spleen itself. Regardless of cause, the pathophysiology ultimately involves destruction of circulating blood elements within the splenic parenchyma. In some cases, the process may also result in splenomegaly, which can create a mass effect on the surrounding organs. When the stomach is compressed between an enlarged spleen and the liver, patient may experience early satiety and weight loss. Elective splenectomy is indicated in cases of hypersplenism, in order to reverse the cytopenia and also to relieve compressive symptoms from splenomegaly.[23]

SURGICAL TREATMENT FOR DISEASES RELATING TO THE SPLEEN

Approximately 25,000 splenectomies are performed in the United States for a variety of indications.[24] In a 2001 study evaluating 6 the indication for splenectomy over a 10-year period, the most common indication was therapeutic splenectomy, including for trauma (44%). The next most common indication was incidental to another procedure (26.3%) and for staging purposes (20.2%).[25] Splenectomy for diagnosis was the least common indication (9.5%). An updated report describing all splenectomies in Olmsted County, Minnesota, over a nearly 50-year period showed that the most common indication for splenectomy was malignancy (35%) followed by trauma (19%).[26] With practice changes both for therapeutic and diagnostic purposes, the landscape of indication for splenectomy is shifting. For example, trauma splenectomy is less commonly performed due to the increased understanding of the natural history of splenic trauma, and splenectomy for staging purposes is less commonly performed. In this section, we will discuss the indications for splenectomy as well as now these indications have changed over time. Similarly, splenectomy used to be

included as part of the staging work-up for lymphoma but has largely been replaced by imaging. A summary of indications for splenectomy is included in **Table 73.5**.

Table 73.4 Causes of Hypersplenism

I. Primary diseases of blood cells; normal spleen
    A. Congenital
        i. Erythrocyte abnormalities
            a. Hereditary spherocytosis
            b. Hereditary elliptocytosis
            c. Glucose 6-phosphate dehydrogenase deficiency
            d. Pyruvate kinase deficiency
        ii. Hemoglobin abnormalities
            a. Thalassemia major
            b. Sickle cell anemia (eventually results in splenic infarction and hyposplenism)
        iii. Platelet abnormalities
            a. Wiskott–Aldrich syndrome
    B. Acquired
        i. Autoimmune hemolytic anemia
        ii. Autoimmune neutropenia—Felty syndrome
        iii. Immune thrombocytopenia purpura
        iv. Thrombotic thrombocytopenia purpura
II. Primary disorders of the spleen
    A. Neoplastic
        i. Hairy cell leukemia
        ii. Chronic lymphocytic leukemia
        iii. Chronic myelogenous leukemia
        iv. Non-Hodgkin lymphoma
    B. Cellular infiltrative (hematopoiesis)
        i. Agnogenic myeloid metaplasia
        ii. Mastocytosis
        iii. Chediak–Higashi
    C. Metabolic infiltration
        i. Gaucher disease
        ii. Sarcoidosis
    D. Vascular
        i. Splenic vein thrombosis
        ii. Portal vein hypertension (cirrhosis)

Historically, the only available option was open splenectomy. The first laparoscopic splenectomy was described in 1991,[27] and now is the preferred approach in many centers. Similarly, robotic splenectomy is described as well for some indications. In addition to the technical advances in approach, there has also been an increased recognition of the immune function of the spleen. This has led to efforts to preserve the spleen when at all possible. We will begin by discussing specific conditions and indications for splenectomy then proceed to discuss the role of the spleen as a diagnostic or therapeutic specimen. The specific categories that will be discussed are trauma, autoimmune and erythrocyte disorders, hypersplenism, vascular abnormalities, as well as miscellaneous indications.

Table 73.5 Indications for Splenectomy in Two Large Series

	Kraus et al.	Hernandez et al.
N	1,280[25]	724[26]
Dates	1986–1995	1966–2011
Trauma	167 (13%)	139 (19%)
Malignancy	386 (30%)	256 (35%)
Benign hematologic disease	219 (17%)	83 (11%)
Intraoperative iatrogenic injury or incidental	336 (26%)	90 (12%)
Other	172 (13%)	156 (22%)

Trauma to the Spleen

In the United States, the spleen is the most commonly injured abdominal organ due to blunt trauma, and approximately 8% of injuries are due to penetrating trauma.[28] Of the 1.5 million U.S. adults who suffer from blunt trauma, nearly 40,000 are diagnosed with a splenic injury.[29] The management

of traumatic injury to the spleen has evolved over time, mirroring general trends in trauma surgery. The first reported splenectomy reported in the United States was in fact for penetrating trauma. In 1816, a man was attacking a woman when she stabbed him in the left flank, resulting in splenic protrusion from the wound. The protruding spleen was successfully ligated and the patient reportedly recovered.[30] Since that time, splenectomy for trauma was the norm for more than 100 years. In 1962, a Brazilian surgeon, Dr. Campos Christo, reported a case of partial splenectomy with splenic salvage in cases of trauma.[31] As trauma systems evolved to become more sophisticated, and with the advances achieved in cross-sectional imaging techniques, there was a gradual shift from mandatory splenectomy for every patient with an injured spleen toward an emphasis on splenic preservation when possible.[28]

Splenic injury should be high on the list of suspected injuries for patients who sustain blunt trauma, particularly in those with left upper quadrant tenderness or peritonitis. Vital sign abnormalities, particularly hypotension, can be present and should heighten suspicion of an injury but are not required for the diagnosis of a splenic injury. The standard advanced trauma life support assessment of airway, breathing, and circulation should be applied to all patients at risk for a splenic injury. The diagnostic evaluation is predicated on the patient's underlying hemodynamic state. For hemodynamically normal patients, diagnostic evaluation should include a complete blood count, chest x-ray to evaluate for rib fractures, and CT scan which can diagnose splenic injury as well as other potential sources of intra-abdominal injury. CT scan will also allow for assessment of the severity of the splenic injury. The grading system for splenic trauma is summarized in **Table 73.6**.

According to guidelines from the Eastern Association for the Surgery of Trauma (EAST), patients who present after blunt trauma with hemodynamic instability or diffuse peritonitis should be brought the OR urgently for exploratory laparotomy.[32] The operative approach consists of a generous midline incision followed by abdominal packing to contain ongoing hemorrhage. Rapid mobilization of the lateral attachments of the spleen, typically accomplished using blunt dissection, should be performed to bring the spleen into the operative field. The hilar vessels can then be controlled

and ligated to stop hemorrhage. This will be discussed in more detail in the section describing operative approaches to the spleen.

Table 73.6 Grading of Splenic Injuries

Grade	Laceration	Hematoma
I	<1-cm depth	Subcapsular <10% surface area
II	1–3 cm not involving a trabecular vessel	Subcapsular 10–50% surface area or intraparenchymal <5 cm
III	>3-cm depth or any depth involving a trabecular vessel	Subcapsular, >50% surface area or ruptured subcapsular or intraparenchymal laceration ≥5 cm
IV	Segmental or hilar vessel involvement	
V	Shattered spleen or hilar vessel disruption	

The majority of patients with splenic injury (85% to 90%) are managed nonoperatively.[29] Patients with diagnosed splenic injuries who are managed nonoperatively must be closely monitored (such as in an intensive care unit) while adhering to institutional protocols to minimize morbidity. Importantly, nonoperative management should only be conducted in a setting where an operating room is rapidly available should the patient decompensate. Serial abdominal examinations in combination with serial complete blood counts will help to determine need for additional intervention such as laparotomy. A change in patient status (e.g., drop in hemoglobin, development of

hypotension, increased pain) should prompt immediate reevaluation to determine the need for additional diagnostic tests or intervention. Depending on the stability of the patient, this may warrant immediate transfer to the operating room.[29]

An important adjunct to nonoperative management of splenic injury is the availability of splenic artery embolization. Guidelines recommend consideration of angiography in patients with grade III or worse injury, those who have a contrast blush on their initial CT scan, patients with a moderate amount of hemoperitoneum, or in patients who demonstrate evidence of ongoing hemorrhage.[32] This technique can be especially useful for high-grade injuries (Grade IV/V), which have a high rate of failure with observation alone.[33] In a 2011 meta-analysis evaluating outcomes for more than 10,000 patients with blunt splenic injury, 68% were managed nonoperatively. Among patients who underwent observational therapy without splenic artery embolization, there was an overall failure rate of 8.3%, but varied based on the degree of injury with an 83.1% failure rate for grade V injury. For patients who underwent splenic artery embolization, there was an overall failure rate of 15.7% but no variation was seen in injury severity. The conclusion was that splenic artery embolization more frequently allowed for splenic preservation for high-grade injuries.[33] Splenic artery embolization is not standard of care and its use varies among centers. Among level I trauma centers, utilization rates vary from 1% to 19%. In a study of four level I trauma centers, patients treated at centers with higher utilization were significantly more likely to successfully undergo nonoperative management.[34] However, other studies have shown no difference in rates of splenic salvage, leading the EAST to describe splenic artery embolization and other interventional techniques as "important adjuncts to nonoperative management of splenic injuries" rather than endorsing it as a guideline.[32]

The feared complication of nonoperative management of splenic injuries is delayed splenic rupture that occurs in the outpatient setting. Several large observational studies demonstrate that the majority of patients who fail nonoperative management do so within the first 3 to 5 days after injury. In one study where patients were followed up to 6 months after their injury, the rate of rupture in the outpatient setting was 1.4%.[29] Patients who are discharged from the hospital after nonoperative management of splenic injuries should be counseled about the risk of delayed rupture.

Autoimmune and Erythrocyte Disorders

Autoimmune and erythrocyte disorders are two categories of disease that often lead to consideration for splenectomy. In cases of autoimmune disease, antibodies lead to destruction of circulating cells. One common example of this is immune thrombocytopenic purpura (ITP). In intrinsic erythrocyte disorders, cellular defects lead to a shortened half-life in the peripheral circulation due to premature elimination in the spleen. An example of this would be sickle cell disease. In this section, we will review some of the commonly encountered autoimmune and erythrocyte disorders in which splenectomy may be considered as part of the treatment algorithm. A summary of the diagnoses leading to splenectomy can be found in **Table 73.7**.

Immune Thrombocytopenic Purpura

ITP is typically a diagnosis of exclusion, and other potential etiologies of thrombocytopenia must first be ruled out. ITP may be idiopathic but can be secondary to other conditions such as systemic lupus erythematosus, HIV/AIDS, and lymphoma. There are two peaks in disease diagnosis, one between 20 and 30 years of age when females are slightly more affected than males, and one after 60 years of age where there is no difference in sex distribution.[35] The pathogenesis of ITP remains incompletely understood as there are likely several mechanisms leading to the clinical presentation. Traditional models of the disease suggest that antiplatelet antibodies lead to premature platelet destruction in the spleen, liver, or both. However, up to 50% of patients with ITP do not demonstrate antiplatelet antibodies. Other suggested mechanisms include T-cell–mediated abnormalities as well as involvement of CD8 cells.[35]

Table 73.7 Final Pathologic Diagnoses in 122 Spleens Removed for Diagnostic Purposes

Total Number of Diagnostic Splenectomies		122
Indication	**Diagnosis**	
Splenic mass		52
	Lymphomas	17
	Metastatic Cancer	14
	Carcinoma	12
	Sarcoma	2
Benign		21
	Cysts	11
	Hamartoma	3
	Hemangioma	3
	Other	4
Splenomegaly		41
	Lymphoma	24
	Benign lymphoid proliferation	5
	Benign vascular	4
	Granulomatous disease	4
	Infarction/hemorrhage	
Categorize lymphoma		29
	Malignant (successful)	28
	Benign	1

Adapted from Kraus MD, Fleming MD, Vonderheide RH. The spleen as a diagnostic specimen: a review of 10 years' experience at two tertiary care institutions. *Cancer* 2001;91(11):2001–2009.

The hallmark of ITP is isolated thrombocytopenia (platelet count <100,000/mm^3). Patients rarely (<5%) present with life-threatening hemorrhage, but more commonly present with fatigue, easy bruising, and mucocutaneous bleeding.[35] Patients should be evaluated with complete history and physical examination to evaluate for other potential causes of

thrombocytopenia. Peripheral blood smear typically shows reduced numbers of otherwise normal-appearing platelets. Measurement of antiplatelet antibodies and bone marrow biopsy are not part of the routine diagnostic evaluation.

Treatment of ITP is predicated on the patient's clinical presentation. For patients who present with evidence of acute hemorrhage, the primary goal is to stop ongoing bleeding. The standard approach includes platelet transfusion in conjunction with corticosteroids and intravenous immune globulin (IVIG). Because of the ongoing platelet destruction, platelet transfusions are typically only helpful for a few hours at a time and thus ongoing transfusion may be necessary while the corticosteroids and IVIG start to work. In certain life-threatening situations, transexamic acid can help as well.[35] Many patients with ITP do not require any treatment. Severe bleeding typically does not occur until the platelet count is <30,000/mm^3. As such treatment is not initiated until platelet counts fall below this level. The mainstay of treatment is corticosteroids, but unfortunately 70% to 90% of patients will experience relapse when corticosteroids are stopped.[35] Other potential therapies include IVIG and Rh_0(D)-immune globulin but like corticosteroid treatment, it is uncommon to achieve sustained remission.

Several newer treatments have recently become available. These include thrombopoietin-receptor agonists (e.g., eltrombopag, romiplostim) and immunomodulators (e.g., rituximab). Thrombopoietin-receptor agonists are approved for patients with ITP who are refractory to other medical treatments. Randomized trials demonstrate that 70% to 95% of patients will see increased platelet counts and that this will be sustained in 40% to 60%. Similarly, immunomodulators have demonstrated success with up to 40% demonstrating complete response and up to 60% demonstrated some treatment effects. However, rituximab is not currently approved for treatment of ITP by the Food and Drug Administration (FDA).

For patients who do not respond to corticosteroids or other medical treatments, or who cannot tolerate therapy, splenectomy is the next option. While splenectomy is curative for most patients, up to 30% will experience relapse.[35,36] Given the success in development of treatments for ITP as well as the risks of postsplenectomy sepsis, splenectomy as a treatment for ITP has declined in frequency.[36]

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenia purpura (TTP) is a syndrome characterized by microangiopathic hemolytic anemia and severe thrombocytopenia. This results in visceral ischemic symptoms, particularly in the central nervous system. Until recently, its etiology was poorly understood. However, the discovery of the cause of this disease, severe deficiency of a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13 (ADAMTS13), a protein that processes von Willebrand Factor (vWF) in the body, led to advancements in the understanding of this disease. vWF is known to be essential for platelet adhesion and aggregation. Patients who died from TTP were found to have large amounts of vWF within the microthrombi due to the inability of ADAMTS13 to effectively cleave vWF. Thrombocytopenia does not typically occur until levels of ADAMTS13 are <10%.[37,38] Deficiency of ADAMTS13 can be either hereditary or, more commonly, acquired through the development of autoantibodies.

Initial presentation of TTP may be nonspecific with symptoms such as fatigue and headache. Patients may then go on to develop petechiae as well as neurologic symptoms such as confusion and seizures. Rare symptoms of the disease may include myocardial infarction or stroke. Complete blood count will demonstrate thrombocytopenia and hemolytic anemia. Fragmented blood cells will be seen on blood smear.

Treatment of the condition depends on whether the deficiency is hereditary (genetic) or acquired. For hereditary deficiency, the treatment consists of serial infusions of fresh frozen plasma (as no autoantibodies are present). For patients with acquired deficiency and the presence of autoantibodies, the initial treatment consists of plasma exchange. Other immunosuppressive agents such as corticosteroids, rituximab, vincristine, and others have been employed to achieve resmission.[39] While used previously, anti-platelet agents such as aspirin and dipyridamole are less effective in preventing platelet aggregation in TPP. Ongoing work continues in the investigation of additional drugs to treat patients with TTP.

The role of splenectomy for treatment of TTP is not entirely clear as the evidence for its effectiveness varies. While some reports demonstrate relapse-free survival in up to 70% of patients who undergo splenectomy, other reports state that less than 10% achieve remission. The role of the

spleen is not completely known, but it is thought to be a significant site of ADAMTS13 autoantibody production, as well as ADAMTS13 removal in the body.[40]

Autoimmune Hemolytic Anemia

Autoimmune hemolytic anemia exists in two forms: warm autoimmune hemolytic anemia and cold autoimmune hemolytic anemia. It is important to distinguish between the two because the etiology and treatment differ.

In warm autoimmune hemolytic anemia, the primary abnormality is IgG antibodies directed against erythrocytes. Binding is maximal at 37°C which is why it is referred to as "warm." The erythrocytes are then removed in the spleen as the splenic macrophages carry receptors for the Fcγ portion of the heavy chain of IgG. Median age of onset is in the 50s and there is a slight female predominance for disease. About half of cases are primary and idiopathic, while the other half of cases are due to medications or other disorders. Typical presenting signs are often related to the underlying anemia (e.g., fatigue, dyspnea) but can include more severe findings such as venous thromboembolism in up to 15%. Diagnosis includes laboratory findings of anemia, reticulocytosis, hemolysis, and a positive Coombs test. Initial treatment may include transfusion of ABO- Rh-blood for patients with severe anemia (Hbg <6 g/dL). Long-term management includes corticosteroids, rituximab, or both. While splenectomy was historically performed as part of the treatment, guidelines now recommend medical management over splenectomy given the long-term risks associated with splenectomy and the variable effectiveness. Only half of patients will demonstrate remission following splenectomy, and of those 25% will relapse with 1 year.[41]

Cold autoimmune hemolytic anemia is characterized by IgM antibodies that bind to RBCs, ultimately leading to complement activation and RBC aggregation, and accounts for about 15% of autoimmune hemolytic anemia. Because of this mechanism, the spleen features less prominently in this form of the disease and therefore splenectomy is not effective. Diagnosis of cold autoimmune hemolytic disease is based on a combination of clinical presentation and laboratory testing. Laboratory evaluation will indicate evidence of chronic hemolysis, positive direct antiglobulin test, and an elevated cold agglutitin titer. Treatment consists of avoidance of cold

temperature, blood transfusion, and plasmapheresis in acute situations. Corticosteroids are generally not effective. Rituximab has been used with some success. As mentioned previously, splenectomy is not effective for this form of disease.[41]

Autoimmune Neutropenia (Felty Syndrome)

Felty syndrome is the clinical picture of neutropenia and splenomegaly in the setting of rheumatoid arthritis. Fewer than 1% of patients with rheumatoid arthritis go on to develop this syndrome. Abnormalities detected in patients with Felty syndrome include impaired production of neutrophils, increased sequestration and destruction of neutrophils, and excessive neutrophil margination. Patients with Felty syndrome suffer from a high rate of infections due to neutropenia, and up to 36% 5-year mortality rate. Treatment of Felty syndrome starts with antirheumatic drugs such as methotrexate. If this treatment fails, other options include colony-stimulating factor and splenectomy. Splenectomy can improve the degree of neutropenia and decrease the incidence of recurrent infection.[42]

Hereditary Spherocytosis

Hereditary spherocytosis is an autosomal dominant disease that is the most common of the congenital hemolytic anemias affecting 1 in 2,000 individuals. The primary defect is a defect in spectrin and ankyrin that lead to loss of the membrane surface area and decreased erythrocyte deformability. This then leads to increased destruction in the spleen because of the fact that the affected erythrocytes lack of deformability that impacts the passage of erythrocytes through channels of the spleen. Clinical manifestations include anemia, jaundice, gallstones, reticulocytosis, spherocytes on peripheral blood smear, and splenomegaly. Diagnosis is based on thorough history and physical examination in combination with laboratory findings. Because the spleen plays a dominant role in sequestration and destruction of erythrocytes, splenectomy will cure most patients. Patients should be assessed at the time of scheduling a splenectomy for the presence of gallstones and a laparoscopic cholecystectomy should be performed if stones are identified.[43]

Hereditary Elliptocytosis

Hereditary elliptocytosis is less common then hereditary spherocytosis but is similarly caused by defects in membrane proteins that lead to elliptical shaped erythrocytes resulting in reduced deformability. Most patients are asymptomatic and are only diagnosed when peripheral blood smear is performed for other reasons. However, patients may exhibit symptoms related to the disorder such as anemia, jaundice, and splenomegaly. Splenectomy can be considered, but should only be done for patients older than 5 years of age with severe symptoms.[44]

Hereditary Nonspherocytic Hemolytic Anemia

This is a heterogenous group of hemolytic anemias caused by inherited defects in various enzymes involved in glycolysis. The most common variants are glucose 6-phosphate dehydrogenase (G6PD) deficiency and pyruvate kinase deficiency. In G6PD deficiency, patients can be completely asymptomatic. Symptoms of hemolysis are typically brought on by infection, exposure to fava beans, or to oxidative drugs. Treatment is generally supportive and splenectomy is not recommended. Pyruvate kinase deficiency similarly presents with signs and symptoms of hemolysis, as well as complications such as hyperbilirubinemia and gallstones. 80% to 85% of patients have splenomegaly. Treatment consists of supportive therapy, and splenectomy may reduce some symptoms and decrease transfusion requirements.[45,46]

Thalassemia

Thalassemia is an inherited disorder characterized by various structural defects in the globin chains. Previously, thalassemias were divided into subtypes based on the underlying molecular defect, but the current classification system divides them into transfusion-dependent thalassemia (TDT) and non–transfusion-dependent thalassemia (NTDT) based on their need for ongoing blood transfusion to survive. The categories are not mutually exclusive and are based on clinical presentation. In addition, patients with NTDT may intermittently require transfusion, whereas patients with TDT generally require ongoing transfusion for survival.[47] The molecular defects in thalassemia lead to ineffective erythropoiesis and peripheral hemolysis. Clinically, patients may present with iron overload and

anemia. Ineffective erythropoiesis is also associated with bone disease, organomegaly due to extramedullary hematopoiesis, gallstones due to peripheral hemolysis, and hypercoagulability. All of these may result in end organ damage.[48]

Diagnosis of thalassemia is made by analysis of the peripheral blood smear. Erythrocytes will demonstrate variation in cell size and shape, microcytosis, and hypochromia. The specific findings will vary by molecular defect. Hemoglobin analysis is also important but must be performed with the clinical setting in mind. Definitive diagnosis is made by DNA analysis.[47]

Conventional treatment of the thalassemias includes transfusion, iron chelation, and splenectomy. Transfusion functions to not only treat the anemia but also suppress ineffective erythropoiesis. Iron chelation addresses the iron overload that occurs either due to increased intestinal absorption or the iron load from regular transfusion. Splenectomy is rarely used for patients with TDT due to the increased safety and availability of blood. For patients with NTDT, splenectomy may improve anemia and reduce their risk of infection. However, in addition to the standard risks brought on by splenectomy, for patients with NTDT it also confers a hypercoagulable state. Splenectomy is currently only recommended for patients who cannot receive transfusions or undergo iron chelation therapy, or who suffer from hypersplenism or symptomatic splenomegaly.[48]

Sickle Cell Disease

Sickle cell disease is an inherited disease characterized by a missense mutation in the sickle hemoglobin gene. It is increasing in frequency and more than 300,000 infants are born with this disease every year. It is more common in areas of the world with endemic malaria as heterozygosity for the sickle cell mutation is protective against malaria. The variation in the shape of the erythrocyte leads to hemolytic anemia and blockage of small blood vessels leading to vaso-occlusion. This can then lead to tissue ischemia, severe pain, and in some cases organ failure.[49]

While most patients with sickle cell disease are born with normal spleens, over time the spleen can exhibit both functional hyposplenism and splenomegaly. This is because the environment of the spleen promotes sickling which then increases adhesion of the sickled erythrocytes. Sickled

cells are also cleared more regularly by the spleen. While the precise mechanism is not known, splenic injury occurs early on for most patients. Because most patients develop hyposplenism over time, splenectomy is not often required. Most of the vaso-occlusive episodes do not result in sickle cell crisis. However, acute splenic sequestration can occur when RBCs become trapped in the spleen resulting in abdominal pain, distention, and signs of anemia and shock due to an acute drop in the hemoglobin level. Treatment consists primarily of transfusion as well as treatment of any inciting cause such as infection. For patients with recurrent sequestration, splenectomy can be considered.[50]

Treatment of sickle cell disease consists of prophylactic penicillin for children, hydroxyurea, and regular transfusion. Stem-cell transplant may be curative but is currently limited. As described above, most patients do not ever require splenectomy but it can be considered for those who develop hypersplenism. Laparoscopic splenectomy is preferred, and partial splenectomy may be considered for young children with the purpose of preserving immune function.[49,50]

Wiskott–Aldrich Syndrome

Wiskott–Aldrich Syndrome (WAS) is an X-linked immunodeficiency disorder characterized by recurrent infections, eczema, and bleeding diathesis. While males are most frequently affected, females can be carriers and in rare cases may exhibit symptoms. The syndrome has associated abnormalities in T and B cells and may result in hemorrhagic insults, autoimmune disease, as well as a propensity for lymphoma and other malignancies. The associated thrombocytopenia is incompletely understood, but may due to increased platelet destruction by the spleen as well as megakaryocyte dysfunction.[51]

All patients with WAS exhibit thrombocytopenia that typically manifests in the first year of life with easy bruising, spontaneous or prolonged bleeding (particularly after circumcision), as well as petechiae. The other features such as eczema and recurrent infections do not occur in all patients. WAS should be suspected in patients with thrombocytopenia but genetic testing is the gold standard for diagnosis.[52] The definitive treatment for WAS is hematopoietic stem cell transplantation or stem cell gene therapy, ideally

within the first 2 years of life. For adults who have not been treated, hematopoietic stem cell transplantation may also be an option. Additionally, supportive therapy consists of infection prophylaxis, management of thrombocytopenia, and managing other symptoms related to associated autoimmune or other diseases. Because of the potential role of the spleen in thrombocytopenia, splenectomy has been recommended for patients with severe thrombocytopenia such that avoidance of activity (for prevention of bleeding) interferes with their quality of life, particularly for patients with the milder form of WAS termed X-linked thrombocytopenia as this group has lower risk of infection.[52]

Hypersplenism

7 Hypersplenism, or splenomegaly, is enlargement of the spleen. While there are many causes for hypersplenism to occur, these causes can be broadly categorized into neoplastic, hematopoietic, and metabolic or storage disorders. Typical symptoms include abdominal discomfort and tenderness, early satiety, bloating, and other symptoms related to the mass effect of the spleen on adjacent organs. Cytopenias are frequently present due to sequestration.

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in developed countries. Males are more commonly affected, and the median age at diagnosis is 72 years. The disease is caused by a clonal proliferation and accumulation of mature B cells in the spleen, blood, lymph nodes, and bone marrow. Patients are commonly diagnosed incidentally after complete blood count demonstrates lymphocytosis. Symptoms include anemia, thrombocytopenia, neutropenia, lymphadenopathy, and B symptoms. Diagnosis is confirmed with immunophenotyping. Treatment choices are dictated by stage as well as symptoms. Findings that indicate the need for treatment include progressive anemia or thrombocytopenia, autoimmune anemia or thrombocytopenia that does not respond to steroids, enlarging of symptomatic lymphadenopathy, and enlarging or symptomatic splenomegaly. The standard chemotherapy regimen is fludarabine plus cyclophosphamide

(FCR) which will lead to remission for many patients. Alternative regimens are available for patients who do not tolerate FCR.

The spleen is the third-most affected organ in CLL. Both the white and red pulp are diffusely infiltrated. Splenomegaly is common due to the infiltrative nature of the disease (as demonstrated in Figure 73.7) but splenectomy is rarely necessary. It may be indicated for patients with advanced CLL and refractory pancytopenia. Up to 90% of patients who undergo splenectomy demonstrate improvement in thrombocytopenia as well as hemoglobin. For patients who are not surgical candidates, splenic irradiation can be considered. In a review of 27 studies, splenic irradiation was found to be effective for splenic reduction (72% of patients), relief of pain (59% of patients) and improved cytopenia (78% of patients).[53–55]

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) accounts for approximately 15% of adult leukemias and is characterized by the Philadelphia chromosome (Ph). This chromosome results from a translocation that gives rise to BCR-ABL1, a protein with deregulated tyrosine kinase activity. While CML can occur in three phases (chronic, accelerated, and blast), most patients are diagnosed in the chronic phase. Diagnosis is made by history and physical (including palpation of the spleen), complete blood count, chemistry, and liver function tests. Spleen size is used as part of the staging as larger spleens confer higher likelihood of dying from CML. A bone marrow biopsy to confirm the presence of the BCR-ABL1 gene is also recommended to confirm the diagnosis. Clinical features include leukocytosis, thrombocytosis, and splenomegaly in more than half of patients. The standard treatment for CML is with tyrosine kinase inhibitors (TKIs). Second-generation TKIs (e.g., dasatinib, nilotinib, bosutinib) have demonstrated superior outcomes compared to first-generation TKIs such as imatinib, but drug selection should be individualized based on the presenting patient. While not curative, splenectomy can be performed to relieve symptoms associated with splenomegaly and thrombocytopenia, and to reduce transfusion requirements.[56,57]

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma is a heterogeneous disease arising from primarily mature B cells, and in some cases T lymphocytes or natural killer cells. The disease arises from DNA mutation and can be associated with specific mutations, as in the case of the MYC oncogene in Burkitt lymphoma, or due to underlying infections such as Epstein–Barr.[58] Common presenting signs include lymphadenopathy and splenomegaly, and a third of patients will have extranodal disease. Systemic symptoms including B symptoms are present in about half of patients while many patients are asymptomatic. Diagnosis is made with routine blood tests, which can be normal or may exhibit anemia, thrombocytopenia, or neutropenia due to bone marrow involvement. A biopsy of the affected lymph node or organ is required for diagnosis. Staging is based on the number an extent of involved lymph nodes, as well as the presence of B symptoms or extranodal disease. CT scan is the primary method used to assess extent of disease which is important for staging.[59] For most patients with indolent or low-grade lymphoma, chemotherapy is not curative. These patients are followed clinically and many never require treatment.[58] For patients with high-grade lymphoma, immunochemotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) is standard and results in cure for 60% to 70%. For patients who have symptoms related to splenomegaly as described above, or with progressive cytopenia, splenectomy can be considered. While splenectomy was previously used as a diagnostic or staging tool, this is less commonly the case due to advances in imaging.[58,59]

Hairy Cell Leukemia

Hairy cell leukemia is a rare B-cell leukemia so named because of the characteristic appearance of "hairy cells" on peripheral blood smear in 90% of patients. While many patients with hairy cell leukemia are asymptomatic, most patients present with splenomegaly or symptoms related to cytopenia. Splenectomy was previously the mainstay of treatment, leading to complete response in 40% to 62% of patients and 5-year survival of 61% to 68%. Splenectomy continues to play a role for patients with symptomatic splenomegaly, complications related to cytopenias, infections, or pregnancy. However, other therapies have largely replaced splenectomy. Some patients who present with indolent disease do not require treatment at all. For

patients with symptomatic splenomegaly or severe cytopenia, standard treatment includes cladribine and pentostatin.[60]

Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) is a clonal stem cell disorder that primarily occurs in older adults with a median age at diagnosis of 65 to 70 years. Multiple steps involving gene mutations and/or cytogenetic changes resulting in ineffective hematopoiesis. As a result, patients develop cytopenias with a third of patients going on to develop acute myeloid leukemia. The exact cause of MDS is determined in only 15% of cases with linkage to heritable, environmental, or occupational factors for most others. Patients present with nonspecific symptoms related to anemia or thrombocytopenia, as well as increased risk of infection due to neutropenia. Peripheral blood smear will demonstrate small numbers of circulating blasts. Bone marrow analysis is required for diagnosis. Cytogenetic analysis may be useful for cases in which the diagnosis is not clear but also serves to provide valuable prognostic information. Treatment is based on the international prognostic scoring system. For lower-risk patients, the goal of treatment is to reduce consequences of cytopenia, reduce need for transfusion, and improve quality of life. For these patients, treatment includes erythropoiesis-stimulating agents as well as hypomethylating medications in some countries. Some patients also require transfusions to treat cytopenia. Treatment for higher-risk patients aims to extend survival while preventing progression to acute myeloid leukemia. Treatment options include allogeneic stem-cell transplantation, intensive chemotherapy, and hypomethylating agents.[61] As with the other neoplastic processes, patients with MDS can develop significant and symptomatic splenomegaly. Splenectomy can be considered but carries a high risk of morbidity and mortality without demonstrated improvements in survival.[62]

Metastatic Disease to the Spleen

Metastasis to the spleen is thought to occur in less than 10% of patients with cancer, but due to improvements in imaging and follow-up the incidence is increasing. Metastases can be either solitary or as part of a multivisceral presentation. For solitary lesions, the most common primary cancers are

colorectal and ovarian. For multivisceral lesions, the most common primary cancers are breast, colorectal, ovarian, lung, and melanoma. Imagine-guided biopsy of the spleen is preferred for diagnostic purposes, but in some cases splenectomy can be performed to relieve symptoms associated with splenomegaly. Particularly for solitary lesions occurring late after the primary is diagnosed, there is evidence that splenectomy may lead to long-term remission.[63]

Gaucher Disease

Gaucher disease is the most common of the lysosomal storage disease and has three described variants. It is inherited in an autosomal recessive fashion and leads to insufficient activity of the lysosomal enzyme acid β-glucosidase which leads to accumulation of its main substrate, glucosylceramide. Glucosylceramide than accumulates in macrophages in affected organs which can cause bone involvement, hepatomegaly, splenomegaly, as well as anemia and thrombocytopenia. While the underlying abnormality is understood, the mechanism by which this causes disease in specific organs is poorly understood. There are three subtypes. Type I is most common and is usually diagnosed in adults particularly from specific populations such as the Ashkenazi Jewish population; types II and III are diagnosed in infancy or childhood and are more severe. The gold standard of diagnosis is the detection of insufficient enzyme activity. The mainstay of therapy is enzyme therapy, with the goal being to reduce the signs and symptoms caused by the disease. Prior to this, partial splenectomy was a common treatment recommendation but with the development of enzyme therapy, patients can experience reduction in spleen volume of 50% to 60% after 2 to 3 years of treatment.[64]

INCIDENTAL SPLENECTOMY

Incidental splenectomy, or removal of the spleen during the course of another operation, it not uncommon. While these operations are explained in detail in other portions of this textbook, here we make some comments about the reasons why this may occur.

Incidental splenectomy often occurs during distal pancreatectomy due to the intimate association of the splenic vein to the undersurface of the pancreas, as well as the many venous branches to the pancreatic parenchyma. With an increased understanding of the risks associated with splenectomy, there has been renewed interest in distal pancreatectomy without splenectomy. This can be achieved either through the preservation or resection of the splenic vessels. In cases where the splenic vessels are divided, the short gastric vessels are carefully preserved to maintain blood flow to the spleen. It should be noted that these approaches should only be employed when anatomically and oncologically appropriate.[65,66]

Splenectomy may also be employed in conjunction with resection of proximal gastric cancers, tumors involving the left kidney or adrenal gland, and retroperitoneal masses invading the spleen. The purpose of splenectomy in these cases is often to provide adequate exposure to dissect bulky disease posterior to the spleen. It should be recognized that despite the risk that asplenia confers to patients, the spleen can be safely removed to facilitate a complete resection.

IATROGENIC SPLENECTOMY

Because of its proximity to organs in the left upper quadrant of the abdomen, the spleen can be injured during the course of other operations, sometimes requiring removal. This scenario is undesirable not only because the patient will be left asplenic, but they also have not had the opportunity for prophylactic vaccines prior to the operation. While the best method to protect against this is not to injure the spleen at all, understanding the operations that put the spleen most at risk can give a sense of when to be especially cautious.

In a 2019 retrospective study describing all splenectomies at a single hospital over a 17-year period in England, nearly half of all splenectomies were unplanned. Of the unplanned splenectomies, 36% were iatrogenic (vs. emergency for trauma or rupture). Of the 26 iatrogenic splenectomies, 11 occurred during a procedure for benign disease and 15 during a procedure for malignant disease. The most common operation leading to iatrogenic splenectomy was elective open colon resection (n = 12, 46%) followed by

emergency open colonic resection (n = 7, 27%).[67] While the spleen can be damaged due to a variety of factors in colorectal surgery, it is especially high risk in cases where the splenic flexure must be mobilized. A 2018 report from the Cleveland Clinic reported on their series of 2,336 colorectal operations that required splenic flexure mobilization. They reported a 1.1% risk of splenic injuries, most of which (64%) were managed with topical hemostatic agents. Splenorrhaphy was used in 16%, and the remaining 20% underwent splenectomy. The rate of splenic injury was much lower in laparoscopic cases (0.25% vs. 1.5%, p = 0.005), leading the authors to conclude that laparoscopic colon resection may result in fewer iatrogenic spleen injuries due to the increased visualization.[68]

Other operations that place the spleen at risk for injury include left nephrectomy, left adrenalectomy, antireflux procedures, and colonoscopy. In a 2013 study of 4,323 patients undergoing nephrectomy at the Mayo Clinic, they reported iatrogenic splenectomy in 33 patients (0.8%). Of these patients, 94% underwent a radial open left nephrectomy. Iatrogenic splenectomy was associated with longer operative time, more blood loss, higher rate of complications, and longer hospital length of stay.[69] As in this example, understanding risk factors prior to operating is important, but being prudent to avoid injury to the spleen is this most important guiding factor when considering this topic.

DIAGNOSTIC SPLENECTOMY

Diagnostic splenectomy has historically been used in cases when a patient has a splenic mass diagnosed on imaging in which definitive diagnosis was necessary, or in cases where a patient had splenomegaly on physical examination without any clear underlying disorder. In a 2001 series of more than 1,200 patients undergoing splenectomy, diagnostic splenectomy accounted for only 9.5% of the cases.[25] In the 1980s and 1990s, splenectomy was also used to reduce tumor burden in patients with leukemia or to diagnose or stage lymphoma.[70] While most patients can be diagnosed with imaging, laboratory studies, blood smears, and in some cases less-invasive biopsy methods, in some cases of lymphoma the diagnosis is still unclear. Furthermore, studies demonstrate that 37% to 57% of patients with

idiopathic splenomegaly harbor lymphoma. In a 2019 study of 113 patients undergoing diagnostic splenectomy at the Mayo Clinic Arizona, 35 (40%) had an unknown diagnosis prior to surgery. Of these patients, 16 (46%) received a definitive diagnosis following the operation. However, more than half of these patients (56%) underwent a change in their medical management as a result of the findings and 54% reported that their symptoms resolution. Given these findings the authors suggest that for patients who present with equivocal findings, diagnostic splenectomy can be a useful adjunct in their evaluation.[71]

Recognizing the significant morbidity that can accompany splenectomy, less-invasive options for diagnosis such as percutaneous image guide biopsy have been developed. As with indications for diagnostic splenectomy, splenic biopsy is indicated in cases of an indeterminant splenic mass where diagnosis cannot be determined by clinical or other diagnostic methods. Splenic biopsy is successful in more than 90% of cases and is significantly less invasive compared to splenectomy.[72]

VASCULAR DISORDERS OF THE SPLEEN

Vascular problems with the spleen that can lead to splenectomy include both venous and arterial problems. The most common situation would be splenic vein thrombosis and splenectomy in this setting is curative for the patient. Splenic artery aneurysms are one of the more common visceral aneurysms and can be an indication for splenectomy.

Splenic Vein Thrombosis

Splenic vein thrombosis typically occurs secondary to pancreatic disorders due to the close relationship between the splenic vein and the pancreas. It may present in up to 12% of patients with chronic pancreatitis and 22% of patients with acute pancreatitis. It can also occur in cases of pancreas cancer due to invasion of the vein. Splenic vein thrombosis leads to left-sided or “sinistral” portal hypertension. This localized area of venous hypertension can lead to the development of gastric varices (53% to 77% of patients) due to increased pressure in the gastroepiploic system. Clinically, patients with

sinistral portal hypertension may present with upper gastrointestinal bleeding due to rupture of gastric varices in 4% to 12%. In the setting of acute hemorrhage, upper endoscopy may demonstrate gastric varices. The presence of gastric varices in the absence of esophageal varices is also suggestive. Various imaging techniques can then be used to confirm the thrombus within the splenic vein. Because the majority of patients do not experience acute bleeding, most patients are diagnosed via CT, MRI, or ultrasound.

For patients without acute bleeding, anticoagulation should be considered as initial therapy. Splenectomy is typically employed for patients with uncontrollable episodes of bleeding.[73] By removing the spleen, the collateral flow is reduced, releasing the hypertension causing development of gastric varices. Splenectomy was previously recommended for all patients with splenic vein thrombosis to prevent future bleeding episodes, but due to advances in imaging and the realization that a minority of patients present with acute hemorrhage, observation is safe for most patients.[74]

Splenic Artery Aneurysm

Of all the visceral arterial aneurysms, splenic artery aneurysm is the most common and accounts for approximately 60% of such aneurysms. Most splenic artery aneurysms are asymptomatic and are diagnosed incidentally on imaging for other reasons. Women are affected four times more often than men, and there is some thought that this is potentially related to the increased frequency of abdominal ultrasound for women during pregnancy. Women also more frequently have true aneurysms, while men more frequently have pseudoaneurysms, which are more prone to rupture. Typical symptoms include abdominal pain, and aneurysmal rupture should be suspected when patients present with abdominal pain in the setting of anemia. Treatment of splenic artery aneurysms is determined by the size of the aneurysm. Risk of rupture increases substantially when the aneurysm size exceeds 2 cm. Patients who are asymptomatic and have aneurysms smaller than 2 cm can be followed with serial imaging. The special case is in women of child-bearing age who are planning pregnancy, or for women who are already pregnant. There is a high risk of rupture during pregnancy and therefore it is recommended that they be treated even if smaller than 2 cm. Reasons for the increased risk during pregnancy are thought to be related to increased levels

of circulating hormones that lead to increased blood flow and pressure in the splenic artery. Pseudoaneurysms should also be repaired, regardless of size.[75]

For patients that do require treatment, there are a variety of approaches. Aneurysms can be surgically resected or ligated, and endovascular approaches that can be used as well. Splenectomy can be used as an adjunct to aneurysm resection. Both surgical and endovascular options are safe and effective, but endovascular repairs may result in a faster recovery and shorter length of stay.[76]

MISCELLANEOUS INDICATIONS FOR SPLENECTOMY

Less commonly encountered indications for splenectomy include cysts, abscesses, as well as the "wandering spleen." The indications are discussed here.

Cysts of the Spleen

Splenic cysts are typically classified as either parasitic or nonparasitic, as first described by Fowler in 1913. Parasitic cysts are almost always hydatid cysts caused by Echinococcus. Fewer than 5% of all patients with echinococcal infection will develop hydatid cyst of the spleen. Many patients are asymptomatic, but mass effect from an enlarging cyst can cause pain or discomfort due to mechanical displacement of other abdominal organs. Diagnosis is made through a thorough history and physical examination in conjunction with serology and imaging. Ultrasound and CT scan may demonstrate peripheral calcification, daughter cysts within the larger cavity, or additional cysts in the liver. Splenectomy is the most common treatment, and care should be taken intraoperatively to avoid spillage from the cyst which can cause anaphylactic shock. The cyst can be carefully aspirated if it is sufficiently large to prevent adequate mobilization of the spleen. Partial splenectomy may also be considered based on the location of the cyst. Medical therapy such as albendazole is used as an adjunct.[77]

Nonparasitic cysts are classified into several different categories, often based on whether the cyst is primary or secondary. Primary cysts (20% to 30% of all nonparasitic cysts) include congenital cysts and neoplastic cyst. Neoplastic cysts include hemangiomas, lymphangiomas, and dermoid cysts. Secondary cysts (70% to 80% of all nonparasitic cysts) are either traumatic or necrotic.[78] Within the designation of nonparasitic cysts, there are many debates regarding the overall classification without a single accepted classification scheme. For asymptomatic cysts smaller than 5 cm in diameter with typical imaging findings, nonoperative treatment is recommended. Typical findings on imaging include the absence of solid components, regular appearance of the cyst wall, and lack of any contour defect. For larger or more symptomatic cysts there are several proposed approaches. Total splenectomy has historically been the most common treatment but has given way to other treatments. Aspiration has been described but is not generally recommended. Marsupialization can lead to recurrence of the cyst and is therefore not recommended. Total or subtotal cyst resection can prevent the need for partial or total splenectomy and laparoscopic methods are currently described both for cyst removal and partial splenectomy with good success.[79]

Abscess of the Spleen

While uncommonly encountered, splenic abscess carries significant risk of mortality if not adequately treated. Causes of splenic abscess include hematogenous spread of bacteria either due to infectious endocarditis or intravenous drug use; ischemia secondary to trauma; secondary infection from adjacent organs (e.g., pancreas, bowel); and in certain immunocompromised states. Commonly encountered bacteria are *Streptococcus species* and *Escherichia coli*. Typical symptoms include fever and left upper quadrant pain, as well as splenomegaly in some patients. Imaging such as ultrasound or CT scan will show findings of a rim enhancing fluid collection, and treatment consists of appropriate antibiotics followed by source control. While splenectomy was traditionally advocated for source control, percutaneous drainage of splenic abscess has demonstrated success of 67% to 100%. For patients who fail percutaneous drainage, subtotal or total splenectomy is an option.[80]

Ectopic Spleen (Wandering Spleen)

Ectopic, or "wandering," spleen is a condition in which the spleen is located in the lower abdomen or pelvis, rather than the left upper quadrant. The abnormality is due to laxity of the peritoneal attachments. This condition is more commonly encountered in children and is 10 times more common in females. About half of patients with this condition are asymptomatic. Symptoms associated with wandering spleen are typically due to acute torsion, or rupture after trauma. For patients with life-threatening hemorrhage, splenectomy is recommended. For patients who are incidentally found to have wandering spleen, laparoscopic splenopexy has been described.[81,82]

SPLENECTOMY: OPERATIVE TECHNIQUE

Splenectomy remains the mainstay of treatment for many conditions affecting the spleen as described earlier in this chapter. An important decision to make early on is which approach to plan for. For example, a patient presenting in acute trauma with splenic laceration will require an open approach, where a patient with underlying hematologic abnormality may be a good candidate for a laparoscopic or robotic approach. Secondarily, some patients may be a good candidate for a partial splenectomy. In this section we will describe the preoperative considerations, the steps of the operation, and the postoperative care for patient undergoing splenectomy.

Preoperative Evaluation

For patients who are undergoing urgent splenectomy for hemorrhagic shock related to trauma or splenic rupture, rapid evaluation and management should take care following advanced trauma life support approaches.

For all other patients, standard evaluation should include careful history and physical examination. History should include a complete medical history to determine their fitness for undergoing general anesthesia, as well as a more nuanced understanding of the indication for splenectomy. The surgeon should inquire as to prior operative history which may help determine the

approach. Imaging will help determine the size of the spleen as some approaches may not be suitable for extremely large specimens. Importantly, all patients undergoing elective splenectomy should undergo routine vaccination with vaccines to prevent against overwhelming postsplenectomy sepsis from pneumococcus pneumonia, *H. influenzae* type B, meningococcus, and seasonal flu. Ideally these would be administered at least 2 weeks prior to a scheduled splenectomy, but there is debate around the optimal time frame.[24] This will be discussed in detail in the section entitled "Sequelae of Splenectomy and Hyposplenism."

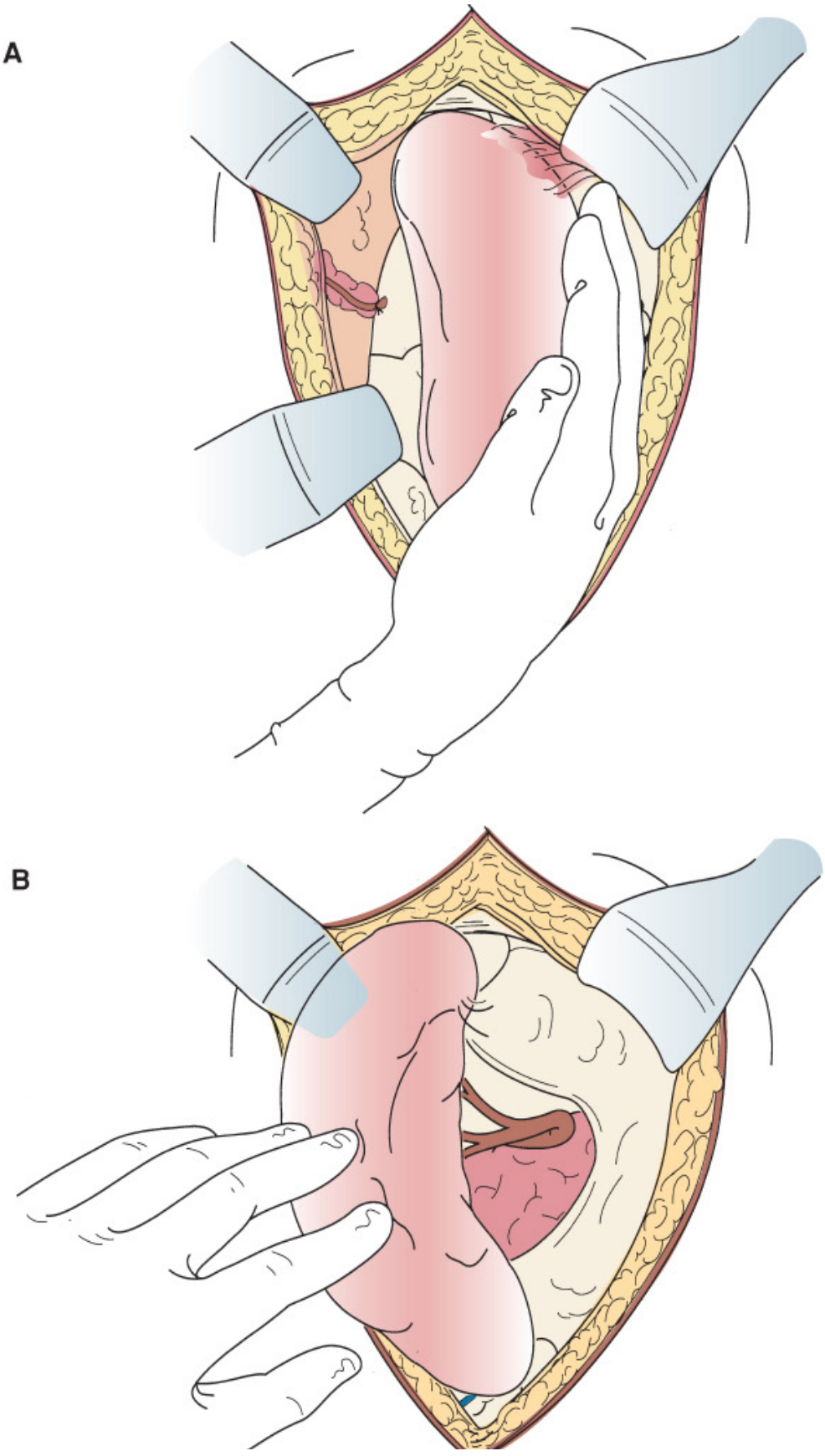
Description of Procedure

Open Splenectomy—Nontraumatic

The patient is positioned supine on the operating room table. The operation begins with either a midline laparotomy incision or a left subcostal incision. Once the abdominal cavity is safety entered, a self-retaining retractor system should be employed to facilitate exposure of the spleen. Retract the stomach medially to gain access to the gastrosplenic ligament and identify an avascular space for entry into the lesser sac. Using an energy device, serially ligate the vessels in the gastrosplenic ligament to gain access to the splenic hilum. Identify the course of the splenic artery and carefully incise the overlying peritoneum to fully expose the vessel. After gaining proximal and distal control, the artery can then be ligated either with silk sutures or a vascular stapler. It is important to ligate the artery before the vein as it allows for drainage of the organ prior to removal, possibly lessening blood loss.

Continue to divide the gastrosplenic ligament to fully mobilize the spleen from the stomach. Care should be taken near the upper pole of the spleen as the stomach is in close proximity, and sometimes completely adherent, to the spleen. Continue to mobilize the spleen by dividing the posterior and lateral attachments to deliver the organ into the surgical field. Take care not to injure the capsule of the spleen as this can cause significant hemorrhage. Finally, divide the splenocolic ligament to fully mobilize the spleen. Once the hilum is visible, the vessels can be serially ligated either with clamps and ties, or with a vascular stapling device. After removing the specimen and

meticulously achieving hemostasis, maintain vigilance for the possibility of an accessory spleen which must also be removed before completing the operation. A schematic of this approach is demonstrated in **Figure 73.9**.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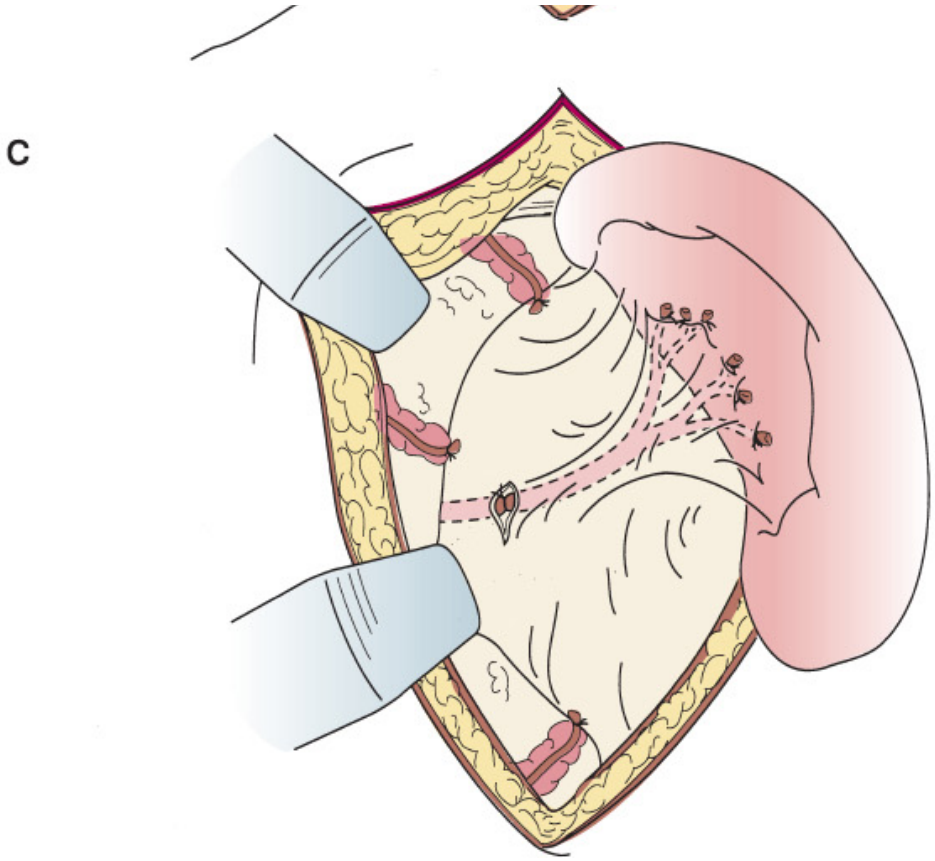


Figure 73.5 **A, B:** Rapid mobilization of a bleeding spleen can be accomplished in most patients by blunt dissection of the lateral attachments. **C:** The splenic hilum can then be quickly controlled.

Open Splenectomy—Traumatic

Open splenectomy for trauma takes place during an exploratory laparotomy. The patient is supine on the operating room take, prepped from neck to knees with arms extended. A generous midline laparotomy is made, immediately packing all four quadrants of the abdomen. Once any ongoing hemorrhage has been controlled, begin a thorough examination to determine the source. If the spleen is determined to be injured and bleeding, elevate the spleen medially using a combination of rolled laparotomy packs and blunt dissection as demonstrated in Figure 73.8. Once in the surgical field, serially clamp and ligate all vessels of the splenic hilum to control bleeding and remove the organ. Unlike the situation for an elective or planned splenectomy, the hemoperitoneum has often facilitated much of the dissection. Once the organ is removed, again meticulously check for ongoing bleeding as missed bleeding from the short gastric vessels can be a significant of ongoing

hemorrhage. A schematic of this approach is demonstrated in **Figure 73.5**. A schematic of techniques to repair superficial splenic lacerations is demonstrated in Figure 73.6.

Laparoscopic Splenectomy

In the elective setting, laparoscopic splenectomy is the preferred approach in many centers. First introduced in the early 1990s, the laparoscopic approach was found to be associated with less blood loss intraoperatively, less pain, shorter hospital length of stay, and lower morbidity.[83] Initially, laparoscopic splenectomy was contraindicated for cases of splenomegaly but as the technology developed and surgeons gained experience it became more common. However, some of the previously cited benefits may not apply for patients with splenomegaly. In a 2019 matched case study, the authors found that for patients with moderate splenomegaly (splenic weight 500 to 1,000 g), the laparoscopic approach was associated with a significantly longer operating time and 14% conversion rate. There was no difference in length of stay, morbidity, or mortality. However, for patients with massive splenomegaly (>1,000 g), the laparoscopic approach was associated with longer operating room time, 35% conversion rate, and a higher rate of readmission compared to open surgery. The authors conclude that for patients with splenomegaly, it is not clear whether the laparoscopic approach is superior.[83]

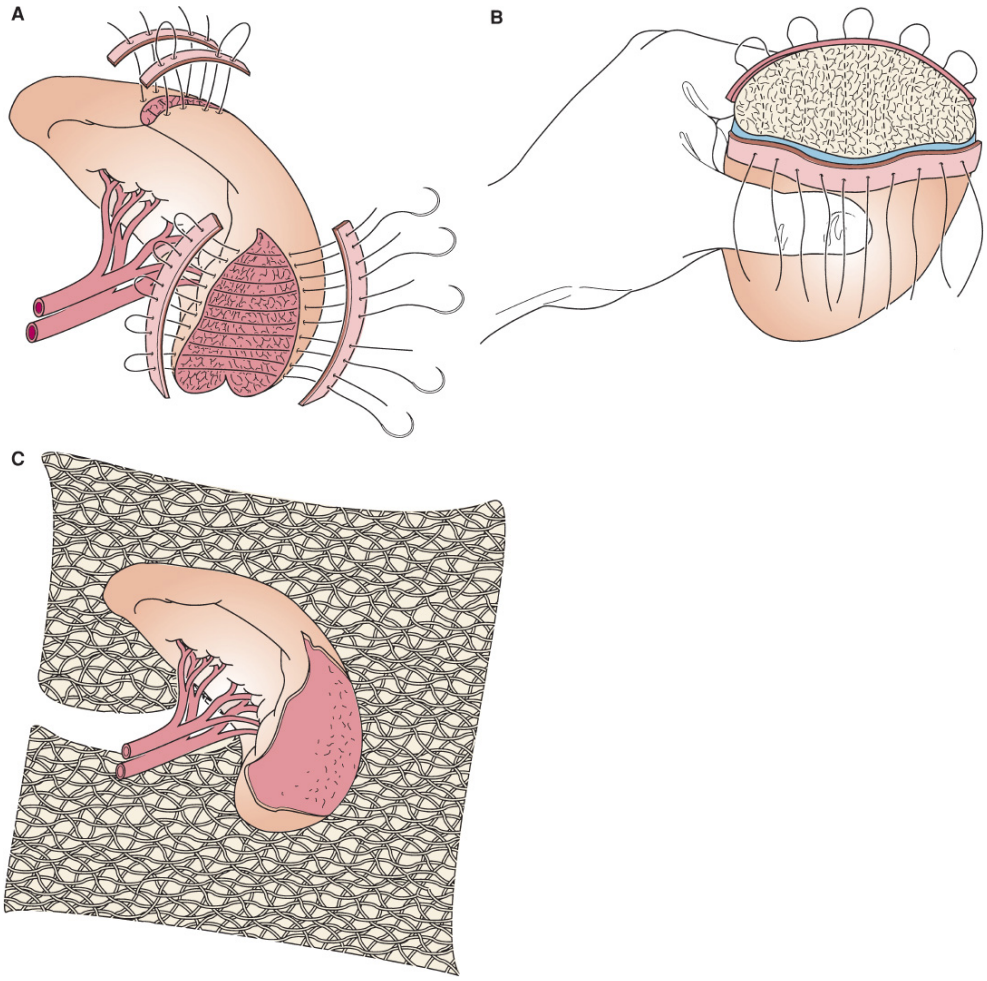


Figure 73.6 **A:** Techniques to suture superficial splenic lacerations. **B:** Technique to control bleeding after hemisplenectomy. The sutures can be interlocked. **C:** Polyglycolic acid mesh sheets or mesh bags can be applied to spleens that have had the capsule stripped away.

Figure 73.7 A massively enlarged, 2.2-kg spleen from a patient with chronic lymphocytic leukemia. Superficial areas of infarction are indicated by *thin arrows* and splenic infarction by the *thick arrow*.

The procedure begins with the patient in a right lateral decubitus position with a flexed table to optimally expose the left flank. Port positions and selection may vary slightly between surgeons, but a commonly described method is to place four to five ports in the left subcostal plane. Entry can be gained either via Hasson or Veress technique. The entry port is placed in either in the periumbilical location or just lateral to Palmer point. After

visual inspection of the abdomen and assessment of the size of the spleen, additional ports are placed just below the left subcostal margin to allow appropriate triangulation of the spleen. Begin by mobilizing the splenic flexure of the colon using an energy device. Carry this dissection medially to enter the lesser sac and divide the short gastric vessels. As in open splenectomy, take care at the upper pole of the spleen as the stomach may be very adherent at this point. Next visualize the splenic artery to allow for dissection. As dissection continues, small branches may be encountered that can be serially clipped and ligated. Once the splenic artery is dissected circumferentially, it is doubly clipped and ligated. Alternatively, a surgical stapling device can be used to divide the artery.

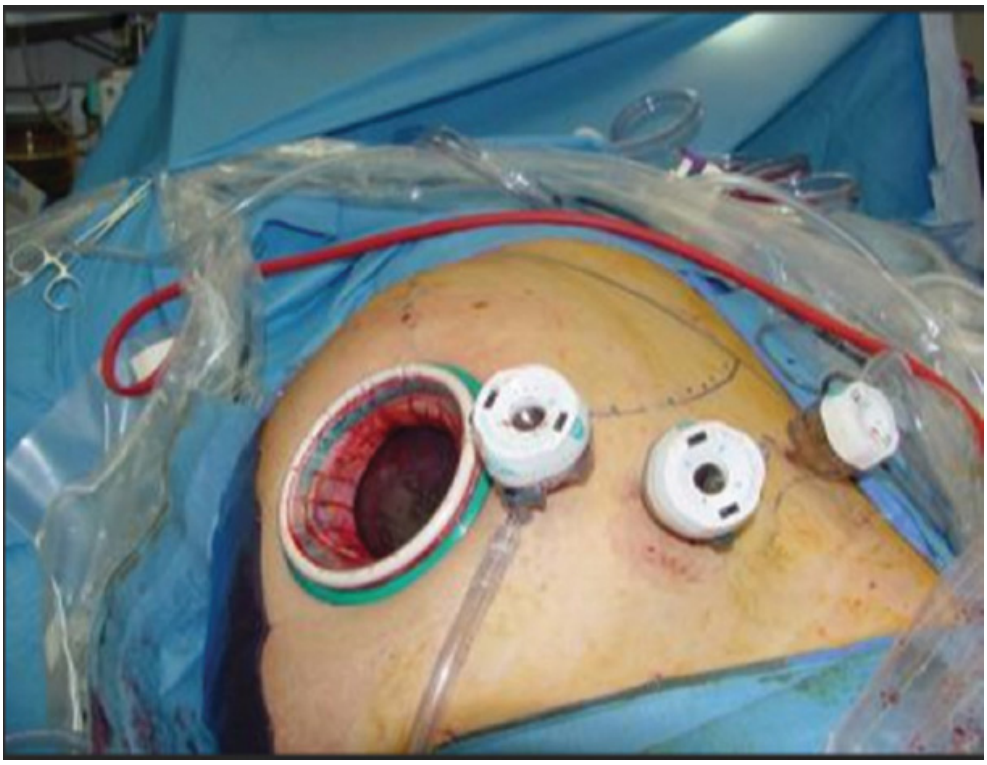
Continue dissection on the medial aspect of the spleen to expose the hilar vessels. Meticulous dissection ensues, clipping and ligating small vessels as the operation proceeds. Further mobilize the spleen by dividing the hilar attachments. Continue to dissect until the splenic vein is identified and encircled. Divide the vein with an endoscopic stapler with a vascular load. Alternatively, the entire vascular pedicle can be divided with an endovascular stapler rather than separately dividing the artery and vein. Once the vessels are ligated, continue dissection around to organ to free any remaining attachments so that the spleen can be removed. A specimen removal bag is then inserted to facilitate removal, brought to skin level, and the spleen is then morcellated to allow for removal. Carefully inspect the splenic fossa for hemostasis before closing the abdomen.

Hand-Assisted Laparoscopic Splenectomy

For cases in which splenomegaly would otherwise preclude the laparoscopic approach, the use of a hand port can help to facilitate laparoscopic splenectomy. In this technique, an additional incision is made to allow for insertion of the surgeon's nondominant hand into the abdomen. Reports of this technique describe a 7- to 8-cm incision (or slightly smaller than the surgeon's hand) located 2 to 4 cm caudal to the lower pole of the spleen. It can be made in the midline, or on the right subcostal area.[84,85] A hand port is then placed in the wound. The use of the hand port allows the nondominant hand to assist in retraction of the spleen. Additionally, the spleen can be

removed through this incision without the need for morcellation in some cases.

The advantage of hand-assisted laparoscopic splenectomy is that it allows for removal of larger spleens that would otherwise require open surgery while still maintaining the benefits associated with standard laparoscopic splenectomy. The additional tactile feedback afforded also may result in a lower incidence of hemorrhage as the vascular pedicle can be directly palpated and controlled.[85] In a meta-analysis of 16 studies with 754 patients undergoing laparoscopic splenectomy and hand-assisted laparoscopic splenectomy, the hand-assisted approach was found to be associated with shorter operative time, less blood loss, and a lower rate of conversion for open surgery in cases of splenomegaly. There was no significant difference in outcome metrics such as complications, hospital length of stay, or mortality, leading the authors to conclude that in cases of splenomegaly the hand-assisted approach is ideal.[86]



Schematic of port placement for hand-assisted laparoscopic splenectomy.

Robotic Splenectomy

Robotic approach to splenectomy is described and is similar in procedure to laparoscopic splenectomy. For normal-sized spleens, the robotic approach in results in longer operating time and higher costs, but no difference in safety, compared to laparoscopy. For splenomegaly, the robotic approach is associated with less blood loss and longer operative time without significant differences in safety.[87] Given the technical challenges presented by splenomegaly, some argue that the best approach in that circumstance remains hand-assisted laparoscopic splenectomy.[88]

Partial Splenectomy

Partial splenectomy has been advocated because it allows for removal of pathology while still preserving the immune function of the spleen and preventing overwhelming postsplenectomy sepsis. Indications for partial splenectomy include cysts, intraparenchymal lesions, hematologic disease, abscess, as well as others. The operation begins with division of the gastrocolic ligament followed by the gastrosplenic ligament to enter the lesser sac. Short gastric vessels are divided to allow visualization and temporary occlusion of the splenic artery. The spleen is then completely mobilized and segmental vascular control at the splenic hilum is achieved. Once the vessels are controlled, the splenic artery is then unclamped to allowed for visualization of the newly created ischemic zone, which can then be resected. That portion of the spleen is transected using an energy device, and subsequently removed. Given the potentially large surface area of splenic parenchyma now exposed, meticulous hemostasis must be achieved before closure. This can be accomplished with energy or hemostatic agents.[89]

SEQUELAE OF SPLENECTOMY AND HYPOSPLENISM

Postsplenectomy Sepsis

For patients who are asplenic, either due to surgical removal or functional asplenia, postsplenectomy sepsis is a significant concern. Hyposplenism, or impaired splenic function, may also occur in patients with HIV infection,

chronic graft-versus-host-disease, and severe celiac disease. Asplenic or hyposplenic patients are at particularly high risk of infection from encapsulated bacteria such as *Streptococcus pneumoniae* and *H. influenzae* type b. Other common high-risk organisms include *N. meningitidis, E. coli, and Staphylococcus aureus*. The reason for this is that the spleen is the organ best suited for removal of IgG-coated bacteria and encapsulated bacteria as these are not effectively opsonized by other methods. It is important to remember that patients who have not undergone surgical splenectomy may be functionally asplenic due to underlying disease, and thus may still be at risk for these infections.[24]

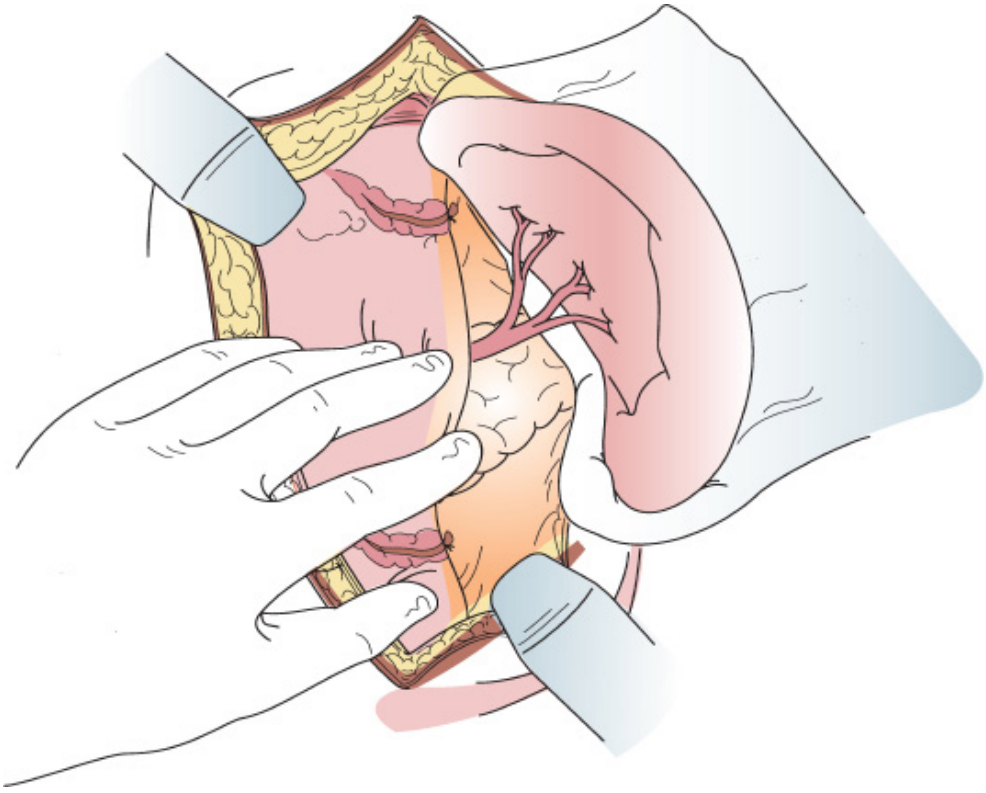
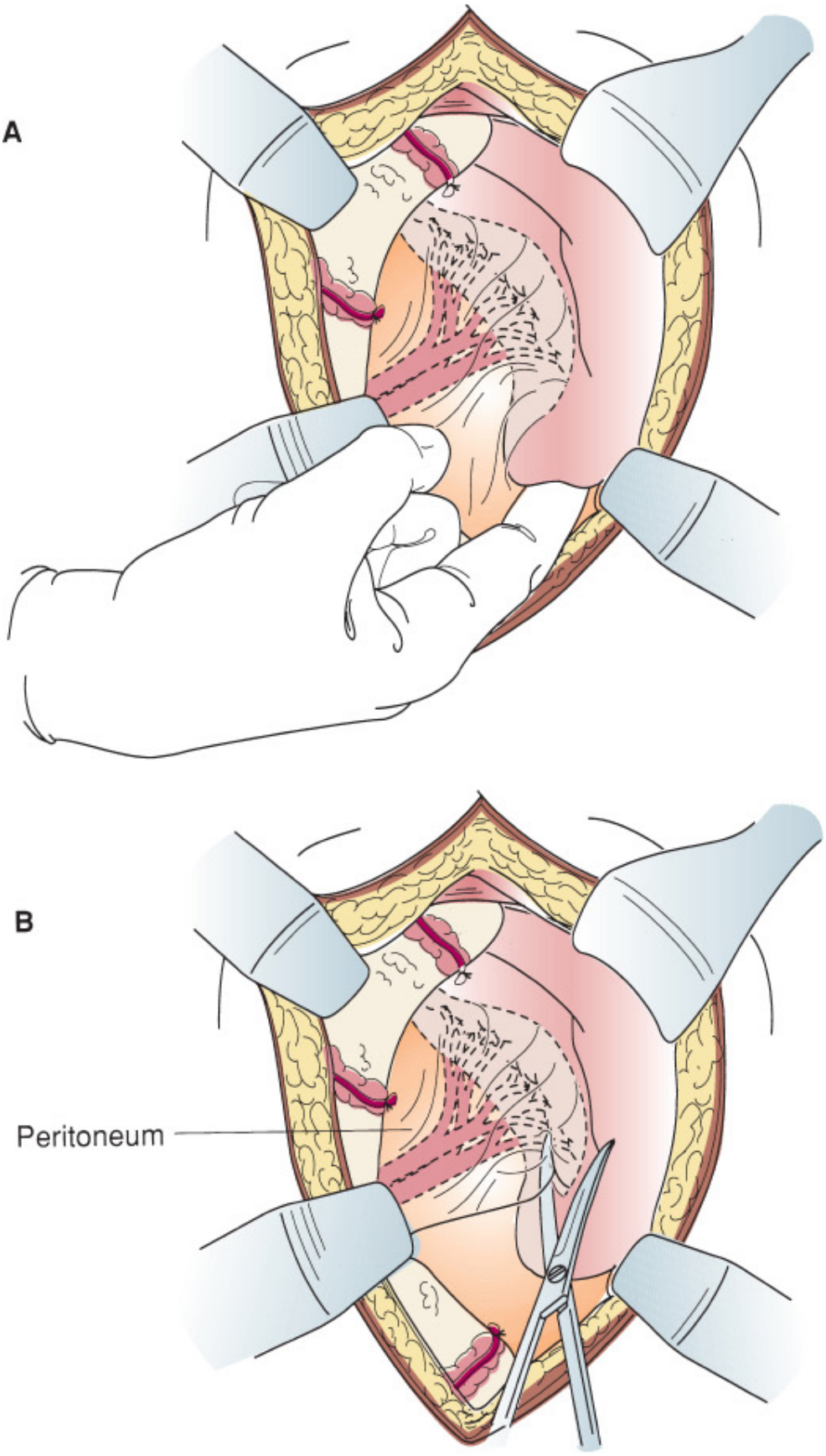


Figure 73.8 Lateral mobilization permits the spleen to reach the surface of a midline wound despite the presence of intact hilar vessels.


A
B
Peritoneum

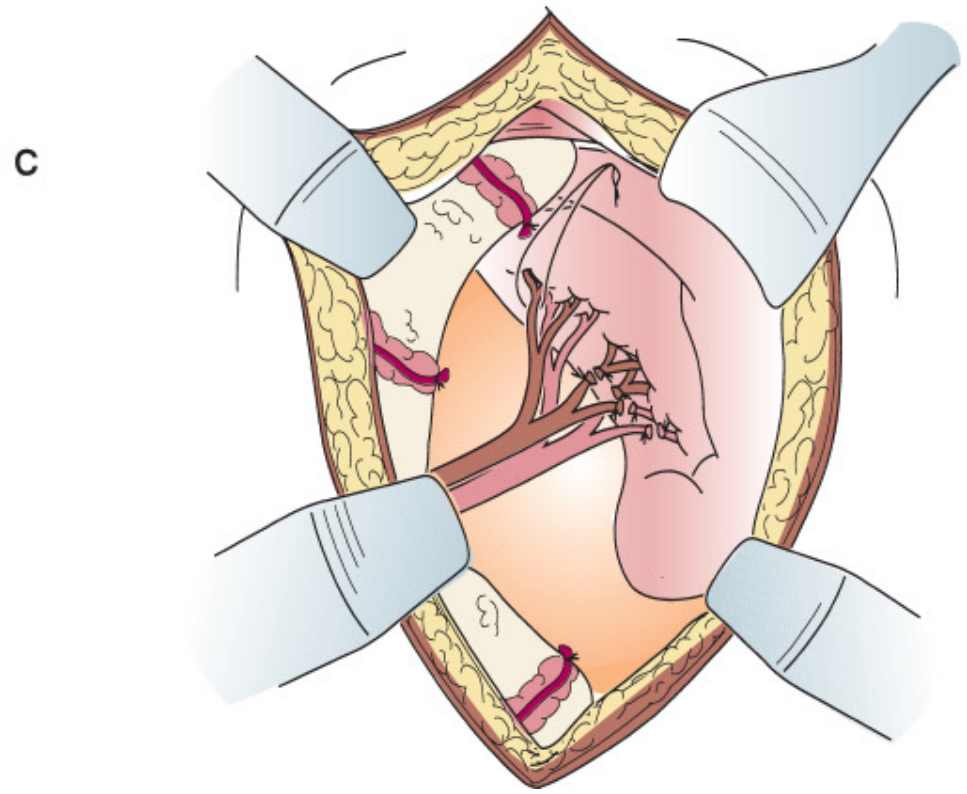


Figure 73.9 Technique for elective splenectomy. **A:** The inferior pole is reflected laterally by the assistant's fingers, exposing the lower edge of the hilar peritoneal envelope. **B:** The hilar peritoneum is opened, here shown progressing from inferior to superior. **C:** Individual vessels are identified and suture is ligated.

The risk of postsplenectomy sepsis depends on the indication for splenectomy. Healthy patients undergoing trauma splenectomy have the lowest risk while patients with surgical asplenia due to sickle cell disease, thalassemia, or portal hypertension are highest risk. Patients with hereditary spherocytosis or ITP are intermediate risk. Children, particularly infants, are at highest risk. The risk of postsplenectomy sepsis is highest in the first year following splenectomy but remains high for at least 10 years or longer. While the overall risk of postsplenectomy sepsis is low, mortality is high. Prior to the availability of effective vaccines, the incidence of postsplenectomy sepsis was 3.2% and led to death in up to two-thirds of affected patients.[24] A 2014 study of more than 20,000 splenectomized patients from 1970–2009 in Sweden indicated that there was a nearly six-fold higher risk of sepsis compared to the general population. As previously described, patients who underwent splenectomy for trauma has a lower risk than patients with

hematologic malignancy. Overall mortality for patients with sepsis was 17%.[90]

Given the high risk of postsplenectomy sepsis and associate mortality routine prophylaxis is recommended. Ideally, these vaccines can be given prior to splenectomy but in many cases (e.g., trauma) this may not be possible. While the exact timing is debated, there is some evidence that vaccination is less effective if administered in the 2 weeks before or after splenectomy. For *S. pneumoniae,* there are two vaccines (PCV13 and PPSV23) given 8 weeks apart. *H. influenzae* type b is a single vaccination while *N. meningitidis* requires two doses. In addition, it is recommended that patients undergo vaccination for the seasonal influenza virus.[24] However, in a 2019 study describing vaccination rates in Minnesota over a nearly 50-year period, only 62% of patients received adequate vaccination with only 32% received booster vaccines. Furthermore, patients who did not receive appropriate vaccination more frequently presented with sepsis and developed sepsis at a shorter time interval following surgery compared to those who were vaccinated.[26]

Initial symptoms of postsplenectomy sepsis include nonspecific viral symptoms such as fever, chills, rigors, diarrhea, and vomiting. However, these symptoms can rapidly progress to fulminant sepsis in 1 to 2 days. Effective treatment begins with early recognizing that a patient might be at risk so that diagnosis can be made quickly. Treatment including blood cultures and early initiation of broad spectrum antibiotics follows standard sepsis bundles.[91]

Vascular Complications Following Splenectomy

A less commonly recognized complication following splenectomy is arterial and venous thrombosis, as well as vascular remodeling leading to pulmonary hypertension. These complications vary by indication and are most common following splenectomy for thalassemia. While the exact mechanism is not well understood, it is thought to be related to a combination of platelet activation, altered lipid profile, hypercoagulability, and changes to vascular endothelium. This may be because damaged cells and particulate matter that

would otherwise be filtered by the spleen are left circulating in the blood. Because the mechanisms underlying this phenomenon are still being explored, there is no universally endorsed strategy to treat or prevent this. Some advocate for thromboprophylaxis or anti-platelet therapy in high-risk patients but this has not been validated in prospective studies.[92]

One specific example of thrombotic disease following splenectomy is portal vein thrombosis. This occurs not only due to the hypercoagulable state induced by splenectomy, but also due to stasis within the splenic vein stump that leads to turbulent blood flow. This is a rare complication of splenectomy (<1%) but can be fatal. Patients may be asymptomatic or show symptoms of abdominal pain and fever. Anticoagulation is the mainstay of treatment.[93]

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Section K: SURGICAL ENDOCRINOLOGY

74

Breast Disease

Thanh U. Barbie and Julie A. Margenthaler

Key Points

1. Any clinically suspicious mass, even in the absence of an imaging abnormality, needs to be biopsied.
2. Core needle biopsy is the preferred strategy for breast cancer diagnosis. Core needle biopsy is less invasive and less expensive than excisional biopsy and facilitates definitive breast cancer treatment planning.
3. The upgrade of lobular neoplasia diagnosed on core biopsy at time of surgical excision to malignancy is 1% to 3% and as such surgical excisional biopsy is no longer indicated if there is radiographic-pathologic concordance.
4. All women should undergo risk assessment by age 35 to determine the best approach for breast cancer screening.
5. Surgical options for the treatment of DCIS include breast-conserving surgery as a component of breast conservation therapy (partial mastectomy and postoperative radiation therapy) or simple mastectomy.
6. Sentinel lymph node biopsy has replaced axillary lymph node dissection for axillary staging, and the therapeutic impact of axillary lymph node dissection may be limited to specific subsets of breast cancer patients.
7. Local regional management of invasive breast cancer consists of breast conservation therapy (partial mastectomy with radiation therapy) or mastectomy, noting that the choice in locoregional management does not typically impact the recommendation for adjuvant medical therapy.
8. Among patient's undergoing partial mastectomy, performing cavity shave margins halved the rates of positive margins and reexcision.
9. A negative surgical margin for invasive breast cancer is now defined as no tumor at the ink margins. Given the potential for gaps between lesions in DCIS, a negative surgical margin is still defined as ≥2 mm, understanding that this practice may evolve pending more study results.

10 Nipple-sparing mastectomy is a safe option for BCRA mutation carriers, with no local regional recurrences at the nipple or areola at up to 37 months of follow-up.

11 Axillary radiation therapy may result in less morbidity than axillary lymph node dissection in patients with early stage breast cancer with clinically negative axillary examinations who have ≤2 positive sentinel lymph nodes.

ANATOMY

Surgical Anatomy of the Breast

The boundaries of the mature adult breast are the 2nd rib superiorly, the 6th rib inferiorly, the sternal edge medially, and the midaxillary line laterally. Breast tissue also extends into the axilla. Posteriorly, the breast lies on top of portions of the deep investing fasciae of the pectoralis major muscle, the serratus anterior muscle, the external abdominal oblique muscles, and the upper extent of the rectus sheath (Fig. 74.1). The breast is composed of skin, subcutaneous tissue, and breast parenchyma. The skin overlying the breast is thin and contains hair follicles, sebaceous glands, and exocrine sweat glands. The subcutaneous tissue is composed of fat, vasculature supplying the skin, lymphatics, and nerves. The breast parenchyma consists of parenchymal components and stroma.

Breast tissue is located within the superficial fascia of the anterior thoracic wall and consists of 15 to 20 lobes of glandular tissue that are divided by connective tissue with adipose tissue filling the space between the lobes (Fig. 74.2). Each lobe is composed of 20 to 40 lobules, which are themselves composed of 10 to 100 alveoli. Each lobe ends in a lactiferous duct that dilates into lactiferous sinuses, which then open through constricted orifices into the nipple. The suspensory ligaments of Cooper are fibrous connective bands that extend from the deep fascia to connect to the dermis, providing the breast with both support and mobility. There is significant variation in breast size with the average nonlactating breast weighing between 150 g and 225 g, whereas the lactating breast may exceed 500 g.[1]

The left breast is commonly slightly larger than the right.[2] The upper outer quadrant of the breast contains more breast parenchyma and is the most frequent site of both benign and malignant breast disease.

The skin of the nipple and areola is highly pigmented and somewhat wrinkled, composed of stratified squamous epithelium. Deep to the nipple and areola are bundles of smooth muscle fibers that are arranged radially, circumferentially, and longitudinally, allowing for erection of the nipple from stimuli. Along the margin of the areola are sebaceous glands and sweat glands. Accessory glands known as Montgomery glands have nodular elevations (tubercles of Morgagni) that open onto the surface of the areola. The nipple and areola are highly innervated, with the nipple containing numerous free sensory nerve endings and Meissner corpuscles, whereas the areola contains both Ruffini-like endings and Krause-end bulbs.[3] The sensory innervation of the breast is mainly the lateral and anterior cutaneous branches of the second through sixth intercostal nerves. There is also a small region of skin over the upper portion of the breast that is supplied by the anterior or medial branches of the supraclavicular nerve that arises from the cervical plexus.

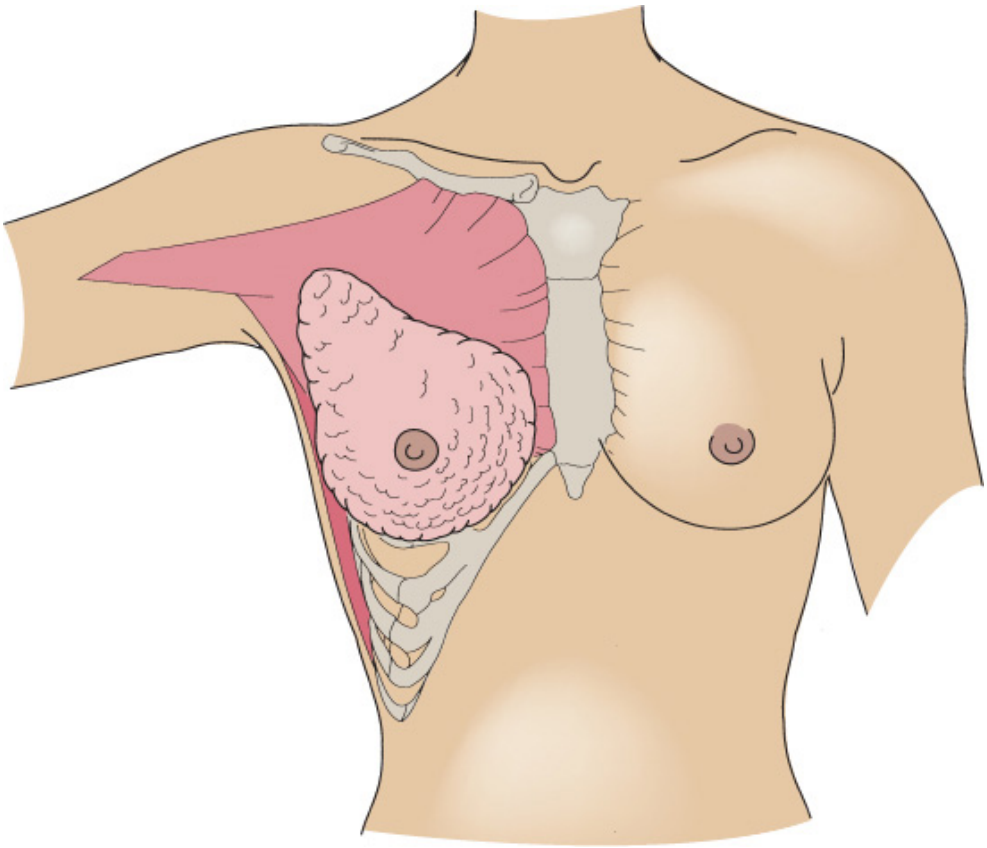


Figure 74.1 The adult female breast. The upper and medial portions of the breast rest on the pectoralis major muscle, and the inferolateral portion rests on the serratus anterior.

The arterial blood supply to the breast consists of the internal mammary artery (perforating branches), the posterior intercostal artery (lateral branches), and several branches of the axillary artery including the superior thoracic artery, the lateral thoracic artery, and the pectoral branches of the thoracoacromial artery. The breast's venous system parallels its arterial system, consisting of the internal mammary veins, the posterior intercostal veins, and the axillary vein tributaries.[4]

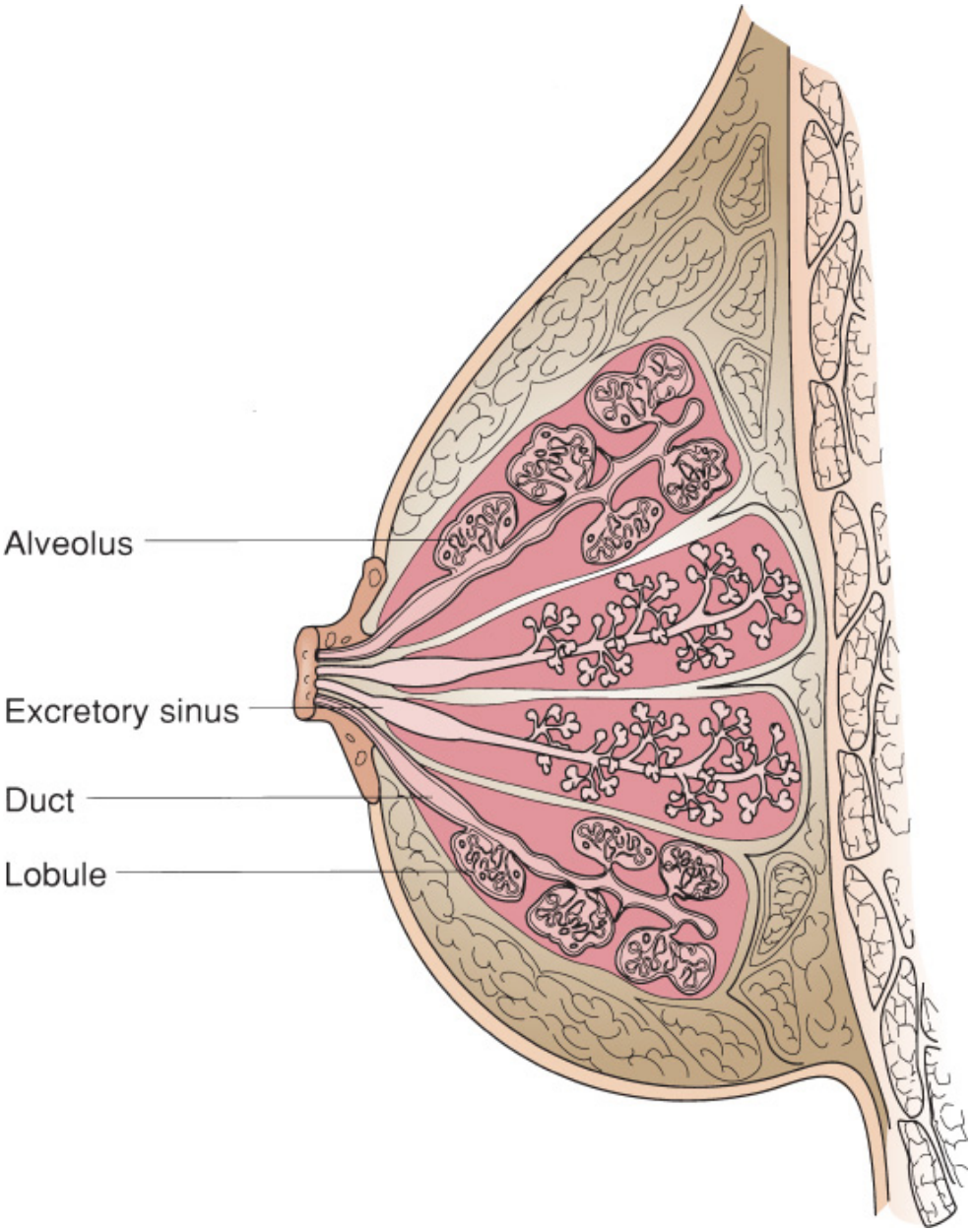


Figure 74.2 The breast consists of 15 to 20 lobes of glandular tissue. Within each lobe, the lobules are composed of branched tubuloalveolar glands. Each lobule ends in a lactiferous duct. These ducts dilate into lactiferous sinuses beneath the nipple.

Lymphatic Drainage

The lymphatic flow from the breast is unidirectional through thin-walled, valveless vessels that are interconnected through three groups. The primary group of lymphatic vessels comes from within the gland in the interlobular spaces and along the lactiferous ducts. The lymphatic vessels that drain the

skin, nipple/areola, and the central portion of the gland constitute the subareolar plexus. The third plexus is on the deep surface of the breast and communicates with small vessels in the deep fascia underlying the breast. More than 75% of the lymph from the breast passes to the axillary lymph nodes, whereas the remainder passes to parasternal nodes. The flow of lymph to either the axillary or the parasternal nodes is independent of the quadrant from where the lymph originated.[5] Occasionally, lymph flow can be found outside of these three interconnected plexuses, occurring along the lateral cutaneous branches of the posterior intercostal arteries, within the rectus sheath or subperitoneal plexus by following branches of the intercostal and musculophrenic vessels, or directly to subclavicular or apical nodes.[6]

The axilla is a pyramidal compartment between the upper extremity and the thoracic walls, which can be thought of as consisting of four walls, an apex, and a base. The anterior wall consists of the pectoralis major/minor and its associated fasciae. The supscapularis muscle, teres major muscle, latissimus dorsi muscle, and associated tendons form the posterior wall. The medial wall consists of the serratus anterior muscle and associated intercostal muscles of the upper four or five ribs. A thin strip of the humerus and the bicipital groove, which is between the insertion of the muscles of the anterior and posterior walls, forms the lateral wall. The apex is an aperture that extends into the posterior triangle of the neck through the cervicoaxillary canal, which is bounded by the clavicle anteriorly, the scapula posteriorly, and the 1st rib medially. The base of the axilla is the axillary fascia and skin.[6]

The axillary lymph nodes have traditionally been divided into three levels, corresponding to their location relative to the pectoralis minor (Fig. 74.3). Level 1 nodes (external mammary, axillary vein, and scapular lymph node groups) are inferior and lateral to the pectoralis minor; level 2 nodes (central lymph node and some subclavicular lymph node groups) are behind the pectoralis minor; and level 3 nodes (subclavicular lymph node group) are medial to the pectoralis minor. The interpectoral nodes (Rotter nodes) are located between the pectoralis major and minor muscles along the lateral pectoral nerve. The supraclavicular nodes are contiguous with the apex of the axilla. The internal mammary nodes are located in the first six intercostal spaces within 3 centimeters of the edge of the sternum, with the highest concentration of nodes found in the first three intercostal spaces.[7,8]

BREAST PHYSIOLOGY

Breast Development

As epidermal appendages, mammary glands likely evolved from ancient apocrine glands that were associated with hair follicles.[9] The mammary gland is a complex secretory organ consisting of multiple different cell types. Epithelial cells form the ductal network of the gland, which is embedded within a fat pad composed of adipocytes. In addition, there are vascular endothelial cells that make up the blood vessels, stromal cells including fibroblasts, and immune cells. During the three stages of mammary development (embryonic, pubertal, and pregnancy/lactation), these cells undergo an intricate series of changes under the regulation of hormones and regulatory factors, resulting in permanent changes to the mammary gland that both modify its architecture and biologic characteristics.[10] Understanding breast development and morphology is extremely important to the study of both premalignant and malignant conditions.

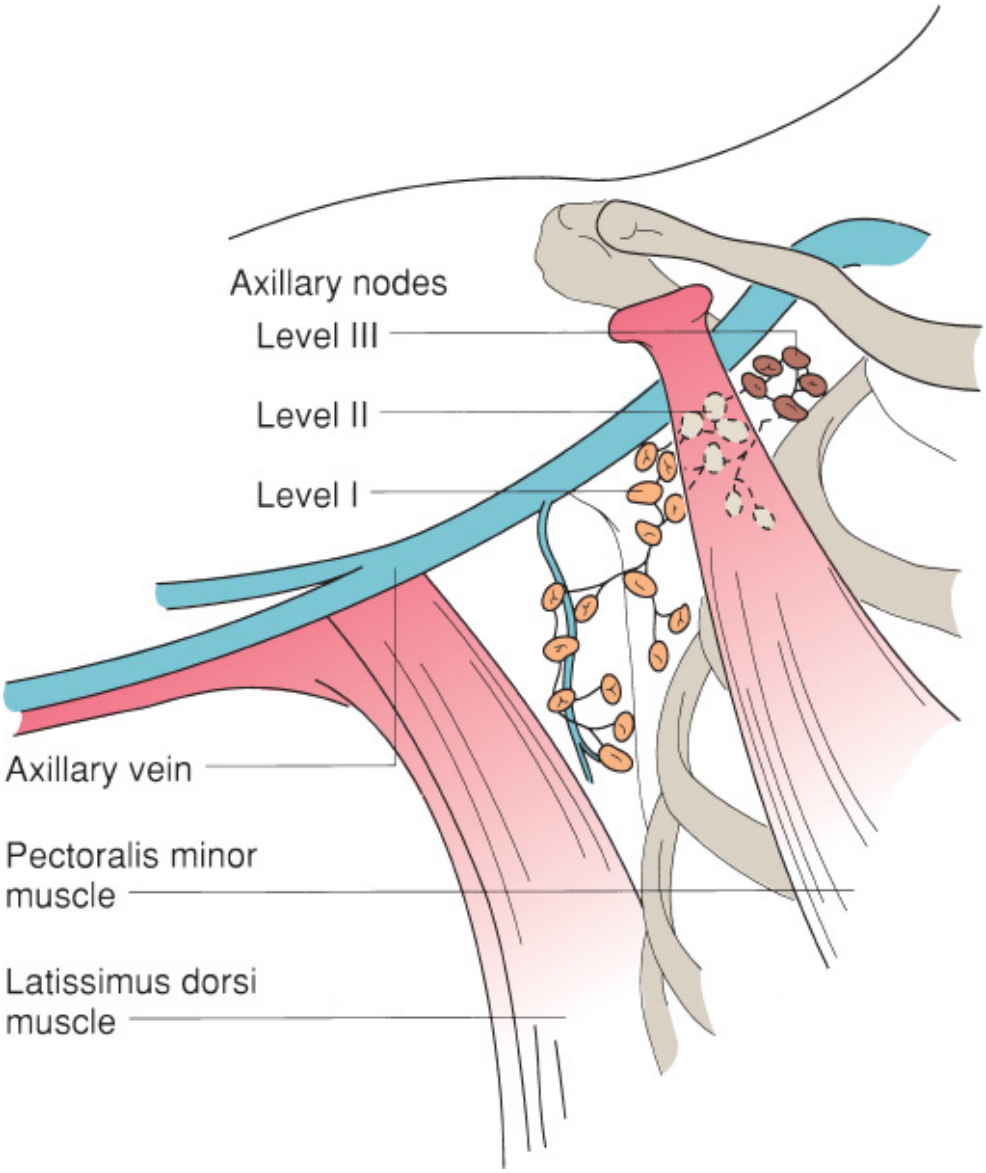


Figure 74.3 The axillary lymph nodes are divided into three levels by the pectoralis minor muscle. The level I nodes are inferior and lateral to the pectoralis minor, the level II nodes are below the axillary vein and behind the pectoralis minor, and the level III nodes are medial to the muscle against the chest wall.

In humans, mammary gland development starts in the sixth week of fetal life with the formation of bilateral milk lines or ectodermal thickenings that extend from the axilla to the groin. These ridges rapidly regress except for those of the thorax, where invagination of ectoderm cells into the mesenchyme results in mammary bud formation. In the human embryo, at about 5 months, the deep layer of the mammary bud epithelium starts to proliferate and produces about 10 to 25 secondary buds, which will later

correspond to lactiferous ducts. Canalization, or the formation of lumens within the solid core of these epithelial structures, occurs later in development. By birth, six to eight of these ducts are patent and empty into the nipple.[11–15] A parallel bundle of an additional 25 smaller ducts also appear and are the precursors to the milk-producing units of the breast.[16] The subareolar lymphatic plexus also develops from the ectoderm in a similar fashion,[17] while the nipple forms from the proliferation of the mesenchyme under the areola.[14]

In infants, only small ductal structures are seen within the stroma and during childhood these structures continue to grow isometrically at a rate similar to the rest of the body until puberty.[18] These initial stages of breast development are not dependent on sex steroids but are likely governed by numerous growth factors that regulate the epithelial-mesenchymal interaction, including Lef-1,[19] parathyroid hormone–related protein, and the type 1 parathyroid hormone/parathyroid hormone–related protein receptor.[20]

During puberty, the female glands enlarge rapidly secondary to maturation of the ductal system into a lobuloalveolar system. This is characterized by thickening of the ductal epithelium, elongating ducts, and an increasing amount of periductal connective tissue. In addition, stem cells at the tips of the ductal tree form terminal end buds, which are highly proliferative and give rise to alveolar buds. In early puberty, these alveolar buds empty into a terminal ductal lobular unit and are referred to as lobules type 1. Under the influence of ovarian hormones (estrogen and progesterone), lobules type 1 will differentiate into lobules type 2, which are characterized by smaller but more numerous buds that are noted as ductules or alveoli. It has been postulated that each menstrual cycle fosters new budding that never fully returns to the baseline of the prior cycle.[21,22] In addition to estrogen and progesterone, pubertal breast development is also dependent on other hormones and regulatory factors including prolactin, growth hormone, glucocorticoids, growth factors (hepatocyte growth factor, IGF-1, IGF-2, FGF, neuregulins especially heregulin), vitamin D receptor, metalloproteinases, and PTEN.[23–28]

As these developmental events are occurring, physical changes in the breast contour and the appearance of the nipple become evident and are illustrated as the five Tanner stages of breast development (Fig. 74.4).[29]

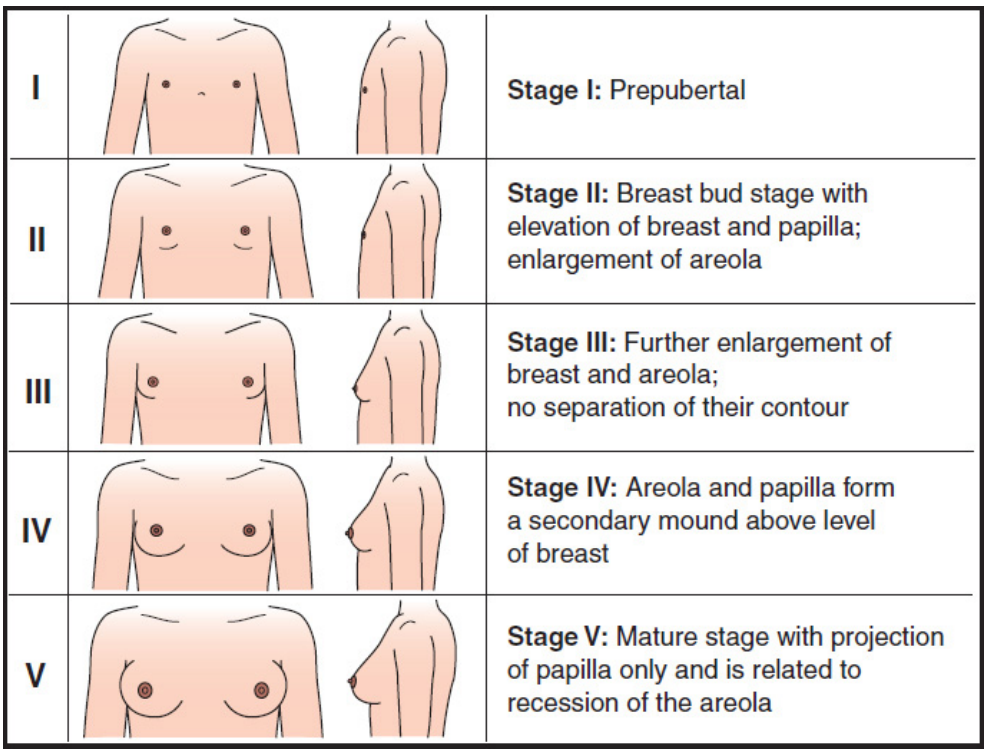


Figure 74.4 Tanner stages of breast development.

Pregnancy and Lactation

Although the pubertal phase is marked by significant lobular development, the mammary gland does not achieve full differentiation until after pregnancy and lactation. In early pregnancy, the distal ducts continue to proliferate resulting in more lobules and more alveoli within each lobule. However, by mid-pregnancy, proliferation of the lobules ceases and instead alveolar cells begin to differentiate into acini by hypertrophy and the ability to secrete colostrum into the lumina of the ductules. By the third trimester, the acini become distended with colostrum and the breast's connective tissue and fat become largely replaced by glandular proliferation. In addition, the connective tissue becomes infiltrated with plasma cells, lymphocytes, and eosinophils. There is also a marked increase in vascularity. The stage of lactogenesis or the ability to synthesize and secrete milk marks the final stage of maturation of the mammary gland (lobule type 4).[30,31] Following lactation or during weaning, the mammary gland involutes with lobules type 4 returning to the prepregnancy state as lobules type 2 and 3.[32,33]

The hormones and regulatory factors that govern mammary development during pregnancy and lactation overlap with those previously discussed for pubertal breast development, with estrogen, progesterone, and prolactin playing chief roles. Other hormones and regulatory factors include intracellular signaling molecules (c-erbB, hox genes, cell–cell adhesion molecules such as E-cadherin, cell cycle protein cyclin D1, RANK-L, slug transcription factor), activins and inhibins including STAT5, hypothalamic peptides, thyrotropic-releasing hormone, and lactogenic hormones.[34–41]

Menopause

By menopause, the mammary gland is mainly replaced by fat as the glandular epithelium undergoes apoptosis. As such, the postmenopausal phase is characterized by both a decrease in lobules and ducts.[42,43]

In summary, human breast development is a progressive process that is initiated during embryonic life, with glandular maturation starting at puberty, and attainment of full breast differentiation only with subsequent pregnancy and lactation.

CLINICAL EVALUATION OF THE PATIENT WITH BREAST DISEASE

Breast disease is an extremely common clinical problem. Most women who present to a breast health specialist will have benign breast disease. One of the primary goals of the evaluation is to determine whether the breast problem represents benign or malignant breast disease. With benign conditions, the goals are to reassure the patient and if indicated provide symptomatic treatment. With a malignant condition, prompt evaluation and treatment should be undertaken, typically involving a breast surgeon, medical oncologist, and radiation oncologist. In this section, clinical breast examination (CBE), diagnostic imaging studies, and biopsy procedures used to evaluate the patient with breast disease are discussed.

During the CBE, it is important to discuss with the patient whether she has any breast concerns and to elicit a gynecological history including

menopausal status (for premenopausal patients, the time in their menstrual cycle) and the use of any hormonal therapies. If a woman has any breast problems, a thorough history needs to be obtained (Table 74.1).

Clinical Breast Examination

Clinical breast examination (CBE) is performed in both the sitting and supine positions. The patient is disrobed from the waist up and then provided a front-opening gown. Visual inspection is first accomplished with the patient sitting upright with the arms relaxed to her side. The bilateral breasts are compared for size and shape. It is normal to find slight differences in breast size, with the left breast often slightly bigger than the right. Breast shape is also contrasted. Recent changes to breast size or alterations in breast shape can be concerning signs and need to be evaluated by the provider, as tumors located superficially can cause changes to the breast contour. The skin of the breasts is inspected for dimpling, edema (peau d'orange), and/or erythema. In cases of significant erythema and peau d'orange, the provider needs to consider the diagnosis of an inflammatory breast cancer (IBC) versus an infectious etiology. This is followed by close inspection of the nipples for symmetry. Although some women have a lifelong history of nipple inversion, any new history of nipple inversion needs to be regarded with a high index of suspicion. Next the nipple–areola complex is evaluated for any eczematous changes or ulcerations (to suggest conditions such as Paget disease of the breast [PDB]). The patient is then asked to raise her arms to allow for a more complete visual inspection of the lower aspect of the breasts bilaterally. The visual examination is completed when the patient is asked to place her hands on the hips and then to contract the pectoral muscles. This allows for a final visual assessment of breast symmetry. Furthermore, tumors deep within the substance of the breast involving Cooper ligaments can result in skin retraction and can sometimes be seen best with contraction of the pectoral muscles.

Table 74.1 Medical History of a Breast Problem

General
Age at menarche
Number of pregnancies
Number of live births
Age at first birth
Family history of ovarian cancer, gynecologic cancers, and other cancers, including affected relative, age of onset, and presence of bilateral disease
History of breast biopsies (and histologic diagnosis, if available)
Premenopausal women
Date of last menstrual period
Length and regularity of cycles
Use of oral contraceptives
Postmenopausal women
Date of menopause
Use of hormone replacement therapy
Specific
Onset
Duration
Frequency
Severity
Relationship to menstrual cycle or use of hormone replacement therapy

With the patient remaining in the sitting position but now with the pectoral muscles relaxed, palpation of the regional lymph nodes of the neck, clavicles (infraclavicular and supraclavicular), and axilla is then performed. To best delineate the axillary lymph nodes, the patient should be examined with the ipsilateral arm supported (Fig. 74.5). Attention is paid to evaluate the size, consistency (soft or firm), and characteristics (mobile or matted, tender or nontender) of the lymph nodes. Bimanual palpation of the breasts for masses and asymmetry completes the sitting examination.

The patient is then placed in the supine position with the ipsilateral arm raised above the head and the contralateral breast covered with the gown. The breast tissue is carefully palpated to evaluate for masses and asymmetry. It must be noted that generalized lumpiness is not a pathologic finding, with most normal breasts having more nodularity in the upper outer quadrants, at the inframammary ridge, and in the subareolar region. Comparing the breasts for symmetry by palpation may help discriminate benign findings from those that require additional evaluation. The area examined extends from the clavicle to the lower rib cage and medially from the sternal border to the midaxillary line. In addition, the axillary tail of the breast should be carefully palpated. The three search patterns that have been described are concentric circles, radial spoke method, and the vertical strip pattern (Fig. 74.6). As the first two methods can result in a less than thorough examination of the nipple–areola complex, we prefer the vertical strip pattern as it incorporates this area. Otherwise, with the other two search patterns, a separate examination of the nipple–areola complex needs to be performed.

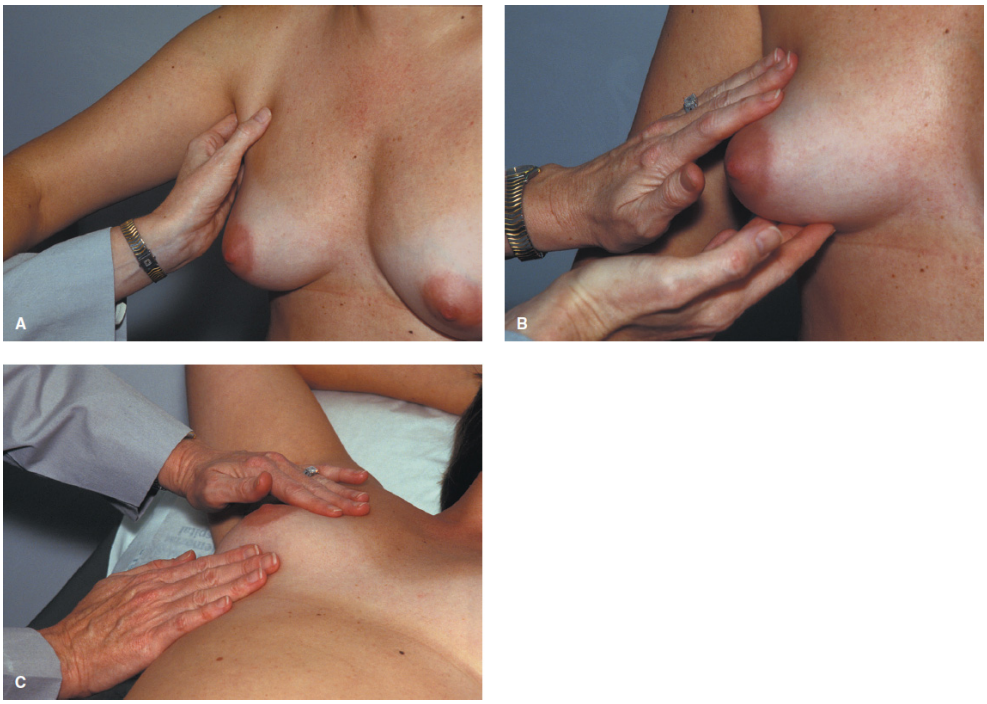


Figure 74.5 Breast examination. **A:** The patient's ipsilateral arm is supported by the examiner to relax the pectoral muscle while the axillary nodes are examined. **B:** Bimanual examination of the breast in the upright position. **C:** Bimanual examination in the supine position with the arm raised over the head.

Figure 74.6 Clinical breast examination search patterns: vertical strip, radial spoke, and concentric circles.

Diagnostic Mammography and Breast Ultrasound

A woman who has an indeterminate or abnormal CBE will typically benefit from a diagnostic imaging evaluation, which can include mammography, targeted ultrasound, and/or MRI. *It is important to note that any clinically suspicious mass, even in* 1 *the absence of an imaging abnormality, needs to be biopsied as up to 15% of breast cancers are mammographically occult.*[44]

Soft tissue densities and clustered microcalcifications are two common mammographic findings suggestive of breast cancer. Soft tissue densities can appear as well-defined round/oval/lobulated masses, spiculated masses, irregular masses, or as areas of architectural distortion without an obvious mass (Fig. 74.7). Nearly 90% of spiculated soft tissue masses are associated with invasive cancer whereas well-defined solid masses are less commonly predictive of malignancy. Microcalcifications can have benign or malignant features, with benign calcifications often appearing rim-like, large, coarse, smooth, round and/or oval in appearance. Calcifications that are associated with malignancy tend to be smaller in size ranging between 0.1 to 1 mm in diameter. They are typically clustered, numbering four to five per cubic centimeter. Histologically, these represent intraductal calcifications in areas of necrotic tumor or calcifications within mucin-secreting tumors. In addition, malignant microcalcifications can often appear in a granular or linear branching pattern, with the linear branching pattern being highly associated with malignancy (Fig. 74.8).

Breast ultrasound is another important diagnostic imaging modality for the evaluation of breast masses and/or mammographic abnormalities. Breast ultrasound is complementary to mammography, and is particularly valuable for the evaluation of breast masses. Breast ultrasound can increase the sensitivity and specificity of mammography for detection of breast cancer.[45] Ultrasound can differentiate a cystic mass from a solid one, characterize a palpable lesion that is not seen on mammography, and can assist with determining the actual size of a lesion. Ultrasonographic features that are used to characterize a lesion include shape (oval, round, lobular, irregular); margin (circumscribed, obscured, microlobulated, ill-defined, speculated); orientation (parallel or not parallel to skin); matrix echogenicity (anechoic, hypoechoic, hyperechoic); homogeneity (homogeneous, heterogeneous); and attenuation (indifferent, shadowing, enhancement).

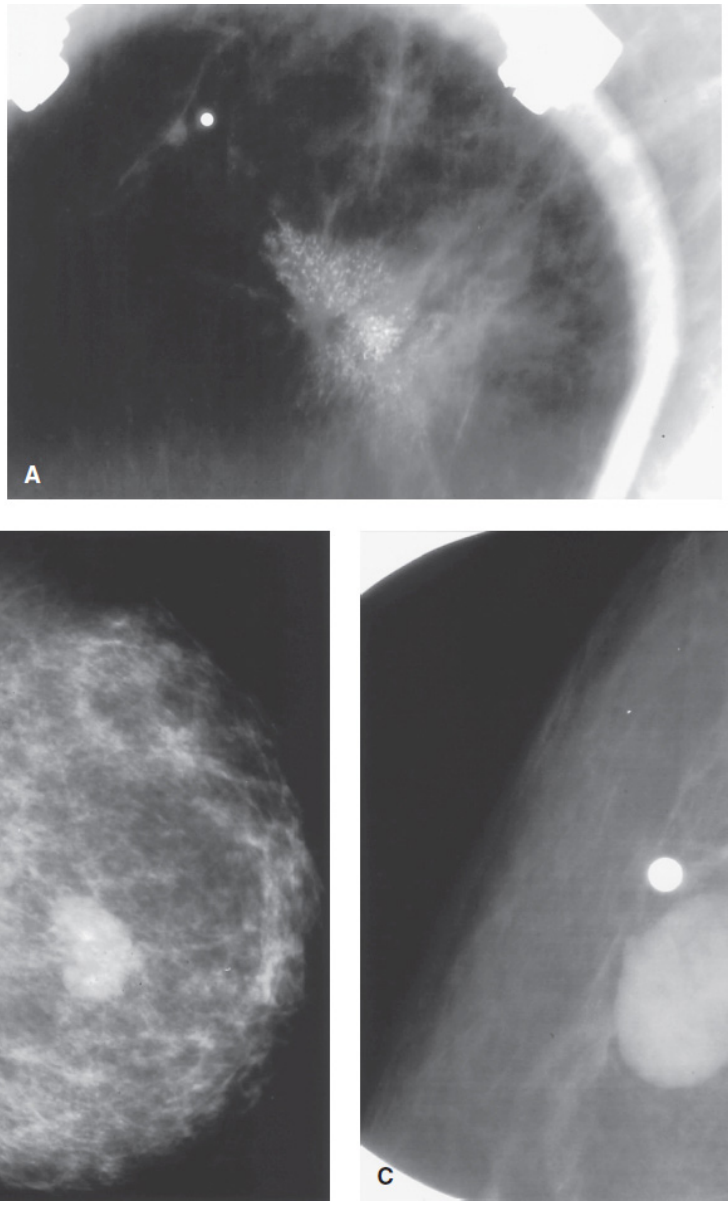


Figure 74.7 Mammographic masses. **A:** Spiculated mass with calcifications. **B:** Lobulated mass with indistinct posterior margin. **C:** Well-circumscribed mass.

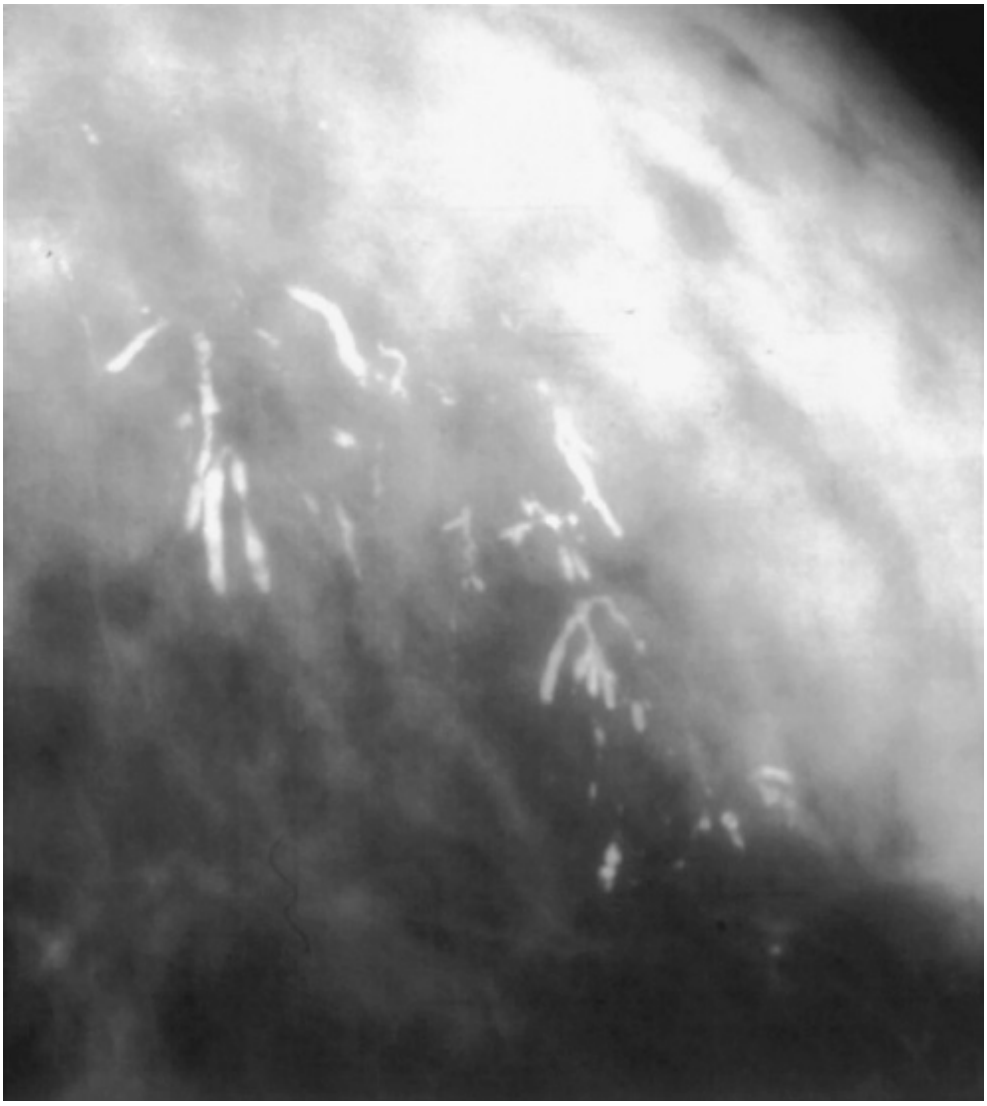


Figure 74.8 Microcalcifications. The branching, irregular appearance is classic for ductal carcinoma in situ.

Diagnostic MRI

Gadolinium contrast-enhanced MRI is complementary to mammography and breast ultrasound. It is not typically used for the evaluation of benign breast masses, but does have a high sensitivity for detection of breast cancer. As such, MRI is most commonly used to evaluate extent of disease and exclude occult breast cancers in patients with newly diagnosed breast cancer. In a meta-analysis of 44 studies, the sensitivity and specificity of diagnostic breast MRI was determined to be 90% and 72%, respectively.[46] The role of

MRI in the evaluation of newly diagnosed breast cancer patients is discussed in ***Evaluation of the Patient with Breast Cancer***.

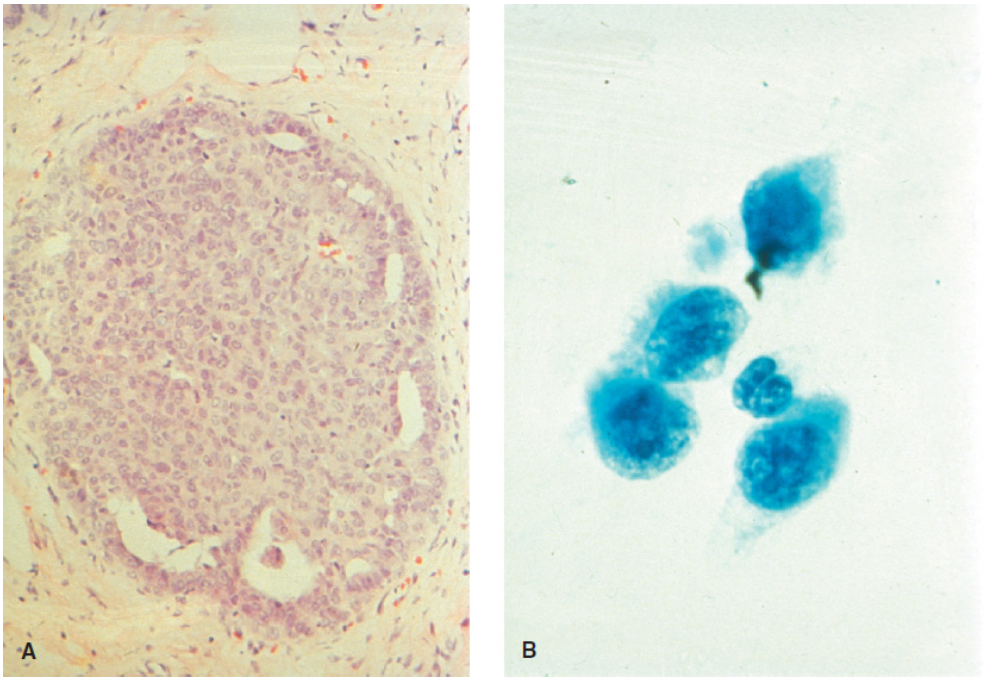


Figure 74.9 Comparison of core needle biopsy specimen (**A**) and fineneedle aspiration specimen (**B**). Only the core specimen can demonstrate the architectural detail.

Biopsy Procedures

Breast biopsy is one of the most common general surgery procedures performed in the United States. There are multiple different types of breast biopsy ranging from fine-needle aspiration (FNA) biopsy to excisional biopsy. The different types of breast biopsy are discussed below.

Fine-Needle Aspiration (FNA)

Fine-needle aspiration of the breast is the least invasive breast biopsy procedure. FNA can be used for both diagnosis and treatment, and can be performed using palpation or image guidance. FNA is commonly used to sample suspicious breast and axillary lesions especially those that are palpable. Other indications include drainage of simple cysts, and small abscesses. In institutions with experienced cytopathologists, diagnostic FNA has a reported sensitivity of 98% and a specificity of 97%.[47] However, as

the tissue architecture cannot be evaluated by FNA, a definitive diagnosis of invasive cancer cannot be made. In the past, FNA was commonly used to sample palpable breast masses as part of the Triple Test for evaluation of palpable masses. Currently, ultrasound can more accurately assess these lesions and low-suspicion lesions are followed with serial imaging. High-suspicion lesions are best sampled by core needle biopsy to allow assessment of tissue architecture (Fig. 74.9).

Core Needle Biopsy

2 Core needle biopsy is also a minimally invasive strategy for breast biopsy. Given the limitations of FNA, core needle biopsy allows for more tissue to be sampled, permitting a histologic diagnosis, and offering the ability to discriminate between invasive and noninvasive breast cancer. Core needle biopsy can be performed by palpation, but ultrasound-guided core needle biopsy typically offers superior results. Ultrasound imaging and patient preparation are similar to that described for patients undergoing FNA.

For nonpalpable lesions that cannot be imaged by ultrasound but are present on mammography (most commonly microcalcifications), stereotactic core biopsy can be performed. Stereotactic techniques use the principle of triangulation, which allows the precise location of a breast lesion to be determined in three dimensions.[48] The patient can be upright or prone depending on the machine. More commonly, the patient is placed in the prone position on the stereotactic table, which has an opening for the breast. A mammography unit is attached beneath the table and compresses the dependent breast. An initial scout image is obtained perpendicular to the compressed breast and evaluated. Following biopsy, repeat images are obtained to ensure the area of concern has been adequately biopsied. The procedure may be repeated to obtain additional cores. Most stereotactic core biopsies are performed with vacuum assistance allowing for greater accuracy. If suspicious microcalcifications are biopsied, the samples can be examined with specimen imaging to ensure the presence of microcalcifications within the biopsy samples.

Failure to obtain an adequate sample can result in a false-negative diagnosis, although the false-negative rate is very low. In some instances the

results of the core biopsy may not be definitive and a surgical excision is required. If the core biopsy demonstrates atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), radial scar, or lobular carcinoma in situ (LCIS) surgical excision is required to exclude a diagnosis of malignancy. In the clinical context of persistent suspicious physical or imaging abnormalities (discordance between clinical and/or imaging findings and pathology results), surgical excision is required. Please see Table 74.2 for indications for surgical excision after core biopsy.

Incisional Biopsy

Incisional biopsy typically involves surgical removal of part of a large mass for diagnosis. With the advent of core needle biopsy techniques, incisional biopsy is rarely required. However, if a core needle biopsy is nondiagnostic and the mass is too large to remove without significant cosmetic compromise, an incisional biopsy can be performed for definitive diagnosis.

INDICATIONS/CONTRAINDICATIONS

Table 74.2 Indications for Surgical Biopsy after Core Biopsy

- Atypical ductal hyperplasia
- Radial scar
- Columnar cell hyperplasia with atypia
- Papillary lesions
- Lack of concordance between appearance of mammographic lesion and histologic diagnosis
- Nondiagnostic specimen (including absence of calcifications on specimen radiograph when biopsy is performed for calcifications)

Excisional Biopsy

Excisional biopsy of the breast is the surgical removal of a breast lesion. Although core needle biopsy has largely obviated the need for excisional biopsy for diagnostic considerations, indications for this procedure still remain. Indications include breast lesions that are presumed to be benign but require excision, discordance between clinical evaluation/diagnostic imaging and pathology requiring further tissue sampling, high-risk lesions

(including atypical hyperplasia, radial scar, papilloma, LCIS) identified on core biopsy, abnormalities that are close to the nipple or chest wall, small breasts that are not amenable to core biopsy (given the needle excursion is often 2 cm), and for patients who cannot tolerate stereotactic core needle biopsy. In addition, excisional biopsy may be considered for complex cysts, aspirated cysts that do not completely resolve, and when follow-up imaging for a lesion with previous benign pathology from a core biopsy shows an increase in size or has suspicious changes. Excisional biopsies may also be performed for likely benign lesions that are greater than 2 cm, painful, or recurring, or where the mass represents growing cysts or fibroadenomas. Patient preference for complete removal of a benign lesion may also be an indication for excisional biopsy.

For nonpalpable lesions, the abnormality can be localized preoperatively using a needle localization wire that is placed with the patient in a sitting position with the breast compressed by a labeled grid plate. Various needles used include the Kopans needle (checkmark wire), the Hawkins needle (multiple barbs and the only retractable wire for repositioning), and the Homer needle (J wire and nontransectable needle). For lesions that are superficial and can be readily imaged by ultrasound, needle localization can be performed under ultrasound guidance. Alternatively, there are other localization techniques including radioactive seeds, magnetic seeds, and radar seeds. There are additional methods in development. The patient is then taken to the operative setting, where excision of the lesion can be performed under local anesthesia (mixture of short- and long-acting anesthetics with epinephrine) with sedation or general anesthesia. In the operating room, the patient is placed in the supine position with the arm ipsilateral to the index lesion positioned at 90 degrees. Appropriate padding of the arm and wrists should be undertaken. The operative site is then prepped and draped in a sterile fashion. Intraoperative localization is performed by evaluating the imaging studies and palpating the needle (for nonpalpable lesions) or by direct palpation. For lesions located in the upper half of the breast, transverse or curvilinear incisions are made along Langer lines. If an incision is needed in the lower half of the breast, radial incisions are used. When possible, periareolar or inframammary incisions are made as they result in the best cosmesis. Prior to incision, an anesthetic of short- and long-acting local anesthesia with epinephrine is injected into the skin and

along the path of the needle localization wire. The incision is then typically made directly above the palpable mass or the tip of the needle (Fig. 74.10). Alternatively, an incision can be made next to the needle and then followed down to its tip to find the target lesion. Once the skin incision is made, the thickest possible flaps, which would still result in fully removing the lesion anteriorly, are developed. The specimen is then excised with electrocautery. The specimen is oriented with sutures, with the short stitch designating the superior margin and the long stitch designating the lateral margin. Palpation of the cavity is performed to ensure complete removal of the lesion. Specimen imaging is performed to confirm excision of the lesion of interest. Hemostasis is then achieved with electrocautery and the cavity is irrigated with saline. The cavity is examined again to confirm hemostasis. The skin is closed in two layers. The dermis is reapproximated with interrupted sutures of 3-0 vicryl and the skin is closed with a subcuticular running stitch of 4-0 monocryl. Cyanoacrylate tissue adhesive is then applied, allowing the patient to take a shower within 24 hours. For allergies to skin glue, adhesive strips can be applied. No pressure dressing is needed. A sports bra may be worn to stabilize the breast for the first 48 hours.

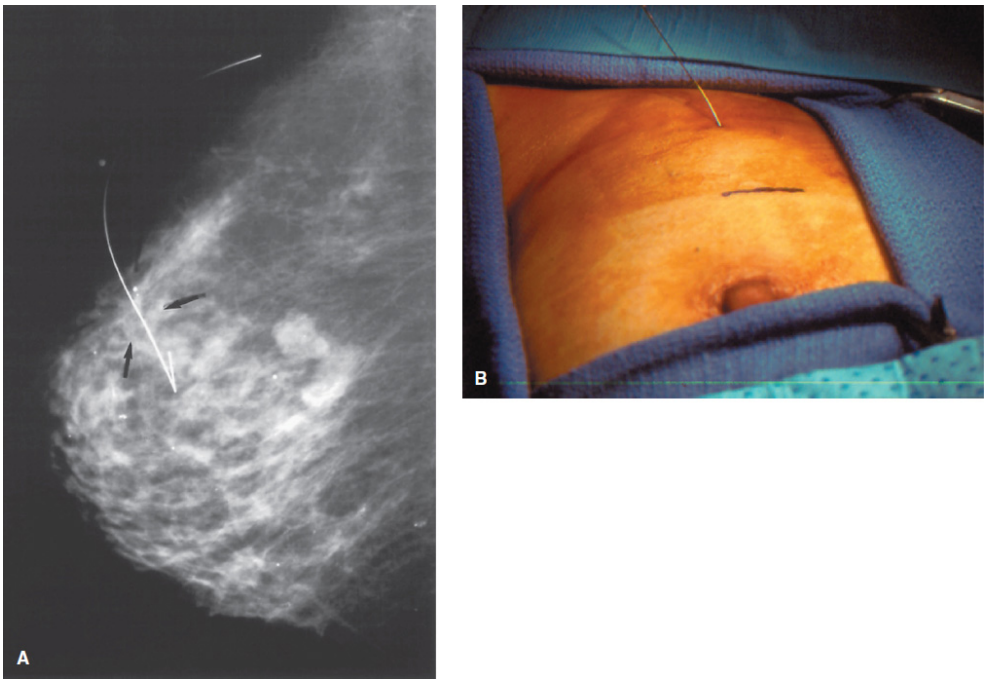


Figure 74.10 Incision placement for needle localization biopsy. **A:** The mammogram demonstrates that the lesion (*arrow*) is inferior to the point of wire entry. **B:** Incision placement inferior to wire entry to allow access to the lesion.

Skin Punch Biopsy

For any suspicious cutaneous lesion of the breast or chest wall, a biopsy can be obtained using a punch biopsy device, which consists of a circular blade. Punch biopsy devices are available in various sizes ranging from 1 mm to 8 mm, with the 4-mm size most commonly used in breast biopsies. The area to be biopsied is first selected. Common sites are the most abnormal-appearing site within a lesion or the edge of an actively growing lesion. The involved skin is cleansed and infiltrated with 2 to 3 mL of 1% lidocaine. The punch device is held vertically over the skin and rotated downward using a twirling motion until the subcutaneous fat or the hub of the device is reached. The specimen is then transected at the base with iris scissors. The skin is approximated with an interrupted stitch or U-stitch of 4-0 monocryl.

COMMON CLINICAL PROBLEMS AND MANAGEMENT ALGORITHMS

The most common clinical breast problems include breast masses, breast pain, nipple discharge, and breast infections. Clinical algorithms for the evaluation of these common breast problems have been developed to facilitate optimal care.

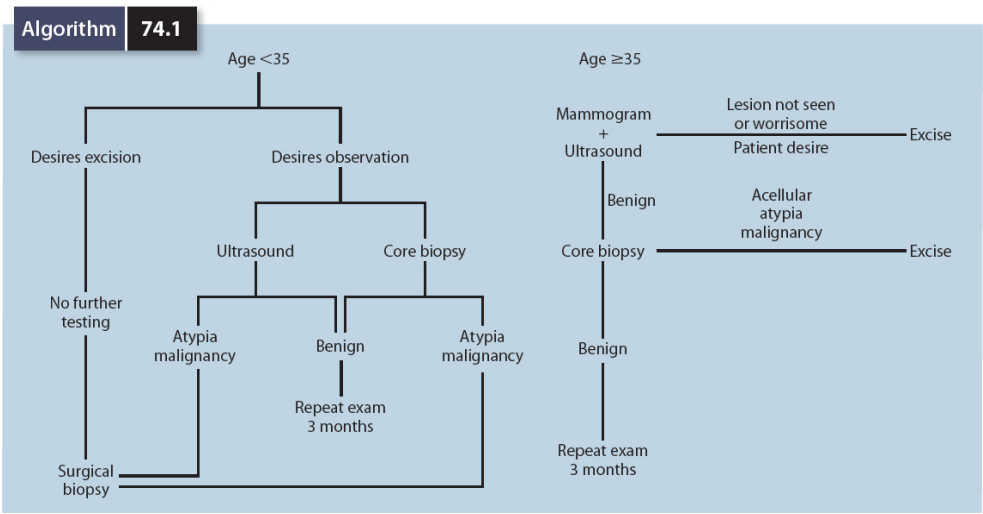
Breast Mass

A breast mass is defined as a palpable area in the breast that may be either benign or malignant. When a woman presents with a palpable breast finding, a thorough history and physical examination needs to be performed. The history should include a thorough review of the patient's medical problems and any risk factors associated with breast cancer (see ***Management of Patients at High Risk for Breast Cancer***).

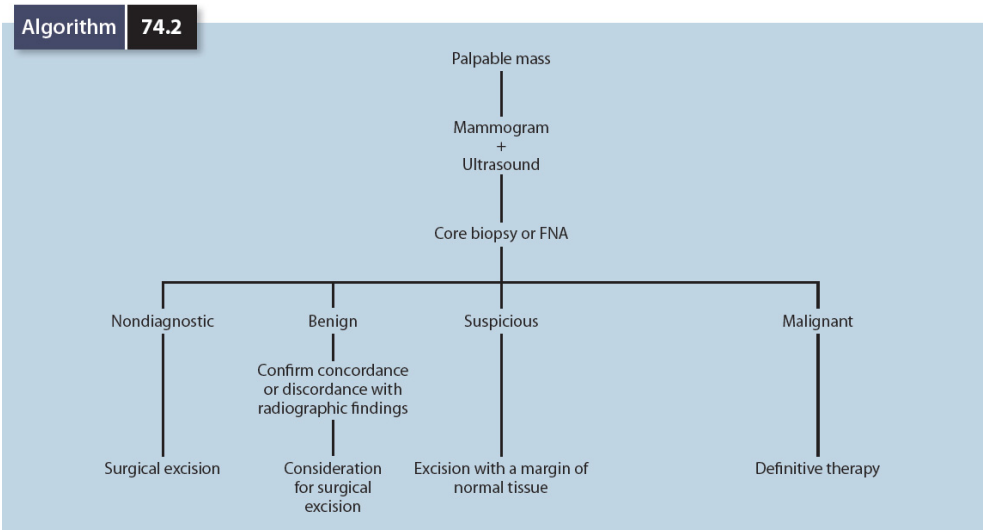
In women less than 40 years old with no family history of premenopausal breast cancer or other risk factors, a targeted ultrasound is an appropriate initial imaging approach for a breast mass that appears clinically benign (Algorithm 74.1). The ultrasound is used to determine if a dominant mass is indeed present, as normal glandular tissue of the breast, especially in young

women, may feel nodular. In a review of 605 women younger than 40 years of age who were referred for evaluation of a breast mass, only 36% of the masses detected by patients had a surgical correlate. Furthermore, only 29% of the masses detected by primary care providers were confirmed.[49] Consideration can then be made regarding the need for additional imaging such as mammography or an MRI. In women aged 40 or older, the initial imaging approach to a palpable mass should include a mammogram and ultrasound. These studies should be obtained prior to any biopsies are performed as post-biopsy changes can distort subsequent imaging evaluation. Of note, all clinically suspicious palpable masses need to be biopsied even in the absence of imaging findings as 15% of breast cancers can be mammographically occult (Algorithm 74.2).[44] Ultrasound also provides important information about the etiology of a breast mass, and can further categorize the mass as either cystic or solid. Workup of a cystic lesion typically involves aspiration of the cyst, with further evaluation based on the results of the aspiration (Algorithm 74.3). The definitive diagnosis of a breast mass is often confirmed by a core needle biopsy, although FNA is an appropriate alternative (Table 74.3). Core needle biopsy is typically preferred to excisional biopsy.

Breast cysts are common causes of dominant masses in premenopausal and perimenopausal women. If a cyst is found in a postmenopausal woman in the absence of hormone therapy use, it should be regarded with a high degree of suspicion. Palpable masses that present as benign solid masses include fibroadenomas, fibrocystic disease, and fat necrosis. Fibrocystic breast disease has been used to describe a variety of benign breast disorders associated with nodular breast tissue. This term, however, should be reserved for women who have a biopsy consistent with one of the histologic components of fibrocystic change. Breast surgery, blunt trauma, injection of native or foreign substance such as fat and silicone, and radiation therapy can result in fat necrosis. On clinical exam and mammographic imaging, fat necrosis can mimic a malignancy, often leading to a biopsy. However, when oil cysts, which are circumscribed masses of mixed soft tissue density and fat with a calcified rim, are present radiographically, a definitive diagnosis of fat necrosis can be made (Fig. 74.11). Please see the section ***Benign Breast Disease***.



Algorithm 74.1 Diagnosis and management of the patient with a clinically benign breast mass. The use of imaging studies varies according to age because breast carcinoma is infrequent in women younger than 35 years old.



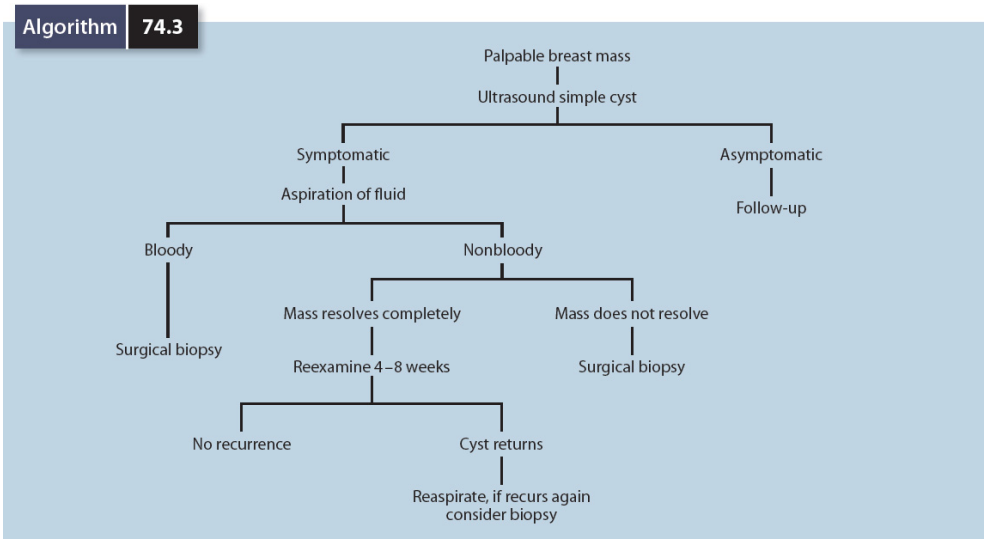
Algorithm 74.2 Diagnosis and management of the patient with a clinically indeterminate or suspicious solid breast mass. In this circumstance, imaging studies are insufficient to exclude malignancy, and tissue sampling is required.

Breast Pain

Breast pain (mastalgia, mastodynia, idiopathic breast pain) is a common concern and is rarely (0.5% to 3.3%) representative of a breast cancer. It is noted that some IBCs can present with pain. While two-thirds of patients present with cyclical breast pain, another one-third has pain that is unrelated

to the menstrual cycle and more likely to be secondary to a breast or chest wall lesion.[50]

Cyclical breast pain is associated with hormonal changes during the menstrual cycle and often occurs the week prior to the onset of menses and often dissipates once menstrual flow is established. During the menstrual cycle, the breast undergoes significant histologic changes as described by Vogel (see ***Menstrual Cycle***).[51] During the secretory phase, luminal cells produce apocrine secretions and the stromal cells become edematous, which may contribute to the pathogenesis of breast pain. However, the exact physiologic events are not understood completely. Furthermore, while most women do experience mild cyclical breast pain, it is not clear why others have more pronounced pain. Cyclical breast pain is typically bilateral and involves the upper outer aspect of the breasts with radiation to the axillae or down the arms.



Algorithm 74.3 Diagnosis and management of the patient with a cystic lesion. Bloody fluid on aspiration, failure of the mass to resolve completely, and prompt refilling of the same cyst are indications for surgical biopsy.

Table 74.3 Management of Breast Masses Based on Core Biopsy Diagnosis

FNA Diagnosis	Treatment
Malignant	Definitive therapy
Suspicious	Surgical biopsy
Atypia	Surgical biopsy
Benign	Possible observation[a]
Nondiagnostic	Surgical biopsy

[a]See discussion in text on clinical approach to the patient with a solid breast mass.

Noncyclical breast pain is more frequently unilateral and variable in its location in the breast. Possible etiologies include large pendulous breasts with pain resulting from stretching of the Cooper ligaments, duct ectasia, macrocysts, medications (including antidepressants, hormones and antibiotics), and infections.[52,53] Thrombophlebitis of the lateral thoracic or superior thoracoepigastric vein (Mondor disease) is an uncommon presentation for breast pain characterized by a tender subcutaneous cord in the lateral aspect of the breast (Fig. 74.12). Mondor disease may result from trauma, radiation to the breast, and/or breast surgery. It can also occur in women with nonpalpable breast cancers, and a mammogram should be obtained when diagnosed.[54] For symptomatic relief, a patient can use anti-inflammatory medications, although Mondor disease often resolves spontaneously without the need for a specific therapy. Referred pain to the breast from the chest wall or ribs can also occur. Spinal or paraspinal problems and medical conditions (biliary, pulmonary, esophageal, and cardiac disease) can also result in referred pain.

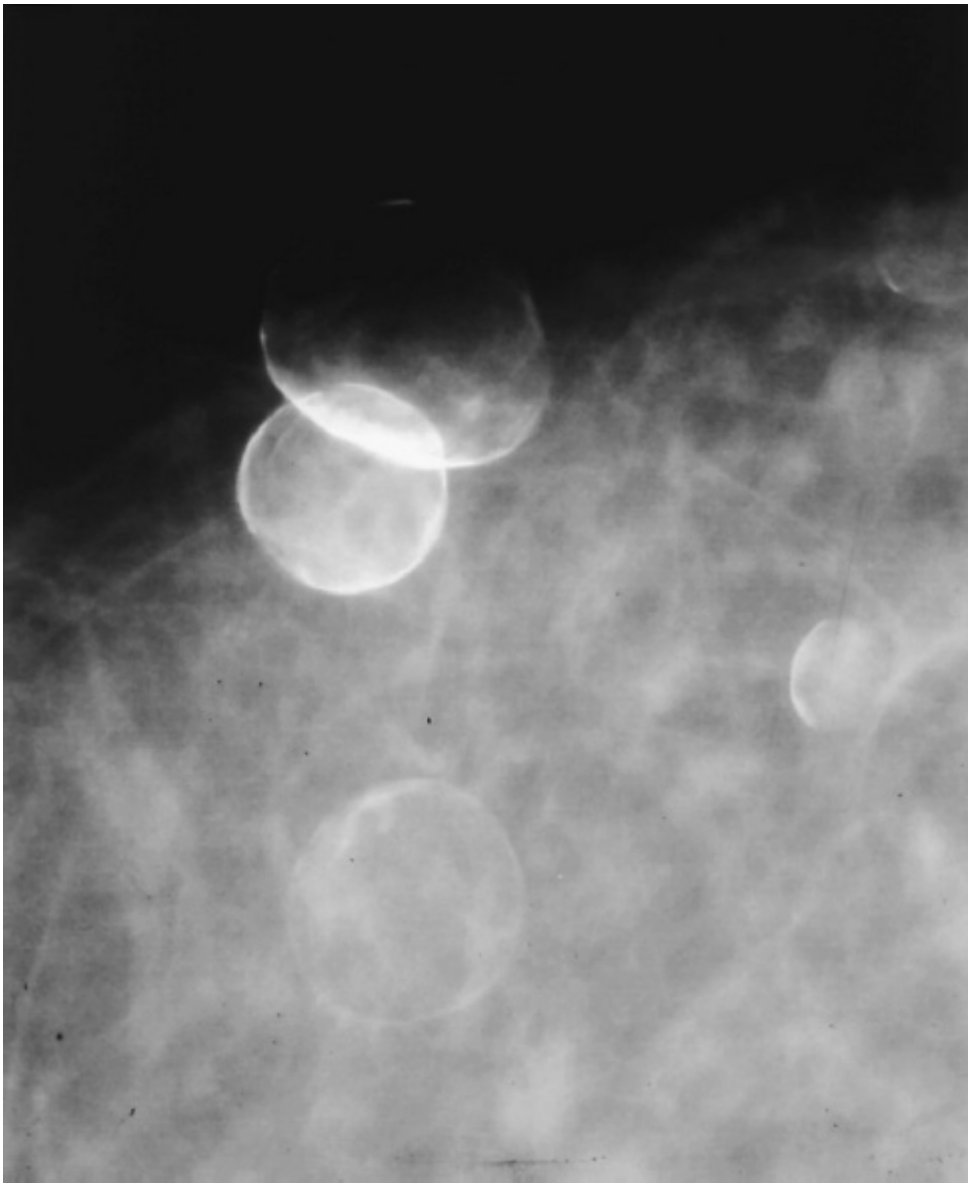


Figure 74.11 Oil cysts. The calcified rims of these cysts in a patient with a history of trauma are diagnostic.

Figure 74.12 Mondor disease. Thrombophlebitis of the thoracoepigastric vein causes retraction of the lateral portion of the breast, which crosses to the midline at the inferior areolar margin and is accompanied by a palpable cord.

The workup for breast pain should include a careful history, including questions related to the menstrual cycle, a thorough physical examination, and in women 35 years and older, a mammogram. If a malignancy is suspected, biopsy should be performed. If the CBE and diagnostic imaging studies are normal, reassurance that the symptoms are not consistent with breast cancer often provides significant relief for the patient.

Initial therapy for idiopathic breast pain includes lifestyle changes, the use of supportive garments such as a well-fitting brassiere with a steel underwire, a low fat–high-carbohydrate diet, and elimination of caffeine and nicotine. Oral analgesics with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) should be initiated. Topical analgesic gels containing diclofenac or salicylate can be applied to the affected breast areas. If a patient is on oral contraceptives or hormone replacement therapy, discontinuation of these medications may improve pain. However, in women not using oral contraceptives with cyclical breast symptoms, the initiation of

this therapy has been shown to reduce breast pain severity and duration. Although inconclusive evidence exists for the role of evening primrose oil (3,000 mg daily),[55,56] it is often part of the initial therapeutic approach. Evening primrose oil needs to be taken for at least 4 to 6 months to achieve a positive effect.

Approximately 5% of women will still have debilitating breast pain despite lifestyle changes and the initial therapies described above. For these women, therapies such as danazol, tamoxifen, bromocriptine, and GNRH agonists can be considered. However, only danazol has been approved by the FDA for the treatment of idiopathic breast pain. Danazol (100 mg to 400 mg daily) is an antigonadotropin that results in a hypoestrogenic state. However, its use is often discontinued as it also induces a hyperandrogenic state, with most women having side effects of increased facial hair, acne, deepening of the voice, and adverse blood lipid profiles.[57] Tamoxifen (10 mg daily) has also been shown to be effective although side effects, including the risk of blood clots, endometrial cancer, and hot flashes limit its use.[58] As both danazol and tamoxifen have significant teratogenic effects, women on these therapies must be counseled to use an effective birth control method. Although bromocriptine and GNRH agonists have been studied for use in breast pain, they are not currently recommended because of significant side effects. Therapies that have been proven to be ineffective include diuretics, progesterone, and vitamins. Surgery to excise trigger spots (in the absence of an identifiable lesion) is not recommended, as the affected area is often by a painful scar.

Nipple Discharge

Nipple discharge is a common breast symptom that often results in surgical consultation. The most common cause of pathologic nipple discharge is an intraductal papilloma, but breast cancer can also present as a pathologic nipple discharge. The first step in evaluation of nipple discharge is to determine whether the nipple discharge is pathologic or physiologic. Physiologic discharge is nonspontaneous or is elicited by manual compression of the nipple. It often involves multiple ductal orifices in the nipple and is present in both breasts. The discharge is commonly white or clear (although it can also present as yellow, green, brown, or gray fluid) and

is negative on occult blood test. In contrast, pathologic nipple discharge is spontaneous, is present in a single breast/ductal orifice, and is often positive on occult blood test. However, any nipple discharge that is spontaneous is considered pathologic. Age is also predictive of breast cancer risk in women with nipple discharge. In a study involving women with pathologic nipple discharge, breast cancer was present in 3% of women <40 years old, 10% in those 40 to 60 years old, and 32% in those over 60 years old.[59]

Clinical evaluation of nipple discharge includes a careful history and physical examination. The history includes questions regarding whether the discharge is spontaneous or elicited, unilateral or bilateral. The patient should be questioned regarding any recent trauma to the breast. The past medical history and medications are reviewed. Medications such as oral contraceptives, metoclopramide, phenothiazines, and selective serotonin reuptake inhibitors can be associated with nipple discharge. A premenopausal woman presenting with milky fluid discharge bilaterally or galactorrhea, should be evaluated for endocrine disease. Hypogonadism as suggested by amenorrhea or hot flashes/vaginal dryness should prompt a workup for hyperprolactinemia. In addition, hypothyroidism, pituitary adenoma and chest trauma (including thoracotomy) can result in galactorrhea. When endocrine disease is suspected, patients should undergo laboratory evaluation including quantitative hCG, prolactin level, and thyroid function tests. The physical examination should include a visual field test as often these patients may show signs of bitemporal field loss or chiasmal syndrome. A careful breast examination is performed to evaluate for any dominant masses, skin changes such as eczema/infections, nipple changes such as Paget disease, or adenopathy. Each of the quadrants of the involved breast is massaged from the periphery to the nipple areolar complex and then pressure is applied to the base of the nipple areolar complex to elicit discharge. This will help define the involved quadrant of the breast and whether the discharge is from a single ductal orifice. The color of any nipple discharge should be noted, and an occult blood test should be performed.

After initial evaluation, no further workup is required in women who have physiologic discharge, and these women should be advised to avoid manual compression of the nipples.

Imaging evaluation is indicated for patients with pathologic nipple discharge and includes an ultrasound, and for patients >30 years old, a

mammogram is also recommended. In patients with an imaging abnormality, a biopsy should be considered. Additional diagnostic tests that may be helpful include ductography and ductoscopy. Ductography is performed by instilling contrast medium into the involved duct to identify any lesions in the ductal system. Lesions will appear as either a complete ductal obstruction, irregularities in the duct wall, or as an intraductal filling defect (Fig. 74.13). However, the absence of a lesion on ductography does not rule out a cancer.[60] Ductoscopy is often performed in the operating room and involves the use of a small fiberoptic ductoscope that is placed into the involved duct. The benefit of ductoscopy is that it allows for direct visualization of any potential lesions, which may result in more precise excision.

The most common etiology of pathologic nipple discharge is a papilloma, which is a benign epithelial lesion with supporting stroma that grows within a duct. When a papilloma is diagnosed by core biopsy, the standard recommendation is to proceed with surgical excision as it may be associated with atypia or ductal carcinoma in situ. Other causes for pathologic nipple discharge include malignancy (most commonly DCIS, 5% to 15% of cases), and ductal ectasia, which is characterized by ductal dilatation with loss of elastin in the duct walls and the presence of chronic inflammatory cells. It is not known however, whether the inflammatory cells result from a primary or secondary infection and antibiotics are not recommended.

If a malignancy is identified as the etiology of a pathologic nipple discharge, it should be managed accordingly, with appropriate cancer surgery typically the first treatment. In the absence of a known malignancy, pathologic nipple discharge should be treated with terminal duct excision. Prior to excision, the patient should refrain from any nipple stimulation. If the involved duct can be identified intraoperatively, a lacrimal duct or instillation of methylene blue may aid with the ductal excision. Terminal duct excision is commonly performed with a circumareolar incision and involves removal of the duct from its proximal to distal extent, which is often a distance of 2 to 3 cm. Alternatively, ductoscopy can be performed as previously prescribed and then the outer sheath of the cannula can be left in place as a guide for surgical excision of the involved duct. If there is difficulty isolating the involved duct or multiple ducts are involved, central or total terminal duct excision may be indicated. The potential risks of

terminal duct excision include inability to breastfeed and hyposensitivity or hypersensitivity of the nipple.

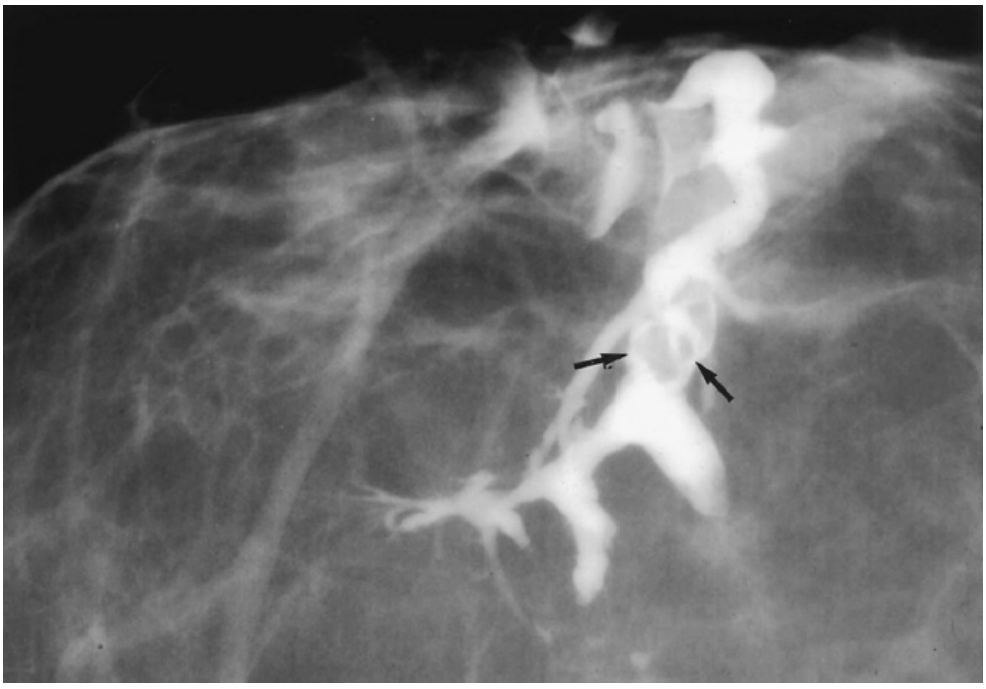


Figure 74.13 Ductogram. A large defect (*arrows*) represents an intraductal papilloma.

Breast Infections

Breast infections are less common outside of the postpartum period. As such, breast infections can be classified as lactating or nonlactating infections. Lactating infections occur commonly during the initial 6 weeks of breastfeeding and during the process of weaning. In the initial stages of infection, a mastitis or cellulitis is typically found, with associated pain, erythema, induration, and fever. A woman should not be counseled to discontinue breastfeeding. Commonly the cellulitis results from *Staphylococcus aureus*. Treatment includes pain management (acetaminophen, NSAIDs) and an antibiotic such as dicloxacillin. Alternative antibiotics include cephalexin and erythromycin. The mastitis should improve within 24 to 48 hours after initiation of antibiotics. If symptoms or fever persists, an abscess should be ruled out. For small or superficial abscesses, needle aspiration may be attempted. However,

incision and drainage should be considered for large or complex abscesses, understanding the risks associated with milk fistula formation.

Nonlactating breast infections can present as periareolar abscesses or less commonly as peripheral abscesses. For small or moderate size abscesses, needle aspiration is the first line of treatment and a drain can be placed if indicated. However for larger and/or deeper abscesses, incision and drainage may be indicated. This is commonly performed in the operating room under general anesthesia, although if the anterior aspect of the abscess is close to the skin it may be possible to perform the incision and drainage at the bedside with infiltration of a local anesthetic. A preoperative ultrasound can be obtained to better evaluate the size and location of the abscess. Often the abscess is not located directly under the area of greatest erythema, and careful breast examination should be performed to localize the area of greatest fluctuance. *Biopsy of the cavity should always be considered, as breast infection may be an unusual breast cancer presentation.* For a subareolar abscess, removal of the sinus tract as well as the segmental duct should be considered. Antibiotics, such as cephalexin 500 mg QID, are commonly prescribed for 7 to 10 days postoperatively, although once a wound is properly drained and cellulitis subsides, the patient can discontinue all antibiotics. For chronic subareolar abscesses, it may be necessary to completely excise the involved duct.

In the setting of recurrent or persistent abscess formation or inflammatory changes despite adequate surgical management, other etiologies need to be considered including idiopathic granulomatous mastitis, Wegener granuloma, sarcoidosis, tuberculosis, and histoplasmosis.

BENIGN BREAST DISEASE

Benign breast lesions can be classified into three groups: (1) nonproliferative breast lesions, (2) proliferative breast lesions without atypia, and (3) proliferative breast lesions with atypia (Table 74.4).

Table 74.4 Classification of Benign Breast Disease

Nonproliferative: No Increase In Risk
Cysts: micro or macro
Ductal ectasia
Simple fibroadenoma
Mastitis
Fibrosis
Metaplasia: squamous or apocrine
Mild hyperplasia
Proliferative: RR 1.5–2.0
Complex fibroadenoma
Papilloma
Sclerosing adenosis
Hyperplasia: moderate or severe
Proliferative with Atypia: RR 4.5–5.0
Atypical ductal hyperplasia
Atypical lobular hyperplasia

RR, relative risk.

Nonproliferative Breast Lesions

Nonproliferative breast lesions include breast cysts, papillary apocrine change, epithelial-related calcifications, and mild hyperplasia of the usual type. These lesions are not associated with an increased risk of breast cancer.[61] Papillary apocrine change is characterized by proliferation of ductal epithelial cells showing apocrine features and has eosinophilic cytoplasm. Benign calcifications found in normal ducts, lobules, breast stroma, and blood vessel walls are referred to as epithelial-related calcifications. Mild hyperplasia of the usual type occurs when the number of epithelial cells within a duct is more than two but not more than four cells in depth, and the epithelial cells do not cross the lumen of the involved space.[62]

The most common nonproliferative lesions of the breast are cysts, which often present clinically as solitary masses that can be associated with pain. They are fluid-filled round or ovoid structures arising from the terminal duct lobular unit when fluid accumulates because of distension and obstruction of the efferent ductule.[63] Given that cysts arise from lobular pathology, they occur mainly during lobular development, menstrual cyclic changes, and lobular involution in pre- and postmenopausal women, with peak incidence between 35 and 50 years of age.[64,65]

The three types of cysts are simple, complicated, and complex. Simple cysts are well circumscribed and on ultrasound have posterior acoustic enhancement. In addition they are anechoic and do not have solid components or Doppler signals. If simple cysts are diagnosed by ultrasound, they are by definition benign and do not require further intervention, although cyst aspiration can be performed if the patient is symptomatic. Alternatively, FNA can also be used to diagnose simple cysts. If the aspirated fluid is nonbloody and the palpable mass completely resolves this is also diagnostic of a simple cyst and no further diagnostic evaluation is required. A follow-up CBE +/– ultrasound can be performed in 3 to 6 months to document stability and the patient may resume routine breast cancer screening.

Unlike simple cysts which are not associated with malignancy, complicated and complex breast cysts are associated with malignancy in <1% and 1% to 23% respectively.[66–68] On ultrasound, complicated cysts appear as masses with homogenous low-level internal echoes due to echogenic debris. However, there are no solid components, thick walls, or thick septa. Complex cysts are defined as cysts with solid components, thick walls, or thick septa. Complex cysts are characterized on ultrasound by the absence of posterior wall enhancement and the appearance of anechoic and echogenic components. Complicated cysts can be confirmed as benign by biopsy, either through FNA, core biopsy, or excisional biopsy. Alternatively, ultrasound imaging and mammography (if the lesion was visualized on mammography) with CBE every 6 months for 2 years can be performed to document stability. If complicated cysts develop any concerning changes such as an increase in size or development of a solid component, biopsy should be performed per consensus guidelines. Complex cysts mandate biopsy. If no fluid is aspirated by FNA, then core biopsy under image guidance should be performed with care to biopsy the solid component. A metallic clip marking

the biopsy site facilitates surgical excision if necessary and facilitates follow up imaging. If pathology is concordant with imaging findings, then follow up with CBE and ultrasound imaging every 6 to 12 months for 1 to 2 years can be performed to document stability. For any concerning changes in the appearance of the lesion or increase in size, excisional biopsy should be performed. In patients that may be noncompliant with follow-up care, surgical excision should be considered for complicated and complex breast cysts per consensus guidelines.

Proliferative Breast Lesions without Atypia

Proliferative breast lesions without atypia include ductal hyperplasia, intraductal papillomas, sclerosing adenosis, radial scars, and fibroadenomas. Ductal hyperplasia is often an incidental finding noted on biopsies obtained for mammographic abnormalities or for breast masses. Ductal hyperplasia is characterized by an increased number of cells within the ductal space, however the cells retain the cytological features of benign cells. Ductal hyperplasia is not associated with a significant risk for subsequent breast cancer and no additional treatment is necessary.[62,70] Women with intraductal papillomas often present with pathologic nipple discharge (see section on ***Nipple Discharge*** above). These lesions consist of a monotonous array of papillary cells that grow from the wall of a duct or cyst into its lumen. Given that intraductal papillomas can harbor areas of atypia or ductal carcinoma in situ (DCIS), surgical excision is recommended when intraductal papillomas are diagnosed by core needle biopsy. If no atypia or DCIS is found at the time of excision, then no further treatment is necessary.[71–75] Sclerosing adenosis typically presents as a mammographic abnormality or a mass and requires no further treatment following biopsy, as it is a benign lobular lesion resulting from increased fibrous tissue and interspersed glandular cells.[76,77] Complex sclerosing lesions or radial scars are often found incidentally when a breast mass or radiologic abnormality is biopsied or excised. These lesions are characterized by a fibroelastic core with radiating ducts and lobules, and radial scars can appear spiculated on mammography.[78] When diagnosed on core biopsy, radial scars should be excised as 8% to 17% are associated with malignancy at surgical excision.[79–81] If the surgical excisional confirms a radial scar, no additional treatment is needed.

Fibroadenomas typically present as well-circumscribed mobile masses that are not fixed to the surrounding breast tissue. They are benign solid tumors made of glandular as well as fibrous tissue, and are found most commonly in women between the ages of 15 and 35 years.[82] Fibroadenomas with benign imaging characteristics can be followed with serial CBE and ultrasound imaging to ensure stability. Alternatively, core needle biopsy can be performed to confirm the diagnosis. If a fibroadenoma is asymptomatic, surgical excision is not necessary. However, if the presumed fibroadenoma is symptomatic or increases in size, excision can be performed for symptomatic relief or to rule out a malignancy such as a phyllodes tumor.[83] Fibroadenomas that are associated with proliferative changes such as sclerosing adenosis, ductal epithelial hyperplasia, epithelial calcification, or papillary apocrine changes are referred to as complex fibroadenomas. Surgically excision of these lesions is often recommended to exclude a diagnosis of breast cancer,[84,85] although this is controversial as some advocate that these lesions can be followed similarly as simple fibroadenomas.[86]

A fibroadenoma that is greater than 10 cm in size is referred to as a giant fibroadenoma and excision is recommended, as these lesions are hard to differentiate from a phyllodes tumor.[62] Juvenile fibroadenomas occur in young women between the ages of 10 and 18 and can vary in size from 5 to 20 cm in diameter. Surgical excision is recommended as these lesions can be cosmetically distressing for the young patient and are difficult to differentiate from a phyllodes tumor, although risk to the prepubertal breast bud is a potential complication.[87]

Proliferative Breast Lesions with Atypia

Proliferative breast lesions with atypia include ADH, ALH, flat epithelial atypia (FEA), and LCIS. Although these lesions are not considered premalignant, they are associated with an increase in the patient's future risk of developing breast cancer (Fig. 74.14).

ADH is characterized by a proliferation of uniform epithelial cells with monomorphic round nuclei filling part, but not all, of the involved duct. ADH often presents as suspicious microcalcifications seen on mammography. In contrast, ALH is often an incidental finding found on breast biopsies

performed for other reasons, such as an abnormal mammogram or breast mass. ALH is characterized by a proliferation of monomorphic, evenly spaced, dyshesive cells filling part, but not all, of the involved lobule.[62] Atypical hyperplasias are associated with an increased risk of subsequent breast cancer (relative risk 3.7 to 5.3) in both the ipsilateral and contralateral breast.[88–92] Atypical hyperplasias are often diagnosed on core needle biopsy, and in this clinical context surgical excision is indicated to exclude a diagnosis of malignancy. Atypical hyperplasias are upgraded to DCIS or invasive breast cancer in 10% to 20% of cases. If the diagnosis of atypical hyperplasia is made by excisional biopsy and the area is adequately sampled, reexcision is not necessary or recommended. Instead, the patient should be counseled toward risk reduction strategies which include CBE every 6 to 12 months, annual screening mammography, and consideration for chemoprevention with a selective estrogen receptor modulator (SERM) or an aromatase inhibitor (AI) per consensus guidelines. In addition, the patient should be counseled to perform consistent breast self-examinations such that she will become familiar with her breasts and report changes promptly to her provider (please see the section on ***Management of Patients at High Risk for Breast Cancer*** below).

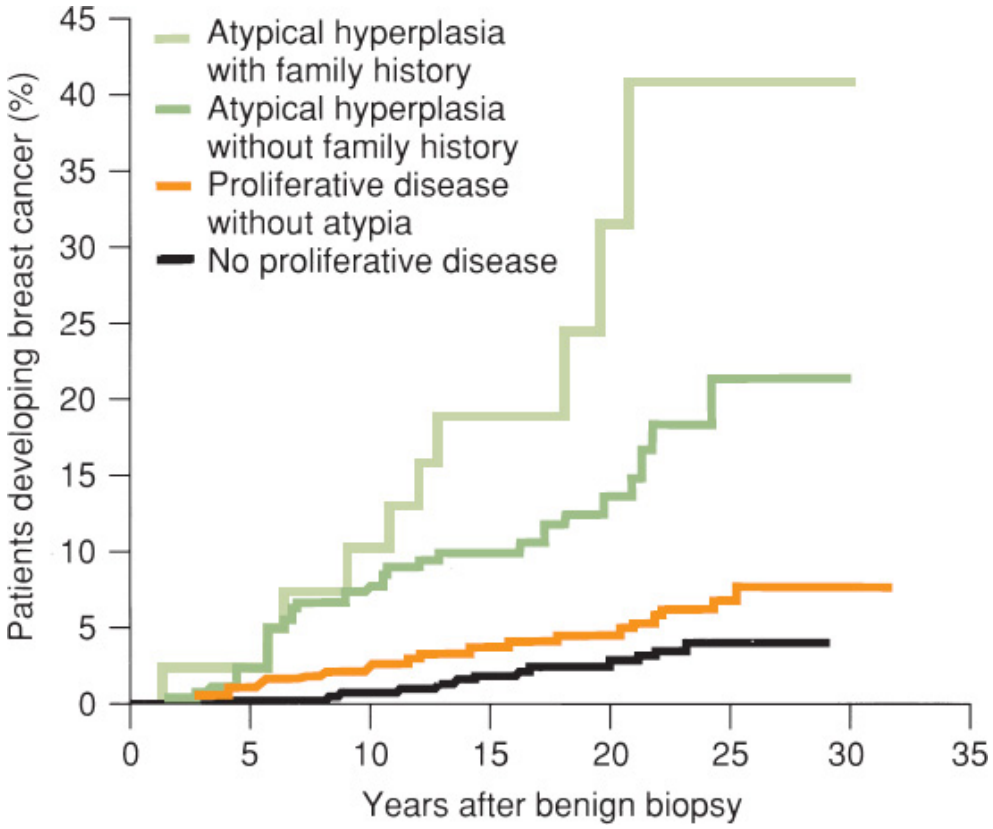


Figure 74.14 Cumulative risk for the development of invasive breast cancer after a biopsy for benign breast disease. Women with atypical hyperplasia (ductal or lobular type) are at a significantly increased risk for the development of breast cancer. (Reproduced with permission from Page DL, Dupont WD. Anatomic markers of human premalignancy and risk of breast cancer. *Cancer* 1990;66:1326.)

Lobular Carcinoma In Situ (LCIS)

LCIS is a noninvasive lesion that arises from the lobules and terminal ducts of the breast. It is characterized by solid proliferation of small cells, with small, uniform, round to oval nuclei, and variably distinct cell borders. The cytoplasm of the cells is clear to lightly eosinophilic and occasionally there are intracytoplasmic vacuoles that may be large enough to produce signet ring cell forms. LCIS tends to have a very low proliferative index and are estrogen-receptor positive.[93] LCIS is more prevalent in premenopausal women and white women.[94,95]

LCIS is often diagnosed as an incidental finding on a breast biopsy that has been performed for another reason, such as an 3 area of fibrocystic change or mammographic abnormality. If LCIS is identified on core biopsy, in the

past excisional biopsy was always recommended given the possible upgrade to DCIS or invasive cancer that was presumed to occur in 15% to 38% of patients.[96–100] However, more recently this risk of an upgrade to malignancy is found to be much lower at a rate of 1% to 3% if LCIS is found as an incidental finding on core biopsy.[101–105] As such, if radiographic and pathologic concordance exists, a possible alternative to surgical excision is imaging and clinical follow-up. If LCIS is found on excisional biopsy, no further surgical intervention is needed. However, if *pleomorphic* LCIS is identified at a surgical margin on excisional biopsy, wide excision with negative margins is recommended as pleomorphic LCIS can be hard to differentiate from DCIS.[106–108]

Although it is not a premalignant lesion, LCIS conveys a substantial increased risk for breast cancer. The relative risk of developing an invasive cancer in women with LCIS is approximately two to three folds higher than for women without LCIS (Table 74.5).[109] LCIS also conveys an increased risk for breast cancer to the contralateral breast. Historically, women diagnosed with LCIS were treated with bilateral prophylactic mastectomies. However this approach has been proven to be too aggressive given that *most* women with LCIS who do not have other contributory factors (e.g., family history of premenopausal breast cancer) will not develop an invasive breast cancer. Instead, a careful lifetime surveillance protocol similar to that described above for atypical hyperplasias can be followed. Chemoprevention with a SERM and/or AI can also be discussed with the patient. There are currently no randomized trials to compare the efficacy of surveillance protocol versus prophylactic mastectomy in women with LCIS.

FEA is an intraductal finding that is characterized by the replacement of native epithelial cells by a single layer, or up to three to five layers of mildly atypical cells (World Health Organization definition).[110] When diagnosed at core biopsy, the risk of upgrade to a malignancy at surgical excision is 5% to 15%.[111–113] When FEA is diagnosed by excisional biopsy, no further surgery is warranted. However, if FEA is diagnosed by core needle biopsy, excisional biopsy should be performed. Alternatively, radiologic surveillance can be performed and if there is absence of a residual mammographic abnormality and core biopsy was felt to be adequate, no further surgery is needed. Excisional biopsy must be performed for any residual lesions seen. When FEA is found at the margins, wider excision is

not needed.[111–114] Although FEA is an atypia, it conveys the same risk of breast cancer that is associated with benign proliferative disease without atypia and as such, patients should continue routine surveillance.[115] There is also no data to support the use of chemoprevention.

MANAGEMENT OF PATIENTS AT HIGH RISK FOR BREAST CANCER

Risk Factors

Breast cancer is the most common cancer in women in the United States. Approximately 200,000 women and 2,000 men are diagnosed with invasive breast cancer each year.[116] Breast cancer is the most common cancer in women of every major ethnic group, and the highest rate is among Caucasian women, with 122 newly diagnosed breast cancer cases per 100,000 women each year.[117] Understanding the risk factors for breast cancer is important, as some of these risks can be modified to decrease a patient's risk either through lifestyle/behavioral changes and/or the use of chemoprevention.

Increasing Age

As a woman ages, her risk for breast cancer increases: birth to age 49, 1.9% probability of developing invasive breast cancer (1 in 53); age 50 to 59, 2.3% (1 in 43); age 60 to 69, 3.5% (1 in 29); age 70 and older, 6.7% (1 in 15). From birth to death the probability of developing invasive breast cancer is 12.3% or 1 in 8.[116]

Estrogen Exposure

A woman's lifetime exposure to estrogens appears to correlate with her risk for breast cancer.[118] Exposure to estrogens can be approximated by age of first menarche, age of menopause, and age of first live birth, with nulliparous women who have an early menarche and a late menopause having the highest risk. Premenopausal women who undergo bilateral oophorectomy are at decreased risk. Given that high endogenous levels of estrogen is known to increase the risk of breast cancer in both premenopausal and postmenopausal

women, the use of exogenous hormones and their associated risk for breast cancer has been studied and debated. The use of hormonal contraceptives does not appear to significantly increase the risk of breast cancer.[119] However, the use of hormone replacement therapy in postmenopausal women has been associated with an increased risk of breast cancer as reported in the Women's Health Initiative Estrogen Alone and Estrogen-Plus-Progestin Studies, which were stopped early secondary to this and other concerns.[120] In the Estrogen-Plus-Progestin study, the HRT used was a combined estrogen-progestin therapy (EPT) that was given to postmenopausal women with an intact uterus. The risk of breast cancer is relatively low as EPT would result in an additional eight cases of breast cancer if 10,000 women took EPT for a year. More recently, it was determined that the rate of death from breast cancer among those taking EPT was 2.6 per 10,000 women per year, compared with 1.3 per 10,000 women per year among those taking placebo.[121] Short-term use of less than 3 years does not appear to significantly increase the risk of breast cancer and after the cessation of EPT use for 3 years a woman's risk returns to baseline.

RESULTS

Table 74.5 Risk for Breast Cancer Development after Lobular Carcinoma in Situ

Study	No. Patients	Invasive Cancer (%)	Follow-Up (yrs)	Relative Risk
Haagensen[406]	287	18	16.3	6.9
Rosen et al.[407]	99	12.5	24	9.0
Andersen[408]	47	26.4	15	12.0
Page et al.[109]	44	23	18	9.0
Salvadori et al.[409]	80	6.3	5	10.3
Ottesen et al.[410]	69	11.6	5	11.0
Bodian et al.[411]	236	26[a]	18	5.4
Fisher et al.[157]	182	33	5	—

[a]Includes intraductal and invasive cancer.

Given that lactation interrupts ovulation and modifies pituitary and ovarian hormone secretion, it has been postulated that breastfeeding can reduce breast cancer risk. This finding remains inconclusive. Limited data suggest that longer duration of lactation in premenopausal women may reduce risk.[122] A pooled analysis consisting of over 50,000 women with breast cancer and 96,000 controls concluded that for every 12 months of breastfeeding there was an associated 4.3% reduction in the relative risk of breast cancer.[123]

Environmental and Lifestyle Factors

Women who were subjected to ionizing radiation of the chest, such as for treatment of Hodgkin lymphoma or through exposure from nuclear plant accidents or the atomic bomb, have an increased risk of breast cancer. The prepuberty stage (age 10 to 14) appears to be the most vulnerable time for exposure, with little associated risk when exposure occurs after age of 45.[124–126] Alcohol use is associated with an increased risk of breast cancer and correlates with the amount of consumption, with differences noted with alcohol intake as low as three drinks per week versus those who abstain from alcohol. A meta-analysis of 110 studies shows a small but significant association (RR 1.05, 95% CI 1.02–1.08).[127,128] The relationship between cigarette use and breast cancer risk remains controversial because of unresolved issues of confounding and dose response, however a recent meta-analysis found that smoking before menarche and before the first birth was associated with an increased risk for breast cancer.[129] Furthermore, in women diagnosed with breast cancer, lifetime cigarette smoking (≥20 pack-years) was associated with an increased risk of recurrence and all-cause mortality.[130] The role of dietary factors such as fat intake, red meat and processed meat, phytoestrogens, calcium/vitamin D, and antioxidants in modifying breast cancer risk remains inconclusive. Regular physical exercise and a diet composed mainly of fruits and vegetables likely provide protection against breast cancer.

Family History

The number of first-degree relatives with breast cancer is strongly associated with a woman's risk for the future development of breast cancer. If one first-degree relative is affected, the risk of breast cancer increases by

approximately twofold, and if two first-degree relatives are affected, the risk of breast cancer is increased by approximately threefold. The age at diagnosis of the first-degree relative is also important, as a women's risk is approximately threefold higher when the diagnosis occurs before age 30 but only 1.5-fold higher if the diagnosis is after age 60.[131]

When evaluating family history, it is important to note that the majority of breast cancers are caused by sporadic mutations (mutations that occur in somatic cells that cannot be inherited). When studying the family tree of women with *sporadic breast cancer*, these women typically have no family history of breast cancer through two generations, including siblings, offspring, parents, and both maternal and paternal aunts, uncles, and grandparents. Less than 10% of breast cancers are hereditary. In families with *hereditary breast cancer*, the family tree is characterized by earlier onset of breast cancer, bilateral breast cancer, a greater frequency of primary cancers such as breast and ovary, and an autosomal dominant inheritance pattern (Fig. 74.15).[132] For women who have first- or second-degree relatives with breast cancer but do not meet the hereditary breast cancer definition noted above, these women have *familial breast cancer* where it is likely that both genetic and environmental factors play a role in their susceptibility.[131]

Most patients with hereditary breast cancer have mutations in the *BRCA1* or *BRCA2* genes which are localized to chromosome 17q21 and chromosome 13q12.3, respectively. Both serve as tumor suppressor genes and function as gatekeepers in controlling gene transcription, regulating repair of DNA damage (especially double strand breaks during cell replication), and may play a role in the maintenance of genomic stability.[133–135] Founder mutations exist in the Ashkenazi Jewish population with specific mutations in *BRCA1* (185delAG, 5382insC) and *BRCA2* (617delT).[136] Other BRCA-specific mutations have been identified in Dutch, Scandinavian, French-Canadian, and Belgian populations.[137,138]

The lifetime risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers is estimated to be as high as 85%, which is markedly elevated from a baseline risk of 12% in the general population (Table 74.6). Ovarian cancer risk is higher in *BRCA1* carriers with an estimated risk of 40% to 60% whereas *BRCA2* carriers have a risk of 15%. Among male patients with breast cancer who have a *BRCA* mutation, one-third of mutations involve

BRCA1 and two-thirds involve *BRCA2*. The risk of breast cancer in males is 1% to 5% with a *BRCA1* mutation, and 5% to 10% with a *BRCA2* mutation, versus a risk of 0.1% in the general population.[139–141] In addition prostate and pancreatic cancer is more common in patients with *BRCA2* mutations.[142,143]

Several commercial tests exist for *BRCA1* and *BRCA2* testing. Prior to genetic testing, patients should undergo genetic counseling where the complexities of testing are discussed along with potential emotional and financial ramifications that can result from positive test results. Ideally, genetic testing should start with a family member affected with breast or ovarian cancer or both. If that individual tests negative, further testing on an unaffected relative is unlikely to be informative. Candidates for gene testing include those with a known *BRCA1* or *BRCA2* gene mutation in the family, a personal history of breast cancer at age 45 or younger, a personal history of breast cancer at age 50 or younger and a family member (parent, sibling, child, grandparent, grandchild, uncle, aunt, nephew, niece or first cousin) diagnosed with breast cancer at any age, a personal history of triple negative breast cancer (TNBC) diagnosed at age 60 or younger, a personal history of ovarian cancer, a personal or family history of male breast cancer, and Ashkenazi Jewish heritage and a personal or family history of breast or ovarian cancer per consensus guidelines. Once an individual tests positive for a mutation, she should inform her first- and second-degree relatives of their risk status and the potential for DNA testing.

Other breast cancer susceptibility genes include *p53*, *ATM*, *CDH1*, and *PTEN*. The Li-Fraumeni or SBLA syndrome corresponds with *p53* mutations and includes a broad spectrum of cancers including sarcoma, breast cancer and brain tumors, lung and laryngeal cancer, leukemia, lymphoma, an adrenal cortical carcinoma.[145] The *ATM* gene mutation results in a childhood neurologic disorder referred to as ataxia-telangiectasia which is characterized by progressive cerebellar and neuromotor deterioration, telangiectasia of the conjunctivae and facial skin, and growth retardation. Females with the *ATM* mutation have a five times higher risk for developing breast cancers than the general population.[146] Females with the *CDH1* or E-cadherin gene mutation have a 70% lifetime risk for diffuse gastric cancer and a 40% risk for lobular breast cancer.[147] Distinctive mucocutaneous lesions referred to as trichilemmomas characterize Cowden disease, which

is associated with an increased risk of breast, thyroid, and genitourinary tract cancers in women, resulting from the *PTEN* gene mutation.[148]

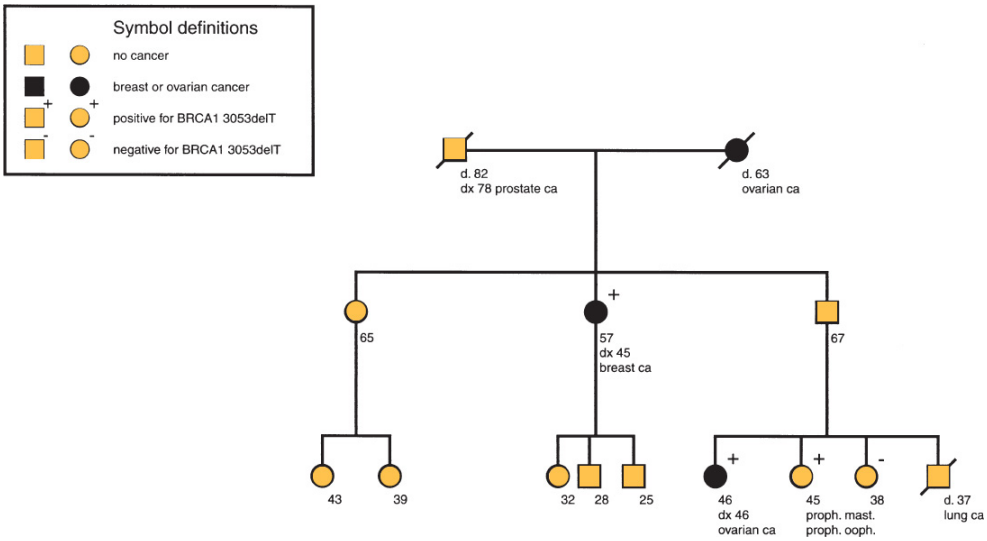


Figure 74.15 Pedigree of genetic breast cancer. The family illustrated in the pedigree carries a mutation of the BRCA1 gene; multiple relatives are affected with breast and ovarian cancer.

Clinical Risk Assessment

4 Through large population studies, numerous factors that can increase breast cancer risk have been identified as summarized in Table 74.7. In an effort to quantitate these potential risks such that preventive strategies can be better tailored, multiple risk assessment tools have been developed including the BCRAT or the Gail model 2,[149] BRCAPRO,[150] BOADICEA,[151] Tyrer–Cuzick,[152] and the Breast cancer surveillance consortium.[153] The Gail model calculates risk over a defined time interval and predicts risk accurately in groups of women 35 years of age and older who undergo annual mammography. The model is not for women who have a strong family history of breast cancer (such as genetic mutation carriers) or those with LCIS. The components of the Gail model include current age, age at menarche, age at time of first live birth, number of first-degree relatives with breast cancer, number of prior breast biopsies, prior breast biopsy with atypia, and race. A sample risk calculation is shown in Figure 74.16. Women are considered to be high-risk if their 5-year risk is >1.7%, or if their lifetime risk of breast cancer is at least 20%.

Management

All women at high risk for breast cancer should undergo genetic counseling, with education provided about the risk factors, genetics and natural history of breast cancer. These women should be followed with enhanced surveillance, and chemoprevention or prophylactic surgery should be considered. For women who have a genetic predisposition, such as those with a *BRCA1* or *BRCA2* mutation, many experts support aggressive surveillance including CBE biannually beginning at age 20, and annual mammography and MRI screening performed in a staggered fashion such that imaging occurs every 6 months starting at age 25. The use of screening MRI for women at high risk is supported by numerous studies. Prophylactic mastectomies can be considered at any age; many women prefer to defer this until after childbearing as they would like to breastfeed. Ovarian cancer screening for *BRCA1* and *BRCA2* carriers includes transvaginal ovarian ultrasound, serum CA-125, and annual pelvic exams starting at age 30. When childbearing is complete, prophylactic oophorectomies should be considered. In women with a family history but no known genetic abnormality, screening mammography should begin 10 years before the age of onset in the youngest diagnosed first-degree relative or at age 40. Furthermore, in the absence of a genetic abnormality, women who have a lifetime risk of breast cancer >20% should also be monitored with annual screening MRI.

Table 74.6 Estimated Lifetime Cancer Risks for BRCA1 and BRCA2 Mutations (To Age 70)

Type of Cancer	General Population (%)	BRCA1 Carrier (%)	BRCA2 Carrier (%)
Breast cancer	8.0	40–85	40–85
Contralateral breast cancer	0.5–1/yr	40–65	40–65
Male breast cancer	0.1	1–5	5–10
Ovarian cancer	1.4	30–45	10–20

Modified from Isaacs C, Peshkin BN, Lerman C. Evaluation and management of women with a strong family history of breast cancer. In: Harris JR, Lippman ME, Morrow M, et al., eds. *Diseases of the Breast*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:316.

Table 74.7 Magnitude of Known Breast Cancer Risk Factors

Relative Risk <2
Early menarche
Late menopause
Nulliparity
Proliferative benign disease
Obesity
Alcohol use
Hormone replacement therapy
Relative Risk 2–4
Age >35 first birth
First-degree relative with breast cancer
Radiation exposure
Prior breast cancer
Relative Risk >4
Gene mutation
Lobular carcinoma in situ
Atypical hyperplasia

In addition to its role in the treatment of breast cancer, endocrine therapy (chemoprevention) can reduce the risk of invasive and/or in situ breast cancers in women at high risk for breast cancer. Women who are known to benefit from chemoprevention include those >35 years with a history of LCIS, DCIS, or atypical proliferative lesions of the breast, women between 35 and 59 years with a Gail model risk of breast cancer >1.7% over 5 years, and women with known *BRCA1* or *BRCA2* mutations who do not undergo bilateral prophylactic mastectomies. Currently, there is no data regarding the risks and benefits of chemoprevention in male patients with breast cancer and as such, the use of these agents in men is not recommended.

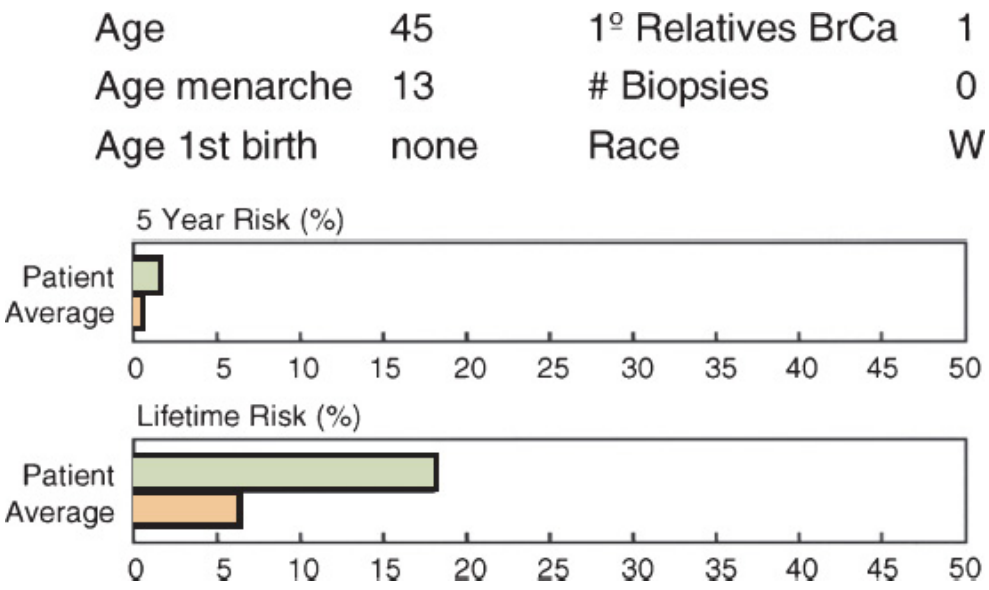


Figure 74.16 Breast cancer risk assessment according to the Gail model. This woman's 5-year risk for the development of breast cancer is 1.6%, and her lifetime risk is 18%.

For pre- and postmenopausal women at increased risk of breast cancer, both tamoxifen and raloxifene can be used. As SERMs, both agents block the effects of endogenous estrogen on normal breast tissue and breast cancer. Using data from four trials in the 2013 U.S. Preventive Services Task Force (USPSTF) meta-analysis, tamoxifen has been shown to reduce the risk of estrogen receptor-positive breast cancer (RR 0.70, 95% CI 0.59–0.82). Similarly, using data from two trials in the 2013 USPSTF meta-analysis, raloxifene reduced the risk of estrogen receptor-positive breast cancers (RR 0.44, 95% CI 0.27–0.71).[154,155] In terms of the choice between tamoxifen and raloxifene, the STAR trial directly compared tamoxifen with raloxifene and showed that the former was slightly more effective at preventing invasive breast cancer (Fig. 74.17). However, neither resulted in a reduction in breast cancer-specific, or all-cause mortality rates.[156]

Both tamoxifen and raloxifene have estrogenic activity on the bone resulting in a decreased incidence of fractures, while only tamoxifen has estrogenic activity on the uterus and coagulation pathways. Therefore, tamoxifen use is associated with an increased risk of endometrial cancer (4 cases in 1,000 women, RR 2.13, 95% CI 1.36–3.32) and thromboembolic events (4 cases in 1,000 women, RR 1.93, 95% CI 1.41–2.64),[154] with a trend toward higher stroke rates and pulmonary embolism.[157] Despite these

risks, quality of life measures (depression, anxiety, major psychosocial outcomes) show no differences in women receiving the drug versus placebo. However, an increase in vasomotor symptoms, gynecologic symptoms, and problems of sexual functioning was noted.[158,159] As congenital anomalies have been associated with tamoxifen, women with childbearing potential must implement an effective contraceptive method. For women desiring a pregnancy, tamoxifen should be discontinued for at least 2 months prior to attempt at pregnancy.

In postmenopausal women, studies show that aromatase inhibitors (AIs) are a reasonable alternative to tamoxifen and raloxifene. AIs suppress plasma estrogen levels by inhibition of aromatase, an enzyme that converts androgens to estrogens. Although AIs are commonly used for breast cancer treatment, they are not approved in the United States for breast cancer prevention at this time. Also, while both the USPSTF and ASCO support the use of SERMs for both premenopausal and postmenopausal women, only ASCO considers the use of exemestane as a reasonable alternative to SERMs for postmenopausal women.[160] More recently, the International Breast Cancer Intervention Study (IBIS-II trial) showed that high-risk postmenopausal women who took the AI anastrozole had a 50% reduction in the number of invasive breast cancers and DCIS compared to placebo. The side effects of anastrozole include musculoskeletal problems, hypertension, vaginal dryness, and vasomotor symptoms.[161] AIs may also be associated with a loss of bone density.

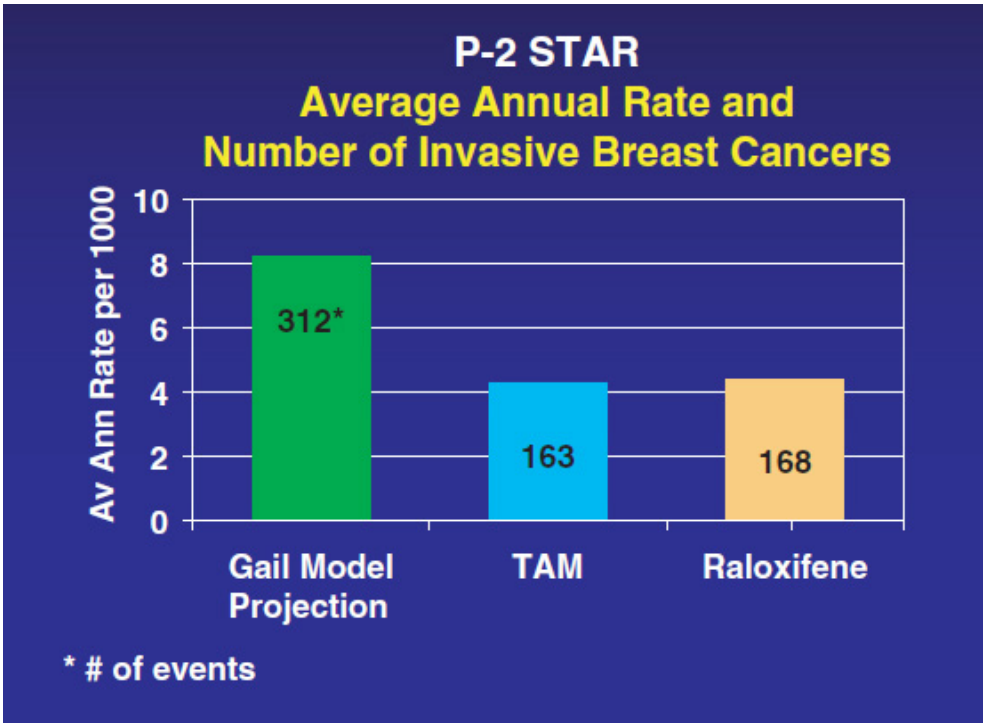


Figure 74.17 Both tamoxifen and raloxifene when taken for 5 years in the National Surgical Adjuvant Breast and Bowel Project P-2 (STAR trial) were equally effective at reducing the risk of invasive breast cancer.

The decision to proceed with endocrine therapy chemoprevention must be individualized. In general, the data support the use of endocrine therapy versus observation. For premenopausal and postmenopausal women, tamoxifen or raloxifene are both reasonable options. If a woman's primary concern is breast cancer prevention, then tamoxifen should be chosen. However, if there are risk factors for uterine cancer and/or thromboembolic complications, raloxifene is a reasonable alternative. If a postmenopausal woman does not want to take a SERM, then an aromatase inhibitor can be prescribed.

DUCTAL CARCINOMA IN SITU (DCIS)

Ductal carcinoma in situ (DCIS) is commonly defined as the proliferation of malignant epithelial cells within the mammary ductal system with no evidence of invasion into the surrounding stroma on routine light microscopic examination (Fig. 74.18). It is further categorized by its size, nuclear grade,

presence and extent of comedo necrosis, and architectural pattern. Common histologic subtypes of DCIS include comedo, cribriform, micropapillary, papillary, and solid.[162] DCIS is designated as Tis (DCIS) by the TNM staging system and considered a Stage 0 breast cancer.[163] The incidence of DCIS increases with age and is uncommon in women younger than 30 years. In women aged 50 to 64 years, the risk is as high as 88 per 100,000 women.[164] Among the breast cancers diagnosed in the United States, 25% are DCIS.[165] The risk of development of metastases and/or death in women with DCIS is rare (<1%).[166]

Most patients with DCIS will present with no breast-related symptoms or findings on physical examination. More than 90% of all cases of DCIS are detected on imaging studies—commonly as microcalcifications on mammography.[167,168] Prior to routine screening mammography, DCIS presented as a palpable mass, in association with nipple discharge, or as Paget disease.[169,170] Although most patients with DCIS have microcalcifications of indeterminate morphology, patterns that are highly suggestive of DCIS include linear branching or segmental types of pleomorphic microcalcifications.[168]

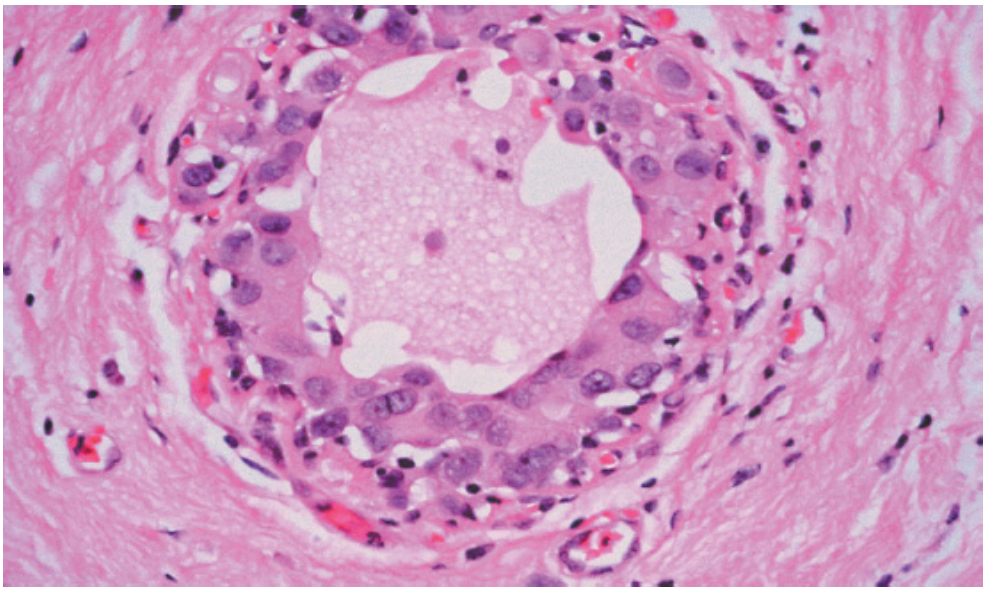


Figure 74.18 Photomicrograph of ductal carcinoma in situ. The abnormal cells do not cross the ductal basement membrane. The necrotic debris in the center of the duct is responsible for the calcification visible on mammography.

Once an abnormal lesion is detected by diagnostic imaging, the diagnosis of DCIS is typically confirmed by breast biopsy. Of note, when DCIS is diagnosed initially by core biopsy, 15% to 20% of lesions will be upgraded to invasive cancer at the time of definitive resection. Large, high-grade DCIS lesions are more likely to have an invasive component.[171]

5 Surgical options for the treatment of DCIS include breast-conserving surgery as a component of breast conservation therapy (BCT) (partial mastectomy and postoperative radiation therapy) or simple mastectomy. Although there is no randomized trial that has ever compared the treatment of DCIS by mastectomy with treatment by BCT, a large number of clinical studies have shown that the local recurrence rate of BCT is 10% to 15% after 10 years and that approximately half of the local recurrences are invasive carcinoma.[172–176] Mastectomy is curative in 98% of patients with DCIS, regardless of the tumor grade or the size of the lesion.[172,173] However, both surgical treatment options are associated with equivalent long-term survival as shown in both retrospective and prospective analyses.[177–179] Given that partial mastectomy is a much less invasive surgical procedure, BCT is typically recommended over mastectomy. Mastectomy should be performed if BCT is contraindicated, or based on patient preference. BCT is contraindicated with multicentric disease, extensive disease where resection would result in poor cosmesis, and in patients who cannot receive radiation therapy. For patients undergoing mastectomy, immediate breast reconstruction options should be reviewed.

BCT typically includes a partial mastectomy with negative surgical margins, followed by radiation therapy to eradicate any residual disease. Radiation therapy is typically recommended, except in rare circumstances (see ***Breast Cancer in the Elderly***). Four prospective, randomized clinical trials—NSABP B-17 (1998, 2001),[175,176] EORTC 10853 (2006),[180] United Kingdom (2003),[181] and the SweDCIS (2008)[182] have focused on the role of radiation therapy in the treatment of DCIS (Table 74.8). Despite differences in study design, the results are very similar, demonstrating a 50% to 60% reduction in local recurrence with surgical excision and radiation therapy compared to surgical excision alone. Furthermore, the results of NSABP B-17 confirm that the reduction in local recurrence persists through 12 years of follow-up. However, no survival benefit from radiation therapy was

observed. Patients with comedo necrosis, uncertain margins, and/or those at highest risk for recurrence appear to benefit most from radiation therapy.[183] However, even in the most favorable subgroup (absent or slight comedo necrosis, clear margins), radiation therapy was associated with a reduction in the absolute incidence of breast recurrence by 7% at 8 years.

Given the risks, inconvenience and cost associated with radiation therapy, attempts have been made to define a subgroup of patients with DCIS who may not require radiation therapy. The ECOG 5194 study investigated patients undergoing local excision alone in women with low-risk DCIS (low- to intermediate-grade DCIS lesions were <2.5 cm, and high-grade DCIS lesions were <1.0 cm). Margins were at least 3 mm and a postexcision mammogram was obtained for all patients to document the adequacy of surgical resection. Tamoxifen following excision was allowed but not required. At a median follow-up of 6.7 years, the local recurrence rate at 5 years was 6.1% (95% CI 4.1% to 8.2%) for patients with low- to intermediate-grade DCIS (n = 565), and 15.3% (95% CI 8.2% to 22.5%) for patients with high-grade DCIS (n = 105).[184] These findings suggest that local excision alone may be sufficient for select patients with low- to intermediate-grade DCIS. However, identifying these patients remains a challenge.

RESULTS

Table 74.8 Results of Randomized Trials of Radiotherapy in Ductal Carcinoma in Situ

			IBTR (%)	
Study	Patients (No.)	Median Follow-up (mo)	E	RT
NSABP B-17[175,176]	813	44	40	17
EORTC 10853[180]	1,010	126	26	15
United Kingdom[181]	1,030	53	14	6
SweDCIS[182]	1,046	96 (mean)	27	12

DCIS, ductal carcinoma in situ; E, excision alone; EORTC, European Organization for Research and Treatment of Cancer; IBTR, ipsilateral breast tumor recurrence; NSABP, National Surgical Adjuvant Breast Project; RT, radiation therapy.

Other models which have attempted to predict the likelihood of local recurrence following excision alone in patients with DCIS include the Van Nuys Prognostic Index (VNPI)[185] and its updated version the University of Southern California Van Nuys Prognostic Index (USC/VNPI).[186] Patients are classified into three groups based on pathologic classification: (1) non–high-grade DCIS without comedo type necrosis, (2) non–high-grade DCIS with comedo type necrosis, and (3) high-grade DCIS with or without comedo type necrosis. The USC/VNPI score (range is 4 to 12) is then calculated based on the pathologic classification score and points given for margins, tumor size, and the patient's age. The study's conclusion is that women with an overall low score (4, 5, 6) did not require radiation therapy. However, attempt to replicate and validate the USC/VNPI score in other datasets have had varying success[187–189] and as such it is not commonly used.

More recently gene expression analysis has been explored in an attempt to distinguish patients who may omit postexcision radiation therapy. The DCIS Recurrence Score is a multigene assay that was developed using tumors from 327 patients who participated in the ECOG5194 trial as described previously.[190] The DCIS Recurrence Score is designed to stratify patients into three groups corresponding to the 10-year risk of developing ipsilateral DCIS or invasive breast cancer. Those with a low score (<39) had a risk of ipsilateral recurrence of 12% and 5% respectively; intermediate score (39–54) had a risk of ipsilateral recurrence of 25% and 9%; and high score (>55) had a risk of ipsilateral recurrence of 27% and 19%. It must be noted that for some patients a 12% risk of an ipsilateral recurrence at 10 years may not justify omission of radiation therapy. Furthermore, validation of this multigene assay is required prior to its implementation into clinical practice.

Axillary lymph node involvement in DCIS is rare, and sentinel lymph node biopsy is not indicated during breast-conserving surgery. In the NSABP B-17 and B-24 trials, the axillary recurrence rates, irrespective of treatment, were 0.83 and 0.36 per 1,000 patient-years of follow-up.[191] If a patient is undergoing a mastectomy following core needle biopsy, SLN biopsy should be considered as it is possible that an occult invasive breast cancer will be identified, and SLNB is often not feasible after mastectomy. Of note, SLNB after a mastectomy has been explored through skin mapping. Radiocolloid with or without blue dye is injected superior to the mastectomy incision into the skin flap, with successful identification of a sentinel lymph node in 13 out

of 20 patients (65% success rate).[192] Our institution has had slightly higher success rates with the injection of both radiocolloid and blue dye.

After breast-conserving surgery, a postexcision mammogram should be performed prior to the initiation of radiation therapy to ensure that there are no persistent residual suspicious calcifications. Treatment for DCIS after breast-conserving surgery is not considered complete without adjuvant radiation therapy (see ***Radiation Therapy***).

There is no role for chemotherapy in DCIS. However, endocrine therapy is commonly recommended. Fifty to 75% of DCIS specimens express estrogen and progesterone receptors.[193,194] In the United States, only tamoxifen has been approved to prevent breast cancer recurrences in women with DCIS. Currently, no data exist to support the use of aromatase inhibitors in this population. The benefit of tamoxifen therapy in decreasing local recurrence rates is supported by both a meta-analysis of two randomized trials and by NSABP B-24. The meta-analysis consists of 3,375 women and shows that tamoxifen after surgery for DCIS reduces recurrence of both ipsilateral DCIS (HR 0.75; 95% CI 0.61 to 0.92) and contralateral DCIS (HR 0.50; 95% CI 0.28 to 0.87) (Fig. 74.19). There is also a trend toward decreased ipsilateral invasive cancer (HR 0.79; 95% CI 0.62 to 1.01) and reduced contralateral invasive cancer (HR 0.57; 95% CI 0.39 to 0.83). The number needed to treat in order for tamoxifen to have a protective effect against all breast events was 15. However, there was no difference in all-cause mortality (RR 1.11; 95% CI 0.89 to 1.39).[195] In a retrospective review of NSABP B-24, it was found that at 10 years of follow-up, patients (n = 732) with ER-positive DCIS treated with tamoxifen had significant decreases in any subsequent (invasive and/or noninvasive; ipsilateral and/or contralateral) breast cancer events compared with those who received placebo (HR 0.58, 95% CI 0.42 to 0.81, $p < 0.0015$).[196]

Management of patients with DCIS who have not undergone bilateral mastectomies include consideration of tamoxifen for 5 years rather than observation, recognizing that although there is an improvement in recurrence rates, there is no proven survival benefit per consensus guidelines. In women who have undergone bilateral mastectomies, the risks associated with tamoxifen use likely outweigh the benefits. Furthermore, tamoxifen is not typically recommended for patients with ER-negative DCIS.

EVALUATION OF THE PATIENT WITH BREAST CANCER

Breast cancer is a heterogenous disease that can be characterized further based on clinical and pathologic features. Further characterization and staging of breast cancer in newly diagnosed breast cancer patients can facilitate definitive treatment. Pathologic, biologic and anatomic characteristics are used in combination to predict prognosis and response to therapy.

AJCC TNM Staging

The eighth edition of the AJCC TNM staging system for breast cancer is an internationally accepted system used to characterize the extent of disease, predict prognosis, and facilitate medical decision-making (Table 74.9).[198] Unlike the seventh edition, this new staging system is no longer just based on anatomic findings (TNM anatomic stage groups) but now includes pathologic prognostic (TNM pathologic prognosis stage groups) and clinical prognostic (TNM clinical prognostic stage groups) factors by incorporating such things as tumor grade and receptor status (esterogen, progesterone, HER2 amplification). The system we will discuss in detail is the TNM anatomic staging system, where breast cancer is classified on the basis of the primary tumor type (invasive or in situ) and size (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastases (M).

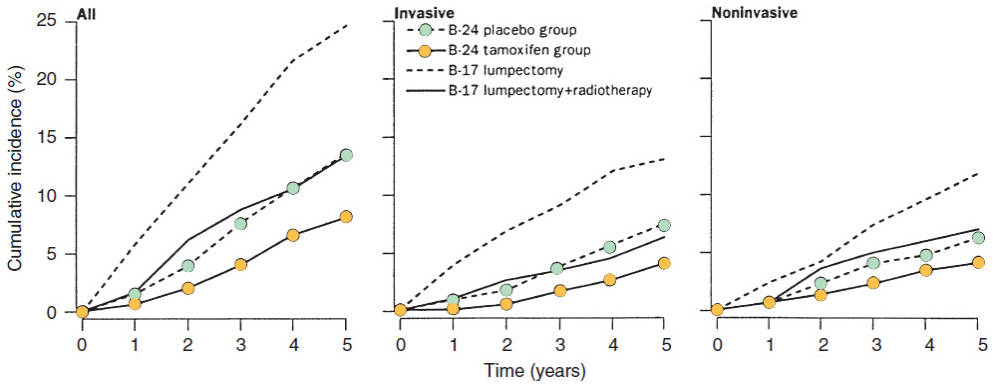


Figure 74.19 Benefits of radiation therapy and tamoxifen in ductal carcinoma in situ. The cumulative incidence of breast cancer events in the ipsilateral and contralateral breasts for patients treated in the National Surgical Adjuvant Breast and Bowel Project B-17 and B-24 trials is shown. The reduction in recurrence is greatest for patients receiving radiotherapy and tamoxifen.

Noninvasive breast cancers are noted as Tis and further classified into Tis (DCIS) and and Tis (Paget). LCIS is now considered a benign entity and as such not classified as Tis. T1 tumors are invasive cancers ≤20 mm; T2 tumors are >20 mm but ≤50 mm; whereas T3 tumors are >50 mm. T4 tumors are any size with direct extension to the chest wall and or the skin, resulting in nodules or ulcerations. Invasion of cancer into the dermis alone does not qualify as T4. IBC, which is defined by typical skin changes involving a third or more of the skin of the breast, is classified as T4d.

Lymph node classification criteria differ depending on whether the lymph nodes were clinically or pathologically assessed and as such are designated as cN or pN respectively. When possible, pathologic classification is preferred. Regional lymph nodes are defined as those of the ipsilateral axilla, ipsilateral intramammary, internal mammary nodes, and supraclavicular nodes. Metastasis to any other lymph node, including cervical or to the contralateral axillary lymph node is classified as distant disease (M1). In regards to the clinical classification of the regional lymph nodes, cN0 refers to no regional lymph node metastases. Mobile level I and II axillary lymph nodes containing metastases that are ipsilateral are considered cN1, whereas fixed or matted nodes are cN2. When metastases occur in the infraclavicular lymph nodes, ipsilateral internal mammary lymph nodes *and* axillary lymph nodes, or to the ipsilateral supraclavicular lymph nodes, it is classified as cN3.

In order to discuss the pathologic classification of regional lymph nodes, it is important to note that breast cancer metastases must be greater than 0.2 mm and exceed 200 cells in a single histologic lymph node cross section to be considered clinically relevant. As such pN0 refers to no regional lymph node metastases, pN1mi is used to describe micrometastases (greater than 0.2 mm or more than 200 cells, but none greater than 2.0 mm), and pN1 is used to describe metastases in one to three lymph nodes, and/or internal mammary nodes with metastases detected by SLN biopsy but not clinically detected. pN2 disease occurs when metastases are present in four to nine axillary lymph nodes or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases. pN3 disease includes metastases in 10 or more axillary lymph nodes, metastases to the infraclavicular (level III axillary) lymph nodes, in clinically detected ipsilateral internal mammary lymph nodes in the presence of 1 or more positive level I, or II axillary lymph nodes, in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometases detected by SLN biopsy but not clinically detected, or in ipsilateral supraclavicular lymph nodes.

Distant metastasis (M1) is defined as detectable metastases as determined by classical clinical and radiographic means and/or histologically proven larger than 0.2 mm. When no clinical or radiographic evidence of distant metastases is present, but deposits of molecularly or microscopically detected tumor cells are found in circulating blood, bone marrow or other nonregional nodal tissue that are no larger than 0.2 mm in a patient with no symptoms of metastases the designation used is cMO(i+).

The particular combination of the T, N, and M characteristics defines the overall breast cancer stage. Although the TNM staging system estimates predicted survival, it should not be used alone to dictate treatment.

Histologic Subtype and Tumor Grade

Most invasive breast cancers arise from epithelial elements and are categorized as carcinomas, consisting of several histologic subtypes. Based on the Surveillance Epidemiology and End Results (SEER) database of the National Cancer Institute between 1992 and 2001, estimated percentages of each histologic subtype of breast cancer in a series involving 135,157

women showed infiltrating ductal carcinoma (IDC) as the most common (76%), followed by invasive lobular (8%), ductal/lobular (7%), mucinous/colloid (2.4%), tubular (1.5%), medullary (1.2%), and then papillary (1%).[199]

IDC is the most common type of invasive breast cancer. On gross pathologic evaluation, these lesions are typically firm, gray-white, gritty masses. Cytologic features of these cells range from low grade to highly malignant. Microscopically these cancers are characterized by cords and nests of tumors cells with varying amounts of gland formation. As these cancer cells infiltrate the breast parenchyma, they induce a fibrous response, resulting in their characteristic irregular, stellate shape. Often IDC is associated with a variable amount of DCIS.

Table 74.9 Tumor, Node, Metastasis (TNM) Classification for Breast Cancer Staging

TNM Definitions

Primary Tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ, ductal or lobular or Paget disease of the nipple with no tumor
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall (not including pectoralis muscle), skin edema, skin ulceration, satellite skin nodules, or inflammatory carcinoma
Regional Lymph Nodes (Pathologic)	
Nx	Nodes cannot be assessed
N0	No regional node metastases histologically, no additional examination for isolated tumor cells (ITCs)
N1	Metastasis to one to three axillary nodes or in internal mammary (IM) nodes with microscopic disease detected by sentinel node biopsy, which is not clinically apparent
N2	Metastases in four to nine axillary nodes or in clinically apparent IM nodes in the absence of axillary node metastasis
N3	Metastases in 10 or more axillary nodes, or in infraclavicular nodes, or in IM nodes in the presence of one or more positive axillary nodes; or in more than three axillary nodes with IM metastases, or in supraclavicular nodes
Distant Metastases	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis

M0 M1	Distant metastasis		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T0 T1 T2	N1 N1 N0	M0 M0 M0
Stage IIB	T2 T3	N1 N0	M0 M0
Stage IIIA	T0 T1 T2 T3 T3	N2 N2 N2 N1 N2	M0 M0 M0 M0 M0
Stage IIIB	T4 T4 T4	N0 N1 N2	M0 M0 M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any T	M1

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Infiltrating lobular carcinomas (ILC) are the second most common type of breast cancer. The incidence rate of lobular carcinoma is rising faster than the rate of ductal carcinoma in the United States. Furthermore, postmenopausal hormone therapy use may be more strongly associated with lobular carcinoma that ductal carcinoma. Although some ILC may appear similar to IDC macroscopically, others may not show a mass lesion with the excised tissue appearing normal or having only a slightly firm consistency. As such, the microscopic size of ILC may be much greater than what is measured grossly. Unlike IDC, ILC induces only a minimal fibrous reaction.

Microscopically, these tumors are characterized by small cells that insidiously infiltrate the mammary stroma and adipose tissue individually and in a single file pattern, often growing in a target-like configuration around normal breast ducts. LCIS or DCIS may be present with ILC. There is a higher frequency of bilateral and multicentric disease with ILC than IDC.[200,201] ILC are more common in older women, and are typically larger but more differentiated than IDC. ILC are almost always estrogen receptor-positive. The prognosis for ILC and IDC appears to be similar, however, recent reports suggest that the short-term prognosis for ILC may be more favorable.[202,203] ILC tend to metastasize later than IDC and spread to unusual locations such as the peritoneum, meninges, and the gastrointestinal tract.[204] Furthermore, lobular breast cancers have been observed in families that carry germline mutations in *CDH1*, the gene that encodes for the E-cadherin protein. The lack of E-cadherin can be used to distinguish ILC from IDC.[205,206]

Mucinous (colloid) carcinoma is a less common histologic subtype that is more common in older patients. On gross examination, these tumors have a soft gelatinous appearance and tend to be well circumscribed. Microscopically, they are characterized by nests of tumor cells, with uniform and low grade nuclei, dispersed in large pools of extracellular mucus. These lesions have a favorable prognosis.[207,208] Another histologic subtype with favorable prognosis is tubular carcinoma, which is characterized by the presence of well-formed tubular or glandular structures infiltrating the stroma. The tumor cells are low grade and are often associated with low-grade DCIS. Metastatic disease is rare with tubular carcinoma.[209]

Medullary carcinomas are well circumscribed, soft, tan masses with areas of hemorrhage and necrosis. Microscopically, the tumor cells are poorly differentiated, grow in a syncytial pattern, and have an intense lymphoplasmacytic infiltrate.[210] These cancers occur more frequently in younger patients and are more frequent in women with *BRCA1* mutations, although the majority of breast cancers in patients with *BRCA1* mutation are not medullary.[211] Despite, their aggressive histologic appearance, medullary carcinomas are associated with a more favorable prognosis than IDC.[212,213]

Other breast cancer subtypes include macropapillary carcinomas which are highly aggressive and have a tendency for lymph node metastasis even when small in size.[214] Also likely associated with a worse prognosis,

metaplastic carcinomas are well circumscribed tumors that contain various combinations of poorly differentiated ductal adenocarcinoma, mesenchymal (sarcomatous), and other epithelial (e.g., squamous cell) components.[215] When the squamous cell component predominates, the tumors tend to be more aggressive and are frequently refractory to treatment when compared with IDC.[216,217] Unlike IDC, metaplastic breast cancers tend to have fewer T1 tumors, more node-negative tumors, more poorly differentiated or undifferentiated tumors, and have fewer estrogen receptor positive tumors.[215] Metaplastic breast cancers are treated similarly to other invasive breast cancers.[218–220]

The grade of a breast cancer is determined by a combination of the architectural and cytologic features, usually assessed by utilizing the Ellston–Ellis modification of the Scarff–Bloom–Richardson scoring system. This system is based on three parameters including tubule formation, nuclear pleomorphism, and mitotic activity. Each category is assigned a score of 1 to 3 and then a summation score of 3 to 9. The lowest possible score is 3 with scores of 3 to 5 defined as grade 1, 6 or 7 as grade 2, and 8 or 9 as grade 3. Cells that infiltrate the stroma as solid nests of glands and where the nuclei are relatively uniform with little or no evidence of mitotic activity are referred to as well differentiated or grade 1 tumors. When the tumor cells infiltrate as solid nests with some glandular differentiation and nuclear pleomorphism is present, the tumor is categorized as grade 2 or moderately differentiated. In addition, the mitotic activity is moderate. In poorly differentiated or grade 3 tumors, solid nests of neoplastic cells without evidence of gland formation are present. In addition, there is marked nuclear atypia and high mitotic activity.[221]

Biomarker Profile (ER, PR, HER2)

As targeted therapies exist targeting breast cancers that express the estrogen receptor (ER), progesterone receptor (PR), and/or the HER2 protein, these biomarkers have significant treatment implications. As such, when an invasive breast cancer is diagnosed, expression of these biomarkers is determined. Using immunohistochemistry and image analysis, ER and PR are considered positive if greater than or equal to 10% of cells stain positive. The Allred score is another method to quantify ER and PR expression. The

Allred score integrates the percentage of cells that stain positive, with the intensity of staining to give a score of 0 to 8.[222] The goal of the Allred score is to quantify ER expression based on the likelihood that a breast cancer patient will respond to endocrine therapy. One of the benefits of the Allred score is that by integrating both the percentage and intensity of staining, patients with <10% staining may be identified who benefit from endocrine therapy.[223] The receptor tyrosine kinase protein HER2 is a member of the epidermal growth factor receptor family and its amplification or overexpression has been shown to contribute to breast cancer development and progression. HER2 can now be targeted using monoclonal antibodies and small molecule inhibitors. Using immunohistochemistry and image analysis, HER2 is scored 0, 1+, 2+, and 3+. Positivity is noted as 3+, whereas scores of 0 and 1+ are considered negative. A score of 2+ is considered indeterminate and further testing for gene amplification can be performed using either FISH (fluorescence in situ hybridization) or CISH (chromogenic in situ hybridization). The HER2 FISH assay is based on the gene copy number and the ratio between the number of HER2 and chromosome enumeration probe 17 (CEP17) sequences, with positivity defined as a HER2/CEP17 ratio ≥2.0. Positivity is also defined as HER2 copy number ≥6.0 signals/cell even if the HER2/CEP17 ratio is <2.0.[224] Alternatively, a more cost effective and comparable method to FISH testing is the HER2 CISH assay.[225,226]

An emerging biomarker is the Ki-67 index. The Ki-67 antigen is present in all phases of the cell cycle except for the G0/resting phase and reflects of the proliferative potential of a breast cancer. Ki-67 is determined by IHC and noted as a percentage, where <10% is considered a low proliferative index, 10% to 20% is considered borderline, and >20% is considered high. The Ki-67 index can also be used to measure the response to endocrine therapy.

Molecular Subtyping

Recent advances in molecular biology, including the development of sophisticated techniques for gene expression profiling, have established a new taxonomy of breast cancer, defining molecular subtypes of breast cancer. This new taxonomy has had a profound impact on the clinical management of breast cancer, as the molecular subtypes differ markedly in prognosis and

response to therapy. As gene expression profiling is not routinely performed on clinical specimens, molecular subtypes have been approximated based on expression of the estrogen receptor, progesterone receptor, HER2 expression, and other biomarkers. Commonly defined subtypes include luminal A (ER+, PR+, HER2–, Ki-67 <14%), luminal B (ER+ and or PR+, HER2+/–, Ki-67 ≥ 14%), HER2 (ER and PR–, HER2+), and basal-like (ER, PR, and HER–).[227–229] Luminal A and B subtypes have estrogen receptor expression, however the former group has a much better overall survival.[230] Luminal B HER2+ and HER2 subtypes benefit from targeted therapies against HER2. Furthermore, both HER2 and basal-like breast cancers are known to have higher initial responses to anthracycline-based chemotherapy than the luminal subtypes but are associated with a decreased disease-free survival.[231]

Table 74.10 Approach to the Axillary Nodes

Finding	Approach
Clinically negative	Sentinel lymph node biopsy
Radiographically suspicious	Fine-needle aspiration (image guided) If no metastatic disease identified, then sentinel lymph node biopsy If metastatic disease is identified, consideration for axillary lymph node dissection
Clinically suspicious	Fine-needle aspiration (image or hand guided) Follow-up management as for radiographically suspicious

Breast MRI

Although there is no data from prospective randomized trials demonstrating improved outcomes with the addition of MRI to the diagnostic evaluation of

newly diagnosed breast cancers, the consensus guidelines suggest that diagnostic MRI should be considered in patients with newly diagnosed breast cancer when (1) the clinical extent of disease appears larger than what is observed on mammography, (2) there is concern about pectoralis muscle involvement, (3) there is no evidence of a breast primary in the presence of axillary lymph node metastases, (4) there is no disease identified on physical examination or mammography in the presence of PDB, (5) in women at very high risk for contralateral breast cancers such as those with *BRCA1/2* mutations, and (6) to help determine the extent of disease prior to treatment. Of note, MRI is associated with a high false-positive rate, and many MRI-detected abnormalities will need to be biopsied in order to meaningfully interpret the results of the MRI.

Sentinel Lymph Node Biopsy

Breast cancer spread to ipsilateral axillary lymph nodes is common, occurring in 15% to 30% of patients. The presence of axillary lymph node metastases has important prognostic implications, and can impact medical, surgical and radiation oncology decision making. However, ALND has significant risks, and the therapeutic impact of axillary surgery remains to be clearly defined.[232–234] Currently SLNB is the procedure of choice for staging of the axilla in breast cancer. Axillary ultrasound has also been used, and can facilitate evaluation of patients with an equivocal physical examination (Table 74.10).

6 The SLN hypothesis predicts that breast cancers metastasize to one or a few lymph nodes prior to involving other lymph nodes in the corresponding lymph node basin. Prospective studies have confirmed this hypothesis, demonstrating that the pathology of the SLN accurately predicts the pathology of the corresponding axillary lymph node basin (Table 74.11). SLNB has significantly fewer complications than ALND, with the risk of lymphedema being significantly lower (2% after SLNB vs. 13% after ALND at 12 months).[235]

The SLNB procedure begins with localization of the SLN through injection of radioactive colloid and/or blue dye. Given that the combined use of both tracers appears to be complementary and that failed SLN identification is minimized when both tracers are used, this is our recommended approach. A

systematic review by an expert panel convened by ASCO concluded that the use of both blue dye and radioactive colloid was associated with a trend toward a lower false-negative rate.[236]

Prior to surgery, radioactive technetium sulfur colloid is injected either peritumorally, intradermally, or into the subareolar plexus. Lymphoscintigraphy can be performed to identify areas of increased radioactivity. Alternatively, a handheld gamma probe can be used to survey the axilla and identify hot spots. The patient is then brought to the operating room and positioned with the ipsilateral arm abducted up to 90 degrees. The breast, anterior chest wall, and axilla are prepped and draped in the usual standard sterile fashion. Five milliliters of blue dye (isosulfan or methylene blue dye) is injected either around the tumor periphery, at the palpable edge of the biopsy cavity, or into the subareolar plexus. Blue dye should not be injected directly into the tumor itself as the lymphatics may be occluded by tumor. Likewise, blue dye should not be injected into the seroma cavity following breast surgery as the seroma cavity may not have sufficient lymphatic drainage. For these reasons, we typically inject into the subareolar plexus. Breast massage is performed for 5 minutes to dilate the breast lymphatics and facilitate lymphatic drainage.

Isosulfan blue can be used for SLNB, however anaphylaxis requiring resuscitation can occur in 0.7% to 1.1% of cases.[237,238] Alternatively, methylene blue can be used. The risks associated with methylene blue include skin necrosis if injected intradermally, pain secondary to caustic reaction, and pulmonary edema.[239–241] These risks can be minimized by diluting the methylene blue, with common dilutions ranging from 2:3 (2 mL of methylene blue mixed with 3 mL of saline, injecting 5 mL total) to 1:4 (1 mL of methylene blue mixed with 4 mL of saline, injecting 5 mL total). In patients taking serotonergic psychiatric mediations, methylene blue should be used with caution as the dye can prevent the action of monoamine oxidase A, resulting in toxic levels of serotonin or serotonin syndrome. This is characterized by mental status changes, muscle twitching, excessive sweating, shivering, diarrhea, trouble with coordination, and/or fever.[242]

Table 74.11 Results of Prospective, Multi-Institutional Studies of Lymphatic Mapping and Sentinel Node Biopsy

Study	No. Patients	% SN Identification	% False Negative
ACOSOG Z10[278]	5,237	98.7	N/A
ALMANAC[412]	803	96.1	6.7
NSABP B-32[413]	5,611	97.1	9.8
Sentinella/GIVOM[414]	697	95	16.7

ACOSOG, American College of Surgeons Oncology Group; ALMANAC, Axillary Lymphatic Mapping Against Nodal Axillary Clearance; GIVOM, Gruppo Interdisciplinare Veneto Oncologia Mammaria; NSABP, National Surgical Adjuvant Breast and Bowel Project; SN, sentinel node.

Using a handheld gamma probe the axilla is systematically surveyed and the skin is marked at the location of the hottest spot. A small incision is then made below the hair-bearing area of the axilla and carried down through the subcutaneous tissue. The clavipectoral fascia is incised with care to visually identify any blue lymphatics. The blue lymphatics are then followed toward the axilla to identify the sentinel lymph node(s). Successful SLN identification by blue dye is defined as the identification of any blue node or nonblue node with a blue afferent lymphatic. These lymph nodes are also evaluated with the gamma probe and the associated counts are recorded. The dissection is continued until all lymph nodes associated with a blue afferent lymphatic are removed and any remaining lymph nodes have less than 10% radioactivity compared to the most radioactive lymph node.[243–245] This often results in more than one SLN being identified and removed. Finally, palpation of the axilla is performed and any suspicious lymph nodes are also removed as gross tumor involvement can interfere with uptake of both radioactive colloid and blue dye. In the case of gross tumor involvement the radioactive colloid and blue dye are may be diverted to a lymph node other than the true SLN, giving rise to a false-negative result if palpation of the axilla and removal of suspicious lymph nodes is not performed.[246,247] Once all SLN have been identified and removed, hemostasis is obtained, and the

clavipectoral fascia is reapproximated with interrupted vicryl stitches. The deep dermal layer is reapproximated with interrupted 3-0 vicryl stitches and the skin closed with a running subcuticular stitch.

TREATMENT OF THE PATIENT WITH BREAST CANCER

Breast cancer is currently treated with a multidisciplinary approach. Most patients benefit from a combination of therapies which may include surgery, medical therapy, and radiation therapy. This multidisciplinary approach has resulted in a significant reduction in breast cancer mortality.[248] One important consideration is optimal coordination of surgery with the other treatment modalities. In the discussion below we will first provide an overview of how the different treatment modalities are coordinated in early stage, locally advanced and metastatic 7 breast cancer. After this overview, surgery, medical therapy and radiation therapy will be discussed in more detail.

Overview

Most patients with newly diagnosed breast cancer have no evidence of metastatic disease and are diagnosed with *early stage* breast cancer. This includes patients with clinical stage I (T1N0), IIA (T1N1 or T2N0), or IIB (T2N1) disease. Local regional management often consists of BCT (partial mastectomy with radiation therapy) or mastectomy, noting that the choice in locoregional management does not typically impact the recommendation for adjuvant medical therapy. For patients with clinical T1N0 disease, surgery is typically the first treatment modality. For patients with clinical T2N0 or T2N1 disease, neoadjuvant chemotherapy or endocrine therapy is often the first treatment modality. The goal of neoadjuvant therapy is to shrink the primary breast cancer prior to surgery, facilitating BCT. For patients with a clinically suspicious axilla, an ultrasound guided FNA may be helpful to determine whether there is metastatic spread to the axilla. If the FNA is negative, then the patient should undergo a SLNB at the time of surgery. For

patients with a clinically negative axilla, a SLNB should be planned at the time of surgery with a decision about further management of the axilla, if any, pending the results of the SLNB. The decision to recommend chemotherapy for patients with early breast cancer is primarily dependent on tumor characteristics but also integrates the patient's overall health status and personal preference. Adjuvant chemotherapy is typically recommended when high-risk features are present such as high-grade tumor, large tumor size (≥1.0 cm), unfavorable biomarker profile, or lymph node involvement. In addition, an Oncotype DX can be obtained in patients with ER+/HER2- negative breast cancers and negative lymph nodes. A score of ≥31 often suggests that adjuvant chemotherapy will be beneficial. For patients with breast cancers that are hormone receptor-positive, endocrine therapy is typically recommended postoperatively. If adjuvant chemotherapy is recommended, then endocrine therapy is given after completion of chemotherapy. For patients with TNBC, adjuvant chemotherapy is commonly given if the tumor size is ≥0.5 cm. Patients who have HER2-positive breast cancers that are ≥1.0 cm are treated with adjuvant chemotherapy plus HER2-directed therapy. The management of HER2-positive breast cancers that are <1.0 cm is controversial and should be decided by the patient and her provider after a discussion of the risks and benefits of treatment. Adjuvant radiation therapy is typically recommended for all patients who are treated with BCT, and a subset of patients who are treated with mastectomy (see ***Radiation Therapy***).

Patients with *locally advanced disease* (clinical stage IIB [T3N0], or stage IIIA–IIIC [T1–T3N2 disease or T4 disease]) are at a higher risk for recurrence and distant metastases, and neoadjuvant and/or adjuvant chemotherapy and radiation therapy are typically recommended (Fig. 74.20). Benefits of neoadjuvant chemotherapy in this clinical context include the ability to treat any potential systemic disease immediately, and the ability to directly assess the response to treatment by physical examination and imaging, allowing for suboptimal regimens to be discontinued and other regimens to be prescribed. In patients with hormone receptor-positive disease, neoadjuvant chemotherapy is associated with a higher response rate in a shorter period of time than endocrine therapy. Endocrine therapy in the neoadjuvant setting is often reserved for postmenopausal women who have

contraindications to chemotherapy. For patients with HER2-positive breast cancer, HER2-directed therapy such as trastuzumab with or without pertuzumab should be given in addition to chemotherapy. If a patient has a limited response or cannot tolerate the neoadjuvant regimen, she should proceed with surgery. Even if patients have an excellent clinical response, they should undergo surgery to remove the area of involvement. Although BCT is an option for patients with locally advanced breast cancer (LABC) who have a significant clinical response to neoadjuvant chemotherapy, mastectomy is typically recommended for those who initially present with breast cancers that are greater than 5 cm.

Figure 74.20 Locally advanced breast cancer. The breast is lifted and the upper half is bulging because of the large tumor. Distortion in the inferolateral contour is evident. The medial skin changes are caused by dermal tumor satellites.

Approximately 5% of patients with newly diagnosed breast cancer will present with stage IV disease, and up to 30% of patients who present with early stage breast cancer at diagnosis will develop distant metastatic disease.[249] The approach to patients with metastatic breast cancer is focused on prolonging survival and improving quality of life by minimizing cancer-related symptoms. As such the treatments plans for these patients are highly individualized.

For patients with hormone receptor-positive, HER2-negative disease, the preference is for endocrine therapy alone. However for patients with rapidly progressing disease, endocrine-resistant disease, or a large tumor burden involving visceral organs, chemotherapy should be considered.[250,251] For patients with $HER2^+$ disease, HER2-directed therapies should be administered along with chemotherapy. For patients with TNBCs, chemotherapy is the only option for treatment of metastatic disease.

When chemotherapy is indicated, the preference is for sequential single agent therapy, which includes taxanes and anthracyclines. Other options, especially for patients with bone-predominant ER^+ metastatic disease that have failed two trials of endocrine therapy, include capecitabine, which is derived from the antimetabolite fluorouracil. Capecitabine also may be indicated for metastatic disease to the brain as it appears to cross the blood–brain barrier.[252–254] Other agents include eribulin, gemcitabine, ixabepilone, etoposide, and platinum agents.

Although combination chemotherapy conveys a higher risk of toxicity, its use is indicated when tumor burden is large or when patients have significant symptomatic disease. This includes anthracycline-containing regimens, nonanthracycline taxane-based regimens, and combination regimens incorporating platinum salts. It is important to note that no prospective study has shown that combination chemotherapy improves overall survival compared with single-agent sequential chemotherapy.

For women with metastatic breast cancer, data exist that extending chemotherapy duration is associated with improved progression-free and overall survival. However, prolonged chemotherapy can be associated with more serious toxicities such as neutropenia and neuropathy.[255,256] As such, an individualized approach should be undertaken weighing tumor response against side effects. During treatment for metastatic disease, the patient needs to be monitored for treatment failure, which includes clinical deterioration during treatment, evidence of new metastatic disease, and increasing size of previously documented metastatic lesions.

Table 74.12 Recommendations for Adjuvant Therapy

Patient Group	Recommended Treatment
Node Negative, Low Risk	
Tumor <0.5 cm	No treatment or endocrine therapy if ER+
1–2 cm, grade 1, ER+	
Special histologic types	
Node Negative, Higher Risk	
ER+	Endocrine therapy OR chemotherapy + endocrine therapy
ER–	Chemotherapy
Any HER2+	Add trastuzumab to chemotherapy
Node Positive	
ER+	
Premenopausal	Chemotherapy + endocrine therapy
Postmenopausal	Chemotherapy + endocrine therapy OR endocrine therapy alone
ER–	Chemotherapy
Any HER2+	Add trastuzumab to chemotherapy

ER+, estrogen receptor positive; ER–, estrogen receptor negative.

The recommendations for adjuvant therapy are summarized in Table 74.12.

Surgical Therapy

Partial Mastectomy

Breast conservation therapy (BCT) consists of breast-conserving surgery (partial mastectomy) followed by radiation therapy (RT) (Fig. 74.21). The use of BCT is supported by six prospective randomized clinical trials demonstrating that partial mastectomy plus radiation therapy offers equivalent survival to mastectomy with a low rate of local recurrence

(Table 74.13).[257–265] The local recurrence rate with BCT is 5% to 22% versus 4% to 14% with mastectomy. Of note, most recurrences after mastectomy occur within the first 3 years, but recurrences after BCT tend to occur later.[266–268] Factors that increase local recurrence rate following partial mastectomy include young age, lymph node involvement, ER^- disease, and absence of radiation therapy.[269] The American College of Surgeons, the American College of Radiology, the College of American Pathologists, and the Society of Surgical Oncology have developed consensus standards of care for BCT.[270] Most patients can be offered BCT except for those with (1) multicentric disease, (2) diffuse suspicious microcalcifications on mammography, (3) a history of radiation therapy that includes a portion of the affected breast such that when combined with the current proposed treatment would result in an excessively high total radiation dose to the chest wall, (4) pregnancy (although if in the third trimester, partial mastectomy can be performed with planned breast irradiation deferred postpartum), (5) IBC, and (6) persistently positive margins after multiple attempts at breast-conserving surgery (Table 74.14).

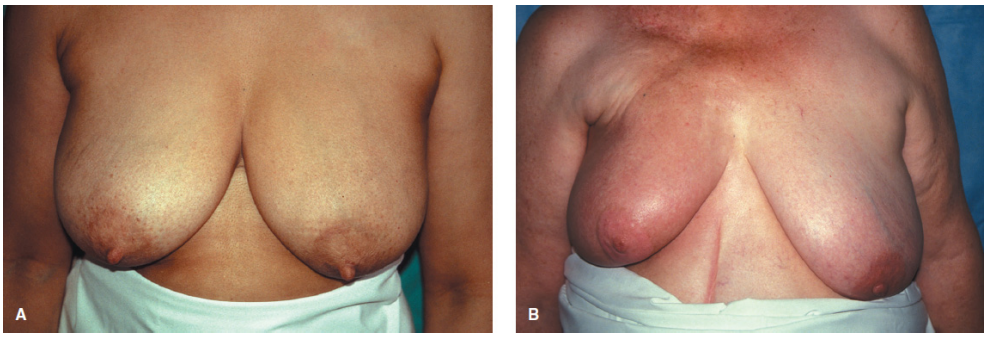

Figure 74.21 Cosmetic outcome after breast-conserving therapy with radiation. **A:** Excellent cosmetic outcome. The treated breast (**left**) is identical to the untreated breast. **B:** Fair cosmetic outcome. Significant shrinkage and loss of ptosis is evident in the treated right breast.

Table 74.13 Survival in Prospective Randomized Trials Comparing Breast-Conserving Therapy with Mastectomy

		Overall Survival		Local Recurrence	
Trial	Follow-Up (Yrs)	BCT (%)	Mastectomy (%)	BCT (%)	Mastectomy (%)
Institut Gustave-Roussy[264]	15	73	65	9	14
Milan I[259]	20	42	41	7	2
NSABP B-06[258]	20	46	47	14	10
NCI[263]	20	54	58	31	6
EORTC[261]	10	65	66	20	12
Danish[265]	6	79	82	3	4

BCT, breast-conserving therapy; EORTC, European Organization for Research and Treatment of Cancer; NCI, National Cancer Institute; NSABP, National Surgical Adjuvant Breast and Bowel Project.

The operative approach for a partial mastectomy is very similar to an excisional biopsy and is sometimes referred to as a wide excision, lumpectomy, or segmental mastectomy. The considerations for placement of the incision are similar to those for excisional biopsy, however it is best to keep the incision within the boundaries of a potential mastectomy incision, and the incision should be made directly over the lesion rather than at the wire insertion site to minimize tunneling. As negative margins are associated with lower rates of recurrence, many techniques have been developed to ensure negative margins at the time of the initial surgery. One common 8 technique is to remove the breast cancer with surrounding normal tissue, and then obtain additional shave margins. Each shave margin is labeled and oriented in relationship to the primary cancer.[271–276] Approaches to evaluate intraoperative margin status include frozen section, cytologic touch prep analysis, and intraoperative ultrasound. However, no method has proven superior and there is no established standard of care. In patients undergoing breast-conserving surgery, it is important to discuss the potential need for re-excision. A histologically positive margin is defined as a margin that has tumor present at the inked margin. Patients with a positive margin have at least a twofold increase in ipsilateral local breast cancer recurrence. As such, controversy has centered on the optimal amount of normal tissue that should be excised around the cancer to minimize local recurrence risk. A recent 9 multidisciplinary consensus panel supports the use of "tumor at

ink" as the criteria for positive margin/re-excision based on a meta-analysis that included 33 studies with 28,162 patients and 1,506 ipsilateral recurrences.[277] Like most other institutions, we have adopted this new definition of a positive margin for invasive breast cancers to guide decisions about reexcision. However, given the concern for gaps between lesions or skip lesions in DCIS, we continue to define a negative margin for this pathology as ≥2 mm, understanding that this practice may evolve pending more study results.

Axillary Lymph Node Dissection

Until recently, axillary lymph node dissection (ALND) was performed in all newly diagnosed breast cancer patients to facilitate staging, medical decision making and minimize locoregional recurrence. More recently, SLNB has replaced ALND for axillary staging, and the therapeutic impact of ALND may be limited to specific subsets of breast cancer patients. In the American College of Surgeons Oncology Group Z0011 trial, eligible patients had T1–T2 invasive breast cancers, no palpable adenopathy, and 1 to 2 SLNs containing metastases identified by frozen section, touch preparation, or H&E staining. Patients were randomized to undergo ALND or no further axillary treatment. Systemic therapy was at the discretion of the treating physician. Patients ineligible for the trial included those with matted lymph nodes, ≥3 positive nodes, gross extranodal disease, and those treated with neoadjuvant therapy.[278] After 6 years of follow-up, SLNB alone was not inferior to ALND in patients with limited sentinel lymph node involvement treated with BCT. Of note, these findings have been compared with those of the NSABP B04 trial that was conducted over a decade ago, which randomized women with clinically negative nodes to treatment with radical mastectomy, total mastectomy plus axillary radiation, or total mastectomy with delayed ALND if nodal recurrences were observed. No statistically significant survival differences were observed between any of the groups initially, or at any of the analyses up to 25 years of follow-up.[232] These studies suggest that for contemporary women, ALND may not provide a survival benefit in patients who are clinically node-negative. Currently, ALND is limited to patients with positive sentinel lymph nodes who do not meet Z0011 criteria, those with a contraindication to SLNB such as pregnant

women, those with clinically palpable pathologic lymph nodes, and patients with IBC.

INDICATIONS/CONTRAINDICATIONS

Table 74.14 Contraindications to Breast-Conserving Therapy in Invasive Carcinoma

Absolute Contraindications

- Two or more primary tumors in separate quadrants of the breast
- Persistent positive margins after reasonable surgical attempts
- Pregnancy is an absolute contraindication to the use of breast irradiation. When cancer is diagnosed in the third trimester, it may be possible to perform breast-conserving surgery and treat the patient with irradiation after delivery
- A history of prior therapeutic irradiation to the breast region that would result in retreatment to an excessively high radiation dose
- Diffuse malignant-appearing microcalcifications

Relative Contraindications

- A history of scleroderma or active systemic lupus erythematosus
- Large tumor in a small breast that would result in cosmesis unacceptable to the patient. In this circumstance, preoperative chemotherapy should be considered.
- Very large or pendulous breasts if reproducibility of patient setup and adequate dose homogeneity cannot be ensured

The boundaries of an ALND are the axillary vein superiorly, the serratus anterior muscle and long thoracic nerve medially, and the latissimus dorsi muscle and thoracodorsal nerve laterally. Contemporary axillary dissection in breast cancer involves removal of the level 1 and 2 lymph nodes (Fig. 74.22).[279] Level 3 nodes are palpated and only in the presence of gross disease is dissection performed, as removal of these nodes greatly increase the risk of lymphedema and are rarely (<1%) involved in the absence of level 1 and 2 disease.[280,281] Typically, a yield of ≥10 axillary lymph nodes is achieved with ALND.

The procedure is performed under a general anesthetic that does not include a muscle relaxant as identification of the long thoracic and thoracodorsal nerves are critical to the dissection. Preoperative antibiotics and deep venous thrombosis prophylaxis with sequential compression devices are employed. The patient is placed in the supine position with the ipsilateral arm abducted ≤90 degrees. Use of a stockinette allows for mobilization of the arm during dissection. If the ALND is performed through a mastectomy incision (modified radical mastectomy), no additional incisions are required. Also, for partial mastectomies performed in the upper outer quadrant, the partial mastectomy incision can be extended to the axilla. For palpable nodes that close to, or have eroded the skin, it is important to take the overlying skin during the dissection.

For an ALND performed during a partial mastectomy or as a separate procedure, a curvilinear skin incision is made 1 to 2 cm below the hair-bearing area of the axilla, following Langer lines from the border of the pectoralis major muscle to the latissimus dorsi muscle. Although flaps can be developed superiorly, inferiorly, laterally, and medially, most surgeons find that this is not necessary. Once the skin incision is made, the lateral edge of the pectoralis major muscle (PM) is palpated and the PM fascia is then opened with electrocautery. The lateral edge of the PM is then retracted medially to expose the pectoralis minor muscle (PMi), with care to avoid injury to the medial pectoral nerve, which innervates both the PM and the PMi. The tissue at the border of the PMi is then incised with care to avoid injury to the axillary vein or brachial plexus superiorly. If the arm is in a stockinette, it should be flexed medially and anteriorly to relax the PMi. The PM and PMi are then retracted and using blunt dissection, the axillary vein at the medial extent of the dissection can be identified. Further blunt dissection can be performed just below the medial aspect of the axillary vein and just lateral to the chest wall to identify the long thoracic nerve. The long thoracic nerve can also be palpated along the chest wall and once it is identified, the nerve is dissected free of surrounding tissue inferiorly to the insertion. To avoid injury, the fascial layer on the serratus anterior muscle which holds the nerve in place should not be opened. Attention is now turned to identification of the thoracodorsal nerve. Dissection is initiated mid-axilla just inferior to the axillary vein. Anterior to the bundle is often the thoracoepigastric vein, which is a large superficial venous tributary arising from the axillary vein.

Although the thoracoepigastric vein may need to be transected to allow for completion of the dissection, it is important to first identify the thoracodorsal nerve. The axillary fat pad/contents can then be dissected away from the thoracodorsal bundle using blunt dissection from superiorly to inferiorly with a long fine tonsil clamp. Once the long thoracic and thoracodorsal nerves are identified and dissected free of surrounding tissue, the axillary contents can be mobilized and removed. Of note, there are usually three to five intercostobrachial nerves that supply sensation to the medial-posterior aspect of the arm and run medial to lateral in the field of dissection. An attempt should be made to spare these nerves but only if they do not directly interfere with the dissection. The axillary contents are retracted inferiorly, and using electrocautery or sharp dissection, it is freed from the teres major posteriorly. The axillary contents are then sent en bloc to the pathologist. The wound is suction irrigated with sterile saline and hemostasis is achieved. A single 19 French round Blake drain can be placed above or below the bra line. However, some surgeons do not place drains for ALNDs, as in the absence of an associated mastectomy, the drainage is often scant. The skin is closed with interrupted 3-0 vicryl sutures and a 4-0 subcuticular stitch. If a drain is placed, it is removed when drainage is less than 30 mL per 24 hours. No antibiotic prophylaxis is necessary.

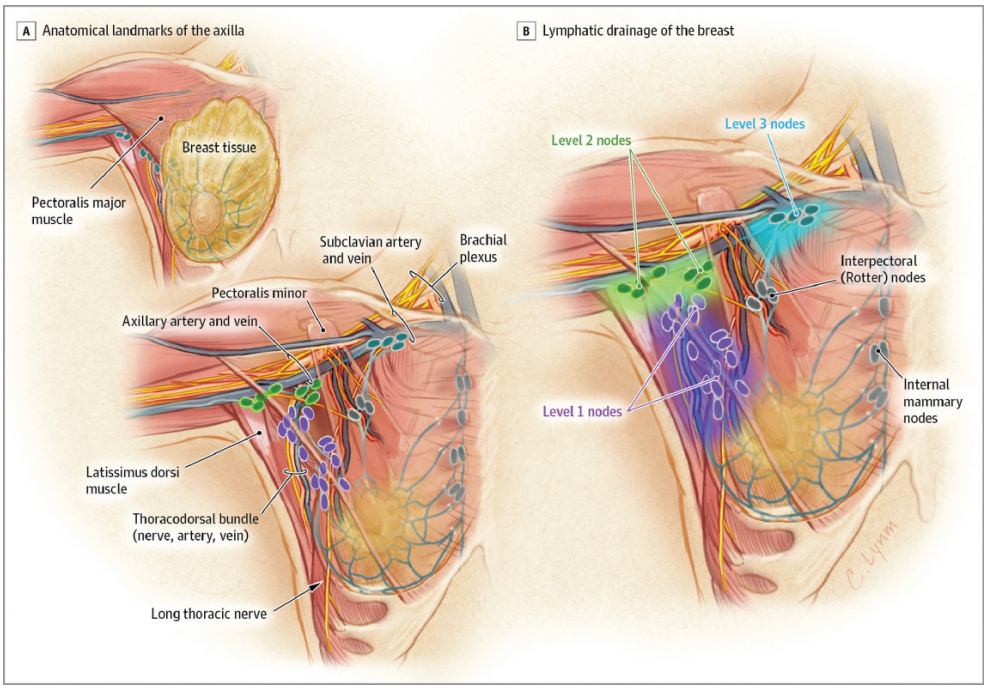

Figure 74.22 **A:** Anatomical landmarks of the axilla. The boundaries of the axillary lymph node dissection are the axillary vein superiorly, the latissimus dorsi and thoracodorsal bundle laterally, and the serratus anterior muscle and long thoracic nerve medially. **B:** Lymphatic drainage of the breast. During an axillary lymph node dissection, level 1 and 2 lymph nodes are removed.

The approach to axillary lymph node dissection described above is a medial to lateral approach with the long thoracic nerve, axillary vein, and thoracodorsal nerve identified in sequence. Alternatively, one can approach the dissection through a lateral to medial approach. With this method, once the clavipectoral fascia is incised to enter the true axilla, the anterior surface of the latissiumus dorsi is identified at the lateral extent of the axillary dissection. The clavipectoral fascia is then incised along the superior and medial aspects of the axilla. Dissection is then performed to first identify the thoracodorsal nerve, then the axillary vein superiorly, and then the long thoracic nerve medially. Once all the nerves and vascular structures are identified, the axillary contents are mobilized and removed.

Complications from ALND include motor and/or sensory nerve injury. Injury to the long thoracic nerve may result in winged scapula, whereas injury to the thoracodorsal nerve leads to weakness of internal rotation and extension, characterized by the functional inability to hold a book under the

arm. Other risks include seroma formation, infection, and lymphedema.[282–284] The risk of lymphedema is lifelong and is as high as 30%.

Simple Mastectomy

A mastectomy is performed for patients with breast cancer who are not candidates for BCT or for patients who prefer a mastectomy. For women at high risk for the development of breast cancer, it can be performed as a prophylactic procedure. The goal of mastectomy is complete removal of the breast tissue while preserving muscle function, and viable skin flaps for primary closure. Preoperatively, the patient is examined in the holding area, where the breast is marked and the correct site of surgery is confirmed. An intravenous antibiotic that covers skin flora, such as cefazolin, given before skin incision has been shown to significantly decrease the risk of infection in patients undergoing mastectomy (relative risk 0.60, 95% CI 0.45 to 0.81).[285] The patient is then placed in the supine position with the arms abducted up to 90 degrees with padding placed beneath the arms and wrist to avoid brachial nerve and radial nerve injury. The skin is then cleansed with a preparation of chlorhexidine gluconate/isopropyl alcohol or betadine solution and the patient is draped in a sterile fashion. The most common skin incision used is an elliptical incision in the horizontal (Stewart Incision) or diagonal plane (Orr Incision), although historically a vertical plane incision for high lying or infraclavicular lesions has also been used (Fig. 74.23). The medial border of this incision is 2 cm from the sternal edge and the lateral border is at the midaxillary line. The elliptical incision should include the skin directly over the tumor, especially if the tumor is superficial. Once the incision is made, a superior skin flap is developed in the relatively avascular plane between the skin and the breast parenchyma, to the level of the clavicle. The fascia of the pectoralis major muscle is then incised from the sternum to the edge of the lateral edge of the muscle with care to preserve the internal mammary perforators. The inferior flap is then developed to the level of the rectus muscle (just at or below the level of the inframammary fold). The underlying fascia is then incised from the sternum to the mid axillary line. The medial flap is then developed similarly, connecting the superior and inferior flaps, with attention to the internal mammary perforators in this area. As these vessels tend to retract, a stick tie should be used to ligate any bleeding

vessel. Unlike the other skin flaps, the lateral dissection tends to be less well defined and slightly thicker. The flap is taken down to the level of the latissimus muscle. Care should be taken to avoid the axillary contents and sensory nerves. The breast is then removed en bloc with the fascia of the pectoralis muscle by retracting the breast downward and dissecting the plane between the muscle fibers and the fascia. The wound is then irrigated with warm sterile saline, and the flaps and chest wall are then systematically inspected to ensure hemostasis. A drain is then placed to prevent seroma formation. Skin closure can be performed in different ways, such as with a 3-0 running polydioxanone suture (PDS) with a 4-0 subcuticular stitch or with interrupted 3-0 vicryl sutures with a 4-0 subcuticular stitch. Post mastectomy, the patient is admitted to the hospital overnight to ensure adequate pain control, and to monitor for acute bleeding. When drain output is less than 30 mL for two consecutive days, the drain is removed (typically between postoperative days 7 and 14). No antibiotic coverage is necessary while drains are in place. In less than 1% of cases, hematomas can occur and if small can be observed. For large or enlarging hematomas (encompassing greater than one-fourth of the chest wall), surgical exploration is required to evacuate the hematoma and stop any sources of bleeding. Other complications associated with mastectomy include skin flap necrosis, pneumothorax, cellulitis, neuropraxia, and lymphedema.

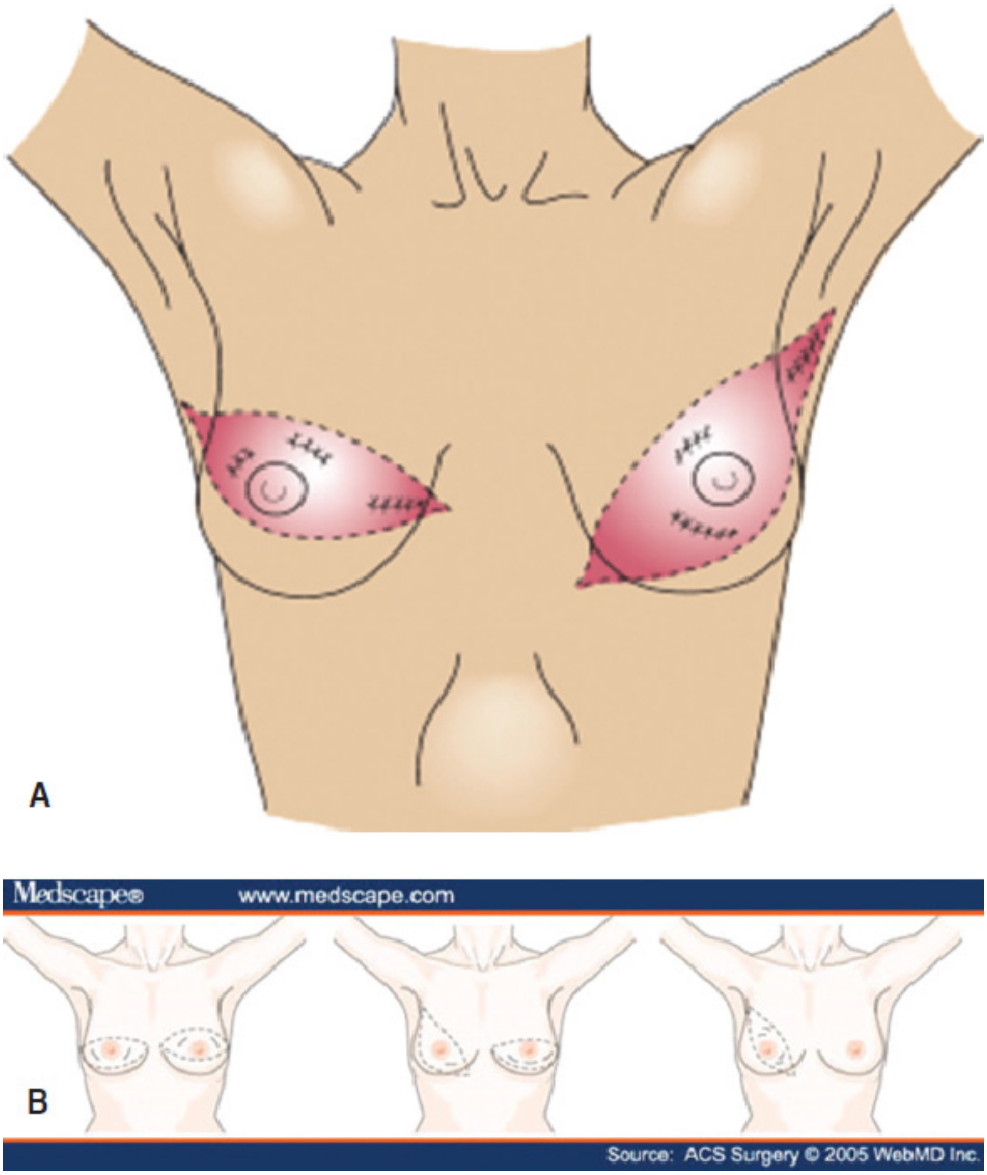

Figure 74.23 Incision placement for modified radical mastectomy. The incision should include the nipple–areola complex, biopsy scar, and excess skin of the breast.

If immediate reconstruction is planned, a *skin-sparing* incision is made, which often consists of making either a smaller horizontal ellipse around the nipple–areola complex, a circular incision just encompassing the nipple–areola complex, or a lollipop incision (Fig. 74.24). In some circumstances, the patient may be a candidate for a *nipple-sparing mastectomy* if her breasts are small to moderate in size, often no larger than a C cup, with minimal ptosis, and the breast cancer is at least 2 cm from the nipple. Tumor size, histology, or lymph node status are no longer considered exclusion

criteria for nipple-sparing mastectomy, and current exclusion criteria include clinical involvement of the nipple areolar complex, PDB, bloody nipple discharge, multicentric disease[286] and/or inflammatory carcinoma.[287] Nipple-sparing mastectomies are often performed through an inframammary fold incision or a radial lateral incision. More recently, a lateral vertical incision has been described. This incision is associated with a significant reduction in hypertrophic scar formation versus the radial lateral incision.[288] Intraoperatively, a biopsy of the retroareolar margin is performed and must be histologically negative 10 for malignancy. BRCA mutation carriers are also candidates for nipple-sparing mastectomies. In a study of 26 patients with BRCA mutations undergoing prophylactic mastectomies, DCIS was identified in one patient compared with two cases of DCIS in the matched control group. There were no locoregional recurrences in the patients with BRCA mutations at 37 months of follow-up.[289] These findings support that nipple-sparing options are reasonable for patients with BRCA mutations.

Although the goal of a mastectomy is to completely remove the breast cancer and normal breast tissue, local recurrence remains a risk. The risk of local recurrence is 6% at 5 years in patients with no lymph node involvement, and 16% at 5 years in patients with one to three lymph nodes involved. With the addition of radiation therapy the risk of local recurrence decreases to 2%. When four or more lymph nodes are involved, the risk of recurrence is 26% at 5 years, decreasing to 6% with the addition of radiation therapy.[290]

In women with a personal history of breast cancer, the absolute risk of contralateral breast cancer is estimated to be 0.5% to 1.0% per year or 5% to 10% during the 10 years following diagnosis.[291] As such, most women will not develop a contralateral breast cancer. As no randomized clinical trials have been performed, it is not known if contralateral prophylactic mastectomy (CPM) is associated with a survival benefit in women with a personal history of breast cancer. However, a survival benefit for CPM has been shown for patients with a deleterious *BRCA1* or *BRCA2* mutation.[292–295] The decision to perform a CPM must be individualized with each individual patient. Of note, a twofold increased risk of major complications exists with CPM when compared with unilateral mastectomy.[296,297]

Breast Reconstruction

All patients undergoing mastectomy should be offered consultation with a plastic surgeon for consideration of breast reconstruction, recognizing that some women may choose to forego this procedure and prefer the use of breast prosthesis. The two main types of breast reconstruction include implant-based and autologous tissue breast reconstruction. Implants include silicone or saline implants. Autologous tissue techniques used for breast reconstruction often include either the transverse rectus abdominus myocutaneous (TRAM) flap or the deep inferior epigastric perforator (DIEP) flap.

Breast reconstruction can be performed immediately after a mastectomy procedure (immediate reconstruction) or at a later time (delayed reconstruction). For implant-based breast reconstruction, the most common technique involves a two-stage method with placement of a tissue expander under the pectoralis major muscle at the time of the mastectomy (Fig. 74.25). The tissue expander can then be filled incrementally with saline with the first fill typically occurring 1 to 3 weeks postoperatively with additional fills every 1 to 2 weeks until the desired expansion is achieved. The tissue expander is then left in place for several months to allow for maximal skin remodeling. During the second stage, the tissue expander is removed and is replaced with a silicone or saline implant. This two-stage reconstruction method is particularly beneficial for women who will need adjuvant radiation therapy as radiation can result in flap necrosis, fibrosis and shrinkage resulting in poor cosmetic outcomes after immediate implant and/or tissue flap reconstruction. Instead, the tissue expander allows for skin preservation and the ability to then proceed with either an implant or autologous reconstruction at a later date. The complications associated with tissue expander placement include infection requiring removal. This occurs at a rate of 1.2%, but may be higher in women being treated with chemotherapy and/or radiation therapy.[298]

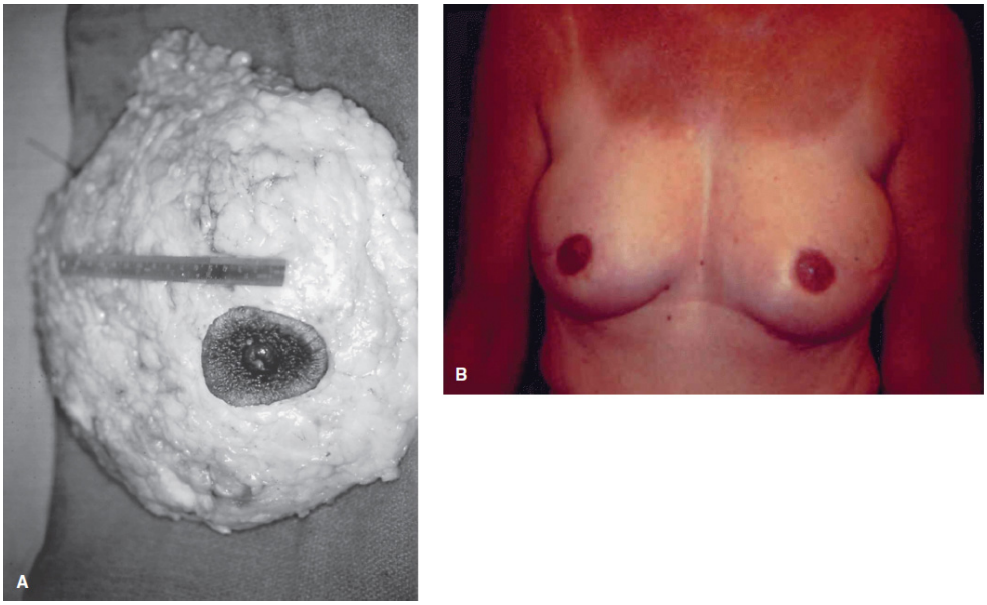

Figure 74.24 Skin-sparing mastectomy. **A:** The only skin removed was the nipple–areola complex. **B:** Cosmetic outcome after bilateral skin-sparing mastectomy and transverse rectus abdominis myocutaneous (TRAM) flap reconstruction.

Figure 74.25 Breast reconstruction with tissue expanders. Although the breasts are not identical, this is not evident when a bra is worn.

Although silicone gel implants are superior to saline implants in terms of offering a more natural contour and texture, the use of silicone implants remains controversial secondary to unsubstantiated claims of a link between silicone implants and autoimmune disease first reported in 1992. Since that time, no studies have shown a causative relationship and the American College of Rheumatology and the FDA have concluded that there is no additional risk of connective tissue disease in patients with silicone implants.[299–301]

A few case reports have noted an association between breast implants (saline or silicone) and anaplastic large cell lymphoma of the breast. There have been 60 cases of ALCL reported among an estimated 5 to 10 million women with breast implants. Although a causal relationship is not proven and the potential risk is extremely low, the FDA does require breast implant manufacturers to include this finding in the product labeling.[302]

The primary benefit of autologous tissue breast reconstruction is that the reconstructed breast appears and feels more natural than following implant-based breast reconstruction. In addition, autologous tissue breast reconstruction may be the only option in patients who have undergone chest wall radiation, as skin fibrosis may preclude implant-based breast reconstruction. A common procedure is the free TRAM flap, which involves removing skin, subcutaneous fat, muscle and associated blood supply from the lower abdomen. The blood supply includes the deep inferior epigastric artery and vein, which are anastomosed to the internal mammary or thoracodorsal arteries and veins. The TRAM flap is contoured to replicate the native breast. Similar to the TRAM flap, the DIEP perforator flap uses the same lower abdominal skin and subcutaneous fat but spares the rectus abdominis muscle. In both methods, the donor site is closed as a modified abdominoplasty.

Radical Mastectomy

In 1907, Halsted presented to the American Surgical Association his results of 232 patients who underwent his radical mastectomy at Johns Hopkins. Halsted's radical mastectomy involved wide excision of skin via a teardrop incision extending across the deltopectoral groove, excision of the entire pectoralis major muscle, resection of the pectoralis minor muscle to expose the axillary contents for dissection, and excision of the supraclavicular lymph nodes. In certain cases, he also removed the mediastinal nodes. Immediate skin grafting was performed to close all of the wounds.[303] With advances in breast cancer screening, adjuvant medical therapy, and radiation therapy, a concomitant evolution toward less radical surgery has ensued. A report by the American College of Surgeons Commission on Cancer demonstrated a dramatic decline in the use of the radical mastectomy from 47.9% of breast cancer cases in 1972 to 3.4% of cases in 1981.[304] Further, the **modified**

radical mastectomy, which consists of a simple mastectomy and axillary lymph node dissection, was considered a satisfactory alternative to the radical mastectomy by 1980.[305] A randomized, prospective clinical study by W.A. Maddox in 1983 showed no significant differences in disease-free survival, overall survival, or local recurrence rates at 5 years for modified radical versus radical mastectomy. These differences are likely secondary to the routine use of chemotherapy for patients with involved axillary lymph nodes by this time period.[306] When patients are not candidates for breast conservation and SLNB, a modified radical mastectomy is indicated. Please see the section on ***Axillary Lymph Node Dissection*** above.

Radiation Therapy

The primary indication for the use of radiation therapy in breast cancer is to reduce the risk of a locoregional recurrence following surgery, and potentially improve survival by eradicating persistent locoregional disease that may be resistant to systemic therapy.

The standard approach for patients who undergo breast-conserving surgery is to deliver whole breast radiation therapy with a dose of 50 to 60 Gy. The regimen is often given in 2 Gy fractions 5 days a week for a total of 5 weeks. A 60 Gy regimen, which also includes a 10 Gy boost to the tumor bed, was found to be more effective for patients 45 years of age or younger, with a local relapse rate of 14% (60 Gy) compared to 28% (50 Gy) ($p < 0.0001$).[307] Alternative radiation therapy strategies are currently under investigation including the use of rapid fractionation schedules, such as the delivery of 41 to 42 Gy over 15 fractions, and accelerated partial breast radiation. Early results show excellent clinical outcomes.[308–310]

Although most women do not require radiation therapy following mastectomy, postmastectomy radiation therapy is often recommended for women at high risk for locoregional recurrence, including women with four or more positive lymph nodes, tumor size greater than 5 cm, or with positive surgical margins. In these instances, postmastectomy radiation can reduce the rate of chest wall recurrence by 65% to 75%.[311–315]

Of note, optimal locoregional management of the axilla remains to be defined. Both surgery and radiation therapy can be used to treat disease in the axilla. Previously, ALND was the preferred treatment modality for

prevention or treatment of axillary disease. More recent studies suggest that radiation therapy may be equally effective with less morbidity. The EORTC 11 AMAROS trial randomized patients with clinical T1–T2 N0 breast cancer to ALND or radiation therapy to the axilla after a positive SLNB.[316] The two arms had comparable axillary control, but patients in the radiation therapy arm had significantly less morbidity. At 5 years 23% of patients in the ALND arm had lymphedema compared to 11% in the radiation therapy arm. Currently, in patients with clinical T1–T2 N0 disease who undergo mastectomy with a positive SLNB, ALND is the standard approach as these patients were not included in the Z0011 study. However, findings from the AMAROS trial suggest that in this group of patients, radiation therapy may provide similar locoregional control with less morbidity.

Chemotherapy

The role of medical therapy is to eradicate breast cancer cells at the primary tumor site, or at any other site in the body. Systemic therapies include but are not limited to chemotherapy, endocrine therapy, and targeted therapy.

The decision as to whether or not to treat breast cancer patients with chemotherapy is complex. Considerations include patient age, menopausal status, AJCC TNM stage, histologic grade, biomarker profile, proliferation index, and medical comorbidities. Fortunately, online calculators exist to estimate the risks and benefits of chemotherapy and other adjuvant therapies. Adjuvant! Online is a popular risk–benefit calculator that is based on population-wide data that focuses on recurrence risk and probability of survival. This is a web-based program that is generated from collective data from the Surveillance, Epidemiology, and End Results (SEER) database, the Early Breast Cancer Trialists Collaborative Group (EBCTCG), individual clinical trial results, and published literature.[317] Other calculators include Cancermath.net[318] and FinProg project.[319] Molecular profiling using Oncotype DX or similar molecular assay can be used for patients with node-negative $ER^+/HER2^-$ breast cancers. For Oncotype DX a score of ≥31 is associated increased risk of recurrence with a recommendation for administration of chemotherapy.

Adjuvant chemotherapy is often initiated 4 to 6 weeks after surgery. Although treatment earlier is not beneficial, a delay of greater than 12 weeks

may be detrimental. If adjuvant radiation therapy is indicated, it is administered starting 3 to 4 weeks after completion of chemotherapy.

Anthracyclines (doxorubicin, daunorubicin, epirubicin)

These compounds are derived from *Streptomyces* bacteria and function by inhibiting DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand, blocking DNA transcription and replication by inhibiting topoisomerase II enzyme, generating free oxygen radicals, and by inducing histone eviction form chromatin. The main adverse effect is cardiotoxicity.

Taxanes (paclitaxel, docetaxel)

These compounds are derived from plants of the genus *Taxus* (yews) and function by disrupting microtubule formation and inhibiting mitosis. The main adverse effect is peripheral neuropathy. Given that these compounds are not water soluble, allergic reactions to the diluent may result.

Cyclophosphamide

This compound is a nitrogen mustard alkylating agent that functions by adding an alkyl group to the guanine base of DNA, resulting in intrastrand and interstrand DNA crosslinks and therefore interferes with DNA replication. The main adverse effects include acute myeloid leukemia, bladder cancer, hemorrhagic cystitis, and infertility.

5-Fluorouracil

This compound is an antimetabolite that works as an irreversible inhibitor of thymidylate synthase and therefore interferes with DNA synthesis. The main adverse effect is mucositis.

Methotrexate

This compound is both an antimetabolite and an antifolate that blocks dihydrofolate reductase and therefore inhibits the synthesis of folic acid, which is essential for DNA, RNA, thymidylate, and protein synthesis. The main adverse effect is ulcerative stomatitis.

Platinum Agents (carboplatin or cisplatin)

These compounds bind to and cause crosslinks in DNA, triggering apoptosis. The main adverse effect is nephrotoxicity, neurotoxity, and ototoxicity.

Endocrine Therapy

Patients with all stages of breast cancer that express the estrogen receptor or progesterone receptor are candidates for endocrine therapy. In the premenopausal setting, the focus is on blocking ovarian function and the effects of estrogen. In postmenopausal women, the ovaries are no longer the predominant source of estrogen, but instead estrogen is synthesized mainly from nonglandular sources such as subcutaneous fat. As such, blocking estrogen production is very effective in the postmenopausal population.

Blocking Ovarian Function (leuprolide, goserelin, buserelin)

As the ovaries are the main source of estrogens in premenopausal women, ovarian ablation can be achieved either surgically by removal of the ovaries or through medical therapy with luteinizing hormone–releasing hormone (LHRH) agonists such as goserelin or leuprolide. These compounds function by binding to the gonadotropin-releasing hormone (GnRH) receptor, resulting in initial FSH and LH release. However, with prolonged drug exposure, desensitization of the pituitary occurs whereby the levels of LH and FSH become profoundly suppressed. This results in inhibition of the growth of ovarian follicles and steroidogenesis.

Blocking Estrogen at the Receptor (tamoxifen, raloxifene, fulvestrant)

As SERMs, tamoxifen and raloxifene competitively bind to the estrogen receptor and prevent estrogen from binding. As a selective estrogen receptor down-regulator (SERD), fulvestrant binds to the estrogen receptor and targets it for destruction. Fulvestrant is used only in postmenopausal women who have hormone receptor-positive metastatic disease who experience progression following endocrine therapy.

Blocking Estrogen Production (anastrozole, letrozole, exemestane)

The enzyme aromatase converts androgenic substrates to estrogen, and therefore its inhibition can effectively decrease plasma levels of estrogen. Nonsteroidal aromatase inhibitors include anastrozole and letrozole, whose binding activity can be reversed. Exemestane is a steroidal aromatase inhibitor that irreversibly binds aromatase and permanently inactivates it.

Targeted Therapy

Targeted Therapy for HER2+ Breast Cancers

Amplification or overexpression of the human epidermal growth factor receptor 2 (HER2) is present in approximately 20% of primary breast cancers. Given that effective targeted therapies exist for these patients, all newly diagnosed breast cancers are routinely tested for HER2 expression/amplification.

Trastuzumab is a monoclonal antibody that targets $HER2^+$ breast cancers by multiple mechanisms including (1) interfering with the homo- and heterodimerization of HER2 and inhibiting mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K/Akt) signaling pathways, (2) immune-mediated killing of tumors that overexpress HER2 by a mechanism referred to as antibody-dependent cellular cytotoxity (ADCC), and (3) triggering HER2 internalization and degradation through promoting the activity of tyrosine kinase-ubiquitin ligase c-Cbl.

Pertuzumab is a monoclonal antibody that interferes with the dimerization of HER2 to HER3, therefore interfering with MAPK and PI3K pathway activation. It also induces ADCC.

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that consists of trastuzumab linked with the cytotoxic agent mertansine (DM1). While trastuzumab binds to the HER2 receptor, mertansine enters the cell and destroys it by binding to tubulin. This allows toxin to be targeted specifically to the cancer cell.

Targeted Therapy for Triple Negative Breast Cancers (experimental options)

Although patients with TNBC often have an excellent response to chemotherapy, overall outcomes are worse compared to patients with ER^+ and/or $HER2^+$ disease.[231,320,321] The lack of effective targeted therapies for TNBC likely contributes to this disparity in outcome. Drugs targeting TNBCs are in clinical trials and include inhibitors targeted to the epidermal growth factor receptor (cetuximab), angiogenisis (bevacizumab), DNA damage or poly adenosine diphosphate-ribose polymerase (olaparib, veliparib, iniparib), the proto-oncogene Src (dasatinib), and histone deacetylase (vorinostat). Given the heterogeneity of TNBC, multi-targeted therapy will likely be needed to eradicate this disease.

Special Issues in Breast Cancer Treatment

Inflammatory Breast Cancer

A common clinical presentation for IBC is *peau d'orange*, characterized by edema, warmth, and erythema. Unlike other types of breast cancer, patients with IBC often have associated pain and tenderness with an enlarged and firm breast. The nipple can also be involved with flattening, erythema, crusting, blistering, and retraction. Despite the reference to inflammation, the skin changes are not secondary to an inflammatory process but rather secondary to tumor emboli within the dermal lymphatics.[322] As noted by Sir Charles Bell in 1812, these cancers tend to be much more aggressive —"when a purple color is on the skin over the tumor accompanied by shooting pains, it is a very unpropitious beginning."[323] By 1924, Lee and Tannenbaum described 28 cases of women presenting with a rare, rapidly progressive breast cancer with inflammatory features and introduced the term "inflammatory breast cancer."[324]

IBC is an aggressive form of LABC that affects approximately 1% to 5% of women with breast cancer.[325] It is designated as primary tumor stage T4d. The consensus-based criteria for the diagnosis of IBC was determined by an international expert panel who proposed the following features: (1) rapid onset of breast erythema, edema, and/or *peau d'orange*, and/or warm breast,

with or without an underlying palpable mass, (2) duration of history no more than 6 months, (3) erythema occupying at least one-third of the breast, and (4) pathologic confirmation of invasive carcinoma.[326] Furthermore, although dermal lymphatic involvement supports the diagnosis of IBC, which can be obtained with a full-thickness skin punch biopsy, it is neither necessary nor sufficient in the absence of the classical clinical findings. The diagnosis of IBC is made with clinical exam findings, followed by breast imaging, which includes mammography and ultrasound to help detect sites within the breast that can be biopsied to confirm the breast cancer. To determine extent of disease, we routinely obtain a breast MRI. A skin punch biopsy can then be performed but is not required for diagnosis. As IBC is a clinically and pathologically distinct form of LABC that is particularly fast growing, invasive, and angiogenic, nearly all women have lymph node involvement at the time of presentation and approximately a third of patients will have distant metastases.[327,328] As such, all women with IBC need to undergo complete staging including a chest/abdomen/pelvic CT scan and bone scan. Head CT should be considered if symptoms are present.

The treatment for IBC is based on multimodality treatments, similar to those described for women with LABC. However, BCT, SLN biopsy, and immediate breast reconstruction are generally considered inappropriate for patients with IBC. Treatment often consists of neoadjuvant chemotherapy that is anthracycline- and taxane-based until all signs of skin inflammation have resolved and the breast and axillary masses are deemed operable. Surgical management with a modified radical mastectomy is then performed with delayed breast reconstruction, if appropriate. Adjuvant radiation therapy follows using standard fields determined by CT planning, ensuring that the chest wall, supraclavicular, infraclavicular, and the internal mammary lymph nodes are radiated.[326] Radiation therapy to the axillary bed after axillary dissection is often individualized. However, if the patient still remains inoperable after neoadjuvant chemotherapy, then radiation therapy ensues, with the goal that the patient will thereafter become operable. For ER^+ IBC, adjuvant endocrine therapy is given. For $HER2^+$ IBC, trastuzumab (+/– pertuzumab) is added to the neoadjuvant regimen and adjuvant trastuzumab is given to complete 1 year of treatment.

Currently there is no optimal systemic regimen (chemotherapy or targeted therapy) identified for IBC. However, patients who obtain a complete

pathologic response from chemotherapy have a significantly higher disease-free survival and overall survival.[329,330] Despite the combination of surgery and radiation therapy improving locoregional control, there is no impact on overall survival.[331] Even with multimodality treatments, the prognosis for patients with IBC remains poor with 5-year disease-free survival rates of 20% to 45% and an overall survival of 30% to 70%.[329,331–334]

Breast Cancer in the Elderly

In the United States, approximately half of newly diagnosed breast cancers are in older women, typically defined as age ≥65 years. Older patients tend to receive less than standard therapy worldwide,[335–338] with decreased rates of surgery and use of adjuvant radiation therapy, but with increased use of primary endocrine therapy.[339] This may be secondary to more indolent tumors present in elderly women versus younger women.[340] However after controlling for confounding factors such as comorbidity, social support, and functional status, older women are still treated less aggressively than their younger counterparts. In general, treatment approaches should not be altered for medically fit older women, except for the use of SLNB and/or radiation therapy in early ER^+ disease.

The ability to omit axillary surgery without an adverse effect on outcome in older women (age ≥70 years) with favorable breast cancers has been well studied and supported by multiple randomized trials. These women had clinically negative axillary examinations, small (<2 cm) ER^+ breast cancers, and were all treated with adjuvant endocrine therapy.[341–343]

The ability to omit adjuvant radiation therapy in older women who have undergone partial mastectomy for early ER^+ breast cancer is supported by CALGB 9343. This phase III study involved 636 women (age ≥70 years) who had T1N0M0 ER^+ breast cancer who were treated with partial mastectomy and then randomly assigned to either receive radiation therapy plus tamoxifen (317 women) or tamoxifen alone (319 women). The primary end points studied included time to local or regional recurrence, frequency of mastectomy, breast cancer-specific survival, time to distant metastasis, and overall survival (OS). At 10 years, 98% of patients receiving radiation therapy plus tamoxifen compared with 90% of those receiving tamoxifen alone were free from local and regional recurrences. However, there were

no significant differences in time to mastectomy, time to distant metastasis, breast cancer-specific survival, or OS between the two groups. Ten-year OS was 67% (95% CI, 62% to 72%) and 66% (95% CI, 61% to 71%), respectively.[344] This led to breast-conserving surgery and endocrine therapy alone being incorporated as a category I recommendation in the current consensus guidelines for older women.

For older women with comorbidities, functional status limitation, or frailty, the Comprehensive Geriatric Assessment (CGA) can serve as an objective measure to aid in treatment decisions. The CGA has been used in elderly cancer patients including those with breast cancer and range from 44 to 84 questions. The ELCAPA study looked at how the CGA could alter an initial treatment plan in 375 patients aged 70 years and older. Treatment plans were modified in 20.8% of cases, with most plans changed to decrease treatment intensity, although there were some regimens (10.8%) that were intensified.[345] Given how extensive the full CGA can be, other screening tools that have been developed include the Vulnerable Elders Survey-13, Barber Questionnaire, Geriatric 8, Cardiovascular Health Study, and the abbreviated CGA.

For medically frail patients, surgical management followed by observation is commonly offered, especially if a patient's life expectancy is limited. If surgical intervention is not an option, endocrine therapy can be offered to patients with ER^+ disease and single agent chemotherapy for those with ER^- disease. In the presence of $HER2^+$ disease, single agent HER2-directed therapy or its addition to systemic therapy can be prescribed, understanding that the latter approach carries additive risks of toxicity. Radiation therapy is not recommended unless local control of disease is needed for symptom management. Lastly, palliative and supportive care services need to be offered to patients who wish to avoid both surgical and systemic therapies.

Breast Cancer during Pregnancy

Gestational breast cancer is a rare disease affecting approximately 1 in 1,000 pregnancies, but may become more common as women delay childbearing.[346–349] It is defined as breast cancer that is diagnosed during pregnancy, within the first postpartum year, or anytime during lactation. Similar to nonpregnant women, women with gestational breast cancer present

most often with a breast mass or skin thickening. Any mass that persists for greater than 2 weeks needs diagnostic imaging and possible biopsy.

The breast becomes engorged and hypertrophied during pregnancy making imaging more difficult. When women present with a mass in pregnancy, ultrasound is first obtained, which can differentiate between a simple cyst, a complex cyst, or a solid tumor. The majority of gestational breast cancers present as a focal solid mass.[350,351] In the presence of an abnormal ultrasound, a diagnostic mammogram can then be obtained to further determine the extent of disease and has been shown to be safe in pregnancy as long as abdominal shielding is used.[352] Although MRI with gadolinium has been shown to be more sensitive than mammography for detecting invasive breast cancer, gadolinium is contraindicated in pregnancy. MRI has also not been systemically studied for the evaluation of breast masses in pregnancy or lactation. All suspicious masses must be biopsied, even in the presence of normal imaging studies, through core needle biopsy, incisional biopsy, or excisional biopsy. In a patient who has a concerning axillary exam, FNA biopsy is indicated.

The most common histologic type of gestational breast cancer is IDCs that are poorly differentiated and diagnosed at an advanced stage. Compared to nonpregnant women, women with gestational breast cancers have less hormone receptor-positive breast cancers (approximately 25% vs. 55% to 60%).[353,354] The association between HER2 disease and gestational breast cancer is not currently known. For pregnant or lactating women with locally advanced disease, staging evaluation is necessary. Given the large cumulative radiation dose that can be associated with CT scans and the contraindication for gadolinium use (therefore limiting the utility of MRI) in pregnancy, staging imaging for pregnant women commonly include a chest x-ray, an abdominal ultrasound of the liver, and a “low-dose” bone scan or a skeletal MRI.

For women diagnosed with breast cancer at an early gestational age, pregnancy termination is an option. However, studies have not shown better outcomes with early termination. In a study involving 176 patients, pregnancy did not directly affect the prognosis of breast cancer, instead poor survival was related to younger age (less than 40 years old) and to the large number of estrogen receptor-negative tumors (71%).[355] Multiple subsequent studies have shown that pregnancy does not have a negative impact on overall

survival.[356–358] In 2012, a meta-analysis involving 3,000 patients with gestational breast cancer who were compared to 37,100 controls, found that gestational breast cancer was associated with a higher risk of death. However, this was limited to women diagnosed in the postpartum period.[359]

The treatment for breast cancer for women diagnosed in the postpartum or lactational period does not differ from that recommended for nonpregnant patients. However, for patients receiving chemotherapy, trastuzumab, or endocrine therapy, breastfeeding is not recommended given the potential toxicity to the infant. The treatment for pregnant women does not differ significantly from established guidelines, but includes modifications to ensure the safety of the developing fetus. During any trimester of pregnancy, surgical and anesthetic risks to the fetus have been shown to be minimal.[360–363] Mastectomy can be performed and for early breast cancers, this can eliminate the need for radiation therapy as it is contraindicated in pregnancy. Typical radiation doses used for breast cancer range from 46 to 60 Gy, which has been shown to convey a first trimester fetal dose of 0.04 to 0.15 Gy or a third trimester dose as high as 2 Gy.[357,364] The threshold determined for prenatal radiation exposure for fetuses under 16 weeks of gestation is 0.10 to 0.20 Gy and after 16 weeks 0.50 to 0.70 Gy to avoid risk of congenital malformations.[365] As such breast conserving treatment (which necessitates radiation therapy) remote from delivery is not a feasible option. Otherwise the choice between breast-conserving surgery versus mastectomy can be guided by a patient's preference and the biology of the tumor.

Isosulfan blue dye is contraindicated in pregnant women, and methylene blue when used in amniocentesis has been associated with fetal complications. However, a small series of studies using methylene blue or double filtered technetium sulfur for SLNB have suggested its safety and success in pregnant women.[366–369] Given the small number of pregnant patients included in these studies, the potential risks of methylene blue and technetium sulfur to the fetus along with the potential inaccuracy of SLNB in pregnancy need to be discussed with the patient preoperatively.

The most common regimens used in gestational breast cancers are anthracycline-based, AC (doxorubicin plus cyclophosphamide) or FAC (fluorouracil plus AC). The exposure of the fetus during organogenesis or the first trimester to chemotherapy can be detrimental and conveys risks including congenital abnormalities, chromosomal abnormalities, and

miscarriage. Although chemotherapy exposure in the second and third trimesters is not associated with organogenesis, risks of intrauterine growth restriction, lower gestational age at birth, and low birth weight occurs in about half of exposed infants.[370–373] As such, chemotherapy is often initiated after the first trimester and given its association with transient neonatal myelosuppression, it should be avoided three to four weeks prior to delivery. When possible, timing of delivery is restricted to 34 or more weeks of gestation and requires confirmation of fetal lung maturity to minimize complications associated with prematurity. Given that gestational breast cancer can present as locally advanced disease, neoadjuvant chemotherapy can be first given, followed by surgery in the postpartum period, and if indicated adjuvant radiation therapy and endocrine therapy can then be initiated. For women who are diagnosed late in pregnancy or the postpartum/lactational period, prior to commencement of chemotherapy, which may impair infertility, these women should be offered consultation with a reproductive endocrinologist to discuss fertility-preserving options.

Trastuzumab is contraindicated in pregnancy given its association with oligohydramnios, which can result in fetal death, pulmonary hypoplasia, and fetal developmental abnormalities.[374,375] The use of methotrexate and endocrine therapy are also contraindicated during pregnancy. These therapies can be initiated in the postpartum period.

Given that the majority of women diagnosed with gestational breast cancers are of reproductive age, many desire additional pregnancies. In a meta-analysis of fourteen studies, 1,244 women who became pregnant following breast cancer were compared to 18,145 control patients. Pregnancy in breast cancer survivors did not convey a worse survival but suggested a protective effect. Some suggest that pregnancy may have an unknown biologic antitumor effect, although more likely this is secondary to healthier women with better prognosis choosing to reproduce over their sicker peers and therefore resulting in a bias toward improved survival. As most recurrences happen within the first two years after diagnosis and treatment, it is generally recommended that pregnant women wait 2 years before contemplating another pregnancy.

Breast Cancer in Men

Male breast cancer in the United States accounts for 0.5% to 1% of all breast cancers diagnosed annually.[376] Risk factors for male breast cancer include family history of breast cancer and genetic mutations including *BRCA1* and *BRCA2*. *BRCA2* is more commonly associated with male breast cancer and conveys a 6% lifetime absolute risk, which is an approximately 100-fold higher risk than in the general male population.[377] As such, all men diagnosed with breast cancer need genetic counseling and BRCA testing. Other genetic mutations include *PTEN* which is linked to Cowden syndrome, *TP53* which is associated with Li-Fraumeni syndrome, mismatch repair genes that are linked to hereditary nonpolyposis colorectal cancer (Lynch syndrome), and *PALB2* mutations.[378,379] Other risk factors include those that increase circulating estrogens such as hormonal therapies, hepatic dysfunction, obesity, marijuana use, and thyroid disease. It is also associated with Klinefelter syndrome, which is characterized by 47XXY genotype. These male patients have atrophic testes and gynecomastia. In addition, they have high serum concentrations of gonadotropins (follicular stimulating hormone, luteinizing hormone) and a low serum testosterone level, resulting in a high ratio of estrogen to testosterone. Those with Klinefelter syndrome have a 19.2- and 57.8-fold increase in the incidence of and mortality from breast cancer.[380] Primary testicular conditions (orchitis, undescended testes, testicular injury) are associated with an increased risk of male breast cancer as it can result in lower androgen production and therefore result in a higher than normal estrogen to androgen ratio.[381,382]

Unfortunately, men are often diagnosed with breast cancer at an advanced stage. They commonly present with a firm retroareolar mass that is painless. Workup for a suspicious breast mass in men is similar to that for a woman and includes a mammogram and biopsy. Ultrasound is typically less informative. The most common histologic subtype is invasive ductal carcinoma (90%). Lobular carcinoma is rarely diagnosed in men. DCIS is also less frequent in men versus women. Most male breast cancers are ER^+ (81.5%).[383] The staging system for male breast cancers is similar to that for women and is classified according to the TNM AJCC staging system.

The treatment for early-stage male breast cancer has generally been a modified radical mastectomy. However for a man with a clinically negative axillary exam, an expert panel from the American Society of Clinical Oncology (ASCO) considers SLN biopsy to be an “acceptable” method.[236] It

is generally accepted that in men who have no evidence of disease in the SLN biopsy, no further axillary surgery is needed. For men who have a positive SLN, given there is lack of data for men in regards to this issue, they should be treated similarly to women with positive SLN biopsies. There is limited data regarding the use of breast-conserving surgery in men. A retrospective study of seven men treated with breast conserving therapy followed for a median of 67 months reported that there was no recurrence of disease. If men do elect for a partial mastectomy, adjuvant radiation therapy is essential and is based on results showing that adjuvant RT after breast-conserving surgery for women conveys a survival advantage.[384] For men with LABC (T3N0, N1-2, or T2N2) or IBC, treatment plans are similar to that for women. Consideration for neoadjuvant chemotherapy prior to surgery should be made. The treatment of metastatic breast cancer in males should parallel that for women.

Adjuvant chemotherapy, radiation therapy, anti-HER2 therapy, and endocrine therapy should mirror those for women. As the majority of male breast cancers are estrogen receptor-positive, endocrine therapy with tamoxifen should be given. In a limited study involving 39 men, those treated with tamoxifen had better 5-year actuarial survival (61% vs. 44%) and disease-free survival (56% vs. 28 %).[385] Although there is limited data, tamoxifen appears to be superior to aromatase inhibitors in the adjuvant setting for male breast cancer.[386] Extrapolating from the ATLAS trial for women,[387] for men with higher risk breast cancers, consideration toward extending tamoxifen to 10 years should be considered.

Male breast cancer patients should undergo similar posttreatment surveillance as that recommended for women. However, the role of screening mammography for the contralateral breast in these men has not been explored. It is important to recognize that male breast cancer patients are at risk for developing secondary cancers such as those of the small intestine, rectum, skin (nonmelanoma), pancreas, and prostate.[388]

Locoregional Breast Cancer Recurrence

Breast cancer recurrence can occur after both mastectomy and BCT (partial mastectomy and radiation therapy), with the median time to recurrence after mastectomy of 2 to 3 years versus 3 to 4 years after BCT.[389–391] When breast

cancer reappears on the chest wall it is defined as a local recurrence. However, breast cancer that involves the lymph nodes such as the ipsilateral axillary, supraclavicular, infraclavicular or internal mammary nodes is referred to as a regional recurrence. Among patients who undergo mastectomy for an operable breast cancer, 5% to 10% of patients will have a local or regional recurrence within 10 years whereas patients who undergo BCT have a risk of 10% to 15%, and in patients who forego radiation therapy after a partial mastectomy, the risk of recurrence is as high as 35%.[392] Although BCT is associated with an increased risk of locoregional recurrence, there are no differences in overall survival as supported by a single institutional NIH randomized study (n = 237)[262] and two European randomized trails (EORTC trial 10801 and DBCG trial 82-TM). The latter involved approximately 1,800 patients with stage I and II breast cancer who were randomized to undergo a modified radical mastectomy or BCT. Patients who developed a local recurrence in these trials were then analyzed for survival and time to subsequent local recurrence after salvage treatment. There were no differences between the two groups in regards to survival and time to subsequent local recurrence after treatment for an early locoregional recurrence.[389]

The primary risk factors for postmastectomy recurrence include the size of the primary cancer and the number of positive axillary lymph nodes, where ≥4 involved nodes have been consistently shown to increase axillary recurrence rate to over 20%.[393] In women with four or more positive lymph nodes, tumor size greater than 5 cm, or those with positive surgical margins, postmastectomy radiation therapy is often recommended as it can reduce the rate of chest wall recurrence by 65% to 75%.[311–313] The most common presenting sign of a postmastectomy recurrence is a clinical mass or multiple small nodules on the chest wall or overlying skin in or near the mastectomy scar/skin flaps. Other signs of a recurrence can include inflammatory changes without an associated mass and painless masses found in the axilla or the supraclavicular fossa. Workup for a recurrence should also be undertaken for patients who present with lymphedema or a brachial plexopathy. When a recurrence is suspected, a core biopsy should be obtained to confirm the diagnosis and to evaluate hormone and HER2 receptor status. In addition, a metastatic workup should be performed. The 5-year survival rate for patients based on site of recurrence is 52% for chest wall alone, 50% for axilla

alone, 28% for supraclavicular nodes alone, 28% for chest wall plus axilla, and 7% when both the supraclavicular nodes and chest wall/axilla are involved.[394] The subsequent treatment plan for patients with recurrent breast cancer is complex and requires a multidisciplinary team.

After BCT, the primary risk factors for recurrence are the use of radiation therapy and pathologic margin status. When an ipsilateral breast cancer is identified it is important to determine whether this is indeed a true recurrence versus a second primary cancer; a true recurrence is often found within the primary tumor site or the boost volume of the treated breast. Unlike postmastectomy recurrences, which are commonly detected on physical examination, post-BCT recurrences are often identified by surveillance mammography. However, it is important to note that any physical examination changes that occur more than one year after completion of radiation therapy warrant further workup, even in the presence of a normal mammogram. In this setting, consideration should be made for MRI and biopsy. For any recurrent disease, biopsy is obtained to confirm diagnosis and tumor receptor status, followed by a complete metastatic staging workup. In the absence of metastatic disease, the standard approach to a local recurrence after BCT is a mastectomy, with most patients surviving at least 10 years.[395] In the setting of more advanced recurrent disease, such as that associated with skin involvement or inflammatory changes of the skin, systemic therapy may need to be considered prior to mastectomy. The decision to proceed with axillary restaging should be considered by a multidisciplinary team. Furthermore, the management of regional recurrence after BCT is complex and should be planned with a multidisciplinary approach.

Figure 74.26 Paget disease of the nipple. Depigmentation and desquamation of the nipple and areola are evident.

Paget Disease of the Breast

Although the presentation of breast cancer is commonly associated with a mass or a mammographic abnormality, it must be considered in the setting of chronic nipple ulceration. PDB was first noted by Sir James Paget in 1874 when he described 15 women with chronic nipple ulcerations who then developed cancer of the involved breast within 2 years.[396] The hallmark of Paget disease is a scaly, raw, vesicular, or ulcerated lesion that begins on the nipple and then spreads to the areola (Fig. 74.26). This is often a unilateral process and can be associated with bloody nipple discharge. Symptoms which can occur prior to the development of clinically apparent disease include pain, burning, and pruritus. PDB is a rare disease accounting for only 1% to 3% of new cases of breast cancer in females in the United States.

The diagnostic workup of PDB is to first establish the diagnosis and then to identify the underlying breast cancer which is present in 85% to 88% of cases, despite often not being associated with a breast mass or a mammographic abnormality.[397] Full-thickness wedge or punch biopsy of the nipple should be performed. PBD is characterized histologically by the presence of large cells with prominent nucleoli and a pale cytoplasm (Paget

cells) occurring singly or in small groups within the epidermis of the nipple. Other characteristics of Paget cells include the presence of low–molecular-weight cytokeratins such as CK7. Approximately 50% of PDB cases express hormone receptors and between 70% and 90% of cases overexpress HER2.

For patients with PDB, a physical examination including bilateral breast examination and mammography should be performed to help identify the underlying breast cancer. Approximately one-half of patients with PDB will have an associated mammographic abnormality. Interestingly, these abnormalities can occur distant from the nipple–areolar complex. If no palpable masses are found and mammography is normal, there is a greater likelihood of DCIS than an invasive cancer.[398] If mammography and breast imaging fail to locate disease, then a MRI can be obtained, recognizing that although it is highly sensitive it is not highly specific. As such, MRI detected lesions should be biopsied to confirm the diagnosis of a breast cancer.

The treatment for PDB is either a mastectomy or breast-conserving therapy, which includes a partial mastectomy and whole breast radiation therapy. Breast-conserving surgery includes resection of the nipple–areola complex and the underlying cancer with negative margins obtained (central lumpectomy). Given that the nipple–areola complex is removed, some women may consider this cosmetically unacceptable. Evaluation and treatment of the axilla is dependent on the underlying cancer identified. Adjuvant systemic therapy is also determined by the involved breast cancer.

Figure 74.27 Breast asymmetry resulting from a benign phyllodes tumor. Skin changes are caused by pressure necrosis.

Phyllodes Tumor

Phyllodes tumors are uncommon (<0.5% of all breast malignancies) fibroepithelial breast tumors first described by Johannes Muller in 1838 as *cystosarcoma phyllodes*.[399] Given that these tumors often do not have cystic components and are not true sarcomas, they are now referred to simply as phyllodes tumors (Fig. 74.27). The malignant potential of phyllodes tumors differ widely, with some behaving like fibroadenomas and others that can degenerate histologically into sarcomatous lesions and metastasize distantly. As such, they are histologically classified as benign (50%), borderline (25%), or malignant (25%) based upon the degree of stromal cellularity and atypia, mitotic rate, and the presence or absence of stromal overgrowth and infiltrative margins. Risk factors for phyllodes tumors are not known, aside from their association with Li-Fraumeni syndrome.[400]

Patients with phyllodes tumors present with a smooth, multinodular, well-demarcated, firm mass that is both mobile and painless. The average tumor size is 4 to 7 cm. Although palpable axillary lymphadenopathy can be found in up to 20% of patients, lymph node involvement is rare.[401] Imaging is

notable for a smooth multi-lobulated mass that resembles a fibroadenoma. Core needle biopsy is recommended for diagnosis. However, it has a false-negative rate of 25% to 30%.[402,403] As such, in the presence of a rapidly enlarging mass, excisional biopsy should be performed.

The treatment for all phyllodes tumors is surgical excision to negative histologic margins; however, the definition of negative margins does differ between institutions ranging from no tumor at ink to 1 cm margins. As such, these cases are best addressed in multidisciplinary fashion with pathology. Even large tumors can be treated with breast-conserving surgery without compromising cancer-specific survival. Lymph node involvement is also very rare, in the SEER database, only 8 of 498 women had involved nodes.[404] As such, most surgeons do not routinely perform SLNB for phyllodes tumors. The use of adjuvant radiation therapy and chemotherapy is controversial, however in the setting of a large borderline or malignant phyllodes tumor these treatments should be considered. If systemic therapy for malignant phyllodes tumor is undertaken, it is based on guidelines for treating sarcomas. Similar to breast sarcomas, malignant phyllodes tumors can metastasize to the lungs and as such patients should undergo chest x-ray every 6 months for 2 years and then annually. Unfortunately once metastasis develops, the mean overall survival is 30 months.[405]

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75

Thyroid Gland

Sarah B. Fisher and Elizabeth G. Grubbs

Key Points

1. A thorough understanding of the anatomy and embryology of the thyroid gland will facilitate identification of the recurrent laryngeal nerves (RLNs) and parathyroid glands, avoiding damage to these key structures.
2. A non-recurrent recurrent laryngeal nerve is most commonly seen on the right and associated with vascular developmental abnormalities (arteria lusoria) whereas a left nonrecurrent nerve (rare) may be observed with situs inversus.
3. A thorough ultrasound (US) that includes the thyroid and the central and lateral neck compartments is vital to assessing thyroid pathology, with fine-needle aspiration (FNA) biopsy of appropriate nodules serving as the gold standard for initial diagnosis.
4. The Bethesda system uses cytopathology to risk stratify FNA biopsy results; molecular testing is a diagnostic adjunct for indeterminate nodules but requires an understanding of the strengths and limitations of the specific test.
5. A diagnosis of medullary thyroid cancer (MTC) should prompt a genetic evaluation, with the genotype/phenotype correlation guiding timing of care for those with hereditary syndromes (MEN2A, MEN2B, and familial MTC).
6. Anaplastic thyroid cancer (ATC) should be suspected in the patient with rapid growth and sudden onset of compressive symptoms, hoarseness, and/or dysphagia; imaging will often demonstrate invasion into local structures. These patients should be rapidly triaged to a multidisciplinary team experienced in treating ATC.
7. When deciding between lobectomy and total thyroidectomy for small well-differentiated thyroid cancers, surgical decision making should take into account the underlying disease process, the necessity of adjuvant radioactive iodine (RAI), and patient preferences.
8. Compartment-based lymph node dissection is therapeutic for patients with histopathologic evidence of lymph node metastases.

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INTRODUCTION

Thyroid lobectomy or total thyroidectomy is appropriate for patients with thyroid cancer or as prophylaxis in the setting of multiple endocrine neoplasia, those with symptomatic nodular disease, selected patients with hyperthyroidism, or as a diagnostic modality for select patients with indeterminate nodules. A concomitant compartmental anatomically based lymph node dissection is appropriate for some thyroid malignancies. An understanding of the

embryology, anatomy, and physiology of thyroid disease and the technical aspects of the operation is essential to avoid complications of thyroid surgery.

EMBRYOLOGY

Primarily composed of foregut endoderm, the thyroid is the first endocrine gland in the body to form during development. The median thyroid component descends from the foramen cecum at the base of the tongue at around 4 weeks of gestation. The lateral portion of the thyroid develops later from the caudal pharyngeal endoderm and 4th and 5th branchial pouches; fusion with the median portion forms the tubercle of Zuckerkandl. By 6 weeks of gestation, the foramen cecum resorbs, leaving a fibrous thyroglossal duct attached to the central hyoid bone; incomplete resorption of the tract may result in a thyroglossal duct cyst, whereas the more common persistence of the distal portion of the tract results in a pyramidal lobe.[1,2] Developmental abnormalities of the aortic arch may lead to altered position of the recurrent laryngeal nerves (RLNs).[2,3] Embryologic anomalies and their surgical implications are summarized in Table 75.1.

ANATOMY OF THE THYROID

The thyroid is a bilobed gland that weighs between 15 and 30 gm and sits anterior to the trachea, just inferior to the cricoid cartilage within the central compartment of the neck. Each lobe is approximately 5 cm in craniocaudal dimension, 2 to 3 cm anteroposterior, and 3 cm in width, although substantial physiologic and pathologic variations exist. Laterally, the thyroid is bordered by the medial aspects of the carotid sheath. Anteriorly, the sternothyroid and sternohyoid muscles cover the gland. The trachea and the esophagus (particularly on the left side) comprise the posterior borders. The pretracheal fascia extends to form a thin layer of connective tissue that invests the thyroid; in the absence of thyroiditis or invasive malignancy, this layer represents an easily mobilized plane of dissection. The sheath condenses as the anterior suspensory ligament of the thyroid above the isthmus; posteromedially to the thyroid gland it condenses to form the firm attachment to 1 the trachea called the ligament of Berry. The RLN and its insertion into the cricopharyngeus muscle are often intimately associated with the ligament of Berry and the RLN is most vulnerable to iatrogenic injury at this relatively fixed point.

Table 75.1 Medical and Surgical Implications of Embryologic Thyroid Anomalies

Condition	Mechanism	Presentation	Treatment
Thyroid agenesis	Failure of the thyroid anlage to form	Congenital hypothyroidism (dwarfism and irreversible brain dysfunction, or cretinism)	Early recognition allows for thyroid hormone replacement
Thyroglossal duct cyst	Failure of the thyroglossal duct to completely resorb	Midline neck mass that elevates with tongue protrusion	Sistrunk procedure: resection of the entire thyroglossal duct including the midportion of the hyoid bone
Lingual thyroid	Failure of the median portion of the thyroid to descend	Mass at the base of the tongue, often combined with absence of thyroid tissue elsewhere	Surgical excision or radioactive iodine ablation, with awareness of the need for thyroid hormone replacement
Ectopic thyroid tissue	Embryologic rests of thyroid tissue in the *central* compartment of the neck	Ectopic thyroid mass (thyroid cancer may also develop in these rests)	Surgical excision; not to be confused with thyroid tissue in the lateral compartment, which is not an embryologic abnormality and instead represents a regional nodal metastasis of differentiated thyroid cancer
Nonrecurrent laryngeal nerve	Abnormal development of the aortic arch; most often right sided (0.3 to	Typically silent; may be associated with dysphagia lusoria (compression of	Preoperative imaging that suggests aberrant arterial anatomy should heighten

	1.6% of patients undergoing thyroid surgery) and associated with an aberrant right subclavian artery that arises directly from the aorta and courses posterior to the esophagus. May occur on the left (0.04%) but requires a right sided aortic arch (as in situs inversus)	the esophagus between the trachea and a retroesophageal right subclavian artery)	awareness of the possibility of a nonrecurrent nerve

Vasculature

The thyroid has a rich blood supply, which is increased in certain pathologic conditions such as toxic goiter. The superior thyroid artery arises off the external carotid artery and courses inferiorly along the inferior pharyngeal constrictor muscles to the thyroid, branching into at least an anterior and posterior branch close to the superior pole of the thyroid gland. The inferior thyroid artery arises from the thyrocervical trunk, courses medially deep to the carotid artery, and branches into several smaller vessels that join the thyroid directly just inferior to the ligament of Berry near the tracheoesophageal groove. These vessels are intimately and variably associated with the RLN, and care must be taken during ligation to avoid iatrogenic nerve injury. Careful ligation of both the superior and inferior thyroid arteries close to the thyroid capsule will allow preservation of branches that supply the parathyroid glands. The thyroid ima artery arises directly from the great vessels and courses anterior to the trachea to the inferior portion of the thyroid gland. It is variable in presence (approximately 10% of patients) and size, but can represent a significant source of blood loss when unrecognized.

The venous drainage of the thyroid is comprised of a plexus of anastomosing vessels that condense into three named veins: the superior and middle thyroid veins drain to the ipsilateral internal jugular vein, and the inferior thyroid vein drains into the ipsilateral brachiocephalic vein. The middle thyroid vein may be absent or duplicated; when present medialization of the thyroid may stretch and tear this vein if unrecognized.

Lymphatics

The lymphatic plexus surrounding the thyroid gland is rich and variable. Intracapsular lymph channels in the thyroid gland provide communication across the isthmus and between lobes. The central lymph node compartment includes levels VI and VII and encompasses the prelaryngeal, pretracheal, and paratracheal lymph nodes. It extends superiorly from the hyoid bone inferiorly to the innominate artery and is bounded laterally by the carotid sheath; level VI is distinguished from level VII at the level of the sternal notch (Fig. 75.1).[4] The prelaryngeal lymph nodes reside in the midline just above the anterior suspensory ligament and the isthmus of the thyroid. Also called Delphian lymph nodes after the Greek Mythology "Oracle of Delphi" for their role as a harbinger of outcome, these are frequently the first nodes encountered upon opening the midline raphe. When associated with metastasis from malignancy, these nodes are associated with adverse pathologic characteristics of the primary tumor and involvement of other central or lateral compartment lymph nodes.[5] Although most lymph node metastases from thyroid cancer occur in the central compartment before spread to the lateral compartment, "skip" metastases to the lateral compartments only have been reported, particularly in tumors located in the superior poles.[6]

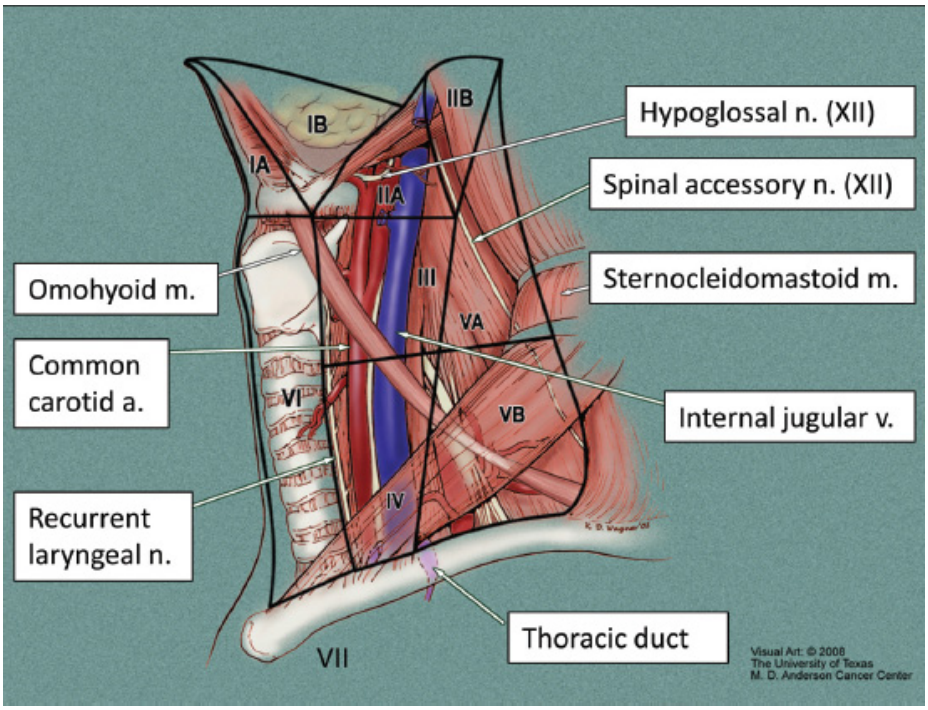

Figure 75.1 The central (VI and VII) and lateral (I–V) compartments of the neck. (Adapted from Fisher and Perrier[4] with permission from Libromed Panama, Republic of Panama. Comprehensive Clinical Oncology, Current Practices, English Edition, 2020.)

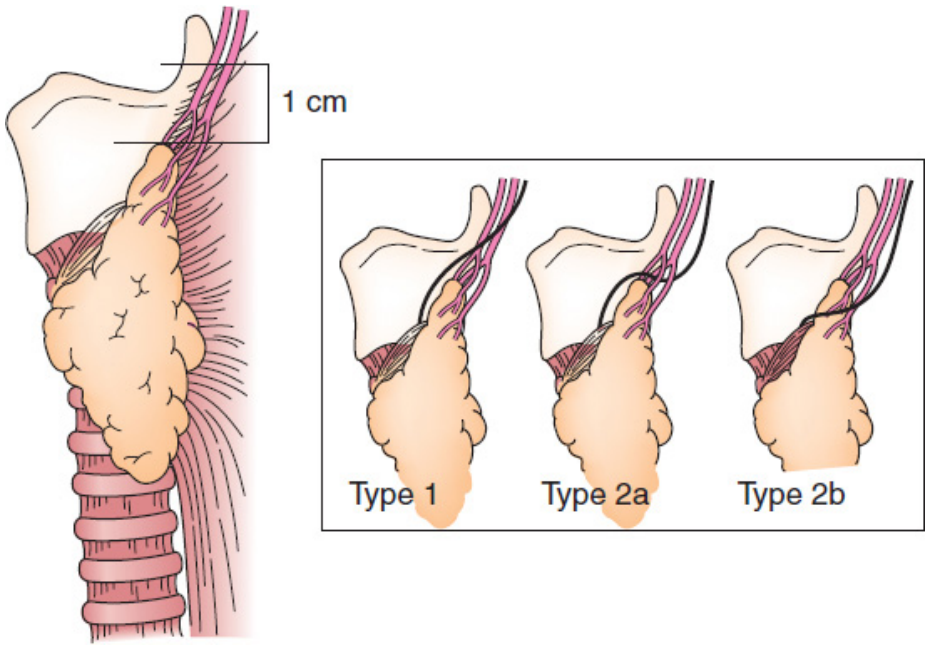

Figure 75.2 The Cernea classification of the external branch of the superior laryngeal nerve highlights the anatomic variability with progressively increasing risk of iatrogenic injury during thyroidectomy. Type I crosses the superior thyroid vessels ≥1 cm above the superior thyroid pole, type II crosses within 1 cm above the pole, and type III crosses below the superior pole.

The lateral compartment includes the submental nodes (level I), upper jugular (level II), midjugular (level III), lower jugular (level IV), and posterior triangle (level V) (Fig. 75.1).[4] The role and extent of prophylactic and therapeutic node dissection for thyroid cancer is discussed later (see Thyroid Surgery: Lymph Node Dissection).

Nerves

The thyroid gland itself is innervated by the cervical sympathetic chain, with two nerves in close vicinity that do not directly innervate the thyroid but are of critical importance: the external branch of the superior laryngeal nerve and the RLN.

The superior laryngeal nerve arises from the vagus and bifurcates into the internal branch (which enters the larynx at the thyrohyoid membrane to provide sensory information to the superior larynx) and the external branch, which contributes to voice pitch and projection by innervating the cricothyroid muscle. The course of the external branch is variable and meticulous dissection close to the superior pole is necessary to prevent iatrogenic injury during thyroidectomy (Fig. 75.2).

An understanding of the course of the RLN is critical for all surgeons who operate in the neck or chest (Fig. 75.3).[4] Inadvertent unilateral injury results in ipsilateral vocal cord paralysis and hoarseness; bilateral injury results in stridor and often requires an emergent surgical airway due to paralysis of the vocal cords in a closed position. On the right, the RLN arises from the vagus at the level of the subclavian artery, passing around it before ascending into the central neck at an oblique angle. The left RLN has a more vertical

trajectory, arising from the vagus nerve at the level of the aortic arch posterior to the ligamentum arteriosum and ascending in the tracheoesophageal groove. Up to 34% of RLNs will branch prior to insertion, with motor fibers carried anteriorly and sensory branches posteriorly.[7] In addition to hoarseness due to motor dysfunction, inadvertent injury to the posterior sensory fibers can result in aspiration.

A nonrecurrent, or direct, laryngeal nerve is most common on the right side (up to 1.6% of patients) and is typically associated with a retroesophageal right subclavian artery (Table 75.1). Left-sided nonrecurrent laryngeal nerves require a right-sided aortic arch (situs inversus) with an aberrant left 2 subclavian and are less common (Table 75.1). When available, preoperative recognition of aberrant vasculature on cross-sectional imaging (i.e., CT of the chest or upper mediastinum) should alert the surgeon to the possibility of a nonrecurrent nerve. As CT of the chest is not routinely performed for most patients undergoing thyroidectomy, thoughtful ultrasound (US) may offer a more accessible alternative. Although operator dependent, in experienced hands, US can correctly identify aberrant neck vasculature (specifically the lack of a brachiocephalic trunk) and preoperatively predict patients with nonrecurrent right-sided laryngeal nerves with minimal examination time (median 5 minutes in one study) and few false positives (associated with obesity, large goiter, or tortuous arteries).[8] Although nonrecurrent laryngeal nerves are rare, their presence is associated with increased risk of iatrogenic nerve injury (12.9%) and it is possible that surgeon-performed US may offer a cost-effective and easily implemented mechanism to augment recognition; this requires further evaluation.

Parathyroid Glands

The location of the parathyroid glands is variable but is often in close proximity to the thyroid, and care should be taken during thyroidectomy to preserve the parathyroid gland and its blood supply. Superior parathyroid glands are typically located superior to the tubercle of Zuckerkandl and posterior to the course of the RLN; they may be encountered adherent to the posterior thyroid capsule, within the tracheoesophageal groove, or directly adjacent to the RLN.[9] Inferior parathyroids are more variable and may be similarly adjacent to the RLN, associated with the inferolateral aspect of the thyroid, or within the thyrothymic ligament. True intrathyroidal parathyroids are rare. Normal parathyroids are often symmetric (80% for superior glands and 70% for inferior glands) and correct identification of their location and preservation of their blood supply is important to prevent postoperative hypocalcemia after thyroidectomy.

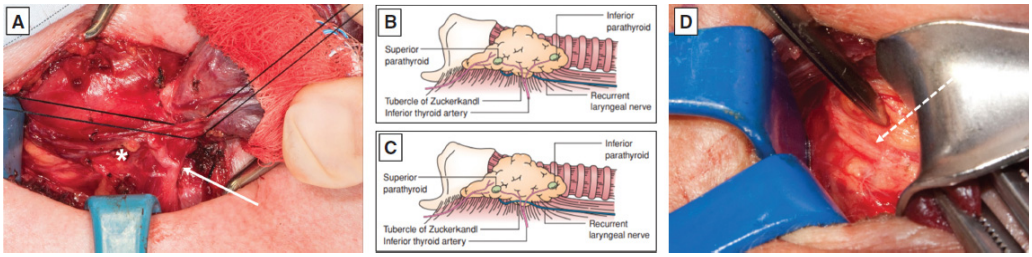

Figure 75.3 **A**: The most commonly encountered course of the right recurrent laryngeal nerve (RLN, *arrow*) with the thyroid rotated medially into the field, and the superior parathyroid preserved (*star*). The course of the nerve may vary with relation to the tracheoesophageal groove as well as the tubercle of Zuckerkandl, in which the nerve passes medial and posterior **(B)** versus **(C),** in which the RLN passes lateral to an enlarged tubercle. In the event of anomalous vasculature, the nerve will be nonrecurrent, as shown in **(D)** by the *arrow*, with the thyroid again retracted medially. (Pictures in **A** and **D** are adapted from Fisher and Perrier[4] with permission from Libromed Panama, Republic of Panama. Comprehensive Clinical Oncology, Current Practices, English Edition, 2020.)

THYROID PHYSIOLOGY

The follicular cells of the thyroid produce thyroxine (T4) and triiodothyronine (T3) under the stimulus of thyrotropin (or thyroid-stimulating hormone, TSH), which is secreted by the anterior pituitary. The process is dependent on dietary iodide, which in most developed regions typically far exceeds the daily requirement of 100 to 150 µg, with excess excreted by the kidneys. On a cellular level, thyroid follicles are comprised of epithelial cells (thyrocytes), which are organized in an ovoid structure with the interior containing iodinated thyroglobulin (colloid). The active uptake of iodide in cells occurs via a Na^+/I- symporter mediated by a Na^+/K^+-adenosine triphosphatase pump on the basolateral plasma membrane. After entry into the cell, thyroid peroxidase (TPO) catalyzes an oxidative reaction to couple iodide with tyrosine, leading to the production of T4 and T3, which are then coupled to thyroglobulin for storage (Fig. 75.4). The release of thyroid hormone into the circulation is mediated through micropinocytosis stimulated by TSH.

In humans, T4 is produced in excess of T3 by a ratio of 13:1 under normal physiologic conditions. A less active but more stable hormone, T4 is converted to T3 in the periphery (primarily liver and plasma) by type 1 deiodinase enzymes. The half-life of T3 is between 8 to 12 hours, whereas the half-life of T4 is approximately 7 days. The majority of circulating T4 and T3 (>99%) is bound to plasma proteins (thyroglobulin, albumin, thyroxine-binding prealbumin).

CLINICAL EVALUATION OF THE PATIENT WITH A THYROID DISORDER

A thorough history should include questions about prior thyroid-related concerns, medication use, previous thyroid biopsies, and history of head and neck or upper esophageal/thoracic surgery or radiation. Medications such as amiodarone or lithium can induce hyperthyroidism.

A history of transient hypothyroidism requiring exogenous thyroid hormone should alert the clinician to the possibility of thyroiditis. Previous thyroid biopsies or the presence of known nodules on previous imaging studies provide information regarding patterns of growth and natural history that can be used to assess the risk of malignancy. Previous surgical procedures in the region should prompt evaluation of RLN function with laryngoscopy or videostroboscopy. Radiation exposure history (therapeutic or environmental), in addition to potentially creating fibrosis within the surgical field, is an important risk factor for later development of papillary thyroid cancer (PTC).[10,11] Family history of thyroid disorders or syndromic patterns that suggest an increased risk of thyroid cancer should be evaluated (e.g., multiple endocrine neoplasia type II, Cowden syndrome, Carney complex, familial adenomatous polyposis and/or Gardner syndrome, Werner syndrome, *DICER1* syndrome) and referral to genetic counseling considered.

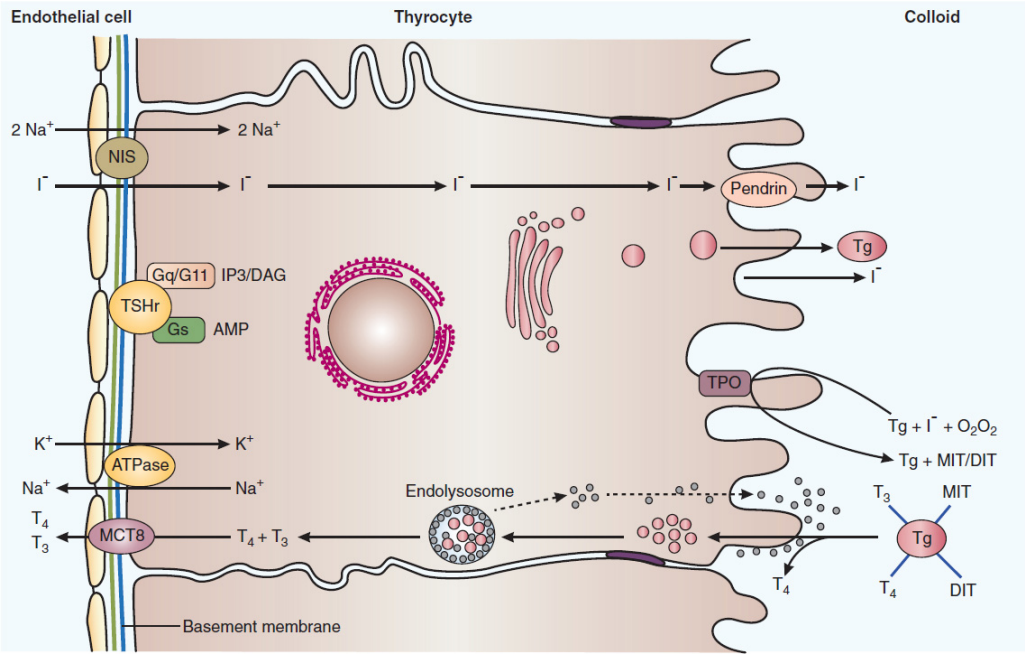

Figure 75.4 Thyroid hormone metabolism. Thyroxine (T_4) and Triiodothyronine (T_3) are produced by the thyroid follicular cell in a complex biochemical pathway. It is dependent on the movement of circulating iodide through the follicular cell and into the intracellular colloid space. T_3 and T_4 are then bound to Thyroglobulin (Tg) for eventual transport back through the follicular cell to be released into the intravascular space.

Table 75.2 Symptoms of Hypo- or Hyperthyroidism

	Hypothyroidism	Hyperthyroidism
Symptoms	Fatigue Sensitivity to cold Weight gain Dry skin/hair/nails Constipation Muscle weakness Depression	Nervousness or irritability Heat intolerance Palpitations Hyperphagia Weight loss Thin skin Diarrhea Weakness Insomnia
Signs	Puffy facies Macroglossia Bradycardia Hypermenorrhea or menorrhagia Delayed relaxation of deep tendon reflexes Hypercholesterolemia Generalized nonpitting edema	Thyromegaly +/− thyroid bruit Tachycardia Sweating Oligo- or amenorrhea Hyperactive deep tendon reflexes Tremor Pretibial myxedema[a] Exophthalmos[a]
Laboratory Findings	Low fT4 Elevated TSH	Elevated fT4 and/or T3 Low/suppressed TSH

[a]In patients with hyperthyroidism related to Graves disease.

fT4, serum free thyroxine; TSH, thyroid-stimulating hormone; T3, serum triiodothyronine.

Symptoms of hypo or hyperthyroidism (Table 75.2) should be assessed and confirmed with laboratory testing. Mechanical symptoms such as dysphagia, dysphonia, dyspnea, compressive symptoms, and neck pain should be clarified with attention to duration, severity, and exacerbating factors. The timeline of symptom presentation provides clues to the etiology. A rapidly growing mass is concerning for either thyroid lymphoma or anaplastic thyroid cancer (ATC), whereas a stable nodule over many years is less suspicious for malignancy.

The physical examination should include a thorough neck examination focusing on the thyroid (size, texture, nodularity, mobility) and evaluation for central and lateral adenopathy. Physical signs of hyper- or hypothyroidism should be noted (Table 75.2). Laboratory workup should include serum TSH and free thyroxine (fT4) levels to screen for hypothyroidism or hyperthyroidism, with additional laboratory testing tailored to the specific diagnosis (see Laboratory Assessment of Thyroid Abnormalities). Previous neck surgery, dysphonia, or perceived voice changes should prompt either laryngoscopy or videostroboscopy to evaluate

the vocal cords and the corresponding function of the RLNs. RLN injury and vocal cord dysfunction can be clinically occult but have significant consequences for future contralateral surgery. Vocal cord dysfunction in the absence of previous surgery should heighten the clinician's suspicion for malignancy.

Imaging of the thyroid should begin with an US that assesses the thyroid as well as the central and lateral compartments of the neck. The accuracy of fine-needle aspiration biopsy (FNA biopsy), if indicated, is usually increased by 3 US guidance (see Radiographic Assessment of Thyroid Abnormalities, below).

LABORATORY ASSESSMENT OF THYROID ABNORMALITIES

Basic thyroid function tests for the patient with any thyroid complaint should include measurement of TSH and free T4 (fT4). Under normal circumstances an inverse relationship between TSH and fT4 is observed, with small variations in fT4 leading to more substantial changes in TSH. Assuming a functional hypothalamic–pituitary axis, an elevated TSH in the setting of low fT4 suggests hypothyroidism (note that TSH measurement will be inaccurate in the patient with panhypopituitarism), whereas a suppressed TSH with high fT4 levels suggests hyperthyroidism.

Thyroid-Stimulating Hormone (Thyrotropin, TSH)

Immunometric assays to measure TSH are highly sensitive and specific, making it the ideal method for detecting thyroid dysfunction in the patient with a functioning hypothalamic–pituitary axis. The range of normal is a spectrum and is usually between 0.27 and 4.20 mIU/mL, although target ranges for treatment during specific conditions (such as pregnancy or as suppressive therapy for differentiated thyroid cancer) are typically lower. Interpretation of TSH, particularly within the spectrum of normal ranges, must be considered with regard to concomitant symptoms of hypo- or hyperthyroidism (Table 75.2).

Free versus Total Thyroxine (T4) and Triiodothyronine (T3)

Levels of total T3 and T4 (defined as both free and protein bound) can vary based on variation in levels of plasma proteins. Multiple medications, including nonsteroidal anti-inflammatories, birth control pills, phenytoin, carbamazepine, furosemide, and aspirin can either alter levels of transport proteins directly or compete with T4 and T3 for binding. These alterations do not typically impact true thyroid function, leading to variability in total T3 or T4. Measuring free T4 improves the ability to detect true physiologic thyroid dysfunction, independent of alterations in transport proteins. Measurement of free T3, while possible, is often unreliable due to the extremely low level of circulating T3 not bound to

plasma proteins. Instead, total T3 is often used as a surrogate, and is most useful when assessing hyperthyroid states—it may be elevated even then TSH and fT4 are normal. Conversely, it is also the last test to become abnormal in the hypothyroid state and thereby less useful in this condition.

Thyroglobulin and Thyroglobulin Antibodies

Thyroglobulin is a protein produced by normal thyroid tissue and differentiated thyroid cancer cells that clinically primarily serves as a tumor marker. After complete removal of native thyroid tissue (i.e., thyroidectomy), thyroglobulin should be undetectable, and, in the absence of thyroglobulin autoantibodies, a rise in thyroglobulin suggests microscopic disease recurrence. Thyroglobulin autoantibodies interfere with the radioimmunoassay commonly used to measure thyroglobulin and may artificially increase or decrease thyroglobulin. Thyroglobulin autoantibodies are present in up to 10% of the general population and up to 20% of patients with differentiated thyroid cancer. Knowledge of their presence is essential when interpreting thyroglobulin; in a patient with autoantibodies the antibody titer may gradually decrease (over years) after complete thyroidectomy. Elevated TSH also tends to stimulate higher levels of thyroglobulin, so interpretation of thyroglobulin must occur simultaneously with measurement of TSH. Measurement of thyroglobulin in the setting of an intact thyroid or after thyroid lobectomy is not informative.[12]

Thyroid Autoantibodies

Both thyroid peroxidase autoantibodies (TPO-Ab) and thyroglobulin autoantibodies are elevated in patients with Hashimoto thyroiditis (HT), whereas thyroid-stimulating immunoglobulins (TSI) and/or TSH receptor autoantibodies (TrAb) are elevated in Graves disease. Conversely, TrAb may also have a blocking effect on the TSH receptor and result in hypothyroidism in other conditions. Thyroid autoantibodies may also be present in the individual without thyroid dysfunction.

Calcitonin

Calcitonin, secreted by the parafollicular cells of the thyroid gland, may help modulate calcium and phosphorus homeostasis but is not the primary driver (parathyroid hormone is) in humans. It is useful as a tumor marker for medullary thyroid cancer (MTC). Given the rarity of MTC, calcitonin should not be used as a screening test for the general population, but tested only when suspicion for MTC exists.[12,13]

RADIOGRAPHIC ASSESSMENT OF THYROID ABNORMALITIES

US is the gold standard imaging modality for the thyroid and is particularly advantageous in that it does not expose the patient to ionizing radiation. Other imaging modalities, including radionuclide imaging, computed tomography (CT), magnetic resonance imaging (MRI), and/or fluorodeoxyglucose positron emission tomography (FDG-PET) have specific roles in the evaluation of the patient with a thyroid complaint.

Ultrasound

Although user dependent, US provides information on the size, location, and radiographic characteristics of thyroid nodules, assessment of thyroid parenchyma, and evaluation of cervical lymph nodes. Regardless of the presence of other imaging, all patients with suspected structural abnormalities (thyroid nodules, thyroid cancer) should undergo a dedicated US that examines the thyroid and the central and lateral compartments of the neck. This is best performed with a high-frequency probe (7.5 to 15 MHz). Assessment of constitution (solid, cystic, spongiform, or mixed), presence of microcalcifications, and evaluation of echogenicity, shape, and borders (smooth vs. irregular) are important when assessing risk for malignancy (Fig. 75.5).[12] Hypoechogenicity, irregular borders, and subtle microcalcifications are concerning for malignancy, whereas hyperechogenicity, smooth borders, or a "halo sign" (an anechoic rim) are more often benign. Large macrocalcifications, associated with posterior acoustic shadowing are often benign. Combined with size, US characteristics inform the decision to perform FNA (Table 75.3).[14] Routinely performing FNA biopsy on all nodules results in unnecessary procedures, whereas overly stringent criteria for biopsy may miss a clinically relevant cancer. In general nodules above 1 cm, those with particularly concerning US characteristics, or those that are increasing in size over time merit FNA biopsy. US should also be used to evaluate and/or FNA-biopsy lymph nodes (suspicious findings include loss of fatty hilum, microcalcifications, hyperechoic change, rounded shape, or necrosis),[15] which alters the planned operation in up to one-third of patients with thyroid nodules.[13]

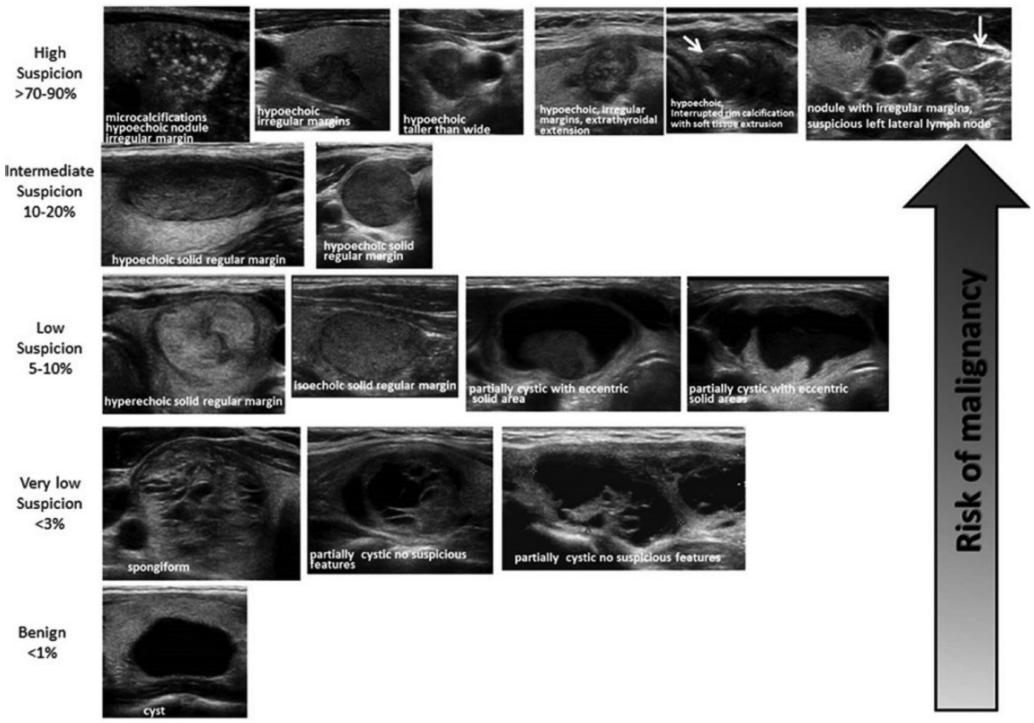

Figure 75.5 Ultrasound characteristics concerning for malignancy. (Reprinted with permission from Haugen et al.[12])

Table 75.3 Guidelines for Fine-Needle Aspiration Biopsy of Thyroid Nodules

American Thyroid Association	Society of Radiologists in Ultrasound	Three-Tiered System	White Paper of the American College of Radiology
Solid hypoechoic nodules ≥1 cm with or without one or more: irregular margins, microcalcification, taller than wide shape, rim calcifications with soft tissue extrusion, or extrathyroidal extension OR solid isoechoic or hyperechoic nodules ≥1.5 cm without the above features OR spongiform or partially cystic nodules ≥2 cm without the above features[a]	Solid nodules ≥1 cm with microcalcifications OR solid nodules ≥1.5 cm OR mixed solid cystic nodules ≥2 cm	Solid nodules ≥1 cm with microcalcifications, hypoechoic features, increased vascularity, infiltrative margins, or taller than wide dimensions OR PET avid nodules OR any nodule associated with lymphadenopathy, extrathyroidal spread, lung metastases, or signs of ipsilateral vocal cord palsy	Any PET avid nodule OR Biopsy based on US characteristics (not further specified)

[a]May consider observation with serial ultrasound rather than biopsy if desired.

PET, positron emission tomography; US, ultrasound.

Adapted with permission from Fisher and Perrier.[14]

Radionuclide Imaging

Radionuclide uptake scans provide information regarding thyroid function but do little to delineate anatomy. The most commonly performed examination, technetium (Tc) pertechnetate scintigraphy, uses ^{99m}Tc pertechnetate, an isotope that emits primarily gamma (γ) radiation and is rapidly absorbed by the thyroid. In contrast to iodine, ^{99m}Tc is not incorporated into thyroglobulin and therefore scintigraphy must be performed within 20 to 30

minutes after injection. Normal uptake scans demonstrate uptake of the radiotracer symmetrically across the thyroid. In patients with toxic adenoma the uptake will concentrate at the area with the nodule (a hyperfunctioning or "hot" nodule), whereas patients with hypofunctioning nodule(s) ("cold" nodule) will demonstrate relative photopenia.[16,17] While a hot nodule is rarely malignant, a "cold" nodule was historically considered suspicious for malignancy. Today with the sensitivity and specificity of FNA biopsy the use of scintigraphy in the evaluation for malignancy is outmoded.

The oral administration of ^{123}Iodine (^{123}I) allows for measurement of iodine uptake over time using the x-rays, β particles, and γ rays transmitted by this radiotracer, with images obtained at 4 and 24 hours. In patients with hyperthyroidism from Graves disease the thyroid will demonstrate increased symmetric uptake throughout the gland, which most often remains elevated 24 hours later.[16] The fraction of dose retained by the thyroid is calculated as the 24-hour radioactive iodine (RAI) uptake.

In contrast to ^{123}I, ^{131}I has a longer half-life (~8 days) and emits more β and γ radiation. It is thoroughly cleared from background tissues and is the isotope of choice when performing nuclear imaging for differentiated thyroid cancers. A diagnostic dose (1 to 5 mCi) allows for evaluation of iodine uptake, whereas therapeutic doses (30 to 150 mCi) ablate residual thyroid cells. Ablative ^{131}I scintigraphy may also be used for selected patients with Graves disease, often with resulting hypothyroidism.[18]

In summary, thyroid scintigraphy is most useful in patients with hyperthyroidism to distinguish the source of overproduction (i.e., a toxic adenoma vs. toxic multinodular goiter [MNG] vs. Graves disease).

Positron Emission Tomography

Although FDG-PET is routinely employed for staging and surveillance of many cancers, it is not a first-line imaging modality for well-differentiated thyroid cancers.[12] In contrast, for poorly differentiated thyroid cancers with loss of iodine uptake, in which ^{131}I scintigraphy will be falsely negative, FDG-PET has a sensitivity of up to 84%, which increases to 93% when combined with CT.[19] Another unique instance in which FDG-PET or other PET modalities such as ^{68}Ga-labeled somatostatin analogs (^{68}GA-DOTATATE or -DOTATOC) may be useful is in the case of locally advanced, recurrent, or metastatic MTC, particularly in patients with elevated or rising tumor markers without radiographic evidence of disease using conventional imaging.[20,21]

When an FDG-PET performed for other reasons identifies a thyroid nodule, the concern for malignancy is greater than for incidentally found nodules identified by other radiographic modalities. One systematic review of 55,000 patients identified PET-avid thyroid nodules in 1%, with 33% of those representing malignancy (most commonly PTC).[22] It is important to note that the pattern of uptake also provides information—diffuse tracer avidity within the thyroid gland in general represents benign disease, whereas uptake in a specific nodule is concerning for malignancy. Further evaluation of PET-avid thyroid nodules with US and FNA biopsy is necessary.[12]

Computed Tomography and/or Magnetic Resonance Imaging

Cross-sectional imaging with CT (most commonly) or MRI (in select instances) is indicated for patients with findings concerning for locoregionally advanced disease (bulky primary tumor, extensive nodal metastases, concern for RLN palsy or tracheal invasion) or for evaluation of substernal pathology (i.e., MNG) not well visualized on US (Fig. 75.6).

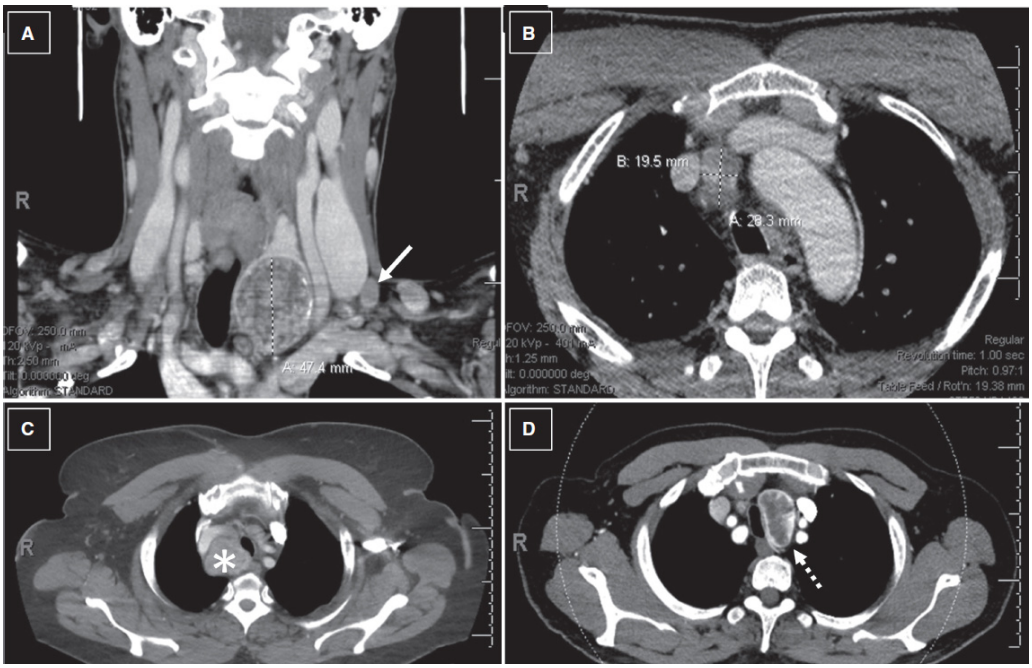

Figure 75.6 Utility of computed tomography in evaluating thyroid disease. **A**: Coronal view of a large left sided tumor (4.7 cm) causing mild tracheal deviation and a pathologic left level IV lateral neck lymph node (*arrow*). **B**: Identification of a pathologic mediastinal/level VII lymph node (1.9 × 2.8 cm). **C**: A substernal goiter (*star*) causing tracheal compression, and (**D**) a left-sided substernal thyroid nodule (*dashed arrow*) not palpable on physical examination.

THYROID DISORDERS CHARACTERIZED BY HYPERTHYROIDISM

Common causes of hyperthyroidism include toxic adenoma (a single hyperfunctioning nodule), toxic MNG, or diffuse toxic goiter (Graves disease). Less common causes include amiodarone-induced thyrotoxicosis (AIT), TSH secretion by a pituitary adenoma, or exogenous thyroid hormone supplementation. Presentation is variable and may range in severity from incidental detection on laboratory studies to thyroid storm. Elderly patients in particular may present with atrial fibrillation, angina, or congestive heart failure, and thyroid function should always be evaluated during initial presentation of these illnesses.

Initial treatment focuses on restoring normal physiology. Antithyroid drugs (ATDs) such as methimazole and propylthiouracil inhibit thyroid hormone synthesis with an onset of action

over a 2- to 6-week period. Patients should be monitored carefully for adverse effects including agranulocytosis (1 in 500 patients), which presents with fever and pharyngitis, and hepatotoxicity (0.3 to 0.7 per 1,000 patients). Hepatotoxicity is typically cholestatic when associated with methimazole, whereas propylthiouracyl may cause hepatocellular injury and/or fulminant liver failure. Both agranulocytosis and hepatotoxicity are most common within the first 90 days of use.[18] Rash, pruritus, and arthralgias are less severe but more commonly encountered with ATDs. Beta blockade is useful in controlling tachycardia, tremors, heat sensitivity, and anxiety, and may inhibit peripheral conversion of T4 to T3 at high doses.[23] Titration of therapy should be based on T3 and T4 levels, as TSH may remain suppressed for several months after normalization.

After stabilization, continuation of ATDs, ablation with RAI, or surgical resection offer potential definitive treatment for the patient with hyperthyroidism. The underlying etiology, patient-specific factors and preferences, and available healthcare infrastructure influence the optimal therapy for hyperthyroidism (Table 75.4).[24]

Toxic Adenoma

Typically toxic adenomas grow to at least 2 cm in size before becoming biochemically apparent. Although RAI is a potential therapeutic option, it has several disadvantages as compared to thyroid lobectomy, including the possibility of leaving behind a palpable nodule and the probability of inducing hypothyroidism (see Table 75.4).[24] Thyroid lobectomy for patients with toxic adenoma has a much lower rate of postoperative hypothyroidism (2% to 3%) as compared to when performed for other indications (20%). Thyroid lobectomy also has a faster return to the euthyroid state (2 to 3 days postoperatively, vs. 75% response rate at 3 months for RAI) and a lower risk of disease recurrence (<1% vs. 3% to 5.5% for RAI).[18]

Toxic Multinodular Goiter

Toxic MNG, in which hyperthyroidism results from more than one autonomously functioning nodules, may develop in a patient who was previously euthyroid either spontaneously or after exposure to an iodine load (Jod-Basedow phenomenon). Historically, efforts to iodinate salt or flour in iodine-deficient populations were followed by the development of toxic MNG over a time course of several years. Clinically, toxic MNG may be difficult to discern from Graves disease with nodular degeneration, however patients with toxic MNG are more often female and older than 50 years of age, with a history of MNG. Laboratory testing demonstrates the absence of TSI and/or TrAb. Patients with toxic MNG often have concomitant indications for thyroidectomy, including compressive symptoms and/or substernal extension. While RAI remains a possible treatment option, requirement of repeated doses because of goiter size and poor iodine uptake is more common. ATDs are less likely to achieve remission in patients with toxic MNG than in Graves disease.

Table 75.4 Comparison of Thyroidectomy, Radioactive Iodine Ablation, and Medical Therapy for Thyrotoxicosis

	Thyroidectomy	Radioactive Iodine Ablation (RAI)	Medical Therapy
Time of Onset	▪ Immediate	▪ 4–6 mo	▪ 4–6 wks
Advantages	▪ Immediately curative with quick onset ▪ May be beneficial for patients with limited access to care ▪ Lobectomy is appropriate for toxic adenoma, and may avoid iatrogenic hypothyroidism	▪ Less invasive than surgery ▪ May be more cost effective (dependent on geographic area)	▪ Noninvasive ▪ Nonablative (potential to retain native thyroid function) ▪ Achieves remission in 40–50% of patients with Graves after 12–18 mo; less likely in patients with toxic multinodular goiter
Disadvantages	▪ Typically requires medical therapy preoperatively ▪ Invasive—risk of surgical injury ▪ Results in iatrogenic hypothyroidism	▪ Requires medical therapy preprocedure in selected patients due to the risk of transient worsening of thyrotoxicosis ▪ May result in hypothyroidism (80% by 16 wks, up to 90% by 10 yrs) ▪ 5–15% require repeat treatment ▪ Requires isolation ▪ Avoid radioactivity in women who are pregnant or lactating ▪ 15–20% risk of inducing/aggravating Graves orbitopathy[a]	▪ Medication nonadherence ▪ Side effects Rare but serious: ▪ Agranulocytosis ▪ Hepatotoxicity ▪ Birth defects (methimazole) ▪ Vasculitis More common but less serious: ▪ Rash ▪ Arthralgias
Patient Preferences	Patients choosing surgery likely place a higher relative value on prompt and	Patients choosing RAI likely place a higher relative value on definitive control of symptoms with	Patients choosing medication likely place a higher relative value on the possibility of

	definitive control of symptoms and avoidance of radioactivity and/or side effects from medications, with less relative concern for potential surgical risks and need for lifelong hormone replacement	avoidance of surgery and/or side effects from medications, with less relative concern for the rapid resolution of symptoms, need for lifelong hormone replacement, and worsening of Graves orbitopathy	remission and avoidance of lifelong hormone replacement, and avoidance of surgery or radioactive exposure, with less relative concern for medication side effects and/or disease recurrence

[a]Exacerbation of orbitopathy may be ameliorated by concomitant steroid use.

RAI, radioactive iodine.

Adapted with permission from Fisher et al. Surgery for Thyrotoxicosis. In: Wass J, Owen K, eds. *Oxford Handbook of Endocrinology and Diabetes*. United Kingdom: Oxford University Press, 2014.[24]

Graves Disease

Initially described by Robert Graves in the 1830s as an enlarged thyroid gland, accelerated heart rate, and ocular changes, Graves disease is an autoimmune disorder characterized by thyroid-stimulating antibodies. These antibodies bind to the TSH receptor to stimulate thyroid hormone release and cause hypertrophy of the thyroid. Graves disease occurs in 20 to 50 individuals per 100,000, affecting women more frequently than men (lifetime risk 3% vs. 0.5%).[25] In addition to hyperthyroidism, Graves disease has several distinct manifestations, including eye disease and localized dermopathy. Thyroid-associated eye disease (TED) is thought to be mediated by the accumulation of immune cells and fibroblasts within the orbit, and presentations include eyelid retraction (92%), exophthalmos (62%), extraocular muscle dysfunction (43%), ocular pain (30%), increased lacrimation (23%), and optic neuropathy (6%).[25] Thyroid dermopathy, or thickening of the skin (which is most commonly observed on the shins—pretibial myxedema—but may develop elsewhere) occurs less commonly (1% to 4%) and typically in conjunction with severe TED.

Therapeutic options for patients with Graves disease include ATDs, RAI, and total thyroidectomy; lobectomy is not appropriate. Practice patterns vary geographically and by access to specialists, and should take patient preferences into account. Patients with a high likelihood of remission (women with mild disease, small goiters, and negative or low-titer antibodies) may benefit most from ATDs, whereas those with severe adverse reactions to ATDs, known liver disease, or medication noncompliance may favor RAI or thyroidectomy.

Patients with life-limiting comorbidities, previous neck surgery or irradiation, or those without access to a high-volume thyroid surgeon may favor either RAI or ATDs. The presence of TED may be worsened by RAI, and although this effect may be ameliorated by corticosteroids,[23] thyroidectomy is often preferred in these patients. The presence of larger thyroid nodules, compressive symptoms, known or suspected malignancy, or concomitant hyperparathyroidism is an indication for thyroidectomy. Thyroidectomy is also favored for women who are pregnant, planning a pregnancy, or lactating, as RAI is contraindicated during pregnancy or lactation, and most experts recommend avoiding it within 6 months of a pregnancy. When surgery is pursued thyroidectomy should be delayed until second trimester (if disease severity allows) when the risk of preterm labor or pregnancy loss is lowest. Pediatric patients are often treated initially with ATDs but the rate of remission is lower than that observed in adults.[26] Hesitation to treat with RAI, which unlike external radiation has not been definitively associated with an increased risk of later development of thyroid cancer, exists, and thyroidectomy is often favored in the pediatric patient in whom ATDs are insufficient. Finally, thyroidectomy is appropriate in situations in which immediate control of symptoms is necessary (i.e., thyroid storm or cardiovascular exacerbation refractory to medical management) as ATDs require 2 to 6 weeks and RAI may take 4 to 8 weeks to normalize thyroid function.[18]

In an elective situation a patient with Graves disease should be rendered euthyroid prior to thyroidectomy with ATDs. Adjunct measures, which may be particularly useful for the management of the patient with severe Graves disease refractory to ATDs, include beta blockade, iodine, cholestyramine, and hydrocortisone. With the exception of iodine, the specific pros and cons of each of these are outside of the scope of this chapter. Most commonly given as Lugol solution (LS, a combination of elemental iodine and potassium iodide) or saturated solution of potassium iodide (SSKI), an iodine load preoperatively suppresses thyroid hormone synthesis and release (Wolff–Chaikoff effect). The American Thyroid Association (ATA) supports preoperative treatment with LS or SSKI in most patients with Graves disease to reduce thyroid blood flow and vascularity,[27] although the benefits of it in the setting of modern surgical technique have been contested.[28] While two early randomized studies demonstrated decreased blood flow on Doppler US and less operative blood loss in patients treated with LS[29–31] later retrospective studies failed to identify differences in blood loss or postoperative complications.[32,33] It is plausible that excellent surgical technique minimizes clinically relevant blood loss and iodine supplementation is unnecessary, however there are minimal side effects from a short course of LS or SSKI. When utilized, either may be administered as three to five drops every 8 hours for 7 to 10 days preoperatively, and are most palatable dissolved in juice.

Hypoparathyroidism, either transient or permanent, is a risk after total thyroidectomy (discussed in detail below in Complications) and merits specific mention with regard to Graves disease. Retrospective studies demonstrate a higher incidence of transient hypocalcemia in patients with Graves disease as compared to euthyroid patients undergoing thyroidectomy for other reasons,[34] with rates as high as 28% in one experienced tertiary care center.[35] The specific reasons for the increased risk are not clearly defined but are thought to be related to increased complexity of the operation due to increased thyroid gland size and

vascularity, and increased calcium metabolism and bone turnover due to hyperthyroidism.[36] Concomitant vitamin D deficiency, which may be observed at higher frequencies in patients with autoimmune thyroid disease including Graves disease,[37] likely also contributes to higher rates of postoperative hypoparathyroidism. Although not specific to patients with Graves disease, one randomized trial demonstrated reduction in transient hypocalcemia and related symptoms after thyroidectomy with the use of perioperative alfacalcidol (1α-hydroxy-vitamin D3).[38] Another prospective study treated patients with Graves disease with calcium carbonate for 2 weeks before thyroidectomy and demonstrated less symptomatic hypocalcemia than historic counterparts treated at the same institution.[39] When planning elective thyroidectomy vitamin D deficiency should be corrected and selective preoperative calcium supplementation may be considered, particularly in patients with Graves disease at higher risk for postoperative hypoparathyroidism.

Thyroid Storm

Thyroid storm is most often associated with uncontrolled Graves disease or AIT, and may be triggered by cessation of ATDs and/or physiologic stressors (illness or surgery), or RAI therapy (rare). The diagnosis is clinical and requires a high index of suspicion as many other critical illnesses have overlapping characteristics, including thermoregulatory dysfunction (hyperpyrexia), cardiovascular instability (tachycardia, arrhythmias, congestive heart failure), central nervous system disturbance (agitation, delirium, psychosis, stupor, coma), and/or gastrointestinal dysfunction (nausea, vomiting, diarrhea, hepatic failure). Associated with a mortality of 8% to 25%, thyroid storm requires both supportive intensive care and therapy aimed at inhibiting thyroid hormone secretion and synthesis.[18] Propylthiouracil, which is typically considered second line to methimazole in treatment of *stable* patients with thyrotoxicosis, is favored in treatment of thyroid storm due to the additional inhibition of peripheral conversion of T4 to T3. Beta blockade, with its antiarrhythmic properties and inhibition of peripheral conversion is also useful. Other adjuncts include steroids which may also block peripheral conversion; cholestyramine, which enhances enterohepatic clearance of thyroid hormone; and/or iodine, which should be started after initiation of ATDs and temporarily blocks new hormone synthesis and thyroid hormone release. Supportive therapy includes cooling blankets, volume resuscitation, cardiovascular and respiratory monitoring and invasive support as indicated, and nutritional support.

THYROID DISORDERS ASSOCIATED WITH HYPOTHYROIDISM

Hypothyroidism may be primary, arising from intrinsic thyroid disease, iatrogenic destruction or removal of the thyroid, or administration of ATDs; or secondary due to pituitary dysfunction. Tertiary hypothyroidism, in which the hypothalamus does not produce sufficient thyrotropin-releasing hormone, is a rare cause of hypothyroidism. Treatment is largely medical with replacement of T4.

THYROIDITIS

Inflammation of the thyroid, or thyroiditis, is frequently encountered and rarely an indication by itself for surgery. Although most often associated with hypothyroidism, thyroiditis may also present with transient hyperthyroidism due to the destruction of thyroid follicles and release of preformed thyroid hormone. Multiple factors contribute to the development of thyroiditis, which can be nonspecific or follow several distinct variations with specific clinical, laboratory, and imaging characteristics.

Hashimoto Thyroiditis

As the most common cause of hypothyroidism in adults, HT affects up to 10% of the population and may also be called autoimmune or lymphocytic thyroiditis. It is more common in women than men (9:1) and most commonly presents between 30 and 50 years of age but may occur across all age ranges. A typical presentation includes painless symmetric enlargement of the thyroid that is often characterized as rubbery and is sometimes accompanied by fullness or compressive symptoms. Laboratory studies may demonstrate a transient hyperthyroidism at the initial presentation (5% of patients), often followed by subclinical or clinical hypothyroidism; anti-TPO antibodies are typically elevated. US demonstrates a heterogeneous echotexture, and benign pseudonodules due to the autoimmune destruction of thyroid follicles and resulting architectural fibrosis and distortion may be observed. Nodular disease in a patient with HT should be evaluated with FNA biopsy to rule out malignancy. It is not clear whether patients with HT have an increased risk of well-differentiated thyroid cancer—surgical studies influenced by selection bias show a link between HT and malignancy, but population-based studies do not support a relationship.[40] Patients with HT are at a higher risk for the rare thyroid lymphoma, although the overall incidence (0.37% of patients with HT) remains low.[41]

Postpartum Thyroiditis and Painless Sporadic Thyroiditis

Postpartum thyroiditis affects up to 8% of pregnant women and is distinguished by presentation with pregnancy or during the year following pregnancy. The degree of cellular destruction (fibrosis, follicular atrophy) in postpartum thyroiditis is typically less than is observed in HT. Women with postpartum thyroiditis may demonstrate a relapsing clinical course, with periods of mild hyperthyroidism, euthyroidism, and/or hypothyroidism. Care is supportive, with thyroid hormone replacement as indicated by symptoms and laboratory assessment. One-third of women will remain hypothyroid 1 year after delivery; for those with spontaneous resolution relapse is often triggered by future pregnancies. Painless sporadic thyroiditis represents the same autoimmune process observed in postpartum thyroiditis, except it occurs independent of pregnancy or the postpartum period. Women

remain more frequently affected than men (2:1) and it is most common between the ages of 30 and 40. As with postpartum thyroiditis, treatment is supportive.

Subacute Thyroiditis

Also called de Quervain thyroiditis, giant cell thyroiditis, pseudogranulomatous thyroiditis, or subacute painful thyroiditis, subacute thyroiditis may be triggered by a virus (often coxsackievirus or echovirus). Women are more commonly affected than men (5:1) and the age of onset is typically 20 to 60 years. Following a prodromal upper respiratory illness, the patient often presents with fever, malaise, and painful and firm goiter that is ultimately transient over a period of weeks to months. Pain radiating to the jaw or ears and/or associated with specific movement may be observed. Laboratory studies may demonstrate transient hyperthyroidism followed by hypothyroidism; while antithyroid antibodies may be present they are often normal. Inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are often elevated in subacute thyroiditis. Treatment involves salicylates or nonsteroidal anti-inflammatory medications, with steroids reserved for more severe symptoms. Recurrence is rare.

Amiodarone-Induced Thyrotoxicosis or Thyroiditis

Amiodarone causes thyroid dysfunction in 15% to 20% of patients and may present as hypothyroidism or hyperthyroidism. Management of amiodarone-induced hypothyroidism is supportive; management of AIT may be more challenging. In contrast to many forms of thyroiditis, AIT is more common in men than women. Two forms of AIT exist with distinct mechanisms. In type I AIT, the iodine load from the drug itself exacerbates thyroid autonomous function, typically in the setting of a pre-existing MNG. Type I AIT is more common in iodine-deficient areas and can be treated by cessation of amiodarone (when feasible), ATDs, and/or LS or SSKI. Type II AIT is more common and develops independent of structural thyroid disease. Because type II AIT is a destructive process, ATDs are ineffective at controlling the hyperthyroidism and treatment consists of cessation of amiodarone (when feasible) and/or corticosteroids. Mixed or indefinite AIT may also occur with features of both type I and type II.[42] Thyroidectomy is appropriate for patients with medically refractory disease, but is associated with a higher complication rate.[43]

Acute Thyroiditis

Also called suppurative, pyogenic, bacterial, or infectious thyroiditis, acute thyroiditis is a rare condition caused by bacterial, fungal, mycobacterial, or parasitic infection. It is common in children and young adults aged 20 to 40 years. Patients may experience fever, malaise, and/or pain radiating to the ear, with enlargement of the thyroid related to abscess formation. Given the rich vasculature and lymphatic drainage of the thyroid, infection is rare and is most often seen in patients who are immunosuppressed, or those with congenital abnormalities predisposing to infection such as a pyriform sinus fistula. Thyroid function is

typically within normal limits, and antithyroid antibodies are rarely present. FNA biopsy with Gram stain and culture confirms the diagnosis and guides antibiotic therapy. Thyroidectomy, particularly in resistant cases or those in which a structural abnormality predisposes, may be appropriate.[44,45]

Riedel Thyroiditis

Also known as fibrosing thyroiditis, this form of thyroiditis presents with a painless progressive goiter. Women are more commonly affected than men (3 to 4:1) and the peak age of onset is between 30 and 60 years of age. The cause is unknown. Patients are typically euthyroid but may progress to hypothyroidism over the course of the disease. Physical examination reveals a firm, fixed goiter that is best described as "woody." The fibrous process may extend to surrounding tissues and cause tracheal or esophageal compression or hypoparathyroidism. Other focally sclerotic conditions (retroperitoneal fibrosis, mediastinal fibrosis, or sclerosing cholangitis) may also occur. Surgical resection may be necessary to rule out malignancy or alleviate symptoms, but total thyroidectomy may not be feasible due to infiltration with other structures. Medical adjuncts to therapy include corticosteroids, methotrexate, and/or tamoxifen.[45]

NODULAR THYROID DISEASE

Thyroid nodules, whether clinically evident or incidentally discovered, are commonly encountered by medical providers across multiple specialties. The prevalence of thyroid nodules identified by palpation is estimated to be between 4% and 7%,[46,47] with up to 10 times more identified by imaging studies. Autopsy studies estimate that thyroid nodules may be present in up to 50% to 60% of all adults.[48] Women are more frequently affected than men (4:1), with the prevalence of thyroid nodules increasing with age to 50% in women over 70 years.[46] Although most thyroid nodules are benign, appropriate risk stratification and identification of patients who need further evaluation, biopsy, and/or surgical intervention is essential. In addition to assessing the risk of malignancy, evaluation should include attention to the presence or absence of related symptoms, which may be mechanical (such as dysphagia, dysphonia, or compressive symptoms) or related to autonomous production of excess thyroid hormone (see *Hyperthyroidism*).

Multinodular Goiter

Endemic goiter, or goiter due to iodine deficiency, remains a world health problem, although it is less likely in developed areas with dietary fortifications (iodination of salt, bread, flour, or vegetable oil). Thyromegaly from TSH stimulation occurs along with an adaptive response in which the thyroid shifts production of thyroid hormone from T4 to the more biologically potent T3. Therapy involves support with exogenous thyroid hormone therapy and/or iodine supplementation, which may not be practical in populations with limited

access to care. Access to surgeons is similarly limited, and thyroidectomy in these areas is typically reserved for patients with very large goiters in whom symptoms have developed (compression, dyspnea, stridor, hoarseness, or dysphagia). In an iodine-deficient setting recurrence rates are high (25% to 30%) and reoperative thyroid surgery accounts for 16% of all thyroidectomies.[49]

In iodine-replete areas of the world goiter may occur independent of TSH stimulation, and it is unlikely to shrink with exogenous thyroid hormone or iodine. Management depends on assessment of risk of malignancy and presence of symptoms. When more than one nodule is present each must be assessed for risk of malignancy based on physical examination, patient risk factors, US characteristics, and/or FNA biopsy. Both benign and malignant lesions can grow over time, so change in size alone is not necessarily an indication for resection. Symptoms including a feeling of neck pressure or compression, dyspnea on exertion or at baseline or stridor thought to be related to tracheal compression, and/or dysphagia merit discussion of total thyroidectomy. In the patient with an asymmetric goiter in which the contralateral lobe is homogenous or characterized only by small, benign-appearing nodules who wishes to preserve thyroid function, thyroid lobectomy may be appropriate.

Uninodular Disease

The management of a single dominant thyroid nodule is similar to that of an MNG, in that risk assessment for malignancy and evaluation of symptoms should guide therapy in the euthyroid patient. In contrast to MNG, diagnostic lobectomy (in the case of indeterminate risk of malignancy) or therapeutic lobectomy (in the case of compressive symptoms) is the first choice of surgical management.

Substernal or Intrathoracic Thyroid Nodular Disease

Accurate preoperative assessment of the inferior extent of a multi- or uninodular goiter is imperative to avoid unwanted surprises in the operating room. Physical examination should include palpation of the inferior-most extent of the thyroid (or observation that it is not clearly assessable), which can be aided by neck extension and/or deglutition. Definite palpation and/or clear delineation of the inferior border on US suggests lack of a clinically meaningful intrathoracic component. In situations of uncertainty, CT of the neck and chest will clearly delineate the inferior-most extent of disease. The prevalence of substernal goiter ranges widely in the literature (2% to 19%), and sternotomy (partial or full) may be required in 5% (range 1% to 11%).[50]

Thyroid Cytopathology

FNA biopsy is the cornerstone of cytopathologic evaluation of structural thyroid abnormalities and is indicated for most solid or hypoechoic nodules greater than 1 cm in diameter, or for smaller nodules with radiographically suspicious features (Table 75.3,[14] Fig. 75.5).[12] The accuracy of FNA biopsy can be improved with image-guided techniques

(most commonly using US), which decrease the nondiagnostic rate from 15% to 20% to approximately 7%.[46,51,52] Onsite cytopathology can further improve diagnostic yield of FNA biopsy by evaluating adequacy of the obtained tissue and, if needed, prompting repeat passes in a single setting.[53] In the event of a nondiagnostic result, one repeat FNA biopsy is reasonable and may yield diagnostic material in more than half of the patients[54]; this is often best performed after a short surveillance interval to allow resolution of any associated hemorrhage from the initial biopsy. In addition to increasing diagnostic accuracy, US guidance during FNA biopsy also allows the clinician to select the most suspicious nodule, or area of the nodule, for biopsy, and to discern (and biopsy) multiple sites. With the exception of lymphoma, in which a core needle biopsy is often more appropriate, FNA biopsy is generally sufficient to yield diagnosis within the limits of cytopathology. Specific indeterminate lesions (see Bethesda Classification) require evaluation of the architecture of surrounding cells, and therefore are unlikely to be definitively diagnosed on FNA biopsy, which relies on aspiration of single cells. The false-negative rate for FNA biopsy ranges between 1% and 6% at high-volume centers, and the false-positive rate should be between 0% and 0.5%.

Bethesda Classification

The ATA recommends that thyroid FNA-biopsy cytology should be reported using the Bethesda system for reporting thyroid cytopathology.[12,55] The Bethesda system includes six categories with an associated range of risk of malignancy for each 4 (Table 75.5).[14] Bethesda V and VI represent clinically suspicious (V) or overt malignancy (VI) and should be addressed surgically in most situations. Bethesda I represents a nondiagnostic result and may be managed by repeat FNA biopsy (with management guided by specific results), or diagnostic lobectomy in the event of persistent nondiagnostic findings. Benign findings such as adenomas, colloid nodules, complex cysts, hyperplastic nodules, and thyroiditis, which are unlikely to be malignant (<3%), are categorized as Bethesda II. The majority of Bethesda II nodules may be safely observed with serial physical examination and US, although resection (thyroid lobectomy) remains an appropriate therapy for patients who are symptomatic. Repeat FNA biopsy during surveillance of Bethesda II nodules is not routinely indicated and should be reserved only for significant changes in nodule characteristics (with or without accompanying change in size) that may suggest original sampling error. A higher index of suspicion may be necessary for patients with nodules greater than 3 to 4 cm in size as the risk of sampling error and false-negative results increases with nodule size (>3 to 4 cm). Retrospective surgical series of patients with initially benign cytology identified malignancy in 11% to 13% of patients with tumors greater than 3 to 4 cm, although this is influenced by selection bias and likely overestimates the rate of false-negative findings.[56,57]

Table 75.5 The Bethesda System for Reporting Thyroid Cytopathology with Suggested Management and Corresponding Risk of Malignancy

Diagnostic Category	Usual Management	Predicted Risk of Malignancy (%)[b]	Actual Risk of Malignancy in Surgically Excised Nodules, % Median (Range)[°]
Nondiagnostic/unsatisfactory	Repeat FNA with US guidance	1–4	20 (9–32)
Benign	Clinical follow-up	0–3	2.5 (1–10)
Atypia or follicular lesion of undetermined significance	Observation, with or without molecular studies, and/or lobectomy	5–15	14 (6–48)
Follicular neoplasm or suspicious for follicular neoplasm	Lobectomy, with molecular diagnostics and or observation employed in select situations	15–30	25 (14–34)
Suspicious for malignancy	Lobectomy or thyroidectomy[a]	60–75	70 (53–97)
Malignancy	Lobectomy or thyroidectomy[a]	97–99	99 (94–100)

FNA, fine-needle aspiration; US, ultrasound.

[a]Based on tumor size, histopathologic characteristics, and anticipated need for postoperative radioablative iodine therapy.

[b]As predicted by the Bethesda system.[55]

[°]As summarized in Haugen et al.[12]

Adapted with permission from Fisher and Perrier.[14]

Patients with Bethesda III nodules comprise an indeterminate category in which the findings do not clearly meet criteria for benign or malignant lesions. Interpathologist variability is most pronounced in this category, with preparation quality and cellular adequacy heavily influencing interpretation.[58] Repeat FNA biopsy may yield a specific diagnosis in more than half of Bethesda III cases. Molecular diagnostics, discussed below,

may add additional risk stratification to persistently indeterminate findings. With appropriate patient counseling either diagnostic lobectomy or observation are reasonable therapeutic approaches.

Bethesda IV nodules represent follicular neoplasm or findings suspicious for follicular neoplasm. Although this category was created to signify the possibility of follicular thyroid cancer (FTC) and prompt diagnostic lobectomy, which remains standard of care, a majority will be benign on final pathologic evaluation. With appropriate patient selection and counseling, molecular diagnostics and/or close observation may be appropriate management strategies.

Molecular Evaluation

Up to 70% of PTCs display point mutations of the B-Raf proto-oncogene (*BRAF*, 45%) or RAS proto-oncogene family (*RAS*, 10%) or *RET/PTC* rearrangements (20%), with a smaller proportion demonstrating mutations in the promoter region of the telomerase reverse transcriptase (*TERT)* gene (10% to 12%).[59] FTC is more likely to demonstrate *RAS* mutations (45%) or paired box 8-peroxisome proliferator–activated receptor gamma (*PAX8-PPARγ*, 35%) rearrangements, with a higher prevalence of *TERT* promoter mutations (17%) than PTC.[59] Debate exists regarding the specific clinical implication of each mutation, and the prognostic significance of each is likely confounded by the presence of other adverse clinicopathologic factors. Mutations in *BRAF*, for example, are more frequently identified in patients with lymph node metastases and/or those with recurrence than in patients without metastases and/or recurrence, and *BRAF*-mutated patients are also more likely to have concomitant extrathyroidal extension and higher stage than non-*BRAF* mutated patients. Yet *BRAF* mutations may also be identified in a patient with an indolent microcancer, leading some to propose that specific combinations of mutations (i.e., the combination of *BRAF* and *TERT*) may be more prognostic.[12] It is likely that improved understanding of the molecular profile of the tumor rather than a single oncogene will provide better prognostic information, but further studies are necessary.

As to the indeterminate nodule, molecular diagnostics may aid in diagnosis. Currently multiple molecular panels, the majority of which use gene expression classification with or without additional evaluation for specific mutations or fusions which may be associated with thyroid cancer, are commercially available as a tool to augment decision making regarding indeterminate thyroid nodules. The two most commonly used tests in the United States currently are Thyroseq™ and Afirma™. When interpreting test results, it is essential to understand that positive and negative predictive values of tests depend on the underlying prevalence of disease, that is, the underlying prevalence of thyroid cancer, which may differ between institutions.

Thyroseq v3 (CBLPath, Rye Brook, NY, USA), tests for point mutations, insertions/deletions, copy number variations, gene fusions, and gene expression variations across 112 proprietary genes and is built upon a series of previous versions.[60] Internal validation studies suggested high sensitivity (92.9%) and adequate negative and positive predictive values (85.5% and 83.0%, respectively), with a relatively high prevalence of

malignancy (49.6% to 61.7%).[60,61] Multi-institution validation supported these results with a 94% specificity in Bethesda III/IV nodules and negative and positive predictive values of 97% and 66%, respectively, with an overall cancer prevalence of 28%, leading the authors to conclude that benign results on the classifier may obviate diagnostic surgery in up to 61% of all patients with Bethesda III/IV nodules.[62]

The Afirma Gene Expression Classifier™ (GEC, Veracyte, South San Francisco, CA) assesses expression of 167 genes (proprietary panel) with a high negative predictive value (95% and 94% for Bethesda III and IV, respectively), making it most useful in ruling out malignancy in cytologically indeterminate nodules.[63] Initial concern regarding performance for Hurthle cell tumors in particular was addressed with The Afirma Gene Sequencing Classifier™, which built on the original assay and added cassettes to aid in the detection of MTC, follicular and Hurthle cell neoplasms, RET fusion transcripts and BRAFV600E mRNA, and parathyroid tissue.[64] The initial reports cite improved specificity and an increased overall *benign* call rate particularly in Hurthle cell tumors (from 12% to 59%), while maintaining negative predictive value (96.1%).[64,65] If the greatest utility of this test is to identify benign lesions, the inherent drawback of it is the inability to definitively prove the diagnosis with resection and formal histopathologic evaluation. Currently only a small percentage of patients with Afirma GEC or GSC benign determinations undergo resection (6% to 13%), leading to the possibility that some of these patients may have an indolent malignancy that has not yet declared.[66] Patients electing for observation of a cytologically indeterminate nodule, with or without reassuring molecular testing, should undergo regular follow-up.

DIFFERENTIATED THYROID CANCER

The incidence of thyroid cancer in the United States has tripled over the past three decades[67] with a recent stabilization, possibly related to incorporation of more conservative diagnostic practices.[68] PTC is the most common form of thyroid cancer, accounting for 85% of the estimated 52,890 new cases per year in the United States, followed by FTC (12%), poorly differentiated or insular thyroid cancer (3%), MTC (1% to 2%), and ATC (<1%).[68,69] Thyroid cancer exhibits a wide range of behavior, from the very indolent papillary thyroid microcarcinoma to the extremely aggressive ATC. Fortunately, well-differentiated thyroid cancers form the bulk of the cancer burden with excellent long-term survival, and thyroid cancer accounts for only 0.4% of cancer deaths worldwide.[70]

Papillary Thyroid Cancer

PTC affects people of all ages with a peak incidence in the third and fourth decades and a female predominance (3:1). Microscopically, PTC is characterized by papillary architecture, calcifications, psammoma bodies, squamous metaplasia, and fibrosis. Large overlapping nuclei that are optically clear (Orphan Annie nuclei) and intranuclear grooves are common findings on cytology. Histopathologic variants include the follicular variant of

PTC, which is notable for its diagnostic ambiguity on FNA biopsy. This particular form of PTC combines architectural feature of a follicular tumor and is often characterized as a follicular lesion. Clinically it behaves in the same manner as classic PTC (not to be confused with the noninvasive, or encapsulated form, which is discussed below). Other histopathologic variants are associated with more aggressive clinical behavior, including the hobnail, tall cell, columnar, and solid variants. Often these histopathologic features are identified in the setting of other adverse factors, including larger tumor size, extrathyroidal extension, angiolymphatic invasion, lymph node metastases, and distant metastases.[71] The presence of these variants, in addition to other clinical factors, should be taken into consideration when planning extent of surgery (i.e., lobectomy vs. total thyroidectomy, discussed later).

Treatment for PTC localized to the thyroid and/or the cervical lymph nodes is surgical (thyroid lobectomy or thyroidectomy, with compartment base lymph node dissection as appropriate), with selective use of adjuvant RAI to minimize risk of recurrence. Excellent long-term oncologic outcomes for most patients with PTC have allowed discussion of quality of life to factor into surgical planning. For example, the extent of thyroidectomy must be balanced between the concern for recurrence and need for RAI versus the desire to maintain native thyroid function and/or minimize extent of surgery and surgical risks. Unlike many other cancers, multifocality (within the thyroid) and/or lymph node involvement does not necessarily convey a poorer prognosis. Interestingly, the size of the tumor also does not correlate with the risk of lymph node metastases, and the incidence of metastases varies depending on the extent of lymph node dissection performed. While therapeutic lymph node dissection for clinically evident disease is standard of care,[72] the value of prophylactic central neck dissection, which may identify micrometastases in as many as 30% to 80% is debated[73] (see Lymph Node Dissection).

In a small subset of patients (1% to 8%) PTC may present with metastatic disease, most commonly with lung metastases.[74] Thyroidectomy may be appropriate even for patients with distant metastases, as removal of native thyroid tissue will facilitate treatment with RAI therapy.

Papillary Thyroid Cancer: Nonoperative Management

In contrast to the more aggressive histologies, papillary thyroid microcancer is defined as a PTC that is ≤1 cm in diameter. Often found incidentally during thyroidectomy for other reasons, these are generally not life-limiting. Ten-year disease-specific survival for patients with surgically treated papillary thyroid microcancer is >99%,[75] and some have questioned the clinical impact of these cancers if left in situ. Active surveillance, which involves serial physical examination, US, and laboratory assessment, was first proposed in Japan for patients with small tumors (≤ 1 cm on US) located away from vital structures (RLNs, trachea, esophagus) without evidence of extrathyroidal extension or lymph node involvement, who wished to avoid surgery and its potential complications. In this highly monitored population of 1,235 patients, only 4.6% demonstrated tumor growth and 1.5% developed lymph node metastases with over 10 years of follow-up.[76] Importantly, no patient

developed distant metastases or died of thyroid cancer.[77] The first North American group to examine active surveillance showed similarly promising results with tumor growth observed in 3.8% of 291 patients over 25 months, and no regional or distant metastases.[78,79] Although promising, the oncologic safety of active surveillance and the efficacy of salvage surgery for tumor progression require further evaluation, and this method should be used with caution outside of a well-designed multidisciplinary trial.

Follicular Thyroid Cancer

FTCs comprise 10% to 15% of all thyroid cancers, present with a female predominance, and are most common in the fifth decade of life. The histologic diagnosis hinges on the identification of vascular and capsular invasion, which is not readily identified on FNA biopsy or frozen section determination. FTC tends to demonstrate hematogenous spread and these patients have a higher lifetime risk of distant metastases (10% to 15%) and are less likely to manifest regional nodal disease (10%) than patients with PTC. Surgical planning, staging, and adjuvant therapy (RAI, to which up to 80% are sensitive) decisions should take this propensity for distant metastasis into consideration and most patients with FTC are treated with total thyroidectomy, with therapeutic lymph node dissection as indicated by preoperative imaging.

Noninvasive Follicular Thyroid Neoplasm with Papillary-Like Nuclear Features

In 2012, the National Cancer Institute recognized the public health burden of the overdiagnosis of cancer and encouraged efforts to revise terminology when data supported a more indolent classification. In 2016, Nikiforov et al.[80] proposed that the *encapsulated* follicular variant of PTC, which comprises 10% to 20% of all thyroid cancers in North America and is characterized by lack of capsular or vascular invasion, be reclassified as a nonmalignant entity, and introduced the term “noninvasive follicular thyroid neoplasm with papillary-like nuclear features,” or NIFTP. That study, and others since, have demonstrated that for patients who meet the strict histologic criteria of NIFTP and were treated with surgery alone, long-term retrospective follow-up failed to show recurrence or distant metastasis.[81] Although the goal of the noncancer nomenclature is to reduce the number of unnecessary operations, diagnosis of NIFTP currently still requires complete histologic assessment, and therefore lobectomy. Improved understanding of the molecular profile of these tumors in the future may allow a less-invasive diagnostic option.

Hurthle Cell Cancer

Hurthle cell cancers are characterized by the presence of oncocytic cells (abundant eosinophilic granular cytoplasm and hyperchromatic nuclei) and evidence of capsular and vascular invasion, whereas Hurthle cell adenomas lack invasion. By definition, FNA biopsy

cannot evaluate the entire periphery of the lesion and therefore cannot distinguish benign from malignant for Hurthle cell neoplasms. It is also important to note that the specificity of available molecular diagnostics is the lowest for Hurthle cell neoplasms as compared to other indeterminate nodules (specificity for Afirma GSC 59%; Thyroseq v3 internal validation specificity 69.3%),[61,65] and as such diagnostic lobectomy is most commonly utilized for a "Hurthle cell neoplasm." Frozen section analysis has similar limitations to FNA biopsy, and final histopathology must make the diagnosis of Hurthle cell cancer. Once invasion is evident and the diagnosis of Hurthle cell cancer is made, the extent of invasion observed in the tumor can be used to further subdivide Hurthle cell cancer into two types: minimally invasive (<4 foci of angioinvasion) and widely invasive (>4 foci). Often the distinction between the two is subject to interobserver variability, but is no less important given the relatively indolent behavior of the former and the more aggressive behavior of the latter. Hurthle cell cancers are more likely than PTC or FTC to demonstrate lymph node metastases and less likely to take up radioiodine (10% radioiodine avid), making surgery the mainstay of treatment.

MEDULLARY THYROID CANCER

MTC is rare (~1% to 3% of all thyroid cancers) and derives from the calcitonin-producing parafollicular C cells of the thyroid. In contrast to PTC, the development of nodal metastases correlates with tumor size (central and lateral compartment nodal disease are present in 14% and 11% of patients with T1 tumors, and 86% and 93% of patients with T4 tumors, respectively) and nodal and distant disease is more common. When presentation is associated with a palpable nodule up to 70% of patients will have cervical metastases and 10% will have distant disease.[21]

Table 75.6 Disease Phenotypes Associated with Medullary Thyroid Cancer

Syndrome	Clinical Features (% Penetrance)
MEN2A	MTC (>90%), pheochromocytoma (40–60%), parathyroid hyperplasia (20–30%), cutaneous lichen amyloidosis, Hirschsprung disease
MEN2B	MTC (>98%), pheochromocytoma (40–60%), intestinal and mucosal neuromas (98%), marfanoid habitus, inability to produce tears, everted eyelids and/or ptosis, prominent corneal nerves
Familial MTC	Isolated MTC with typically later age of onset and less aggressive clinical course

MEN, multiple endocrine neoplasia; MTC, medullary thyroid cancer.

Adapted with permission from Kiernan and Grubbs.[82]

Of the 25% of patients in whom MTC is hereditary (multiple endocrine neoplasia [MEN] 2A and 2B or familial MTC) germline-activating point mutations of the *RET* proto-oncogene can be identified in the majority (95%). The specific mutation associated with hereditary MTC has a strong genotype–phenotype correlation and, when known, will guide timing of therapeutic interventions (Table 75.6).[82] Similar *RET* mutations may be identified in the remaining 75% of patients with sporadic disease, but at a lower frequency (40% to 50%), with *RAS* mutations accounting for an additional 10% to 15% and unknown or unidentified driver mutations in the remainder. Because a diagnosis of MTC may present as the initial proband in a family, any adult patient with MTC should undergo genetic counseling as well as screening for pheochromocytoma and hyperparathyroidism regardless of family history. In 5 children, in whom genetic counseling and testing of a family member often leads to subsequent presentation and diagnosis at a young age, prophylactic thyroidectomy should be performed within the first year of life for those with RET codon *M918T* mutations (ATA highest risk) and prior to age 5 for those with RET codon *C634* or *A883F* mutations (ATA high risk). For the remaining patients with moderate risk (mutations other than those mentioned above), the timing of thyroidectomy may be influenced by patient and family preferences, the natural history of other affected family members, and serial observation may be appropriate for those with normal US findings and a normal serum calcitonin.[21] In addition, screening for pheochromocytoma and hyperparathyroidism should be considered in children above the age of 10 depending on mutation profile, whereas it is not indicated in children under the age of 5 given the sequence of presentation.[82] Such care should occur in the context of a multidisciplinary center with providers who are familiar with the disease and its associated physiologic and psychosocial impacts.

As with other thyroid pathology, all patients with suspected MTC should undergo a thorough neck US that includes the draining central and (bilateral) lateral nodal basins. In addition to routine thyroid function tests, both calcitonin and carcinoembryonic antigen (CEA) should be evaluated. The baseline levels of these two tumor markers are valuable for assessing disease burden (calcitonin levels >400 pg/mL should prompt a metastatic workup with cross-sectional imaging, with particular attention to the liver as the most common site of metastasis) and over time yield insight into the rate of disease progression by allowing the calculation of doubling time. The ATA provides a calculator to assess the rate at which each biomarker doubles (https://www.thyroid.org/professionals/calculators/thyroid-cancer-carcinoma/). In general, doubling time is best calculated with at least four data points over a minimum of 2 years, and calcitonin is better correlated with outcome than CEA. Patients with a doubling time of less than 6 to 12 months most often demonstrate structural disease progression and decreased progression-free and overall survival, whereas those a doubling time greater than 2 years is associated with disease stability and improved survival.

Surgical resection is the mainstay of therapy for MTC, with prophylactic thyroidectomy for patients with known hereditary syndromes, ideally timed to be performed prior to detection of disease, and total thyroidectomy with bilateral central neck dissections performed for known disease, with lateral neck dissection guided based on the presence of biopsy-proven disease in the associated compartment. Postoperative radioiodine ablation is not indicated, except in the case of combination histology in which locoregional or distant metastases include a proportion of PTC or FTC. Adjuvant external-beam radiation is reserved for the patient judged to be at high risk of recurrence who has exhausted all surgical options, and is typically administered only after multiple operations. For those with distant metastatic disease and evidence of progression, two multitargeted tyrosine kinase inhibitors, vandetinib (a RET, epidermal growth factor [EGFR], and vascular endothelial growth factor receptor [VEGFR] inhibitor) and cabozantinib (a RET, MET proto-oncogene, and VEGFR2 inhibitor) are approved as single-agent therapy by the United States Food & Drug Administration, with ongoing promising phase I/II clinical trials for others (selpercatinib and pralsetinib).[83–85] Antimotility drugs and somatostatin analogs may be helpful for symptom relief of the hypersecretory diarrhea and flushing that may be seen with advanced MTC. Localized therapies (hepatic embolization strategies, surgical metastasectomy) may be employed in well-selected patients to palliate symptoms or delay disease progression. Although still in its therapeutic infancy, peptide receptor radionuclide therapy has shown promising results with improved survival in highly selected patients.[86]

ANAPLASTIC THYROID CANCER

ATC is a rare and aggressive malignancy which has traditionally been treated with palliative measures. Approximately 46% of patients present with known distant metastases, and often those without definite distant metastases have radiographically occult disease. The median overall survival for all patients is 3 to 5 months, with 1-year survival of 20%.

Traditionally surgical therapy for ATC has been limited to the palliation of acute airway compromise, although occasionally a small ATC limited to the thyroid or with limited extension to immediate surrounding tissues may be identified and 6 treated aggressively with curative intent. For those with disease amenable to resection, multimodal adjuvant therapy with taxane or platinum-based chemotherapy and radiation has been associated with improved overall survival as compared to palliative care, although often with limited overall impact (1-year OS 42%).[87]

Recently novel multidisciplinary efforts are extending survival and the discovery of the targetable BRAFV600E mutation in 25% to 45% of ATCs has provided at least some hope for life-prolonging therapy. In 2018, the dual-agent BRAF/MEK inhibitors dabrafenib and trametinib became the first FDA-approved targeted agents for ATC based on the results of a phase II open label trial in 16 patients that showed an overall response rate of 69% (1-year estimate of OS 80%, median not reached).[88] Since then, investigators at the same institution have utilized this regimen in a neoadjuvant fashion to downstage patients with initially unresectable disease, with six of six patients responding sufficiently to allow complete surgical resection. Overall survival was 100% at 6 months, and 83% at 1 year, with two patients dying of complications from distant metastases without evidence of locoregional recurrence.[89] The addition of checkpoint inhibitors such as pembrolizumab at the time of progression has been used to further extend survival.[90] Future investigations of the combination of immunotherapy and targeted agents are needed, and care of the patient with ATC should take place in a multidisciplinary setting with experience in management of this rare and aggressive disease.

OTHER THYROID MALIGNANCIES

Primary thyroid lymphoma, most commonly non-Hodgkin lymphomas of B-cell origin, comprise <5% of thyroid cancers. Patients often describe a rapidly enlarging mass with compressive symptoms and commonly have a history of hypothyroidism with evidence of HT. Distinguishing a thyroid lymphoma may be accomplished with FNA biopsy and/or core needle biopsy, with surgical resection reserved for diagnostically ambiguous cases. Definitive therapy mirrors the treatment of the lymphoma with chemotherapy and radiation.

Metastases to the thyroid from renal cell carcinoma, breast, lung, gastrointestinal cancers, melanoma, and sarcoma have been reported. Definitive treatment is based in the appropriate therapy for the primary disease process, with resection reserved for palliation of compressive symptoms.

STAGING OF DIFFERENTIATED, MEDULLARY, AND ANAPLASTIC THYROID CANCER

In 2018 the American Joint Committee on Cancer (AJCC) released the 8th edition[91] update for the staging of thyroid cancer, with several key changes. For differentiated thyroid cancers

(papillary, follicular, and Hurthle): (1) the age stratification between prognostic groups was dichotomized at 55 years (previously 45); (2) microscopic perithyroidal soft tissue invasion (extrathyroidal invasion) was removed from the tumor (T) classification, reserving the T3b status to tumors with gross extrathyroidal extension visualized at the time of surgery only; (3) superior mediastinal nodal disease (level VII) was combined with level VI as N1a disease (previously N1b); and (4) N1 disease no longer upstages patients to stage III: patients with N1 disease are stage I if they are <55 years of age, and stage II if they are ≥55 years of age, as summarized in **Table 75.7A–C**.[91,92] Recently a large retrospective single-institution analysis corroborated the anticipated 10-year disease-specific survival estimated by the AJCC, however further evaluations and refinements will continue to be necessary.[92,93]

For patients with MTC, the same tumor-node-metastasis (TNM) staging system is currently in use, without the stratification by age (**Table 75.7D**).[94] The limitations of applying a system designed primarily for PTC to a different disease process are inherently evident. Recently a large analysis using the National Cancer Database (NCDB) and the United States Surveillance, Epidemiology, and End Results program (SEER) showed that the current staging system upstages a large proportion of patients with MTC to stage IV and does not accurately stratify groups based on survival. The authors used recursive partitioning to propose new staging groups and demonstrated improved separation of survival curves by grouping patients with T1 and T2 tumors without nodal disease into stage I, expanding stage II to include patients with nodal disease or larger tumors without nodal disease, and limiting stage IV to only patients with distant metastases.[94] As with other rare cancers, continued refinements to a universal staging system will require assumptions based on large databases.

The ATC staging system follows the same definitions for TNM categories as PTC and MTC, however, all patients with ATC are considered to have stage IV disease (Table 75.7E).[91]

NONSURGICAL THERAPEUTIC ADJUNCTS FOR THYROID CANCER

TSH Suppression

Considered a trophic factor, TSH may be suppressed below physiologic levels by exogenous administration of thyroid hormone (levothyroxine) in patients with moderate- to high-risk differentiated thyroid cancer (papillary, follicular, and Hurthle cell cancers). The goal TSH range for patients with high-, moderate-, and low-risk disease are <0.1 mU/L, 0.1 to 0.5 mU/L, and 0.5 to 2 mU/L, respectively.[12] The suppressive effects of TSH therapy must be balanced against the long-term health effects of occult hyperthyroidism, including the risks of arrhythmias and osteoporosis, and the degree of suppression is typically reduced in patients without evidence of disease over time. Historically TSH suppression was thought to reduce the size of benign thyroid nodules, but the effect on nodule size is modest and potential side effects from suppression outweigh the benefit. Suppression for patients with benign nodules is not recommended.

Radioiodine Therapy

Radioiodine may be used in a dose-dependent manner to diagnose residual thyroid tissue, ablate remnant thyroid tissue, or treat residual or recurrent disease in patients with follicular-derived thyroid cancers. As thyroid cells should be adequately stimulated by TSH and deprived of iodine, the timing of postoperative RAI uptake scans and/or therapeutic administrations depends on the patient and specific sequence of therapy. Evaluation should be delayed at least 4 to 8 weeks after an iodine-rich contrasted CT scan is performed. Withdrawal of thyroid hormone replacement will allow the TSH to rise to stimulatory levels, but requires a 4- to 5-week period given the long half-life of levothyroxine and may result in significant hypothyroid symptoms. Replacement with T3 (liothyronine) during this time period allows a shorter withdrawal period of 2 weeks, or alternatively recombinant human TSH can be administered to avoid the withdrawal period entirely.

Selection for administration of adjuvant RAI is a careful risk assessment that requires close communication between surgeon and endocrinologist and an understanding of interobserver variability. Extent of disease at presentation, histopathologic factors, and postoperative structural or biochemical evidence of disease, influence the decision to administer RAI (Fig. 75.7).[12] In general, RAI is encouraged for patients with distant metastases, primary tumors >4 cm or with gross extrathyroidal extension, and lymph node involvement.

External-Beam Radiation Therapy

External-beam radiation therapy (EBRT) is rarely indicated for the treatment of locoregional differentiated thyroid cancer, and should only be used in the neck after all surgical options are exhausted. For poorly differentiated tumors that are anticipated to be RAI resistant and that have invaded the trachea or esophagus, surgical awareness of the possible need for EBRT and subsequent planning with flap placement is beneficial to prevent fistula. In contrast, EBRT is employed more often for the palliation of distant bony metastases, which are less likely to be fully treated by RAI. Bone-directed therapeutics (i.e., zoledronic acid or denosumab) may be combined with EBRT in the treatment of bony metastases with synergistic effect.

Metastatic Disease and Systemic Therapy

RAI therapy is a cornerstone of therapy for patients with locally advanced/unresectable or distant metastatic disease. Unfortunately, while 5% to 15% of patients with differentiated thyroid cancer display loss of differentiation and subsequent inability to uptake iodide (RAI-refractory disease), up to 50% of patients with metastatic disease will be RAI refractory. Patients with RAI-refractory disease have poorer prognosis, with 5-year disease-specific survival rates between 60% and 70%.[95]

Table 75.7 The American Joint Committee on Cancer Tumor-Node-Metastasis 8th Edition Staging System for Papillary Thyroid Cancer, (A) Tumor Staging, (B) Nodal Staging, and (C) Stage Grouping and Anticipated 10-yr Disease-Specific Survival, with modifications for Medullary Thyroid Cancer (D), and Anaplastic Thyroid Cancer (E)

Table 75.7A Tumor Staging

T Stage	Description
T0	No evidence of tumor
T1	<2 cm, confined to the thyroid
1a	<1 cm
1b	≥1 cm but <2 cm
T2	>2 cm but ≤4 cm
T3	>4 cm, confined to the thyroid or with gross extrathyroidal extension to the strap muscles only
3a	>4 cm without extrathyroidal extension
3b	Presence of gross extrathyroidal extension
T4	Gross extrathyroidal extension beyond the strap muscles
4a	Invasion into the soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
4b	Invasion into the prevertebral fascia or encasement of the carotid artery or mediastinal vessels

Table 75.7B Nodal Staging

N Stage	Description
N0	No evidence of nodal metastases
N0a	Histologic evidence of benign lymph nodes
N1	Presence of nodal metastases
1a	Metastases in levels VI or VII
1b	Metastases in levels I–V or retropharyngeal nodes

Table 75.7C Stage Grouping and Anticipated 10-Yr Disease-Specific Survival

Age (Yrs)	Stage	Tumor-Node-Metastasis Description	Anticipated 10-Yr Disease-Specific Survival (%)[91]	10-Yr Disease-Specific Survival (Tam et al.)[92]
<55	I	$T_{any}N_{any}M_0$	98–100	99.8%
	II	$T_{any}N_{any}M_1$	85–95	88.3%
≥55	I	$T_{1-2}N_0M_0$	98–100	99.8%
	II	$T_{1-2}N_{1a/b}M_0$ $T_{3a/b}N_0M_0$	85–95	88.3%
	III	$T_{4a}N_{any}M_0$	<50	72.4%
	IVa	$T_{4b}N_{any}M_0$	<50	71.9%[a]
	IVb	$T_{any}M_{any}M_1$	<50	–[a]

[a]Analyzed as stage IV inclusively.

Table 75.7D Staging Groups for Medullary Thyroid Cancer

Stage	TNM	Overall Survival (Adam et al.) (%)[94]
I	$T_1N_0M_0$	95
II	$T_{2-3}N_0M_0$	91
III	$T_{1-3}N_{1a}M_0$	89
IVa	$T_4N_{any}M_0$ $T_{1-3}N_{1b}M_0$	68[a]
IVb	$T_{4b}N_{any}M_0$	–[a]
IVc	$T_{any}N_{any}M_1$	–[a]

[a]Analyzed as stage IV inclusively in this retrospective analysis of 1,252 patients from the National Cancer Database.

Table 75.7E Staging Groups for Anaplastic Thyroid Cancer		
Stage	**TNM**	**Clinical Description**
IVA	$T_{1\text{-}3a}N_0M_0$	Intrathyroidal, surgical resectable
IVB	$T_{1\text{-}3a}N_1M_0$ $T_{3b}N_{any}M_0$ $T_4N_{any}M_0$	Extrathyroidal (due to locoregional nodal disease or direct extension) but without distant metastases
IVC	$T_{any}N_{any}M_1$	Distant metastases

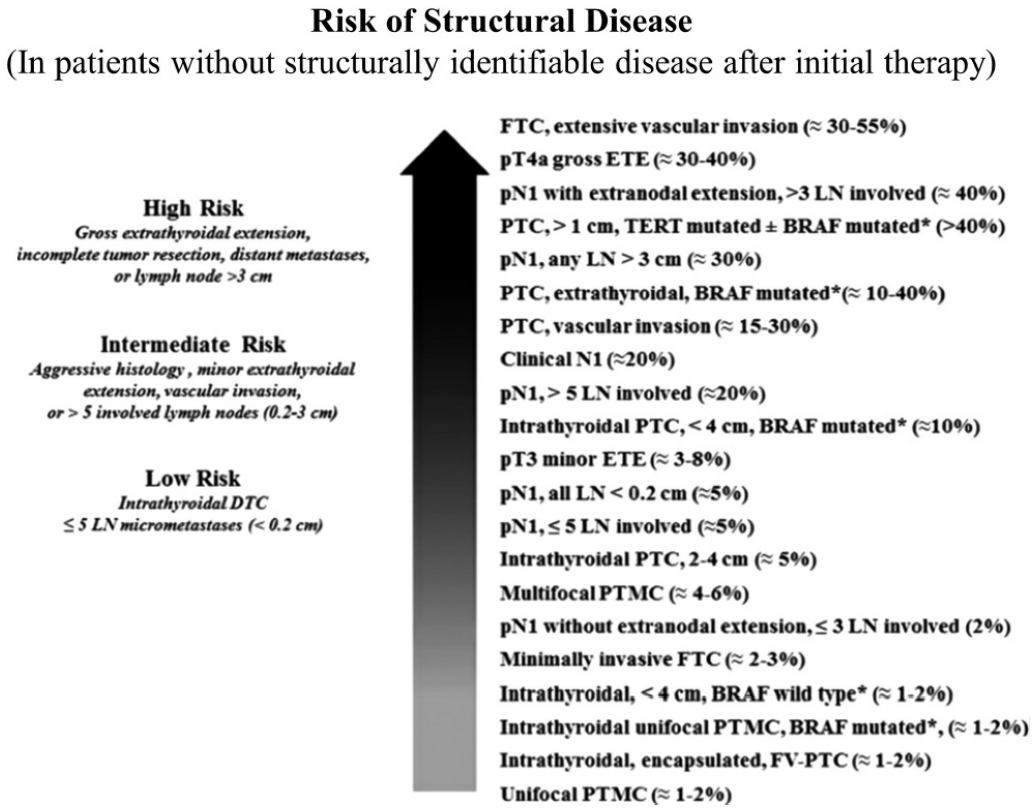

Figure 75.7 The American Thyroid Association risk stratification. In general, radioactive iodine (RAI) is encouraged for high-risk patients, considered for intermediate-risk patients, and avoided for low-risk patients. (Reprinted with permission from Haugen et al.[12])

The cornerstone of systemic therapy for thyroid cancer is based on an understanding of the altered signaling pathways, including point mutations in *BRAF* (40%) and the *RAS* family of proto-oncogenes (38%), rearrangement of *RET/PTC* (10% to 20%), rearrangements and mutations in anaplastic lymphoma kinase (*ALK*) and neurotrophic tropomyosin receptor kinase (*NTRK*)*1-3*.[85] Oral multitargeted tyrosine kinase inhibitors such as sorafenib (VEGFR, platelet-derived growth factor receptor [PDGFR], and RAF kinase inhibitor) and lenvatinib (VEGFR1-3, fibroblast growth factor receptors 1–4, PDGFRα, RET, and c-kit

signaling pathway inhibitor) are FDA approved for RAI-refractory differentiated thyroid cancer and poorly differentiated thyroid cancer. Both drugs were approved on the basis of phase 3 randomized placebo-controlled trial that demonstrated longer progression-free survival; Lenvatinib was also associated with improved overall survival in select subsets of patients (age >65 and follicular histotype).[85]

For patients with *BRAFV600E* mutated thyroid cancer either single-agent vemurafenib or dabrafenib (BRAF inhibitors) or combination therapy with trametinib or cobimetinib (MEK inhibitors, typically combined with dabrafenib) have demonstrated partial responses and promising progression-free survival (as opposed to placebo). The addition of the MEK inhibitor blocks the paradoxical activation of MAPK signaling and the increase in cutaneous malignancies observed with single-agent BRAF inhibitors. Additionally, the combination of BRAF and MEK inhibitors is thought to promote redifferentiation—or restoration of the ability of thyroid cancer cells to uptake RAI—and has great interest as adjuvant therapy for RAI-resistant disease.[85]

Other potential avenues of systemic therapy that are undergoing promising exploration currently include the mammalian target of rapamycin (mTOR) inhibitors (everolimus and temsirolimus), NTRK inhibitors (larotrectinib or entrectinib, relevant for the patient with gene fusions in NTRK, ALK, and ROS1), and selective RET inhibitors (selpercatinib and pralsetinib, as discussed in the MTC section). Immunotherapy and specifically anti-programmed cell death protein 1 (PD-1) inhibitors are also under investigation in combination with other targeted therapy.[85]

THYROID SURGERY

Shaped by contributions from Theodor Billroth, Theodor Kocher, and William Halsted, modern thyroid surgery is safe and effective. Thyroid lobectomy, total thyroidectomy, and occasionally isolated thyroid isthmusectomy may be performed. Historically, subtotal thyroidectomy (the Hartley-Dunhill procedure, in which approximately 2.5 gm of tissue is left on one side to avoid postoperative hypothyroidism) was performed for thyrotoxicosis, with the end objective to preserve native thyroid function. While this approach may still be useful in geographic areas in which thyroid hormone replacement is not readily available, subtotal thyroidectomy is rarely performed today. Near-total thyroidectomy, in which a conscious decision is made to leave a minor amount of thyroid tissue at the insertion of the RLN, is appropriate for patients with benign disease and anatomy such that further dissection may compromise the nerve.

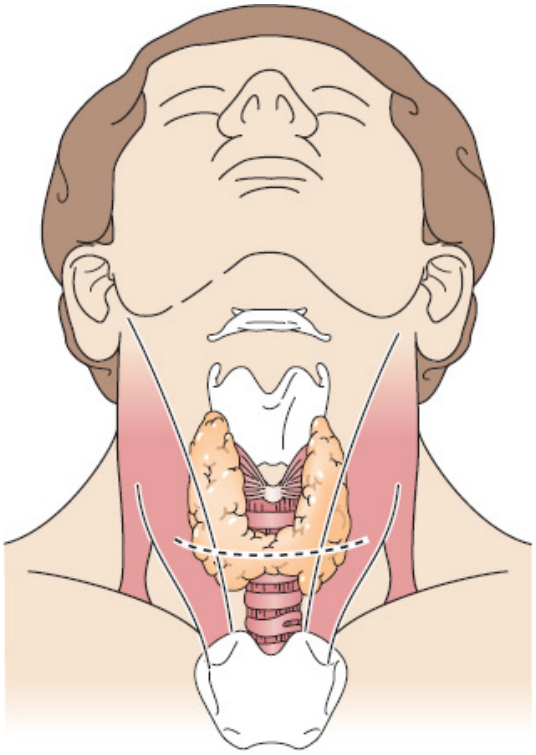

Figure 75.8 With the patient's neck extended, the *dashed line* indicates the appropriate site of incision for thyroid resection. Camouflage within an existing skin crease is often possible.

Technique

The patient is placed in the semi-Fowler position with the neck gently hyperextended and a horizontal shoulder roll placed to open the surgical field. A natural skin crease one- to two-finger breadth above the clavicles and approximately 1 cm below the cricoid cartilage is made (Fig. 75.8) and the subcutaneous tissue and platysma are divided. Subplatysmal skin flaps may be developed, extending to the thyroid cartilage, sternal notch, and laterally to the sternocleidomastoid muscles, prior to dividing the midline raphe. As an alternative to subplatysmal skin flaps, the avascular space between the sternohyoid and sternothyroid muscles may be gently dissected after the midline raphe is divided. Attention should be paid to the presence of a pyramidal lobe (which should not be inadvertently left during a total thyroidectomy) and/or midline prelaryngeal (Delphian) lymph nodes (which should be assessed early during an operation for malignancy). The middle thyroid vein is divided and the thyroid is rotated medially into the field, taking care to identify and dissect parathyroid glands laterally.

Normal parathyroid tissue is subtle and may be difficult to identify; it is characterized by a slight brownish color with a fine capillary vascular pattern not typically seen in adjacent lymph nodes, fat, or thymus. Knowledge of their common locations and careful dissection along the capsule of the thyroid will prevent inadvertent injury to the parathyroids or their blood supply. In the event of inadvertent resection or devascularization, the parathyroid should be confirmed with frozen section, morselized, and reimplanted—most commonly into

the sternocleidomastoid muscle. Deliberate marking of the reimplantation site with a Prolene suture facilitates future exploration in the event of hyperparathyroidism and marking the pocket with a radiopaque clip allows radiographic identification.

The superior pole is approached with close dissection along the capsule of the gland to avoid injury to the external branch of the superior laryngeal nerve. Although the external branch of the superior laryngeal nerve is not always directly visualized, in cases where it is observed, a nerve stimulator can be used to elicit contraction of the cricothyroideus muscle. The RLN should be directly visualized consistently and is often identified approximately 1.5 cm away from its insertion, facilitated by gentle traction of the surrounding tissues. Careful dissection along the anterior surface of the nerve and meticulous attention to early branches will preserve function (including attention early branching which may separate sensory fibers posteriorly toward the esophagus; injury of this posterior branch is associated with aspiration due to sensory dysfunction). Awareness of the possibility of a nonrecurrent laryngeal nerve, although rare (<1%), is important. More commonly found on the right side, a nonrecurrent laryngeal nerve is associated with an aberrant subclavian artery (most commonly retroesophageal).[2,3,96] Following identification of the course of the RLN, the inferior thyroid pole vessels can be divided near the thyroid capsule. Careful mobilization of the thyroid to the midline continues and Berry ligament is encountered along the anterior surface of the trachea just medial to the insertion of the RLN. Attention to hemostasis is important, as small vessels in this area in particular may bleed and obscure visualization of the RLN. The operation, as appropriate, proceeds in similar fashion on the contralateral side.

Surgical Energy Devices

There is variation in the use of specific energy devices during thyroidectomy, without a standard consensus regarding an optimal energy technique. In general, literature supports the use of energy devices with decreased operative time and similar complication rates.[97–99] The surgeon should be familiar with the use of electrocautery, bipolar electrocautery, and/or surgical energy devices such as the Harmonic Scalpel or Ligasure and the heat generation and lateral thermal spread of each. Successful thyroidectomy requires knowledge of the operation and relevant anatomy and facile use of more than one technique with the ability to adapt according to need.

Intraoperative Nerve Monitoring

Intraoperative nerve monitoring (IONM) has been proposed as an adjunct measure to provide dynamic functional feedback to enhance surgical decision making. It is not designed or proposed to replace surgeon familiarity with anatomy, gentle tissue handling, and meticulous dissection of the RLN. In the most commonly used form, intermittent IONM involves a hand-held probe that can be used to stimulate the RLN (or the vagus nerve). The transmitted signal is detected via an electrode attached to the endotracheal tube that is in contact with the vocal cords. Successful use of this system requires both the surgeon and

anesthesiologist understanding of the anatomy and positioning, as well as the ability to evaluate and troubleshoot the circuit and correctly interpret the signals. When used appropriately, feedback from the system may alert the surgeon to neuropraxia not readily recognized visually, although it is important to note that IONM has not been shown to consistently reduce the rate of nerve injury.[100–103] Information from IONM may be particularly useful in high-risk patients, including patients with bulky thyroid disease, thyrotoxicosis, or extensive malignancy, patients with known unilateral vocal cord palsy, and in reoperative settings. Both the American Academy of Otolaryngology Head and Neck Surgery[96] and the ATA[12] support the consideration of IONM during thyroidectomy.

Extent of Operation

Historically total thyroidectomy was the procedure of choice for most patients with thyroid cancer, with lobectomy reserved for very small unifocal tumors in low-risk patients. With improved understanding of the often indolent disease course of well-differentiated PTC, examination of large-scale datasets supports performing thyroid lobectomy for broader indications, with minimal impact on long-term survial.[104–107] The ATA encourages the consideration of lobectomy for well-selected younger patients (age ≤45 years) without family history or excess radiation exposure who have solitary tumors smaller than 4 cm, without evidence of extrathyroidal extension, lymphadenopathy, high-risk histopathology (i.e., tall cell variant, poor differentiation), or distant metastases, as RAI is unlikely to be required in these patients, and salvage completion thyroidectomy is a tenable option in the event of locoregional 7 recurrence.[12] The possibility of immediate or delayed completion thyroidectomy should be discussed in any cancer patient considering lobectomy. In addition to disease-related factors, discussion should also consider patient values regarding the possibility of postoperative hormone supplementation (which is required in about 20% of patients undergoing lobectomy, and is utilized more frequently in those who require TSH suppression as part of their oncologic therapy). The decision to proceed with lobectomy also mitigates the value of thyroglobulin as a postoperative tumor marker, as native thyroid tissue will also produce the protein. Finally, healthcare accessibility and compliance with follow-up should also be factored into the decision of lobectomy versus total thyroidectomy.

Lymph Node Dissection

Clinically and radiographically occult cervical lymph node metastases may be present in 24% to 82%[73] of patients with differentiated thyroid cancer selected for lymph node dissection, yet the prognostic value of prophylactic nodal dissection in these patients is controversial. Proponents cite the eradication of any microscopic disease (that would otherwise present as persistent or potentially recurrent) at the initial operative setting, thereby avoiding a reoperative field. Likely due to selection bias, retrospective analyses of prophylactic central node dissection have conflicting results, with some showing improved locoregional control,[108,109] and others showing minimal if any difference.[73,110] The information gained from additional dissection increases the likelihood of receiving adjuvant

RAI,[111] but also increases the risk of postoperative hypoparathyroidism[112–114] (3.45% vs. 1.55% in one meta-analysis).[73] The ATA recommends consideration of prophylactic central node dissection for patients with differentiated thyroid cancer who are most likely to demonstrate clinically relevant nodal metastases (T3/T4 tumors, extrathyroidal extension).[12] In contrast, prophylactic central node dissection should be performed for patients with known MTC.[21]

Therapeutic nodal dissection should be compartment based and performed when there is presence of radiographic biopsy-proven 8 disease. The anatomic boundaries of the central compartment begin superiorly at the hyoid bone, extend inferiorly to the innominate vein, and are bounded medially by the corresponding carotid artery to the midline of the trachea. The RLN should be identified and skeletonized, and care should be taken when sweeping the fibrofatty tissue to preserve the parathyroids and their blood supply.

Lateral neck dissection is most commonly performed for levels II–IV, with the decision to include levels I or V based on the presence of disease. The relevant anatomic boundaries include the belly of the digastric muscle superiorly, the sternocleidomastoid laterally, the clavicle inferiorly, the sternohyoid muscle medially, and the precervical fascia investing the scalene posteriorly. Identification and preservation of the spinal accessory, vagus, and phrenic nerves is essential. Awareness of the marginal mandibular nerve at the angle of the jaw will prevent injury (often related to pressure from a retractor). The hypoglossal nerve is not commonly seen but the surgeon should be cognizant of it. Lymphatic channels and the thoracic duct, (in the left neck) when visualized, should be carefully ligated.

COMPLICATIONS

Thyroid surgery is associated with low rates of overall morbidity (6% to 12%) and mortality (<1 in 10,000).[115,116] The most common serious complications after thyroidectomy include hypoparathyroidism, RLN injury, and/or postoperative hematoma.

Hypoparathyroidism

Hypoparathyroidism, or impaired/inadequate PTH secretion leading to hypocalcemia and hyperphosphatemia, is the most common thyroid-specific complication after thyroid surgery and may be transient or permanent. Estimates in the literature describe hypoparathyroidism in 0.33% to 68% of patients undergoing thyroid surgery.[36] This wide variability is multifactorial, influenced by differences in patient disease and risk factors, extent of the operation and surgeon experience, and a lack of consensus regarding a uniform definition of either transient or permanent hypoparathyroidism. Patients with hypoparathyroidism experience paresthesias of the hands, feet, or lips and may progress to tetany; laboratory evaluation confirms hypocalcemia. Treatment involves supplementation with oral calcium and/or calcitriol, with intravenous calcium infusion reserved for severe cases. Perioperative assessment of parathyroid hormone levels assists in identification of patients at risk for postthyroidectomy hypoparathyroidism.

Recurrent Laryngeal Nerve Injury

Loss of function of a unilateral RLN can result in voice changes, aspiration, dysphagia, and difficulty breathing. While some patients compensate well and the injury may be silent, many experience symptoms that impair their quality of life with far-reaching impacts on emotional and socioeconomic well-being. Bilateral loss of function of the RLNs results in a substantially morbid outcome, as paralysis of the cords in a paramedian position causes glottic obstruction and requires tracheotomy. Rates of VCP in the literature are highly variable due to differences in symptom severity, divergent practice patterns (i.e., routine postoperative laryngoscopy vs. symptom elicited), and lack of consensus in definition (transient vs. permanent). In general, in experienced hands the rate of permanent unilateral VCP should be <1%.

Hematoma

Postoperative hematoma can create a life-threatening airway emergency through both direct compression of the cartilaginous trachea and impaired venous and lymphatic drainage with resulting laryngopharyngeal edema. Hematoma after thyroid surgery fortunately occurs only rarely in experienced hands (0.7% in one national series of >19,000 patients,[117] range 0.49% to 4.3%).[118] Meticulous attention to hemostasis is essential.

In general, thyroid surgery is an elective and well-tolerated procedure. Surgeon experience with thyroid surgery correlates with outcomes,[115,119] with patients undergoing surgery by low-volume surgeons (≤25 cases per year) more likely to experience any complication (odds ratio 1.51, $p = 0.002$). In addition to surgeon experience, operative risk is dependent on multiple factors, including the underlying diagnosis, the impetus for and extent of surgery, and patient age and comorbidity. A thorough understanding of anatomy and careful attention to surgical technique is essential to ensuring optimal outcomes for patients undergoing thyroid surgery.

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76

Parathyroid Glands

Gerard M. Doherty

Key Points

1 The normal parathyroid glands are flat, ovoid, and red-brown to yellow. Their dimensions are 5 to 7 mm × 3 to 4 mm × 0.5 to 2 mm, and they weigh between 30 and 50 mg each.

2 Parathyroid hormone (PTH) is the single most important hormonal regulator of calcium and phosphate metabolism in humans with direct effects on the skeleton and kidney and indirect effects on the intestine, mediated through vitamin D.

3 The demonstration of an elevated plasma PTH concentration alone does not establish the diagnosis of hyperparathyroidism; with a simultaneous elevated serum calcium level, this finding is virtually diagnostic.

4 A large proportion of patients with the diagnosis of hyperparathyroidism is minimally or asymptomatic and the appropriate treatment for these patients remains controversial.

5 It is routinely possible to identify abnormal parathyroid glands prior to operation for most patients, allowing the surgeon to know where to start the exploration; intraoperative PTH measurement can be used to confirm removal of all hyperfunctioning parathyroid tissue, that is, when to stop the operation.

ANATOMY

Typically, each person has four parathyroid glands—two superior and two inferior (**Fig. 76.1**).[1] The normal parathyroid glands are flat, ovoid, and red-brown to yellow. They measure 5 to 7 mm × 3 to 4 mm × 0.5 to 2 mm and weigh between 30 and 50 mg each. 1 The lower glands are usually larger than the upper glands. The superior glands are most often embedded in the fat on the upper posterior surface of the thyroid lobe near the site where the recurrent laryngeal nerve enters the larynx. The inferior glands are usually more ventral and lie close to or within the portion of the thymus gland that extends from the inferior pole of the thyroid gland into the chest. Although

this anatomy is fairly consistent, substantial variations from the usual can occur, and it is essential that the surgeon have a thorough understanding of these anatomic variations.

Variations in parathyroid gland anatomy are primarily caused by differences in patterns of embryogenesis. During the fourth and fifth weeks of fetal development, a series of four pharyngeal pouches develop (**Fig. 76.2**). The superior parathyroid gland arises from the fourth pharyngeal pouch in conjunction with the lateral thyroid, and the inferior gland arises from the third pouch along with the thymus. The derivatives of each pouch then migrate together so that the superior parathyroid gland usually remains in close association with the upper pole of the thyroid, although it may occasionally be loosely attached by a long vascular pedicle, migrating caudad along the esophagus into the posterior mediastinum. Occasionally, a gland may be totally embedded in the thyroid parenchyma. The inferior parathyroid gland descends with the thymus, but this migration is extremely variable. Inferior glands can be found anywhere from the pharynx to the mediastinum. Regardless of their location, they usually adhere to the thymus or are within the thyrothymic ligament. Supernumerary glands can be identified in up to 15% of patients, most often in association with the thymus. Autopsy studies suggest that four parathyroid glands are virtually always present.

The arterial supply to both the superior and inferior parathyroid glands is usually from the inferior thyroid artery, although it may arise from the superior thyroid or thyroidea ima arteries or from the rich anastomosis of vessels supplying the larynx, trachea, and esophagus. A mediastinal parathyroid gland that descended during embryonic development usually receives its blood supply from either the internal mammary artery or small arteries within the thymus; however, an enlarged parathyroid gland that grows into the mediastinum usually carries with it the corresponding branch of the inferior thyroid artery. The inferior, middle, and superior thyroid veins, which drain the parathyroid glands, empty into the internal jugular vein or the innominate vein.

Histologically, the normal adult parathyroid gland is about half parenchyma and half stroma, including fat cells (**Fig. 76.3**). In children, the gland is almost entirely composed of parenchymal chief cells. Beginning at puberty, adipocytes appear and, with age, occupy an increasing proportion of

the gland. Also with increasing age, acidophilic, mitochondria-rich oxyphil cells are present in increasing numbers and are intermixed with the glycogen-laden, polygonal, water-clear cells. The functional significance of the various cell types remains unclear, although the water-clear cells and oxyphil cells are probably derived from the chief cells and secrete parathyroid hormone (PTH).

PHYSIOLOGY

The primary physiologic role of the parathyroid gland is the endocrine regulation of calcium and phosphate metabolism. Average daily exchanges of these ions from the gastrointestinal tract, bone, and kidney are shown in **Figure 76.4**.

Calcium

Calcium ion plays a critical role in all biologic systems. It participates in enzymatic reactions and is a mediator in hormone metabolism. Calcium is intimately involved in the physiology of neurotransmission, muscle contraction, and blood coagulation. It is the major cation in bone and teeth. It represents about 2% of the average body weight, and almost all calcium is contained in the skeleton. The normal range of serum calcium is 9 to 10.5 mg/dL (4.5 to 5.2 mEq/L), and the daily variation in a normal person is generally less than 10%. About half of the total serum calcium is in an ionized, biologically active form; 40% is bound to serum protein, mainly albumin, and 10% forms compounds with organic ions, such as citrate. The total serum calcium concentration is a function of the serum protein content, and because hydrogen ion competes with calcium for the same binding sites on albumin, the body fluid pH is important. In general, for every change of 1 g/dL in the serum albumin level, a direct alteration of 0.8 mg/dL occurs in the serum calcium concentration. Almost all the physiologically important activity of calcium is represented by the unbound, or free, fraction.

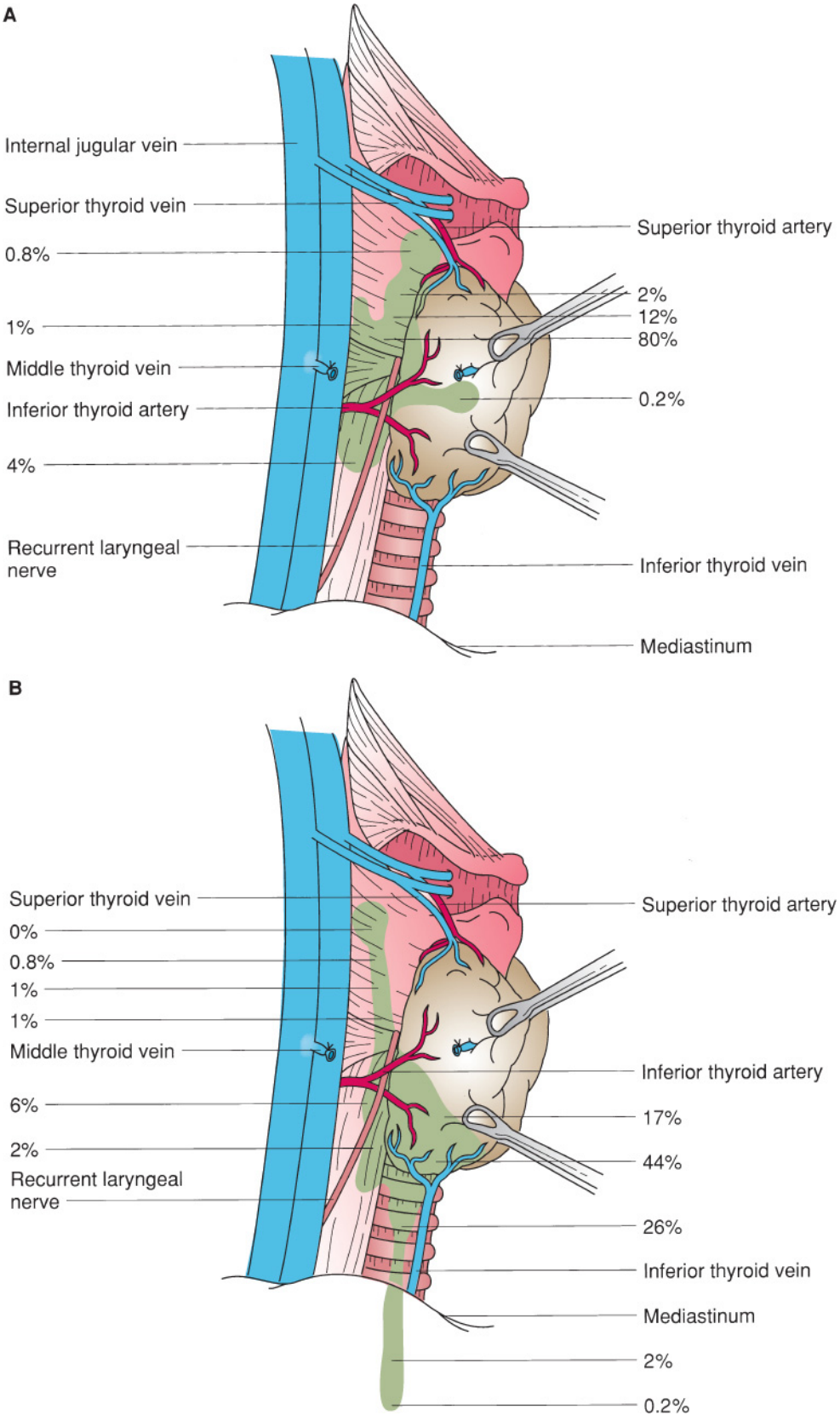
A
Internal jugular vein
Superior thyroid vein
0.8%
1%
Middle thyroid vein
Inferior thyroid artery
4%
Recurrent laryngeal nerve
Superior thyroid artery
2%
12%
80%
0.2%
Inferior thyroid vein
Mediastinum
B
Superior thyroid vein
0%
0.8%
1%
1%
Middle thyroid vein
6%
2%
Recurrent laryngeal nerve
Superior thyroid artery
Inferior thyroid artery
17%
44%
26%
Inferior thyroid vein
Mediastinum
2%
0.2%

Figure 76.1 Schematic illustration of the location of the superior (**A**) and inferior (**B**) parathyroid glands from 503 autopsy studies. The more common locations are indicated by the shaded areas. The numbers represent the percentage of glands found at each location. Typically, the glands were posterolateral to the thyroid and above or below the junction of the inferior thyroid artery with the recurrent laryngeal nerve.

Calcium is absorbed in its inorganic form from the duodenum and proximal jejunum. The rate of absorption is precisely regulated according to body calcium status. The calcium in the extracellular fluid is constantly being exchanged with that in the intracellular fluid, the exchangeable bone, and the glomerular filtrate. Calcium reabsorption by the kidney is closely related to that of sodium, and about 99% of the filtered load is reabsorbed under normal conditions.

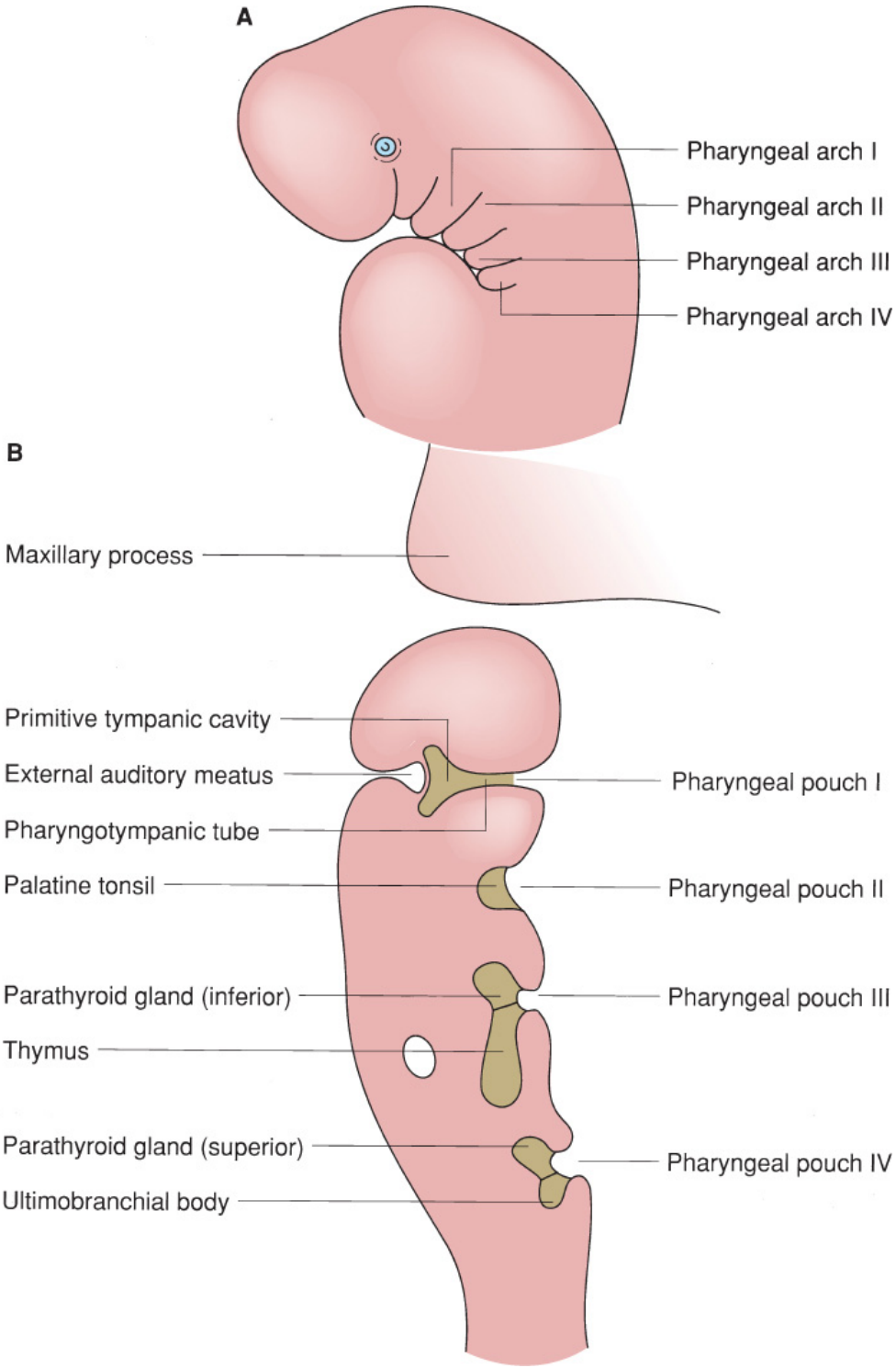

Figure 76.2 **A:** Pharyngeal arches in a 5-week embryo. The corresponding pouches extend from within the pharynx into each arch. **B:** Schematic representation of the differentiating epithelium of the respective pharyngeal pouches.

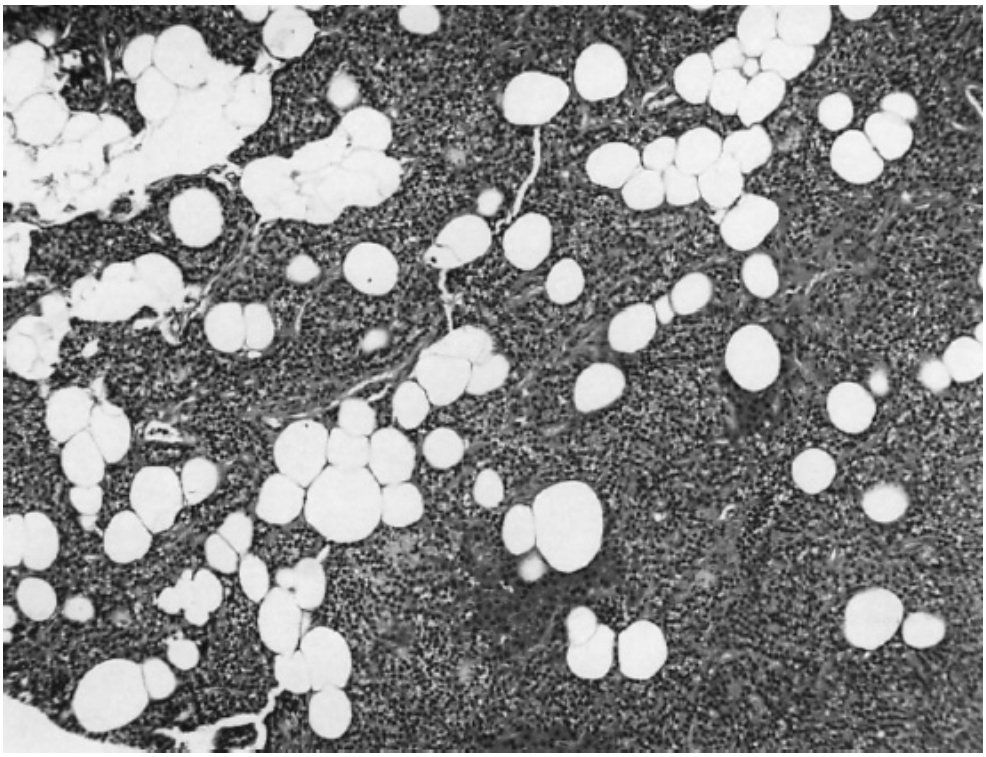

Figure 76.3 A normal adult parathyroid is composed of about half parenchyma and half fat (×150).

Phosphate

Phosphate anion is also an integral component of most biologic systems. It is critical to the pathways of glycolysis and is the functional group for a number of high-energy transfer compounds, including adenosine triphosphate. It is also the major anion in crystalline bone. Normal levels of plasma phosphate range from 2.5 to 4.3 mg/dL, and the level varies inversely with the serum level of calcium. The relation is such that the product of plasma calcium and phosphate is relatively constant ranging between 30 and 40 (with calcium and phosphate both expressed in mg/dL). When the product is above this level, the potential for the precipitation of calcium phosphate in body tissues increases.

In contrast to the percentage of calcium absorbed, the percentage of phosphate absorbed from the diet is relatively constant, and excretion usually provides the major mechanisms for regulating phosphate balance (**Fig. 76.4**). Unlike stores of calcium, the readily exchangeable soft tissue stores of phosphate, such as those in muscle, are large.

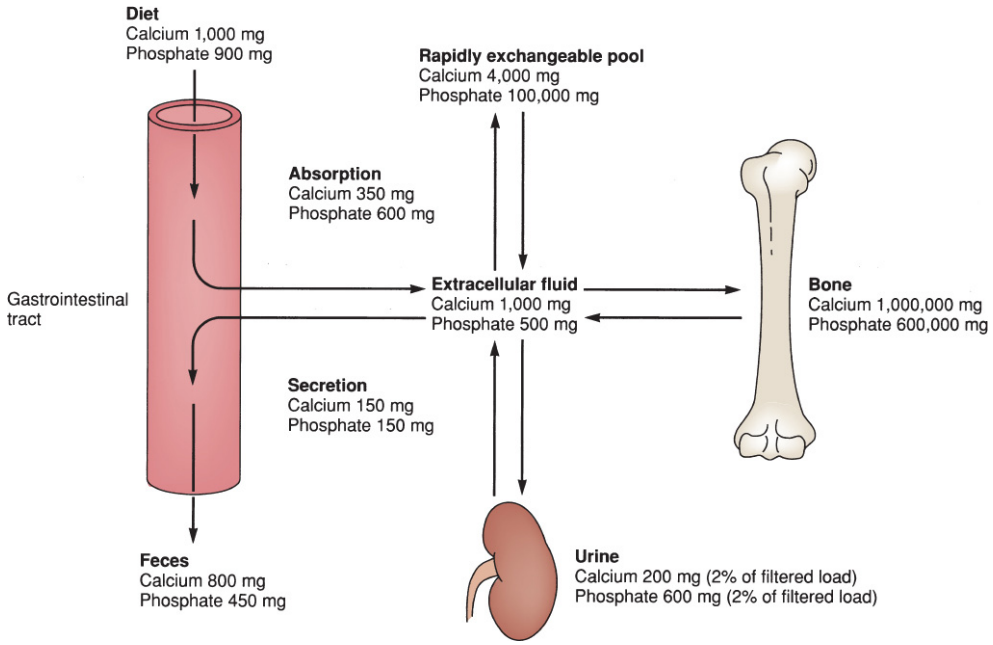

Figure 76.4 Average daily calcium and phosphate turnover in humans.

Regulation of Calcium and Phosphate Metabolism

The maintenance of calcium and phosphate homeostasis depends on major contributions from three organ systems—the gastrointestinal tract, the skeleton, and the kidneys—with minor contributions from the skin and liver.[2] The primary hormonal regulators of this metabolism are PTH, vitamin D, and calcitonin. The actions of each of these hormones in the organs are summarized in **Table 76.1**.

Parathyroid Hormone

PTH is the single most important hormonal regulator of calcium and phosphate metabolism in humans 2 . It has direct effects on the skeleton and kidney and indirect effects on the intestine, mediated through vitamin D. In target tissues, PTH binds first to membrane receptors, activating adenyl cyclase to generate cyclic adenosine monophosphate (cAMP), which regulates other intracellular enzymes.

In bone, the effects of PTH are complex, stimulating both resorption and the formation of new bone. However, sustained elevations of PTH stimulate

osteoclasts and inhibit osteoblasts. Osteocytes, in the matrix of cortical bone, may also act to reabsorb matrix in response to PTH, a process referred to as *osteocytic osteolysis*. Calcium and phosphate mobilization in response to PTH occurs in two phases. Initially, mineral is mobilized from areas of rapid equilibrium. This phase is followed by a more sustained release mediated by newly synthesized lysosomal and hydrolytic enzymes. In the kidney, PTH increases the reabsorption of extracellular fluid calcium at any given concentration, although excess secretion, because of hypercalcemia, increases the net daily amount of urinary calcium excretion. Reabsorption in the proximal tubule and loop of Henle is linked with sodium transport such that factors that alter sodium transport concomitantly alter calcium reabsorption. In contrast, reabsorption in the distal nephron is independent of sodium and directly influenced by PTH. PTH also increases phosphate excretion. This action is accompanied by enhanced bicarbonate secretion. PTH probably has only indirect effects on the gastrointestinal tract, by stimulating the hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D in the kidney.

PTH is synthesized initially as a precursor, prepro-PTH, which is sequentially cleaved in the parathyroid gland to pro-PTH and then to PTH (**Fig. 76.5**). Secretion of this 84-amino-acid molecule is controlled by a negative feedback loop with extracellular fluid calcium. Most PTH is secreted in this form and then cleaved in the liver into N- and C-terminal fragments. The N-terminus contains most of the biologic activity and is rapidly degraded by the liver, whereas the inactive C-terminus is slowly metabolized by the kidney.

Table 76.1 Hormonal Regulation of Calcium and Phosphate Metabolism

Location	Parathyroid Hormone	Vitamin D	Calcitonin
Gastrointestinal tract	No direct effect	Stimulates calcium and phosphate absorption	No direct effect
Skeleton	Stimulates calcium and phosphate resorption	Stimulates calcium and phosphate resorption	Inhibits calcium and phosphate resorption
Kidneys	Stimulates calcium resorption	No direct effect	Inhibits calcium and phosphate resorption

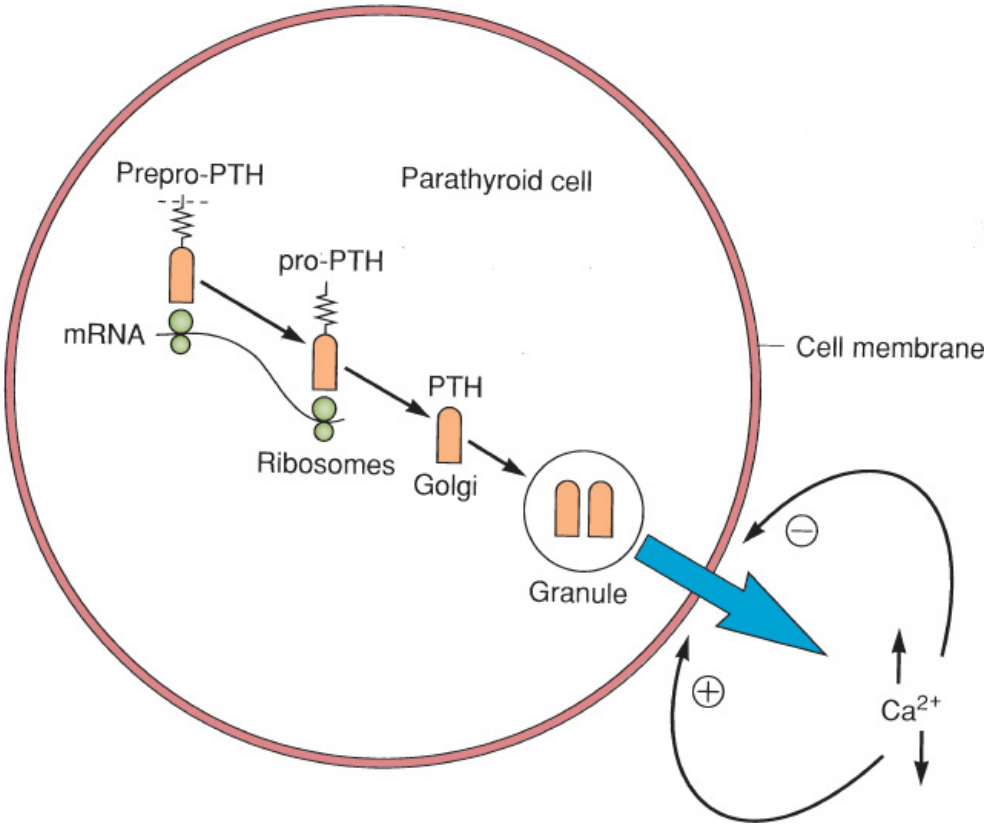

Figure 76.5 The parathyroid gland produces a precursor of PTH, prepro-PTH, that is sequentially cleaved to pro-PTH and PTH. PTH secretion is controlled by the extracellular fluid calcium concentration.

Vitamin D

Vitamin D acts at two major sites. It increases intestinal absorption of calcium and phosphate. In addition, in the skeleton, it promotes mineralization and enhances PTH-mediated mobilization of calcium and phosphate. It has no known direct effect on the kidney.

Vitamin D_3, or cholecalciferol, is produced normally by the action of sunlight on 7-dehydrocholesterol in the skin (**Fig. 76.6**). It is then hydroxylated in the liver (25 position) and kidney (1 position) to form the active 1,25-dihydroxyvitamin D_3 (calcitriol). Vitamin D_2 is normally present in yeast and fungi but not in humans. It is the major pharmacologic source of vitamin D. Pharmaceutical preparations include vitamin D_2 (ergocalciferol), 25-hydroxycholecalciferol (calcifediol), and 1,25-dihydroxycholecalciferol (calcitriol). 1-Hydroxycholecalciferol and dihydrotachysterol are synthetic preparations that require only 25-hydroxylation for activity and so are useful

for supplementation in patients with renal failure, who lack the 1-hydroxylase.

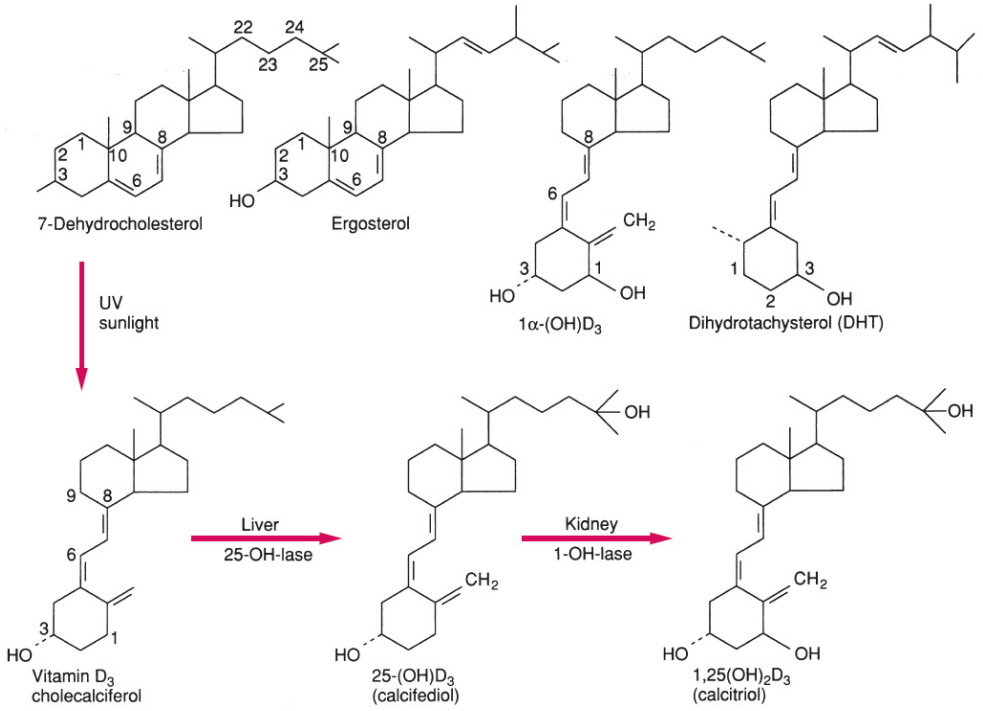

Figure 76.6 Schematic illustration of the synthesis of vitamin D_3. Ergosterol, 1-α-hydroxyvitamin D_3, and dihydrotachysterol are synthetic preparations of vitamin D.

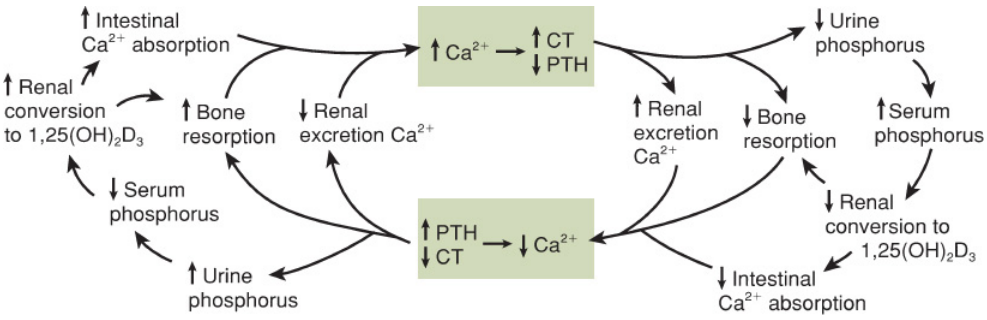

Figure 76.7 Feedback loops involved in the regulation of serum calcium and phosphorus. PTH, parathyroid hormone; CT, calcitonin.

Calcitonin

Calcitonin is a 32-amino-acid protein produced by the parafollicular C (calcitonin) cells of the thyroid. The C cells are embryologically derived from the neural crest and, in lower animals, are found in the ultimobranchial bodies, which are glandular structures derived from the lowest branchial

pouch. In humans, these structures are incorporated into the superior and lateral aspects of the thyroid lobes.

Total thyroidectomy, with removal of all the C cells, is well tolerated. Calcitonin is not essential for the normal control of calcium metabolism in adult humans. It does inhibit bone resorption and can produce hypocalcemia in experimental animals. It also increases urinary calcium and phosphate excretion. These effects are mediated primarily through cAMP. Several secretagogues for calcitonin have been identified, including catecholamines, gastrin, and cholecystokinin, but the most potent appear to be calcium and pentagastrin. Exogenously administered calcitonin can be useful pharmacologically to reduce serum calcium levels.

Mineral Homeostasis

Under normal conditions, serum calcium and phosphate levels vary minimally during the course of the day. Regulation occurs primarily through PTH but also through a series of feedback loops involving vitamin D and calcitonin (**Fig. 76.7**). A fall in serum-ionized calcium increases PTH secretion and stimulates the production of 1,25-dihydroxyvitamin D_3. Conversely, increases in serum calcium inhibit PTH secretion and the formation of active calciferol.

Pathophysiology

Diseases of the parathyroid glands present almost exclusively as disorders of calcium metabolism. Hypercalcemia is the most common manifestation, and in the patient who presents with an elevated serum calcium level, the differential diagnosis can be complex. A thorough understanding of both hypercalcemia and hypocalcemia is essential for the successful treatment of patients undergoing parathyroid surgery. Primary disorders of plasma phosphate are not usually related to surgical disease and are not discussed in detail here.

HYPERCALCEMIA

Hypercalcemia is a relatively common clinical problem.[3,4] In the general population and in hospital outpatients, the incidence is between 0.1% and 0.5%. Most patients in this group have primary hyperparathyroidism. In contrast, hypercalcemia is identified in almost 5% of hospitalized patients, and nearly two-thirds of them have a malignancy.

Clinical Manifestations

The symptoms of hypercalcemia are varied and nonspecific (**Table 76.2**). Severity is a function of both the magnitude and rapidity of onset of the hypercalcemia. Many of the manifestations are subtle and are evident only in retrospect, after the patient has been successfully treated for the cause of the elevated calcium. Specific symptoms and diagnostic tests are addressed in more detail in the section on hyperparathyroidism.

Differential Diagnosis

Although the diagnosis of primary hyperparathyroidism can, after appropriate investigation, be established with confidence in most patients, all causes of hypercalcemia must be considered and excluded. The multiple causes of hypercalcemia are listed in **Table 76.3**.

Etiology

Hyperparathyroidism

The diagnosis of hyperparathyroidism is discussed in detail later. Patients typically have elevated plasma concentrations of calcium and PTH, increased urinary excretion of calcium, and a low plasma concentration of phosphate.

Malignancy

Generally, patients with hypercalcemia and malignancy (humoral hypercalcemia of malignancy) can be classified into two groups.[5–7] Patients with solid tumors, such as lung carcinoma (25% of all cases of humoral hypercalcemia of malignancy); breast carcinoma (20%); squamous cell

carcinoma of the head, neck, esophagus, or female genital tract (19%); or renal cell cancer (8%), account for three-fourths of all cases. Humoral hypercalcemia of malignancy in this setting generally appears late in the disease, with nearly all patients having known, or readily evident, malignancy. These patients have elevated levels of serum calcium, low levels of serum phosphorus, and elevated levels of urinary cAMP, consistent with increased PTH activity but normal or low-serum PTH levels. The hypercalcemia is now known to be caused by PTH-related protein secreted by the tumor, rather than by the bony metastases that many of these patients have because of the advanced nature of their cancers. In the second group, accounting for one-fourth of cases, are patients with hematologic malignancies, such as multiple myeloma, certain lymphomas and leukemias, and a subset of the patients with breast cancer. These patients have elevated levels of serum calcium, but in contrast to most patients with solid tumors and humoral hypercalcemia of malignancy, they have elevated levels of serum phosphate and low levels of urinary cAMP. These patients always have lytic bony lesions and histologically demonstrate increased osteoclast bone resorption adjacent to tumor cells. This osteoclast-activating activity is an effect of cytokines, mainly interleukin-1 β and tumor necrosis factor-β (lymphotoxin). These cytokines promote local net bone resorption and thus produce hypercalcemia and hyperphosphatemia.

Table 76.2 Clinical Features of Hypercalcemia

Neurologic

- Lethargy
- Confusion
- Coma
- Headache
- Depression
- Paranoia
- Muscle weakness
- Hyporeflexia
- Incontinence
- Memory loss
- Hearing loss
- Ataxia

Gastrointestinal

- Constipation
- Anorexia
- Nausea and vomiting
- Polydipsia
- Weight loss
- Pancreatitis
- Peptic ulcer
- Abdominal pain

Cardiovascular

- Electrocardiogram changes (short QT interval, widened T wave)
- Bradycardia
- Heart block
- Hypertension

Renal

- Polyuria
- Uremia
- Renal colic
- Nephrocalcinosis

Other

- Band keratopathy

- Conjunctivitis
- Change in vision
- Pruritus
- Thrombosis
- Myalgia

Table 76.3 Causes of Hypercalcemia

- Hyperparathyroidism
- Malignancy
- Vitamin A or D intoxication
- Thiazide diuretics
- Hyperthyroidism
- Milk–alkali syndrome
- Sarcoidosis and other granulomatous diseases
- Familial hypocalciuric hypercalcemia
- Immobilization
- Paget disease
- Lithium therapy
- Addisonian crisis
- Idiopathic hypercalcemia of infancy

Vitamin D and Vitamin A Intoxication

When administered in excess, vitamins A and D can produce hypercalcemia. Affected patients tend to have normal or elevated serum phosphate levels associated with a low PTH level. Metastatic calcification may occur.

Thiazide Diuretics

Thiazides may increase serum calcium levels to a mild degree, primarily through hemoconcentration and decreased renal excretion. Serum phosphate may also be depressed. It often takes several weeks for the hypercalcemia to resolve after the medication is discontinued.

Hyperthyroidism

Hyperthyroidism is associated with increased bone resorption. Often, the plasma PTH is low, and a history of other thyrotoxic symptoms can be elicited. The hypercalcemia usually resolves as the patient becomes euthyroid.

Milk–Alkali Syndrome

Typically, the milk–alkali syndrome occurs in patients with peptic ulcers who consume large quantities of milk and absorbable antacids. Usually, some degree of renal failure is present. PTH levels are low. This syndrome has become much less common with the increased use of nonabsorbable antacids, histamine 2-receptor antagonists, and proton pump inhibitors as therapy for peptic ulcer disease.

Sarcoidosis and Other Granulomatous Diseases

These syndromes are associated with hypersensitivity to vitamin D. The granulomas can convert inactive vitamin D to its active form. Patients have elevated plasma globulins and low PTH levels. The administration of large doses of corticosteroids for 10 days usually reduces the hypercalcemia. Biopsy of lymph nodes or the liver may confirm the diagnosis.

Familial Hypocalciuric Hypercalcemia

This disease is an asymptomatic, autosomal dominant condition characterized by mild to moderate hypercalcemia, hypocalciuria, and normal or only slightly elevated PTH levels. It develops in people heterozygous for a mutation in the calcium-sensing receptor.[8–10] The mutation causes an increase in the set point for extracellular calcium concentration, so that the "normal" calcium level is higher in these people than in the normal population. No treatment is necessary, although people with this disease should receive genetic counseling. Neonatal severe hyperparathyroidism, which can be fatal, develops in children homozygous for mutations in this receptor. Treatment for neonates with this disease is controversial, but they appear to benefit from early surgical management.

Immobilization

Immobilization produces hypercalcemia by increasing the ratio of bone resorption to bone formation. These patients can usually be distinguished by history, although on laboratory evaluation they have elevated serum levels of calcium and phosphate and a decreased serum concentration of PTH. Often, hypercalciuria is present, which may lead to the development of renal stones. Treatment is early mobilization and forced diuresis.

Other Causes

A variety of other diseases may produce hypercalcemia. For example, Paget disease (osteitis deformans) typically causes mild elevations in serum calcium. Paget disease can be diagnosed on the basis of the characteristic radiographic lesion. Adrenal insufficiency may be associated with hypercalcemia, although the symptoms are typically those of the primary abnormality. Lithium therapy appears to produce hypercalcemia by altering the parathyroid set point for inhibition by calcium, and, over long courses of therapy, may also be associated with hyperparathyroidism. Idiopathic hypercalcemia of infancy is a rare disorder that is probably the result of hypersensitivity to vitamin D. It occurs in infants with mental retardation and is satisfactorily treated with glucocorticoids. Other causes include aluminum-induced renal osteomalacia and a host of analytic errors related to improper specimen collection with prolonged tourniquet times, tube contamination, and instrument drift.

Medical Treatment

Although the choice of therapy is tailored to the cause of the hypercalcemia, several general measures can prove effective.[11,12]

For the patient with mild hypercalcemia, a trial of a decrease in dietary calcium is indicated. A reduction in intake of milk and other dairy products is suggested, along with discontinuation of thiazide diuretics and vitamin D preparations. Mobilization prevents bone demineralization.

Patients with more marked hypercalcemia or severe symptoms should be admitted to the hospital for treatment, with careful observation and monitoring. In the patient with severe hyperparathyroidism, although the definitive therapy is surgical, it is unwise to proceed with neck exploration

until the calcium has been reduced to near-normal levels. The mainstay of therapy is intravenous hydration, preferably with normal saline solution in sufficient quantities to maintain the urine output above 100 mL/hr. These patients are often dehydrated before therapy, and fluid can be administered intravenously at a rate of 200 mL/hr. Caution must be exercised in older patients, whose cardiac reserve may be marginal. This therapy exploits the parallel handling of calcium and sodium by the kidneys. The diuretic furosemide also increases sodium and calcium excretion but should not be used until the patient is well hydrated.

The end points of therapy are a decrease in the serum calcium level and a reduction of symptoms. Diuresis with saline solution is usually effective when the hypercalcemia results from hyperparathyroidism or a benign cause. In contrast, the hypercalcemia of malignancy may produce severe symptoms associated with extremely high-serum calcium levels that are difficult to control. In this setting, a variety of other measures may be considered (**Table 76.4**). Some of the agents used to treat hypercalcemia cause significant toxicity, and close patient monitoring is required during treatment. Calcitonin is a fairly weak hypocalcemic agent, but it acts rapidly and is associated with less toxicity than many of the other drugs.[12] Salmon calcitonin is the most potent preparation. Treatment with glucocorticoids is particularly efficacious in patients with sarcoidosis and other granulomatous diseases. Plicamycin has proved useful in patients with hypercalcemia of malignancy, but it causes a cumulative toxicity (thrombocytopenia, hepatotoxicity, and nephrotoxicity). Bisphosphonates inhibit osteoclast activity directly. These agents are administered orally or parenterally and are particularly efficacious, although long-term use may be associated with significant osteomalacia.[7] Prostaglandin synthetase inhibitors were initially considered useful, but their efficacy has proved to be limited. Intravenous phosphates and chelating agents have largely been abandoned because of their severe toxicity; however, oral phosphates may be beneficial in patients requiring prolonged therapy.

HYPOCALCEMIA

Hypocalcemia can occur as a consequence of various acquired and hereditary diseases.[13,14] Generally, these disorders produce a deficiency or defect in the action of either PTH or vitamin D. It is most commonly a significant clinical problem after neck operation for thyroid disease. Chronic vitamin D deficiency is associated with compensatory PTH excess. The end result is rickets in children or osteomalacia in adults.

Clinical Features

The major signs and symptoms of hypocalcemia are a direct consequence of the reduction in plasma levels of ionized calcium, which increases neuromuscular excitability (**Table 76.5**). The earliest clinical manifestations are numbness and tingling in the circumoral area, fingers, and toes. Mental symptoms are also common. Patients become anxious, depressed, and occasionally confused. Tetany may develop, characterized by carpopedal spasm, tonic–clonic convulsions, and laryngeal stridor. The magnitude of symptoms at any given plasma concentration of ionized calcium varies from patient to patient. On physical examination, contraction of the facial muscles is elicited by tapping anterior to the ear, over the facial nerve (Chvostek sign), although this sign may be present in 10% of normocalcemic patients. Trousseau sign is elicited by occluding blood flow to the forearm for 3 minutes. The development of carpal spasm indicates hypocalcemia, although the test is unpleasant and clinically impractical.

Table 76.4 Treatment of Hypercalcemia

Therapy of Primary Disease
- Tumor resection (hypercalcemia of malignancy)
- Parathyroidectomy (primary hyperparathyroidism)

Expansion of Extracellular Volume
- Infusion of saline solution
- Enhancement of urinary calcium excretion
- Extracellular volume expansion
- Loop diuretics (furosemide and ethacrynic acid)

Inhibition of Bone Resorption
- Calcitonin
- Glucocorticoids
- Plicamycin (mithramycin)
- Bisphosphonates
- Gallium nitrate

Reduction of Intestinal Calcium Absorption
- Low-calcium diet
- Glucocorticoids

Other Treatments
- Dialysis
- Mobilization
- Oral phosphate
- Estrogens or progestogens (postmenopausal women with primary hyperparathyroidism)
- Chloroquine (sarcoidosis)

Modified from Attie MF. Treatment of hypercalcemia. *Endocrinol Metab Clin North Am* 1989;18(3):807–828.

Etiology

Some of the causes of hypocalcemia are listed in **Table 76.6**. The most common cause of hypocalcemia by far is excision of or damage to the

parathyroid glands during thyroid surgery.

Postoperative Hypoparathyroidism

Postoperative hypoparathyroidism commonly develops after total thyroidectomy.[15,16] Most patients undergoing operation on the thyroid experience some alteration in serum calcium, although they often are asymptomatic; the low calcium probably represents contusion or temporary alteration of the blood supply to the parathyroid glands. The hypocalcemia is usually transient and is not treated unless significant symptoms develop. Occasionally, in hyperparathyroid patients who have parathyroidectomy and significant bone disease, a marked skeletal deposition of calcium and symptomatic hypocalcemia occurs, the so-called *bone hunger*. The plasma calcium usually reaches its nadir at 48 to 72 hours after surgery and then slowly returns to normal within several days. These patients may require calcium and vitamin D therapy for weeks or months after parathyroidectomy.

Table 76.5 Clinical Features of Hypocalcemia

Neurologic

- Circumoral paresthesia
- Light-headedness
- Depression
- Anxiety
- Confusion
- Chvostek sign
- Trousseau sign
- Irritability
- Laryngeal spasm
- Seizures

Musculoskeletal

- Tetany
- Cramps
- Involuntary twitching
- Osteomalacia

Cardiovascular

- Electrocardiogram changes (prolonged QT interval, T-wave peaking)
- Arrhythmia
- Tachycardia, hypotension

Other Features

- Lenticular cataracts

Table 76.6 Causes of Hypocalcemia

- Hypoparathyroidism
- Vitamin D deficiency
- Pseudohypoparathyroidism
- Hypomagnesemia
- Malabsorption
- Pancreatitis
- Hypoalbuminemia
- Chelation of calcium
- Osteoblastic metastases
- Toxic shock syndrome
- Hyperphosphatemia

Idiopathic Hypoparathyroidism

A less common form of hypoparathyroidism is idiopathic lack of function. It occurs both sporadically and in families. In some cases, it develops as part of a polyglandular disorder and is thought to have an autoimmune basis. DiGeorge syndrome is a group of congenital disorders involving the branchial pouches that produce partial or complete agenesis of the thymus and parathyroid glands. Hypoparathyroidism can also develop in newborns as a result of prenatal suppression of the fetal parathyroid glands as a consequence of maternal hypercalcemia.[17] It is also common in otherwise normal but premature infants.

Vitamin D Deficiency

Vitamin D deficiency can occur as a result of dietary deficiency or lack of sun exposure. Likewise, renal disease produces a decrease in the 1-hydroxylase activity necessary for the formation of active vitamin D. The result is a decrease in calcium absorption and an increased secretion of PTH by the stimulated parathyroid glands. Osteomalacia, abnormal fractures, and the deformities of rickets may result.

Pseudohypoparathyroidism

Pseudohypoparathyroidism is a familial disease characterized by a rotund appearance, shortening of the extremities, and sometimes mental deficiency. The defect is not in PTH secretion; in fact, most patients have elevated plasma levels of PTH with evidence of increased bone resorption. Rather, the kidney is unresponsive to the hormone, and as a consequence, hypocalcemia and hyperphosphatemia develop. The deficit appears to be in the renal adenyl cyclase system.

Hypomagnesemia

This unusual deficit may result from chronic alcoholism, malabsorption, parenteral nutrition, or increased renal clearance during therapy with aminoglycosides. The deficit appears to block the physical response to PTH in addition to its release from the parathyroid gland.

Other Causes

In short-gut syndrome, after extensive small-bowel resection or bypass, or after some forms of bariatric surgery, vitamin D and calcium may be absorbed in insufficient quantities. In pancreatitis, the massive soft tissue destruction and saponification that occur with hemorrhagic disease may sequester significant amounts of calcium in the retroperitoneum. Some undefined systemic factor also appears to contribute to hypocalcemia in these patients. Hypoalbuminemia causes a reduction in the total plasma calcium level, although the level of ionized calcium remains within the normal range and patients are asymptomatic. Circulatory substances, such as the citrate used to anticoagulate banked blood and radiographic contrast media, may bind to calcium. In patients with osteoblastic metastases, particularly associated with prostate carcinoma, hypocalcemia has been attributed to increased calcium flux into the lesions. Toxic shock syndrome is sometimes associated with hypocalcemia, but the mechanism has not been defined. Acute hyperphosphatemia, as a consequence of exogenous administration of phosphate or during the cytolytic chemotherapy of highly responsive tumors (e.g., Burkitt lymphoma and acute lymphoblastic leukemia), may produce symptomatic hypocalcemia associated with soft tissue calcification.

Treatment

The treatment of hypocalcemia is summarized in **Table 76.7**. For acute symptomatic hypocalcemia, calcium should be administered intravenously. Calcium gluconate is less irritating to the veins than calcium chloride, and the calcium release is slower, without a risk for overcorrection. Usually, 20 to 30 mL of 10% solution is infused over a 15- to 20-minute period, and then 50 to 100 mL is administered over the next 12 hours in adults. A practical guide after an initial bolus dose includes 60 mL of 10% calcium gluconate in a 500-mL bag of dextrose 5% in water, infused at 1 mL/kg/hr, and adjusted every 4 hours based on the serum level of calcium and patient symptoms. Bicarbonate precipitates any calcium infused through the same intravenous line. Serum magnesium should always be measured, and hypomagnesemia should be corrected if present. In patients with convulsions from advanced tetany, diphenylhydantoin therapy is useful, but symptoms should never be allowed to progress to this point.

Long-term therapy is gauged on the basis of symptoms. In the postoperative patient, the continued stimulus of mild hypocalcemia to any remaining parathyroid gland tissue may prove useful. Concomitant therapy with calcium and vitamin D is effective in a timely fashion. A starting dose of 2 g of oral calcium carbonate per day in divided doses is usually well tolerated. Vitamin D can be administered as calcitriol, an active synthetic vitamin D analog. Most adults respond to a dose of 0.5 to 1.0 mcg/day; reduced doses may be necessary for patients with renal dysfunction.

Table 76.7 Treatment of Hypocalcemia

Symptom or Goal	Treatment
Symptomatic hypocalcemia	Oral calcium carbonate or intravenous calcium gluconate, and possibly vitamin D supplements to increase the efficiency of absorption of oral supplements
Symptomatic tetany	Intravenous calcium gluconate
Correction of hypomagnesemia	Intravenous magnesium chloride
Vitamin D supplementation	Ergocalciferol, calcifediol (liver disease), calcitriol (renal disease)
Long-term therapy	Calcium carbonate; low-phosphate, low-oxalate diet; parathyroid grafting (immunosuppressed or cryopreserved autograft)

HYPERPARATHYROIDISM

Definitions

Parathyroid neoplasms are rarely identified by physical enlargement but rather are sought because of the peripheral effects of excess hormone. Primary hyperparathyroidism develops spontaneously, without apparent cause but possibly in response to exogenous stimuli. When the normal control of serum calcium is disturbed and the autonomous production of PTH is increased, the state is referred to as *primary hyperparathyroidism.* This category includes both benign single- and multiple-gland enlargements and the much rarer parathyroid carcinoma. In some cases, the disease is familial. In contrast, *secondary hyperparathyroidism* occurs when a defect in mineral

homeostasis leads to a compensatory increase in parathyroid function. This occurs most commonly in response to renal disease but may also develop as a consequence of the hypocalcemia associated with some diseases of the gastrointestinal tract, bones, or other endocrine organs. Occasionally, with prolonged secondary stimulation, the hyperfunctioning glands are no longer physiologically responsive to an increase in ionized calcium. This uncommon (affecting about 2% of patients after renal transplantation), relatively autonomous state referred to as *tertiary hyperparathyroidism,* develops most commonly after renal transplantation when the renal defect in calcium homeostasis is corrected.

Incidence

The advent in the 1970s of the widespread assessment of serum calcium as part of automated multichannel analysis has considerably altered our understanding of hyperparathyroidism. Before that time, primary hyperparathyroidism was thought to be a relatively rare condition. Most patients presented with symptoms of disease, usually renal stones or bony manifestations. Currently, most patients are asymptomatic or have only vague symptoms or signs that can be related to hyperparathyroidism.[18,19] Occasionally, patients recognize that they had symptoms only after their well-being improves following parathyroidectomy. Incidence varies with both age and gender, but hyperparathyroidism is believed to develop in about 50 to 100 people per 100,000 in the general population, with approximately 50,000 new cases occurring annually in the United States.[20] Marked variations have been noted worldwide; the reasons for these differences remain unclear.

Etiology

The cause of primary hyperparathyroidism is not known. Although the sequence of progression from secondary to tertiary disease in response to chronic stimulation has a logical appeal, it is difficult to draw parallels with primary disease. Most patients with primary hyperparathyroidism have disease of a single rather than of multiple glands, which is not what might be predicted if an external stimulus were part of the pathophysiology.

Hyperparathyroidism is most common in postmenopausal women, the population group with the highest incidence of osteoporosis and the most significant alterations in calcium and phosphate metabolism. Loss of renal function with aging is associated with elevations in PTH and decreases in phosphate clearance. It has been suggested but not demonstrated that a renal calcium leak, if sufficient, might result in a chronic calcium deficit stimulating the parathyroid glands.

Genetic studies of parathyroid adenomas have described an oncogene (*PRAD1*) that may be one step in the path to neoplasia in these tumors. Overexpression of the normal *PRAD1* gene, also known as *cyclin D1,* allows progression of the cell cycle from the G1 phase to the S phase, thus promoting cellular growth and division. *PRAD1* is overexpressed in 20% to 40% of parathyroid adenomas; further research may reveal other genetic alterations that contribute to the neoplastic growth. The *MEN1* tumor-suppressor gene has also been implicated in the molecular pathogenesis of sporadic hyperparathyroidism. About 15% to 20% of sporadic parathyroid adenomas have either somatic mutation or biallelic deletion of the *MEN1* gene.[21,22]

Hyperparathyroidism occurs in several familial forms. It is a major component of the multiple endocrine neoplasia (MEN) syndromes types 1 and 2A. The parathyroid disease of MEN-1 syndrome is multiple parathyroid adenomas that appear with increasing frequency over the patient's lifetime.[23] In other families, hyperparathyroidism is inherited in an autosomal dominant fashion without other manifestations of MEN-1 or MEN-2; some have osseous abnormalities (tumor–jaw syndrome) and some apparently have isolated disease.

Pathology

Single-Gland versus Multiple-Gland Disease

Microscopically, the cell most commonly involved in primary hyperparathyroidism is the chief cell. Less frequently, the oxyphil cell is the predominant cell type. Diseased glands typically have an increase in the proportion of stromal cells and a reduction in the proportion of stromal fat. Single diseased glands, or adenomas, have been classically described with a

predominance of chief cells centering in a single focus, with a compressed rim of surrounding normal tissue (**Fig. 76.8**). In contrast, parathyroid hyperplasia has been characterized as a diffuse proliferation of clear cells in multiple glands, with little remaining normal tissue (**Fig. 76.9**). These criteria have proved totally unreliable. Although pathologic studies can usually distinguish parathyroid glands from other tissue, they may not prove useful beyond this capacity. Intraoperative decisions frequently depend on recognizing disease of one or more parathyroid glands, and in this regard, the histologic description of adenoma or hyperplasia is generally unreliable in primary hyperparathyroidism.[24]

Patients with multiple-gland disease may have one gland that appears to be an adenoma and another that appears diffusely involved or even histologically normal with gross enlargement. The most reliable index of abnormality is the determination of glandular enlargement by visual inspection. The incidence of single- and multiple-gland enlargement as judged by visual inspection in 66 consecutive patients with hyperparathyroidism is shown in **Table 76.8**. The visual assessment and judgment of the experienced surgeon have proved to be an effective basis for intraoperative decisions. This approach requires that all four parathyroid glands be evaluated at the time of operation. However, the recent ability to rapidly measure PTH during operation has provided a method to assess gland function rather than size. This experience indicates that there may be more enlarged glands than there are hyperfunctioning glands.[25]

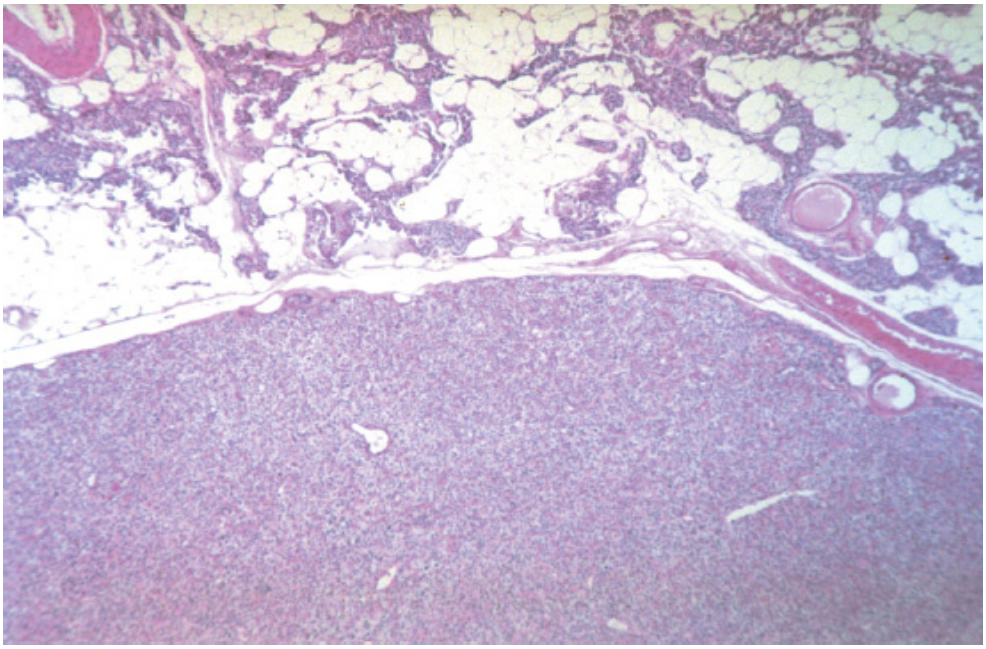

Figure 76.8 Parathyroid adenoma. The tumor consists of sheets of neoplastic chief cells and is separated from normal parenchyma by a thin capsule.

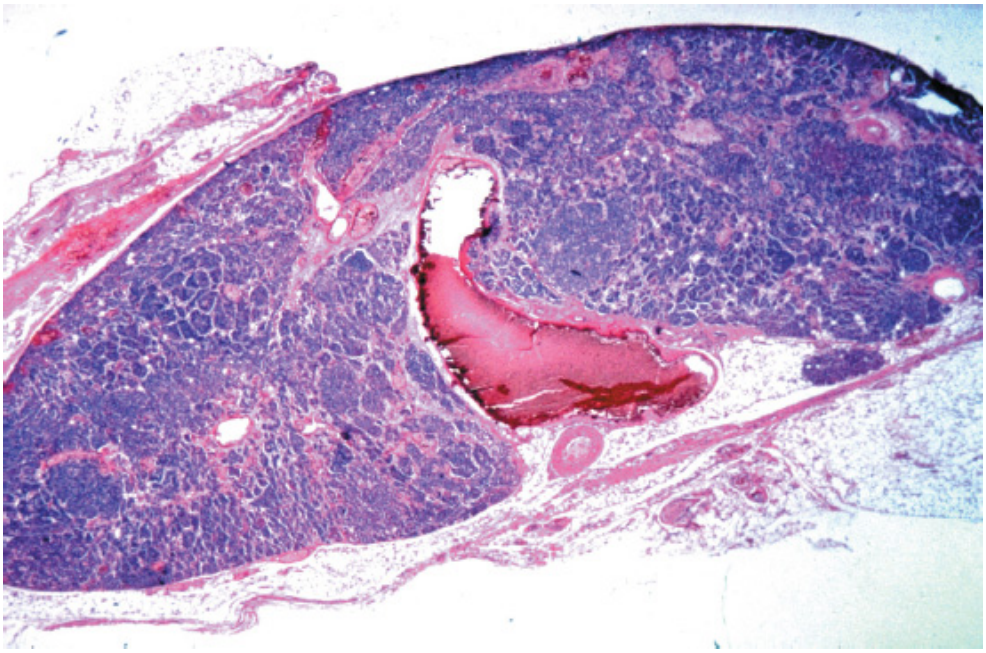

Figure 76.9 Primary parathyroid hyperplasia. The normal adipose tissue of the gland has been replaced by sheets and trabeculae of hyperplastic chief cells.

Carcinoma

Parathyroid carcinoma is a rare entity, and the histologic diagnosis can be exceedingly difficult. The surgeon may suspect the diagnosis when dense

invasion and scarring are encountered, although this may also be secondary to some other inflammatory disease in the neck. Pathologic criteria include marked mitotic activity, dense fibrous stroma, and evidence of local invasion into the capsule or surrounding vessels.[26] Malignant-appearing tumors, however, may pursue an apparently benign clinical course; the converse is less frequently true. The only reliable criteria of malignancy are metastases, most commonly to the lymph nodes, lung, or liver, and true local invasion.

Systemic Effects

The use of automated technology for determining serum calcium has changed not only the estimated incidence of hyperparathyroidism but also the usual mode of presentation. Before screening, three-fourths of patients presented with renal disease, particularly nephrolithiasis; one-third to one-half had skeletal manifestations, and rare patients had both. Most recent series suggest that at least half of the patients in whom hyperparathyroidism is diagnosed do not have renal or osseous disease and many are minimally symptomatic or asymptomatic. Manifestations of the disease are protean but generally nonspecific, and they may be difficult to elicit in the history. A significant proportion of patients present without a readily quantifiable index of disease severity. This finding has created some controversy about the need for surgery in the asymptomatic patient and particularly for the elderly or high-risk patient.[20,27]

Table 76.8 Gland Enlargement in 1,002 Consecutive Patients with Primary Hyperparathyroidism

Pathology	Patient, *n*	Percentage (%)
Adenoma	788	78
Double adenoma	98	9.8
Hyperplasia	116	11.6

From Hughes DT, Miller BS, Park PB, et al. Factors in conversion from minimally invasive parathyroidectomy to bilateral parathyroid exploration for primary hyperparathyroidism. *Surgery* 2013;154(6):1428–1434.

The earliest complaints are often the vague symptoms of hypercalcemia. These vary with the magnitude of plasma calcium elevation and can include muscle weakness, anorexia, nausea, constipation, polyuria, and polydipsia. These nonspecific symptoms may or may not cause the patient to seek medical attention. Some symptomatic patients have evidence of chronic disease involving the kidney or skeleton. Usually, only one of these systems is significantly involved in any individual patient. The treatment of hyperparathyroidism is designed to eliminate or halt the progression of the complications of the disease. Symptomatic patients can be divided into two groups. Members of the first group have renal manifestations, a slower onset of symptoms, and generally lower serum calcium concentrations. Patients in the second group have a more rapid onset of symptoms, higher-serum calcium levels, and significant bone disease. No recognizable histologic or physiologic characteristics distinguish patients with renal disease from those with bone disease.

Renal Manifestations

Renal complications develop because the hypercalcemia leads to an increase in urinary calcium excretion and because PTH increases the excretion of phosphate and produces urinary alkalosis. Both these events predispose to stone formation. Urinary stones can be treated surgically or with lithotripsy, and subsequent definitive treatment of the hyperparathyroidism reduces the rate of reformation. Of patients who present for the first time with renal colic, 5% to 10% are found to have primary hyperparathyroidism. Nephrocalcinosis (**Fig. 76.10**) is calcification of the renal parenchyma and occurs in 5% to 10% of patients with hyperparathyroidism. It causes more significant renal damage than nephrolithiasis does. In general, the more severe the renal damage, the less likely it is that nephrocalcinosis will regress after parathyroidectomy.

The incidence of hypertension in hyperparathyroidism increases with the degree of renal impairment. Hypertension may be a significant cause of the morbidity associated with hyperparathyroidism, but although a decrease in blood pressure has been demonstrated in some patients after parathyroidectomy, the correlation between the two conditions is not clear.

Figure 76.10 Abdominal film demonstrating nephrocalcinosis, or diffuse calcification of the renal parenchyma (*arrows*).

Figure 76.11 Magnification radiograph of the fingers in hyperparathyroidism. Subperiosteal cortical resorption (*arrows*) typically is most visible on the radial aspect of the middle phalanges.

Skeletal Manifestations

Parathyroid bone disease in its most classic and severe form, osteitis fibrosa cystica, is seldom encountered; however, 5% to 15% of patients with parathyroid bone disease present with significant symptoms of skeletal disease. Most commonly, these symptoms include bone pain and pathologic fractures.

Bone changes are often demonstrable on detailed plain radiographs of the hands (**Fig. 76.11**). Characteristically, subperiosteal resorption is evident on the radial aspect of the middle phalanx of the second or third finger. Because of tufting of the distal phalanges, clubbing may be evident on physical examination. Other findings that typically involve the skull and long bones include bone cysts, "brown" tumors (i.e., localized proliferations of osteoclasts), and diffuse demineralization or granularity. More subtle bone loss can be detected by iliac crest bone biopsy or dual-energy x-ray absorptiometry scan. The risk of bone fracture increases with increasing severity of bone loss.

Gastrointestinal Manifestations

Hypercalcemia is clearly associated with nonspecific gastrointestinal complaints, including nausea, vomiting, constipation, and anorexia, but attempts to demonstrate a definite relation between hyperparathyroidism and either peptic ulcer disease or pancreatitis remain unconvincing. Hypercalcemia stimulates gastric acid secretion experimentally and clinically, and has been associated with pancreatitis. Therefore, a theoretic rationale for the complex of hyperparathyroidism and gastrointestinal symptoms does exist.

Neuromuscular Manifestations

Neurologic and muscular complaints are those of hypercalcemia in general. Fatigability and proximal muscle weakness are among the most debilitating manifestations. Atrophy of type II muscle fibers, consistent with a neuropathic and not a myopathic cause, has been demonstrated. Sensory complaints include dysesthesia, a reduced vibratory sense, and stocking–glove sensory deficits.

Psychological Manifestations

The emotional disturbances of hyperparathyroidism are often subtle and difficult to quantify. As with other forms of hypercalcemia, they range from depression or anxiety to psychosis and coma. Patients undergoing parathyroidectomy frequently experience a sense of well-being and relief

from fatigue and dullness postoperatively, even if they may have had no noticeable complaints preoperatively.

Other Manifestations

A variety of signs and symptoms of soft tissue calcification have been described. Nonspecific arthralgia, particularly involving the proximal interphalangeal joints of the hands, is characteristic. The incidence of chondrocalcinosis is increased. Pruritus, vascular and cardiac calcification, and band keratopathy of the cornea have all been noted. Some reports have suggested an increased risk of malignancy and coronary artery disease, but the effects remain unsubstantiated, and it is not clear if the mortality risk is modifiable by correction of hyperparathyroidism.[28–31]

Physical Findings

Except in patients with the classic deformities of advanced bone disease, the physical examination is seldom helpful. Diseased parathyroid glands are infrequently palpable, except in patients with parathyroid carcinoma. A mass in the anterior neck in a patient with primary hyperparathyroidism is most commonly a thyroid nodule.

Laboratory Findings

Tests for calcium, PTH, phosphate, bicarbonate, and magnesium, in addition to other laboratory tests, are useful to establish the diagnosis of hyperparathyroidism.

Calcium

Hypercalcemia is the single most important diagnostic finding; however, particularly in early or mild cases, serial analysis may show fluctuations in and out of the normal range. Coexistent hypoalbuminemia and acidosis may produce an apparently normal total serum level of calcium, even though the ionized fraction is actually elevated. Serum concentrations of ionized calcium may be helpful in the patient with intermittent or mild hypercalcemia.

Parathyroid Hormone

PTH measurement is an important method for establishing the diagnosis of hyperparathyroidism. Because of the heterogeneity of the various circulating forms of PTH, measurement of C-terminal or N-terminal fragments give conflicting and confusing results. Intact hormone assays and whole molecule assays are the most dependable. The demonstration of an elevated plasma PTH concentration alone does not establish the diagnosis of hyperparathyroidism. 3 With a simultaneous elevated serum calcium level, this finding is virtually diagnostic (**Fig. 76.12**).

Phosphate

PTH increases renal phosphate excretion and, in about half of patients, produces hypophosphatemia. In the presence of renal disease, however, the serum phosphate levels may be normal or significantly elevated.

Bicarbonate

PTH also increases bicarbonate excretion, so that a hyperchloremic metabolic acidosis may develop. It has been suggested that the finding of an elevated serum chloride-to-phosphate ratio may be helpful in the differential diagnosis of hypercalcemia. A ratio greater than 30 is considered highly suggestive of hyperparathyroidism.

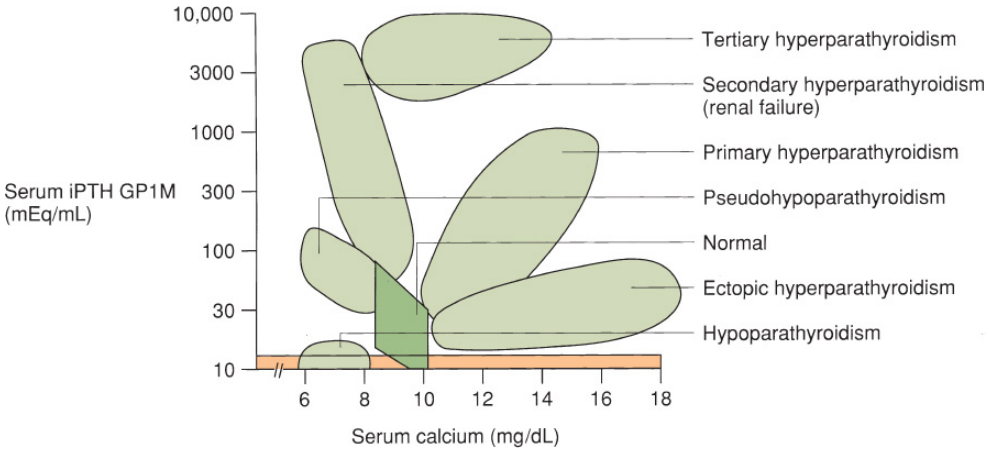

Figure 76.12 Relation between serum immunoreactive parathyroid hormone and serum calcium in patients with hypoparathyroidism, pseudohypoparathyroidism, ectopic hyperparathyroidism, and primary, secondary, and tertiary hyperparathyroidism. GP1M, guinea pig antiserum 1M.

Magnesium

Hypomagnesemia develops in 5% to 10% of patients with hyperparathyroidism. After parathyroidectomy, if both hypocalcemia and hypomagnesemia are present, it may be difficult to correct the calcium until the serum magnesium has been corrected.

Other Diagnostic Tests

A variety of special diagnostic tests for hyperparathyroidism are available. None is more specific than the measurement of serum concentrations of calcium and PTH, although they may be useful in equivocal cases. For example, the 24-hour urinary calcium excretion is usually elevated, but may be normal, in patients with hyperparathyroidism, although the finding is not specific for this disease. This test is helpful in identifying patients with familial hypercalcemic hypocalciuria, in whom the rate of urinary calcium excretion is low. Measurements of tubular reabsorption of phosphate below 30% suggest primary hyperparathyroidism. Urinary cAMP is generated specifically as a consequence of PTH activation of renal tubular adenyl cyclase. Increased urinary concentrations are identified in most patients with primary hyperparathyroidism. These measurements are rarely necessary because of the reliability of the intact PTH measurement.

Localization with Imaging Techniques

In order to try to simplify the operative approach to hyperparathyroidism, an attempt is usually made to localize enlarged glands preoperatively. In the hands of an experienced surgeon, the cure rate for hyperparathyroidism at the initial operation without preoperative localization exceeds 95% with the conventional full-neck exploration. However, technologic developments have led surgeons to pursue alternatives to the full-neck exploration. These innovations are increasingly accurate preoperative localization with ^{99m}technetium sestamibi scintigraphy, computed tomography scans with carefully timed intravenous contrast administration, or high-resolution ultrasound, combined with intraoperative intact PTH measurement that allows termination of the operation without visualization of all four parathyroid glands. Surgeons have used these technologies in various combinations to limit the extent of the neck exploration. All of the current alternative strategies, however, depend on a preoperative parathyroid localization study to direct the exploration.

The study most frequently used for imaging previously unoperated patients is ^{99m}technetium sestamibi scintigraphy (**Fig. 76.13**). Sestamibi scanning can identify the site of abnormal tissue in 75% to 80% of patients but has limitations in patients with small adenomas or multiple-gland disease. Sestamibi was originally developed for cardiac imaging. The use of a single nuclide with a short half-life and a high-energy profile has advantages in lateral, oblique, and three-dimensional imaging that technetium–thallium scanning, which was formerly used, does not provide. However, the availability of a CT scan with carefully timed contrast injection ("4D-CT") has replaced sestamibi scan in many centers.[27]

High-resolution ultrasound examination of the neck is also used for localization of abnormal parathyroid tissue, particularly when it is available for use by the clinician. The current machines scan at high frequencies (10 to 13 MHz) that allow demonstration of small abnormalities in the neck (**Fig. 76.14**). The examination is best done by a clinician in real time, as that allows the most complete assessment of the neck, rather than scans performed by a technician for later review of still pictures by the physician. The sensitivity of cervical ultrasound for abnormal parathyroid glands is about the same as for sestamibi scanning. Ultrasonography is an operator-dependent technique. It is rapid and relatively inexpensive and can direct fine-needle aspiration for cytologic confirmation and immunoassay for PTH.

In patients with persistent or recurrent hyperparathyroidism, preoperative imaging is important to guide the exploration. High-resolution real-time ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), and sestamibi scanning all appear to have comparable sensitivities of 50% to 60%. The results of these examinations may be less successful at centers without significant experience in their use.

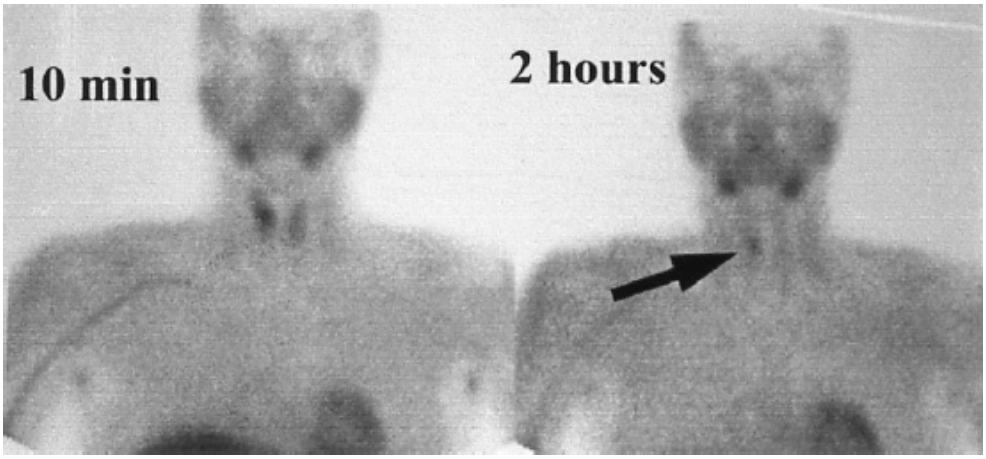

Figure 76.13 99mTechnetium sestamibi scan of a patient with a parathyroid adenoma. The radionuclide is present in both thyroid and parathyroid tissues on the 10-minute film; however, by 2 hours, the radionuclide has washed out of the thyroid and remains only in the right-sided parathyroid gland. This scan shows a 794-mg right upper parathyroid adenoma (*arrow*).

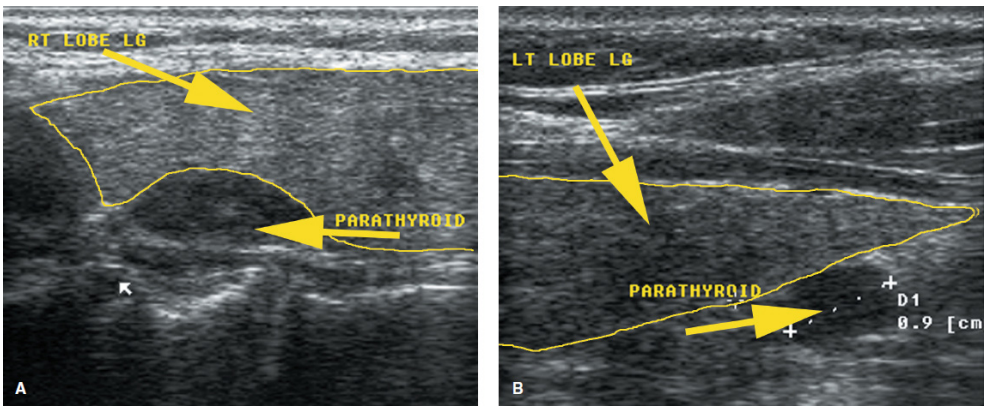

Figure 76.14 Ultrasound views of parathyroid adenomas. **A:** Sagittal image of the upper pole of the right lobe of the thyroid gland, demonstrating a hypoechoic parathyroid adenoma posterior to the thyroid parenchyma. **B:** Sagittal image of the lower pole of the left lobe of the thyroid gland with an adjacent hypoechoic parathyroid adenoma measuring 9 mm in greatest dimension.

Computed tomography is more expensive but less operator dependent than ultrasonography. It clearly is superior in identifying deeper structures and for examining the retrosternal mediastinum. MRI is considerably more expensive than CT and has not been shown to be superior. Most surgeons prefer to have results of two or more imaging tests that confirm an abnormality before exploration in the reoperative setting.[27]

Treatment

Indications for Surgery

Generally, the only practical therapeutic option is surgery. Nephrolithiasis, bone disease, and neuromuscular symptoms all respond well to surgical intervention.[32] In contrast, surgery in patients with renal failure, hypertension, and psychiatric symptoms is not so uniformly successful, although it benefits some patients and is usually indicated in all except those at highest risk. The question of how to manage the large group of patients with apparently asymptomatic disease requires particularly careful consideration.

Management of Asymptomatic Hyperparathyroidism

A large proportion of patients with the diagnosis of hyperparathyroidism are minimally symptomatic or asymptomatic. 4 The appropriate treatment for these patients remains controversial. Although little evidence indicates that irreversible complications, such as renal failure, eventually develop in patients with asymptomatic mild disease, the natural history of the disease remains incompletely defined. Many of the manifestations of this disease may go unrecognized until they are corrected surgically. Still unanswered is the question of how much asymptomatic disease may contribute to generalized osteopenia in this predominantly postmenopausal female population.

A report detailing the 15-year natural history of 116 patients with asymptomatic hyperparathyroidism was published in 2008. Operation was recommended for those in whom symptoms or findings developed, according to the prevailing guidelines. During the monitoring period, 51% of the patients had operation, and biochemical normalization and increased bone mass were observed in those who underwent surgery. However, the patients who did not undergo operative correction continued to have biochemical abnormalities and the cortical bone mass fell significantly. These data confirm the impression of most clinicians that mild hyperparathyroidism rarely takes a precipitously worsening clinical course; however, the differential bone effects that are evident by 15 years call into question how long such patients can be monitored without correction.

In October 1990, a National Institutes of Health Consensus Development Conference reviewed the available evidence regarding the management of asymptomatic primary hyperparathyroidism.[33] After interval developments, a panel of experts reconvened in 2002, and revisited this issue.[34] The panel agreed that operation is the indicated treatment for all patients with symptoms; however, they recognized a subgroup of patients who have no symptoms attributable to hyperparathyroidism, and their conclusions included several indications for surgical intervention in these asymptomatic patients (**Table 76.9**).

The panel mandated close (every 6 months) follow-up for those patients not treated by operation. In addition, they recommended surgery for cases in which medical surveillance is neither desirable nor suitable, such as when a patient requests surgery, consistent follow-up is unlikely, coexistent illness complicates management, or a patient is younger than age 50 years.

This remains an area of considerable controversy, and subsequent reviews have supported similar plans with only minor revisions.[27,35] The complication rate of operation by an experienced surgeon is very low. Within a short period, the financial cost of medical follow-up exceeds that of treatment by operation. Based on these considerations, most patients should undergo operation, and those who do not must be closely followed.

Table 76.9 National Institutes of Health Consensus Development Conference Indications for Surgical Intervention in Patients with Asymptomatic Primary Hyperparathyroidism

- Markedly elevated serum calcium (>1.0 mg/dL above normal)
- History of an episode of life-threatening hypercalcemia
- Reduced creatinine clearance
- Presence of one or more kidney stones detected by abdominal radiography
- Markedly elevated 24-hr urinary calcium excretion
- Substantially reduced bone mass as determined by direct measurement (dual-energy x-ray absorptiometry T-score ≤2.5)

Principles of Surgical Correction

Although neck exploration for hyperparathyroidism may be straightforward, it sometimes becomes an arduous procedure requiring considerable patience because of the variability in both the location and the number of diseased glands. Persistent hyperparathyroidism and the necessity for reexploration can usually be avoided by a meticulous initial procedure. Reoperation is predictably more difficult than the initial operation, and the risks for damage to the recurrent laryngeal nerves and hypoparathyroidism are greater during reoperation.

It is essential that the surgeon be confident of the preoperative diagnosis and prospectively discuss the procedure with the patient. The potential complications of damage to either the recurrent laryngeal nerve or the superior laryngeal nerve and the development of hypocalcemia require discussion. Likewise, the possibility of an unsuccessful initial operation must be explained, and the patient should recognize that reexploration, including median sternotomy, may be required. Although alternatives to full-neck exploration are often now applied, no patient should be explored by a surgeon who is unfamiliar with the principles and techniques of the conventional full-neck exploration.

For a full-neck exploration, the patient is placed under general anesthesia with a roll beneath the shoulders and the neck extended. The neck is opened through a transverse incision overlying the thyroid isthmus, and the platysma is similarly divided. Superior and inferior flaps are developed. The strap muscles are separated in the midline and retracted laterally; division is unnecessary. One lobe of the thyroid is chosen and rotated medially. Important landmarks include the tracheoesophageal groove, the recurrent laryngeal nerve, the inferior and superior thyroid arteries, and the middle thyroid vein (**Fig. 76.15**). In most patients, the nerve lies in the tracheoesophageal groove or just laterally. Occasionally, it may be situated more anteriorly. Uncommonly, it may originate directly from the vagus without passing around the right subclavian artery. Both of these latter variations make the recurrent nerve more susceptible to injury. The external branch of the superior laryngeal nerve, which innervates the cricothyroid muscle, usually lies medial to the superior thyroid vessels and should be carefully preserved.

For a full-neck exploration, all four glands should be identified at the initial exploration because of the possibility of multiple-gland disease.

Supernumerary glands may be present and should be sought at the initial procedure. Although a frozen section has not been helpful in differentiating diseased from normal glands, it is generally reliable for confirming the presence or absence of parathyroid tissue. Small, thin biopsy specimens are sharply incised from the gland, with extreme care taken to avoid damaging its delicate blood supply. Most surgeons use a frozen section selectively to confirm suspected abnormal parathyroid tissue or to document difficult or confusing situations.[27]

The upper glands are usually located far dorsally on the surface of the thyroid lobe at the level of the upper two-thirds of the gland. The lower glands are less constant and may be located anywhere from well above the thyroid to the anterior mediastinum. The lower glands are most typically in the region where the thyrothymic ligament attaches to the lower pole of the thyroid lobe. If the inferior glands cannot be localized, the thymic pedicle should be carefully examined and mobilized. Because of their common embryologic origin, the inferior gland is frequently associated with the thymic remnant. Parathyroid glands within the mediastinum sometimes can be removed by mobilizing the thymus through the cervical incision. If this technique is unsuccessful in identifying the parathyroid gland, the thyroid lobe on the side of the missing gland is mobilized and palpated. Intraoperative ultrasonographic examination may identify an intrathyroidal parathyroid gland. As a last resort, excision of the thyroid lobe may be indicated.

If after meticulous exploration of all these areas three or four parathyroid glands have been identified, none of which is enlarged, most surgeons favor terminating the operation.

Limited Surgical Exploration

With the availability of accurate preoperative localization methods, it has become routinely possible to identify abnormal parathyroid glands prior to operation for most patients. 5 This allows the surgeon to know where to start the exploration. Then, intraoperative PTH measurement can be used to confirm removal of all hyperfunctioning parathyroid tissue, that is, when to stop the operation. This strategy of directed, limited neck exploration is applicable to about 75% of initial parathyroid explorations, and has about

the same success rate as full-neck exploration. The preoperative localization can be done by either ^{99m}technetium sestamibi nuclear medicine scan or by high-resolution ultrasound. The intraoperative PTH measurement is first assessed at the outset of the procedure, and/or immediately preceding parathyroid gland excision (the pre-excision baseline). Blood samples are obtained at time intervals after parathyroid gland resection. A decrease of the PTH level by 50% from the higher of the incision or pre-excision baseline predicts long-term normocalcemia.[36] Other investigators use more sensitive criteria for the detection of multigland disease, including reduction of the PTH level into the normal range and kinetic assessments of the rate of PTH decrease.[37] This increase in sensitivity comes with the cost of decreased specificity, however. Blood samples can be obtained either centrally or peripherally.[38]

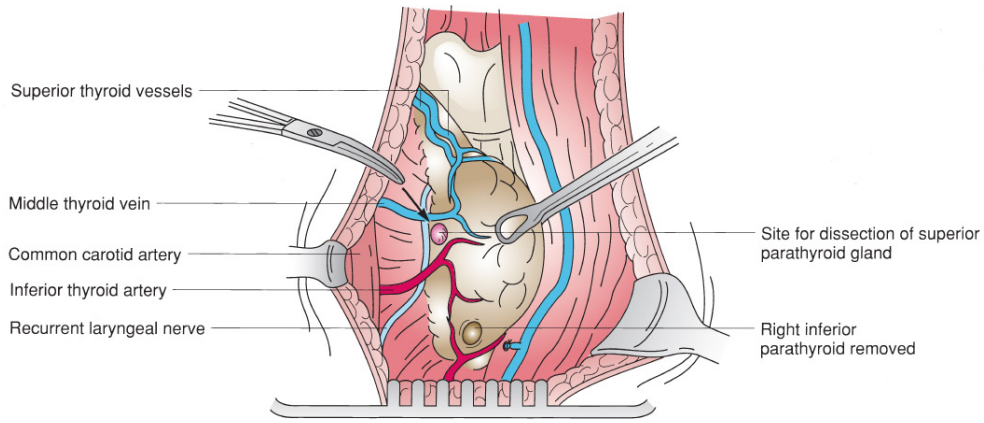

Figure 76.15 Lateral view of the right side of the neck after rotation of the thyroid lobe. The important anatomic landmarks are emphasized.

The limited nature of this operative approach also makes it easier to perform this operation under regional or local anesthetic in an ambulatory setting. However, because of the possibility of multiple-gland disease or inaccurate preoperative localization, all surgeons undertaking this approach should also be skilled in the full-neck exploration for hyperparathyroidism.[39]

Extent of Resection

The operative procedure performed has been based on the number of enlarged glands identified at full-neck exploration; however, with the use of intraoperative PTH monitoring, it has become clear that not all enlarged

parathyroid glands are hyperfunctioning.[40] In contrast, nearly all hyperfunctioning glands are enlarged and hypercellular. The full-neck exploration experience has demonstrated that removing all enlarged glands is a highly successful approach to curing hyperparathyroidism. In the absence of PTH monitoring, this remains an accepted approach. Typically, single-gland disease has been treated by simple excision, whereas any combination of two- or three-gland enlargement is treated by resecting the diseased tissue and leaving the normal glands in place. The question of whether two- or three-gland enlargement implies the presence of disease in all glands (hyperplasia) has not been resolved. If one gland is large and the remaining three are normal in size, resection of the single parathyroid cures virtually all patients. Of XX patients with two- or three-gland disease treated by excising the large glands and leaving the normal glands, only eight (10.5%) had recurrent hypercalcemia, which tended to be mild (follow-up of 12 to 140 months postoperatively). This approach seems satisfactory in most patients.[41]

Treating patients with four-gland disease has been more difficult. In many of these patients, the disease occurs as a component of one of the familial syndromes, particularly MEN-1. Patients with four-gland parathyroid disease can be treated by subtotal parathyroidectomy (removing three and a half glands) or by total parathyroidectomy with autotransplantation of some parathyroid tissue into the nondominant forearm. Both operations depend on meticulous identification of all parathyroid tissue for adequate results. The putative advantage of the subtotal parathyroidectomy is that it leaves the remaining parathyroid tissue with its native blood supply. Total parathyroidectomy with autograft has the advantage of removing all the abnormal parathyroid tissue from the neck and placing it in a site where reoperation for recurrent hyperparathyroidism is simpler. Over time, subtotal parathyroidectomy has become the more common approach.

The reported incidence of recurrent hypercalcemia after subtotal parathyroidectomy for nonfamilial parathyroid hyperplasia is 0% to 16%; the incidence of permanent hypoparathyroidism is 4% to 5%. Total parathyroidectomy with autograft is associated with a similar risk for permanent hypoparathyroidism in the sporadic setting (5%) and a higher reported risk for recurrent hypercalcemia (20%). Reoperation for recurrent hypercalcemia is simplified by the approach of total parathyroidectomy with autotransplantation. Thus, given the current data, sporadic parathyroid

hyperplasia can be acceptably treated by either operation. In patients with MEN-1, the disease is not the same as sporadic hyperplasia. Rather, defects in the MEN-1 gene cause multiple parathyroid adenomas that arise independently over the life of the patient.[23] The operative results reflect this independent capability of all parathyroid tissue in these patients to become neoplastic. The hypercalcemia recurrence rate is 26% to 36% with long-term follow-up after subtotal parathyroidectomy, and similar after total parathyroidectomy with autograft. However, the incidence of permanent hypoparathyroidism after autograft in MEN-1 is also significant (reported as high as 46%). While both approaches are currently accepted, most experienced centers now advocate subtotal parathyroidectomy as the initial operation in MEN-1 hyperparathyroidism, and anticipate that recurrent disease is likely, manageable, and less problematic than permanent hypocalcemia.[42]

Technique of Parathyroid Autotransplantation

The parathyroid gland is sliced into 15 to 20 pieces and autografted into a forearm muscle bed. This location permits easy subsequent access under local anesthesia if recurrent hypercalcemia develops; the grafts are easily identified by ultrasound. Function of the autograft is documented by (a) normocalcemia, with the autograft as the only source of PTH, (b) by measuring higher concentrations of hormone in the antecubital vein draining the graft bed than in the corresponding vein in the opposite arm, or (c) “transient parathyroidectomy,” by placing a venous occlusive tourniquet on the arm above the graft, and measuring changes over several minutes in the PTH levels drawn from the contralateral arm.[43] Lack of function is unusual outside of the MEN-1 patients; hypoparathyroidism develops in about 5% of patients. Glands can also be cryopreserved in dimethyl sulfoxide and serum. If in the postoperative period it becomes clear that the patient is aparathyroid, the cryopreserved tissue can be reimplanted under local anesthesia, though this technique is rarely used now in the era of available intraoperative PTH measurement.

Special Situations

Persistent or Recurrent Hyperparathyroidism

Persistent hyperparathyroidism occurs in fewer than 5% of patients after exploration by an experienced surgeon. Most commonly, it is the result of a single diseased gland remaining in the neck or the mediastinum. Recurrent disease develops after an interval of normocalcemia and may be the result of regrowth of diseased tissue, implantation from a tumor broken at the initial procedure, or recurrent parathyroid carcinoma.

In the evaluation of these patients, it is essential to document that the initial diagnosis was correct. Familial hypocalciuric hypercalcemia should be excluded by measuring urinary calcium excretion.

Reviewing the original operative notes and pathology reports may provide clues to the position of missed glands. The locations of parathyroid tumors not found at the initial operation but identified on subsequent exploration in one large series are shown in **Figure 76.16**.

It is generally agreed that localization studies have an important role in the management of recurrent disease. Noninvasive methods are used first, and if these are unsuccessful in identifying the diseased gland, selective angiography and venous sampling for PTH are used. The utility of the techniques vary across institutions, dependent on local experience, expertise, and preference. Selective angiography localizes 50% to 80% of parathyroid glands that cannot be detected by any other modality. Venous sampling may also be helpful in some patients, although interpretation can be complicated by the alteration in venous drainage that occurs postoperatively. Because it provides no direct image but indicates the side and level of the neck where the hyperfunctioning tissue is located, it may help to direct the interpretation of other imaging studies, and the exploration to one or the other side of the neck. Both of these invasive radiographic techniques require considerable expertise. Transient cortical blindness, transverse myelitis, and cerebrovascular accidents have all been reported as complications of arteriography. Angiographic ablation of mediastinal parathyroid tissue with large doses of ionic contrast has been successful in selected patients. This technique may be used in some patients with mediastinal parathyroid adenomas who are at increased surgical risk and who have other functional parathyroid tissue remaining.[44]

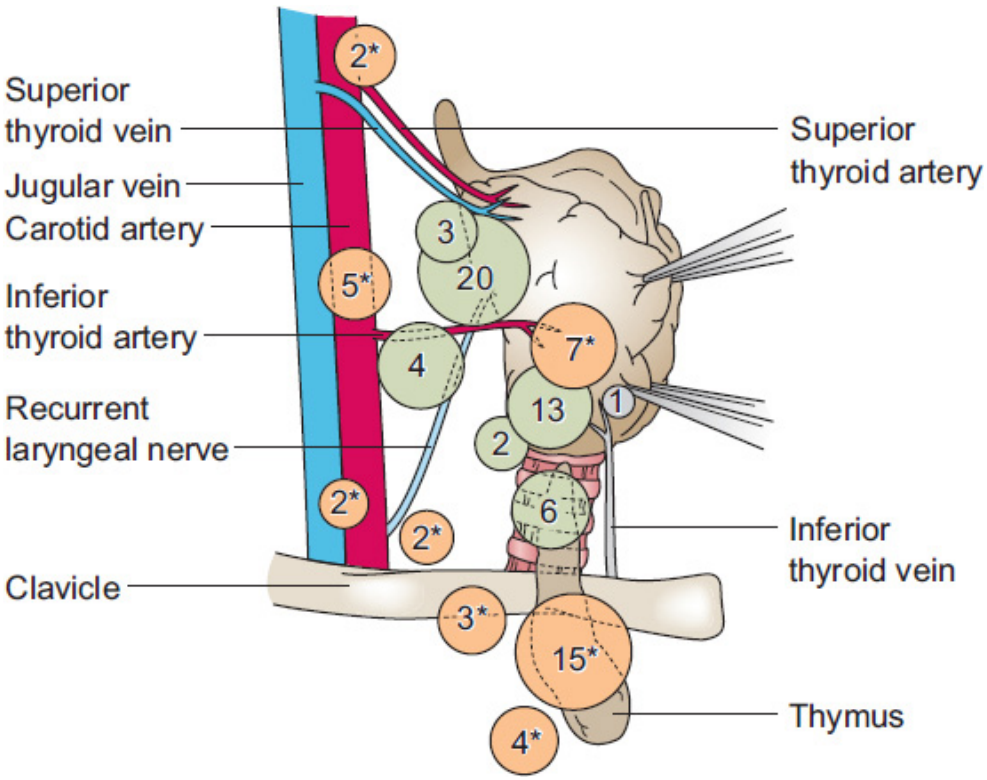

Figure 76.16 Location of parathyroid tumors missed on initial exploration but identified on subsequent operation.

Surgical reexploration can be a difficult procedure. The neck should almost always be reexplored first. If the thymic remnant has not already been removed, it should be excised at this time. Two adjunctive techniques, intraoperative ultrasonography to locate glands and intraoperative measurement of PTH to document the adequacy of resection, may be useful in patients undergoing operation for persistent disease.[27]

If the gland is not identified in the neck by means of the maneuvers described, the mediastinum is examined; most surgeons do this only if there is imaging evidence of disease in the mediastinum, rather than unguided exploration. Median sternotomy and exploration are necessary in very few patients with hyperparathyroidism. Successful transcervical mediastinal exploration is sometimes possible with use of the Cooper thymectomy retractor, a substernal retractor that permits more extensive mediastinal exploration and thymectomy through a cervical incision or using videoscopic techniques. Any remaining thymic tissue is first isolated and examined. Inferior parathyroid glands most commonly migrate into the anterior mediastinum. If the results of this exploration are negative, the area posterior

and lateral to the trachea is then explored. The location of superior parathyroid glands may be as far posterior as the esophagus and as far superior as the pharynx.

Surgical reexploration is successful in experienced hands in about 80% of cases. The incidence of complications is increased. Unilateral recurrent nerve injury occurs in 5% to 10% of patients postoperatively, and permanent hypoparathyroidism in 10% to 20% of patients. Cryopreservation of excised tissue may be included as a component of the management of these patients because it allows later autotransplantation if the patient becomes hypoparathyroid postoperatively. However, the demonstration of continued PTH production by intraoperative PTH measurement makes cryopreservation unnecessary. The risks of these complications must be clearly outweighed by the clinical improvement in patients with advanced disease. Reoperation in asymptomatic patients with mild disease is controversial.

Hypercalcemic Crisis

Occasionally, patients with hyperparathyroidism become acutely hypercalcemic with severe symptoms. The pathogenesis appears to involve a cycle of uncontrolled PTH secretion followed by hypercalcemia and secondary polyuria, dehydration, and reduced renal function, which exacerbate the hypercalcemia. Serum calcium concentrations may reach 16 to 20 mg/dL, and the syndrome is manifested by rapidly developing muscle weakness, nausea and vomiting, lethargy, fatigue, and even coma. Ultrasonography, sestamibi scan, or CT scan may help to identify the enlarged gland to allow expedient correction.

Definitive treatment involves resecting the diseased parathyroid tissue, which is almost always curative. Generally, however, it is safer to lower the serum calcium level before operation.

Hyperparathyroidism in Pregnancy

Hyperparathyroidism in pregnancy is a rare disorder that not only causes hypercalcemia in the mother but also is associated with increased morbidity and mortality rates in the fetus. Even the newborn is at risk for the development of tetany. The risk for fetal complications is higher if the hyperparathyroidism is left untreated. The mother should undergo operation

in the second trimester, though the outcome for the pregnancy with modern management is good overall.[45]

Neonatal Hyperparathyroidism

Neonatal hyperparathyroidism occurs in infants who are homozygous for a mutation of the calcium-sensing receptor and is characterized by hypotonia, poor feeding, constipation, and respiratory distress. Each parent of these children is affected by familial hypocalciuric hypercalcemia. The 1-year survival rate in children with symptoms is less than 50%, and patients without symptoms appear to have significant bone disease. Total parathyroidectomy appears to be the treatment of choice, although experience is very limited.[46]

Secondary Hyperparathyroidism

Secondary hyperparathyroidism develops as a consequence of chronic renal failure. Phosphate retention and hyperphosphatemia reduce the serum calcium levels. This effect is aggravated by the reduction in 1-hydroxylase activity in the kidney, necessary for the activation of vitamin D_3. The secondary increase in PTH levels to compensate for the hypocalcemic effects is exacerbated by aluminum accumulation in bone. Aluminum, present both in the dialysate fluid and in phosphate-binding medications, contributes to the osteomalacia (renal osteodystrophy) that develops in all these patients after several years of dialysis. Therapy includes controlling the hyperphosphatemia with dietary restriction and phosphate-binding gels, calcium supplementation orally and in the dialysate bath, correction of acidosis, administration of vitamin D sterol, and reduction in aluminum intake in both the dialysate and the diet. Therapy should be initiated carefully because metastatic soft tissue calcification can occur. Indications for surgical therapy include persistent, symptomatic hypercalcemia that cannot be controlled medically, particularly in prospective renal transplant patients; bone pain and abnormal fractures; ectopic calcification; and intractable pruritus. Subtotal parathyroidectomy and total parathyroidectomy with heterotopic autotransplantation both appear to be acceptable options, although reexploration for recurrent disease is less complicated after total parathyroidectomy with autotransplantation. Parathyroidectomy can enhance

aluminum deposition, so any excess should be corrected preoperatively through chelation.

Parathyroid Carcinoma

Parathyroid carcinoma is a rare condition, accounting for less than 1% of all cases of hyperparathyroidism. Histologic criteria remain controversial, and the diagnosis is securely made only on the basis of local invasion or distant metastases. In comparison to patients with benign disease, these patients tend to be somewhat younger and more symptomatic. In contrast to the marked female predominance in benign disease, the male-to-female ratio in carcinoma is equal. Serum calcium, PTH, and alkaline phosphatase levels are relatively more elevated, and patients often have an elevated level of human chorionic gonadotropin. Patients may have manifestations of both renal and bone diseases. The affected gland is palpable in almost half of patients.

Initial treatment should include radical resection of the involved gland, ipsilateral thyroid lobe, and regional lymph nodes. Neither chemotherapy nor radiation therapy has shown any benefit. If the disease recurs, resection should be attempted because without treatment these patients usually succumb to uncontrolled hypercalcemia. The long-term prognosis is poor, and the opportunity for survival depends on complete initial resection.[47,48]

MULTIPLE ENDOCRINE NEOPLASIA

Although these familial disorders are typically characterized by a predisposition to the development of tumors of multiple endocrine organs, the parathyroid is characteristically involved in two of them. The disorders are all inherited in an autosomal dominant fashion, and the tumors tend to be multicentric. The tumors can be benign or malignant and can occur metachronously or synchronously. MEN-1 is characterized by the concurrence of parathyroid hyperplasia, pancreatic islet cell tumors, and pituitary adenomas. MEN-2A consists of medullary thyroid carcinoma (MTC), pheochromocytoma, and parathyroid hyperplasia. MEN-2B includes MTC, pheochromocytoma, mucosal neuromas, and a distinctive marfanoid

habitus. Together these syndromes encompass much of the spectrum of endocrine neoplasia.

Pathogenesis

The genetic abnormality in MEN-1 has been identified and described in detail.[49,50] As a tumor-suppressor gene, the first mutation is inherited and becomes unmasked only when a second mutation, in some cases a deletion, develops in susceptible tissues. The resulting complete loss of the tumor suppressor allows neoplasia to develop. The occurrence of multiple second mutations explains the characteristic multicentric involvement of these diseases. Direct genetic testing is now available for some families with known mutations.

Mutations of the *RET* protooncogene are the cause of MEN-2A.[51] Genetic testing is now available to identify affected family members and provide the opportunity for early treatment of MTC in affected persons.

Clinical Features and Management of Multiple Endocrine Neoplasia Type 1

Characteristically, MEN-1 presents in the third and fourth decades, without any gender predilection. The syndrome is expressed with nearly complete penetrance, and autopsy studies suggest that all three organs are affected in more than 90% of patients. The phenotype varies, however; more than 90% of patients have hyperparathyroidism, but evidence of islet cell neoplasms (30% to 80%) and pituitary tumors (15% to 50%) is less common. The cause of death in carriers of the MEN-1 mutation is related to MEN-1 in about 45% of patients and often caused by malignant islet cell or carcinoid tumors.[52]

Parathyroid Disease

Hypercalcemia secondary to hyperparathyroidism is usually the first biochemical abnormality detected in MEN-1 and represents the best screening opportunity for members of affected kindreds until direct genetic screening is available in a specific family. Many of these patients are

asymptomatic and have relatively mild hypercalcemia. When symptoms do develop, they typically involve the urinary tract rather than the skeleton.

Typically, the patients have four-gland disease, which may be particularly difficult to manage. The disease is characterized by metachronous development of multiple parathyroid adenomas. There is no curative operation; the two accepted approaches (subtotal parathyroidectomy and total parathyroidectomy with autograft) each have faults (see earlier). Over time, the subtotal parathyroidectomy approach is becoming the preferred choice by most surgeons.

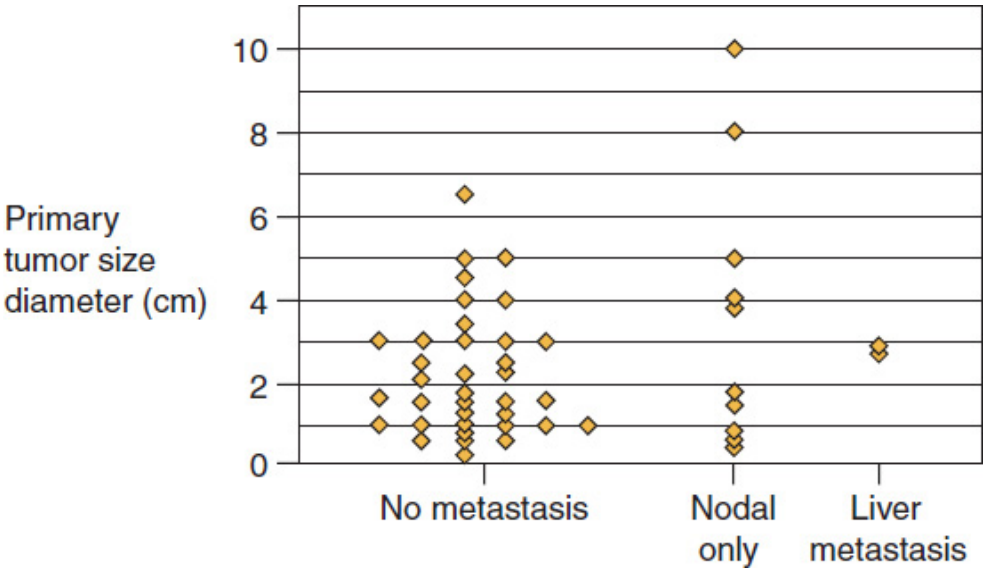

Figure 76.17 Scatter plot of largest primary tumor size versus metastatic status in 43 patients with pancreatic islet cell tumors associated with multiple endocrine neoplasia type I. Each point represents a single patient. Tumor size is not correlated with the presence of liver or lymph node metastases. (From Lowney JK, Frisella MM, Lairmore TC, et al. Pancreatic islet cell tumor metastasis in multiple endocrine neoplasia type I: correlation with primary tumor size. *Surgery* 1998;124:1043–1049.)

Pancreatic Tumors

In patients with pancreatic tumors, multicentric and diffuse hyperplasia of the pancreatic islets may occur in areas distant from any grossly evident tumor. The management of these tumors is controversial because although some patients have aggressive, malignant tumors, many patients have a fairly benign course. No reliable criteria are available to detect malignant tumors. Tumor size is often cited as a useful marker of prognosis, but substantial

overlap has been noted between the sizes of primary benign and malignant tumors (**Fig. 76.17**). Because of the difficulty in identifying the more aggressive subset, some authors have chosen a liberal policy of early operation to try to prevent metastasis and death. Pancreatic tumors are typically multicentric and frequently malignant. Somatostatin receptor scintigraphy can be a useful imaging technique to demonstrate the extent of tumor (**Fig. 76.18**).

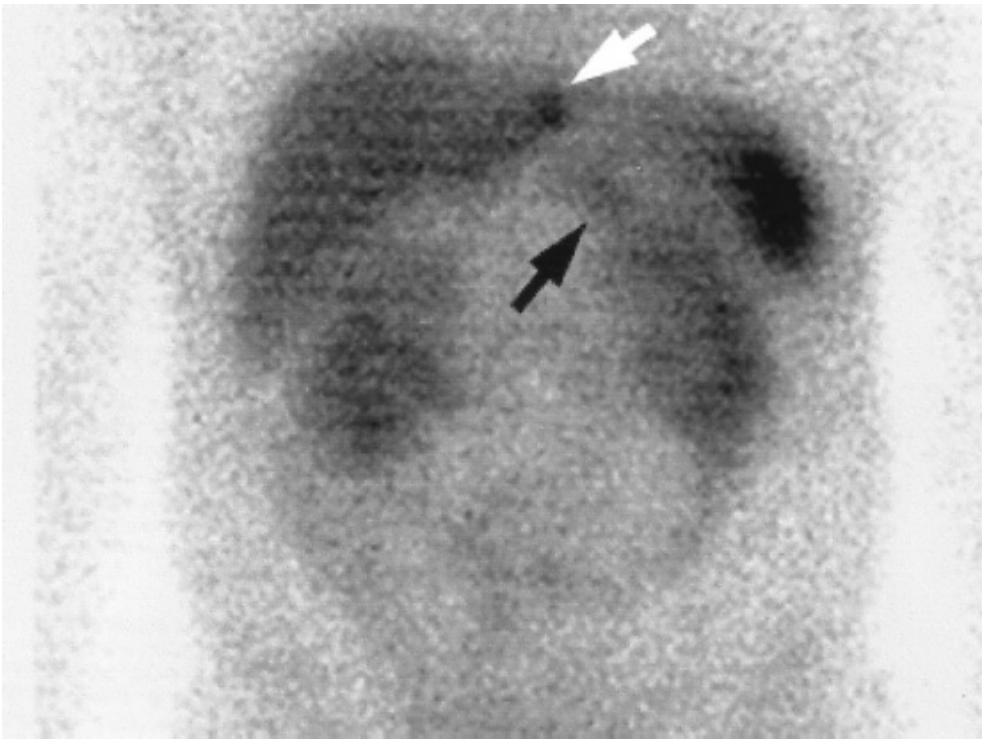

Figure 76.18 Somatostatin receptor scintigraphy in a patient with multiple endocrine neoplasia type I. This scintiscan detected an otherwise unrecognized metastasis to the left lateral segment of the liver (*white arrow*), which was resected along with the small primary tumor (*black arrow*).

Gastrinoma is the most common functional tumor in MEN-1; typically, a severe ulcer diathesis (Zollinger–Ellison syndrome) develops that is associated with secretory diarrhea. Serum gastrin levels are usually markedly elevated (>1,000 pg/mL); when levels are equivocal (250 to 1,000 pg/mL), provocative testing with secretin (2 m/kg) may be useful. An absolute serum gastrin increase of 200 pg/mL is diagnostic. The primary tumors are often in the submucosa of the duodenal wall.

Biochemical cure of these gastrinomas is almost never possible, which is different than patients with sporadic gastrinomas, although exploration can reduce the need for antisecretory medications and may reduce the risk for liver metastasis. Histamine 2-receptor antagonists or proton pump inhibitors are effective in controlling acid secretion, although very high doses may be necessary; the malignant disease is often indolent. Total gastrectomy is no longer ever necessary to eliminate acid secretion.

Insulinoma is the next most common functional pancreatic neoplasm in MEN-1. Patients present with a history of sweating, dizziness, confusion, and syncope, consistent with neuroglycopenia; these symptoms are relieved by consuming carbohydrates. The diagnosis is verified by documenting fasting hypoglycemia associated with inappropriately elevated plasma insulin levels. Preoperative tumor localization is usually achieved by a combination of CT and arteriography. Calcium is injected into various pancreatic arteries and plasma insulin levels in the hepatic vein plasma are measured to detect a gradient after the injection of specific pancreatic arteries localizing the area of the pancreas containing the functional tumor.

Because the available medical therapy for insulinoma is limited, patients are treated operatively. Lesions in the tail of the gland can be enucleated if they are small; however, distal pancreatectomy carries little morbidity. Tumors of the head can usually be enucleated, so that pancreaticoduodenectomy can be avoided. In patients with malignant disease, metastases may respond to streptozocin, diazoxide, verapamil, or octreotide may successfully reduce insulin secretion and control symptoms. A diet of complex carbohydrates can also help stabilize serum glucose levels in the hyperinsulinemic patient.

Nonfunctional tumors are the most common pancreas lesions in MEN-1. Their management is specific to their size and risk of malignancy.

Pituitary Adenomas

Prolactin-secreting tumors occur most commonly in this setting, although Cushing disease or acromegaly develops in an occasional patient. Symptoms may result from compression of the optic chiasm, which produces bitemporal hemianopsia, or from prolactin excess, which produces amenorrhea and galactorrhea in female patients and hypogonadism in male patients.

Bromocriptine inhibits prolactin secretion and shrinks many prolactinomas. Refractory tumors and those producing other hormones can be managed by pituitary ablation or radiation.

Other Tumors

MEN-1 is associated much less frequently with adrenocortical tumors and benign thyroid adenomas. Lipomas and carcinoid tumors may also occur.

Clinical Features and Management of Multiple Endocrine Neoplasia Type 2

Like MEN-1, the MEN-2 syndromes are inherited in an autosomal dominant fashion with complete penetrance but variable phenotype. Bilateral MTC occurs in every affected patient. More frequently than the other syndromes, MEN-2B can arise as a new mutation that can be transmitted to subsequent generations.

Figure 76.19 Medullary thyroid carcinoma. Coronal section of a total thyroid resection shows bilateral involvement by a firm, pale tumor.

Medullary Thyroid Carcinoma

MTC accounts for about 10% of all thyroid malignancies, and 20% of cases occur in the familial setting of MEN-2A, MEN-2B, or familial non-MEN MTC. It is usually the first tumor that develops in these patients and typically appears in the second or third decade. Tumors are virtually always bilateral and develop in multiple areas of the middle and upper portions of the thyroid lobe (**Fig. 76.19**). Occasionally, in young people, a diffuse proliferation of parafollicular C cells, termed *C-cell hyperplasia,* is present without frankly invasive carcinoma. This finding is highly suggestive of one of the familial MTC syndromes. Patients typically present with a neck mass and may have hoarseness, dysphagia, or palpable cervical adenopathy. MTC may produce a variety of hormones, including calcitonin, adrenocorticotropic hormone, prostaglandin, and serotonin. The hypercalcitoninemia is often asymptomatic, although severe diarrhea can develop.

By detecting minimal elevations of plasma calcitonin, it is possible to diagnose MTC at a clinically occult stage. Basal plasma calcitonin levels in normal subjects are in the range of 30 to 100 pg/mL. An increase to levels of 150 to 200 pg/mL occurs, however, after the administration of the potent secretagogues, calcium and pentagastrin. The plasma calcitonin levels of patients with MTC show striking increases (>1,000 pg/mL) after provocative testing, so that they can be identified readily. Patients with occult disease may have only minimally elevated basal calcitonin levels that increase in response to secretagogues. The combined infusion of calcium and pentagastrin was the most effective screening test for familial MTC before genetic testing became available. By means of provocative testing in kindred members at risk for disease, MTC was diagnosed at a preclinical stage, and a greater percentage of these patients were cured by surgical therapy. With genetic testing now available, prophylactic thyroidectomy to prevent the development of MTC is possible for all affected people.

Postoperatively, the presence of residual MTC can be readily detected by provocative testing. Meticulous reoperation in patients with recurrent or persistently elevated plasma calcitonin levels postoperatively, including mediastinal dissection on occasion, can normalize elevated plasma calcitonin levels and apparently cure many of them. For the patient with unresectable metastases, few therapeutic options are available. Neither radiation nor chemotherapy is of significant benefit.[53]

The clinical course of patients with the MEN-2 syndromes is determined primarily by the status of their MTC. In the setting of MEN-2A, the tumors are often indolent and survival prolonged, even in the presence of metastatic disease. By contrast, the tumors in patients with MEN-2B occur at an earlier age and are generally more aggressive neoplasms. Patients may succumb to the disease at a young age. As a consequence of this aggressiveness, the size of kindreds with the disease is typically small, and usually only a few generations are affected.

Figure 76.20 **A,B:** Characteristic appearance of patients with multiple endocrine neoplasia type IIB, including thick lips. **C:** Multiple mucosal neuromas on the tongue of a patient with MEN-2B. (From Norton JA, Froome LC, Farrell FE, et al. Multiple endocrine neoplasia type 2b: the most aggressive form of medullary thyroid carcinoma. *Surg Clin North Am* 1979;59:109–118.)

Pheochromocytoma

Pheochromocytomas are usually detected during the initial screening or follow-up of patients in whom MTC has already been diagnosed. They typically appear in the second or third decade of life, and about 80% are bilateral. Usually, pheochromocytomas are benign but multicentric, and they

almost always arise in the adrenal medulla. In patients with MEN-2A or MEN-2B, hyperplasia of the adrenal medulla may develop first, grossly characterized by thickening of the medullary tissue in both adrenal glands.

Pheochromocytomas can be asymptomatic, but most commonly, patients have pounding frontal headaches, episodic diaphoresis, palpitations, or anxiety. Hypertension also occurs and is often episodic.

The diagnosis is made by measuring the plasma concentration of metanephrines. Patients with MEN-2A or MEN-2B and MTC should be evaluated for pheochromocytoma before they undergo thyroidectomy. If a patient is found to have both lesions, adrenalectomy should be performed first, followed by neck exploration. The abdomen is explored through a bilateral subcostal incision or, more typically, with a laparoscope. Bilateral pheochromocytomas are treated by bilateral adrenalectomy. In patients with MEN-2A or MEN-2B and a unilateral pheochromocytoma, only the diseased adrenal gland is removed. In about 30% of patients treated in this manner, a tumor eventually develops in the opposite gland. In the remaining patients, this approach avoids the need for glucocorticoid and mineralocorticoid replacement and the risk for addisonian crisis. After unilateral adrenalectomy, patients are carefully screened at 6-month or 1-year intervals with plasma metanephrine measurements.

Parathyroid Disease

Hyperparathyroidism develops in about one-third of patients with MEN-2A, although it is usually asymptomatic. Occasionally, nephrolithiasis develops. Bone disease is unusual. Frequently, enlarged parathyroid glands are found at operation for MTC, although the patient is still normocalcemic. Multiglandular chief cell hyperplasia is the predominant histologic finding in MEN-2A. Significant parathyroid disease rarely develops in MEN-2B.

Total parathyroidectomy and heterotopic autotransplantation are performed in hypercalcemic patients with MEN-2A. In normocalcemic patients with MEN-2A undergoing thyroidectomy for MTC, total parathyroidectomy and heterotopic autotransplantation are performed in one session to ensure that the complete thyroidectomy does not compromise the parathyroid blood supply and to avoid reoperation in the neck for subsequent hyperparathyroidism. Evidence suggests that these patients are more easily

treated, with a lower incidence of recurrent hyperparathyroidism, than patients with MEN-1.

Nonendocrine Manifestations of Multiple Endocrine Neoplasia Type 2B

In addition to MTC and pheochromocytoma, marked abnormalities of the nervous and musculoskeletal systems develop in patients with MEN-2B. The classic phenotype is characterized by thick lips and a thin, marfanoid habitus (**Fig. 76.20A,B**). The incidence of associated skeletal abnormalities is high; these include kyphosis, pectus excavatum, pes planus or cavus, and congenital dislocation of the hip. Diffuse autonomic nervous hypertrophy is another feature. Mucosal neuromas appear on the tongue (**Fig. 76.20C**), eyelids, lips, and pharynx. Slit-lamp examination may reveal hypertrophied corneal nerves. Ganglioneuromatosis develops in the submucosal and myenteric plexuses of the gastrointestinal tract. Constipation is common, and radiographic findings may suggest megacolon or Hirschsprung disease.

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77

Adrenal Gland

Hadiza S. Kazaure and Sanziana A. Roman

Key Points

1. Adrenocortical steroid hormones, glucocorticoids, mineralocorticoids, and androgenic steroids are all synthetic derivatives of cholesterol that are either extracted from plasma or synthesized intracellularly.
2. Catecholamines of the adrenal medulla include epinephrine, norepinephrine, and dopamine, the vasoactive synthetic derivatives of the amino acid tyrosine.
3. Unsuspected adrenal masses (incidentalomas) are detected by computed tomography (CT) in up to 1.9% of healthy patients; the goal of evaluation is to determine hyper-functionality and/or malignancy, and determine which need surgical intervention and which can be observed.
4. Hypercortisolism is due to Cushing disease, in 80% to 90% of cases. This is an adrenocorticotropic hormone (ACTH) dependent disorder. Cushing syndrome occurs in 10% to 20% of cases; it is not usually ACTH dependent and primarily due to an adrenal cause.
5. Primary hyperaldosteronism occurs in the setting of either a unilateral aldosterone-producing adrenal adenoma (Conn syndrome) in 60% to 70% of cases, or bilateral idiopathic adrenal hyperplasia.
6. Surgical removal by minimally invasive adrenalectomy of an aldosterone-secreting adenoma results in durable improvement of hypertension and hypokalemia in 70% to 90% of patients; management of idiopathic adrenal hyperplasia is usually medical, because fewer than 20% to 30% of patients with this disease are cured by adrenalectomy.
7. Adrenocortical carcinoma has an estimated incidence of 0.5 to 2 cases per million per year, is very aggressive, and hormone overproduction syndromes are frequent, including virilizing hormones, hypercortisolism, hyperaldosteronism, and can be multihormonal.
8. Recent advances in genetics and oncology have revealed that up to 40% of pheochromocytomas/paragangliomas are hereditary. The *rule of tens* is no longer a useful way to characterize pheochromocytoma. Determination of plasma-fractionated metanephrines is the best test for screening of pheochromocytoma.

ANATOMY

The adrenal glands are bilateral, retroperitoneal, endocrine organs located adjacent to the superior pole of each kidney. These glands appear grossly as flat, triangular structures each weighing approximately 4 g. Each adrenal gland is composed of two distinct endocrine organs, the cortex and medulla. The outer adrenal cortex is bright yellow and nodular, whereas the adrenal medulla is red brown in color and is sandwiched between the thin layers of the cortex. The adrenals are embedded in retroperitoneal perinephric fat but can be identified as distinct structures by their golden brown, nodular appearance. The right adrenal gland abuts the inferior vena cava medially and lies in close proximity to the diaphragmatic crus posteriorly and the liver anteriorly. The left adrenal gland resides between the kidney and aorta, immediately deep to the tail of the pancreas and spleen.

Embryologically, fetal and definitive adrenal cortices arise from coelomic mesoderm near the urogenital ridge during the fourth to sixth weeks of gestation. Postnatally, the fetal cortex involutes, leaving only the definitive cortex to differentiate into the three adult zonae, the glomerulosa, fasciculata, and reticularis. The adrenal medulla develops from the neural crest during the fifth gestational week and migrates along paraaortic and paravertebral routes to join the developing cortex. Ectopic adrenal cortex and medulla may be found anywhere along their respective paths of embryologic migration. Most neural crest tissue regresses, however, extraadrenal neural crest derivatives may be found along the retroperitoneum and at the aortic bifurcation (organ of Zuckerkandl).

The adrenal cortex is composed of three distinct zones. The outer zona glomerulosa, located just beneath the fibrous gland capsule, is the site of mineralocorticoid production. The middle zona fasciculata, composed of linear arrays of large, foamy cells with lipid inclusions, is the predominant site of glucocorticoid and adrenal sex steroid biosynthesis. The inner zona reticularis is the primary location of synthesis of adrenal androgens. Both the zona fasciculata and zona reticularis respond to stimulation by adrenocorticotropic hormone (ACTH). Throughout life, adrenocortical cells proliferate under the adrenal capsule as steroidogenic cells, and are then slowly displaced centripetally, until they undergo apoptosis at the adrenocortical–medullary

boundary. In the past decade, much has been learned about adrenocortical stem and progenitor cells and their roles in normal development, adrenal homeostasis, and in adrenal diseases, however, more research is needed to translate these major scientific advances to the clinical setting.

The adrenal medulla is smaller than the cortex. Cells of the adrenal medulla appear as homogeneous sheets, with large, irregular, atypical-looking nuclei. The cytoplasm of these cells has numerous secretory granules containing catecholamines, neuron-specific enolase, and chromogranin. Catecholamines in these granules precipitate chromium salts, which is the basis for the term *chromaffin cells*.

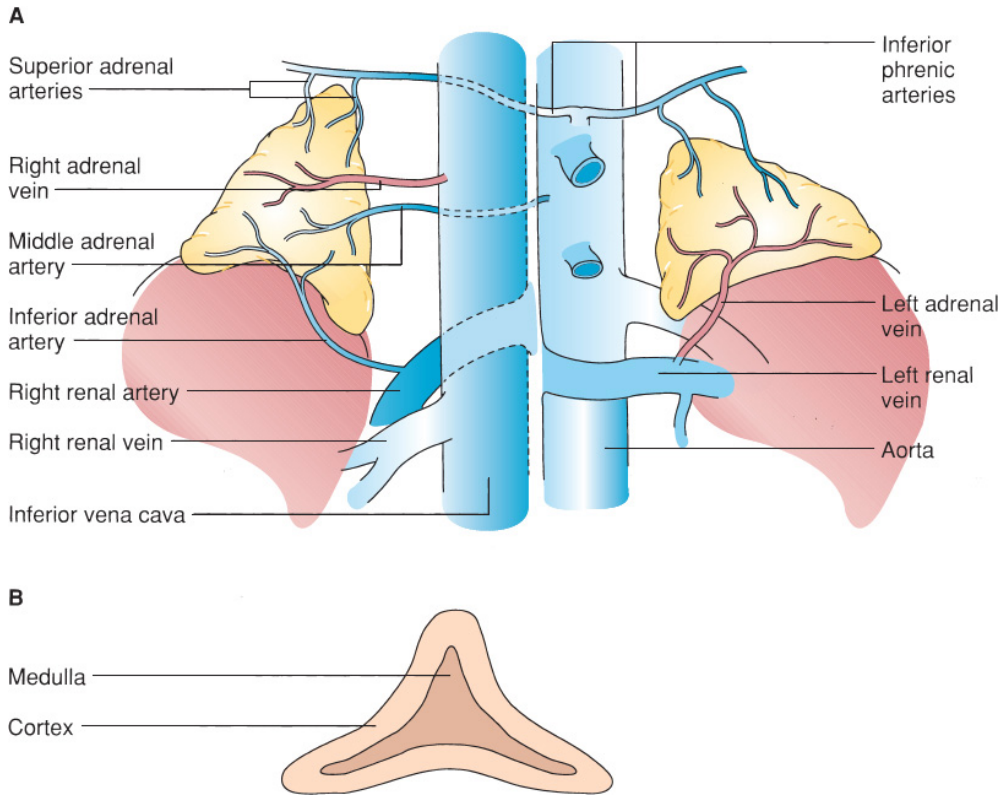


Figure 77.1 **A:** Arterial (*dark shaded*) and venous (*light shaded*) anatomy of the adrenal glands. **B:** Schematic showing outer adrenal cortex (*light shaded*) and inner adrenal medulla (*dark shaded*).

The adrenal glands have an extensive vascular supply derived from branches of the inferior phrenic artery superiorly, the aorta medially, and the renal artery inferiorly. Venous return from the right adrenal gland empties directly into the inferior vena cava through a wide but short central vein. Venous drainage from

the left adrenal gland empties into a smaller vein that shares a common trunk with the left phrenic vein. Together they join the left renal vein (**Fig. 77.1**).

BIOCHEMISTRY AND PHYSIOLOGY

Adrenal Cortex

1 Adrenocortical steroid hormones, glucocorticoids, mineralocorticoids, and androgenic steroids are all synthetic derivatives of cholesterol that are either extracted from plasma or synthesized intracellularly (**Fig. 77.2**). In mitochondrial cells of the adrenal cortex, cholesterol is converted by desmolase (CYP11A1) to delta-5-pregnenolone, the common parent compound for all adrenal cortex steroids. Pregnenolone is then shunted to the three biosynthetic pathways, each compartmentalized within the adrenal according to synthetic capabilities within each zone. In the zonae fasciculata and reticularis, pregnenolone is either converted to progesterone by 3-beta-hydroxysteroid dehydrogenase or is oxidized at position 17 by 17-alpha hydroxylase (CYP17) to form 17-hydroxypregnenolone. In the zona fasciculata, progesterone is hydroxylated by CYP17 at position 17 to form 17-hydroxyprogesterone. Subsequently, 17-hydroxyprogesterone is sequentially hydroxylated at the 21 position by 21-beta hydroxylase (CYP21A2) and at position 11 by 11-beta hydroxylase (CYP11B1) to form cortisol. In the zona reticularis, the androgenic steroids dehydroepiandrostenedione (DHEA) and androstenedione are made from 17-hydroxypregnenolone and 17-hydroxyprogesterone, respectively. Collectively, the glucocorticoid and androgenic steroids are known as *17-hydroxy corticosteroids and 17-hydroxy ketosteroids*. In the zona glomerulosa, progesterone is not hydroxylated at the 17 position owing to the lack of enzyme at this location. Instead aldosterone is made from progesterone by a sequential series of hydroxylation steps at position 21 by CYP21A2, position 11 by CYP11B1, and position 18 by aldosterone synthase (CYP11B2 and P450c11as). The zona glomerulosa is well suited to aldosterone biosynthesis because of the relative lack of 17-hydroxylase and the exclusive expression of aldosterone synthase, required for the conversion of corticosterone to aldosterone.

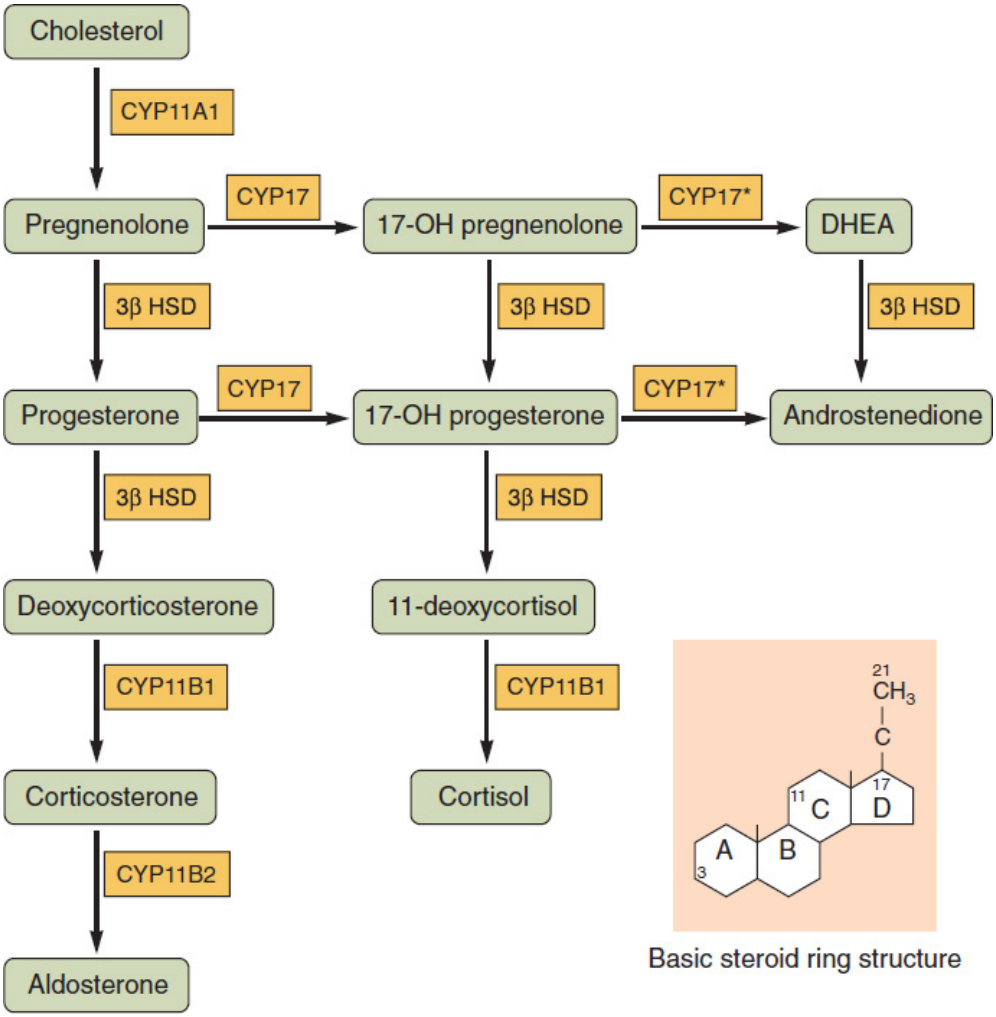


Figure 77.2 Steroid biosynthetic pathways in the adrenal cortex. Steroids and precursors are shown in *square boxes*. Enzymes are shown in *stippled boxes*. Enzyme gene symbol designations are: CYP11A1, desmolase; CYP17, 17α-hydroxylase (±17,20 lyase*); 3β-HSD, 3β-hydroxysteroid dehydrogenase; CYP21A2, 21-hydroxylase; CYP11B1, 11β-hydroxylase; CYP11B2, Aldosterone synthase. *Inset:* Basic steroid ring structure. The four basic carbon rings are designated A, B, C, and D. Individual carbons at sites of steroidegenic enzyme activity are designated numerically.

Cortisol

Cortisol is the predominant glucocorticoid in humans. Production and release of cortisol is tightly regulated by a complex feedback relationship between the hypothalamus, corticotrophs of the anterior pituitary, and cells of the adrenal cortex zonae fasciculata and reticularis. This endocrine system is called the *hypothalamic–pituitary–adrenal (HPA) axis*. Communication within the HPA axis is mediated by synthesis and secretion of corticotrophin-releasing hormone (CRH) by the hypothalamus and ACTH production by corticotrophs of the

anterior pituitary (**Fig. 77.3**). ACTH is a cleavage product of a precursor polypeptide, proopiomelanocortin (POMC) that is built of 241-amino-acid residues within corticotroph cells of the anterior and intermediate lobes of the pituitary. Several derivatives of POMC are important biologically active substances, including ACTH. Under stimulation of hypothalamic CRH stimulus, POMC can be cleaved into ACTH and β-lipotropic hormone in the anterior lobe. ACTH acts directly on the adrenal to regulate cortisol production by cells within the zonae fasciculata and reticularis. Feedback loops involving cortisol, hypothalamic CRH, and pituitary ACTH keep the concentration of cortisol in plasma within a narrow range of 10 to 15 μg/dL. Typical daily production of cortisol in humans ranges from 10 to 30 mg and can increase to as high as 300 mg/day under conditions of maximal stress.

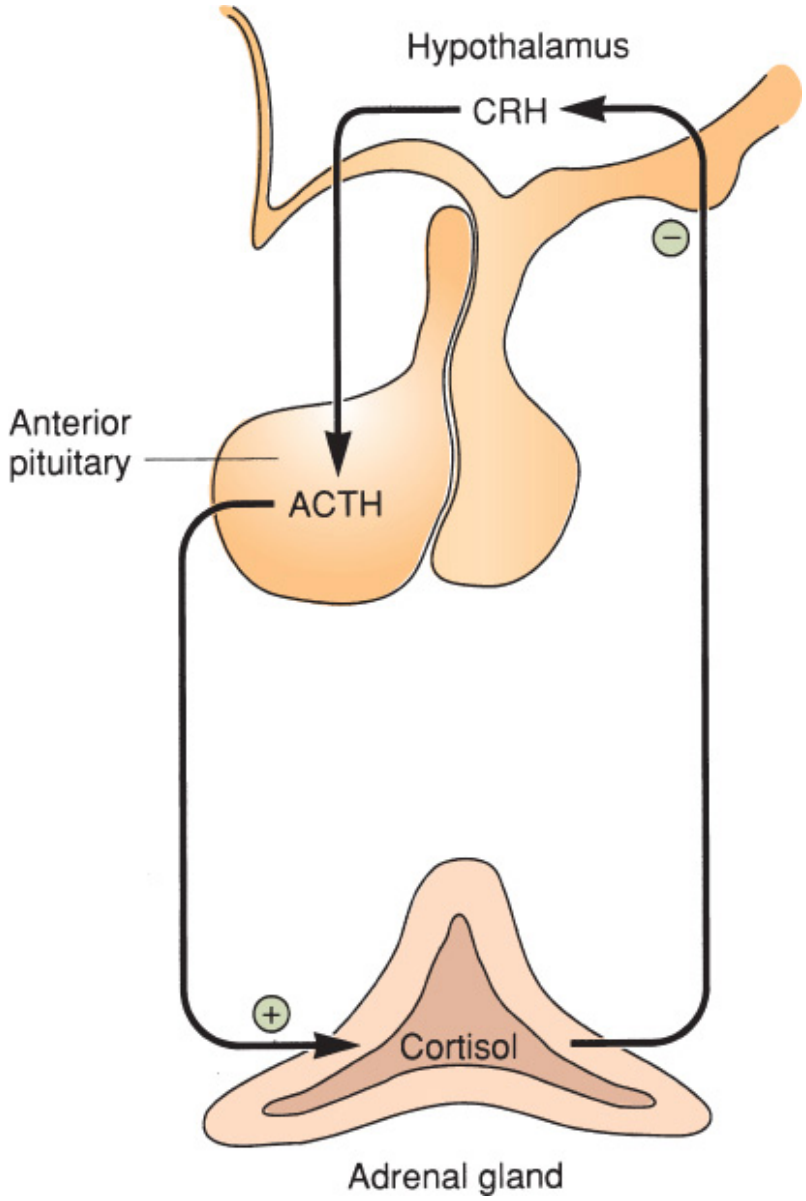


Figure 77.3 Schematic of hypothalamic–pituitary–adrenal axis for cortisol. Regulatory feedback relationships are designated with *arrows*.

In circulation, cortisol is protein bound to transcortin and albumin with a small percentage of free cortisol available to target tissues. The half-life of cortisol in circulation is 90 minutes. Cortisol is metabolized in the liver to the inactive metabolites dihydrocortisol and tetrahydrocortisol, which become conjugated to glucuronidate and excreted in the urine. These urinary metabolites, collectively known as *17-hydroxycorticosteroids,* as well as free cortisol, can be measured in the urine.

Cortisol binds to specific intracellular cytoplasmic receptors, causing translocation of activated receptor–ligand complexes to the nucleus. Biologic effects result from transcriptional activation of genes and may be grouped into intermediary metabolism, immunomodulation, and regulation of intravascular volume (**Table 77.1**). Important effects of cortisol on intermediary metabolism center on raising blood glucose directly and indirectly by providing substrate for gluconeogenesis by the liver. These effects include (a) stimulation of glucagon and inhibition of insulin-stimulated glucose uptake by cells; (b) decrease in peripheral protein synthesis and increase in proteolysis, thus delivering gluconeogenic amino acids to the liver; and (c) stimulation of peripheral lipolysis. In effect, cortisol acts anabolically in vital organs to preserve glucose supply and catabolically in peripheral tissues to mobilize gluconeogenic substrates. Cortisol also possesses profound anti-inflammatory and immunosuppressive activities. Impairment of cellular immunity is due to inhibition of interleukin production, impairment of monocyte and neutrophil chemotaxis despite raised leukocyte counts, and reduction of T-cell activation. Humoral immunity is inhibited by inhibition of T-cell stimulation of B cells and by direct inhibition of B-cell proliferation and activation. These immunomodulatory effects may also underlie the impairment of normal wound healing seen in states of cortisol excess. Cortisol also regulates intravascular volume through renal retention of sodium and maintains blood pressure through inotropic and chronotropic effects on the heart as well as by increasing peripheral vascular resistance. In bone, glucocorticoids promote osteopenia by inhibition of bone formation by osteoblasts.

Table 77.1 Systemic Effects of Cortisol

Function	Normal Amounts	Excessive Amounts
Metabolic Protein Glucose Fat	Proteolysis Gluconeogenesis Low-use peripheral lipolysis Central lipogenesis	Muscle wasting Hyperglycemia Limb thinness Truncal obesity
Gastrointestinal	Mucosal cells Prostaglandin	Ulceration Pancreatitis
Cardiovascular	Chronotropic, inotropic Vascular resistance	Hypertension
Renal	Sodium resorption	Hypertension
Bone	Osteoblastic development	Osteoporosis
Inflammatory and immune	Circulating cells Soluble mediators Antigen processing	Infection
Wound healing	Fibroblasts Epithelial cell	Striae Dehiscence

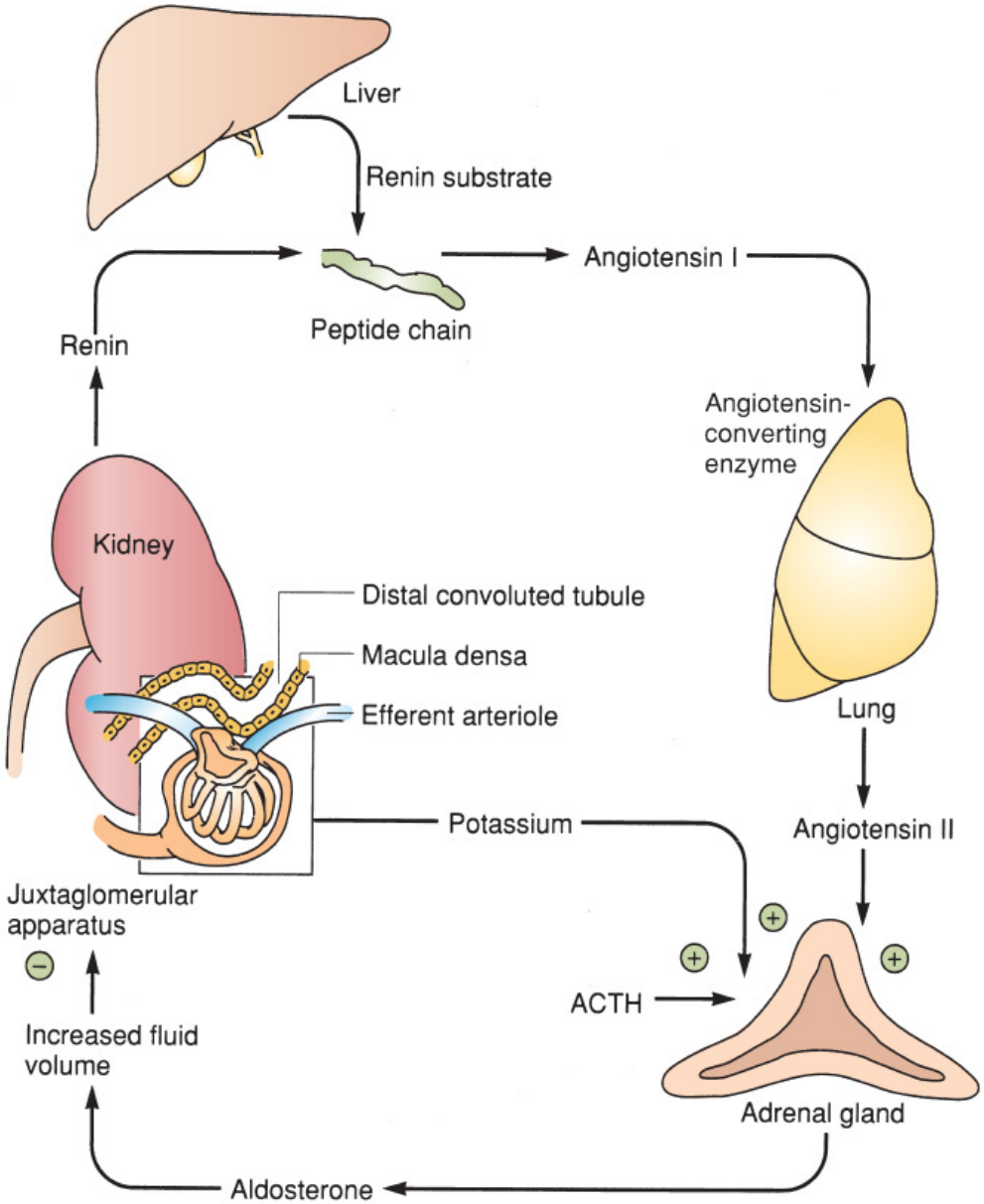


Figure 77.4 Regulatory relationships of renin, the angiotensins, and their sites of production and enzymatic conversion.

Aldosterone

Aldosterone is the principal mineralocorticoid in humans. Aldosterone secretion by the cells of the adrenal zona glomerulosa is regulated by the renin–angiotensin system and by plasma potassium (**Fig. 77.4**). Aldosterone is also regulated to a lesser degree by ACTH and plasma sodium concentration. Juxtaglomerular myoepithelial cells lining afferent arterioles of the kidney sense renal blood flow and pressure, and they secrete renin in response to decreased

perfusion. Renin enzymatically activates angiotensinogen to the inactive decapeptide precursor, angiotensin I. Angiotensin I is converted to angiotensin II by angiotensin-converting enzyme in the lung. Angiotensin II has three major effects: (a) arteriolar vasoconstriction; (b) renal sodium retention; and (c) increased aldosterone biosynthesis, each of which results in sodium retention and potassium excretion by the kidney. These effects work together to maintain arterial blood pressure as well as blood volume. Physiologic conditions that stimulate the renin–angiotensin cascade and aldosterone release include dehydration, upright posture, and hemorrhage. Inhibitory factors include volume repletion. Postural changes in renin–angiotensin and aldosterone are mediated by the sympathetic nervous system.

Under normal circumstances, aldosterone secretion is controlled by total body sodium and potassium levels. Excess sodium intake suppresses renin activity and leading to decreased aldosterone levels and increased renal excretion of sodium. Conversely, sodium depletion stimulates the renin–angiotensin system and aldosterone production, which promotes sodium retention by the kidney. Increased potassium intake directly decreases renin release and aldosterone production; decreasing potassium intake increases renin release. Humans with normal sodium intake typically produce 100 to 150 mg of aldosterone per day.

In circulation, aldosterone is bound to albumin and transcortin with a small percentage of free aldosterone available to target tissues. The half-life of aldosterone in plasma is 15 minutes. Aldosterone is metabolized rapidly in the liver and conjugated to glucuronidate, which is excreted in the urine. In liver failure, metabolism of aldosterone is impaired leading to elevated levels and fluid retention.

Aldosterone is the major regulator of extracellular fluid volume and potassium homeostasis (**Table 77.2**). Aldosterone binds to high-affinity aldosterone receptors in target tissues, including cells of the distal convoluted tubule in the kidney (the major site of action), the salivary glands, and colonic mucosa (minor sites). Stimulation of these cells results in retention of sodium and excretion of potassium. Retention of sodium in the kidney leads to passive reabsorption of water and an increase in extracellular fluid volume. To balance aldosterone-mediated retention of positively charged sodium ions, the kidney epithelium releases intracellular potassium into the distal convoluted tubule for excretion in the urine. Hydrogen ion is also released causing acidification of the urine.

Table 77.2 Effects of Aldosterone Secretion

Tubular Action	Normal Amounts	Excessive Amounts
Increased resorption of sodium	Protects against low-volume states	Hypertension Positive sodium balance Hyporeninemia
Decreased resorption of potassium	Protects against hyperkalemia	Hypokalemia Metabolic alkalosis Hyperglycemia Nocturia, polyuria Muscle weakness

Adrenal Androgens

Adrenal C-19 androgenic steroids, include DHEA and delta-4-androstenedione, are synthesized in cells of the zona reticularis. These steroids promote secondary sexual characteristics in men and virilization in women. DHEA is the major adrenal androgen, while androstenedione is relatively minor. Both are relatively weak androgens and exert their effects on target tissue after local tissue conversion to testosterone. Unlike gonadal androgens, adrenal androgens are regulated by ACTH, not gonadotropins, and can therefore be inhibited by glucocorticoid administration.

Adrenal Medulla

2 Catecholamines of the adrenal medulla include epinephrine, norepinephrine, and dopamine. These vasoactive hormones are synthetic derivatives of the amino acid tyrosine (**Fig. 77.5**). The biosynthetic pathway that converts tyrosine to active catecholamines involves four sequential enzymatic reactions: (a) tyrosine is converted to L-dihydroxyphenylalanine (dopa) by tyrosine hydroxylase; (b) dopa is converted to dopamine by aromatic-L-amino acid decarboxylase; (c) dopamine is converted to norepinephrine by dopamine beta hydroxylase; and (d) norepinephrine is converted to epinephrine by phenylethanolamine-N-methyltransferase (PNMT). Epinephrine is the major (80%) catecholamine stored in the adrenal medulla, followed by norepinephrine (20%) and dopamine (<1%). Tissue expression of the enzyme

PNMT is limited to cells of either the adrenal medulla or organ of Zuckerkandl, located near the aortic bifurcation, thus most extraadrenal pheochromocytomas produce norepinephrine, rather than epinephrine.

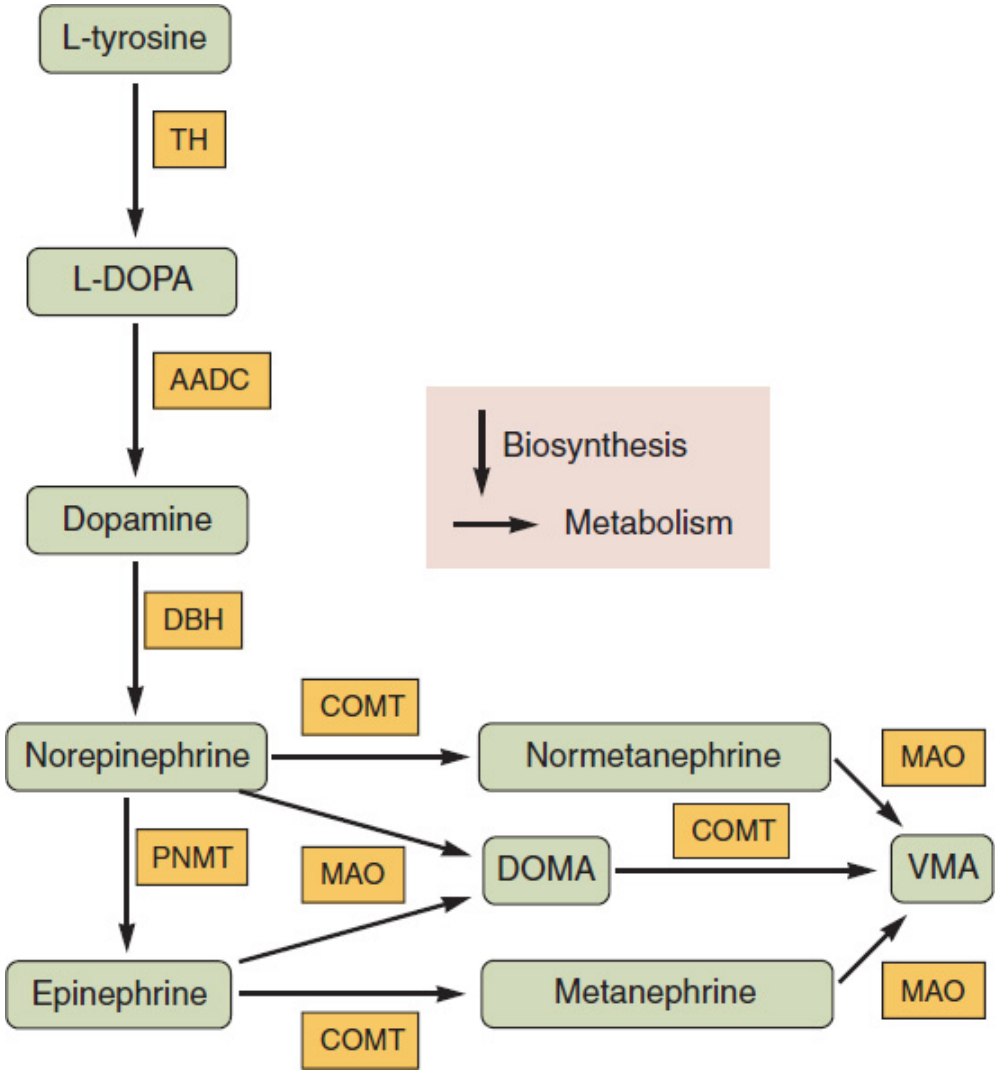


Figure 77.5 Catecholamine biosynthetic and metabolic pathways. Precursors, catecholamines, and metabolites are shown in *square boxes*. Enzymes are shown in *stippled boxes*. Enzyme gene symbol designations are: TH, tyrosine hydroxylase; AADC, aromatic-L-amino acid decarboxylase; DBH, dopamine-β-hydroxylase; PNMT, phenylethanolamine-N-methyltransferase; COMT, catechol-O-methyl-transferase; MAO, monoamine oxidase. VMA, 3-methoxy-4-hydroxy-mandelic acid.

A complex regulatory network governs synthesis and secretion of catecholamines. Factors that increase catecholamine release include splanchnic nerve stimulation, stress, and glucocorticoids. The metabolic milieu within the adrenal medulla also greatly influences catecholamine synthesis by regulating

enzymatic activity: glucocorticoids, phospholipids, cyclic adenosine monophosphate, adenosine triphosphate, protein kinase, and magnesium increase activity of PNMT and decrease catecholamine negative feedback. Catecholamines are stored and secreted from granules within cells of the medulla in association with the matrix protein chromogranin. Chromogranin A is measurable in the blood and their measurement may support the biochemical testing for pheochromocytoma, as well as other functional neuroendocrine tumors.

Catecholamines act on target tissues through membrane-bound receptors. Pharmacologic distinction of adrenergic receptors is made based on their relative responsiveness to natural and artificial bioamines. Alpha-adrenergic receptors show highest affinity for norepinephrine, less for epinephrine, and least for isoproterenol. Beta-adrenergic receptors are most responsive to isoproterenol and least to norepinephrine. In addition, specific antagonists recognize each receptor class: alpha receptors are antagonized by phentolamine and phenoxybenzamine, and beta receptors are blocked by propranolol and related compounds. Beta-adrenergic receptor subtypes include beta-1, which is present in cardiac muscle, adipose tissue, and small intestine, and beta-2 receptors, which are found in vascular, tracheal, and uterine smooth muscle, skeletal muscle, and liver. Alpha-adrenergic receptors are similarly subdivided: alpha-1 receptors mediate vasoconstriction whereas alpha-2 receptors modulate presynaptic norepinephrine release and platelet aggregation (**Table 77.3**).

Table 77.3 Catecholamine Effects

Receptor Class	Normal Amounts	Excessive Amounts
β_1	Chronotropic, inotropic Sweat glands Decreased glucose use	Tachycardia Sweating Hyperglycemia
β_2	Smooth muscle relaxation	Hypotension
α_1	Smooth muscle contraction Gluconeogenesis Glycogenolysis Suppressed insulin effects	Hypertension Hyperglycemia
α_2	Smooth muscle contraction[a]	Pallor

[a]Platelet aggregation.

Metabolism of catecholamines occurs through three mechanisms: by specific uptake by sympathetic neurons, by nonspecific uptake and degradation by peripheral tissues, and by excretion in the urine. Catecholamines are metabolized in liver and kidney by two enzymes, monoamine oxidase and catechol-O-methyltransferase (**Fig. 77.5**). In these tissues, monoamine oxidase and catechol-O-methyltransferase convert epinephrine or norepinephrine to normetanephrine, and metanephrine, 3,4-dihydroxy-mandelic acid, and 3-methoxy-4-hydroxy-mandelic acid. These inactive metabolites are excreted by the kidney and are measurable in the urine either as free compounds or as conjugates of glucuronide or sulfate.

ADRENAL NEOPLASMS AND DISEASES

Incidental Adrenal Mass

Clinically occult adrenal masses (also called *adrenal incidentalomas*) have become commonplace over the past 25 years with the increased use of abdominal imaging such as computed tomography (CT) and magnetic resonance imaging (MRI). The estimated prevalence of incidental adrenal neoplasms varies by population studied and method of detection. Unsuspected 3 adrenal masses are detected by CT in between 0.6% and 1.9% of healthy patients. Patients with a prior history of malignancy have a prevalence of adrenal masses of up to 4.4%. Adrenal masses increase in frequency with advancing age, ranging from 3% in midlife to 10% in the elderly. The combination of an aging population and increased application of abdominal imaging promises to create a significant public health challenge.

The goal of evaluation is to distinguish and remove those adrenal masses that are functioning or likely to be malignant versus those that are neither, and may be observed. Expectations of the yield for the workup of adrenal masses may be informed by epidemiologic reports and reports of pathologic findings in resected incidentalomas. A review of 44 reports describing over 3,000 such cases reported that 41% were cortical adenomas, 19% were metastases from other primary cancers, 10% were adrenocortical carcinomas, and 8% were pheochromocytomas, with the remainder including myelolipomas and cysts.

Diagnosis

In the evaluation of incidental adrenal masses, two simple questions must be answered: Is it functional? Is it malignant? The diagnostic approach should proceed to answer these questions sequentially (**Table 77.4**). Current opinion is that all asymptomatic patients with adrenal masses should be screened for pheochromocytoma, hypercortisolism, and hyperaldosteronism (**Algorithm 77.1**).

All patients require a complete personal and family history, physical examination, biochemical evaluation of pertinent hormones, and select imaging studies. Attention must be paid to episodes of hypertension, tachycardia, and anxiety that suggest pheochromocytoma. Physical findings such as muscle wasting, purple striae, hirsutism, and gynecomastia may suggest either Cushing syndrome or a virilizing tumor. Secondary metastases from underlying malignancy must be considered and evaluated with appropriate history, physical examination, and select tests including mammograms in women and chest radiography in all patients, especially smokers.

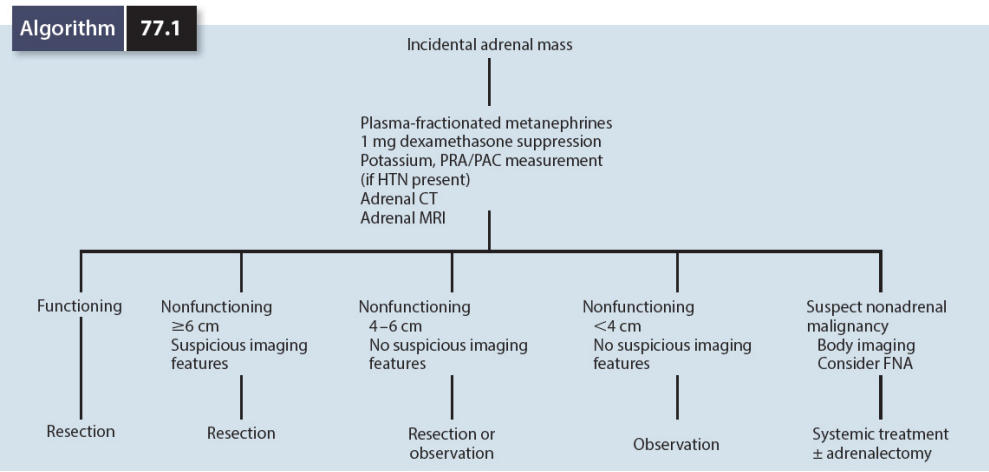
Biochemical testing should routinely exclude pheochromocytoma, hypercortisolism, and hyperaldosteronism. Pheochromocytoma is evaluated either by 24-hour urine collection for catecholamines, metanephrines, and 3-methoxy-4-hydroxy-mandelic acid, or by plasma fractionated metanephrines. Subclinical or clinically apparent Cushing syndrome is best evaluated with the overnight 1-mg dexamethasone suppression test. Hyperaldosteronism is best assessed by concurrent measurement of serum or plasma aldosterone and PRA while assuring that the serum potassium is normalized.

Imaging studies usually include cross-sectional imaging with either CT or MRI. Abdominal CT (noncontrast) is the best initial test for identifying and characterizing most adrenal masses. Using a fast scanner and 1-mm scanning intervals, both adrenal glands can be seen in 97% to 99% of patients and lesions as small as 5 mm can be readily identified. Currently, attenuation values expressed in Hounsfield Units (HU), along with mass size and margins have good performance to differentiate adenomas from adrenal malignancy or pheochromocytoma. Adenomas are usually lipid rich and have attenuation values less than 18 HU on unenhanced CT, a threshold with high sensitivity and specificity (85% to 95% and 93% to 100%, respectively). Generally, further workup is unnecessary when an adrenal lesion has an attenuation of less than 10 HU suggesting a lipid-rich adrenal adenoma. A notable exception is the lipid-poor or atypical adenoma, which has higher HU density. In these cases, rapid washout of intravenous contrast suggests a benign process. Using a 10- to 15-minute delayed enhanced CT, a washout value of 50% to 60% of the initial enhancement is used to distinguish adenoma from other mass etiologies.

MRI can differentiate adenomas, metastases and pheochromocytomas, although the best MRI technique for evaluating adrenal masses is complex and controversial. Adenomas usually show a loss in signal intensity on chemical shift MRI because of high lipid content. Malignant masses tend to be bright on T2-weighted images because of higher fluid content. Secondary metastases to the adrenal are hypointense to liver on T1-weighted images and are brighter than liver on T2-weighted images. Metastases also typically show strong contrast enhancement. Pheochromocytomas most often have low lipid content and high water content, giving low T1 signal intensities and very bright T2 signal intensities. Comparison of the adrenal mass to liver and spleen intensities on various sequences adds to specificity and sensitivity of the test.

Table 77.4 Diagnosis Summary of Tests for Evaluation of Incidental Adrenal Mass

Question	Best Test	Alternative Test	Diagnosis
Is it functioning?	Plasma-fractionated metanephrines 1-mg dexamethasone suppression test Serum potassium Plasma renin/plasma aldosterone ratio	24-hr urine for fractionated catecholamines, metanephrines, dopamine, VMA 24-hr urine for free cortisol 24-hr urine for potassium	Pheochromocytoma Hypercortisolism Hyperaldosteronism
Is it malignant?	Computed tomography	Magnetic resonance imaging Positron emission tomography	Cortical adenoma Adrenocortical Carcinoma Pheochromocytoma Myelolipoma Cyst
	Fine-needle aspiration		Metastasis



Algorithm 77.1 Diagnosis and management of the incidental adrenal mass. PRA, plasma renin activity; PAC, plasma aldosterone concentration; HTN, hypertension; CT, computed tomography; MRI, magnetic resonance imaging; FNA, fine-needle aspiration.

Fine-needle aspiration biopsy may be of value in patients with known extraadrenal malignancy; and with suspicion of harboring an adrenal metastasis; however, it is not indicated in the evaluation of primary adrenal neoplasms as it is not helpful, and is contraindicated if pheochromocytoma is suspected due to the possibility of inducing an adrenal crisis.

Treatment

Resection is indicated for all functioning adrenal incidentalomas and those suspected of harboring primary adrenal cancer. The prevalence of primary adrenal carcinoma in adrenal incidentalomas is related to mass size. The risk of primary adrenal carcinoma is <2% in lesions under 4 cm while the incidence rises to 25% for lesions larger than 6 cm. Lesions that are hormonally nonfunctional and <4 cm with benign imaging characteristics can be followed nonoperatively. For lesions between 4 and 6 cm, either resection or observation is acceptable. Decisions should not be based on size alone, but also on imaging characteristics including CT attenuation values, patient age (older patients with small benign nonfunctional lesions should be followed, but younger patients with relatively larger tumors may be considered for resection) and degree of hormonal activity. Resection of secondary adrenal metastases is recommended in selected patients for whom metastasectomy would confer significant benefit.

DISEASES OF THE ADRENAL CORTEX

Hypercortisolism

The term *hypercortisolism* refers to the physiologic state of glucocorticoid excess. The most common cause of hypercortisolism is the administration of exogenous steroids as immunosuppressive therapy for inflammatory disorders or after organ transplantation. Endogenous hypercortisolism in all cases is caused by increased adrenal production of cortisol, which may be ACTH dependent (ACTH-elevated Cushing *disease*) or independent (ACTH-suppressed Cushing *syndrome*). Some patients with major depression or chronic alcoholism have abnormally high cortisol secretion and may have clinical and biochemical features of Cushing syndrome.

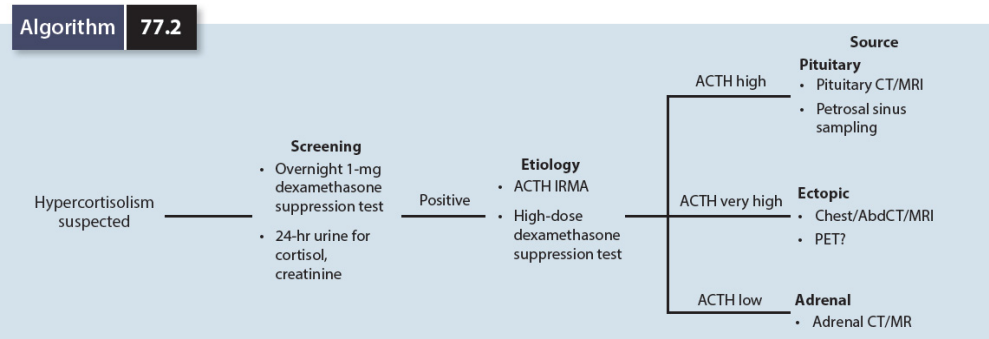
4 ACTH-dependent hypercortisolism is caused by an ACTH-secreting pituitary adenoma in 80–90% of cases. Ectopic ACTH-producing nonendocrine tumors (mostly non–small-cell lung cancer and bronchial carcinoids) represent 10% to 20% of cases of ACTH-dependent Cushing syndrome. All causes of ACTH-dependent Cushing syndrome involve bilateral adrenal hyperplasia in response to ACTH stimulation. Occasionally, a primary adrenal cancer may produce multiple hormones, including ACTH, which could lead to contralateral hyperplasia.

Among patients with endogenous Cushing syndrome, 10% to 25% have ACTH-independent disease caused by a primary adrenal cause. A solitary adrenal adenoma is present in the majority of these patients and is often associated with atrophy of both adjacent and contralateral adrenocortical tissue. Nodular cortical hyperplasia of both glands causes the remaining cases of primary adrenal Cushing syndrome. Although nodular hyperplasia represents a diffuse process, one or more distinct nodules may simulate adenomas. Rarely tumors secrete CRH ectopically, leading to ACTH-independent (though ACTH is elevated) Cushing syndrome with secondary adrenal hypertrophy.

Signs and Symptoms

Clinical features of cortisol excess are listed in **Table 77.1**. Truncal obesity with thinning of the limbs, accumulation of fat around the head and neck (*moon facies* and *buffalo hump*), and muscle wasting are present in most patients. Patients often have purple striae and purpura on the abdomen and extremities. Hirsutism may be present in women. High blood pressure is common and is

usually moderate, although malignant hypertension has been observed. Bone pain and muscle weakness (caused by proximal muscle wasting and hypokalemia) are also common. Osteoporosis is frequently diagnosed and pathologic fractures are observed in advanced cases. Neurologic symptoms, including headache, emotional lability, depression, and even psychosis may be observed. Glucose intolerance is common but can often be managed by alterations in diet alone. The serum potassium level may be low secondary to the weak mineralocorticoid properties of cortisol. Autonomous glucocorticoid production without specific signs and symptoms of Cushing syndrome is termed subclinical Cushing syndrome. This condition is being diagnosed with increased frequency because of the detection of adrenal incidentalomas by routine CT. A substantial percentage of incidentalomas are hormonally active, with 5% to 20% of the tumors producing glucocorticoids. The estimated prevalence of subclinical hypercortisolism is substantially higher than classic Cushing syndrome. Depending on the amounts of glucocorticoids secreted by the tumor, the clinical spectrum ranges from slightly attenuated diurnal cortisol rhythm to atrophy of the contralateral adrenal gland. Patients with subclinical Cushing syndrome lack the classical stigmata of hypercortisolism but have a high prevalence of obesity, hypertension, and type 2 diabetes.



Algorithm 77.2 Diagnosis of hypercortisolism. ACTH, adrenocorticotropic hormone; IRMA, immunoradiometric assay; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

Diagnosis

The investigation of suspected hypercortisolism should answer two questions: (a) Does the patient indeed have cortisol excess? (b) If the answer is yes, then what is the cause? The diagnosis of hypercortisolism is biochemical, however a careful history and physical examination form the basis for suspecting this condition. The laboratory approach to this diagnosis is summarized in

Algorithm 77.2. Radiologic investigations should not be undertaken until hypercortisolism has been confirmed and its likely etiology characterized biochemically.

Hypercortisolism insensitive to suppression by administration of exogenous glucocorticoid is the *sine qua non* of Cushing syndrome. Due to the circadian rhythm of the HPA axis, plasma cortisol levels can normally vary considerably during a 24-hour period, therefore a single random plasma cortisol level is not helpful in establishing a diagnosis of hypercortisolism. There are currently three screening tests for hypercortisolism: low-dose (1-mg) dexamethasone suppression test, 24-hr urinary free cortisol excretion, and late night/bedtime salivary cortisol levels. The low-dose dexamethasone suppression test is the best test in patients with suspected Cushing syndrome. For this test, 1 mg of dexamethasone is administered orally at 11 PM and plasma cortisol is obtained at 8 AM the following day. Normal individuals suppress cortisol to below 1.8 μg/dL. False-positive test results may occur if the patients metabolize the dexamethasone faster than normal, or if the timing of taking the pill is erroneous. A concomitant serum dexamethasone can be obtained in the morning to assure the serum dexamethasone level is in the adequate range. False-positive test results occur in 10% to 15% of cases with the overnight test and occur especially in patients with obesity or alcoholism or in those taking estrogens or phenytoin. Measurement of urinary-free cortisol (not metabolites) is an alternative screening test for Cushing syndrome. Collections should include concurrent creatinine measurement and urinary volume to evaluate the completeness of the collection. This test may be less sensitive than the low-dose dexamethasone suppression test in mild hypercortisolism. The salivary cortisol test quantifies the level of unbound, biologically active form of serum cortisol. The test should be done late at night when the HPA axis reaches a nadir. The salivary cortisol test relies on the fact that the circadian rhythm of the HPA axis is impaired in Cushing syndrome patients, who therefore feature higher cortisol values at night, which are easy to measure in saliva.

Once the presence of hypercortisolism is established, the next task is to determine whether this is ACTH-dependent (pituitary or ectopic source) or ACTH-independent (primary adrenal). Measurement of basal ACTH by radioimmunometric assay is the best test to make this distinction. Plasma ACTH levels are normally between 10 and 100 pg. Suppression of the absolute level of ACTH below 5 pg/mL is nearly diagnostic of adrenocortical neoplasms, which secrete high levels of cortisol and inhibit ACTH release by the pituitary.

Patients with pituitary neoplasms and secondary bilateral adrenocortical hyperplasia have ACTH levels that may range from the upper limits of normal (15 pg/mL) to 500 pg/mL. The highest plasma levels of ACTH (more than 1,000 pg/mL) are in patients with ACTH-producing nonendocrine tumors, such as non–small-cell lung cancer.

Although 80% to 90% of patients with ACTH-dependent Cushing syndrome have Cushing disease, a high-dose dexamethasone suppression test may be required to exclude ectopic ACTH syndrome. Hypercortisolism caused by ACTH-secreting pituitary adenomas is suppressed at least partially by high dexamethasone, whereas hypercortisolism caused by adrenal tumors and ectopic ACTH-producing tumors is not suppressed. For this test 2-mg dexamethasone is administered orally every 6 hours for 2 days, and a 24-hour urine collection for free cortisol is taken during the second day. About 90% of patients with pituitary source Cushing disease have a 50% reduction in urine-free cortisol. The specificity of the test can be improved to 100% for diagnosing pituitary disease if more than 90% suppression in urinary-free cortisol is used.

Biochemical testing of suspected Cushing syndrome is followed by radiologic studies. Pituitary adenomas are best imaged with gadolinium-enhanced MRI of the sella turcica, which has a sensitivity approaching 100%, although small pituitary microadenomas may be missed. Patients with ACTH-independent Cushing syndrome require thin-section CT or MRI of the adrenal, which identifies adrenal abnormalities with more than 95% sensitivity. CT or MRI of the chest may identify a source of ectopic ACTH and should be undertaken in patients with elevated ACTH and hypercortisolism that cannot be suppressed by high-dose dexamethasone.

Despite the accuracy of biochemical testing and radiographic localization, a pituitary versus ectopic source of ACTH sometimes cannot be determined. Bilateral inferior petrosal sinus sampling would need to be done by experienced physicians. An inferior petrosal sinus to peripheral plasma ACTH ratio of 2.0 at basal stimulated or of 3.0 after CRH administration is 100% sensitive and specific for pituitary adenoma. Comparison of right and left inferior petrosal sinus ratios may also lateralize the adenoma.

Treatment

ACTH-dependent Cushing syndrome is best treated by removing the source of ACTH excess. In the case of Cushing disease, transsphenoidal resection of the

pituitary microadenoma is successful in 80% or more of cases. If a microadenoma is not found, then hemihypophysectomy may be performed with the understanding that fertility may be impaired. Pituitary irradiation is a good treatment option when fertility is desired, when a tumor is not found or is unresectable, or cure is not achieved by transsphenoidal resection of a tumor. Debulking of unresectable primary lesions or recurrences with or without bilateral adrenalectomy may provide palliation in some patients. Treatment of ectopic ACTH syndrome involves removal of the primary lesion. Medical adrenalectomy with metyrapone, aminoglutethimide, and mitotane has been used to suppress production of corticosteroid in inoperable cases for both pituitary and ectopic sources of ACTH. Bilateral adrenalectomy could be considered for patients intolerant of mitotane.

ACTH-independent Cushing syndrome is best treated by removal of the adrenal tumor and affected gland, which can be done minimally invasively for most benign-appearing. Resection of cortisol-producing benign adrenal adenomas is curative and prognosis is good following resection. Cortisol-producing adrenocortical carcinomas recur frequently following adrenalectomy, heralded by the reemergence of hypercortisolism. Micronodular-pigmented hyperplasia and macronodular adrenal hyperplasia may involve both adrenal glands. If medical treatment cannot control the hypercortisolism, occasionally adrenal venous sampling may detect a unilateral adrenal gland that is the dominant secretor, and therefore a unilateral adrenalectomy may ameliorate the hypercortisolism for some time. If patients have symmetrical hyperfunction and medical treatment is not satisfactory, bilateral adrenalectomy can be performed. This procedure has the clear consequence of lifetime dependence on exogenous steroid replacement. All patients who undergo bilateral adrenalectomy should wear a medical alert bracelet warning of their adrenal status.

Whether patients with subclinical Cushing syndrome should undergo adrenalectomy is not always clear. Several small series have demonstrated weight loss, an improvement in hypertension and glucose control following adrenalectomy for subclinical Cushing syndrome. Patients with subclinical Cushing syndrome may progress to overt Cushing syndrome as frequently as 12.5% at 1 year. Accordingly, adrenalectomy for subclinical Cushing syndrome may be beneficial and is reasonable in young patients, patients with suppressed plasma ACTH, and patients with recent weight gain, substantial obesity, arterial hypertension, diabetes mellitus, and osteopenia. Truly asymptomatic patients

with normal plasma ACTH concentrations, the elderly, or those who are unfit for surgical intervention may be observed.

All patients who undergo adrenalectomy for Cushing syndrome require postoperative glucocorticoid replacement, since the contralateral gland is suppressed. A cortisol suppression test could be used to establish the need for glucocorticoid replacement. Replacement therapy with hydrocortisone, 12 mg/m^2 per day, may be required as long as 2 years postoperatively. Adequacy of replacement is monitored clinically. The duration of replacement therapy is guided by normalization of the ACTH stimulation test and patient symptoms.

Hyperaldosteronism

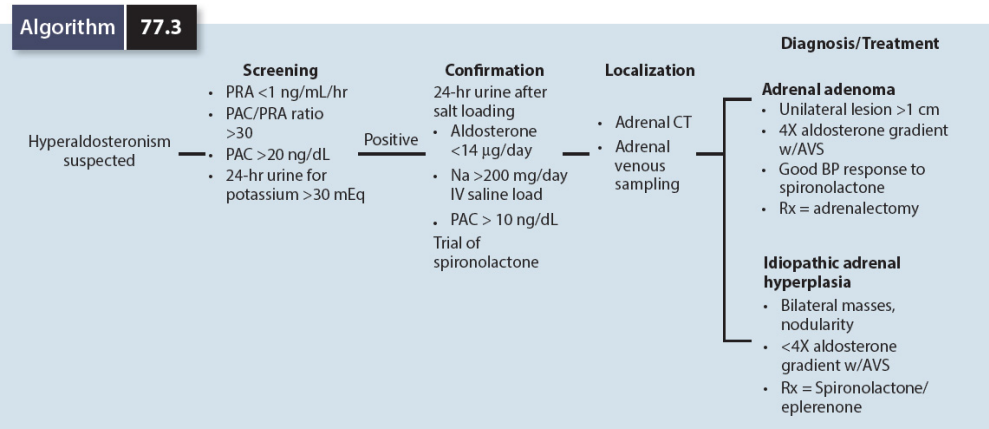
Hyperaldosteronism is a syndrome of hypertension and hypokalemia caused by autonomous adrenal secretion of the mineralocorticoid aldosterone. Hyperaldosteronism may be primary, as a result of an adrenal neoplasm with suppressed plasma renin, or may be secondary, as a result of elevated plasma renin. Primary hyperaldosteronism usually occurs between the ages of 30 and 50 years and is an important and increasingly prevalent cause of hypertension. Screening of hypertensive patients with plasma aldosterone and plasma renin activity (PRA) has suggested that primary hyperaldosteronism may be the underlying cause of up to 20% of cases of essential hypertension.

5 Primary hyperaldosteronism cases are attributable to either idiopathic adrenal hyperplasia or, more commonly, aldosterone-producing adenomas (Conn syndrome, 60% to 70% of all cases). Primary hyperaldosteronism affects both men and women with equal prevalence, although aldosterone-producing adenoma specifically has been shown to have a higher prevalence in women. Although the cause of either adenoma or idiopathic hyperplasia is not entirely understood, basic science research has elucidated various somatic mutations in aldosterone-regulating genes (i.e., *KCNJ5*, *CACNA1D*, *ATP1A1*, *ATP2B3*, *CTNNB1*) that can be present in either subtype of primary hyperaldosteronism. Familial hyperaldosteronism (types I to III) has been described but is rare. Other rare causes of primary hyperaldosteronism include adrenocortical carcinoma and ectopic aldosterone-secreting tumors. Autosomal dominant glucocorticoid-suppressible hyperaldosteronism is another rare cause of hyperaldosteronism resulting from the fusion of the ACTH-responsive 11-beta hydroxylase gene promoter to the aldosterone synthase gene in cells of the adrenal cortex.

Secondary hyperaldosteronism is a physiologic response of the renin–angiotensin system to decreased renal perfusion due to renal artery stenosis, cirrhosis, congestive heart failure, and normal pregnancy. The adrenal cortex functions normally and secretes aldosterone in response to the elevated plasma renin and angiotensin caused by these conditions. Secondary hyperaldosteronism responds to treatment of the underlying cause.

Signs and Symptoms

Clinical manifestations of primary hyperaldosteronism are attributable to hypersecretion of aldosterone by the adrenal gland (**Table 77.2**). Aldosterone-mediated retention of sodium and excretion of potassium and hydrogen ion by the kidney causes moderate diastolic hypertension. Edema is absent. Significant hypokalemia occurs in less than 40% of patients with primary hyperaldosteronism and is even less frequent in cases caused by adrenal hyperplasia, therefore hypokalemia is neither a sensitive nor specific marker of primary hyperaldosteronism. Potassium depletion causes symptoms of muscle weakness and fatigue, polyuria and polydipsia, as well as impaired insulin secretion and fasting hyperglycemia. Primary hyperaldosteronism should be suspected in hypertensive patients with spontaneous hypokalemia (serum concentration <3.5 mEq/L), moderate hypokalemia (serum potassium concentration <3.0) during diuretic therapy despite concomitant use of oral potassium or potassium-sparing diuretics, or refractory hypertension without explanation.



Algorithm 77.3 Diagnosis and management of hyperaldosteronism. PRA, plasma renin activity; PAC, plasma aldosterone concentration; CT, computed tomography; AVS, bilateral adrenal venous sampling.

Diagnosis

The clinical hallmarks of primary hyperaldosteronism are (a) medically refractory hypertension without edema; (b) suppression of plasma renin in the face of volume depletion; and (c) hypersecretion of aldosterone that fails to suppress with intravascular volume expansion. To establish a diagnosis of primary hyperaldosteronism, it is important to discern surgically correctable adrenal adenoma from medically treatable idiopathic hyperplasia, and localize an adrenal tumor (**Algorithm 77.3**).

Demonstration of an elevated plasma aldosterone concentration (PAC) in the setting of suppressed PRA is the best test to establish primary hyperaldosteronism. The ratio in normal subjects and patients with essential hypertension is 4:10 compared with more than 30 in most patients with primary hyperaldosteronism. A PAC of greater than 20 ng/dL and a PAC/PRA ratio of greater than 30 are diagnostic for aldosteronoma with almost 90% sensitivity. A serum potassium value less than 3.5 mEq/L and urinary potassium excretion greater than 30 mEq/day also support a diagnosis of primary hyperaldosteronism. Before biochemical evaluation, patients need to be potassium repleted and have an adequate sodium intake. Medications including ACE inhibitors and spironolactone should be withheld for at least 4 weeks before study.

An elevated PAC/PRA ratio alone does not establish the diagnosis of primary hyperaldosteronism. Although there is no optimal confirmatory test or gold standard, there are four confirmatory tests approved for the diagnosis of primary hyperaldosteronism: oral sodium loading, saline infusion test, fludrocortisone suppression test, and captopril challenge. The oral salt loading test involves a 24-hour urine collection for sodium and aldosterone after 3 days of a high-sodium diet. The 24-hour urinary excretion of aldosterone should be greater than 14 μg per 24 hours after a high-salt diet for patients with primary hyperaldosteronism.

After the diagnosis of primary hyperaldosteronism is made, imaging of the adrenal gland is indicated. High-resolution adrenal CT is a key noninvasive method used to localize an adrenal tumor (**Fig. 77.6**). An adrenal-based CT will detect an aldosterone-producing adenoma in 90% of cases overall, however CT has lower sensitivity for microadenomas (tumors <1 cm). MRI may be useful during pregnancy or in situations in which intravenous contrast medium injection is undesirable. Although idiopathic adrenal hyperplasia is bilateral

and often appears multinodular on CT, distinguishing an aldosteronoma from idiopathic adrenal hyperplasia can be difficult by imaging alone due to the possibility of asymmetric nodularity.

Adrenal vein sampling is an invasive procedure used to lateralize the source of aldosterone production. It is recommended for all patients with a working diagnosis of primary hyperaldosteronism but may be deferred in young patients (<40 years old) who have a unilateral adenoma (>1.0 cm) on CT with a normal contralateral adrenal gland in the setting of biochemical evidence primary hyperaldosteronism. Adrenal vein sampling is particularly crucial in patients with hyperaldosteronism when there is no adrenal abnormality on CT or MRI or when both adrenal glands are abnormal but asymmetric. Percutaneous transfemoral cannulation of both adrenal veins is performed and intravenous ACTH (50 μg/hr) may be administered. Cannulation of the right adrenal vein can be challenging due to the shorter, more posterior superior course. Simultaneous adrenal vein blood samples for aldosterone and cortisol are taken before and after ACTH injection, and their ratios are determined. The PAC is markedly higher (at least fourfold) on the side of an adenoma, whereas there is little or no left–right gradient present in cases of bilateral adrenal hyperplasia. A 10-fold gradient of cortisol in adrenal veins to a peripheral sample ensures adequacy adrenal vein cannulation. This study is greater than 90% accurate and has been shown to alter management in 30% to 50% of patients, even in those with an apparent unilateral adenoma. However, adrenal vein sampling is technically difficult and may be unsuccessful in 25% of patients. In addition, adrenal vein sampling may have some complications such as superficial skin burns from prolonged fluoroscopy, adrenal hemorrhage from cannulating too deeply into segmental adrenal veins, among others.

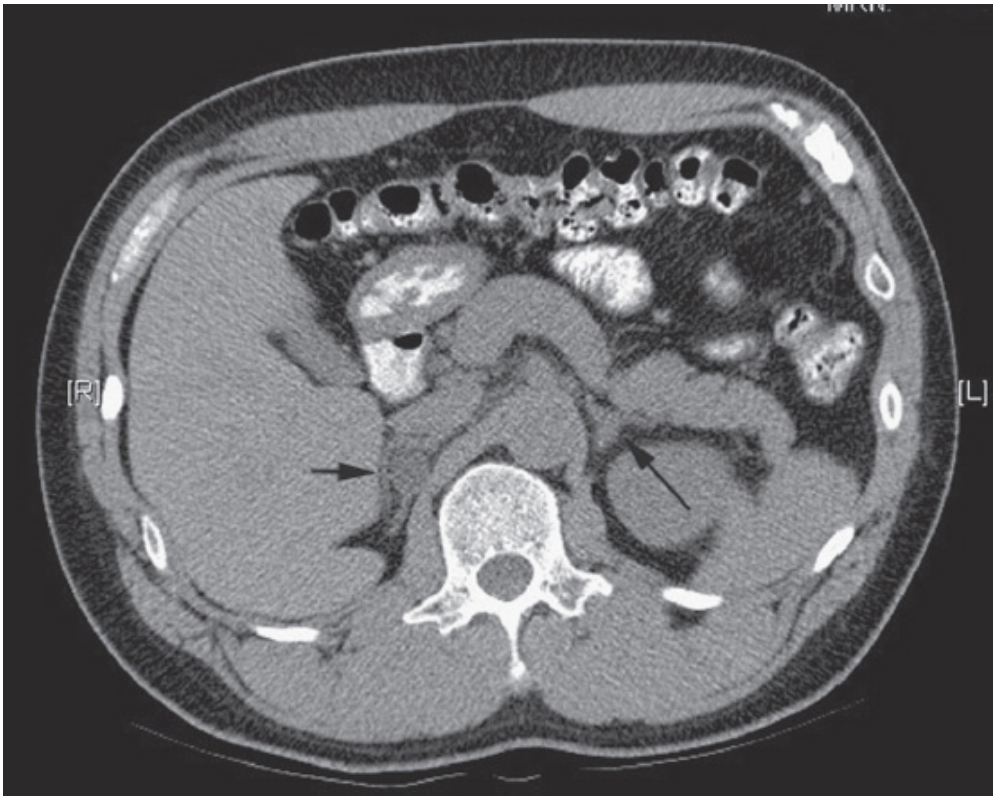


Figure 77.6 Computed tomography scan of right adrenal aldosteronoma. *Short arrow* shows aldosteronoma. *Long arrow* shows normal contralateral adrenal gland.

Figure 77.7 Aldosteronoma within right adrenal gland shown in **Figure 77.6**.

Treatment

6 Surgical removal of an aldosterone-secreting adenoma (**Fig. 77.7**) results in durable improvement of hypertension and hypokalemia in 70% to 90% of patients. Minimally invasive adrenalectomy is the preferred approach to

remove these tumors. Morbidity and mortality following these procedures are almost negligible. Preoperative spironolactone or eplerenone and potassium may be given to replenish potassium stores and correct alkalosis before anesthesia. Preoperatively, a significant fall in blood pressure with aldosterone receptor antagonists predicts a successful outcome after adrenalectomy. Response to adrenalectomy is also influenced by the duration and severity of hypertension and by the presence of histologic changes in the kidney. Factors associated with poor response to surgery include age greater than 50 years, male sex, the necessity for more than two antihypertensive medications prior to surgery, and the presence of multiple nodules within the adrenal gland.

Management of idiopathic adrenal hyperplasia is medical because fewer than 20% to 30% of patients with this disease are cured by adrenalectomy. Idiopathic adrenal hyperplasia is treated with spironolactone or with newer aldosterone antagonist eplerenone. Other potassium-sparing diuretics may be used including triamterene and amiloride. Exogenous administration of physiologic doses of glucocorticoids is the first-line therapy for glucocorticoid-suppressible hyperaldosteronism.

Adrenocortical Carcinoma

7 Adrenocortical carcinoma is a rare malignancy with an estimated incidence of 0.5 to 2 cases per million per year. Presentation peaks in the first and fifth decades of life and is more common in women. The cause of adrenocortical carcinoma is unknown, however somatic mutations in *P53*, *ERCC1*, and *IGF2* have been reported in the pathogenesis of the tumor.

Signs and Symptoms

Adrenocortical carcinoma is a very aggressive malignancy, and up to 75% of patients present with locoregionally advanced or distant disease. Syndromes of adrenal hormone overproduction are frequent (up to 60%) and may include hypercortisolism, hyperaldosteronism, or virilization. Patients with rapidly progressive Cushing syndrome or mixed presentations with signs of both Cushing syndrome and virilization should be suspected of having adrenocortical carcinoma. Nonfunctioning adrenocortical carcinomas present most commonly as abdominal pain or mass with vague symptoms of nausea, weight loss, and fatigue.

Diagnosis

Patients with suspected adrenocortical carcinoma should have biochemical testing to identify hormone overproduction followed by staging investigations including cross-sectional imaging and bone scans. Contrast-enhanced CT of the abdomen and chest is important to preoperatively diagnose local tumor invasion and metastatic lesions as well as to confirm a functioning contralateral kidney (**Fig. 77.8**). In the absence of distant metastases or local invasion, preoperative distinction between large adenomas and carcinomas can be difficult, although large (>6 cm) adrenal masses that have irregular shape and extend to nearby structures on CT scanning should be approached as carcinomas. Biopsy of adrenal lesions suspected of being adrenocortical carcinoma should be avoided as this is not helpful in distinguishing adenoma from carcinoma, and carries a high risk of tumor seeding. Biopsy of extraadrenal lesions may be performed to confirm metastatic disease. Positron emission tomography (PET) scans are often helpful in demonstrating distant disease in cases that are highly suspicious for adrenocortical carcinoma.

Figure 77.8 Computed tomography scan of right adrenocortical carcinoma showing invasion of liver and inferior vena cava. Note that a contralateral kidney is present and functioning.

A definitive diagnosis of adrenocortical carcinoma requires pathologic demonstration of tumor invasion to adjacent organs or spread to lymph nodes or distant sites. Practically, any adrenal neoplasm larger than 6 cm or weighing more than 100 g may be considered malignant. Histologic features of tumor necrosis, hemorrhage, and local invasion are gross pathologic evidence of carcinoma, while cells with large, hyperchromatic nuclei and more than 20 mitoses per high-power field suggest malignancy.

Treatment

Surgical resection is the mainstay of treatment for most stages of adrenocortical carcinoma. Open resection is preferred to minimize tumor spillage and seeding. Complete resection of locally confined tumor is the only chance for cure from adrenocortical carcinoma. However, distant or local spread is evident in 65% of cases at presentation and a minority of patients is resectable with curative intent. Recurrence rates after surgery range from 38% to 85%, depending on stage at presentation (**Table 77.5**).

Many patients with adrenocortical carcinoma present with metastatic disease, involving the lung, lymph nodes, liver, or bone. Resection or surgical debulking of locally advanced or oligometastatic lesions may provide symptomatic relief for selected patients, especially those with low-grade, slow-growing, hormonally productive cancers. Symptomatic locally recurrent or oligometastatic disease is best treated by resection when feasible. Overall median survival following diagnosis is approximately 18 months.

Mitotane is an adrenolytic drug that has high efficacy for adjuvant therapy in patients with adrenocortical carcinoma. Patients at high risk of recurrence include those with vascular or capsular invasion, histologically high-grade disease (high Ki-67, de-differentiation, or high mitotic figure rate), and those whose operation was complicated by intraoperative tumor spillage. These patients may additionally benefit from chemotherapy. Cisplatin, etoposide, and streptozosin have been trialed for the management of adrenocortical carcinoma, with varying success. Adjuvant radiation therapy may be considered in patients with advanced disease stage.

Table 77.5 American Joint Committee on Cancer Staging of Adrenocortical Carcinoma

TNM	Criteria
Tumor	
T1	Tumor <5 cm, no invasion
T2	Tumor >5 cm, no invasion
T3	Tumor with invasion to fat
T4	Tumor with organ invasion
Lymph nodes	
N0	No lymph node metastasis
N1	Lymph node metastasis present
Metastasis	
M0	No distant metastasis
M1	Distant metastasis present

Simplified AJCC Staging Schematic for Adrenocortical Carcinoma

	T1	T2	T3	T4
N0, M0	Stage I	Stage II		
N1, M0	Stage III			
Any N, M1	Stage IV			

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DISEASES OF THE ADRENAL MEDULLA

Pheochromocytoma/Paraganglioma

Pheochromocytomas are functional adrenal tumors that arise from neuroectodermal cells of the adrenal medulla (80% to 85%) or in certain extraadrenal sites (paraganglioma, 15% to 20%). These tumors are uncommon, occurring in 0.005% to 0.1% of persons, but occur with increased frequency in hypertensive populations (0.2% incidence) and in heritable endocrine tumor syndromes. The peak incidence of pheochromocytoma/paraganglioma occurs during the fourth and fifth decades of life, and men and women are affected about equally.

Historically, the *rule of tens* was a useful way to characterize pheochromocytoma tumors (bilateral in 10% of cases, extraadrenal in 10%, familial in 10%, multicentric in 10%, and malignant in 10% and occur in children in 10% of cases). However, recent advances in genetics and oncology have revealed that 8 up to 40% of pheochromocytomas/paragangliomas are hereditary, and at least 19 susceptibility genes have been identified. These susceptibility genes include *RET* proto-oncogene, *VHL* tumor suppressor gene, neurofibromatosis type 1 (*NF-1*) tumor suppressor gene, and succinate dehydrogenase genes (*SDH*).

Approximately 10% of pheochromocytomas are extraadrenal and are called paraganglioma. However, most (98%) are still located within the abdomen. Paraganglioma can occur at any site in the abdomen where chromaffin tissue is located and have been found in the paravertebral ganglia, the organ of Zuckerkandl, and the urinary bladder. Clues to the presence of paraganglioma are predominance of norepinephrine secretion because extraadrenal sites lack the phenylethanolamine-N-methyltransferase (PNMT) enzyme necessary to convert norepinephrine to epinephrine.

Hereditary pheochromocytoma and paraganglioma tend to occur bilaterally, in synchrony or metachrony, have an early onset, may involve multiple disseminated primary tumors or manifest as part of a syndrome involving extraadrenal tumors. Familial transmission is generally autosomal dominant. Patients with von Hippel–Lindau syndrome have pheochromocytoma (usually bilateral), retinal angiomas, cerebellar hemangioblastoma, epididymal cystadenoma, renal and pancreatic cysts, and renal cell carcinoma. Patients with MEN 2A develop pheochromocytoma (usually bilateral), medullary carcinoma of the thyroid (MTC), and primary parathyroid hyperplasia. Patients with MEN 2B develop pheochromocytoma (usually bilateral), MTC, mucosal neuromas, intestinal ganglioneuromatosis, and have a characteristic Marfanoid body habitus. Pheochromocytoma also occurs in neurofibromatosis type 1 and

familial paraganglioma. The frequency of pheochromocytoma in these disorders is 10% to 20% in von Hippel–Lindau syndrome, 50% in MEN 2, and 1% to 3% with neurofibromatosis type 1. Patients with mutations of *SDHx (SDHA, SDHB, SDHC, SDHD, SDHAF2*), transmembrane protein 127 (*TMEM127*), or MYC-associated factor X (*MAX*) generally have only pheochromocytomas and paragangliomas. A minority of *SDHx* mutation carriers have been reported to have gastrointestinal stromal tumors (GISTs), renal cell carcinomas, or pituitary adenomas.

The diagnosis of malignant pheochromocytoma remains a challenge. Histologic features such as growth patterns, mitoses, and atypia of cells and nuclei correlate with malignant biologic features in pheochromocytomas and paragangliomas. However, it is difficult to predict the clinical behavior of individual tumors, and no single risk-stratification scheme is endorsed or in widespread use. The development or presence of metastasis is the proof for a malignant pheochromocytoma or paraganglioma. Metastases are located where chromaffin tissue is normally not found (e.g., lymph nodes, lung, liver, and bones), and frequently are not confirmed histologically but are instead documented on nuclear imaging. The typical metastatic sites for pheochromocytoma are bones and lymph nodes, whereas when paraganglioma is the primary tumor, hepatic metastases are more common.

Signs and Symptoms

Symptoms of pheochromocytoma are attributable to the effects of excessive circulating catecholamines on target tissues (**Table 77.3**), however the clinical occurrence of symptoms may not always correlate with the active release of catecholamines from the tumor. The classic triad of symptoms in patients with a pheochromocytoma is episodic headache, sweating, and tachycardia. Hypertension is common with pheochromocytoma and is sustained in roughly half of patients, is paroxysmal in one-third, and is absent in one-fifth. Orthostatic hypotension results from diminished plasma volume and blunted autonomic reflexes. Other symptoms include palpitations, anxiety, irritability, and tremulousness. Cardiovascular sequelae include myocardial infarction, cardiac dysrhythmias, and stroke. Gastrointestinal motility is also impaired, as is glucose tolerance. Asymptomatic patients with functioning tumors are rare, and nonfunctioning tumors are distinctly uncommon, however very small tumors may be very mildly functioning, and therefore may not become symptomatic until the tumors are larger. Sudden death has been reported in patients with

pheochromocytoma who have undergone surgical procedures or childbirth. Undiagnosed pheochromocytoma may also lead to spontaneous abortion in pregnant women.

Diagnosis

Elevation of catecholamines and their metabolites in either urine or blood is essential for the diagnosis of pheochromocytoma. Either a 24-hour urine collection for fractionated catecholamines and their metabolites (metanephrines) or plasma-fractionated metanephrines can be used to make the diagnosis. Urine catecholamines/metanephrines are the most reliable tests with a sensitivity and specificity of 98%. Plasma-fractionated metanephrines is similarly sensitive (99%), but lacks specificity (85%). Measurement of plasma catecholamines is not as useful in distinguishing patients with pheochromocytoma from those with essential hypertension. Measurement of plasma chromogranin A is nonspecific and a poor diagnostic but potentially helpful confirmatory test.

Many medications alter or interfere with measurement or either plasma or urine catecholamines. Such medications should be discontinued to ensure accurate testing. These drugs include acetaminophen, labetolol, clonidine withdrawal, tricyclic antidepressants, antipsychotics, and ethanol. To control blood pressure, other antihypertensives such as calcium channel blockers or alpha blockers may be substituted.

In normotensive or mildly hypertensive patients with elevated plasma catecholamine levels (1,000 to 2,000 pg/mL), a clonidine suppression test may be used to distinguish from pheochromocytoma. An oral 0.3-mg dose of clonidine suppresses centrally mediated release of catecholamines to less than 500 pg/mL within 2 to 3 hours but does not affect release of catecholamines by a pheochromocytoma.

Biochemical confirmation of the diagnosis should be followed by radiologic evaluation to locate the tumor. Tumor localization can be done using functional or nonfunctional imaging techniques such as CT or MRI. CT or MRI is often the first line of imaging. Contrast-enhanced CT readily detects tumors 1 cm and larger and has sensitivity of 87% to 100% for pheochromocytoma (**Fig. 77.9A**). On adrenal protocol CT, a pheochromocytoma often has attenuation values of >20 HU, however cases of pheochromocytoma with low HU (<10) have been reported. MRI is similarly sensitive, and a T2-weighted image brightness three times greater than liver is highly specific for pheochromocytoma

(**Fig. 77.9B,C**). MRI is useful in suspected malignant pheochromocytoma to evaluate for inferior vena cava thrombus or liver invasion.

Functional nuclear imaging with iodine-131-metaiodobenzylguanidine (131-I MIBG) is a useful adjunct to cross-sectional imaging for pheochromocytoma (**Fig. 77.9D**). MIBG resembles norepinephrine and is taken up by adrenergic tissues including pheochromocytoma. An MIBG scan can detect tumors not detected by CT or MRI or multiple tumors when CT or MRI is positive. Multi-institutional experience with this technique has demonstrated an overall sensitivity of 77% to 87% and a specificity of 96% to 100%. This test is usually not necessary for sporadic pheochromocytoma unless urinary or plasma catecholamines and metabolites are marginally elevated, or if malignant or extraadrenal pheochromocytoma is suspected. 131-I MIBG scanning is also useful to screen patients with metastatic pheochromocytoma for high-dose 131-I MIBG therapy. 111-In-pentetreotide scintigraphy (Octreoscan) may also identify pheochromocytoma and can be used therapeutically as with 131-I MIBG. Because pheochromocytomas and paragangliomas express somatostatin receptors, in recent years, PET-CT imaging tagged with ^{18}F-DOPA, ^{18}F-FDG, and ^{68}Ga-labeled somatostatin analogs (such as ^{68}Ga-DOTATATE) has been used, with better sensitivity and resolution than SPECT scintigraphy.

Treatment

Surgical resection is the only cure for pheochromocytoma. When the diagnosis of pheochromocytoma has been established and localization studies are completed, preoperative preparation of the patient centers on blood pressure control. Alpha-adrenergic blockade is initiated 1–3 weeks before the operation. Phenoxybenzamine, a nonspecific alpha-adrenergic blocking agent, has been a stalwart for decades in the medical treatment of pheochromocytoma, starting at 10 mg twice a day, and increasing by 10 to 20 mg per day until blood pressure normalizes and the patient becomes orthostatic. Alternatives to phenoxybenzamine include selective alpha blockers such as doxazosin and terazosin, which work very well, are cheaper, and better tolerated than phenoxybenzamine; calcium channel blockers (nifedipine and nicardipine) may be used, but are less effective. Side effects of nonselective alpha blockade include postural hypotension, reflex tachycardia, prostration, nasal congestion, and an inability to ejaculate. Preoperative alpha blockade also reverses the relative hypovolemia that is usually present in patients with pheochromocytoma and prevents severe blood pressure swings during intraoperative manipulation

of the tumor. Metyrosine inhibits the enzyme tyrosine hydroxylase and, therefore, catecholamine synthesis, consequently depleting the levels of the catecholamines dopamine, epinephrine, and norepinephrine in the tumor. This can be added preoperatively to alpha blockade to potentiate the control of catecholamine excess. Metyrosine is very expensive as it is produced by a single pharmaceutical company, but is very effective in patients who have very significant levels of catecholamine excess, and should be reserved for the week before surgery.

Beta-adrenergic blockade with propranolol added after alpha blockade can manage patients who develop tachycardia or who have inducible cardiac arrhythmias or ischemia. Propranolol may enhance pressor response to endogenous norepinephrine and thus should not be given until adequate alpha blockade has been established. Propranolol can also produce profound bradycardia, myocardial depression, and congestive heart failure.

Patients with pheochromocytoma can be expected to have blood pressure volatility and high intravascular volume requirements during and immediately after surgery. To avoid some of these fluid shifts, given patients with pheochromocytoma oral salt tablets several days before surgery helps restore intravascular volume and avoid very significant intraoperative hemodynamic shifts due to volume contraction.

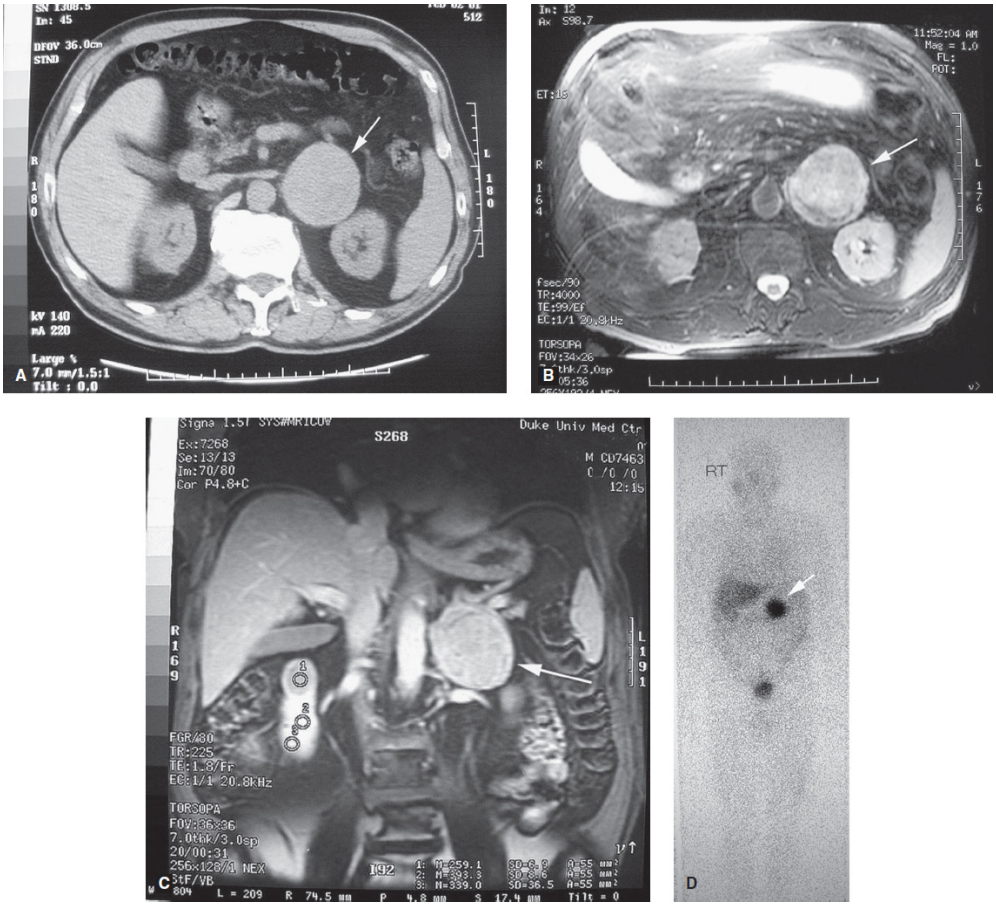

Figure 77.9 Imaging of pheochromocytoma (*arrows*). **A:** Computed tomography scan shows well-circumscribed left adrenal mass. **B:** T2-weighted magnetic resonance imaging shows the mass to be heterogeneously bright, consistent with pheochromocytoma. **C, D:** Coronal contrast-enhanced MRI and near-simultaneous 131I-metaiodobenzylguanine (131I-MIBG) scanning show location of the pheochromocytoma and relationship to surrounding structures.

Patients who have very high levels of circulating catecholamines or have had a longstanding history of undiagnosed pheochromocytoma should undergo a cardiac echocardiogram to evaluate for the potential of catecholamine-excess cardiomyopathy. Whenever available, anesthesiologists with experience in the perioperative management of pheochromocytomas should be selected for these cases. Patients require active hemodynamic monitoring with arterial line placement for careful monitoring of blood pressure and arterial pH, as well as possibly a central line for monitoring of central venous pressures. Anesthetic agents may trigger the release of catecholamines from pheochromocytomas. Intraoperative hypertension is best treated with a sodium nitroprusside drip, and

cardiac arrhythmias are best managed with short-acting beta blockers (esmolol) or lidocaine.

Recurrent, malignant pheochromocytoma can include locally advanced disease or metastasis to bone, liver, lymph nodes, lungs, and the central nervous system. Treatment of malignant pheochromocytoma involves resection of metastases when feasible and medical control of hypertension. Radiation therapy may be helpful to ameliorate pain from bony metastases. Ablative therapy with 131-I MIBG may also produce partial responses and palliation of hormonal symptoms. Radiofrequency ablation of hepatic and bone metastases can be effective in selected patients. Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine can also be effective. Overall 5-year survival for patients with malignant pheochromocytoma ranges from 36% to 60%.

Metastasis to the Adrenal Glands

The adrenal glands are frequent sites for metastases from many cancers. Carcinoma of the lung and breast account for most adrenal metastases; however, virtually any cancer including melanoma, lymphoma, renal, and ovarian carcinoma can spread to the adrenals. Autopsy series of patients with carcinoma show that the adrenal glands are involved in more than 25% of cases. Among cancer patients, 50% to 75% of newly discovered adrenal masses represent metastases. Usually, either a primary site is obvious, or widespread disease is apparent. Biopsy of adrenal masses in patients with a history of carcinoma may be performed after pheochromocytoma is excluded. Resection of isolated adrenal metastases in selected patients with long disease-free intervals from lung cancer, renal cell carcinoma, and melanoma can be considered, although subsequent extraadrenal disease usually develops. Median survival after complete resection of isolated adrenal metastases from a variety of tumors ranges from 13 to 60 months with actuarial 2- and 5-year survival of 40% and 20%, respectively.

ADRENALECTOMY

Surgical indications for adrenalectomy include adrenal tumors that are large or enlarging, worrisome for a malignancy, and those that exhibit evidence of

autonomous hormonal secretion. Surgical approaches to the adrenal glands include the laparoscopic approach, open anterior transabdominal approach, and less commonly, the combined open thoracoabdominal approach. Regardless of approach, important surgical principles include confirmation of the correct site of surgery during the preoperative and intraoperative timeouts, minimal handling of the tumor, early isolation and ligation of the adrenal vein, and avoidance of capsular rupture. Capsular rupture can lead to incurable tumor spread even for benign tumors. Surgeon volume is an important consideration in adrenalectomy: surgeons who perform at least six adrenalectomies per year have better outcomes as compared to lower-volume surgeons.

Minimally invasive adrenalectomy is the gold standard of surgical management of most adrenal tumors, and has advantages including reduced postoperative pain, earlier resumption of oral intake, shorter hospital stay, earlier resumption of baseline activity, and superior cosmesis. Minimally invasive adrenalectomy may be performed via a transabdominal (with or without robot-assistance or hand-assistance) or posterior retroperitoneoscopic approach. At all times, the surgeon must be prepared to convert from a laparoscopic to an open procedure, if necessary. An open approach is recommended in large tumors or in suspected cases of adrenocortical carcinoma.

Laparoscopic Transabdominal Adrenalectomy

Laparoscopic transabdominal adrenalectomy begins with induction of general anesthesia, placement of a urinary catheter and orogastric tube, and positioning of the patient in the lateral decubitus position with the affected side up. Exposure is facilitated by flexion of the operating table at the patient's waist to enhance the space between the rib cage and the iliac crest. A total of three or four intraperitoneal ports (one camera, two working ports, and one liver retractor particular for the right side) are placed at least 5 cm apart in a transverse line from the lateral edge of the rectus sheath to the midaxillary line between the costal margin and iliac crest (**Fig. 77.10A**). Visual four-quadrant exploration of the peritoneal cavity is first performed with the videoscope through the medialmost port, and the videoscope is then transferred to the middle port. If robot assistance is being used, the robot is docked at this time. A retractor is placed through the medial most port to retract the viscera medially. Operating instruments are alternately placed within the abdomen through the

lateral ports. Right adrenalectomy begins with mobilization of the liver to open the retroperitoneum and allow retraction of the right lobe of anteriorly and medially using the most medial port. Left adrenalectomy is performed with mirror-image patient and port-site orientation as right adrenalectomy. Dissection begins with mobilization of the splenic flexure of the colon and spleen from the left retroperitoneum. Subsequent medial retraction of the spleen, tail of the pancreas, and stomach is accomplished with the fan or similar retractor if necessary. In both cases, the adrenal vein should be clearly identified and then doubly clipped and divided. The transabdominal laparoscopic approach has the benefit of being able to have a hand port modification for patients who may have very friable tumors and/or large tumors. The hand port can replace one of the existing outer trocars. This can be considered a technique that preserves a minimally invasive approach with the benefits of manual manipulation (**Table 77.6**).

Table 77.6 Critical Steps in Laparoscopic Transabdominal Adrenalectomy

Left Adrenalectomy	Right Adrenalectomy
▪ After general anesthesia induction, place patient in lateral decubitus position. ▪ Obtain laparoscopic access, confirm no injuries upon entry and place other ports. ▪ Mobilize and retract the spleen medially. ▪ Mobilize the splenic flexure and distal transverse colon inferiorly. ▪ Identify and mobilize the tail of the pancreas off the retroperitoneum. ▪ Create plane medial to the adrenal and lateral to the aorta. ▪ Identify the left renal vein inferiorly. ▪ Continue dissection medially until left adrenal vein is identified. ▪ Clip and divide the adrenal vein. ▪ Mobilize the rest of the adrenal gland from surrounding attachments, carefully assessing for any potential renal polar arterioles, which should be avoided. ▪ Remove adrenal gland from abdomen. ▪ Confirm hemostasis and close. ▪ Use back table to confirm that adrenal gland is in specimen.	▪ After general anesthesia induction, place patient in lateral decubitus position. ▪ Obtain laparoscopic access, confirm no injuries upon entry and place other ports. ▪ Mobilize and retract right lobe of liver. ▪ Create plane medial to the adrenal and lateral to the vena cava. ▪ Identify the right renal vein inferiorly. ▪ Continue dissection medially until right adrenal vein is identified. ▪ Clip and divide the adrenal vein. ▪ Mobilize the rest of the adrenal gland from surrounding attachments, carefully assessing for any potential renal polar arterioles, which should be avoided. ▪ Remove adrenal gland from abdomen. ▪ Confirm hemostasis and close. ▪ Use back table to confirm that adrenal gland is in specimen.

Potential intraoperative complications of laparoscopic transabdominal adrenalectomy:

- Entry site injury from placement of ports
- Injury to surrounding viscera (on left: spleen, kidney, tail of pancreas, colon; on the right: liver, colon, duodenum, kidney)
- Injury or wrongfully clipping/dividing major vessels (renal vessels, vena cava, and aorta)

- Excessive handling of adrenal gland resulting in capsular rupture and tumor spillage
- Hemodynamic instability during adrenalectomy for pheochromocytoma

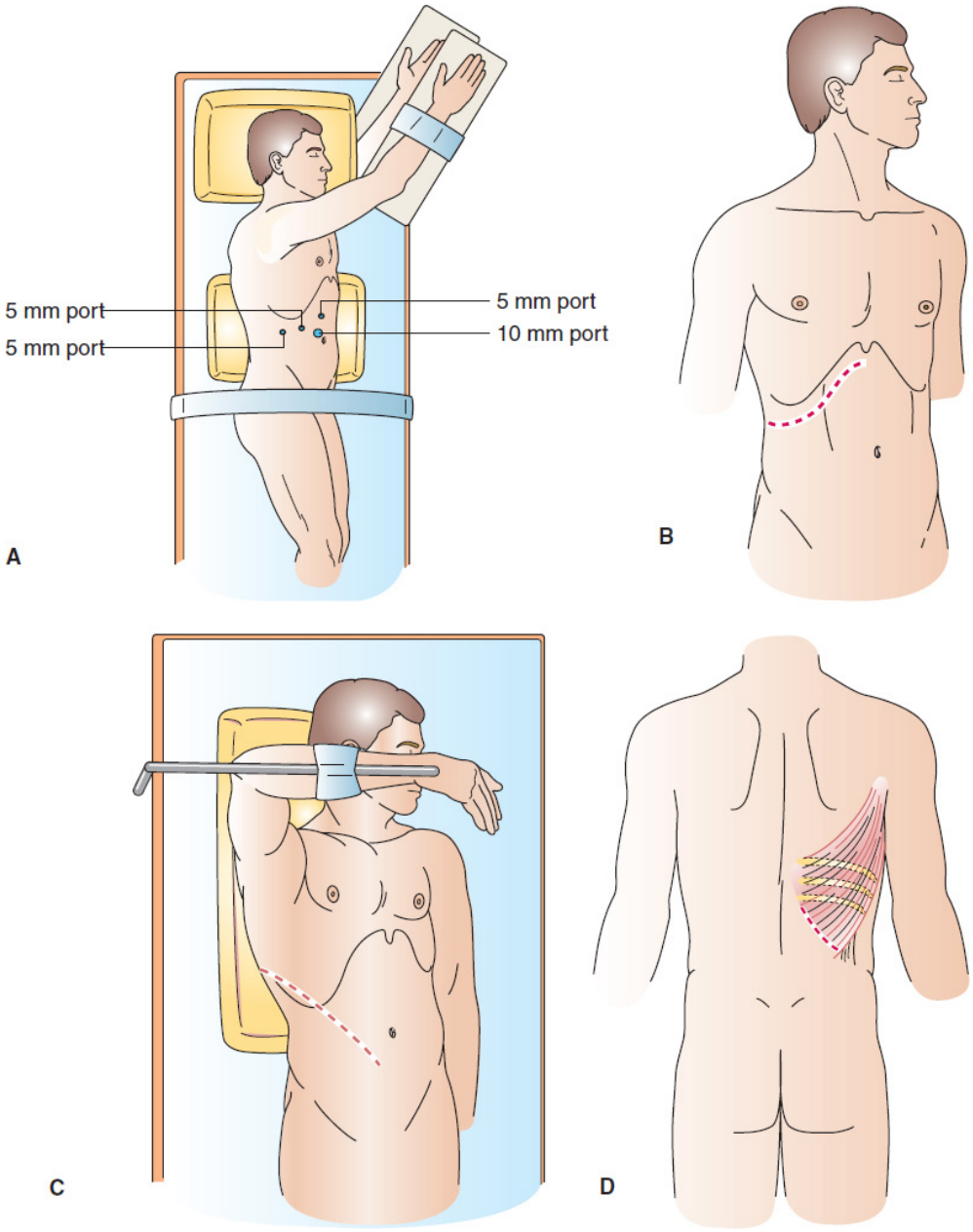

Figure 77.10 Incisions for right adrenalectomy. Shown are typical incisions for (**A**) laparoscopic approach, (**B**) open, anterior approach, (**C**) thoracoabdominal approach, and (**D**) posterior, open approach. Incisions for left adrenalectomy are positioned opposite.

Posterior Retroperitoneoscopic Adrenalectomy

Posterior retroperitoneoscopic adrenalectomy has the advantages of a minimally invasive approach while avoiding the abdominal cavity. This approach is ideal for patients with prior abdominal surgery or for bilateral adrenalectomy as both adrenal glands can be removed without repositioning the patient. It is more difficult in patients who have tumors larger than 6 cm, and should not be attempted if there is any suspicion for malignancy.

Posterior retroperitoneoscopic adrenalectomy begins with placing the patient in the prone jackknife position on a spinal table allowing the abdominal contents to fall by gravity forward. The hips and knees are positioned at 90-degree angles to the spine and femur and carefully padded. The first port is placed just below the tip of the 12th rib; after the incision is made the retroperitoneal space is entered sharply, a space is created bluntly with the index finger. This will become the middle trocar. A blunt 5- or 10-mm trocar is placed under digital guidance just medial to the paraspinous muscle and medial to the psoas internally at a 45-degree angle anteriorly toward the adrenal gland. A lateral 5-mm port is placed 5 cm lateral to the first port in a similar fashion. In the middle port, an 11-mm blunt balloon trocar is inserted. Pneumoretroperitoneum is achieved to 20 to 24 mm Hg to create an adequate working space. The videoscope is transferred from the initial middle port to the medial port to complete the dissection. The retroperitoneal space beneath the diaphragm is created bluntly and sharply. The superior border of the kidney is immediately identified and Gerota fascia is entered. The upper pole of the kidney is pushed caudally and the tissue superior to the kidney, which contains the adrenal gland is completely separated from the kidney. The medial dissection is then begun by carefully bluntly dissecting the adrenal gland and identifying the adrenal vein and dividing it between clips. Identification of the adrenal vein for both sides is easier in this approach than with the transabdominal laparoscopic approach. Dissection is completed circumferentially around the gland using electrosurgical or harmonic energy to coagulate any small vessels. Once the gland is completely free, it is placed in an endoscopic bag and removed through the middle port.

Anterior Open Approach

Anterior, open adrenalectomy begins with an ipsilateral or bilateral subcostal incision (**Fig. 77.10B**). The abdomen is opened and explored for evidence of metastatic disease, including biopsy or excision of suspicious lesions. Resection of the right adrenal gland proceeds with full mobilization and anteromedial retraction of the right hepatic lobe (**Fig. 77.11A**). In order to uncover the inferior vena cava, the right kidney and the right adrenal gland, the hepatic flexure and transverse colon and are retracted inferiorly, usually without need for extensive mobilization. The retroperitoneal space is entered behind the liver to expose the adrenal gland. Subsequent adrenalectomy is performed as in the laparoscopic approach.

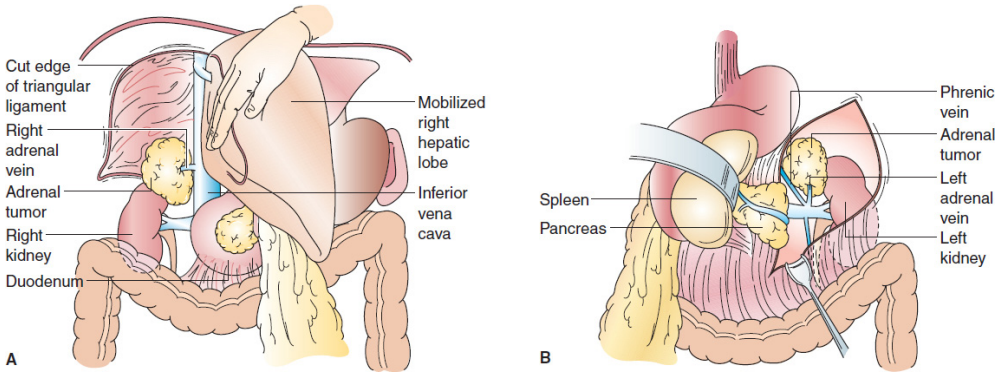

Figure 77.11 Anterior approach to right (**A**) and left (**B**) adrenalectomy. Note position of phrenic vein in relationship to the left adrenal vein and tumor.

Resection of the left adrenal gland requires mobilization of the spleen, tail of pancreas, and left colon. The left colon is freed from its peritoneal attachments and is reflected inferiorly. The spleen is then delivered from the left upper quadrant medially, and the splenocolic ligament is divided. The spleen, stomach, and pancreatic tail are retracted medially en bloc to expose the left kidney and adrenal (**Fig. 77.11B**). The left adrenal vein is ligated and divided at its junction with the left renal vein. The gland is dissected and the arterial vessels are ligated and divided sequentially, beginning at the superolateral aspect of the gland and continuing medially.

Thoracoabdominal Approach

The thoracoabdominal approach is used for large adrenal lesions with invasion of surrounding structures including the IVC, liver, and diaphragm on the right side, and the diaphragm or high gastric cardia on the left side, if control and

access to thoracic structures is necessary. The patient is positioned with the ipsilateral flank raised and arm-extended cephalad. Incision is made in the 10th or 11th intercostal space beginning at the posterior axillary line and is extended toward the midline of the abdomen (**Fig. 77.10C**). Retractors are placed and subsequent adrenalectomy is performed as for the anterior approach.

ADRENAL INSUFFICIENCY

Adrenal insufficiency reflects inadequate glucocorticoid and mineralocorticoid production by the adrenals, either secondary to suppression of the HPA axis or by destruction or surgical removal of the adrenal glands. The most common causes of primary adrenal insufficiency are autoimmune adrenalitis, infection, and, less commonly, gland replacement with metastatic disease. Chronic exogenous steroid use with HPA suppression and surgical resection of adrenal glands are important causes of secondary adrenal insufficiency.

Clinical signs and symptoms usually do not become manifest until at least 90% of the gland is destroyed. Adrenal insufficiency usually occurs gradually unless the patient experiences stress which may precipitate acute crisis.

Signs and Symptoms

Acute adrenal insufficiency usually manifests as shock in a patient with undiagnosed chronic adrenal insufficiency who has been subjected to physiologic stress. Similarly, patients with established adrenal insufficiency caused by exogenous steroid use may experience crisis if they do not increase glucocorticoid replacement during times of stress or illness. Symptoms of adrenal insufficiency reflect glucocorticoid and mineralocorticoid deficiencies. Signs and symptoms of acute insufficiency include fever, nausea, vomiting, refractory hypotension, and lethargy (**Table 77.7**). Acute adrenal insufficiency is a life-threatening emergency and should be suspected in stressed patients with a history of either adrenal insufficiency or exogenous steroid use. Chronic adrenal insufficiency presents more subtly, with fatigue, weight loss, anorexia, nausea and vomiting, abdominal pain, and diarrhea.

Diagnosis

Laboratory findings of adrenal insufficiency include hyponatremia, hyperkalemia, azotemia, and fasting or reactive hypoglycemia. Hypercalcemia may also be present. The rapid ACTH stimulation test is the best test for both acute and chronic adrenal insufficiency. Synthetic ACTH (250 μg) is administered intravenously, and plasma cortisol levels are measured 30 and 60 minutes later. Normal peak cortisol response should exceed 20 μg/dL. Measurement of ACTH by IRMA is then used to distinguish primary from secondary and tertiary adrenal insufficiency. High plasma concentration of ACTH (>200 pg/dL) and low plasma cortisol (<10 mg/dL) are diagnostic of primary adrenal insufficiency. Low levels of plasma ACTH indicate secondary (pituitary) or tertiary (hypothalamic) adrenal insufficiency.

Table 77.7 Symptoms and Signs of Acute Adrenal Insufficiency

Symptoms

- Extreme fatigue, lethargy
- Confusion or disorientation
- Nausea and vomiting
- Abdominal pain
- Coma, death

Signs

- Hypotension
- Hyponatremia, hyperkalemia, azotemia
- Hypoglycemia
- Fever
- Anemia

Treatment

Acute adrenal insufficiency is based on clinical suspicion before laboratory confirmation is available. Intravenous volume replacement with isotonic fluids and immediate intravenous steroid replacement therapy with 4-mg dexamethasone is essential. A rapid ACTH stimulation test is then performed to establish the diagnosis of adrenal insufficiency after resuscitation and corticosteroid replacement. Hydrocortisone acetate is detected in laboratory measurement for cortisol so dexamethasone should be used for replacement of

glucocorticoid function until ACTH testing is complete. Thereafter, 100 mg of hydrocortisone is administered intravenously every 6 to 8 hours and is tapered to standard replacement doses as the patient's condition stabilizes. Mineralocorticoid replacement is not required until oral intake resumes. Chronic adrenal insufficiency requires both corticosteroid and mineralocorticoid replacement. Usual daily dosing is 12 mg/m^2 of hydrocortisone and 0.05- to 0.10-mg fludrocortisone.

Patients who have known adrenal insufficiency or who have received supraphysiologic doses of corticosteroid recently in the period preceding surgery should receive perioperative stress-dose corticosteroids. Administration of 100-mg hydrocortisone the morning of major surgery followed by 100 mg of hydrocortisone every 8 hours during the perioperative 24 hours is usually more than sufficient. Steroids can be rapidly tapered to replacement levels as the patient's condition permits.

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Pituitary Surgery

Benjamin I. Rapoport, Georgiana A. Dobri, and Theodore H. Schwartz

Key Points

1. Clinical manifestations of sellar masses may include local mass effect and pituitary hormone excess or deficiency.
2. Pituitary adenomas account for the vast majority (>90%) of sellar lesions in surgical series, although the differential diagnosis includes a variety of pathologies.
3. Incidental sellar lesions are common findings on cranial imaging.
4. Despite recent advances in genetics and molecular biology, the pathogenesis of most sellar masses remains incompletely understood.
5. Thorough clinical, radiologic, and endocrine testing can help significantly narrow the differential diagnosis before pituitary surgery.
6. There are a number of surgical techniques and approaches in current use with similar outcomes; the trend is toward increasing use of endoscopy.
7. Medical therapy is available for several types of hormone-secreting pituitary adenomas, and is generally considered first-line treatment in patients with prolactin-secreting tumors.
8. With the exception of many prolactin-secreting pituitary adenomas, transsphenoidal pituitary surgery remains first-line therapy for pituitary adenomas associated with mass effect or hormone excess.
9. Medical therapy has an adjuvant role in patients with conditions caused by other types of secretory adenomas (including acromegaly and Cushing disease) when pituitary surgery is not curative.
10. Management of pituitary adenomas is most effective in a multidisciplinary setting, in which the multiple treatment options available can be individualized to a given patient. Comprehensive care of these patients routinely involves collaboration among endocrinology, ophthalmology, rhinology, and neurosurgery.

Revised from a prior edition written by Brooke Swearingen and Nicholas A. Tritos.

INTRODUCTION

The pituitary, as the "master gland," is responsible for the control of much of the body's endocrine function. It affects the function of the thyroid, adrenals, and ovaries or testes, and regulates growth, lactation, and ovulation. Its posterior lobe helps to regulate water homeostasis and parturition. Surgical disorders of 1 the pituitary can manifest as either endocrinopathy, with syndromes of hormone hypo- or hypersecretion, or as abnormalities caused by mass effect, especially visual field deficits (classically, bitemporal hemianopsia due to compression of the optic chiasm). This chapter will review the anatomy and endocrine physiology of the pituitary gland, as well as the diagnosis, imaging, and pathology of pituitary disorders, and will describe the medical and surgical management of pituitary tumors.

ANATOMY

The pituitary gland lies within the sella turcica, a bony cavity in the posterior sphenoid bone. Anatomic boundaries are formed anteriorly and inferiorly by the sphenoid sinus, posteriorly by the dorsum sella and posterior clinoid processes, anterosuperiorly by the tuberculum sella, and superiorly by the diaphragm sella (a thin dural reflection over the superior margin of the gland) (**Fig. 78.1A,B**). The lateral boundaries are formed by the cavernous sinuses. The gland itself is composed of anterior, intermediate, and posterior lobes (the adenohypophysis, pars intermedia, and neurohypophysis or pars nervosa, respectively). The anterior lobe consists of the pars distalis, the bulbous portion of the gland located within the sella, and the pars tuberalis, the stalk-like segment along the anterior infundibulum, which penetrates the diaphragm sella and connects the gland to the hypothalamus. The vascular supply is formed by the inferior hypophyseal arteries, which arise bilaterally from the intracavernous segments of the carotid arteries and are classically described as supplying the neurohypophysis; and by the superior hypophyseal arteries, which supply the median eminence and infundibulum and also form the capillary network of the hypophyseal-portal system. This portal system carries hypothalamic-releasing hormones along the infundibulum to the anterior lobe. Venous drainage exits through the cavernous and superior and inferior petrosal sinuses bilaterally, and thence to the sigmoid sinuses and internal jugular veins.

There is often a variably developed dural venous sinus, the circular sinus, usually at the level of the tuberculum sella, connecting the two cavernous sinuses, and there may be dural venous plexi of variable size and location beneath and posterior to the sella.

Several anatomic relationships are particularly important with regard to pathologic effects and surgical approaches. These include the cavernous sinuses, located lateral to the pituitary and containing the cavernous segments of the carotid arteries; and the suprasellar cistern, located superior to the gland and containing the optic nerves and chiasm. The cavernous sinuses are venous plexi formed by venous drainage from the ophthalmic veins, middle and inferior cerebral veins, and sphenoparietal sinuses. Structures traversing the cavernous sinuses include the intracavernous segment of the carotid artery, as well as multiple cranial nerves, including cranial nerve III (oculomotor), cranial nerve IV (trochlear), the ophthalmic branch of the trigeminal (V1), and the maxillary branch of the trigeminal (V2). These nerves, from superior to inferior, respectively, travel in the dural reflection that forms the lateral wall of the cavernous sinus. The VIth cranial nerve (abducens) runs along the lateral aspect of the intracavernous carotid artery. Nerves III, IV, VI, and V1 exit into the superior orbital fissure, while V2 exits through the foramen rotundum. The relationship of the cavernous segment of the carotid artery to the cavernous sinus is important to understand; this segment of the artery is completely surrounded by the venous plexus. The optic nerves and chiasm are situated above the gland, within the suprasellar cistern. Superior extension of the sellar contents, for example, from a pituitary neoplasm, can compress the chiasm from below, leading to visual abnormalities. Axons from the nasal retinal ganglion cells (which receive input from the ipsilateral temporal visual fields) cross in the chiasm en route to the opposite occipital cortex. Compression of these crossing fibers at the level of the chiasm leads to bitemporal hemianopsia, the pathognomonic neurologic manifestation of a sellar mass.

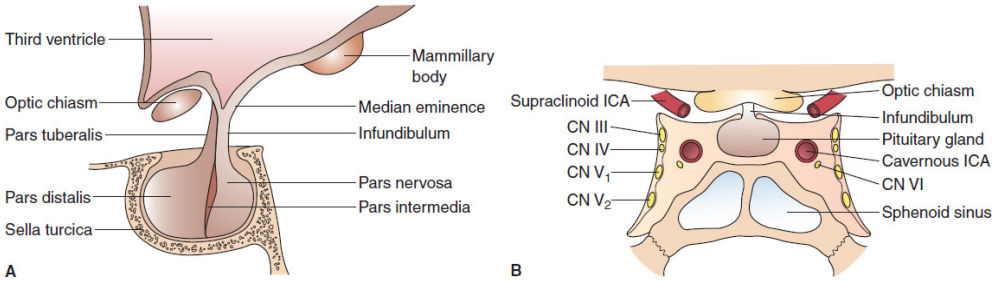


Figure 78.1 Sellar and parasellar anatomy. **A:** Sagittal view. **B:** Coronal view. ICA, internal carotid artery; CN, cranial nerve.

PATHOLOGY OF SELLAR LESIONS

Pituitary Adenomas

2 Pituitary adenomas are the most common tumors of the sella and most important surgical pathology of the sellar region, but the differential diagnosis of sellar lesions includes a variety of other pathologic entities (**Tables 78.1 and 78.2**). The true incidence of pituitary adenomas is difficult to determine as estimates differ depending on whether data are obtained from series of clinically significant tumors, autopsy findings, or imaging data. The prevalence of incidental sellar masses found in imaging 3 studies is about 10% to 22%, while it is about 14% in autopsy series.[1] The original pathologic classification was based upon staining affinity for histologic dyes, that is, acidophilic, basophilic, or chromophobe. A more recent and clinically useful pathologic classification from the WHO is based upon immunocytochemistry of various hormone subtypes.[2] The latest WHO classification of pituitary tumors (2017) includes the use of pituitary transcription factors to further characterize the adenomas.[3,4] Although not readily available in all centers, this new approach has led to diagnosis of more corticotroph, somatotroph, and gonadotroph adenomas and decreased the number of null cell adenomas, formerly called "null" because of weak immunocytochemistry staining.

Table 78.1 Tumors of the Pituitary Gland

Tumors of the Anterior Pituitary
Prolactin-producing adenoma
Growth hormone–producing adenoma
Adrenocorticotropin-producing adenoma
Gonadotropin-producing adenoma
TSH-producing adenoma
Null cell adenoma
Plurihormonal adenoma
Tumors of the Posterior Pituitary
Granular cell tumors
Pituicytoma
Spindle cell oncocytoma of the anterior pituitary
Sellar ependymoma

Modified from Lloyd RV, Osamura RY, Kloppel G, et al. *WHO Classification of Tumours of the Endocrine Organs*. 4th ed. Lyon: International Agency for Research on Cancer; 2017.

Prolactinomas (Lactotroph Adenomas)

Although less important in surgical series since the advent of dopamine agonist (DA) treatment, these are one of the most common pituitary adenomas with an incidence of 6 to 10 per million per year and a prevalence of 60 to 100 cases per million.[5] Also known as lactotroph adenomas, they arise from the prolactin-secreting cells of the adenohypophysis. They are commonly microadenomas in women, but especially in men may become large and invasive.

Table 78.2 Differential Diagnosis of Nonpituitary Sellar Lesions

Tumors
Craniopharyngioma
Meningioma
Neurohypophyseal gangliocytoma
Neurohypophyseal glioma
Granular cell tumor
Germ cell tumor
Chordomas and other soft tissue and bone tumors
Metastatic tumor
Cysts and malformations
Rathke's cleft cyst
Arachnoid cyst
Epidermoid cyst
Dermoid cyst
Vascular Lesions
Saccular aneurysm
Cavernous malformation
Inflammatory Conditions (lymphocytic hypophysitis, granulomatous hypophysitis)
Infiltrative Conditions (sarcoidosis, tuberculosis, Langerhans cell histiocytosis)

Modified from Gejman R, Hedley-Whyte T. Pathology of pituitary adenomas and other sellar masses. In: Swearingen B, Biller BMK, eds. *Diagnosis and Management of Pituitary Disorders*. Totowa, NJ: Humana Press; 2008.

Growth Hormone–Secreting Adenomas (Somatotroph Adenomas)

These tumors secrete excess levels of growth hormone (GH), leading to gigantism in children and acromegaly in adults. The incidence of acromegaly is about two to four cases per million per year.[6] These tumors may sometimes coexpress prolactin (mammosomatotroph adenomas) and rarely thyroid-stimulating hormone (TSH), as these cellular subtypes appear to arise from a common stem cell origin. They are typically invasive macroadenomas.

ACTH-Secreting Adenomas (Corticotroph Adenomas)

These tumors secrete excess levels of adrenocorticotropic hormone (ACTH), leading to excess production of cortisol by the adrenal glands (Cushing disease). They are uncommon, with an estimated incidence of 1.2 to 1.7 cases per million per year.[7] Pathologic diagnosis can be difficult, given that these tumors are often quite small and surgical specimens limited. Corticotroph adenomas typically exhibit loss of normal glandular architecture, with positive immunocytochemistry for ACTH.

TSH-Secreting Adenomas (Thyrotroph Adenomas)

These tumors are uncommon and typically comprise less than 1% of surgical series. Patients sometimes present with hyperthyroidism, but TSH staining without clinical hyperthyroidism is a more common scenario.[8]

Gonadotroph Adenomas

These tumors are common and comprise most of the "nonfunctioning" adenomas, as they express primarily hormone subunits, including beta-follicle stimulating hormone (FSH), luteinizing hormone (LH), or alpha subunits. They become symptomatic via mass effect, with compression of normal gland leading to pituitary hypofunction, or compression of the chiasm leading to visual field abnormalities. Very rarely, patients with these tumors may present with symptoms attributed to excess gonadal steroids, such as precocious puberty, irregular menses, or psychiatric manifestations.

Null Cell Adenomas

These tumors are uncommon; they manifest no clinical or immunocytochemical evidence of hormone secretion, but this may be a function of the sensitivity of the immunocytochemical technique.

"Atypical" Adenomas and Pituitary Carcinomas

Pituitary carcinoma is extraordinarily rare.[9] It is defined by the presence of distant metastases or cerebrospinal fluid (CSF) dissemination. While pituitary carcinomas may demonstrate extensive pleomorphism and/or necrosis, these pathologic findings are also seen in benign adenomas. The factors correlated with aggressive clinical behavior include an elevated Ki-67 labeling index

(MIB-1 fraction, proliferation index) and extensive p53 reactivity.[10] The previously used designation "atypical pituitary adenoma" has been abandoned by the current WHO classification system, in favor of "high-risk pituitary adenomas," describing their clinically aggressive behavior. This class includes the sparsely granulated somatotroph adenoma, the lactotroph adenoma in men, the Crooke cell adenoma, the silent corticotroph adenoma, and the newly introduced plurihormonal Pit-1-positive adenoma.[3]

Nonadenomatous Lesions of the Sella

Although pituitary adenomas are the most common neoplasms of the sella, a variety of other lesions can occur (**Table 78.2**).[11,12] We review them here briefly, maintaining our focus on lesions of the pituitary gland itself.

Neoplasms

Other neoplasms of the sella are uncommon but remain important in the differential diagnosis. *Craniopharyngiomas* are benign, solid, or partially cystic masses which presumably arise from remnants of Rathke's pouch.[13] They occur in a bimodal distribution with peaks in childhood and in older adults. The adamantinomatous type is typical in children, and is often cystic and partially calcified. The cysts contain a "motor oil"–appearing fluid, which can produce severe chemical meningitis when in contact with the CSF. The epithelium produces keratinaceous debris and cholesterol clefts. There is often a pronounced inflammatory reaction. The papillary type is seen almost exclusively in older adults, and is now known to be closely associated with the oncogenic BRAF V600E mutation, and to respond to treatment with BRAF and MEK inhibitors.[14] Papillary craniopharyngiomas may be cystic and/or solid, and can be adherent to surrounding neural structures, especially the optic nerves and hypothalamus. Surgical resection is challenging, recurrence is particularly common in children, and multidisciplinary treatment is essential. *Meningiomas* can arise anywhere along the intracranial dura, including within the sella. Meningiomas arising from the diaphragm sella or tuberculum sella can resemble pituitary adenomas and lead to endocrine dysfunction and chiasm compression. *Germ cell tumors* are most common in children and young adults and occur predominantly in males. The sella is the second most common location after the pineal region, and in many cases germ cell tumors arise

concurrently in both locations; the most common subtype is the germinoma followed by teratomas. *Metastases* to the sella are rare.[15]

Cysts

A variety of nonneoplastic cysts can arise within the sella. Although most are incidental findings seen on routine MRI imaging, large cysts can sometimes lead to endocrine dysfunction or chiasm compression. The most common cystic structure is *Rathke's cleft cyst,* arising from a remnant of Rathke's pouch within the pars intermedia. Rathke's cleft cysts can enlarge and may require drainage and/or resection. Most, however, are incidental findings, and require no treatment. *Epidermoid* or *dermoid cysts* arise from ectopic squamous or dermoid tissue and can fill with keratinaceous debris. *Arachnoid cysts* are CSF-containing structures which may also occur within the sella, presumably arising by means of a "one-way valve" mechanism allowing CSF to enter the cyst cavity but not exit; enlarging cysts may become clinically symptomatic. These must be distinguished from Rathke's cleft cysts and can be more challenging to treat. In contrast with Rathke's cleft cysts, which are self-contained and may be treated with fenestration, fenestration of arachnoid cysts results in a CSF leak that must be repaired at the time of surgery.

Inflammatory Lesions

Inflammatory lesions of the sella are rare. *Lymphocytic hypophysitis,* the most common, is thought to represent an immune-mediated phenomenon. It is sometimes seen in women during or after pregnancy, often in association with autoimmune disorders (Hashimoto's thyroiditis, atrophic gastritis). Lymphocytic hypophysitis has also been observed with increasing frequency in patients treated with immunotherapy.[16] The stalk and gland are enlarged and infiltrated with inflammatory cells, and pituitary dysfunction may occur. *Granulomatous hypophysitis* can arise from infections, tuberculosis or fungal, or as idiopathic granulomatous inflammation, either alone or in association with sarcoidosis. Other uncommon types of hypophysitis include xanthomatous, necrotizing, and IgG4 related.

MOLECULAR PATHOGENESIS

4 The molecular pathogenesis of pituitary adenomas remains incompletely understood.[17,18] The majority of pituitary adenomas are monoclonal in origin,[19,20] but the relative contributions of intrinsic genetic events and stimulation by hypothalamic hormones and local growth factors remain to be determined. Progression to malignancy with metastasis is rare, although local invasion is common. Genetic mutations predisposing to the development of pituitary adenomas include mutations in the *AIP* gene (aryl hydrocarbon receptor interacting protein) which has been found in some familial pituitary adenoma cohorts as well as some sporadic adenomas, especially in young acromegalic patients. The *MEN1* (multiple endocrine neoplasia) gene is also associated with familial adenomas, but is uncommon in sporadic disease, as is the *GNAS* mutation associated with McCune Albright syndrome. The *PRKAR1A* gene encodes a type 1A regulatory subunit of protein kinase A. Inactivating mutations of this gene are identified in 60% to 70% of patients with Carney complex, a condition of dominant inheritance, which may lead to acromegaly as a result of somatotroph hyperplasia or adenoma, as well as a variety of extrapituitary manifestations. Epigenetic modification has been suggested as a mechanism to influence gene expression without alteration in the underlying genome. Altered expression of genes encoding CDKN2A (cyclin-dependent kinase inhibitor), DAPK (death-associated protein kinase), FGFR2 (fibroblast growth factor receptor 2), among others, have been associated with sporadic pituitary adenomas. Loss of tumor suppressor genes may also be involved in adenoma pathogenesis. Loss of the *GADD45y* gene expression occurs in the majority of human pituitary adenomas, and products of the *AIP, PRKAR1A,* and *MEN1* genes may also act as tumor suppressors, with loss of these products in familial syndromes predisposing to the development of pituitary adenomas, in a "two-hit" model. Dysregulation of microRNAs, which can regulate translation of target mRNAs, has recently been found in pituitary adenomas, and differential expression can be associated with specific tumor subtypes. It is unclear which, if any, of these abnormalities are primary as opposed to epiphenomena in pituitary tumorigenesis.

ENDOCRINE EVALUATION

5 All patients with a sellar mass greater than 1 cm in diameter require endocrine evaluation for pituitary hypofunction, and patients with possible

pituitary adenomas of any size require evaluation for hypersecretory syndromes as well.[21] This is best done in conjunction with an endocrinologist experienced in the management of pituitary disease.

Pituitary Hypofunction (Hypopituitarism)

A complete history with questions targeted at change in energy, weight, appetite, thirst, urination as well as irregular menses or sexual dysfunction, along with physical examination and morning blood draw, are very important in diagnosing pituitary hypofunction. The key labs are sodium, free thyroxine (free T4) and 8 **AM** cortisol, especially in patients requiring surgical treatment, as unrecognized hypothyroidism or hypoadrenalism may have a profound effect on response to anesthesia and complicate recovery from surgery and can also cause hyponatremia. To avoid repeated blood draws one might add TSH, ACTH, estradiol/testosterone, LH, FSH, GH, and insulin-like growth factor 1 (IGF1) to fully characterize the pituitary axes.

Central (secondary) hypothyroidism is characterized by low free T4 levels in association with inappropriately low or normal TSH. Central hypogonadism is characterized by low morning testosterone levels in men, and low estradiol levels in women, associated with inappropriately low or normal FSH and LH. Central hypoadrenalism is characterized by low morning cortisol levels in association with inappropriately low or normal ACTH. Morning serum cortisol ≤3 mcg/dL is strongly suggestive of adrenal insufficiency (in the absence of corticosteroid or opioid medications), whereas morning serum cortisol ≥18 mcg/dL assures sufficient adrenal function. Intermediate cortisol levels are indeterminate with regard to adrenocortical function and require further evaluation, including stimulation, based on clinical suspicion. GH deficiency diagnosis requires a low IGF1 in the setting of other deficient pituitary axes, or a GH stimulation test, as GH is highly pulsatile and random levels are rarely useful.

Replacement therapy, especially levothyroxine and glucocorticoid (prednisone or hydrocortisone), should be considered as soon as the diagnosis of insufficiency is confirmed, especially in those patients who require surgery. Glucocorticoid replacement should precede thyroid hormone replacement in order to avoid precipitating adrenal crisis. Posterior pituitary dysfunction, typically diabetes insipidus (DI) is uncommon as a presenting symptom and points away from pituitary adenoma and toward alternative etiologies, such as

germ cell tumor, in the differential diagnosis of a sellar mass. DI is characterized by polyuria with polydipsia, dilute urine, and tendency to hyperosmolar dehydration if access to water is limited or thirst is deficient; confirmation may require a water deprivation test in uncertain cases.

Hypersecretory Syndromes

Pituitary adenomas may be associated with excess hormone secretion, giving rise to well-characterized clinical syndromes. It is important to recognize these preoperatively, especially since surgical treatment in some instances is not first-line therapy. In particular, patients with prolactin-secreting pituitary adenomas may be offered a trial of medical therapy, as DAs are effective in controlling tumor size and relieving mass effect.

Excess Prolactin (Prolactinomas)

Excess prolactin leads to the syndrome of amenorrhea and galactorrhea in women, and the syndrome of hypogonadism with sexual dysfunction in men. Mildly elevated prolactin levels may be related to medication effects (e.g., dopamine antagonists, psychotropic medications), macroprolactin (an inactive macromolecule, prolactin bound to IgG, with no physiologic effect and requiring no intervention), a microprolactinoma (<1 cm), or "stalk effect" (**Table 78.3**). Prolactin release from the anterior pituitary is, under normal circumstances, regulated by continuous inhibition; dopamine is continuously needed to inhibit the secretion of prolactin from the lactotrophs. The "stalk effect" occurs when a non–prolactin-secreting mass exerts pressure on the infundibulum and thereby diminishes the amount of dopamine that reaches the anterior pituitary (diminished inhibition), resulting in increased prolactin release. Usually the serum prolactin level associated with "stalk effect" is less than 150 ng/mL, and this must be distinguished from a prolactinoma, as the treatments are potentially different.[22] A large tumor in the setting of a mildly elevated prolactin level likely represents "stalk effect" rather than a true prolactinoma; a mildly elevated prolactin level in the setting of a microadenoma likely represents a true microprolactinoma.

Giant macroprolactinomas may secrete prolactin exuberantly, giving rise to the "hook effect," an immunoassay artifact that occurs in the presence of very high serum concentrations of prolactin, leading to substantial underreporting of

prolactin levels and potentially erroneous diagnosis. To avoid this artifact, prolactin should be measured in serially diluted serum specimens.[23]

Table 78.3 Causes of Hyperprolactinemia

Physiologic	Pathologic (Pituitary)	Pathologic (Other)
Pregnancy	Prolactin-secreting adenoma	Medications (e.g., antipsychotics, antidepressants, metoclopramide, verapamil, opioids, oral contraceptives)
Lactation	Growth hormone and prolactin-cosecreting tumor	Polycystic ovary syndrome
Physical stress	Any sellar mass causing "stalk effect"	Primary hypothyroidism
Sexual intercourse	Empty sella	Renal insufficiency
Nipple or breast stimulation	Hypothalamopituitary irradiation or trauma	Hepatic insufficiency (as in chronic liver disease)
Macroprolactin	Hypothalamopituitary infiltrative conditions (e.g., hypophisitis, sarcoidosis or tuberculosis)	Chest wall lesions

Excess Cortisol (Cushing Syndrome)

Hypercortisolemia of any cause is known as "Cushing syndrome." Patients with this condition may present with manifestations of various kinds, including metabolic (central adiposity, glucose intolerance), catabolic (muscle wasting, bone loss, skin thinning, spontaneous ecchymoses), cardiovascular (hypertension, thromboembolism, coronary artery disease), mineralocorticoid

(edema, hypokalemia), hypogonadal, hyperandrogenic (hirsutism, acne), increased risk of infections, and psychiatric symptoms. Most commonly the cause is iatrogenic administration of corticosteroids; the second-most-common etiology is a functioning adenoma. Approximately 80% of patients with neoplastic causes of Cushing syndrome have a pituitary adenoma (Cushing disease). The remainder have adrenal tumors (adenoma, carcinoma) or ectopic tumors (nonpituitary ACTH production).[24]

The diagnosis of Cushing disease can be difficult and is best made by an endocrinologist experienced in neuroendocrine disorders. Hypercortisolemia is determined by measurement of 24-hour urine free cortisol levels, nonsuppressed serum cortisol level after low-dose dexamethasone, and elevated late-night salivary cortisol levels. These tests help establish the presence of cortisol excess and differentiate between Cushing syndrome and other states associated with high cortisol levels (**Table 78.4**). An ACTH level is the next step in investigating the source of Cushing syndrome: low ACTH levels (<5 pg/mL), implying ACTH-independent etiology, are seen with adrenal disease, as the autonomous production of excess cortisol results in normal feedback inhibition of pituitary ACTH. High or inappropriately normal ACTH levels (>15 pg/mL), implying ACTH-dependent etiology, are seen with pituitary or ectopic etiologies. ACTH levels between 5 and 15 pg/mL, although not very common, fall into a grey area and cannot clearly point toward a central or adrenal source, necessitating further dynamic testing.

If the ACTH level is elevated an MRI of the pituitary is the next step. If no pituitary lesion is found (up to 40% of cases), or if an adenoma <6 mm is identified, further testing to confirm a pituitary source of ACTH is warranted. Bilateral inferior petrosal sinus sampling (IPSS) is the gold standard in such cases.[25] This is a catheter-based endovascular procedure in which ACTH levels obtained from the inferior petrosal sinuses (both before and after the intravenous administration of a corticotropin-releasing hormone [CRH] analog) are compared to levels obtained in the vena cava. A central-to-peripheral ACTH ratio of greater than 3:1 after the administration of CRH is considered diagnostic of a central (pituitary) source, even in the absence of tumor visualization on MRI.[26] The value of this procedure in predicting the laterality of the microadenoma is debated, but newer protocols, incorporating prolactin gradients, have improved the accuracy of lateralization predictions into the 80% range.[27] If IPSS is not available a CRH stimulation test in

combination with a high-dose dexamethasone suppression test can help to confirm a pituitary source.

Excess Growth Hormone (Acromegaly)

Excess GH secretion by a pituitary adenoma prior to epiphyseal closure leads to gigantism, while GH excess in adulthood leads to acromegaly. Adult patients typically report increased ring and shoe size, dental and jaw abnormalities with malocclusion, coarsening of facial features, headache, hoarseness, skin tags, increased sweating, carpal tunnel syndrome, arthralgias, snoring, and sleep apnea. Higher rates of hypertension, diabetes, hyperlipidemia, kidney stones, cardiomyopathy, gallstones, colon polyps, and thyroid nodules are all related to the excess of GH. Because these changes occur slowly over time, diagnosis can be delayed, and these tumors are often large and invasive at the time of detection. Acromegalic patients have a mortality risk on the order of two to three times that of the general population if GH excess is not adequately controlled. Many of these changes are reversible with successful control of the disease, but skeletal abnormalities are not.

Table 78.4 Conditions Associated with Cortisol Excess

Cushing Syndrome	Cortisol Excess in Patients with Some Manifestations of Cushing Syndrome (but No Tumor): "Pseudo-Cushing"	Cortisol Excess in Patients without Manifestations of Cushing Syndrome
Pituitary adenoma (Cushing disease)	Depression, anxiety, obsessive–compulsive disorders	Acute illness, injury, or surgery
Ectopic ACTH secretion	Alcoholism	Hospitalization
Adrenal tumor (adenoma, carcinoma) or hyperplasia	Severe obesity	Anorexia nervosa
Iatrogenic	Poorly controlled diabetes mellitus	High corticosteroid–binding globulin (CBG) levels
Surreptitious	Polycystic ovary syndrome Familial glucocorticoid resistance	

Because GH secretion is pulsatile, random GH measurements are not useful. The diagnosis is made by an elevated serum IGF1, produced by the liver overstimulated by the excess of GH. IGF1 assays are technically challenging and require gender and age adjustment.

Inadequate suppression of GH after a glucose load (administered in an oral glucose tolerance test as a 75-g bolus) confirms the diagnosis when the IGF1 is less than two times upper level of normal. Whether a GH nadir cutoff of 1

mg/L, 0.4 mg/L, or even lower can be used in patients with diabetes or other comorbidities is still a matter of debate, and in these situations the patient should be referred to an endocrinologist with more in pituitary diseases.[28]

TSH Adenomas

While immunocytochemical staining for TSH is not uncommon, secretion of active thyrotropin leading to central hyperthyroidism is rare. The hyperthyroidism tends to be mild, with palpitations, tremor, heat intolerance, and a diffuse goiter being more frequently found at diagnosis. The majority of these tumors are macroadenomas and may therefore be associated with mass effect. Biochemically, they demonstrate a nonsuppressed (inappropriately normal or increased) TSH level. This syndrome needs to be distinguished from resistance to thyroid hormone which can lead to a similar hormone profile.

Endocrine Evaluation of a Pituitary "Incidentaloma"

With the widespread availability of MRI, it is not uncommon for the radiologist to report the incidental finding of a pituitary mass. The endocrine evaluation requires screening of pituitary hormone levels to determine possible hypo- or hyperfunction, which will help to guide further therapy. Pituitary hyperplasia (which occurs when the pituitary is stimulated to produce a pituitary hormone in much higher quantity than usually) can be difficult to distinguish from a true pituitary adenoma, but requires an appreciation of the clinical setting to guard against unnecessary surgical intervention. Typically it is found in women going through puberty into early adulthood, menopause (proliferation of gonadotroph cells), pregnancy and lactation (proliferation of lactotrophs), or severe primary hypothyroidism (thyrotroph hyperplasia). Rarely, ectopic secretion of GH-releasing hormone or CRH may lead to somatotroph or corticotroph hyperplasia, respectively. All these conditions need to be distinguished from true pituitary adenomas.

NEUROLOGIC EVALUATION IN PITUITARY ADENOMAS

The primary neurologic manifestation of a pituitary mass is ophthalmologic, from compression of the optic nerves or chiasm traveling through the suprasellar cistern. Because the ipsilateral retinal ganglion cell axons cross in the optic chiasm en route to the contralateral occipital cortex, the pathognomonic finding on visual field examination is bitemporal hemianopsia. The chiasm may sometimes be associated with a relatively short intracranial optic nerve segment ("prefixed") or a relatively long intracranial optic nerve segment ("post fixed"). Depending upon the relative position of the tumor and chiasm, compression may also lead to uni- or bilateral optic nerve dysfunction, or compression of an optic tract, with resulting homonymous hemianopsia. Patients may sometimes report decreased acuity, although central vision is usually preserved unless compression is severe. Painless, unilateral decrease in color vision is a sensitive sign of early optic neuropathy, as is an afferent pupillary defect (Marcus Gunn pupil). This can be demonstrated by the "swinging flashlight test," in which light shown into the affected eye leads to a paradoxical increase in pupillary size, as the ipsilateral pupilloconstrictor fibers have been damaged by ipsilateral optic nerve compression and transmit relatively decreased retinal activity. Although pituitary adenomas often invade the cavernous sinus and displace the cranial nerves within, dysfunction of cranial nerves other than the optic nerve is uncommon. When other cranial neuropathies, such as oculomotor dysfunction, are present, and especially if they are of sudden onset, one should suspect a rapidly expanding mass, that is, pituitary apoplexy, or a more aggressive tumor, for example, a malignancy. Similarly, pituitary adenomas often circumscribe but rarely constrict the cavernous carotid artery, and rarely cause neurovascular dysfunction; when neurovascular dysfunction is present an alternate pathologic diagnosis (especially meningioma) should be considered.

Headaches can be part of the presentation for pituitary tumors, possibly via stretching of the surrounding dura mater, dural inflammation in apoplexy, or a form of trigeminal neuralgia. The headaches tend to be daily, retro-orbital or frontal, and throbbing. Such headaches are more frequently associated with cystic lesions and functioning adenomas (especially acromegaly), and resolve with surgery in only slightly more than 50% of patients.[29]

IMAGING OF PITUITARY ADENOMAS

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) represents the standard of care in evaluating pituitary tumors. Useful sequences for imaging the sella include T1 coronal and sagittal imaging before and after gadolinium contrast administration. Other sequences (e.g., T2 coronal) may be useful, especially in the evaluation of cystic structures (fluid is generally hyperintense on T2) and previous hemorrhage (which may be dark on T2). Because of the relatively decreased vascularity of adenomas compared with the normal gland, timing of scanning relative to the administration of gadolinium is important; adenomas are generally focally hypointense to normal gland. Dynamic scanning using thin section gradient echo sequences may improve the sensitivity of visualization with small microadenomas (in Cushing disease, for example), but gland heterogeneity may lead to decreased specificity. When preparing for surgery, it is essential to establish the location of the tumor with respect to the carotid arteries. Contrast-enhanced MRI sequences assist in assessing the extent of tumor invasion of the cavernous sinuses, and, if present, the degree of circumferential contact between the tumor and the cavernous segment of one or both carotid arteries.

Computerized Tomography

Computerized tomography (CT) scanning has largely been supplanted by MRI, but remains useful in the delineation of bony anatomy relevant to surgical planning and intraoperative navigation. At many centers it is common for pituitary surgery to be performed by a team comprising an otorhinolaryngologist and a neurosurgeon, the former performing the approach and the latter performing the tumor resection. Particularly when endoscopic sinus surgical approaches are used, preoperative CT is useful in defining the bony septations of the nasal sinuses, which are often poorly defined on MRI. Additionally, in those few patients who cannot undergo MRI, thin section coronal CT after contrast administration can be used to demonstrate a pituitary lesion. The presence of calcification on CT scanning can assist in the differential diagnosis; for example, a calcified cystic lesion, especially in a child, is highly likely to represent a craniopharyngioma.

MRI Characteristics of Pituitary Tumors and Other Sellar Lesions

The normal gland enhances relatively homogenously. It should be no greater than about 8 mm in coronal height in males and 10 mm in females. The infundibulum should be midline. The posterior pituitary may be bright on T1 without contrast (thought to represent secretory granules in axon terminals), although this is not a constant finding.

Pituitary adenomas should be focally hypointense relative to normal gland on T1 sequences after contrast. Microadenomas (<1 cm) may not significantly disrupt gland architecture. Macroadenomas (>1 cm) show upward bowing of the diaphragm sella associated with stalk deviation, and larger macroadenomas often demonstrate compression of the chiasm. The normal gland can be compressed, usually superiorly and posteriorly. The cavernous sinuses are variably involved; it can be difficult to distinguish invasion from compression. Lesions surrounding the cavernous carotid are obviously invasive; lesions which circumscribe less than 25% are usually compressive. It has been suggested than lesions which circumscribe less than 67% of the carotid diameter are not invasive, but this is very variable. Adenomas can also be cystic, and in such cases may show T1 bright signal before contrast consistent with high protein fluid or hemorrhage.

Craniopharyngiomas may be cystic or solid, and intra- or suprasellar. Characteristics of the cyst fluid can vary with the protein content, with greater T1 hyperintensity associated with higher protein. The cyst wall is commonly calcified (easily verifiable on CT), especially in children. Since the tumor is often suprasellar, involving the stalk and hypothalamus, the gland is typically compressed inferiorly from above.

Pituitary cysts can demonstrate variable imaging characteristics, also depending upon their protein content. Rathke's cleft cysts arise posteriorly in the sella, or sometimes along the stalk. They can be T1 hypo- or hyperintense depending on protein content, and can compress the gland anteriorly or from above. The cyst wall is usually thin, with minimal enhancement. If there is a solid component or calcification, the diagnosis is more likely to represent a craniopharyngioma. Arachnoid cysts of the sella contain fluid isointense to CSF. They exhibit minimal if any enhancement of the wall, as the cyst is lined

with a thin arachnoid layer. The gland is usually compressed inferiorly or anteriorly.

Germinomas usually involve the posterior gland, stalk, and/or hypothalamus. They are typically brightly enhancing, and the borders are relatively indistinct. An enhancing lesion of the posterior sella associated with a pineal mass is highly likely to represent a germinoma. Germ cell tumors may disseminate along CSF pathways, leading to enhancement around the fourth ventricle. *Meningiomas* are usually brightly enhancing, often more so than the gland itself. As they arise from the dura, they can be variably located in and around the sella. If they arise from the diaphragm, they can be difficult to distinguish from adenomas, but usually compress the gland from above. Meningiomas are often associated with a dural "tail," which spreads out from the central mass of the tumor, sometimes with focal hyperostosis. Meningiomas of the cavernous sinus can lead to carotid constriction, whereas adenomas rarely do. This phenomenon is best seen on coronal images when comparing the transverse diameter of the intracavernous carotid arteries. *Metastases* are typically locally invasive, brightly enhancing, rapidly growing, and associated with a clinical history of cancer. They can spread hematogenously to the gland, but more frequently represent focal metastases to parasellar bony structures. When invading the cavernous sinus they can lead to a cavernous sinus syndrome, whereas adenomas rarely do.

SURGICAL TECHNIQUE

6 Although the first reported pituitary operation was a craniotomy done in 1889 by Sir Vincent Horsley,[30] the first transsphenoidal approach was described in 1907 by Hermann Schloffer, a Viennese otolaryngologist, when he reached the sphenoid via a lateral rhinotomy incision.[31] Less disfiguring approaches were devised by the American neurosurgeon Harvey Cushing, who, with William Halsted, devised the sublabial approach in 1910, and another Viennese otolaryngologist, Oscar Hirsch, who described a fully endonasal procedure.[32] Variants of these approaches remain in use today. Cushing performed over 200 transsphenoidal operations with an overall mortality rate of 5%—amazingly low given the lack of imaging, antibiotics, hormone replacement, and modern visualization—but decided in 1927 that the craniotomy was the more preferred procedure. With his decision, the

transsphenoidal approach fell into relative disfavor, although kept alive by Dott in Edinburgh and Guiot in Paris, who introduced the use of intraoperative fluoroscopy as a navigation technique. Jules Hardy of Montreal described the use of the operating microscope and reported the first removal of a pituitary microadenoma in 1962, bringing pituitary surgery into the domain of microneurosurgery.[33] Since the 1990s, pituitary surgery has been reshaped by endoscopic techniques developed collaboratively by otorhinolaryngologists and neurosurgeons. With improvements in endoscope technology and compatible surgical instrumentation, purely endoscopic operations became commonplace in the field of sinus surgery, and these advances led to the use of endoscope-assisted and eventually purely endoscopic techniques for the management of pituitary adenomas and other lesions of the anterior skull base.[34]

The transsphenoidal approach is relatively noninvasive, as it employs the nasopharynx and sphenoid sinus to access the skull base, but the surgeon is constrained to operate through a narrow corridor, to a relatively deep target, surrounded by important structures (the carotid arteries and optic apparatus). The surgeon must (1) approach and navigate to the tumor, (2) visualize the pathology, and (3) maximally resect the tumor while minimizing damage to adjacent structures, including the normal gland and infundibulum.

Approach

There are two principal transsphenoidal approaches to the sella in use today, both of which are endonasal (**Fig. 78.2**). The sublabial approach, as well as the subfrontal craniotomy, deserve mention primarily for their historical significance. The pterional craniotomy remains useful for certain sellar lesions with significant suprasellar extension.

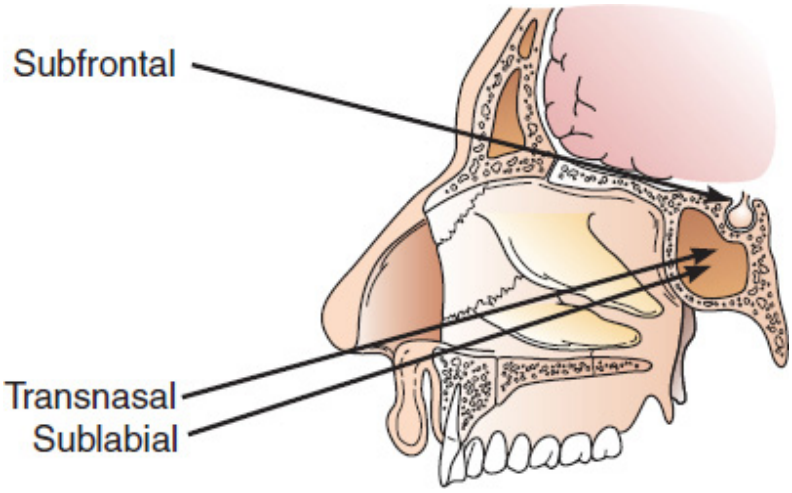


Figure 78.2 Surgical approaches to the sella.

The two endonasal approaches are limited to some degree by the width of the nasal apertures, but the advent of endoscopic systems allows contemporary surgeons access to adequate corridors for visualization and manipulation, through the nasal sinuses to the sella and anterior skull base. One endonasal approach, favored in some centers at which neurosurgeons perform both the approach and the tumor resection, uses a submucosal tunnel along the septum through an anterior mucosal incision immediately posterior to the columella. Postoperatively, nasal packing is used to reapproximate the mucosa to the septum. The direct endonasal approach, typically favored in centers at which endoscopic surgery is the norm, with the endonasal approach being performed by an otorhinolaryngologist, uses either an incision at the insertion of the septum into the face of the sphenoid, or an enlargement of the natural ostia, with a posterior septectomy. This approach facilitates bimanual surgery and operation through both nares.

Navigation

It is critical to maintain accurate orientation in the sellar approach, as the face of sella is bounded immediately laterally by the carotid protuberances, and superolaterally by the optic canals. The insertion of the nasal septum posteriorly is usually a midline structure and can be used for orientation, while the sphenoid septations are very variable, and can be used for orientation only when correlated with preoperative imaging. Lateral intraoperative fluoroscopy was used at some centers in the era before neuronavigation. In the last two

decades, neuronavigational devices have become a ubiquitous standard of care. These systems establish a three-dimensional (3D) reference frame by registering facial and bony anatomy with preoperative imaging, and they can be used to correlate intraoperative anatomy with preoperative imaging by means of a navigational "stylus" recognized by the device in real time. This gives 3D information to guide the approach, but is dependent on the accuracy of the registration, and is less valuable in determining the adequacy of resection and orientation within the tumor, as tumor anatomy can change during resection.

VISUALIZATION

Hardy introduced the use of the intraoperative microscope to pituitary surgery and it remains in widespread use today. After the introduction of the rigid endoscope to field of sinus surgery by otorhinolaryngologists, its use in transsphenoidal surgery was reported by Jankowski in 1992[35]; its utility and efficacy were confirmed in multiple studies and reviews in the ensuing two decades. In the present generation, endoscopy has replaced microscopy at many centers as the preferred mode of surgical visualization in transsphenoidal surgery. Advantages of the microscopic approach are the superb optics and binocular vision; a major disadvantage is the requirement for direct line-of-sight viewing, though for smaller tumors, including the microadenomas of Cushing disease, this disadvantage may not be significant. The endoscope affords a wider field of view and the ability to see at angles off the primary visual axis. Early endoscopes offered only monocular vision with no depth of field, though 3D endoscopes are under development. Although the endoscopic technique has the potential to be less invasive, the need to provide a surgical corridor sufficient for both the endoscope and working instruments may at times require greater dissection within the nasal sinuses. A number of meta-analyses have been published comparing endoscopic and microscopic techniques. The overall results for secretory tumors, where there are defined biochemical criteria for remission, appear similar, whereas endoscopy offers advantages in the setting of larger nonsecretory tumors and those invading the cavernous sinuses.

Determining the Adequacy of Resection

As most pituitary tumors are removed by internal decompression allowing collapse of the tumor capsule, there may be no direct visualization of the adequacy of resection. Endoscopic inspection of the tumor capsule can sometimes provide an indication, but prolapse of the diaphragm as the capsule collapses (itself an indication of adequacy of decompression) can make thorough internal visualization difficult. Intraoperative MRI (iMRI) has been used in the determination of resection adequacy, as the technique allows the surgeon to visualize areas of residual tumor not seen with direct inspection. A number of studies have reviewed the utility of intraoperative imaging. Most report that additional tumor resection can be achieved in about 20% of cases, but this is partly a function of when, during the course of the procedure, the surgeon chooses to image, as premature imaging may bias the results in favor of iMRI.[36] In addition, intraoperative imaging can show whether the chiasm has been adequately decompressed (which correlates with postoperative visual improvement) and may assist in the avoidance of postoperative complications. The iMRI equipment is costly, however, and requires significant alterations in surgical workflow and operative time, with the small but present risk of operating in close proximity to a high-strength magnetic field. It has been debated whether resection can be better optimized with the use of the iMRI versus the endoscope, although these technologies are not mutually exclusive and are used in combination at some centers. Each approach has its adherents. In those few studies combining the use of endoscopy with the iMRI, most suggest that some degree of additional resection can be achieved after imaging.[37–39]

A comparison of preoperative, immediate postoperative, and 1-year–postoperative MR images in a patient with a nonfunctioning macroadenoma causing elevation and compression of the optic chiasm is shown in **Figure 78.3**.

Surgical Technique

There are a number of variations in surgical technique, determined by the preference of the surgeons and the dictates of the anatomy. The patient is given antibiotics and stress-dose steroids preoperatively. Protocols for antibiotic use are not standardized, but a typical neurosurgical antibiotic regimen is almost universally extended to broad-spectrum coverage when a high-flow CSF leak is expected or encountered. A lumbar drain may be placed preoperatively if a

high-flow CSF leak is anticipated, and the abdomen may be prepared for harvest of a fat graft to be used in repairing the associated skull base defect. In selected cases, intrathecal fluorescein may be administered in order to assist in the detection of small CSF leaks. Almost all patients, except for patients with Cushing disease, are given stress-dose corticosteroids. After the induction of general endotracheal anesthesia, the patient is positioned supine. The head may be turned toward the surgeon or in a neutral position if two surgeons will together be performing an endoscopic approach while standing on opposite sides of the patient. At some centers, following the endonasal approach, the otorhinolaryngologist maneuvers the endoscope while the neurosurgeon performs the tumor resection; others prefer to place the endoscope on a fixed holder during the tumor resection. The head of the patient can be held in a gel headrest or pinned using the Mayfield clamp. If neuronavigation is used, the reference fiducials or surface anatomy is registered. The area of the proposed nasal mucosal incision is infiltrated with local anesthesia with epinephrine as a vasoconstrictor.

With a direct endonasal approach the incision is made along the posterior septum, and either the septum is fractured and deviated contralaterally, or a posterior septectomy is performed.[40,41] The microscopic approach employs either a sublabial incision or an endonasal transseptal approach. In both cases a nasal speculum is introduced, fracturing the septum and compressing the turbinates laterally. With the endoscopic approach, the middle turbinate may require removal to increase access. The face of the sphenoid is opened, and any septations impeding access are removed. Anatomy of the sphenoid septations gleaned from preoperative imaging can be useful in guiding the approach to the midline sella, which is drilled to dura. Diamond burr drill bits are used near the dura. The dura may be lightly cauterized prior to the dural incision.

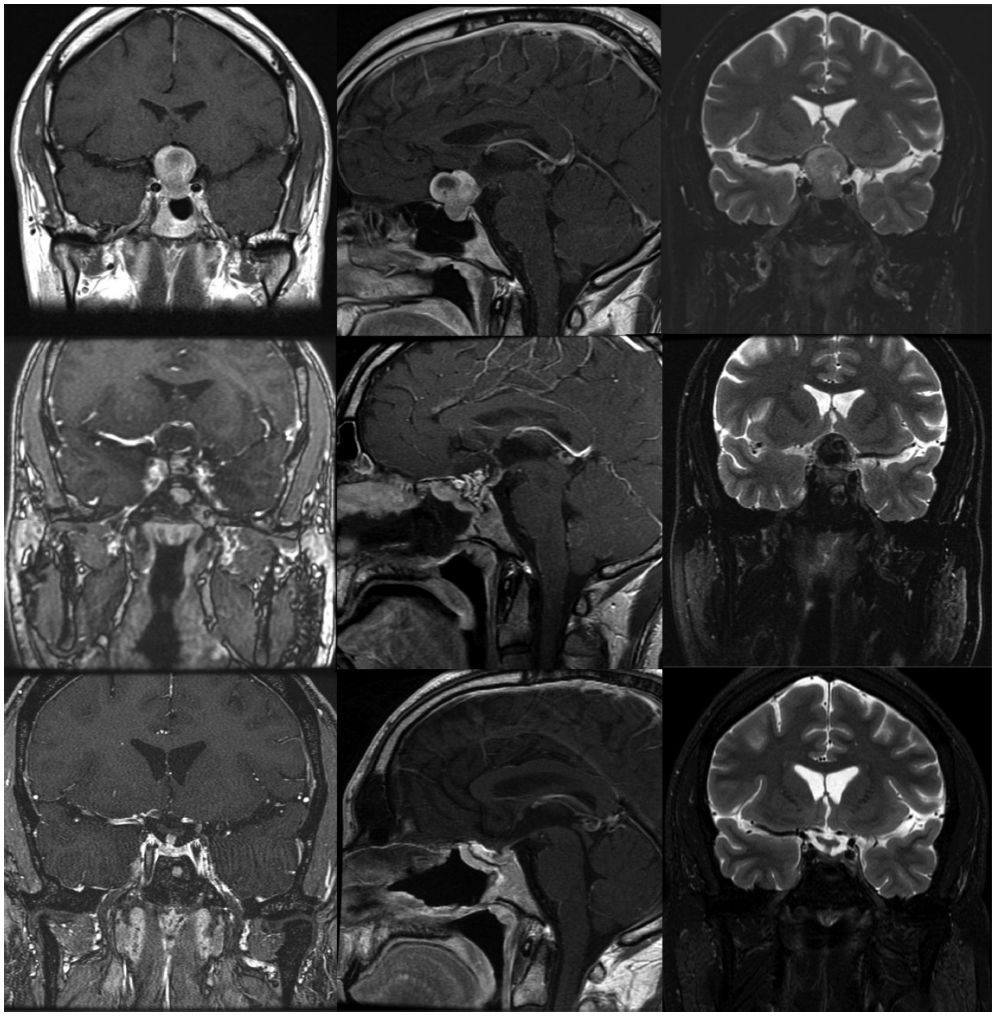


Figure 78.3 MR imaging of the sella before and after resection of a pituitary macroadenoma.

For macroadenomas, the tumor is usually immediately evident. The typical strategy involves dissecting the tumor from the dural leaflets, defining the interface between the tumor and normal gland, internally debulking the tumor with ring curettes, then completing the resection in a manner that preserves the normal gland. The normal gland can usually be distinguished by color and consistency, and in the case of macroadenomas is usually compressed posteriorly and superiorly. As the resection proceeds the diaphragm should prolapse into the operative field, particularly in cases in which the chiasm has been compressed. After tumor removal, the resection cavity is inspected for residual tumor; angled endoscopes can be useful in visualizing areas not in the direct line of sight.

When approaching microadenomas, especially those causing Cushing disease, detection can be difficult. If there is strong evidence from preoperative imaging, dissection in the indicated region may be attempted. Some surgeons approach microadenomas by dividing the gland into quadrants and taking biopsies from each quadrant. If no tumor is found on frozen section analysis, a hemihypophysectomy can be performed guided by IPSS.

Hemostasis is achieved by packing with any number of available hemostatic materials. After achieving hemostasis, many surgeons pack the tumor cavity with fat, muscle, or absorbable hemostatic material. A water-tight seal is essential if a CSF leak has been created. Many techniques have been described for achieving a water-tight reconstruction of the anterior skull base in this context.[42] When a microscopic approach is used, a fat graft is buttressed in place and the sellar floor reconstructed with septal cartilage or bone, titanium mesh, or proprietary, commercially available materials. Fibrin glue or other sellar sealant can be used if needed. When an endoscopic approach is used, such techniques are often supplemented by rotating a vascularized nasoseptal flap over the reconstructed skull base defect. Displaced turbinates and septum are then returned to their physiologic positions. With a direct endonasal approach, nasal packing is not always used. If a submucosal tunnel was created during the approach, nasal packing is placed. The use of iMRI can be timed at the discretion of the surgeon. Some surgeons maintain the sterile field and image before final closure; others complete the closure (since reopening is usually straightforward) and image prior to reversal of anesthesia.

Postoperative Management

Careful monitoring in the postoperative period is essential. Most patients require only one to two nights of hospitalization; an ICU stay is usually not necessary. Potential complications include postoperative hemorrhage, CSF leakage, meningitis, epistaxis, and endocrine dysfunction (including DI, the syndrome of inappropriate antidiuretic hormone secretion [SIADH], and hypopituitarism).

1. *Cavity Hemorrhage and Visual Compromise.* Postoperative hemorrhage can occur into the tumor resection cavity with resulting visual compromise. Thus, frequent testing of postoperative acuity and confrontational fields is necessary. Subjective reporting by the patient must also be taken seriously. Immediate

reexploration may be required, even in the absence of convincing findings on neuroimaging.

2. *Cerebrospinal Fluid Fistula.* CSF leakage can be sometimes difficult to differentiate from postoperative nasal drainage. Positional drainage (nose-down) and CT evidence of pneumocephalus are suggestive of persistent CSF leak. The classic confirmatory test to differentiate CSF from nasal drainage involves assaying collected fluid for tau protein (beta transferrin), which is found in CSF but not in nasal secretions or blood. Management options include the insertion of a lumbar drain to lower intracranial pressure and reduce flow through the fistula for several days, in order to allow for spontaneous closure of the leak, while maintaining antibiotic coverage. In the presence of a persistent, high-flow leak the optimal course is often reexploration and repacking of the tumor bed with closure of the fistula.
3. *Meningitis.* Infection in the immediate postoperative period is rare. Prophylactic antibiotic coverage is maintained for 24 hours, or until the nasal packing is removed. Delayed fever, especially with signs of meningitis, requires evaluation with a lumbar puncture; an occult CSF leak should be suspected. Patients may be at increased risk of sinus infection for many months.
4. *Epistaxis.* Bloody nasal secretions are common, and usually clear with nasal irrigation. Frank epistaxis is rare, usually occurs 2 or 3 weeks after surgery, and is most often caused by delayed hemorrhage from a septal branch of the sphenopalatine artery. It can sometimes be managed with nasal packing, but may require cauterization or clipping, or rarely embolization.
5. *Postoperative Endocrine Changes.* Postoperative endocrinologic changes are best managed in conjunction with an experienced endocrinologist.
   5.1. *Diabetes Insipidus.* Water/sodium imbalances occur in up to 75% of the patients who undergo transsphenoidal surgery in the first 14 days after surgery, with transient DI being the most common abnormality. Transient DI usually resolves spontaneously within days and permanent DI is unlikely (1% to 2% of patients). It is important to monitor liquid intake and urine output, urine specific gravity, and serum sodium levels in the immediate postoperative period, and to treat with hypotonic fluid and desmopressin if needed. Mild cases can be treated with ad lib fluid intake if the thirst mechanism is intact.

5.2. *Hyponatremia.* Immediate postoperative hyponatremia appearing on postoperative days (PODs) 1 to 3 tends to be mild and self-limited. Delayed hyponatremia is thought to be secondary to inappropriate release of the stored antidiuretic hormone (SIADH) following mechanical manipulation of the posterior pituitary. This syndrome typically starts between PODs 5 and 8 and can be severe (from nausea and headache to confusion and seizures). It is a significant cause of morbidity and is the leading cause of readmission after transsphenoidal surgery. More recently different regimens of fluid restriction have decreased the severity of hyponatremia and readmission (e.g., 1 L daily fluid restriction started POD 4 and maintained until sodium is checked and found normal POD 5–8).[43] Mild SIADH usually responds to fluid restriction and oral salt supplements. In more severe cases furosemide, urea, or hypertonic saline need to be used. It is important not to correct the hyponatremia too quickly in order to avoid central pontine myelinolysis. The hyponatremia usually resolves within 1 week with supportive care.[44]

5.3. *Hypopituitarism.* Immediate postoperative monitoring for pituitary insufficiency, especially hypoadrenalism and hypothyroidism, is necessary. Some centers prophylactically treat with replacement steroids until adequate cortisol levels can be proven. Another approach is to check an 8 AM cortisol POD 1–2, at least 24 hours after any steroids have been administered, and to discharge on physiologic corticosteroid replacement only patients with cortisol below a certain level (e.g., 13 to 15 mg/dL).[45] Central hypothyroidism might take longer to become evident on laboratory testing and it is recommended to check free T4 later (this test can be obtained concurrent with the sodium level required to monitor for delayed hyponatremia on POD 5–8). Complete postoperative hormone assessment is usually performed at 6 to 8 weeks postoperatively in order to establish remission of hormone excess and reassess pituitary function. New pituitary hormone deficiencies develop in in 5% to 10% of patients, while pre-existing pituitary hormone deficiencies may resolve in 30% to 40% of patients postoperatively.

5.4. *Biochemical Remission.* Patients treated for hyperfunctioning adenomas require special attention in the immediate postoperative period, especially patients with Cushing disease. Surgical remission leads to immediate lowering of ACTH and cortisol levels, and steroid replacement is required as the normal gland will remain suppressed for months. Patients can develop hypoglycemia, hypotension, tend to be hypercoagulable, and need higher doses of corticosteroid at the time of hospital discharge. Patients with acromegaly in remission postoperatively may have polyuria as GH levels fall, without developing DI.

RESULTS AND COMPLICATIONS

In considering the results of pituitary surgery, the most important outcome measures relate to resolution of presenting symptoms (visual, endocrine, or other), rates of gross total tumor removal and of biochemical remission in the case of functioning adenomas, and the durability of these results. The incidence, severity, and management of each of the principal complications are also important to understand, as are considerations of cost and postoperative quality of life. Additional questions relate to whether outcomes have changed over time, and whether contemporary evidence favors particular surgical techniques. Results from a number of meta-analyses addressing these outcome measures are summarized in **Table 78.5**.

Table 78.5 Comparison of Outcomes and Complications in Endoscopic and Microscopic Approaches for Resection of Pituitary Adenomas

		Meta-Analyses of Retrospective Series													
Study															
	Author (Yr)	Goudakos et al. (2011)		DeKlotz et al. (2012)		Ammirati et al. (2013)		Gao et al. (2014)		Li et al. (2017)		Almutairi et al. (2018)		Li et al. (2019)	
	Methodologic Comments					Incomplete reporting of vascular complications in M				Only comparative odds ratios reported		Complications not assessed		Only comparative odds ratios reported	
	Number of Studies Included (Total Cases)	11 (806)		38 (4,900)		38 (5,643)		15 (1,014)		23 (2,272)		70 (8,257)		17 (1,177)	
		Endoscopic	*Microscopic*	*Endoscopic*	*Microscopic*	*Endoscopic*	*Microscopic*	*Endoscopic*	*Microscopic*	*Endoscopic*	*Microscopic*	*Endoscopic*	*Microscopic*	*Endoscopic*	*Microscopic*
	Endoscopic/ Microscopic Cases	369	437	2,335	2,565	2,125	3,518	487	527	Not Reported Separately	Not Reported Separately	Not Reported Separately	Not Reported Separately	582	595
Results															
	Gross Total Removal	71%	69% (NSD)	79% (favoring E*)	65%	69%	64% (NSD)	71.8% (favoring E*)	58.0%	OR 1.52 (favoring E*)		74.0% (favoring E*)	66.40%	66.4%	66.5% (NSD)
	Endocrinologic Cure (%)	66	60 (NSD)	71	71 (NSD)							75.8	75.5 (NSD)		
	Visual Improvement (%)			71 (favoring E*)	56										
	Recurrence									NSD					
Complications															
	Overall	RR 0.18 (favoring E*)												RR 1.29 (favoring E*)	
	Death (%)					0.49	0.23(NSD)			NSD					
	Cerebrospinal Fluid Leak (%)	NSD		5 (favoring E*)	7	7.00	6.34 (NSD)	12.8	12.2(NSD)	NSD				NSD	

	Meningitis (%)			1	1 (NSD)	1.11	2.08 (NSD)	1.40	2.1 (NSD)	NSD			NSD
	Transient Diabetes Insipidus (%)	15 (favoring E*)	28			9.10	10.23 (NSD)	11.30	14.0(NSD)	NSD			
	Permanent Diabetes Insipidus (%)	2 (favoring E*)	10	2	3 (NSD)	2.31	4.25 (NSD)			NSD			
	Hypopituitarism (%)					8.51	11.64 (NSD)	3.00	6.1 (NSD)	NSD			
	Visual Loss (%)					0.72	0.60 (NSD)						
	Cranial Nerve Injury (%)					0.28	0.53 (NSD)						
	Vascular Incident (%)					1.58	0.50 (favoring M*)						
	Rhinologic Complications	Favoring E*		Favoring E* (<septal perforation, <epistaxis)			Favoring E* (<septal perforation)	OR 0.29 (favoring E*) (<septal perforation)			2.0% (favoring E*)	8.30%	
	Hospital Stay	1.5 d shorter (favoring E*)	3.3 d (favoring E*)	5.9 d			3.8 d (favoring E*)	6.3 d					
	Total Cost												

Randomized Controlled or Prospective Studies

Study													
	Author (Yr)	Cho et al. (2002)		Jain et al. (2007)		Enseñat et al. (2009)		Kahilogullari et al. (2013)		Little et al. (2014)			
	Methodologic Comments	Prolactinomas randomized to microsublabial/endoscopic		Randomized to microendonasal/endoscopic		Randomized to microsublabial/endoscopic		Prospective nonrandomized		Prospective nonrandomized			
	Number of Studies Included (Total Cases)	1 (44)		1 (20)		1 (50)		1 (50)		1 (166)			
		Endoscopic	*Microscopic*	*Endoscopic*	*Microscopic*	*Endoscopic*	*Microscopic*	*Endoscopic*	*Microscopic*	*Endoscopic*	*Microscopic*		
	Endoscopic/Microscopic Cases	22	22	10	10	25	25	25	25	67	99		

Results													
	Gross Total Removal (%)			50	50 (NSD)	60 (favoring E*)	35						
	Endocrinologic cure (%)	66	75 (NSD)	NSD									
	Visual Improvement (%)	63	60 (NSD)	NSD									
	Recurrence												
Complications													
	Overall	4.5% (favoring E*)	27% M	Favoring E*		NSD							
	Death												
	Cerebrospinal Fluid Leak			NSD									
	Meningitis												
	Transient Diabetes Insipidus			NSD									
	Permanent Diabetes Insipidus			NSD									
	Hypopituitarism			NSD									
	Visual Loss			NSD									
	Cranial Nerve Injury												
	Vascular Incident												
	Rhinologic Complications			Favoring E*									
	Hospital Stay	3.2 d (favoring E*)	5.3 d			3 d shorter (favoring E*)		0% Hyp-/0% anosmia (favoring E*)	52% Hyp-/25% anosmia				
	Total Cost									NSD in total hospital charges			

E, endoscopic; M, microscopic.
Boldface E*/M* indicates statistically significant difference favoring endoscopic/microscopic approach.
NSD, no/not significant difference.
RR, risk ratio; OR, odds ratio; d, days.

Reviews of the literature on outcomes after transsphenoidal surgery require recognition of a number of factors potentially affecting the interpretation of the results. Endocrine diagnostic techniques, biochemical criteria for remission for secretory tumors, and surgical techniques have changed over time, which can make comparisons difficult. Publication and reporting biases typically favor newer over older techniques, and some series may selectively report certain classes of complications. Meta-analyses can be useful but need to be interpreted with an eye to the underlying data, and with an awareness that the overwhelming majority of these analyses review retrospective case series rather than prospective or randomized controlled studies.

Gross Total Resection. Pituitary surgery has been a mature field for decades, so an important question concerns the extent to which surgical outcomes have changed over time. A notable meta-analysis published in 2012 reviewed short-term remission and recurrence data over the preceding 25 years. No trend toward improvement in short-term remission was observed over time, but a reduced rate of tumor recurrence was noted.[46] Because of the historical time frame, the majority of series included in that analysis used a microscopic approach. In the last decade, however, a growing body of evidence has emerged suggesting that higher rates of gross total resection are being achieved with the use of endoscopy, particularly in the setting of larger tumors and those with suprasellar extension or cavernous sinus invasion.[47] In perhaps the largest meta-analysis to date comparing endoscopic and microscopic outcomes, published in 2018 and involving 70 studies and 8,257 patients, gross total removal was achieved at a rate of 74.0% for pituitary adenomas removed endoscopically as compared with 66.4% for those removed microscopically.[48]

Biochemical Remission. On the other hand, it is not clear that historical success rates for resection and biochemical remission in the management of hormone-secreting adenomas have improved over time or with the advent of endoscopic techniques.[49] The same 2018 meta-analysis found no difference in the rates of complete removal of functioning adenomas; both endoscopic and microscopic techniques achieved this endpoint at a rate of 75%. The risk of recurrence per patient year at risk has been reported to be 3.4% for prolactinomas, 0.7% in acromegaly, and 2.3% in Cushing disease, as compared with 2.2% for nonfunctioning adenomas.[46] A meta-analysis of 9 endoscopic series involving 821 patients indicated that biochemical (endocrinologic) remission was achieved in greater than 80% of cases.[50] However, it is notable

that the classic pseudocapsular resection technique pioneered by Oldfield was established using microscopic technique via a sublabial approach, and his results remain the gold standard: biochemical remission was achieved in all 261 cases of Cushing disease in which an encapsulated adenoma was identified at surgery.[51]

Visual Improvement. Visual improvement following decompression of the optic apparatus in patients with pituitary tumors causing visual field deficits is believed to depend more on the timing of the decompression than on the surgical technique. Multiple studies have suggested that microscopic and endoscopic approaches yield approximately equivalent visual outcomes.[47]

Recurrence versus Durability of Outcomes. With respect to the durability of surgical outcomes, several important findings are consistent across multiple series and meta-analyses. The most significant prognostic factors for long-term remission in functioning adenomas are low postoperative level of the relevant hormone and gross total resection.[46] Additionally, even accounting for observation bias, multiple studies have suggested that most adenomas that ever recur do so within the first 5 years after surgery.

Microscopic versus Endoscopic Techniques. Multiple meta-analyses have addressed the relative efficacy of endoscopic versus microscopic techniques.[52–64] The findings of these and others are summarized and cited in **Table 78.5**. Early analyses often compared results from newer endoscopic series to results from older or historical microscopic series. In recent years these studies have begun to favor endoscopic over microscopic approaches, but it is not entirely clear whether this trend reflects publication bias. Few controlled trials have been published, and a recent meta-analysis[65] identified only five: two randomized and three nonrandomized, involving a total of 328 patients. There was no evidence for superiority of either surgical technique with respect to gross total tumor removal or biochemical control, but endoscopic pituitary surgery was associated with a significantly reduced risk of complications (RR 0.37) relative to microscopic approaches. It is important to note that this finding is consistently, though not universally, supported by multiple large meta-analyses of retrospective case series, as we will presently discuss.

Cerebrospinal Fluid Leak. CSF leak, in the early years of endoscopic pituitary surgery, was considered a major potential liability of the newer technique. This concern drew extensive attention from the surgical community,

and a variety of techniques emerged and matured, including multilayer skull base reconstruction ("gasket" and "button" closures), use of vascularized nasoseptal flaps, and selective use of lumbar drainage and intrathecal fluorescein to identify small CSF leaks intraoperatively. Because many pituitary adenomas remain extra-arachnoid, pituitary adenoma surgery is typically associated with fewer CSF leaks than extended approaches to nonadenomatous lesions of the sellar and parasellar region. Recent series suggest that the risk of postoperative CSF leak in pituitary adenoma surgery is approximately 1%, as compared with 1% to 3% for microscopic approaches.[47]

Meningitis, Visual Loss, and Death. The rate of postoperative meningitis, which is often a sequela associated with CSF leak, is approximately 1% to 2% following pituitary surgery and has not been shown to differ as a function of technique. Similarly, the rates of permanent new visual loss, cranial nerve injury, and death are all less than 1%, with no significant difference in complication rates between microscopic and endoscopic approaches.

Diabetes Insipidus and Hypopituitarism. The rate of postoperative endocrine dysfunction has not consistently been shown to differ significantly as a function of surgical technique. Transient DI (posterior pituitary dysfunction) occurs in approximately 10% of cases. This condition resolves in most patients, with only approximately 2% to 4% developing permanent DI. The rate of anterior pituitary dysfunction (hypopituitarism) varies more substantially across meta-analyses, with estimates ranging from 3% to 11%.

Vascular Complications. One large meta-analysis has reported a significantly higher rate of vascular complications associated with endoscopic (1.58%) as compared with microscopic (0.5%) pituitary surgery. The study incorporated 38 studies involving a total of 5,643 patients.[64] The size of the reported effect may be called into question, however, given that at least one of the included microscopic series, accounting for 592 (19.6%) of the 3,023 microscopic cases pooled for analysis,[66] was credited with zero vascular complications even though the original series does not report on this outcome at all. This finding of a difference in rates of vascular complications has not been reproduced in other meta-analyses, and no meta-analysis has suggested a difference in the rates of visual loss or surgical mortality (feared consequences of carotid artery injury) between endoscopic and microscopic approaches.

Rhinologic Complications, Hospital Stay, Cost, and Quality of Life. Rhinologic complications, including septal perforations and impaired

olfaction, have consistently been shown to be less common following endoscopic pituitary surgery than following microscopic resection. This difference in the rate of common, non–life-threatening complications largely account for the observed difference in complication rates between endoscopic and microscopic approaches. Rhinologic quality of life outcomes favor endoscopic approaches. Hospital stay has consistently been shown to be shorter by 2 to 3 days following endoscopic surgery, though surgical and total hospitalization costs are not significantly different for endoscopic and microscopic pituitary surgery.

Prolactinomas

Given the efficacy of DA treatment, surgery for prolactinomas is rarely indicated. Nonetheless, it remains effective in selected cases, especially in smaller tumors. A large surgical series reported initial remission of 91.3% in microadenomas, with a recurrence rate of 7.1%. The overall remission rate was 53.2% including giant prolactinomas.[67]

Acromegaly

Surgery remains the most effective treatment for acromegaly, despite the availability of medical therapy. Multiple surgical series in the literature report remission rates of the order of 50% to 65% for macroadenomas, and 70% to 90% for microadenomas.[68–75] It is difficult to compare results as definitions of remission have changed over time from postoperative random GH levels, to GH nadir in the setting of oral glucose challenge, to yet lower GH cutoff levels, and the assays used to measure GH levels have also changed over time. Results from specialized centers are generally better than those results reported from tumor registries.

Cushing Disease

Surgical results for Cushing disease have been reported in multiple surgical series.[46,76–80] Remission rates for microadenomas from 70% to 90% are generally reported. Neither the definition of remission of Cushing disease nor the tests used for postoperative surveillance have been standardized. These remain variable from center to center, making it difficult to compare results. In

those patients not in remission after the initial procedure (reported rates range from approximately 2%[46] to 25% per year[81]), a second exploration is sometimes recommended, which can achieve remission in an additional 50% to 70% of patients.[82–85] While early as opposed to late reoperation is technically less challenging, delayed remissions have been reported, and it is important to determine that postoperative levels have plateaued at an elevated level before proceeding with reexploration.[86]

MANAGEMENT OF PITUITARY ADENOMAS BY SYNDROME

7 With the advent of medical therapy for some of the secretory tumors, surgical indications have changed, and surgical decision making needs to be considered in the context of the available treatment options.

Prolactinomas

Medical treatment with DAs is considered first-line therapy for most patients with prolactinomas, even those with large and invasive tumors.[87] Not all patients require treatment: patients with asymptomatic, stable microadenomas, who are not pursuing fertility (e.g., postmenopausal women), can often be followed expectantly. The commonly used agents, bromocriptine and cabergoline, are both oral agents with excellent efficacy, are relatively inexpensive, and have minimal side effects (gastrointestinal disturbances and dizziness, although depression, anxiety, and impulsivity have been reported). Cabergoline is more effective and generally better tolerated than bromocriptine. Quinagolide is another agent similar in efficacy to cabergoline. High doses of cabergoline (>3 mg/d) have been associated with cardiac valvular dysfunction, but this does not appear to be a significant risk in the dose range usually prescribed for prolactinomas (typically 0.5 to 2.0 mg/wk, **Table 78.6**). The duration of the treatment is at least 2 years with 50% to 70% remission rate at 5 years after discontinuation; for many patients lifelong therapy is required.[88] Tumor regression in response to these agents is often dramatic. Long-standing visual dysfunction will often improve after tumor regression from medical treatment.

Surgical treatment is indicated if there is an insufficient response to medical therapy (persistent neurologic deficit in the setting of inadequate tumor shrinkage, persistently elevated prolactin even on high-dose medication, or intolerance to the medications), and in selected cases with high surgical cure rate when the patient prefers surgery over long-term or potentially lifelong medical treatment. Other indications for surgery include CSF leak and pituitary apoplexy, which may rarely complicate the treatment of large prolactinomas with DAs. Relative indications include cystic tumors, which may not shrink with medical treatment, and infertility in women who wish to become pregnant without medication. Surgical remission rate is >80% for intrasellar tumors but falls to <20% for tumors with an extrasellar component or with abnormal visual fields.[67] Radiation therapy can be recommended for tumors unresponsive to medical and surgical treatment.

Acromegaly

8 Surgery remains first-line treatment in patients who are good surgical candidates, likely to be cured by surgery, or have large macroadenomas, as debulking has been shown to improve subsequent biochemical control with medical therapy.[56,89–92] Surgery is rapidly effective in reducing GH levels, leads to immediate relief of symptoms from mass effect (visual loss), and has the potential to be curative, depending upon the size and degree of tumor invasiveness.

Table 78.6 Medications Used to Treat Prolactin-Secreting Pituitary Adenomas

Name	Mechanism of Action	Usual Dose Range	Adverse Effects
Bromocriptine	Dopamine receptor agonist	1.25–10 mg/d (given orally, once–twice daily)	Nausea, vomiting, dizziness, headache, nasal congestion, constipation, digital vasospasm, vivid dreams, anxiety, depression, impulsivity
Cabergoline	Dopamine receptor (D2 selective) agonist	0.5–>2.0 mg per wk (given orally several times per wk or daily)	Similar to bromocriptine (often better tolerated); high doses (>3 mg/d) have been associated with cardiac valvulopathy
Quinagolide (not available in United States)	Dopamine receptor agonist	0.075–0.9 mg/d (oral, once–twice daily)	Similar to bromocriptine. No risk of valvulopathy
Pergolide (not available in United States)	Dopamine receptor agonist	0.05–0.1 mg/d (oral, once daily)	Similar to bromocriptine. Withdrawn in United States in 2007

	because of higher risk of valvulopathy

Table 78.7 Medications Used to Treat Acromegaly

Name	Mechanism of Action	Usual Dose Range	Adverse Effects
Octreotide acetate	Somatostatin receptor agonist (sstr2 and sstr5)	100–500 µg subcutaneously every 8 hrs	Gastrointestinal side effects, cholelithiasis, hyperglycemia, hypoglycemia, vitamin B12 deficiency, hypothyroidism, bradycardia, hair loss
Octreotide LAR	Somatostatin receptor agonist (sstr2 and sstr5)	10–40 mg intramuscularly every 4 wks	Similar to octreotide acetate
Lanreotide depot	Somatostatin receptor agonist (sstr2 and sstr5)	60–120 mg deep subcutaneously every 4 wks	Similar to octreotide acetate
Pasireotide LAR	Somatostatin receptor agonist (sstr2 and high sstr5)	20–60 mg intramuscularly every 4 wks	Same as octreotide acetate. Higher risk of hyperglycemia (50%)
Octreotide capsule	Somatostatin receptor agonist (sstr2 and sstr5)	40–80 mg orally, twice daily	Same as octreotide acetate. Needs to be taken on empty stomach
Cabergoline[a]	Dopamine receptor (D2 selective) agonist	0.5–7.0 mg by mouth weekly	Nausea, vomiting, dizziness, headache, nasal congestion,

			constipation, digital vasospasm, vivid dreams, anxiety, depression, impulsivity; high doses (>3 mg/d) have been associated with cardiac valvulopathy
Pegvisomant	Growth hormone receptor antagonist	5–40 mg subcutaneously daily	Lipohypertrophy, skin rash, hepatotoxicity

[a]Cabergoline is not approved by the FDA for use in acromegaly.

Pretreatment of surgical cases with somatostatin analogs (SSAs) both for improving postoperative remission rates and anesthetic risk have been debated without consensus. A meta-analysis, including 10 studies, both randomized and retrospective, showed a borderline positive effect with pretreatment that did not reach statistical significance, while analysis of the prospective controlled trials (with historically low pretreatment remission rates) demonstrated a statistically significant benefit.[93] Pretreatment in symptomatic acromegalic patients, especially those with cardiomyopathy and potential difficult airway management due to an enlarged tongue, is sometimes worthy of consideration as it may improve anesthetic risk.[94]

9 The available medical treatments include SSAs, DAs, and GH receptor antagonists.

The SSAs are usually the first line of medical treatment and are comprised of first-generation injectable agents (short-acting octreotide acetate, long-acting octreotide LAR, and lanreotide depot), second-generation injectable agents (pasireotide LAR) as well as oral agents (octreotide capsule). First generation agents normalize IGF1 levels in 20% to 50% of cases and reduce tumor size in 50% of cases. The long-acting forms are given every 4 weeks and

usually are well tolerated; the most common side effects are gastrointestinal disturbances and occasionally cholelithiasis and hyperglycemia.[90] The second-generation injectable agent pasireotide achieves better biochemical and tumor control but a majority of the patients develop hyperglycemia as a complication so it is usually used when first-generation agents fail.[95] Oral octreotide is the newest approved SSAs and is less efficacious than the injectable agents, though useful in milder acromegaly.[96]

Cabergoline, the most potent DA, is sometimes effective in acromegaly (leading to endocrine remission in up to 30% of cases), usually when the IGF1 level is not very elevated (<2.5 times the upper level of normal). It is an oral agent, well tolerated and relatively inexpensive. Its use in acromegaly is not FDA approved.[97]

The GH receptor pegvisomant blocks the peripheral action of GH and leads to dramatic lowering of the IGF1 level in 75% to 95% of patients, but has no direct antitumoral effect. It is administered daily, subcutaneously, and can cause rash, insomnia, or hepatotoxicity. It can be used as monotherapy or as adjunctive to SSAs or cabergoline (**Table 78.7**).[98]

Radiation therapy is usually a third-line option for patients who are not in remission after surgery and do not respond to or tolerate medical therapy. A flowchart for the management of acromegaly is shown in **Algorithm 78.1**.

Cushing Disease

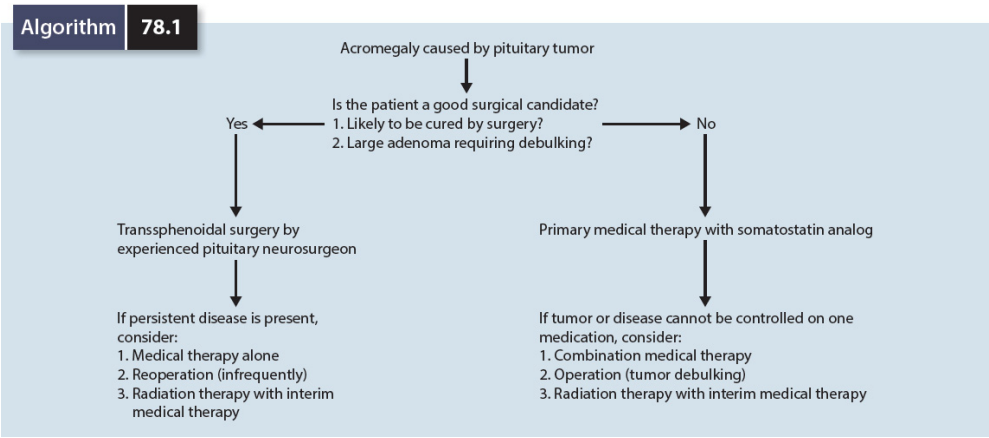
Surgical excision is generally considered to be first-line treatment for Cushing disease. Recurrent Cushing disease after initially successful surgery remains a significant problem and reexploration for recurrence is a reasonable option.

If transsphenoidal surgery is unsuccessful, a number of medications are available by acting at the level of the tumor (decreasing ACTH) and adrenals (inhibiting production of cortisol) or by blocking the cortisol receptors. Each medication has an associated set of side effects and none represents optimal therapy, but each may offer advantages in the individual patient. Combination therapy is at times used when hypercortisolemia cannot be controlled (**Table 78.8**).

Pasireotide and pasireotide LAR work at the level of the tumor as somatostatin receptor agonists, providing a modest degree of cortisol control and good tumor control, but 73% of patients develop hyperglycemia (severe in

some cases). It is not usually used as first-line therapy but it is a good option for locally aggressive tumors.[99]

Cabergoline works at the level of the tumor as a dopamine receptor agonist and controls hypercortisolemia in about 30% of patients, but higher doses are needed (2 mg/wk) that increase the side effect frequency. Control may escape after 2 years of treatment.[100] It is not FDA approved for treatment of Cushing disease.



Algorithm 78.1 Treatment algorithm for acromegaly.

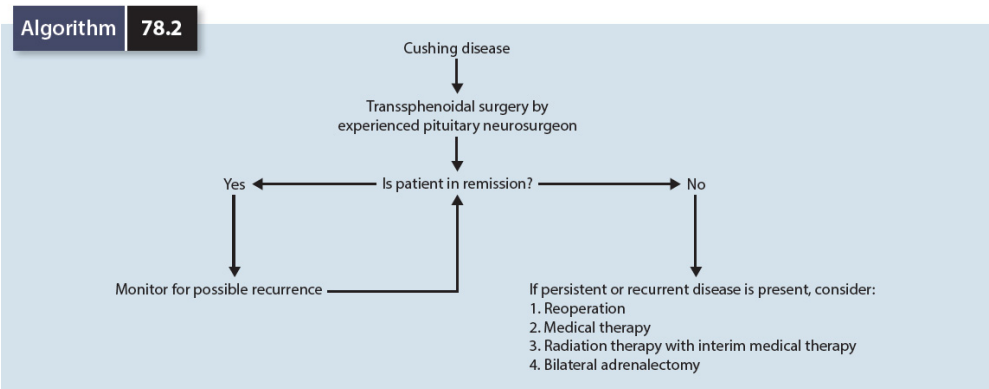
Table 78.8 Medications Used to Treat Cushing Disease

Name	Mechanism of Action	Usual Dose Range	Adverse Effects
Pasireotide	Somatostatin receptor agonist (sstr1, 2, 3, and 5)	0.3–0.9 mg subcutaneously twice daily	Gastrointestinal side effects, cholelithiasis, hyperglycemia (70%), vitamin B12 deficiency, hypothyroidism, bradycardia, hair loss
Pasireotide LAR	Somatostatin receptor agonist (sstr1, 2, 3, and 5)	10–40 mg intramuscularly every 4 wks	Similar to pasireotide
Cabergoline[a]	Dopamine receptor (D2 selective) agonist	0.5–7.0 mg/wk (oral, several times weekly or once per d)	Nausea, vomiting, dizziness, headache, nasal congestion, constipation, digital vasospasm, vivid dreams, anxiety, depression, impulsivity; high doses (>3 mg/d) have been associated with cardiac valvulopathy
Ketoconazole*	Adrenal steroidogenesis inhibitor	200–600 mg by mouth two to	Nausea, dyspepsia, skin rash,

		three times daily	hepatotoxicity, hypogonadism, gynecomastia
Metyrapone*	Adrenal steroidogenesis inhibitor	250–1,000 mg by mouth three to four times daily	Nausea, dizziness, hirsutism, hypertension, edema, hypokalemia
Mitotane*	Adrenal steroidogenesis inhibitor	0.5–3.0 g by mouth three times daily	Nausea, diarrhea, dizziness, ataxia, confusion, hepatotoxicity, rash, gynecomastia, dyslipidemia, teratogenicity
Osilodrostat	Adrenal steroidogenesis inhibitor	4–60 mg orally twice daily	Similar to metyrapone
Etomidate*	Adrenal steroidogenesis inhibitor	0.03 mg/kg intravenously as a bolus, followed by infusion: 0.1–0.3 mg/kg/hr	Sedation
Mifepristone[a]	Glucocorticoid receptor antagonist	300–1,200 mg by mouth daily	Fatigue, headache, nausea, hypokalemia, vaginal bleeding, endometrial thickening, pregnancy

	termination, abnormal thyroid function tests, dyslipidemia

[a]Only pasireotide and mifepristone are approved by the FDA for use in Cushing disease.



Algorithm 78.2 Treatment algorithm for Cushing disease.

Several medications that inhibit different steps in cortisol synthesis in the adrenal are available, some FDA approved, some not. Ketoconazole normalizes cortisol levels in about 50% of patients but has a black box warning for liver failure,[101] and a purified compound levoketoconazole is now in clinical trials. Metyrapone is used off-label, and an updated compound, osilodrostat, was recently FDA approved. It achieves eucortisolemia in close to 80% of patients, with hypertension and hypokalemia as side effects to monitor.[102] Etomidate is a parenteral compound used for severe hypercortisolemia in critically ill patients with Cushing syndrome, and mitotane is very rarely used outside of adrenal cancer due to the severe side effects and adrenolytic effects.

Mifepristone is a cortisol and progesterone receptor blocker FDA approved for treatment of patients with Cushing syndrome and hyperglycemia.[65,103,104] Hypertension, hypokalemia, and uterine hyperplasia are side effects to monitor. A purified cortisol receptor blocker is now in clinical trials.

Bilateral adrenalectomy remains a viable option, with immediate resolution of hypercortisolemia, but requires lifelong mineralocorticoid and glucocorticoid replacement. It is associated with radiographic progression of

the pituitary adenoma in about half of cases, and a smaller number of patients may develop Nelson syndrome.[105]

Radiosurgery with interim medical control is often a reasonable option after unsuccessful transsphenoidal surgery; normalization of cortisol levels occurs in about 50% to 70% of patients within 2 years of treatment, but with a significant risk of anterior hypopituitarism.[106,107]

A flowchart for the management of Cushing disease is shown in **Algorithm 78.2**.

Nonfunctioning Tumors

Surgical removal remains first-line treatment; there are no good medical options (as the response to DAs or SSAs has been poor). Small nonfunctioning tumors (<1 cm) can be followed with serial imaging, but macroadenomas should usually be resected, especially those which are close to the chiasm or enlarging on serial scans, even without visual abnormalities. After subtotal resection it is in many cases reasonable to follow the residual tumor, with reoperation or radiation therapy reserved for those which later enlarge.[108]

Thyrotropin-Secreting Pituitary Adenomas

Pituitary surgery is first-line therapy in most cases. Patients with hyperthyroidism can be pretreated with SSAs or methimazole in order to control hyperthyroidism preoperatively, if present. After surgery, patients with residual tumors or persistent hyperthyroidism may benefit from SSA therapy, which is very effective in controlling hyperthyroidism and also affords some degree of tumor control.[109] Cabergoline can be tried if SSAs are not tolerated but efficacy seems to be low. Radiation therapy and thyroidectomy are alternative options in patients who fail to enter remission after pituitary surgery and medical therapy.

SOCIOECONOMIC CONSIDERATIONS

A number of socioeconomic considerations now affect the practice of pituitary surgery. The volume–outcome relationship, which has been shown to be manifest in a number of surgical subspecialties, holds true in pituitary surgery

as well. This was originally suggested by a study showing improved outcomes for acromegaly with a dedicated pituitary surgeon.[110] Further studies have demonstrated a decrease in complication rate with increased experience,[111] and a significant decrease in operative mortality after pituitary surgery in high-volume as opposed to low-volume centers.[112] A recent study has demonstrated that surgeon and institutional performance continue to demonstrate improvements with respect to gross total removal, biochemical remission, and complication rates, even after many hundreds of operations over more than a decade.[113] With the multiplicity of available treatment modalities, comparative cost–benefit analyses are now being performed. Treatment algorithms in acromegaly which incorporated transsphenoidal surgery were shown to be less expensive than those using medical therapy alone, and algorithms using primary surgery followed by adjunctive medical treatment as opposed to the converse approach were shown to be 30% less costly overall.[114] In Cushing disease, the economic burden of managing patient comorbidities was shown to significantly decrease after successful surgery.[115] Despite the introduction of new pharmacologic agents, it is likely that surgery will continue to play a major role in the treatment of pituitary disorders; given the multiplicity of options, however, care is 10 best individualized for a given patient in a multidisciplinary setting.

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Section L: LUNG

79

Lung Neoplasms

Robert E. Merritt

Key Points

1. Lung cancer remains the leading cause of cancer-related death in the United States.
2. Advances in detection of somatic mutations in NSCLC have yielded targeted therapeutic molecular treatments for patients with metastatic lung carcinoma.
3. Non-small lung cancer is the most common lung neoplasm followed by small cell lung carcinoma (SCLC).
4. The common sites of metastatic spread include the brain, bone, adrenal glands, and liver. A metastatic evaluation includes positron emission tomography and computed tomography (PET-CT) scan, CT scan of the chest and abdomen, and a brain magnetic resonance imaging (MRI).
5. Anatomical lung resection remains the gold standard treatment for early-stage non–small cell lung carcinoma (NSCLC). Thoracoscopic and robotic assisted approaches are increasing in utilization with similar results to thoracotomy.
6. Pulmonary carcinoid tumors are relatively indolent neoplasms of the lung that are effectively treated with surgical resection.
7. Benign neoplasms of the lung, such as hamartomas, are very slow growing and can be managed with observation or surgical resection.

INTRODUCTION

Lung neoplasms can be classified histologically as malignant or benign.[1] NSCLC is the most common malignant lung neoplasm 1 encountered in clinical practice. The histologic classifications of lung neoplasms are further classified as SCLC and large cell lung carcinoma (**Table 79.1**). Carcinoid and carcinoma of the salivary glands are also classified as malignant lung neoplasms. Benign lung neoplasms that are commonly encountered in clinical practice include hamartoma, adenoma, and myelolipoma (**Table 79.2**).

Although population estimates of both the incidence and mortality of lung cancer have begun to decline, lung cancer remains second only to heart disease among all causes of mortality. With 228,150 new cases and 142,670 deaths projected for 2019, lung cancer remains the leading cause of cancer-related death in the United States. Lung cancer is second in cancer prevalence only to prostate cancer among men and breast cancer among women, and remains the leading cause of cancer-related death for both sexes. Since 2005, both the annual incidence and mortality rates due to lung cancer have started to decrease in the United States, reflecting improvements in cancer control and prevention, particularly efforts to reduce the prevalence of smoking.[2] There is also significant regional variation in both lung cancer incidence and mortality. Among men, lung cancer mortality has decreased from 1996 through 2005 in over 80% of the 50 states and the District of Columbia, whereas among women over the same period, mortality decreased in only three states (California, New Jersey, and Texas) and has increased in 13 other states, primarily in the Midwest and South, although more recently consistent rates of decline have been noted for both men and women.[3]

The best predictor of survival for patients with lung cancer is based on staging and effective treatment strategies. Anatomical pulmonary resection remains the gold standard treatment for lung cancer, yet only approximately 37% of all patients diagnosed with lung cancer are considered surgically resectable at the time of presentation. Even among patients who have undergone complete surgical resection with curative intent for early-stage lung cancer, as determined using pathologic *T*umor–*N*ode–*M*etastasis (TNM) criteria, a substantial number will have recurrence of their cancer (**Table 79.3**).[4]

Multiple randomized clinical trials have demonstrated that adjuvant chemotherapy has improved overall survival over surgery alone for early-stage lung cancer in patients with positive lymph nodes.[5,6] In addition, lung cancer screening low-dose chest computed tomography (CT) appears to improve early detection of resectable lung cancer with an improvement in overall survival in a high-risk population.[7–9] As understanding of molecular changes occurring in lung cancer evolves, new strategies that allow for early detection and classification of lung cancer will provide valuable information for the treatment of patients.

EPIDEMIOLOGY

Lung carcinoma is the leading cause of cancer-related death in the United States. The Surveillance, Epidemiology, and End Results (SEER) program estimated that 222,500 people were diagnosed with lung cancer in 2017, and lung cancer comprised 13.2% of all new cancer cases.[10] The prevalence of lung cancer is the Unites States is estimated to be at 408,800 people and accounted for 25.9% of cancer deaths, which is estimated to reach 155,870 cases in 2015. From 2005 to 2015, the number of lung cancer cases per 100,000 individuals has decreased from 63.0 to 54.5, and the number of lung cancer deaths has decreased from 52.9 to 45.0. Despite the improvements in the incidence and death rate for lung cancer, the lung cancer still accounts for more cancer-related deaths than the combined cancer-related deaths for breast cancer, prostate cancer, colon cancer, bladder cancer, and melanoma combined. The current median age for the diagnosis of lung cancer in the United States is 70 and 30% of cases occur in patients between the ages of 65 to 74. The current survival rate for lung carcinoma is 18.1% for patients in the United States. The highest incidence of lung cancer occurs in African-American males with 83.7 cases/100,000 persons. The incidence of lung cancer in Caucasian males is 65.9 cases/100,000 persons.

Table 79.1 WHO Histologic Classification of Malignant Lung Neoplasms
1. Keratinizing squamous cell carcinoma
2. Nonkeratinizing squamous cell carcinoma 2.1 Basaloid
3. Adenocarcinoma 3.1 Acinar adenocarcinoma 3.2 Papillary adenocarcinoma 3.3 Lepidic adenocarcinoma 3.4 Solid adenocarcinoma 3.5 Invasive mucinous 3.6 Minimally invasive adenocarcinoma 3.7 Adenocarcinoma in situ
4. Small cell carcinoma 4.1 Combined small cell carcinoma
5. Large cell neuroendocrine carcinoma
6. Adenosquamous carcinoma
7. Carcinoma with pleomorphic, sarcomatoid, or sarcomatous elements
8. Carcinoid tumor of the lung 8.1 Atypical 8.2 Typical
9. Carcinoma of salivary gland type 9.1 Mucoepidermoid carcinoma 9.2 Adenoid cystic carcinoma 9.3 Epithelial-myoepithelial

Table 79.2 WHO Histologic Classification of Benign Lung Neoplasms
1. Papillomas 1.1 Squamous cell papilloma 1.2 Exophytic 1.3 Inverted 1.4 Mixed squamous
2. Adenomas 2.1 Sclerosing pneumocytoma 2.2 Alveolar adenoma 2.3 Papillary adenoma 2.4 Mucinous cystadenoma
3. Pulmonary hamartoma
4. Chondroma
5. Teratoma
6. PEComa 6.1 Benign 6.2 Clear cell

MOLECULAR TUMOR GENOMICS

2 The origin of carcinogenesis caused by a series of genetic alterations in metabolic pathways in individual cells resulting in defective cell growth and differentiation served as the basis for modern molecular therapy for lung cancer.[11] The epidermal growth factor receptor (EGFR) consists of four different transmembrane kinases that regulate the cell cycle and overexpression of the EGFR receptor has been detected in NSCLC.[12] Targeted molecular therapy has been shown to have clinical benefit notably for patients with advanced NSCLC. For example, among patients whose tumors are shown to carry specific somatic mutations in the EGFR gene, treatment with small molecule tyrosine–kinase inhibitors targeting EGFR has

been associated with improved progression-free survival as demonstrated by several randomized trials.[13] Whether such treatment regimens might be effective in the adjuvant setting for patients with early-stage NSCLC who have undergone curative-intent lung resection has yet to be established, but is the focus of a recently initiated cooperative group trial. The Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials (ALCHEMIST) will evaluate patients with resected lung adenocarcinomas (stage IB to stage IIIA). Those subjects found to have tumors carrying activating EGFR mutations or the echinoderm microtubule-associated protein-like 4 (EML4-ALK) fusion gene will be randomized to maintenance therapy with either erlotinib (EGFR) or crizotinib (ALK fusion), respectively, following completion of standard-of-care adjuvant chemotherapy with or without radiation therapy. Enrolled patients found to have neither of the targeted mutations will be followed in an observational study until tumor recurrence. These studies represent an exciting potential application of gene expression studies for use in determining patient prognosis, as well as guiding the clinical management of lung cancer and preventing the under treatment of patients with NSCLC.

3 NON–S MALL CELL LUNG CARCINOMA

Overview

Patients with suspected lung carcinoma typically present with a constellation of clinical findings.[14] In some cases, symptoms may not be present. The clinical evaluation for lung cancer includes history, physical examination, radiographic imaging studies, and risk factor assessment. The history should focus on symptoms such as cough, hemoptysis, weight loss, and cigarette smoking status. In addition, neurologic symptoms such as headache, gait imbalance, and motor weakness could indicate central nervous system involvement. The physical examination should focus on the cardiopulmonary system and the supraclavicular and cervical lymph nodes. Diagnosis and staging of lung carcinoma is typically achieved with a combination of diagnostic imaging studies, such as CT and PET. Histologic confirmation of the primary lung carcinoma may require fine-needle aspiration (FNA) with

CT guidance, bronchoscopy with biopsy, or video-assisted thoracoscopic surgery (VATS). In order to determine staging and extent of tumor involvement, the elements of the tumor (T), the regional and distal lymph nodes (N), and distant metastatic disease need to be elucidated. The determination of effective treatment depends on a careful evaluation of clinical staging for optimal results. Various professional medical organizations have created evidence-based clinical guidelines for the diagnosis, staging, and management of lung carcinoma.[15–17]

Diagnosis for Non–Small Cell Lung Carcinoma

The diagnosis of lung carcinoma is accomplished with a combination of diagnostic tools that can determine the histologic diagnosis. Sputum cytology is a rarely used diagnostic test, but is safe and noninvasive. The diagnostic specificity of sputum cytology is 99% but the specificity is relatively low in most cases; therefore, the test is not widely utilized in the diagnostic workup for lung carcinoma.[19] Flexible fiberoptic bronchoscopy is a commonly utilized safe and effective diagnostic technique for the diagnosis of lung carcinoma. The overall complication rate for flexible bronchoscopy is relatively low and many diagnostic procedures can be performed. Endobronchial biopsy, brushings, bronchoalveolar lavage, and transbronchial needle aspiration can be performed with fiberoptic bronchoscopy. For central lung tumors, flexible bronchoscopy is very effective for diagnosis, and the overall sensitivity is high as 88%.[14] Flexible bronchoscopy is most effective for lung carcinoma located in the central airways; however, peripheral lung tumors are difficult to access with standard flexible bronchoscopy. Image-guided biopsy technology such as electromagnetic navigational bronchoscopy (ENB) allows surgeons and pulmonologist to navigate to peripheral lung tumors and perform FNA biopsy. The reported sensitivity for ENB is 77% due to the limitation of not having real-time imaging available during the performance of the FNA biopsy.[20]

Table 79.3 Comparison of 8th and 7th Editions of TNM Classification for Lung Cancer

Descriptor	7th Edition TNM	8th Edition TNM
T Component		
0 cm (pure lepidic adenocarcinoma ≤3 cm in size)	T1a if <2 cm; T1b if >2–3 cm	Tis (adenocarcinoma in situ)
≤0.5 cm invasive size (lepidic predominant adenocarcinoma <3 cm total size)	T1a if <2 cm; T1b if >2–3 cm	T1 mi (minimally invasive)
≤1 cm	T1a	T1a
>1–2 cm	T1a	T1b
>2–4 cm	T1b	T1c
>3–4 cm	T2a	T2a
>4–5 cm	T2a	T2b
>5–7 cm	T2b	T3
>7 cm	T3	T4
Bronchus <2 cm from carina	T3	T2
Total atelectasis/pneumonitis	T3	T2
Invasion of diaphragm	T3	T4
Invasion of mediastinal pleura	T3	—
N Component		
No assessment, no involvement, or involvement of regional lymph nodes	NX, N0, N1, N2, N3	NX, N0, N1, N2, N3

M Component		
Metastasis within the thoracic cavity	M1a	M1a
Single extra thoracic metastasis	M1b	M1b
Multiple extra thoracic metastasis	M1b	M1b

For the diagnosis of peripheral lung nodules, transthoracic needle aspiration (TTNA) is utilized in conjunction with CT to enhance diagnostic yield. The technique is very safe and effective; however, there is a 15% risk of postprocedure pneumothorax and 7% risk of developing a pneumothorax that requires chest tube thoracostomy.[21] The diagnostic sensitivity of TTNA is greater than 90% and the false-negative rate can be as high a 20% to 30%.[22] TTNA is very effective in obtaining a diagnosis of primary lung carcinomas, particularly for peripheral lung nodules. For patients with lung nodules that are located in areas of the lung that are not accessible with TTNA, VATS offers a minimally invasive approach to perform a wedge resection. Lung nodules that are located on the outer third of the lung parenchyma are easily accessible for a diagnostic wedge excision; however, lung nodules that are located deeper in the lung parenchyma are more challenging to access with the VATS approach. Smaller lung nodules that are less than 1 cm in diameter pose a challenge to localize and perform a wedge excision for diagnostic biopsy. Needle localization, methylene blue injection, and radio-opaque fiducial marker placement can greatly enhance the ability to localize small lung nodules with the VATS technique.[23,24]

Staging of Non–Small Cell Lung Carcinoma

4 The clinical staging of lung carcinoma is paramount to determining the extent of tumor dissemination which has implications on treatment decisions and overall prognosis. Optimal clinical staging can be determined with a careful assessment of tumor (T), node (N), and metastasis (M) utilizing invasive and noninvasive diagnostic methods. The lung cancer staging system

has changed and undergone many revisions over the past several years. The original survival analysis was led by Mountain and colleagues.[25] The definitions for TNM staging system were further refined by Goldstraw and colleagues through the International Association for the Study of Lung Cancer (IASLC) staging project to develop a statistically valid foundation for the 8th edition of the TNM staging system.[26,27] The American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) utilizes the IASLC-TNM staging system recommendations into an international staging system for lung carcinoma. For the current AJCC 8th edition staging system of lung carcinoma, the IASLC collected over 94,708 NSCLC cases from multiple institutions from multiple countries between 1990 and 2010.

The aims of the initial evaluation of a patient with NSCLC are to determine whether distant metastatic disease is present and to assess the extent of intrathoracic disease. A multidisciplinary approach, involving input from pulmonary medicine, chest radiology, medical and radiation oncology, and thoracic surgery, should be undertaken in the selection of the most appropriate diagnostic testing for any individual patient. A thorough history and physical examination, combined with a plain chest radiograph and baseline laboratory data (complete blood cell count and measurement of serum sodium, calcium, alkaline phosphatase, and lactate dehydrogenase levels), can suggest the presence of distant metastatic disease. The most common sites for metastatic for NSCLC include the brain, supraclavicular lymph nodes, bones, liver, adrenal glands, and contralateral lungs. An extensive metastatic workup is recommended and should include a CT scan of the chest and abdomen, a magnetic resonance imaging (MRI) of the brain, and a whole-body fluorodeoxyglucose (FDG)-PET Scan. In order to confirm the histologic diagnosis, a biopsy by FNA or bronchoscopy can be performed to obtain confirmation of malignancy and to determine the extent of disease.

If the initial clinical evaluation does not demonstrate evidence of distant disease, the extent of further evaluation by additional imaging studies is controversial. Some clinicians routinely perform a complete metastatic workup with a CT scan of the chest and abdomen, CT or MRI of the brain, and FDG-PET scan. A CT scan of the chest and upper abdomen as well as FDG-PET scan have become standard to evaluate the extent of the primary

tumor and the status of the mediastinal lymph nodes and to detect metastases in the contralateral lung, liver, bones, or the adrenal glands. Additional imaging studies in asymptomatic patients may detect the 5% to 10% of metastases that are occult, but these imaging studies are not clearly cost effective in patients with clinical stage I tumors. In patients who are acceptable candidates for pulmonary resection and have a suspicious solitary pulmonary nodule that is indeterminate despite appropriate evaluation, an excisional biopsy with a wedge resection and subsequent lobectomy for surgically resectable lung cancer should be pursued.[28]

The evaluation of the mediastinal lymph nodes for NSCLC is very critical for accurate staging and multimodality treatment which consists of neoadjuvant chemoradiation.[29] Chest CT scans provide only anatomic confirmation for tumor involvement of mediastinal lymph nodes based on enlarged size greater than 10 mm. A meta-analysis of over 3,400 evaluable patients demonstrated a pooled sensitivity of 57% and specificity of only 82% for CT scans. This meta-analysis also demonstrated that FDG-PET scanning appears to provide increased sensitivity of 84% and specificity of 89% in over 1,100 patients studied for the detection of mediastinal malignancy.[30] Several prospective studies have also demonstrated a superior diagnostic accuracy of FDG-PET imaging.[31–33] Although the overall sensitivity and specificity of FDG-PET mediastinal lymph node staging was 61% and 84%, respectively, there was a significant improvement with FDG-PET over chest CT scans in the detection of both hilar (N1) lymph node (42% vs. 13%, $p = 0.0177$) and mediastinal (N2 and N3) tumor involvement (58% vs. 32%, $p = 0.004$). Whereas FDG-PET scanning can increase the suspicion of malignancy, the negative predictive value for mediastinal lymph node metastasis does not appear to be sufficient with a false-negative rate reported as high as 13%.[34] FDG-PET evaluation of the solitary pulmonary nodule also appears to be somewhat insensitive, with a negative predictive value for benign lesions of only 57%, indicating a false-negative rate of 47%. Reliance on this modality could lead to delayed treatment for resectable early-stage NSCLC.[35]

Clinical staging for NSCLC can be accomplished by needle aspiration utilizing several approaches, including endobronchial ultrasound (EBUS) and endoscopic ultrasound (EUS). EBUS-guided transbronchial biopsy has been shown to be safe, effective, and similar in accuracy to cervical

mediastinoscopy.[36] EUS with FNA (EUS-FNA) can be utilized to biopsy the mediastinal lymph nodes in the subcarinal, paratracheal, and aortopulmonary window. Cervical mediastinoscopy remains an important diagnostic modality for sampling mediastinal lymph nodes. This modality has a procedural sensitivity greater than 90%, and specificity of 100%.[37]

Treatment

5 Pulmonary resection remains the gold standard treatment for stage I, II, and selected stage III NSCLC. The extent of resection, segmentectomy, lobectomy, bilobectomy, or pneumonectomy, is determined by the location and size of the primary tumor and also whether adjacent bronchopulmonary nodes are involved. At operation, tumor extent is evaluated by examination of the parietal pleura, pericardium, and mediastinal structures. Complete resection must achieve microscopically negative bronchial and vascular margins. If a tumor extends directly into the chest wall, diaphragm, or pericardium, an en bloc resection of the adjacent involved structures should be performed with the pulmonary resection. If there is endobronchial involvement present, the tumor can be surgically resected by lobectomy with segmental resection of the bronchus and/or pulmonary artery (bronchovascular sleeve resection), thus preserving lung function.

Patients with centrally located tumors should undergo sleeve lobectomy rather than pneumonectomy if complete resection can be achieved and such an approach is technically feasible. Several retrospective studies have demonstrated that operative mortality is reduced among patients undergoing sleeve lobectomy (0% to 5.2%) when compared with patients undergoing pneumonectomy (1.7% to 8.9%).[38–41] Moreover, overall 5-year survival is improved among patients undergoing sleeve resection, particularly among those with N0 or N1 nodal status. For peripherally located clinical stage I tumors, particularly among patients with limited pulmonary reserve or those at high risk from other comorbidities, segmental or nonanatomic wedge resection can be performed. Whether such patients are at greater risk for locoregional recurrence as suggested in earlier series, sublobar lung resection is under investigation in an ongoing multi-institutional prospective and randomized cooperative group clinical trial (CALGB 140503).[42–45]

Long-term survival after resection for NSCLC is linked to the pathologic stage of disease. The overall 5-year survival rates range from 60% to 70% for stage I tumors, from 40% to 50% for stage II tumors, and from 15% to 30% for stage IIIA tumors. Nodal involvement has the strongest adverse influence on survival. Large peripheral tumors that extend directly into the chest wall without nodal involvement (T3N0) are associated with a 5-year survival rate of 40% after complete resection, whereas involvement of mediastinal nodes is associated with only a 20% survival rate.

Some series suggest that histology also affects survival. In node-negative NSCLC, large cell neuroendocrine differentiation conferred worse survival than other types of NSCLC.[46] Different adenocarcinoma subtypes, particularly in more advanced tumors, also appear to confer worse prognosis, but the influence of histology has not been described uniformly in series to date.[47] Delineation of tumor biology by more refined histologic and molecular analyses will be needed to define which patients might be at increased risk for recurrence or treatment resistance.

The predominant sites of relapse for all stages of NSCLC after resection are distant metastases. Approximately 30% of recurrences are locoregional with tumors of both squamous and nonsquamous histology.[48] For all stages of disease, the brain is the single most common site of relapse, and brain metastases occur more frequently with nonsquamous tumors. Other common metastatic sites include bone, ipsilateral or contralateral lung, liver, and the adrenal glands.[49] At least 60% of recurrences develop in the first 2 years after operation, and virtually all recurrences related to the original primary tumor occur within 5 years after surgical resection. Even the small proportion of patients with stage II or III disease who survive 5 years are likely to survive 10 years or more postoperatively. Recurrences of the original primary tumor are uncommon after 5 years, and after that time the occurrence of new pulmonary cancers becomes the dominant problem. The risk for development of a second lung cancer in patients with a prior history of cancer resection for NSCLC is estimated to be 2% to 3% per patient per year, with a second lung cancer developing rarely in never-smokers at the time of initial resection, and at rates of 1.8% per patient-year in former smokers and 2.7% per patient-year in current smokers.[50,51] Patients also face a consistent risk for the development of new, nonpulmonary primary cancers during the first 5 years after operation.

PULMONARY CARCINOID TUMORS

6 Carcinoid tumors, which are neoplasms with a low-grade malignant potential, account for about 2% of lung tumors in the United States. They arise from neuroendocrine stem cells of the bronchial epithelium and are classified as either typical or atypical. Histologically, typical carcinoids consist of uniform polygonal cells with round nuclei and fine granular chromatin (**Fig. 79.1**). Mitotic figures are rarely seen. Atypical carcinoids show increased mitotic activity, nuclear pleomorphism, and areas of disorganized architecture and tumor necrosis (**Fig. 79.2**).[52]

Carcinoid tumors occur equally in both sexes and at a median age of 55 years. Half of patients present with pulmonary symptoms, including hemoptysis, dyspnea, and recurrent or persistent pneumonitis because 40% of lesions are centrally located in the main or lobar bronchi. The lesions may be diagnosed by bronchoscopy, appearing as pink or purple friable endobronchial masses covered by intact epithelium. In the other half of patients, carcinoid tumors are diagnosed when radiologic abnormalities are detected on a chest roentgenogram as part of a routine examination.[53] Lymph node metastases occur in approximately 10% to 15% of patients at diagnosis but are more frequent in atypical carcinoids. Carcinoid syndrome is associated with bronchial carcinoids in only 2% of cases, usually in patients with metastatic disease, particularly to the liver. The most common sites of metastases are lung, bone, liver, adrenals, and brain.[53]

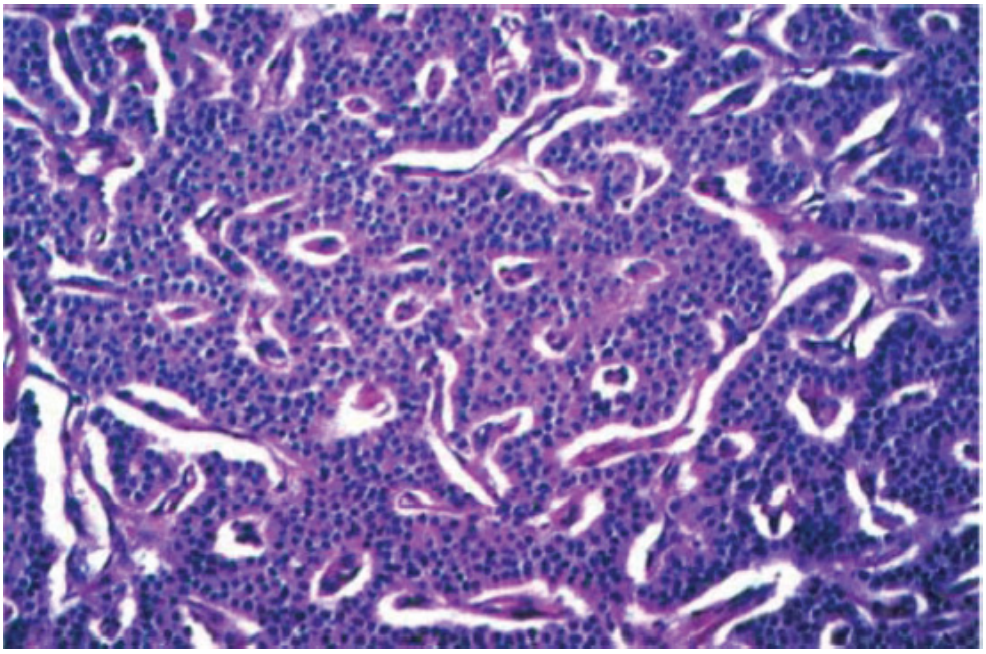

Figure 79.1 Typical carcinoid tumor of the lung. A microscopic view shows ribbons of tumor cells embedded in vascular stroma. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

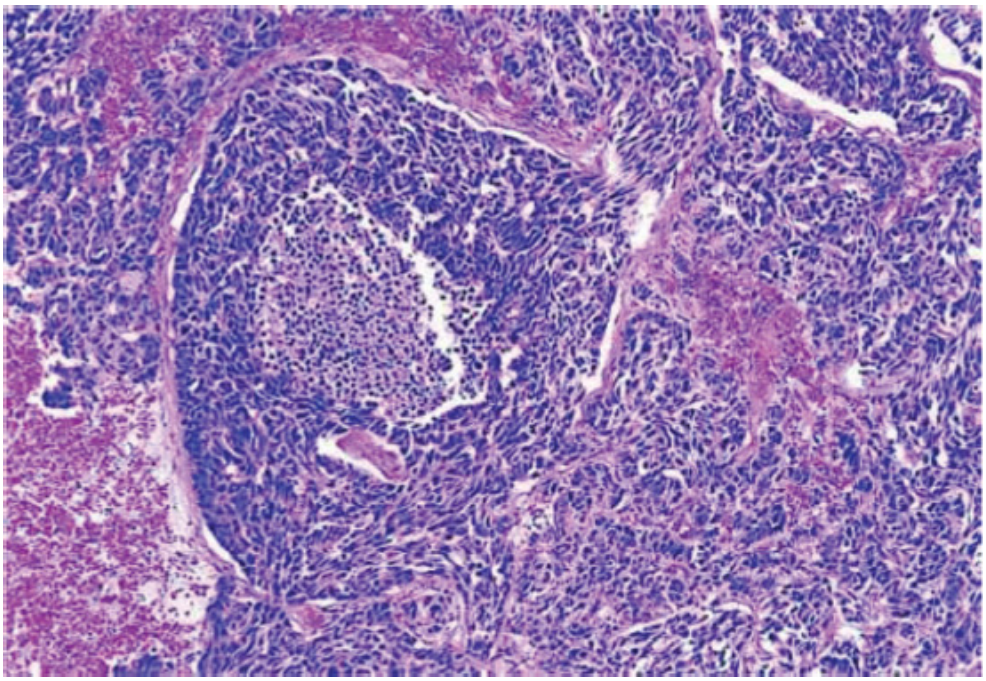

Figure 79.2 Atypical carcinoid tumor of the lung. A cellular tumor shows central necrosis and disorganized architecture. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

The standard treatment for bronchial carcinoids is complete resection, regardless of the presence of nodal involvement, with mediastinal lymph node sampling or dissection. Lobectomy can be accomplished in the majority of patients with resectable disease, although parenchymal-sparing segmentectomy or nonanatomic wedge resection can be considered particularly for patients with a typical carcinoid tumor.[54] For patients who have centrally located tumors and for which pneumonectomy might be performed, bronchoplastic techniques should be considered instead.[55] Endoscopic resection is invariably associated with local recurrence and should be used only as a palliative maneuver in patients whose general medical condition precludes thoracotomy and pulmonary resection.

The long-term survival rate after resection exceeds 90% in patients with typical carcinoids, even when hilar or mediastinal nodal metastases are present. In contrast, patients with atypical carcinoids have a 5-year survival rate of 60% after complete resection. The outcome is more closely linked to histology than to tumor size, location, or nodal involvement. Recurrence is more frequent with tumors larger than 3 cm and in patients who present with lymph node metastases.[55,56]

LARGE CELL NEUROENDOCROINE CARCINOMA

Large cell neuroendocrine carcinoma is characterized by the microscopic features of neuroendocrine tumors, but the tumor cells are large, have a high mitotic rate, and frequently show necrosis (**Fig. 79.3**).[52,57] According to Travis and colleagues, large cell neuroendocrine carcinomas are related to smoking, as is SCLC, and are high-grade tumors with 5- and 10-year survival rates of 27% and 9%, respectively, despite complete resection.[58,59] There is very minimal data available concerning adjuvant therapy. For the time being, the management of large cell neuroendocrine carcinoma is identical to that of NSCLC.[60]

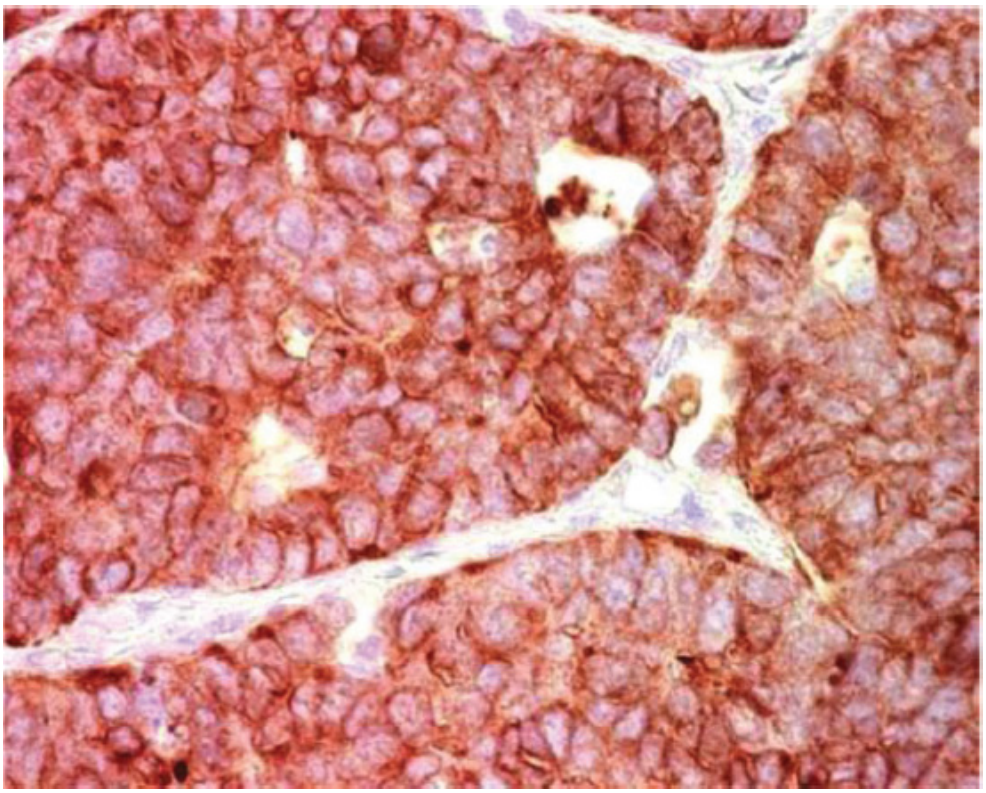

Figure 79.3 Large cell neuroendocrine carcinoma of the lung demonstrates positive immunostaining with synaptophysin antibody. (From Cagle PT. *Color Atlas and Text of Pulmonary Pathology*. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.)

SMALL CELL LUNG CARCINOMA

SCLC has the most aggressive clinical course of any type of pulmonary tumor and is often widely disseminated by the time of diagnosis. The proportion of patients with SCLC has been decreasing from 17% in the 1980s to 13% of lung cancer cases in 2002.[61] In contrast to non–small cell lung tumors, these lesions are notably responsive to chemotherapy and radiotherapy. Surgical resection is rarely indicated for SCLC since the tumor typically presents with advanced disease. The staging system for SCLC was developed by the Veterans Administration Lung Cancer Staging Group and divides patients into those with limited-stage (LS) and those with extensive-stage (ES) disease. This distinction was first based on what could be encompassed by a tolerable radiation portal. After clarification by the IASLC, LS disease includes patients with tumors confined to one hemithorax and regional lymph

nodes (hilar, ipsilateral, and contralateral mediastinal nodes, and ipsilateral and contralateral supraclavicular nodes) as well as patients with ipsilateral pleural effusion, regardless of whether the cytology is positive or negative.[62] On the other hand, both pericardial and bilateral pulmonary involvement are considered ES disease.[63]

Common sites of distant metastases are bone, liver, bone marrow, and the central nervous system, and therefore the metastatic evaluation includes a bone scan, CT of the chest and abdomen, and brain MRI. Some oncologists also perform bone marrow biopsies, but because the marrow is the sole site of extensive disease in fewer than 5% of patients, biopsies are usually judged unnecessary. After the staging process, approximately 30% to 40% of patients are found to have LS disease. For patients with LS SCLC, response rates of 85% to 90% and complete response rates of 50% to 60% can be expected with the combination of etoposide and cisplatin and radiation therapy.[64] The median survival is 18 to 24 months, and the 2-year survival rates are 40% to 50%. The addition of definitive-dose thoracic radiation therapy, particularly when administered concurrently or within several weeks of completing chemotherapy confers a 5% 2- to 3-year overall survival benefit.[65–67] In ES SCLC treated with chemotherapy, response rates reach 75% to 85%, although complete response is seen in only 15% to 25% of patients. The median survival is between 7 and 11 months, with a 2-year survival less than 5%.[61] Although the prognosis in SCLC depends primarily on the anatomic extent of disease, after a review of prognostic variables in its 2,580-patient SCLC database, the Southwest Oncology Group (SWOG) determined that the two-stage system should be extended into a four-stage system, with serum lactate dehydrogenase level, age, and pleural effusion used as additional staging criteria.[68]

The small numbers of patients with SCLC evaluated by surgeons represent fewer than 10% of all patients with SCLC. These patients have peripheral tumors with no nodal involvement or only hilar nodal involvement, which would be classified as Tl–2 N0–l (stage I or II) tumors in the TNM staging system. In the past, such tumors were often diagnosed at exploratory thoracotomy for an asymptomatic coin lesion, but with the increasing use of diagnostic percutaneous needle aspiration, more patients with early-stage SCLC are now identified preoperatively. Patients with SCLC should be evaluated by a multidisciplinary team consisting of medical and radiation

oncology, and surgical resection should be considered after distant disease has been excluded. For such potentially operable patients, it has been suggested that the TNM classification be used in future trials and studies.[69,70]

Retrospective series have demonstrated a 5-year survival rate of 30% to 50% after resection of T1N0 or T2N0 SCLC.[69,71,72] Because of the propensity for small cell cancers to disseminate, adjuvant chemotherapy has traditionally been given to patients although no prospective, randomized trials have demonstrated whether this is of any benefit, due to the small numbers of patients available.[72] Relapse at the primary site, which is a problem for most patients with LS SCLC, is distinctly uncommon after complete resection of these early tumors.[73] Radiation therapy to the chest has been suggested after complete resection, but because insufficient information is available in the literature, and local relapse is uncommon, this is not considered standard treatment.[71,72] Given the propensity for patients to develop brain metastases, prophylactic cranial irradiation is recommended for patients with either LS or ES SCLC with good performance status and who have completed initial therapy with either complete or partial response.[74]

As the role of resection in patients with mediastinal nodal involvement (N2 disease) is questionable, mediastinoscopy or EBUS should be considered mandatory to exclude mediastinal nodal disease.[75] This should be performed separately from thoracotomy since it can be difficult for the pathologist to diagnose small cell cancer on a frozen section. The intraoperative management of SCLC is not significantly different from that of NSCLC, and an incomplete resection does not benefit the patient.

The addition of resection after response to induction chemotherapy has been proposed by some surgeons to cure a small number of patients with LS SCLC without mediastinal involvement.[76] Currently, the Lung Cancer Study Group (LCSG) has performed the only prospective, randomized trial evaluating the role of surgery in LS SCLC.[77] All patients enrolled in this study received induction chemotherapy followed by surgical resection. Objective responders were randomized either to lung resection followed by thoracic and cranial radiation or to radiation therapy alone. Because the survival rate was the same in both groups, with 2-year overall survival of 20%, this trial did not support the addition of pulmonary resection to the multimodality treatment of SCLC. More recently, retrospective studies

suggest better long-term survival, in selected patients with stage I SCLC, of over 50% at 5 years.[70]

Finally, the occurrence of a second primary lung carcinoma after treatment for SCLC has been reported in the few patients with prolonged survival. It should not be assumed that the new tumor is of small cell histology, and these patients should be evaluated for the possibility of resection.[78] The average risk for the development of a second lung cancer in patients who survive SCLC is approximately 6% per patient per year.[79]

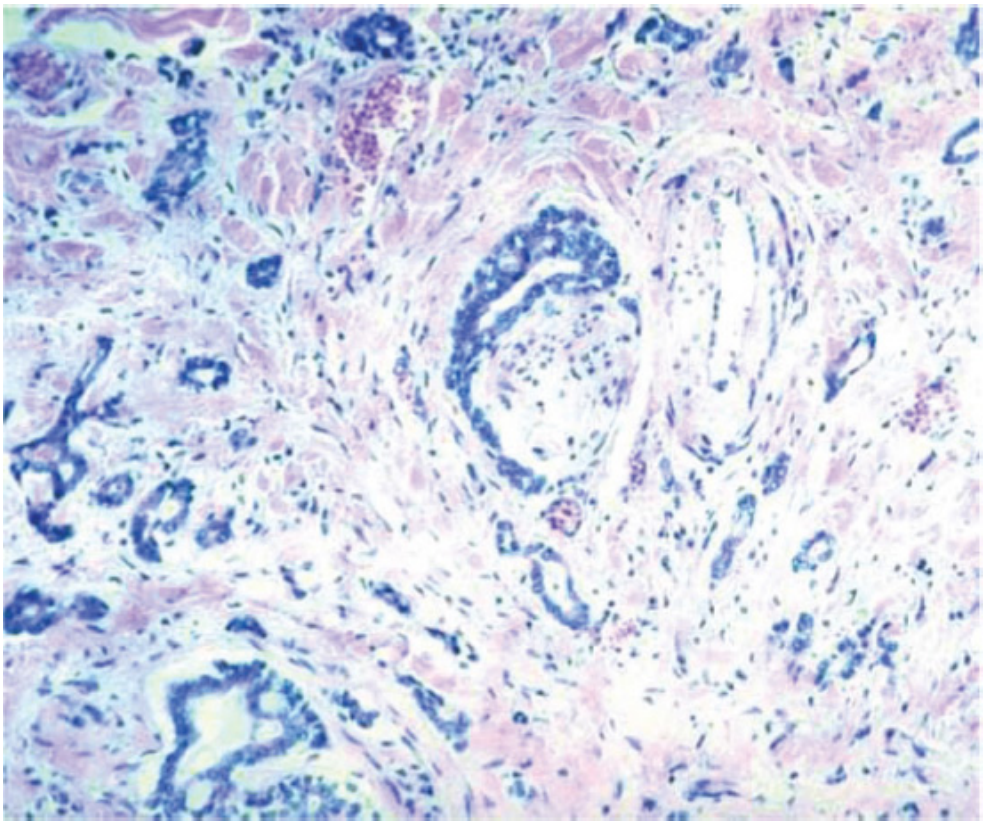

Figure 79.4 Adenoid cystic carcinoma. A photomicrograph demonstrates perineural infiltration of the tumor. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999.)

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinomas are slowly growing malignant tumors that arise from the submucosal glands of the trachea and main bronchi (**Fig. 79.4**). They have also been called cylindromas, adenoid cystic basal cell carcinomas,

adenomyoepitheliomas, and pseudoadenomatous basal cell carcinomas. Adenoid cystic carcinomas behave much like the major and minor salivary gland tumors, to which they are microscopically identical. An important aspect of their clinical behavior is that they tend to spread in the submucosal plane along the perineural lymphatics, well beyond the obvious endoluminal component of the tumor. In a small biopsy specimen, it can be difficult to distinguish adenoid cystic carcinoma from a conventional adenocarcinoma.

Immunohistochemical stains may assist the pathologist to differentiate the two by showing the presence of the myoepithelial cell immunophenotype in adenoid cystic carcinoma.[79] Whenever possible, total excision by tracheal resection or tracheobronchial resection is the treatment of choice.[80–83] This is not always possible because of the extensive submucosal spread of tumor. In such cases, the tumor should be resected with grossly negative margins along with adjuvant radiation since these tumors are radiation sensitive.

When resection is not feasible because of the extent of the lesion or the functional status of the patient, a palliative treatment option is endoscopic laser removal followed by radiation (brachytherapy, external beam irradiation, or both). When complete resection is possible, the prognosis is excellent. However, because of the indolent nature of adenoid cystic tumors and its responsiveness to radiation, prolonged survival is possible even with incomplete resection or palliative measures. Patients frequently live 10 years or more with persistent disease, including pulmonary metastases. In such cases, repeated efforts at palliation are indicated.

MUCOEPIDERMOID CARCINOMA

Mucoepidermoid carcinomas may be low-grade or high-grade malignancies and have the same microscopic appearance as mucoepidermoid tumors of salivary gland origin. These tumors also arise in the glandular submucosa, presenting as submucosal lesions. The distinction between a low-grade and a high-grade tumor is based on mitotic activity, cellular necrosis, and nuclear pleomorphism.[84] The principles of treatment of mucoepidermoid tumors are similar to those of carcinoid tumors. The more malignant variety must be treated as a bronchogenic carcinoma. Some authors even think that adenosquamous carcinoma is the same entity as mucoepidermoid carcinoma,

but arising in the periphery of the lung.[84] The prognosis for these tumors depends on the grade of malignancy and the stage of the disease. High-grade mucoepidermoid tumors have the same prognosis as bronchogenic carcinoma. Complete surgical resection with negative margins is the mainstay of treatment. Mucoepidermoid tumors are too rare to permit an evaluation of combined modality therapy for more aggressive, high-grade tumors.

Hamartoma

7 Pulmonary hamartomas are benign neoplasms composed of predominantly of chondroid and mesenchymal components and are classified as true pulmonary neoplasms.[1] Pulmonary hamartomas are the most common benign lung tumor and account for up to 7% of solitary lung nodules. They occur more commonly in male patients and have a peak incidence in the fifth to seventh decades of life.[85] The clinical presentation of pulmonary hamartomas is typically asymptomatic and they are usually detected incidentally. Larger tumors can present with cough, hemoptysis, chest pain, and postobstructive pneumonia. Hamartomas in the lung are typically located in the periphery of the lung and are well-circumscribed with smooth borders.[86] Approximately 8% of pulmonary hamartomas can be located in the central airways within the bronchus. In general, hamartomas in the lung are indolent and slow-growing neoplasms. The average growth rate of these benign lung neoplasms has been shown to be 3.2 mm, 0.8 mm, to 5.8 mm per year.[87]

Pulmonary hamartomas typically appear as solitary, peripheral, well-circumscribed lung nodules with characteristic smooth borders. Calcification is present in 10% to 30% of hamartomas of the lung although fat can be present in up to 50% of lesions.[88] CT scan can be an effective diagnostic tool for hamartomas of the lung. Small peripheral and well-circumscribed lung nodules with calcification are pathognomonic for pulmonary hamartomas.[89] MRI can identify a common cleft-like architecture of a pulmonary hamartoma which can increase the confidence of the diagnosis.[90] Endobronchial hamartomas are easily identified with flexible fiberopetic bronchoscopy. CT-guided FNA is the most effective modality for obtaining a histologic diagnosis of pulmonary hamartoma. The diagnostic yield is as high as 85%.[91]

The presence of fibromyxomatous tissue and fragments of cartilage are diagnostic of hamartoma.

The management of pulmonary hamartomas depends on the clinical presentation. The benign tumor typically has slow growth and is asymptomatic. Follow-up with a CT scan of the chest annually is recommended. Patients with a diagnosis of a pulmonary hamartoma are very unlikely to develop symptoms or malignant transformation during their lifetime even without surgical resection.[92] When patients present with pulmonary hamartomas with associated symptoms or lesions with concerning growth rates, surgical resection may be indicated. Limited resections with a wedge resection with negative margins can be achieved for small peripheral pulmonary hamartomas with thoracoscopic or robotic approaches.[93–96] Pulmonary lobectomy is reserved for surgical resection of large, centrally located pulmonary hamartomas.

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80

Nonneoplastic Thoracic Disease

Rishindra M. Reddy

Key Points

1. Surgical intervention for chest wall tumors depends on the type of lesion and goals of surgery (resection vs. diagnosis). Reconstruction varies depending on the size of the defect and location on the chest wall.
2. Thoracic outlet syndrome (TOS) may be arterial, venous, or neurogenic. Neurogenic TOS is the most difficult to diagnose and surgery for this should be performed in high-volume centers.
3. The primary treatment for a lung abscess is antibiotic therapy.
4. Hemoptysis can be life threatening from suffocation due to a low volume of blood in the lungs, not from blood volume loss requiring transfusion.
5. Primary spontaneous pneumothoraces will recur in only 30% of patients after initial treatment. When they recur, the treatment should include a thoracoscopic evaluation and possible pleurodesis.
6. Transudative pleural effusions should be treated medically, while exudative effusions may need more intervention. One-quarter of pleural effusions in a community hospital are due to malignancy.
7. Empyema is a part of a spectrum of disease that may be treated early on with drainage alone, but may require debridement and decortication in more advanced cases.
8. Complications of tracheostomies are usually due to improper placement of the tracheostomy on the trachea (below the 3rd ring, risking a tracheoinnominate fistula) or to the use of high pressures in the cuff of the tracheostomy (causing ischemia and long-term stenosis).
9. Mediastinitis is life threatening and warrants immediate evaluation, antibiotic therapy, and surgical drainage.

INTRODUCTION

This chapter is meant as resource for the general surgery community and surgery residents with regard to pathology in the chest. We will cover a wide variety of topics including most noncardiac congenital disease processes in the thorax.

CHEST WALL ANATOMY

The chest wall is the musculoskeletal structure that contains and protects the structures of the upper trunk or thorax. There are two openings to the thorax, the superior aperture, or the thoracic inlet, and the inferior aperture, which leads to the abdominal cavity. The head and arms connect to the intrathoracic structures via the inlet, whereas the diaphragm separates the thoracic and abdominal cavities at the inferior aperture. The inferior vena cava, esophagus, and aorta travel to the abdomen through the diaphragm at levels T8, T10, and T12, respectively.

The sternum, commonly known as the breast bone, is comprised of three parts, the manubrium, the body, and the xiphoid. The manubrium attaches to the clavicles and the first costal cartilages. The sternal angle, also called the angle of Louis, refers to connection between the manubrium and the sternal body and is an important landmark. The second ribs attach to the sternum at this angle and they allow one to count the ribs from this point down, as the first ribs are not palpable. The body of the sternum contains articular facets for ribs 2 to 7 and connects to the cartilaginous xiphoid inferiorly. The xiphoid may be bifid and will eventually ossify in older adults (**Fig. 80.1**).

The ribs are split into two groups; the upper 7 pairs are the true ribs, with articulations to the sternum, while the lower 5 pairs are the false ribs. Ribs 8, 9, and 10 connect to each other and the upper ribs via their costal cartilage. Ribs 11 and 12 are called floating ribs as they have no anterior connection. Rib 1 is uniquely shaped as it is flat, short, and extremely curved. Ribs 2 through 10 have a more standard configuration with the head containing articular facets for the vertebrae. After the neck, the tubercle contains the facet for the vertebral transverse process. The costal groove along the inferior portion of the shaft houses the intercostal bundle, consisting of the nerve, artery, and vein (**Fig. 80.2**). Because of this inferior placement, most chest wall procedures such as thoracostomy tube placement or

thoracentesis should be aimed at the superior aspect of the rib to avoid injury to this bundle.

There are three intercostal muscles, the external intercostal, the internal intercostal, and the innermost intercostal muscle. The intercostal bundle lays just external to the innermost intercostal layer (**Fig. 80.3**). On the inner aspect of the chest wall, the internal thoracic (mammary) artery and vein run between the innermost intercostal muscle and the transversus thoracic muscles which connect the ribs to the lower half of the sternal body. The intercostal arteries have two sources, posteriorly from the descending thoracic aorta and anteriorly from the internal thoracic arteries. The intercostal nerve is a branch off the ventral ramus after it joins the sympathetic trunk. The intercostal veins follow the arteries and posteriorly drain into the azygos and hemiazygos veins. Lymphatic drainage from the posterior chest wall drains into the thoracic duct on the left and into the right lymphatic duct on the right.

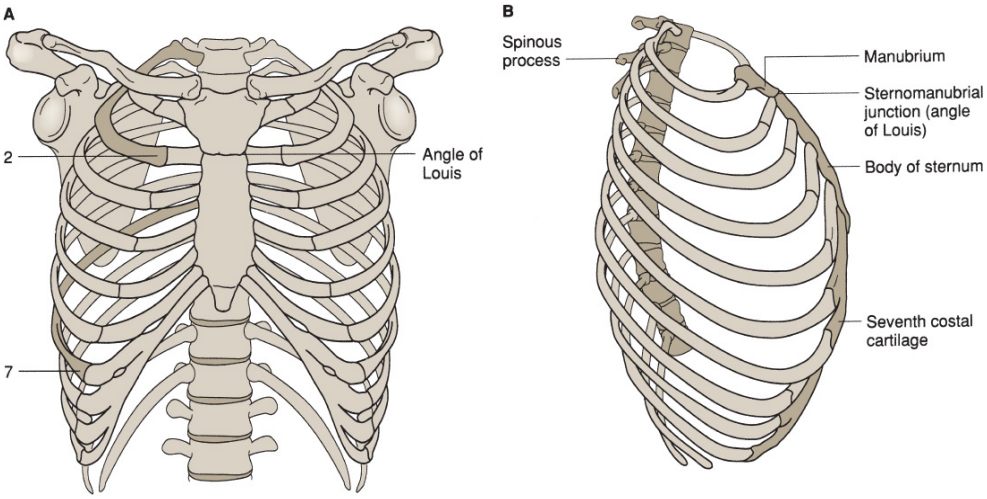


Figure 80.1 Skeletal support of the thorax. Anterior (**A**), and lateral (**B**), views. Note the anterior cartilaginous component of the upper 10 ribs, the fused costal cartilages of ribs 7 through 10, the location of the sternomanubrial junction (angle of Louis) at the level of the second rib, and the oblique course of the ribs laterally from posterior to anterior.

The muscles of the chest wall can be divided embryologically into those from the epimeres, such as the deep back muscles, innervated by the dorsal rami, and those from the hypomeres, such as the intercostals and rectus, innervated by the ventral rami. The musculature can also be classified based

on respiratory function, where the primary muscles of respiration are the intercostals and the diaphragm, and the secondary, or accessory muscles are the sternocleidomastoid, scalenes, pectoralis, serratus, and abdominal wall musculature. The major back muscles include the trapezius and latissimus dorsi (**Fig. 80.4**). In normal breathing, the diaphragm performs a majority of the work with the intercostals supplying about a quarter of the workload. In full inspiration, the pleura extends bilaterally down to the level of the 11th and 12th ribs (**Fig. 80.5**).

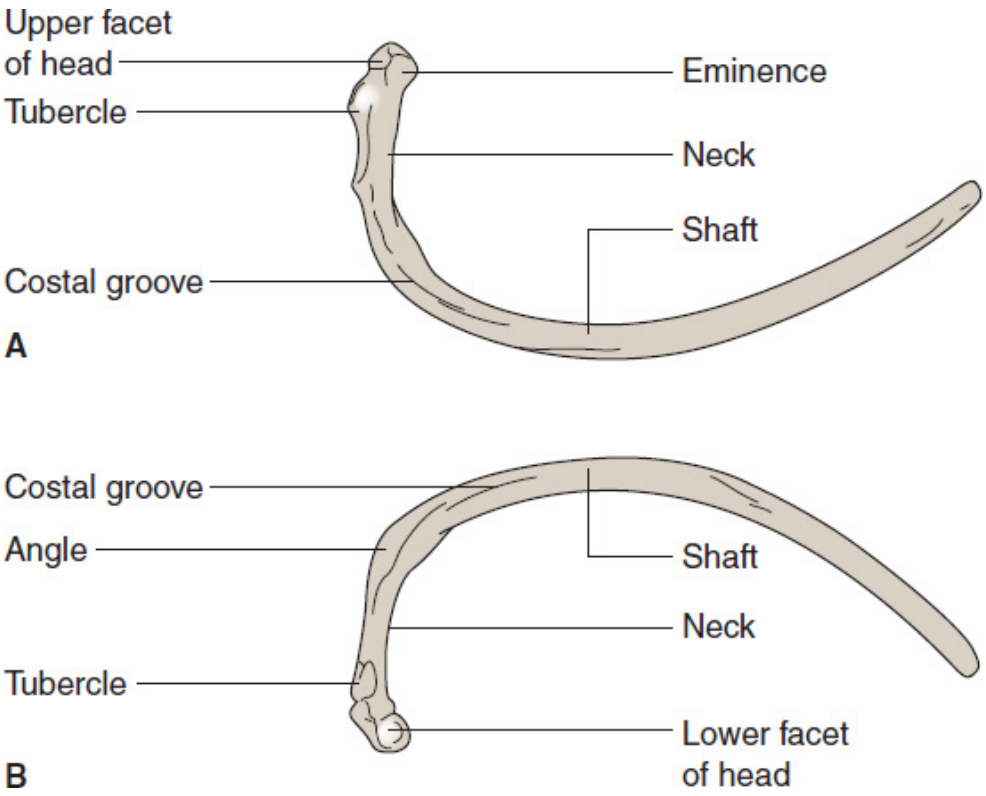


Figure 80.2 Anatomy of ribs 2 to 10 as viewed from above (**A**), and below (**B**).

CHEST WALL NEOPLASMS

Chest wall tumors are very rare. Lesions may be divided into benign and malignant, and then further subdivided into soft tissue versus bony/cartilaginous tumors (**Table 80.1**). Most malignant tumors of the chest wall are either metastatic from carcinomas or sarcomas arising in other sites of the body, or from local extension of lung cancers or breast cancers.[1]

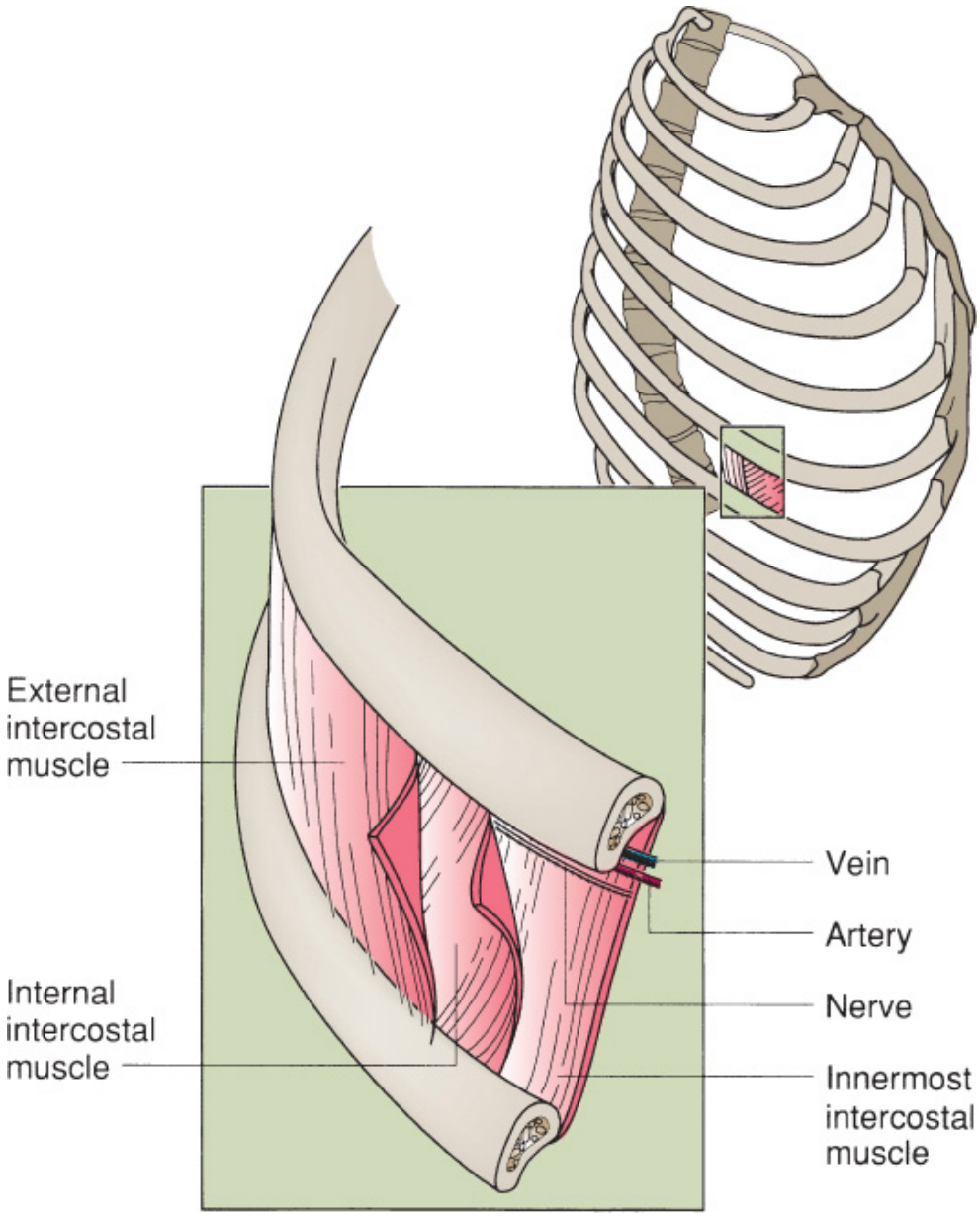


Figure 80.3 Anatomy of the intercostal space. The major intercostal muscles are the external and internal. The neurovascular bundle courses in the costal groove along the inferior aspect of the rib.

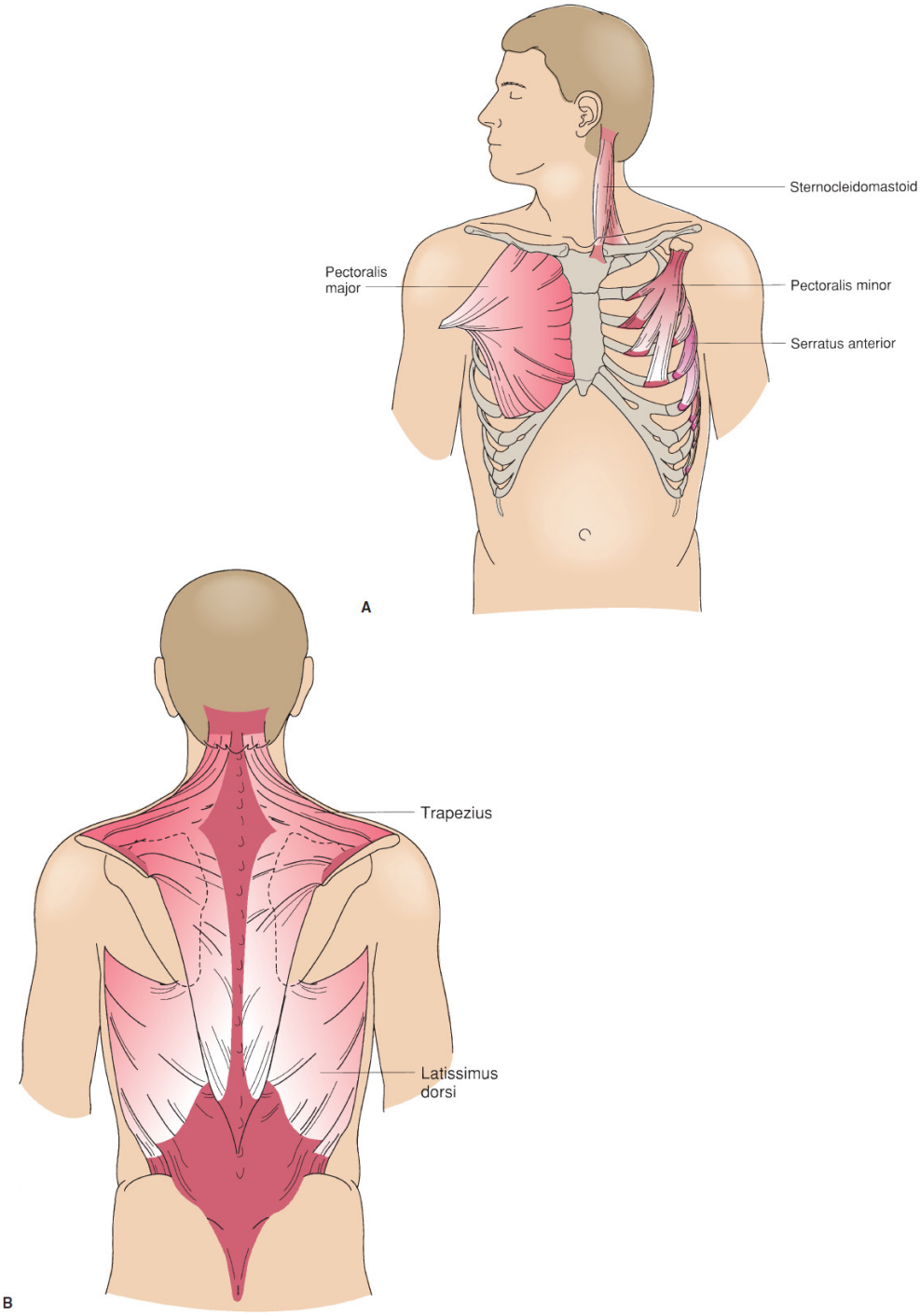


Figure 80.4 Thoracic musculature. Anterior (**A**), and posterior (**B**), views.

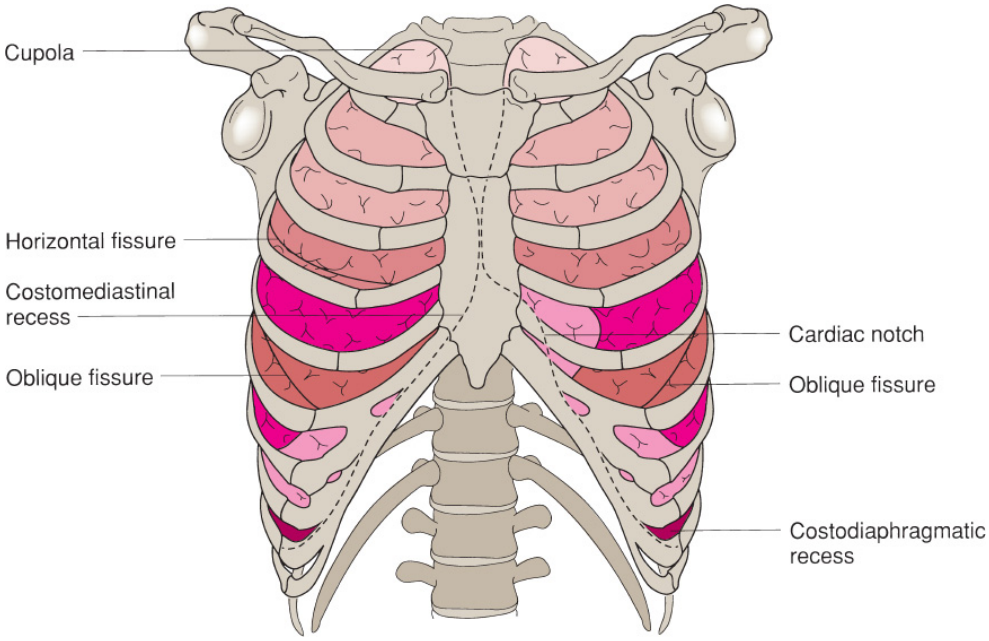


Figure 80.5 Topographic relations of the pleura to the chest wall. Laterally, the pleura extends to the level of the 11th to 12th ribs. The anterior reflection of the mediastinal and costal pleurae forms the costomediastinal recess, whereas the reflections of the costal and diaphragmatic pleurae form the costodiaphragmatic recess.

Table 80.1 Chest Wall Tumor Classification

- Benign tumors
  - Soft tissue tumors
    - Lipomas
    - Fibromas
    - Hemangiomas
    - Neurofibromas
    - Granulomas
    - Inflammatory tumor
    - Tuberculoma
  - Bony/cartilaginous tumors
    - Osteochondromas
    - Chondromas
    - Fibrous dysplasia
    - Eosinophilic granuloma
    - Osteoid osteomas
    - Osteomyelitis
    - Chondro/osteoblastomas

- Malignant tumors
  - Soft tissue tumors
    - Melanomas and other cutaneous cancers
    - Sarcomas
    - Desmoid tumors/low-grade fibrosarcomas
    - Lymphoma
    - Malignant fibrous histiocytoma
  - Bony/cartilaginous tumors
    - Chondrosarcomas
    - Osteogenic sarcomas
    - Ewing sarcomas
    - Solitary plasmocytoma
    - Lymphoma

- Metastatic tumors
  - Breast cancer
  - Lung cancer
  - Mediastinal tumors

Mesothelioma
Other sarcomas or carcinomas

Almost all lesions will present as a mass, as pain, or as a combination of both. Occasionally, they will be asymptomatic and be identified on imaging for cancer surveillance or other reasons.[2] Evaluation of these lesions includes a thorough history and physical and appropriate imaging, which may begin with plain radiographs, but should include three-dimensional imaging such as a CT scan and/or MRI as well as PET scan for staging if clinically indicated.[1]

Surgical intervention depends on the type of lesion and the goal of surgery. Tumors that are suspected metastases may require only a needle or an incisional biopsy to confirm the diagnosis. Lesions that are possible primary tumors, whether benign or malignant, require excisional biopsies. Some low-grade malignant tumors may be underdiagnosed and considered benign if the entire specimen is not removed and examined. If a tumor is proven to be a primary malignant lesion, wide excision is required, with margins up to 4 cm.[3]

BENIGN SOFT TISSUE TUMORS

These tumors include lipomas, fibromas, hemangiomas, and neurofibromas among others. These can be removed by excisional biopsy and require no further treatment unless they recur. Inflammatory osteomyelitis can mimic tumors by causing pain.

BENIGN BONY/CARTILAGINOUS TUMORS

About two-thirds of benign chest wall tumors are either osteochondromas, chondromas, or fibrous dysplasia, with osteochondromas comprising almost 50% of all nonmalignant rib tumors. Osteochondromas usually present as painless masses with a male-to-female predominance of 3:1. If the lesion becomes painful it may indicate malignant degeneration.[3] They are often

found on routine radiographic examinations for other reasons and have a characteristic appearance of a pedunculated bony prominence (**Fig. 80.6**).

Figure 80.6 Osteochondroma of left second rib. The stippled calcification within the tumor and the intact cortex of the rib are characteristic.

Chondromas account for 15% of benign rib lesions and grow from the cartilage at the sternocostal junction.[1] They have an equal male-to-female incidence. Clinically and radiographically, it is impossible to distinguish chondromas from chondrosarcomas. It can be difficult microscopically to distinguish chondromas from low-grade chondrosarcomas as well. As a

result, all chondromas must be treated as if they are potentially malignant and require complete excision.[3]

Fibrous dysplasia arises in the lateral portion or shaft of the rib and can have a "soap bubble" or "ground-glass" appearance on radiographs (**Fig. 80.7**). These lesions may become painful if they enlarge and can result in rib fractures. Surgical excision is needed for diagnosis and symptom relief.[4] Eosinophilic granulomas and osteoid osteomas are rare conditions that affect men more often. Patients may have multiple granulomas, including the skull and may benefit from radiotherapy as opposed to surgical resection. Osteomas may be symptomatic and if so, should be resected.

MALIGNANT SOFT TISSUE TUMORS

These lesions can range from melanomas to desmoid tumors to malignant fibrous histiocytomas (MFHs). Sarcomas also arise in the soft tissue of the chest wall, but they comprise less than 10% of all sarcomas.[2] Desmoid tumors are borderline lesions between a benign and malignant classification, and are sometimes considered low-grade fibrosarcomas.[1] Almost half of all desmoids occur in the chest wall and shoulder where they can encapsulate the brachial plexus. They require wide local excision and have a high rate of recurrence. If they encircle vital structures, they can be treated with radiotherapy after surgical excision.[3]

MFHs are the most common primary chest wall tumors. They are more frequent in men (2:1 ratio) and generally occur after the age of 50. They are slow growing, painless, and spread along the facial planes or between muscle fibers. MFHs are unresponsive to other forms of therapy and require wide local excision. Because of the lesion's propensity for fascial plane infiltration, there is a high rate of recurrence following resection and patients who have undergone resection have a 5-year survival of under 40%.[3] Rhabdomyosarcoma is the second most common soft tissue lesion of the chest wall and usually occurs in children and younger adults. It grows rapidly from the striated muscle, but is usually painless. It is treated with wide excision followed by radiation and chemotherapy with a reported 70% survival at 5 years.[3]

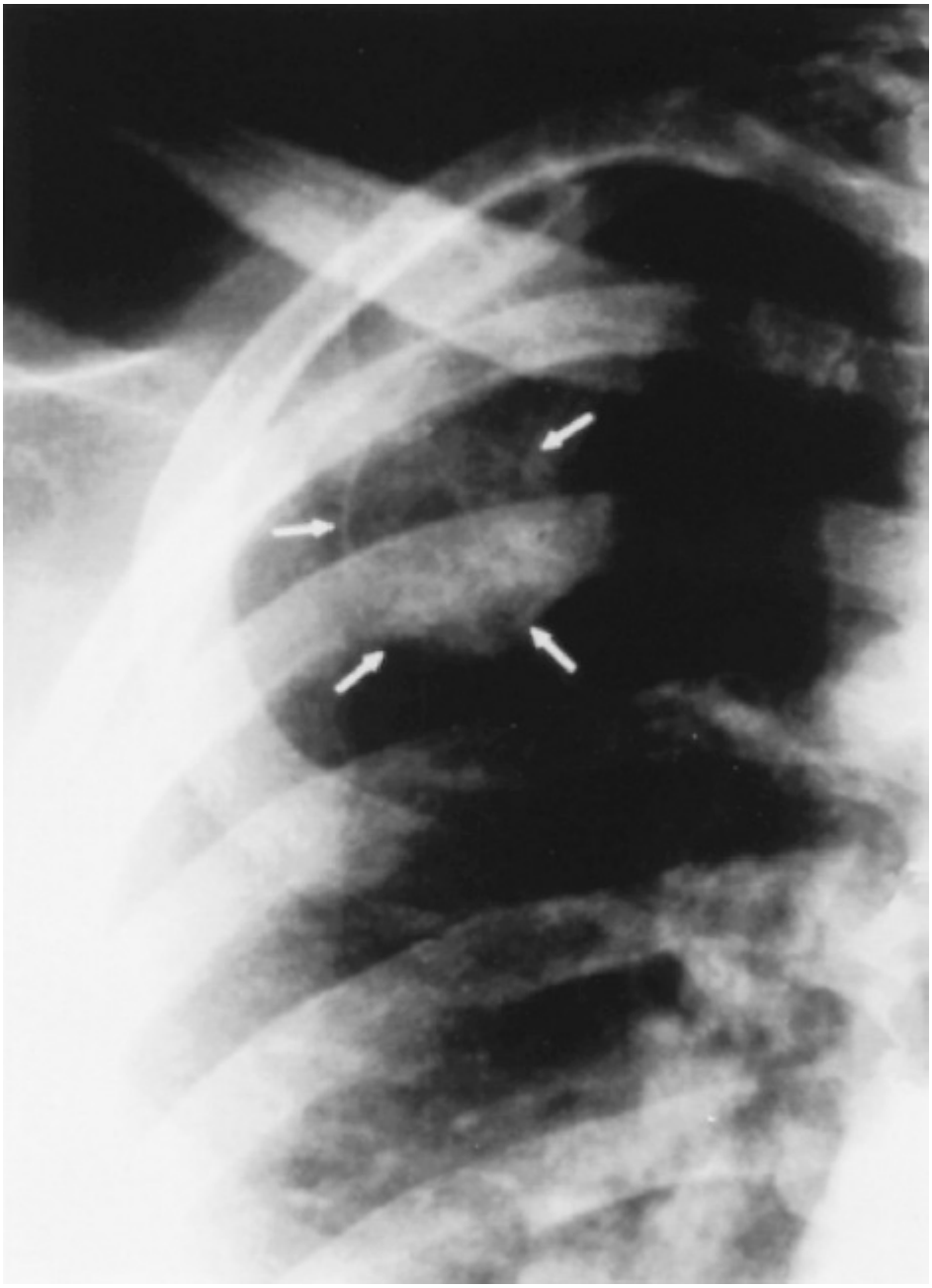


Figure 80.7 Fibrous dysplasia of the rib. Note the characteristic expansion and thinning of the cortex (*arrows*) and the central ground-glass appearance.

MALIGNANT BONY/CARTILAGINOUS TUMORS

Chondrosarcomas are the most common primary malignant bony tumors, accounting for 20% to 30% of lesions. These are well-differentiated tumors and on microscopic examination may be difficult to distinguish from their benign counterparts. Local recurrence can occur after excision and if untreated, distant metastases can develop.[3] Osteogenic sarcomas are more common in the limbs, but also occur in the ribs. Radiographs depict a characteristic "sunburst" pattern. These tend to grow quickly and often have metastases at the time of initial presentation. Patient evaluation should include a CT scan and bone scan to check for the presence of metastatic disease. Surgery with adjuvant chemotherapy is the treatment of choice for local disease.[5] Ewing sarcomas constitute 5% to 10% of chest wall tumors. They occur in children and younger adults with a male-to-female ratio of 1.6:1. Symptoms include pain, fever, and fatigue. Radiographs show a large soft tissue mass with bony destruction. Patients often present with metastatic disease, and ultimately three-quarters of patients will develop metastases. Multimodality treatment is the key to treatment. Survival may be less than 30% at 5 years in patients with metastatic disease.[6]

Solitary plasmocytoma is a rare tumor of the plasma cells and can be part of a systemic disease in multiple myeloma. Lesions can be painful and usually occur in men over the age of 50. X-ray findings show cortical destruction of the rib (**Fig. 80.8**). In the setting of systemic disease, only a needle biopsy may be needed, but if the lesion is small and symptomatic, resection can be offered. For larger lesions, radiotherapy is the primary treatment.[1]

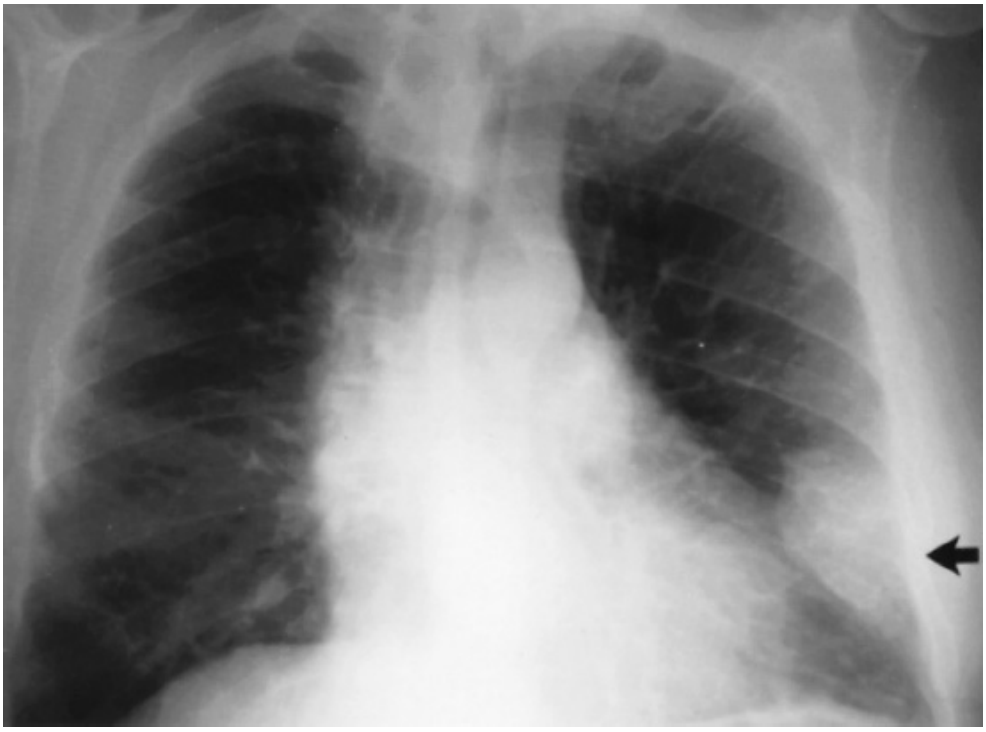


Figure 80.8 Plasmacytoma of the left seventh rib, showing characteristic cortical destruction and relatively large soft tissue component projecting into the chest.

METASTATIC TUMORS

As discussed before, metastatic lesions can arise from a variety of other cancers, and treatment depends on the primary histology, time to recurrence, and goals of intervention. For isolated metastases with a long interval before recurrence, surgical resection may be warranted. Each case should be individualized and discussed within a multidisciplinary team.

CHEST WALL RECONSTRUCTION

Chest wall defects can result from cancer, radiation, trauma, or infection.[7] The goals of repair are to provide stabilization and protection to the thoracic cavity, to minimize complications of respiration due to a flail 1 chest, and to provide cosmetic coverage as needed. Size and location generally determine the need for chest wall stabilization. Defects less than 5 cm anywhere in the chest wall, or defects less than 10 cm in the posterior chest wall that are

anterior to the scapula do not usually need stabilization.[7,8] An alternative criterion is to use the number of ribs resected, and to avoid stabilization when a portion of three ribs or less has been removed.[9] Techniques for closure of the defect include utilizing absorbable Vicryl mesh, used in the setting of infection or if small defects are present. This approach does not provide any stabilization. More definitive repairs utilize polytetrafluoroethylene (PTFE), polypropylene methylmethacrylate (PPM) sandwich mesh, or titanium-plating systems.[10] PTFE is a flexible, soft material, while the PPM sandwich mesh resembles a hardened piece of plaster between two portions of woven mesh. Different surgeons prefer different approaches, but some of the benefits cited for the PTFE repair include greater stretch and the ability to create a water tight seal.[7] The PPM sandwich repair on the other hand allows the ability to mold the prosthetic and provides a firmer stabilization (**Fig. 80.9**).[10] Mortality rates from chest wall reconstruction in the setting of cancer resections have been reported at 4% in multiple series.[7,9]

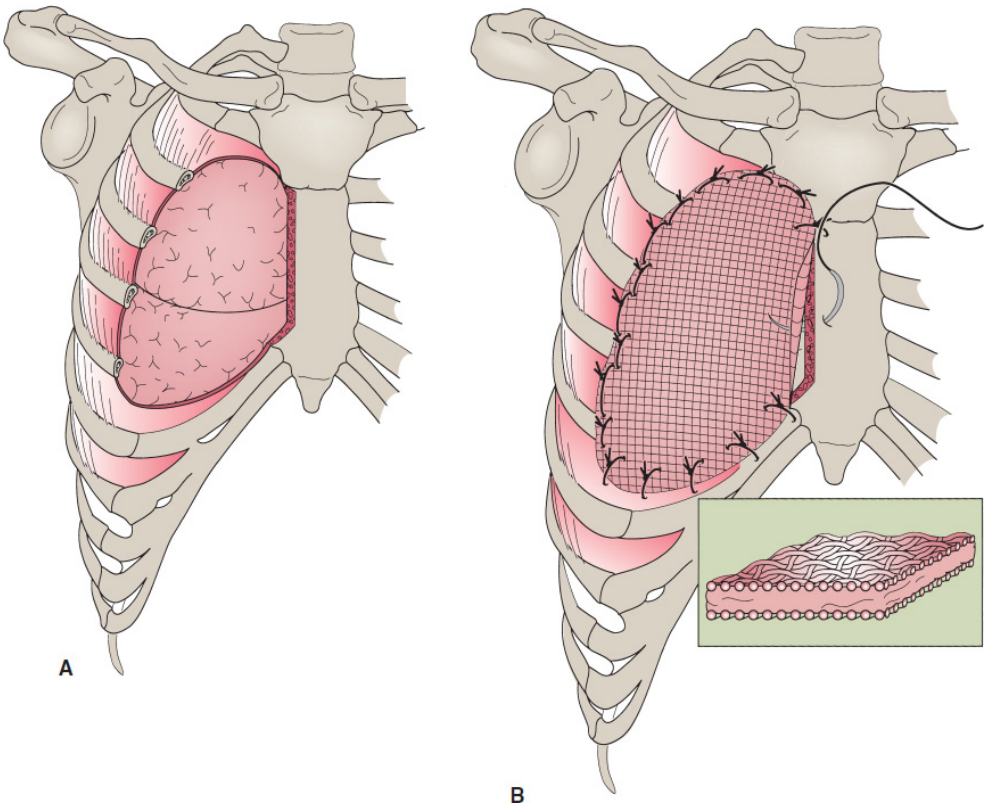


Figure 80.9 Marlex methylmethacrylate sandwich technique for chest wall reconstruction. **A:** Upper anterior chest wall defect resulting from resection of ribs two to five and a portion of sternum. **B:** Marlex methylmethacrylate prosthesis being sutured in place. Heavy, nonabsorbable sutures either encircling the ribs or passed through the sternum are used to anchor the prosthesis in place. *Inset:* Detail of prosthesis showing sandwich of hardened methylmethacrylate between two sheets of Marlex.

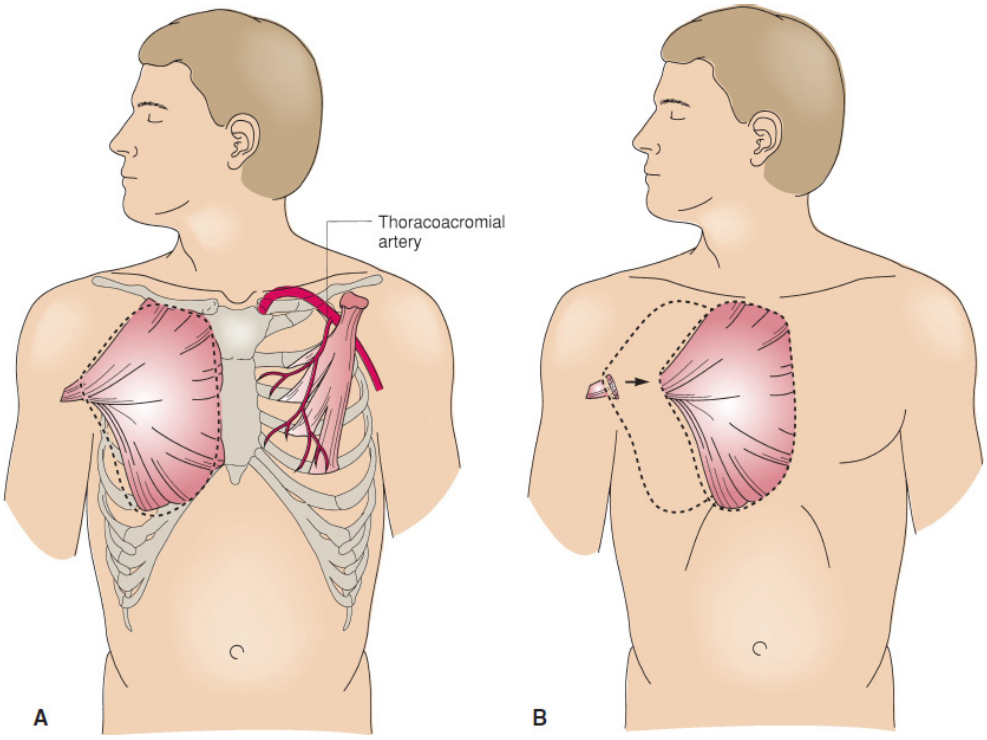


Figure 80.10 Pectoralis major muscle rotation flap. **A:** Mobilization of the flap by detaching the clavicular, sternal, and chest wall origins as well as the insertion of the muscle on the greater tubercle of the humerus. The dominant blood supply, the thoracoacromial artery, which arises from the axillary artery medial to the proximal border of the pectoralis minor muscle, is shown on the left side where the pectoralis major muscle has been removed. **B:** Medial transposition of the muscle flap, preserving the thoracoacromial neurovascular bundle.

Flap coverage of the soft tissue defect will almost always require the assistance of a plastic surgeon, and they should be involved preoperatively in the planning of a chest wall resection and reconstruction. The decision-making process for which flap to use depends on the location of the defect, the size of the defect, the corresponding size of the flap, and its vascular source. Pectoralis major flaps are the most common in the upper chest/neck region. Its blood source can be from the thoracoacromial artery or from intercostal perforators from the internal thoracic arteries (**Fig. 80.10**). The latissimus dorsi flap is also commonly used for large, ipsilateral defects. Its blood source is from the thoracodorsal artery or from perforators from the posterior intercostal vessels. It has a large arc of rotation from the thoracodorsal pedicle and can cover a wide area of the chest wall (**Fig. 80.11**). Also commonly used are rectus abdominal muscle flaps in either a vertical (VRAM) or transverse (TRAM) orientation (**Fig. 80.12**).

External obliques can be used on the lower anterior chest wall, and the trapezius can be used in the mid back.[11] Omental flaps are extremely useful and versatile. They can be used to cover large defects or to fill cavities, such as the pleural space in the setting of a bronchopleural fistula and empyema. The omentum can be taken off of the right or left gastroepiploic artery, but using the right arterial source allows a greater arc of rotation than from the left. The limitations of this flap are that it requires a laparotomy, although laparoscopic techniques have been described,[12] and that the size of the omentum can be variable, and difficult to assess preoperatively (**Fig. 80.13**).[11]

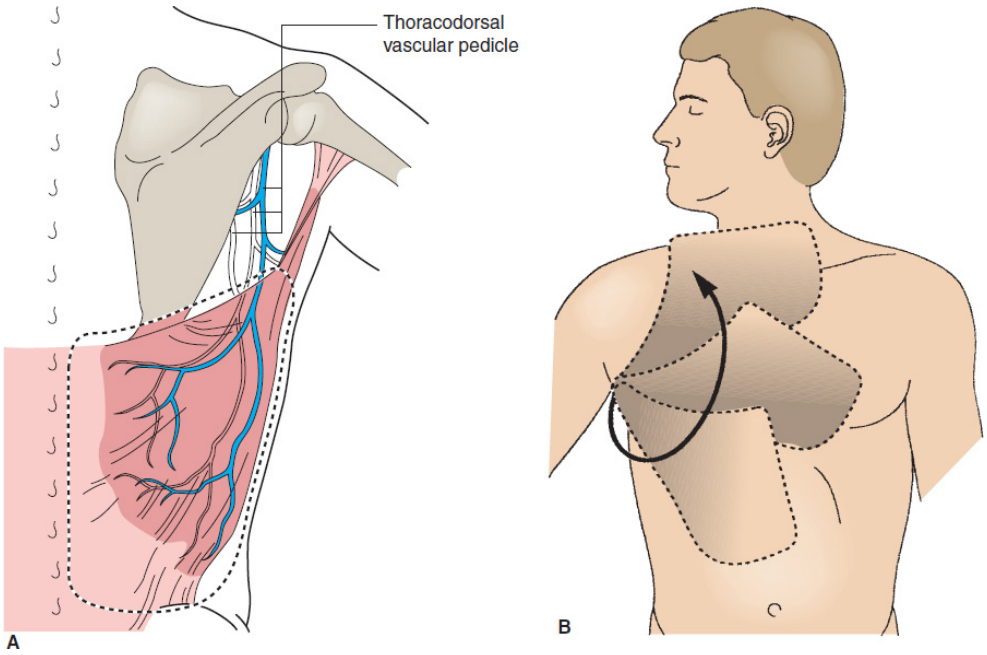


Figure 80.11 Latissimus dorsi muscle rotation flap for chest wall reconstruction. **A:** Posterior view showing detachment of the origins of the muscle. The dominant blood supply, the thoracodorsal artery, is preserved. **B:** Anterior view showing the extent to which the mobilized muscle reaches.

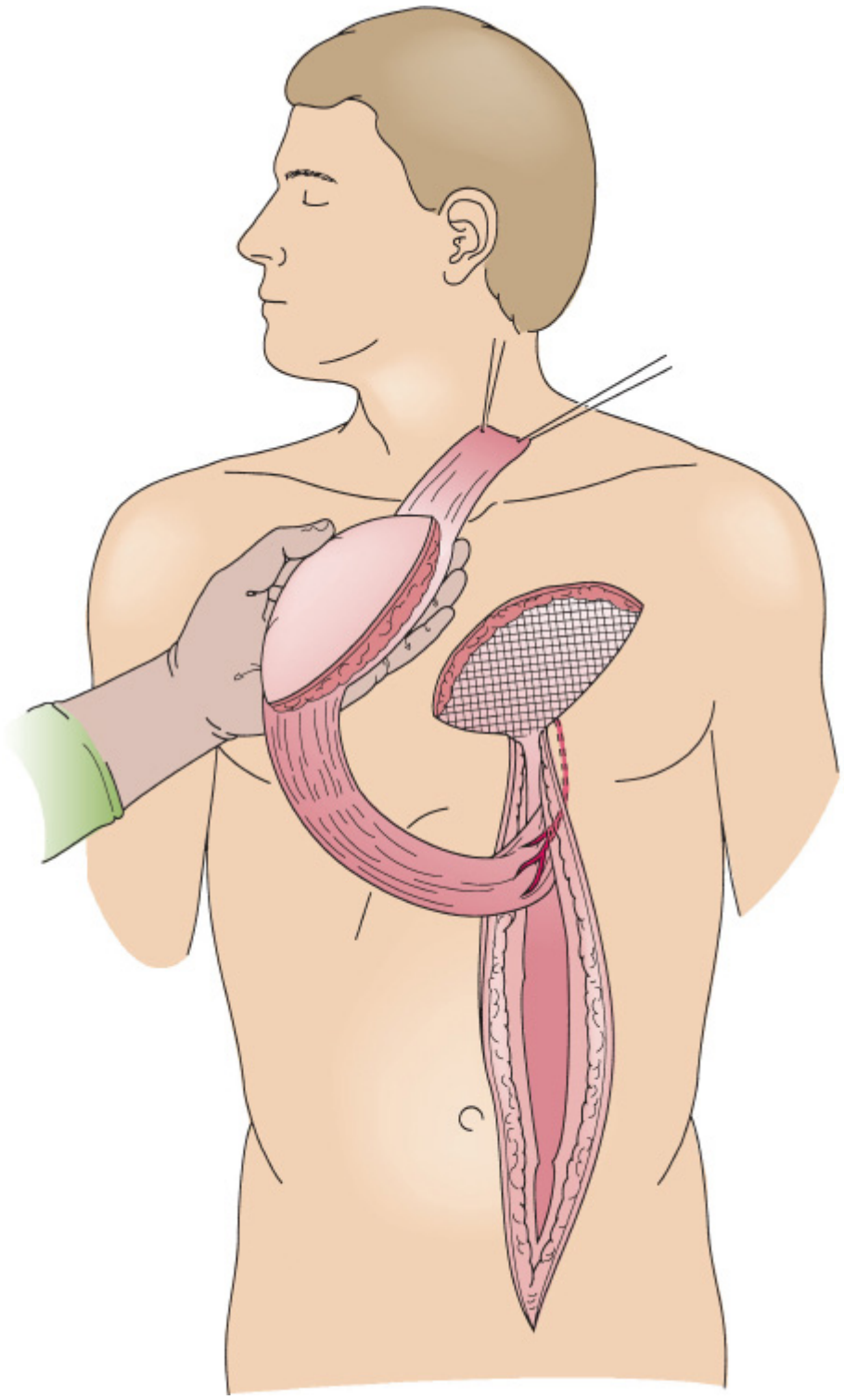


Figure 80.12 Rectus abdominis muscle rotation flap. Shown is the mobilization of the rectus abdominis muscle, which is based on the superior epigastric artery (the continuation of the internal thoracic artery), and rotation of the muscle and overlying skin to fill an anterior chest wall defect.

CHEST WALL CONGENITAL ABNORMALITIES AND THORACIC OUTLET SYNDROME

Pectus Excavatum and Pectus Carinatum

Chest wall deformities occur in 1/1,000 live births. They are five times more common in men than women, and up to 6% of people with these deformities will also have a connective tissue disorder. Pectus excavatum is the most common deformity and appears as a sternal depression that can be off midline approximately 50% of the time. Pectus carinatum is the opposite, with a sternal protrusion, often described as a "pigeon chest" deformity. Pectus excavatum is five times more common than pectus carinatum. Scoliosis is frequently seen in this population.[13] Less common deformities include sternal clefts, which are incomplete fusions of the sternum, and Poland syndrome, where there is an absence of a pectoralis muscle and underlying bony support in the chest wall.

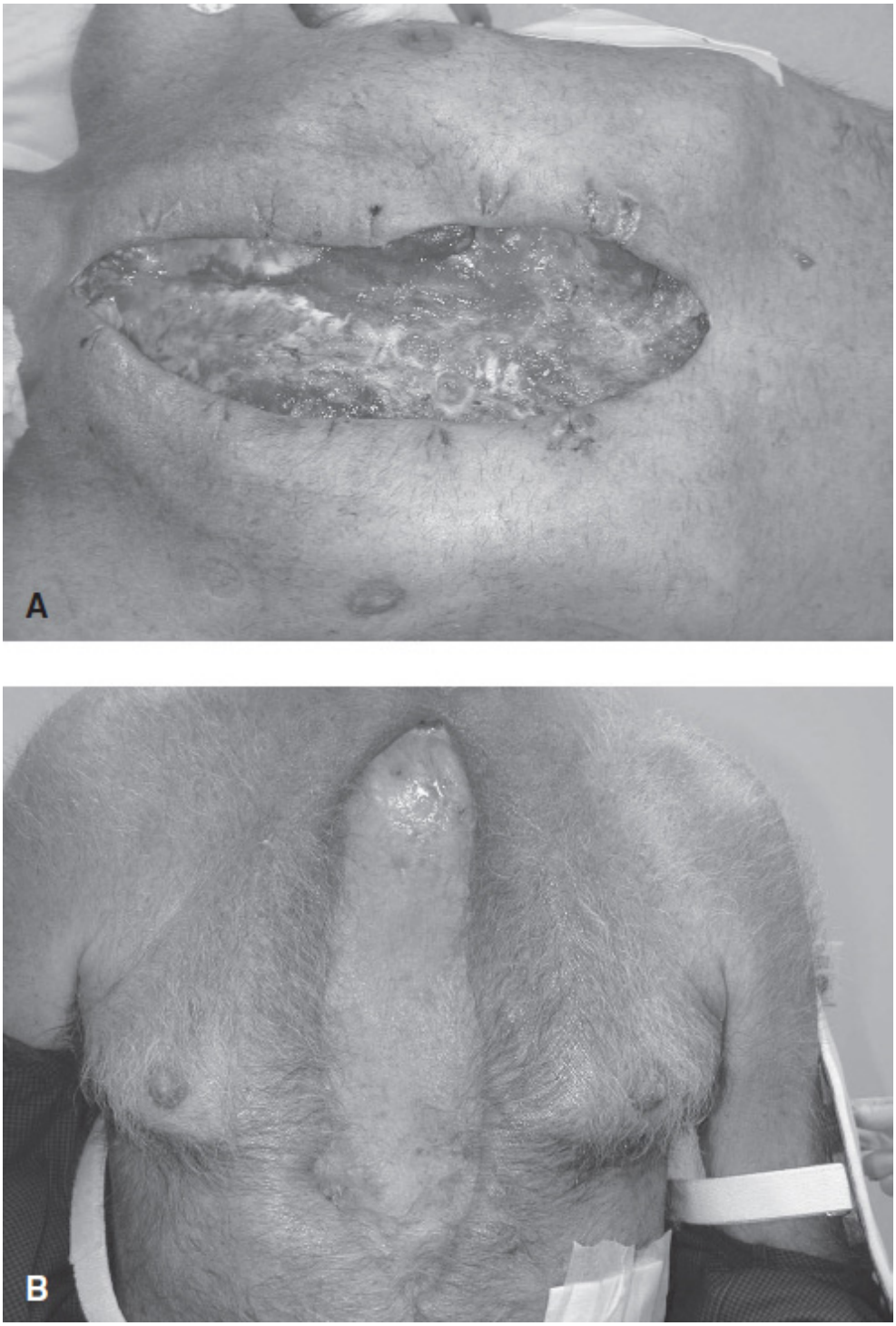


Figure 80.13 The omentum can be used to cover large defects. Shown is an open sternal wound after debridement with failed prior muscle flap (**A**), and wound 6 months after omental flap placement (**B**). (Reproduced with permission from Ghazi B, Carlson G, Losken A. Use of the greater omentum for reconstruction of infected sternotomy wounds: a prognostic indicator. *Ann Plast Surg* 2008;60(2):169–173.)

The techniques for surgical correction of pectus excavatum have been evolving, including the Ravitch and Nuss procedures. Despite this, less than 15% of patients undergo surgery.[14] Most patients present as children with notable deformities. People can be physiologically asymptomatic, but can also present with fatigue, limited stamina, and cardiopulmonary limitations. The workup includes pulmonary function testing, echocardiography, and CT scans. The pectus severity index (Haller index) can be calculated by dividing the inner thorax width by the depth measured from the posterior aspect of the sternum to the anterior aspect of the spine (**Fig. 80.14**). Normal values are 2 to 2.2, and repair is only recommended when the index is at least greater than 3.1.[13,15] The age of the patient at which repair should be performed is also somewhat controversial, as some surgeons advocate waiting until after the age of 10, but many series have reported on a large number of patients treated at a much younger age with good outcomes.[14,16] There is a growing experience with treating adults also, as some patients seek repair at a later age (**Fig. 80.15**).[17,18]

The most commonly used open repair was first described by Dr. Ravitch and is based on removing sections of the deformed cartilage from around the sternum laterally at the ribs, while preserving the perichondrium. Many advocate using a stabilizing bar for a minimum of 6 months, usually placed in an intrathoracic position, to minimize the occurrence of flail chest and to allow the sternum to heal in an anterior position. An essential part of the procedure is a transverse sternal wedge resection through the anterior table to allow the inferior aspect of sternum to bend forward.[13,18] Incisions may be in a vertical midline over the lower half of the sternum or in an inframammary position (**Fig. 80.16**). Recurrences occur in 5% to 10% of patients, with recurrence more common in patients with connective tissue disorders.

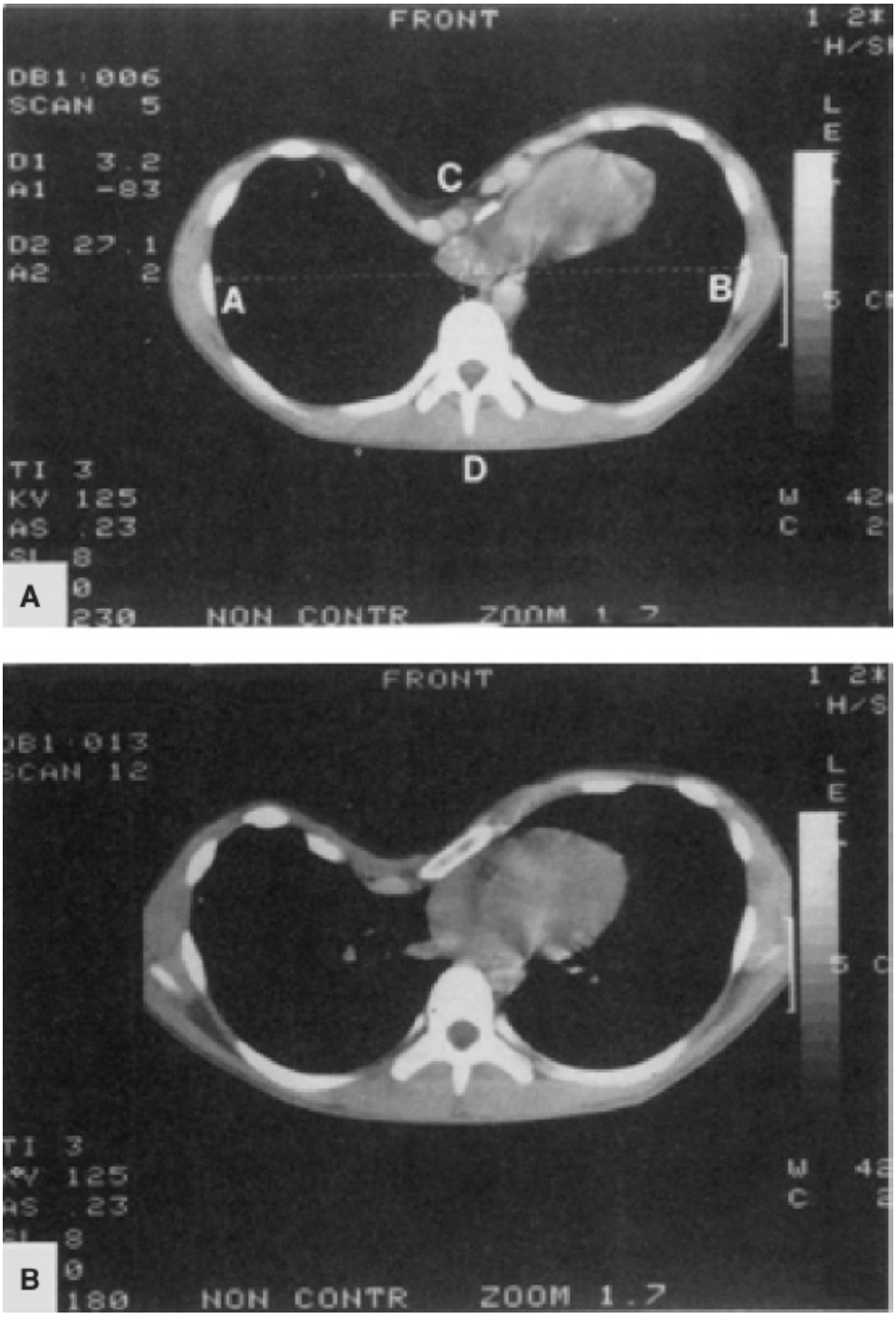


Figure 80.14 Chest CT of pectus excavatum. CT image at xiphoid with A–B (transverse diameter) and C–D (anterior–posterior diameter) indicated for the calculation of the pectus severity index A–B/C–D (**A**). CT image demonstrating angulation of the sternum to the right in the severe defect (**B**). (Reproduced with permission from Haller JA Jr, Scherer LR, Turner CS, et al. Evolving management of pectus excavatum based on a single institutional experience of 664 patients. *Ann Surg* 1989;209(5):578–582.)

Since the 1990s, the Nuss procedure, which utilizes a minimally invasive approach, has been described and performed. The Nuss procedure utilizes one or two stabilization bars, secured to the ribs laterally in multiple points of fixation. It routinely employs thoracoscopy, either unilateral or bilateral. Skin incisions are limited to small lateral locations at the site of the bar insertion and thoracoscopic port sites. In both the Ravitch and Nuss procedures, the stabilization bars stay in for at least 6 months.[19] As the Nuss procedure has grown in popularity, many modifications have been made, including precise shaping of the bars and increased bar stabilization with wire fixation around the ribs to minimize bar displacement.[20]

Pectus carinatum does not have the same cardiac compression concerns as pectus excavatum, but the chest is held in an enlarged position, limiting normal respiration mechanics. Patients can have increased residual lung volumes and their respiratory physiology can mimic emphysema physiology. This can result in breathing difficulties and limited stamina.[18] The Ravitch procedure is most commonly performed to remove the deformed cartilage. Special attention is placed on the transverse sternal osteotomy, to depress the sternum and align it with the anterior ribs (**Fig. 80.17**).[13]

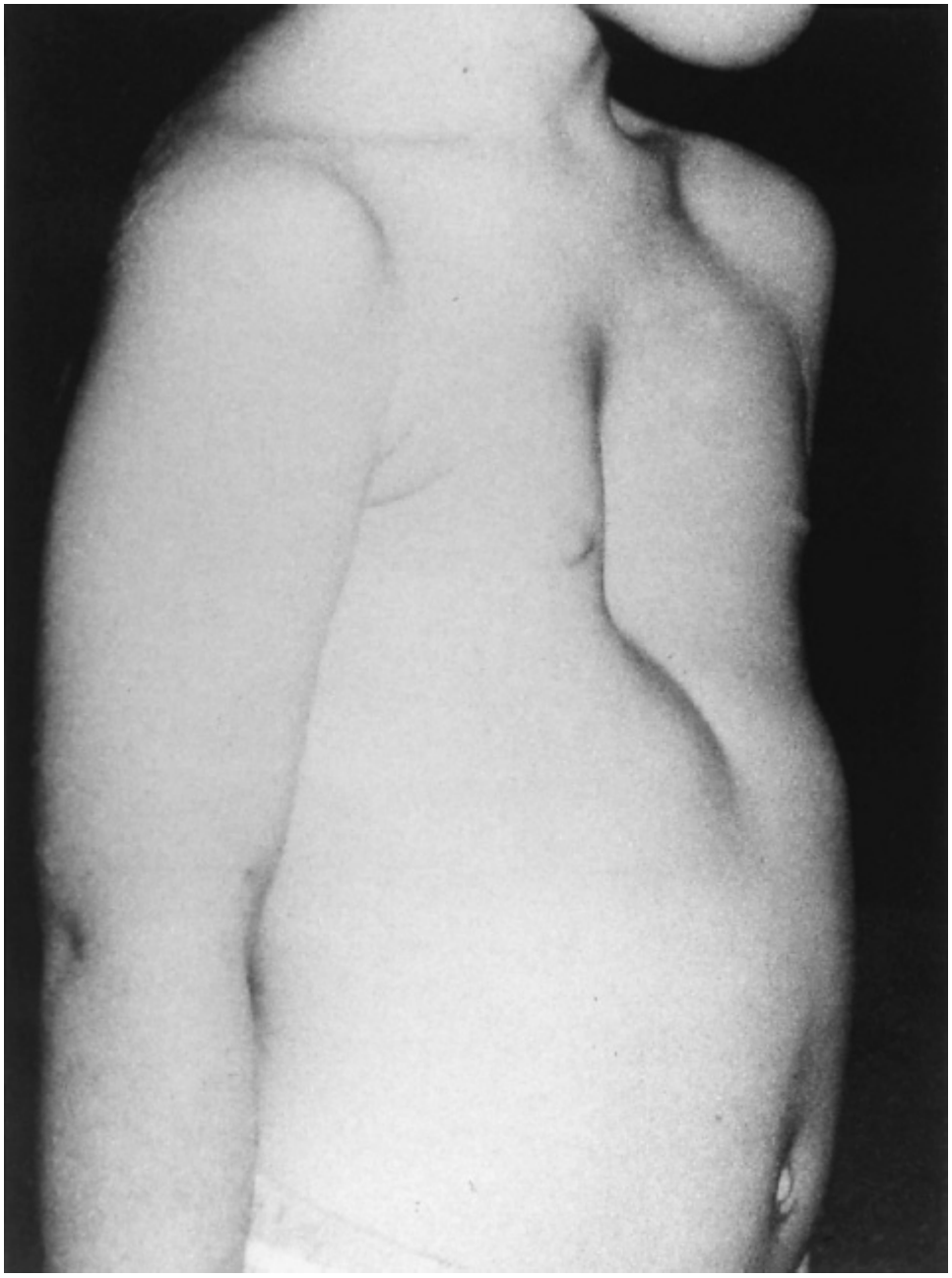


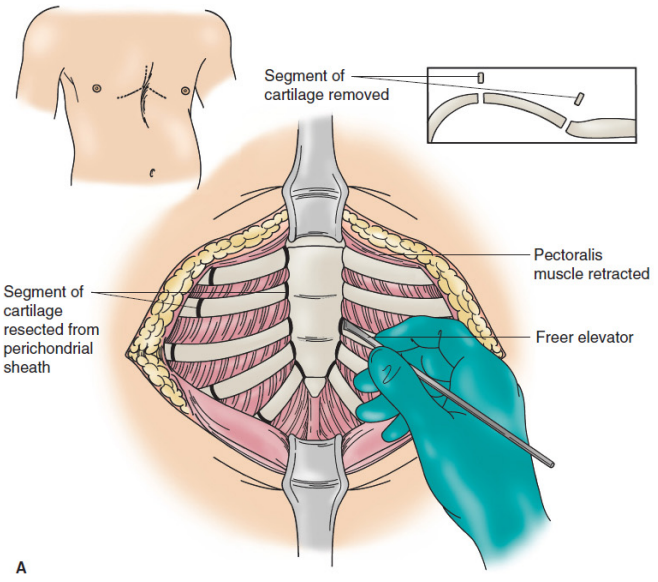
Figure 80.15 Photograph of a 4.5-year-old girl with a symmetric pectus excavatum deformity. Note that the depression extends to the sternal notch. (Adapted with permission from Shamberger RC. Chest wall deformities. In: Shields TW, ed. *General Thoracic Surgery*. 4th ed. Baltimore, MD: Williams & Wilkins; 1994:529–557.)

Sternal Clefts

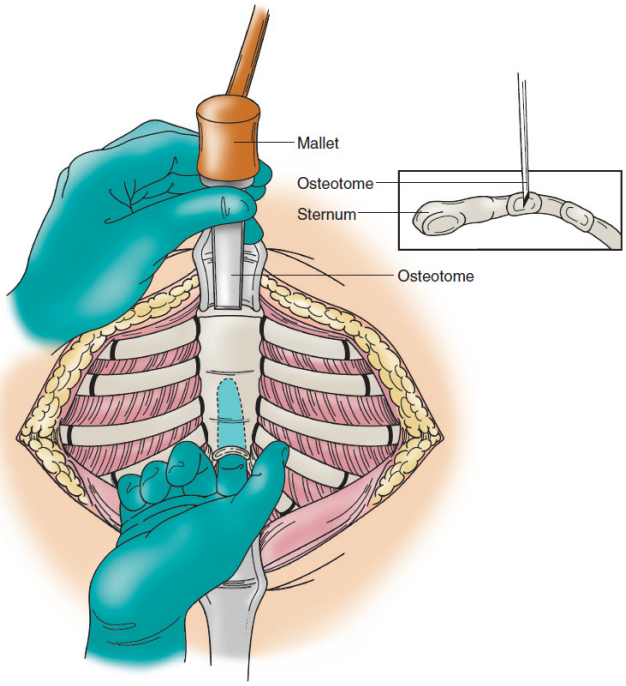
Sternal clefts are much rarer than either pectus deformity. They result from the failure of the sternum to fuse in the midline. They can vary from minor defects with the upper half of the sternum separated, to complete dissociation and thoracic ectopia cordis (the heart being outside the chest wall). Upper sternal defects have a U- or V-shaped appearance and usually extend to the fourth intercostal space (**Fig. 80.18**). Repair of these defects can be easily performed by incision, complete sternotomy, oblique chondrotomies of the sternal halves, and closure. Complete sternal clefts are associated with diastasis recti and an opening between the peritoneal and pericardial cavities. Inferior clefts are associated with the pentalogy of Cantrell, a constellation of defects which include supraumbilical abdominal wall defect, lower sternal cleft, defect in the anterior diaphragm, defect in the associated pericardium, and congenital cardiac defects, often tetralogy of Fallot.[21]

Poland Syndrome

Poland syndrome is the clinical absence of a pectoralis muscle and underlying bony support in the chest wall, and it occurs in 1/30,000 live births. It is usually a right-sided, unilateral defect. Patients commonly have associated limb abnormalities, and may also present with renal and spinal lesions (**Fig. 80.19**). Clinical symptoms may be absent, though lung herniation can occur, requiring a more urgent repair. The surgical approach is usually multidisciplinary and ideally is deferred until after the patient has stopped growing. Repairs typically utilize mesh placement over the defect, and/or muscle flap placement.[22]


Segment of cartilage removed
Pectoralis muscle retracted
Segment of cartilage resected from perichondrial sheath
Freer elevator

A


Mallet
Osteotome
Sternum
Osteotome

B

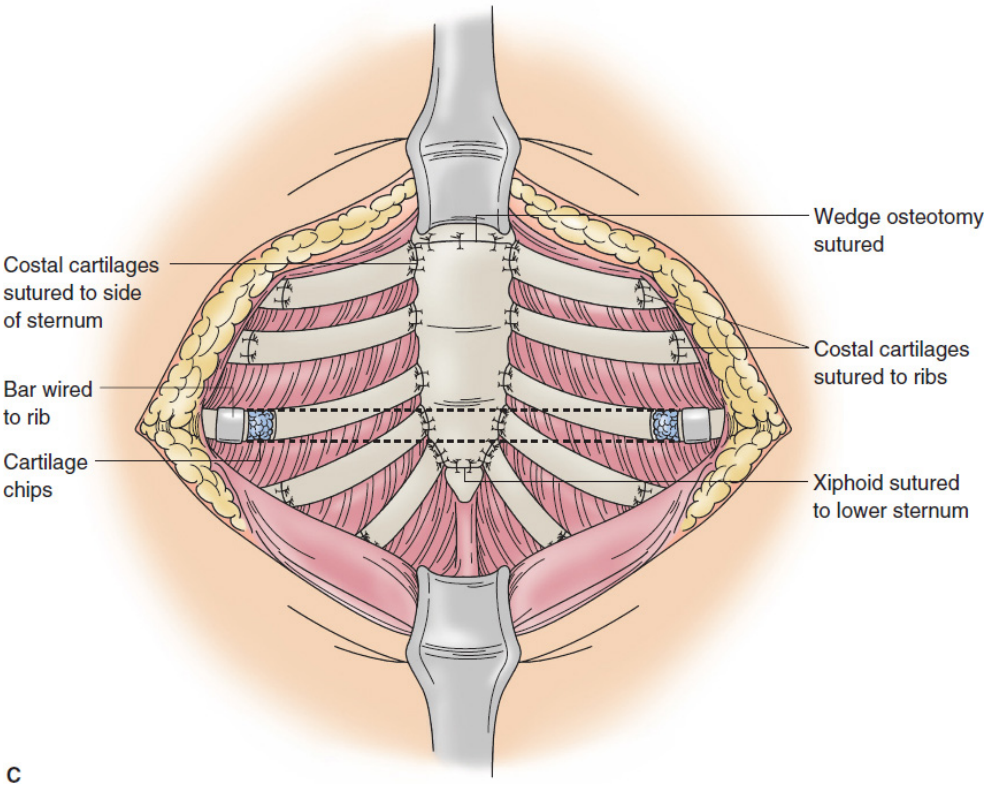


Figure 80.16 A chevron incision is made with flaps elevated. The perichondrium on the deformed cartilage is removed (**A**). A transverse wedge osteotomy is made across the anterior table of the sternum. The lower sternum is elevated to the desired level (**B**). A metal strut is placed posterior to the sternum and attached to the ribs with fine wire (**C**).

Thoracic Outlet Syndrome

The thoracic outlet in thoracic outlet syndrome (TOS) refers to the area described at the beginning of this chapter as the thoracic inlet, the correct anatomic term for the region of the first rib and the middle and anterior scalene muscles. Through these structures, the brachial plexus, subclavian artery, and subclavian vein travel to the upper limbs (**Fig. 80.20**). Because of the close proximity in this area, these conduits may be subjected to abnormal compression by inflammation around the muscles or abnormal bony structures such as cervical ribs, causing pain, thrombosis, and other 2 symptoms that are described as TOS. TOS can be divided into arterial, venous, or neurogenic diseases, or a combination, depending on the symptoms and clinical findings. Vascular TOS is easier to document with vascular imaging. Neurogenic TOS is more difficult to diagnose.

Unfortunately for neurogenic TOS, there is no gold standard diagnostic test to confirm the syndrome. As a result, there has been significant controversy over the diagnosis and the indications for surgical treatment, especially in light of the potential for significant postoperative complications.[23,24]

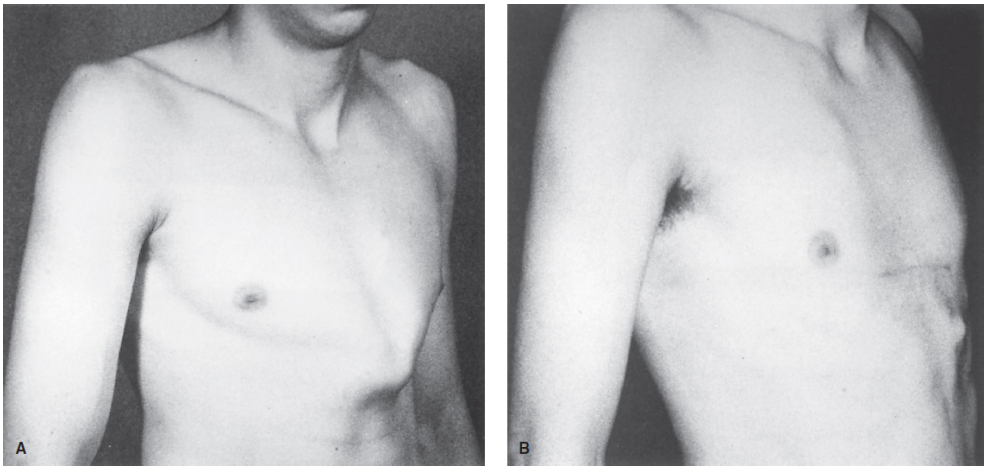


Figure 80.17 Photograph of (**A**) symmetric chondrogladiolar pectus carinatum in a 19-year-old man. Postoperative photograph (**B**) shows correction of the protruding sternum and costal cartilages. (Adapted with permission from Shamberger RC. Chest wall deformities. In: Shields TW, ed. *General Thoracic Surgery*. 4th ed. Baltimore, MD: Williams & Wilkins; 1994:529–557.)

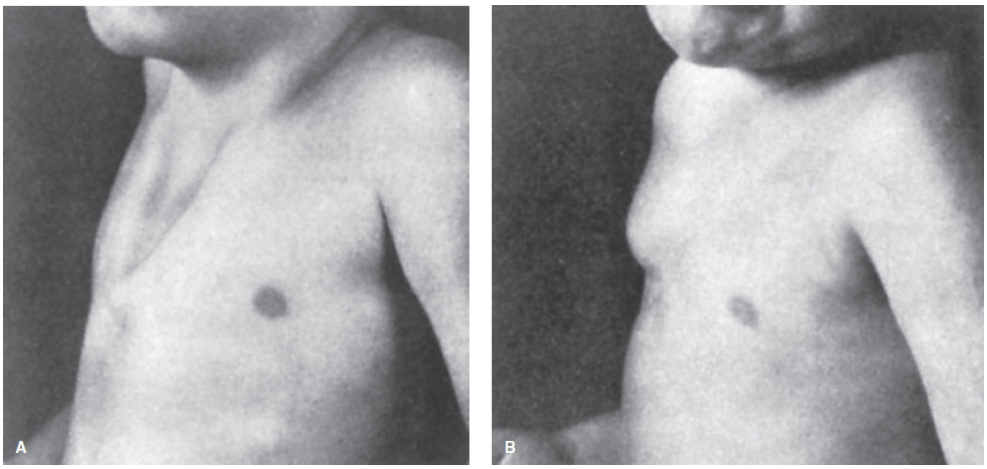
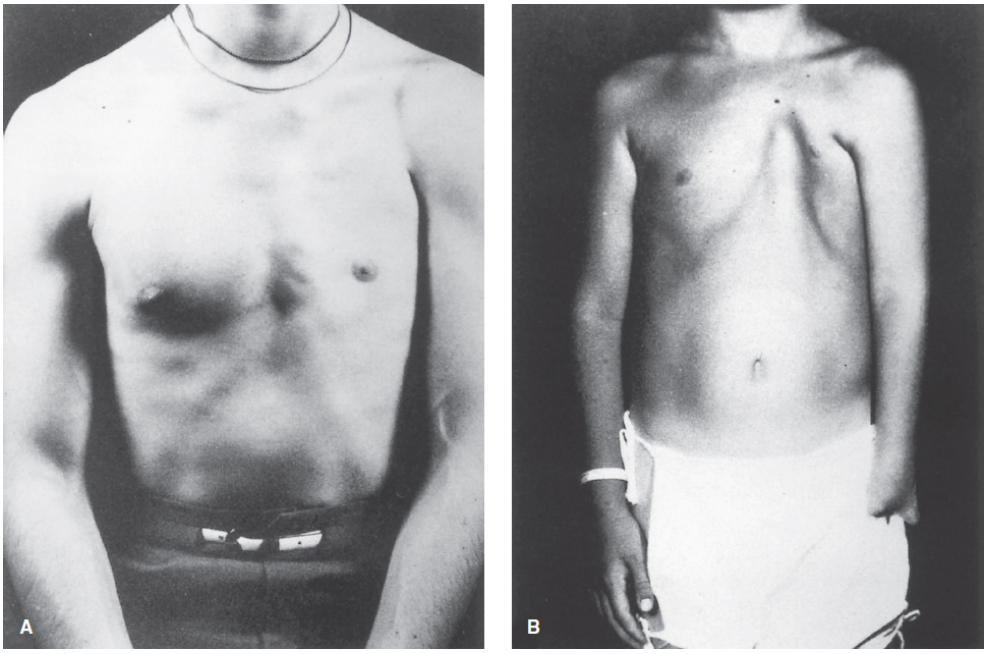


Figure 80.18 Cleft sternum at rest (**A**) and during forced expiration (**B**). Superior clefts of the sternum are variously V- or U-shaped. The appearance of the child as he cries explains the term ectopia cordis, although the heart is actually not misplaced. In the newborn, defects of this kind can be corrected by direct apposition of the sternal halves. In this child, closure of the defect was made possible by sliding chondrotomies on either side. (Reproduced with permission from Sabiston DC Jr. The surgical management of congenital bifid sternum with a partial ectopia cordis. *J Thorac Surg* 1958;35:118–122.)

Vascular TOS can be divided into venous disease and arterial disease. Venous disease results in thrombosis of the subclavian vein and is also called Paget–Schroetter syndrome. This syndrome usually presents in men who use their upper bodies and dominant arm for work. Symptoms may present as pain, swelling, and cyanotic discoloration from venous congestion.[23] Contrast venography is the best test to make the diagnosis, and the radiologist should be instructed to perform positional maneuvers with the patient's arm to replicate narrowing that occurs with arm movement.[24] Arterial TOS accounts for about 5% of all cases of TOS[25] and also may result from repetitive and strenuous use. Patients will present with arm fatigue and may even have evidence of ischemia in their distal digits. Patient evaluation includes pulse examination with the arm relaxed and elevated, bruit examination for poststenotic dilatation, and blood pressure readings in both arms. Duplex scanning and angiography will often confirm the diagnosis. Decompression of the scalene muscles and any abnormal bony structures will alleviate these symptoms.[23]


A
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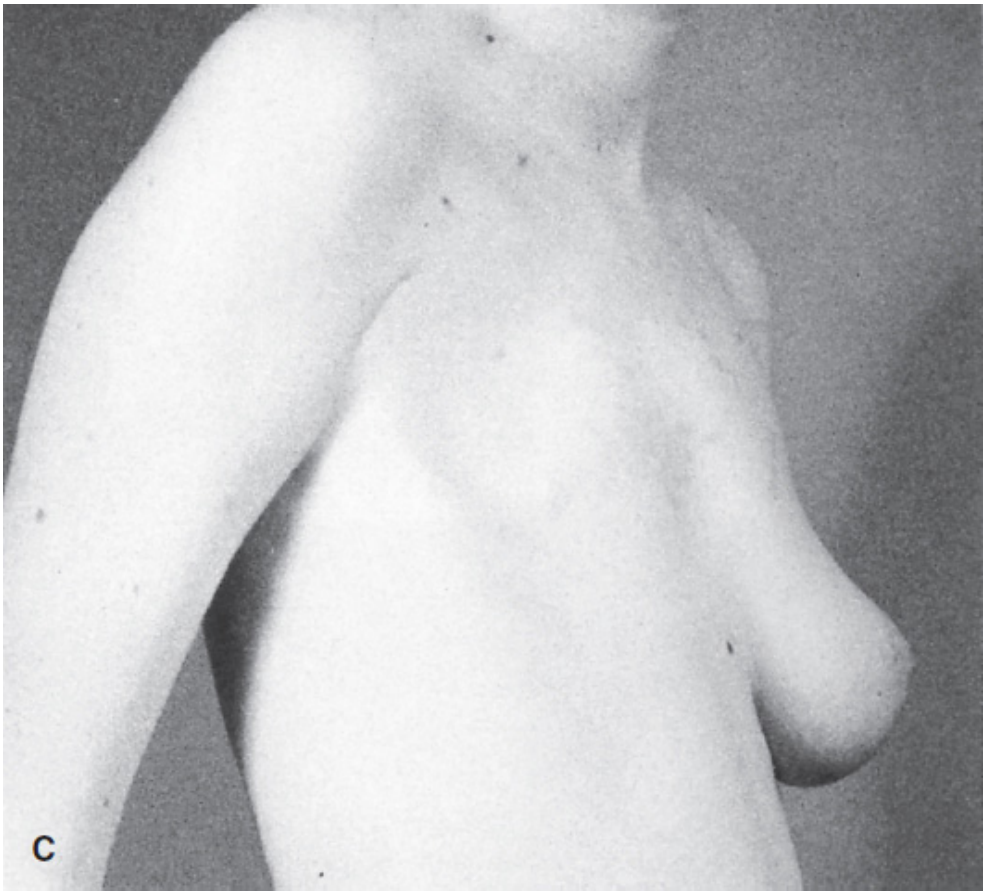


Figure 80.19 **A:** Muscular 15-year-old boy with loss of the left axillary fold, orthotopic sternum, and normal cartilages. He compensates adequately for loss of the pectoralis major and minor muscles. Surgery is not indicated in males with these findings. **B:** An 8-year-old boy with Poland syndrome. The pectoralis major and minor muscles and the serratus to the level of the fifth rib are absent. The boy has sternal obliquity, and the third to fifth ribs are short, ending in points. The corresponding cartilages are absent. The endothoracic fascia lies beneath a thin layer of subcutaneous tissue. Note the hypoplastic nipple and ectromelia of the ipsilateral hand. **C:** A 14-year-old girl with Poland syndrome. Note the high position of the right nipple, amastia, sternal rotation, and depressed right anterior chest. The second to fourth ribs and cartilages were missing, reconstructed with rib grafts. Breast augmentation will be required at full growth. (Reproduced with permission from Shamberger RC. Chest wall deformities. In: Shields TW, ed. *General Thoracic Surgery*. 4th ed. Baltimore, MD: Williams & Wilkins; 1994:529–557.)

ORIENTATION

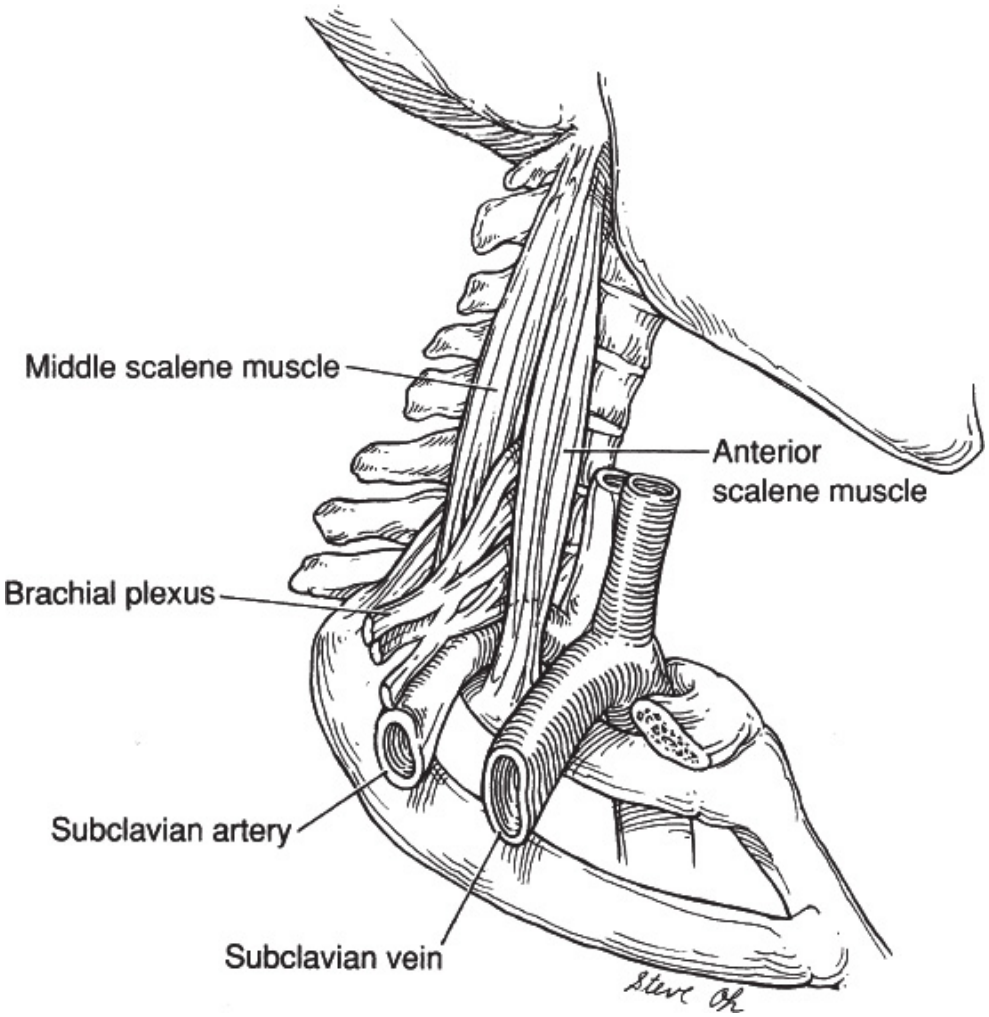


Figure 80.20 Important structures in the thoracic outlet. (Reproduced with permission from Scott-Conner CE, Dawson DL, Shirazi MK, et al. *Operative Anatomy*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.)

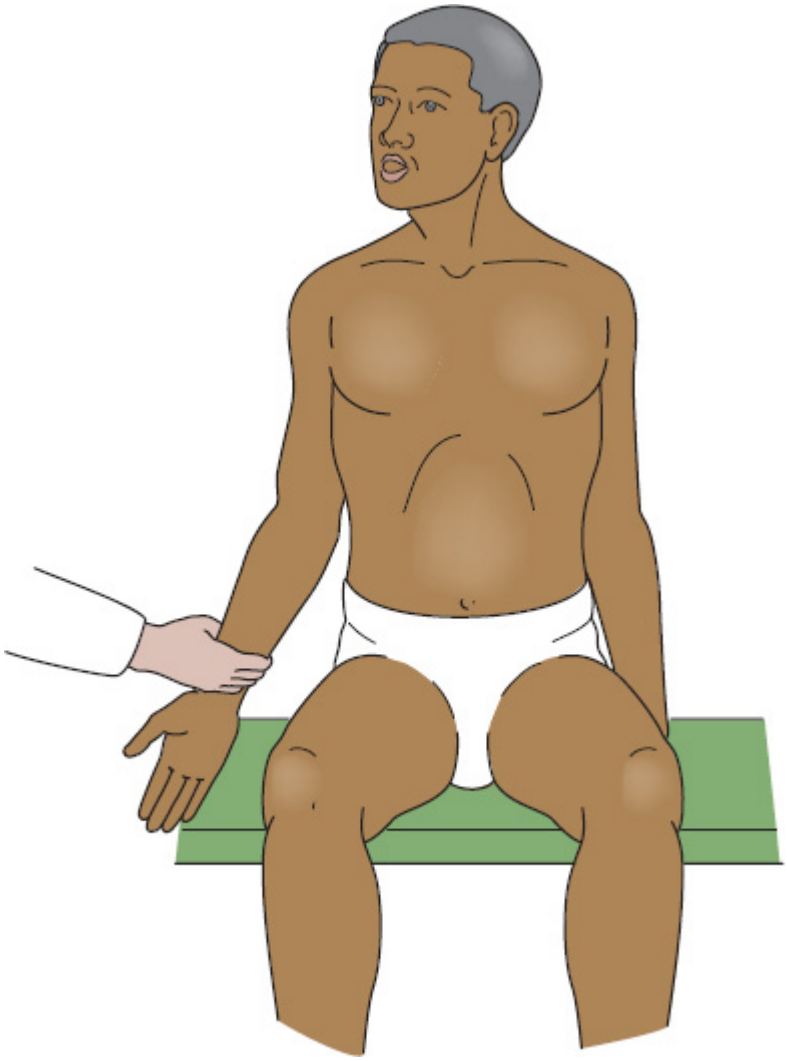


Figure 80.21 The Adson maneuver. Patient inspires and turns head away from the affected arm. The test is positive if the pulse disappears.

Neurogenic TOS presents with limb pain, numbness, or weakness. Symptoms may be bilateral, but are usually worse in the dominant arm. The distribution may not follow a peripheral nerve pattern, thus making the diagnosis confusing, but also ruling out more distal compression syndromes such as carpal tunnel in the wrist or cubital compression at the elbow. The physical examination should be focused on duplicating the patient's symptoms. The Adson maneuver may detect artery compression and is performed by palpating the affected radial pulse, and having the patient take a deep inspiration while turning their head away from the affected arm (**Fig. 80.21**). The test is positive if the pulse disappears, but a positive result can also be seen in asymptomatic people without TOS. Another test requires

the patient to elevate their arms in a "surrender" position and open and close their hands repeatedly. Most people with neurogenic TOS will be fatigued within a minute and be unable to continue (**Fig. 80.22**). Plain radiographs may show bony abnormalities, but no other imaging will help diagnose neurogenic TOS. Physical rehabilitation is the first step to treat patients with neurogenic TOS, and over a third of patients may get a significant improvement in their symptoms. If there is no significant improvement in symptoms, then surgical intervention is suggested.[24]

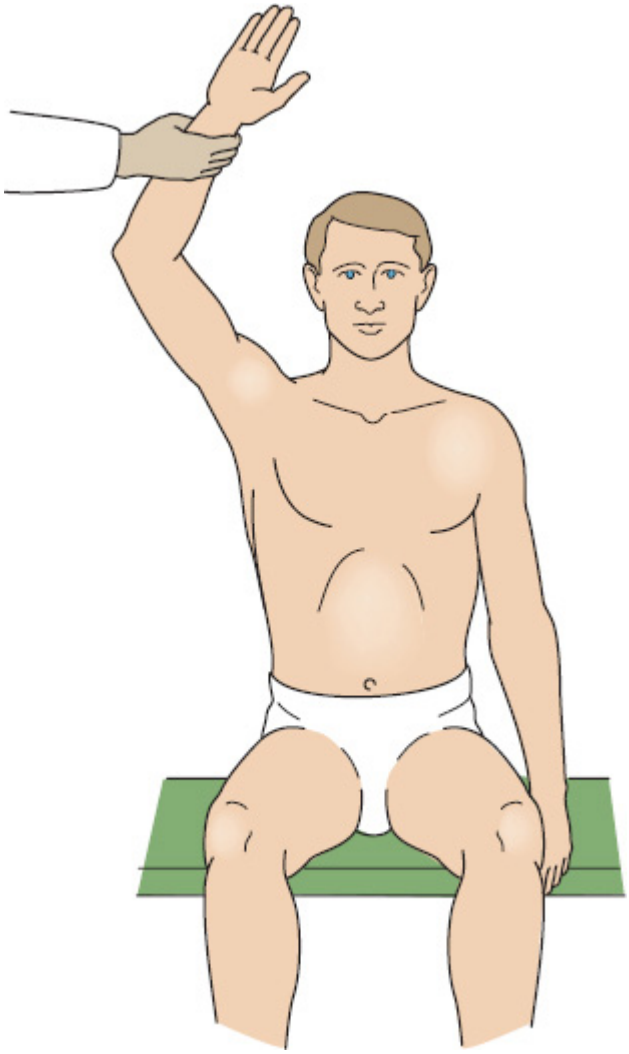


Figure 80.22 Surrender position with opening and closing of hand. Early fatigue is seen in neurogenic TOS.

The surgical approach for TOS was traditionally a transaxillary first rib resection (**Fig. 80.23**). In recent years, a supraclavicular approach has

become increasingly popular as it gives better exposure to the scalene muscles and any cervical ribs. In either approach, the first rib is exposed, attachments to the anterior and middle scalenes are divided, and the rib is removed (**Fig. 80.24**). Special attention must be paid to the phrenic nerve lying along the anterior scalene and the axillary branches off of the brachial plexus. Small drains may be placed in the apex of the thorax if the pleural space is entered.[24,26] The supraclavicular approach also gives access to perform a cervical sympathectomy if indicated for symptoms consistent with sympathetic overactivity. In patients with arterial aneurysms, reconstruction with synthetic grafts or autologous conduits such as an external iliac artery can be performed. For patients with venous TOS, care should be taken to perform a circumferential venolysis and to remove the medial aspect of the first rib.[26]

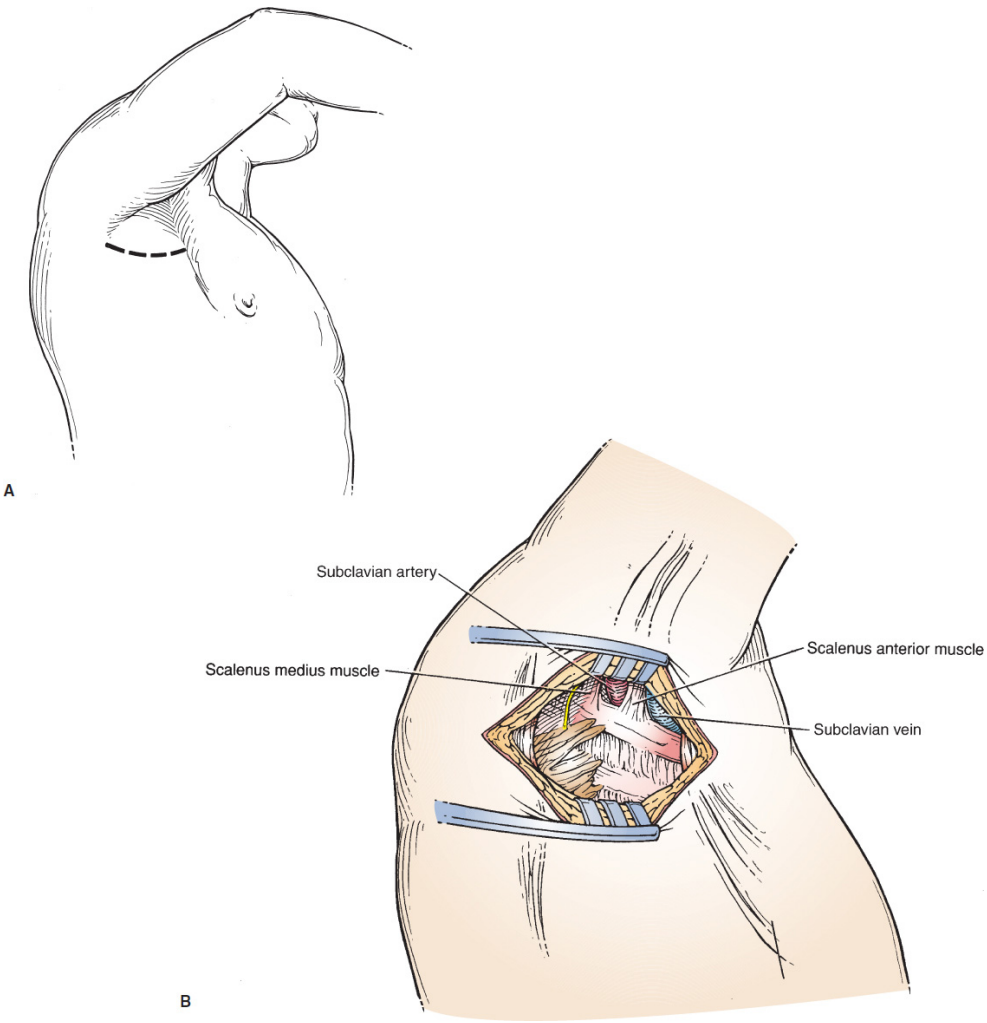


Figure 80.23 Position of the patient (**A**) and skin incision (**B**) for transaxillary approach. (Reproduced with permission from Scott-Conner CE, Dawson DL, Shirazi MK, et al. *Operative Anatomy*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.)

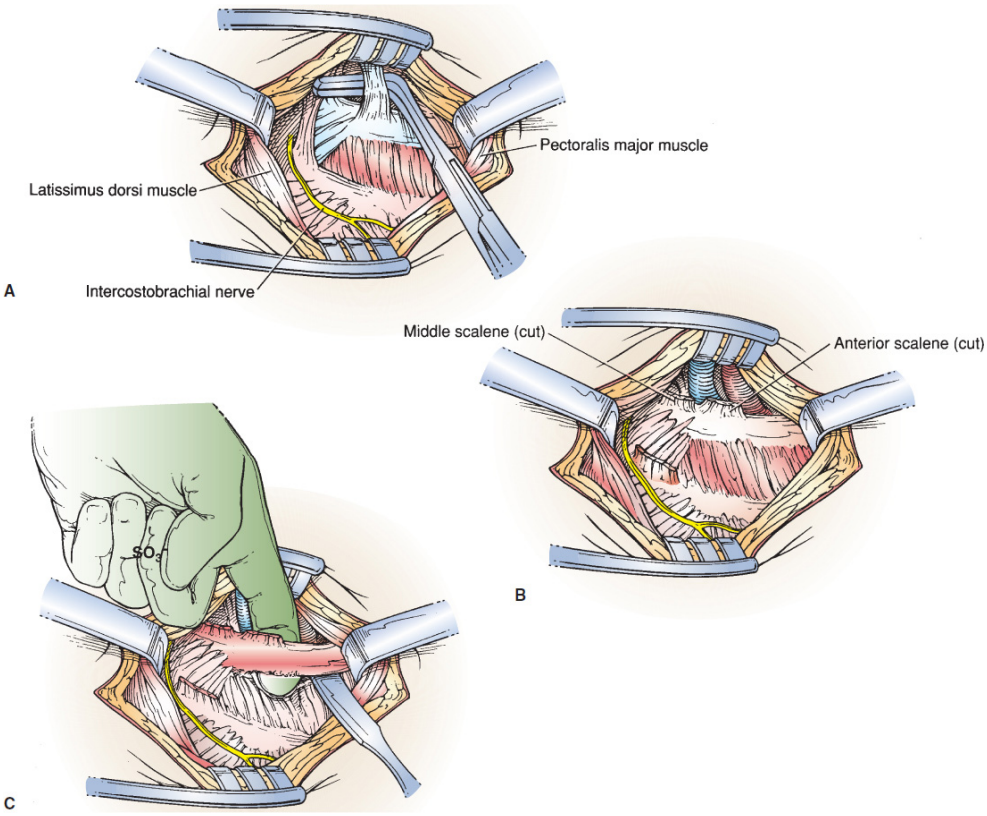


Figure 80.24 Division of the scalene muscles and the first rib. **A:** Mobilization of the scalene muscles off of the first rib. **B:** Exposure of the subclavian vessels. **C:** Mobilization of the first rib, protecting the vessels. (Reproduced with permission from Scott-Conner CE, Dawson DL, Shirazi MK, et al. *Operative Anatomy*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.)

Postoperative complications include pneumothorax, lymphatic leaks, especially on the left side where the thoracic duct enters the operative field, phrenic nerve palsy, and traction injury to the brachial plexus.[25] Rehabilitation and range of motion exercises should begin as soon as possible to reduce the risk of frozen shoulder.[24,26] Up to 12.5% of patients may not get any symptom relief after the surgery, and long-term physical rehabilitation is recommended.[25] Patients with combined symptoms of venous and neurogenic TOS have worse outcomes when compared to patients with only venous disease. A higher percentage of patients had persistent pain in the neurogenic group as might be expected.[27] The treatment of this disease process requires a significant investment into the pre- and postoperative care of these patients and should only be done in centers with a high volume and expertise in this syndrome.

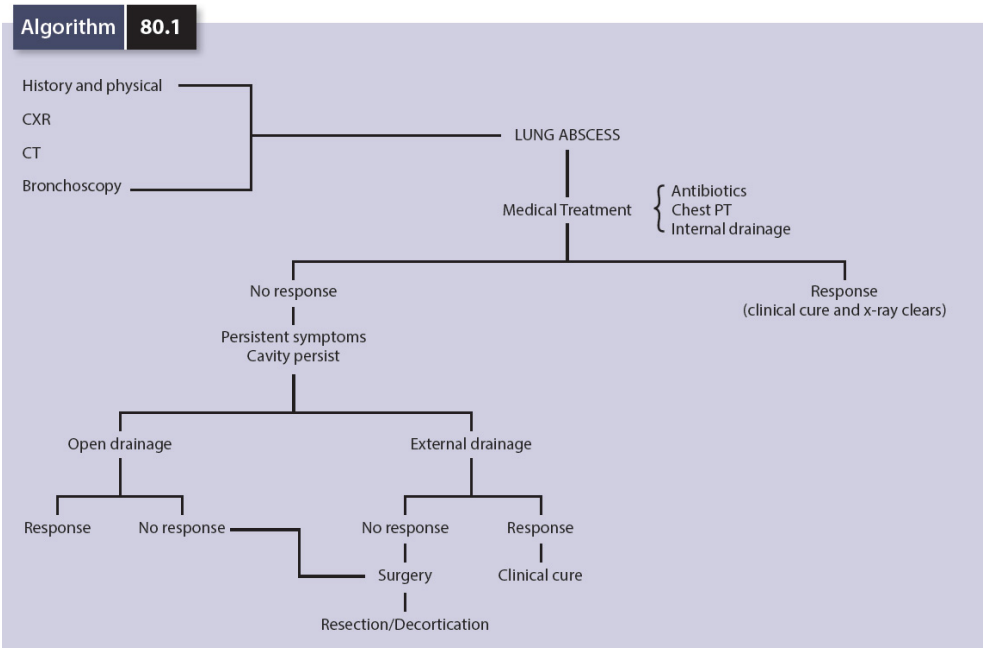
NONNEOPLASTIC LUNG DISEASE

Lung Abscess and Bronchiectasis

Lung abscesses can result from aspiration or occur after necrotizing pneumonia. Patients may present with chest pain and fever. Routine use of antibiotics for pneumonias has dramatically reduced the rate of lung abscess sequelae. In over 80% of cases, a pathogen can be found, and in immunocompromised patients, there are usually multiple organisms involved including *Pseudomonas aeruginosa* 3 and *Haemophilus* species. The primary treatment for lung abscesses is medical therapy with antibiotics. If a patient is clinically not improving with medical therapy alone, a guided drainage tube may be placed. A complication of this approach is the risk of a chronic air leak from a percutaneous tube placed into the lung parenchyma. Surgery may be indicated in the setting of large abscesses causing hemoptysis or other symptoms (**Algorithm 80.1**). Complications from pulmonary infections that require surgery are not common relative to the frequency of pneumonias in both the inpatient and outpatient community. However, some patients may benefit from surgical intervention to treat lung abscesses.[28]

Bronchiectasis is the abnormal dilation of bronchi/bronchioles as the result of multiple episodes of infection and inflammation. Patients can present with respiratory symptoms like dyspnea, hemoptysis, or pleuritic pain, or alternatively may present only with systemic changes such as fatigue and weight loss.[29] Almost all patients will have a chronic cough with or without sputum production.[30] Factors contributing to the development of this disease may be genetic, anatomic, or even systemic. Genetic causes of bronchiectatasis include cystic fibrosis and primary ciliary dyskinesia, which results in reduced mucus clearance, and alpha-1-antitrypsin deficiency which results in destruction of lung parenchyma.[29] Anatomic causes include postsurgical changes or acquired diseases such as chronic obstructive pulmonary disease (COPD) that lead to an increased risk of infection, again by the inability to clear secretions. Autoimmune diseases such as rheumatoid arthritis and inflammatory bowel disease have been associated with increased rates of bronchiectasis.[29,30] Infectious causes include allergic bronchopulmonary aspergillosis and nontuberculous mycobacterium

infections. Reflux disease is also being studied as a potential contributor. Most often the etiology of the disease is idiopathic.[29]



Algorithm 80.1 Algorithm for management of lung abscess. (Adapted from Shields TW, ed. *General Thoracic Surgery*. 6th ed. 2005.)

There are estimated to be 110,000 patients in the United States being treated for noncystic fibrosis bronchiectasis each year. Pulmonary function tests may demonstrate moderate to severe airflow obstruction.[29] A chest CT scan is the optimal test to diagnose bronchiectasis (**Fig. 80.25**), and once the diagnosis is made, the search for an etiology should begin, including obtaining sputum cultures and blood tests for autoimmune markers such as rheumatoid factor.[30]

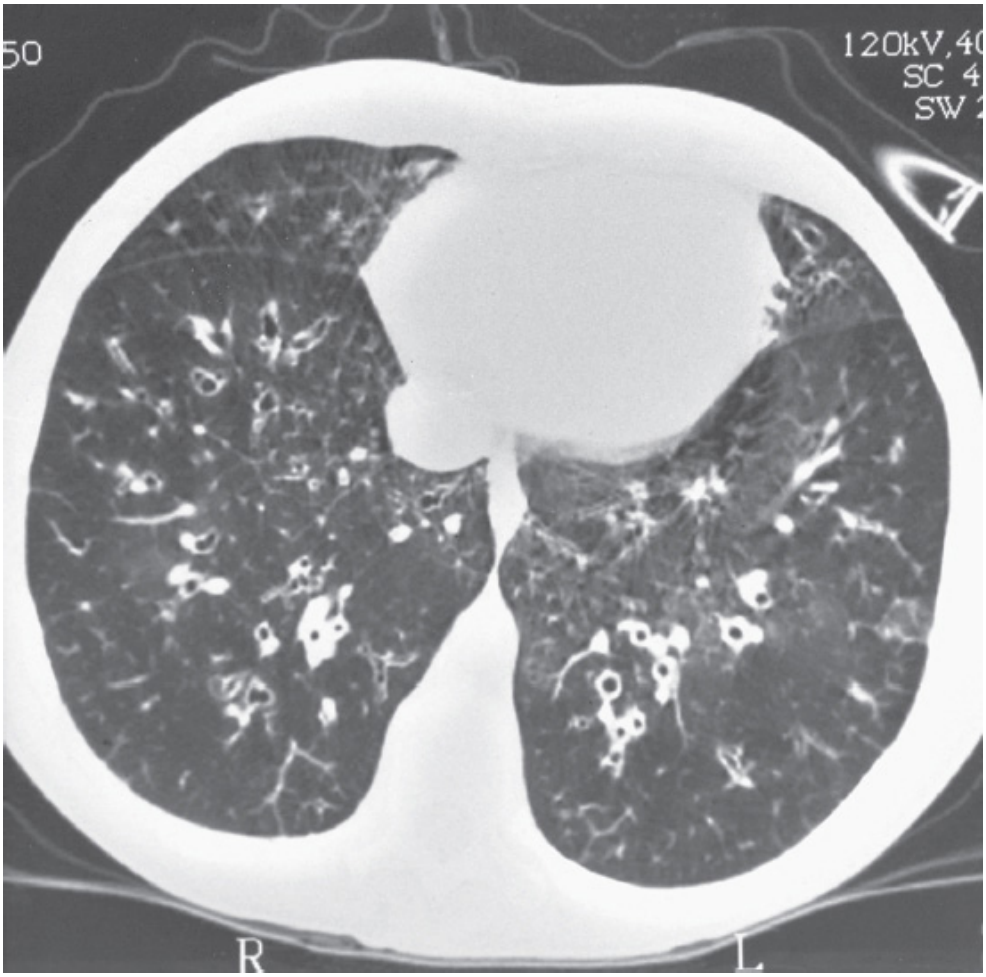


Figure 80.25 CT scan of bronchiectatic lungs. (Reproduced with permission from Shields TW, ed. *General Thoracic Surgery*. 6th ed.)

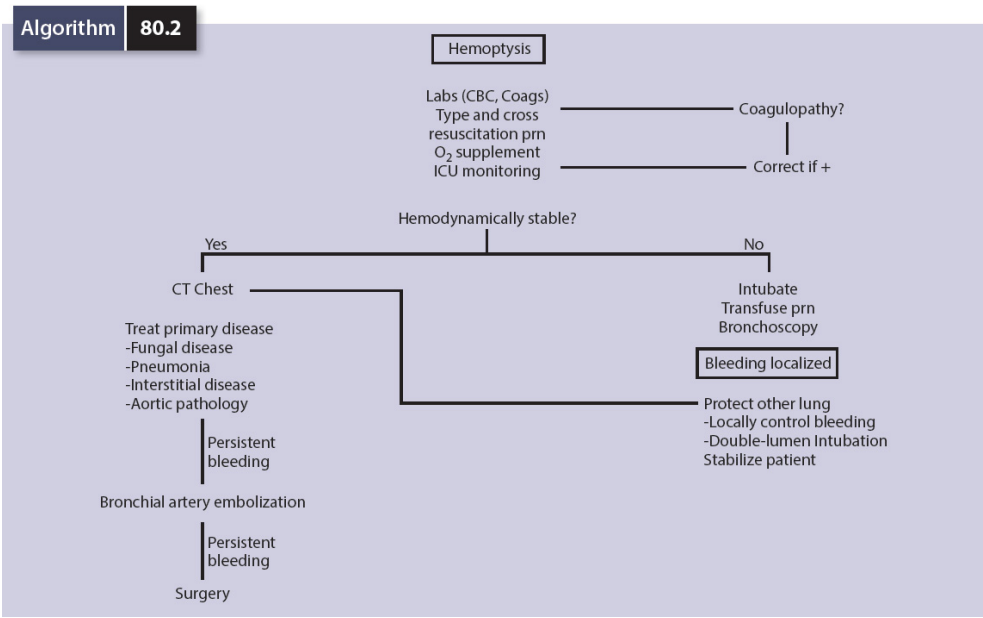
The treatment of the disease includes antibiotic therapy to control infection, the treatment of underlying diseases if they exist, reducing inflammation, improving secretion clearance, and surgery to remove focally damaged areas or transplantation if needed for more diffuse, severe disease. Antibiotic therapy includes inhaled tobramycin and gentamicin.[30] Macrolide antibiotics, like erythromycin and clarithromycin, have been increasingly studied for anti-inflammatory benefits outside for their antibiotic effects. They disrupt the biofilm produced in *Pseudomonas* infections resulting in decreased sputum volume and improved symptoms.[31] Secretion removal is also essential to improving symptoms. Besides the standard treatments of percussive therapy and postural drainage, the use of nebulized

acetylcysteine[30] or hypertonic saline[31] has been shown to improve mucus clearance.

Surgical intervention may occur at many stages of the disease process. Bronchoscopy can be useful to clear secretions or to manage hemoptysis. If the bronchiectasis is localized to a single lobe, resection can eliminate the disease and the source of chronic infection. If a patient has a genetic disease such as cystic fibrosis, a double-lung transplant may be the best treatment if the patient's symptoms are severe enough.[30] Pulmonary tuberculosis can have similar indications for surgical intervention when it results in bronchiectasis or hemoptysis.[32] The rise of more multidrug-resistant tuberculosis strains has led to the increasing need for surgical intervention.[33]

Hemoptysis

Hemoptysis is often used to describe any blood streaking associated with cough. True hemoptysis may only be a few drops of 4 blood, and it requires investigation. Massive hemoptysis is acutely life threatening, not from blood or volume loss, but rather from suffocation secondary to blood in the airway. The causes of hemoptysis include cancer, infections/bronchiectasis, vascular injuries, vasculitides, and coagulopathies.[34] The immediate goals when this is encountered are airway control, improved oxygenation, and resuscitation if needed. Intubation may or may not be necessary, depending on the volume of blood in the airway and the patient's ability to cough.[35] If the bleeding is able to be lateralized, the patient should be placed in a lateral decubitus position with the bleeding site in the dependent position.



Algorithm 80.2 Hemoptysis management. (Adapted from Jean-Baptiste E. Clinical assessment and management of massive hemoptysis. *Crit Care Med* 2000;28(5):1642–1647.)

In patients with hemoptysis, any coagulopathy should be corrected. Early bronchoscopy is essential and the goals are to lateralize the site of bleeding and identify the site and cause of the bleeding. Flexible bronchoscopy may be done, but rigid bronchoscopy is the best approach to maintain airway control, in particular in the setting of large volume hemoptysis.[35] Initial treatment may include topical therapy such as cold saline lavage, bronchial tamponade, and intubation of the contralateral good lung. Double-lumen endotracheal tubes may also be useful to isolate and protect the uninvolved lung from blood from the contralateral side obstructing its lumen. If a patient is stable, a chest CT scan is useful to identify tumors or other potential sources of bleeding.[34]

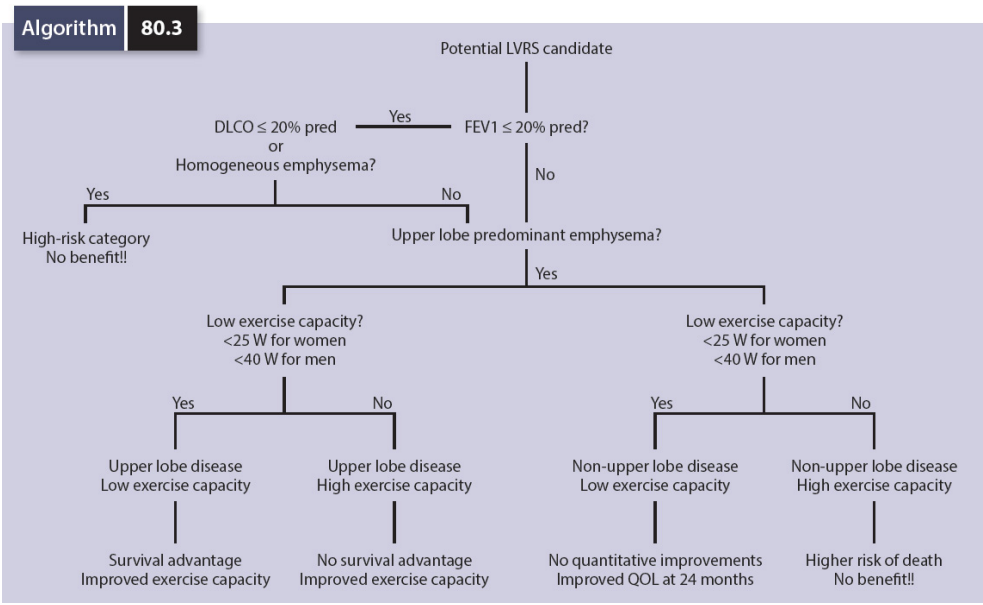
Once a patient is stabilized and appropriate diagnostic tests performed, the treatment of continued bleeding includes the use of interventional radiology and bronchial artery embolization (BAE).[35] First introduced in 1973, BAE is the best nonsurgical treatment of massive hemoptysis, with a success rate of up to 98% within 24 hours, however there is a recurrence rate up to 58% at 30 days.[34,35] Surgery is reserved to treat the underlying condition once the patient has been stabilized and bleeding controlled by other methods. Emergent surgery to treat bleeding may have a mortality rate as high as 38%,[36] and increase to 59% in the setting of malignancy.[34] However, if a

patient undergoes surgery after initial control of hemorrhage by other means the mortality rate decreases to 4%.[35] Depending on the patient's baseline lung function, a lobectomy, let alone a pneumonectomy, may not be tolerated. A risk assessment of the benefits of surgery must be performed. In the setting of a vascular etiology of the hemoptysis such as a ruptured aortic aneurysm, surgical repair is essential and should not be delayed once the patient is hemodynamically stable and the airway is controlled.[34] A detailed algorithm in the assessment and treatment of hemoptysis is shown in **Algorithm 80.2**.

COPD and Lung Volume Reduction

COPD includes a broad group of diseases that result in airflow obstruction and hyperinflation. Medical therapy involves smoking cessation, bronchodilator treatment, steroids, home oxygen, and antibiotics as needed. Despite improvements in the medical management of this condition, patients continue to suffer severe limitations due to their breathing and exercise capacity. As a result, surgical interventions have continued to play a role in trying to ameliorate symptoms and improving survival in these patients.[37,38]

There is a more than 50-year history in the literature recording a variety of surgical approaches to help treat COPD. Interest was diminished, however, because of the high mortality associated with surgical intervention in this patient population. In the 1990s, a renewed interest in lung volume reduction surgery (LVRS) was observed following reports that this procedure was associated with a low published mortality rate and a significant improvement in FEV_1 seen on pulmonary function testing. There was a national increase in interest in the procedure, as many centers began offering it. Despite continued publication of low mortality rates, evaluation of Medicare data in 1996 showed a mortality of 23% in surgically treated patients at 12 months, and Medicare reimbursement for the procedure stopped. This led to the development of the National Emphysema Treatment Trial (NETT), a prospective randomized trial to evaluate the outcomes of LVRS compared to optimal medical treatment (**Algorithm 80.3**).[37]



Algorithm 80.3 LVRS candidate workup. (Adapted from Martinez FJ, Chang A. Surgical therapy for chronic obstructive pulmonary disease. *Semin Respir Crit Care Med* 2005;26(2):167–191.)

The goal of the NETT study was to evaluate short- and long-term survival, lung function, exercise capacity, and quality of life. Patients with upper lobe disease and a low exercise capacity, defined as achieving less than the 40th percentile on exercise testing, 25 W for women and 40 W for men, showed a survival advantage and improved exercise capacity after surgery.

A new technique aimed to provide the same benefit of LVRS but without the surgical risk is the placement of one-way endobronchial valves. These are designed to allow air to escape the hyperinflated apical regions and not allow air to reenter. Endobronchial valves significantly improved pulmonary function and exercise capacity but serious adverse events occur in 21% of patients.[39] Endobronchial stents have been designed to cross bronchioles into hyperinflated regions of the lung and allow decompression. Other approaches being tested include the bronchoscopic introduction of biologic substances such as trypsin or thrombin into hyperinflated regions of the lung with the goal of causing local scarring and reduce the hyperinflation.[40] Other surgical procedures in the treatment of COPD include bullectomy in selected patients and lung transplants in patients with end-stage disease.[38]

Tracheobronchial Foreign-Body Aspiration

Tracheobronchial foreign-body (TFB) aspiration occurs most often in children, but up to 20% of cases have been reported in adults. Risk factors in adults include older age, as elderly patients have a higher incidence of neurologic disease and an impaired cough reflex. Symptoms usually involve an episode of choking, followed by a protracted cough. Fever, dyspnea, hemoptysis, and wheezing can also be present.[41] Chest x-ray may aid in the diagnosis if the aspirated TFB is radio-opaque or if there is associated air trapping, atelectasis, or pneumonia, however, the TFB is visible less than a quarter of the time as most foods are not radio-opaque.[42] Chest CT scans are a more sensitive imaging modality, but not necessarily more specific. Bronchoscopy should be performed if TFB aspiration is suspected. Removal of the TFB can usually be accomplished by flexible bronchoscopy but may require rigid bronchoscopy in difficult cases.[41,42] A recent review found flexible bronchoscopy was successful for removal of TFB in 79% of cases.[43]

Pneumothorax

Pneumothoraces are classified as spontaneous, primary or secondary, traumatic, or iatrogenic. Primary spontaneous pneumothoraces occur in patients with no known lung disease, whereas secondary spontaneous ones occur in patients with underlying lung pathology thought to predispose those patients to a pneumothorax. Iatrogenic pneumothoraces may occur in either the postsurgical or postprocedural setting, typically following central line placement or thoracentesis.[44] Traumatic pneumothoraces are covered elsewhere in this text.

Primary spontaneous pneumothoraces occur more frequently in men than women, with an incidence of 7 to 18 cases per 100,000 people for men, compared to an incidence rate of 1 to 6 cases per 100,000 people in women. Most cases occur in males younger than 30 years of age, and they rarely occur in people over the age of 40. Even though many patients with primary pneumothoraces do not have apparent lung disease, almost all are found to have subpleural bullae, the pathophysiology of which is unknown.[44] Most bullae are apical in location.[45] Patient symptoms can range from minimal to severe, and usually include pleuritic pain, dyspnea, or both. Tachycardia may also be present, and if a person is tachycardic and hypotensive, a tension pneumothorax must be high on the differential and appropriate needle

decompression considered. A tension pneumothorax occurs when air entering the pleural cavity cannot escape and the air compresses the vena cava and even the heart, resulting in hemodynamic instability (**Fig. 80.26**). Urgent needle decompression followed by chest tube placement is the preferred treatment. Most spontaneous pneumothoraces occur while patients are at rest.[44,46]

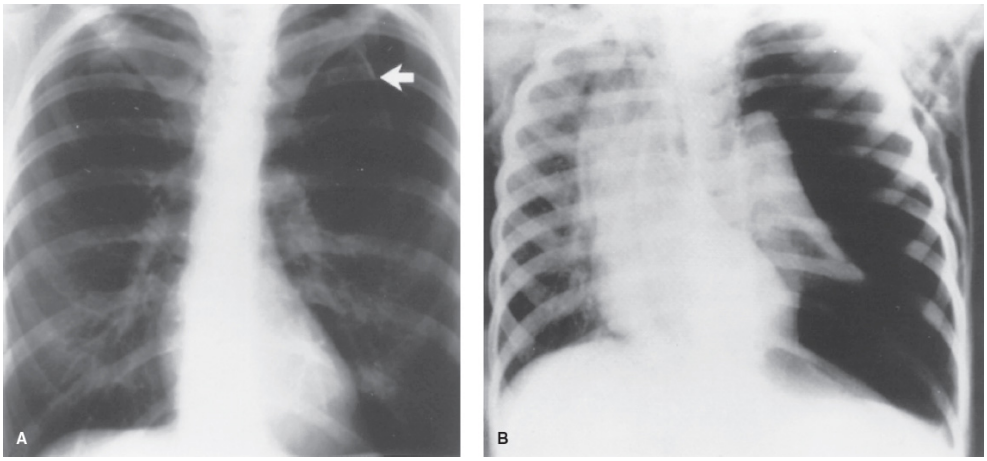
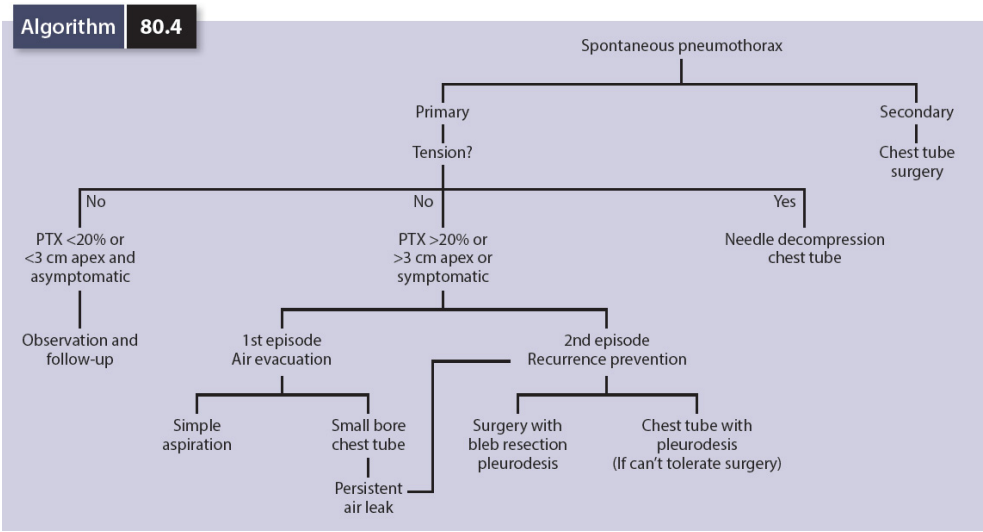


Figure 80.26 **A:** A 40% left-sided spontaneous pneumothorax (*arrow*). **B:** Progression of simple pneumothorax to a tension pneumothorax, showing the characteristic radiographic findings—virtual collapse of the entire involved lung, shift of the mediastinum to the contralateral side, and compression of the contralateral lung. Subcutaneous air dissecting along the left chest wall is also evident.

Observation is often the treatment of a stable, small pneumothorax, defined as being less than 3 cm from the apex. For a larger pneumothorax, chest tube placement is the standard treatment, though some advocate a trial of aspiration. Most patients will have a complete resolution of their pneumothorax 5 and not need further treatment. In the group of patients who have a persistent air leak from the initial pneumothorax, or the 30% who have a recurrent pneumothorax, usually within 2 years, further treatment is warranted. This involves some form of pleurodesis, chemical or mechanical, either via a chest tube (talc infusion), or during a thoracoscopic evaluation where apparent blebs can also be resected (**Algorithm 80.4**).[45,46]

Secondary spontaneous pneumothoraces can occur due to a variety of lung diseases, but COPD is the most common.[47] While primary pneumothoraces can be mild clinical events, secondary ones are much more concerning

because of the baseline lung disease and poor pulmonary reserve. Observation has no role in this patient population who should undergo definitive treatment to prevent a recurrence during the first event. Here a thoracoscopic approach may be more effective in establishing an adequate pleurodesis and allow the evaluation for sources of air leaks.[46] Iatrogenic pneumothoraces can result from transthoracic needle lung biopsies, central line placement, thoracentesis, transbronchial lung biopsies, pleural biopsies, and positive pressure ventilation. Patients with underlying lung disease are at a higher risk of developing a pneumothorax after these procedures. Treatment should follow the same paradigm as for spontaneous pneumothoraces. Patients with a small, asymptomatic, stable pneumothorax and no underlying lung disease may be safely observed, while all others should undergo placement of a chest tube.[46] Some studies have suggested immediate aspiration of air after a CT-guided lung biopsy resulting in a pneumothorax, with an 85% success rate in avoiding the need for chest tube placement.[45]



Algorithm 80.4 Algorithm to treat pneumothorax. (Adapted from Baumann MH, Noppen M. Pneumothorax. *Respirology* 2004;9(2):157–164.)

Table 80.2 Phases of Lung Development Classification

Phase	Gestation Period	Major Developments
Embryonic	26 days to 6 wks	5 lobar bronchi
Pseudoglandular	6–16 wks	Cartilage rings, cilia form
Acinar/canalicular	16–28 wks	Type I and II pneumocytes
Saccular	28–34 wks	Distal airspace development
Alveolar	34 wks to 2 years	Alveoli proliferate from 20 to 600 million

Congenital Lung Disease

Congenital malformations of the lung develop during fetal lung growth. They may be identified during an in-utero evaluation, present as respiratory distress in the newborn, or be completely asymptomatic and found in patients as adults. They can frequently occur with other congenital malformations and may be life threatening. Lung development begins during week 3 from the foregut. It progresses through birth to approximately 2 years of age when alveolar development is complete. The five stages of lung development have been divided into the embryonic, pseuodglandular, acinar, saccular, and alveolar stages (**Table 80.2**). Malformations may occur at each step and lead to different pathologic conditions.[48] Four separate conditions will be discussed here; pulmonary sequestration, lobar emphysema, congenital cystic adenomatoid malformation (CCAM), and bronchogenic cysts.[49]

Pulmonary Sequestrations

Pulmonary sequestrations are defined as pieces of parenchymal lung separated from the respiratory tree, with the sequestration receiving its blood

supply from an anomalous artery arising from the aorta, rather than having the blood supply arising from the pulmonary artery. Sequestrations have been further subdivided into extra- and intralobar lesions, with very distinct anatomic alterations and clinical presentations. Extralobar sequestrations reside outside of the true pleural space. Venous drainage is usually into the azygos or hemiazygos veins. They are most often on the left side between the left lower lobe and diaphragm (**Fig. 80.27**). Up to 80% of extralobar sequestrations occur in males. Most patients present with dyspnea in the first 6 months of life. They may be diagnosed by fetal ultrasound or after birth by chest x-ray. Other congenital abnormalities are found in up to two-thirds of patients, with congenital diaphragmatic hernias present in a quarter of patients.[48] Intralobar lesions reside within the normal lung and within the normal pleura. They are almost always in the lower lobes and occur in the left side just over 50% of the time. Venous drainage is usually through the pulmonary vein. It is suggested that intralobar sequestration may be an acquired disease, caused by repeated episodes of inflammation that lead to bronchiole narrowing and scarring. Ultimately the "lobe" becomes isolated and may develop new feeding blood vessels from collateral arteries in the inferior pulmonary ligament. A complete assessment of a sequestered lesion must be performed prior to resection, and should include assessment of any potential airway or gut connection, determining the vascular supply of the sequestration, and determining if there are any other congenital malformations.[48]

Congenital Lobar Emphysema

Lobar emphysema is the cause of half of the episodes of newborn respiratory distress that are due to structural anomalies. Two-thirds of the cases occur in males. Distension of the distal lung occurs from obstruction of the airway, either from an intrinsic cause, such as meconium or torsion, or an extrinsic cause, such as obstructing lymph nodes. In up to half of the cases, no cause can be found. Almost all cases occur in the upper lobes, with almost equal distribution between sides. Half of the lesions will present in newborns, and the remaining 50% will reveal themselves by 6 months. Chest x-rays are diagnostic (**Fig. 80.28**).[48] Surgical resection may not be immediately necessary, and may be delayed until the child has grown, or until they

develop a failure to thrive. Even after surgical resection, patients may have bronchomalacia and a tendency toward bronchospasm.[50]

Congenital Cystic Adenomatoid Malformation

CCAM lesions are the second most common cause (25%) of newborn respiratory distress, secondary to structural problems. Children will present either at birth or in early childhood with recurrent respiratory infections. The anomalies are due to an overgrowth of bronchioles, likely during the acinar phase of fetal lung development. Lesions can occur on either side and are usually isolated to one lower lobe. The classification system by Stocker (**Table 80.3**) organizes these lesions based on pathologic appearance and clinical outcome. Prenatal MRI best serves to evaluate these lesions, while postnatal chest x-ray and/or chest CT scan can be used to differentiate CCAMs from other lesions.[48] Even though lesions may be small and asymptomatic, these lesions possess the potential for malignant transformation and should be resected (**Fig. 80.29**).[50]

Bronchogenic Cysts

Bronchogenic cysts are formed from primitive foregut tissue present in the airway. They can present as single or multiple cysts in a wide variety of locations in the thorax. They usually present in young children who develop symptoms such as stridor due to airway obstruction or compression caused by the cysts.[49] Alternatively, cysts located within the lung parenchyma can become infected and present as an abscess. Therapeutic aspiration may be temporizing, but ultimately surgery is needed.[51] Resection may have a mortality of up to 14%, but untreated lesions have a 100% mortality.[49] Most cases of congenital lung disease will present in the first 6 months of life. The main symptom is usually respiratory distress, but once children reach 1 year in age, chronic infections become the most common symptom. Diagnostic tests begin with chest x-rays, but can include ultrasound, MRI, CT scans, angiography, and bronchoscopy, depending on the lesion and location.[52] Decision making regarding the timing of surgical resection should

incorporate the patient's acuity due to symptoms and their overall ability to tolerate surgery based on size.

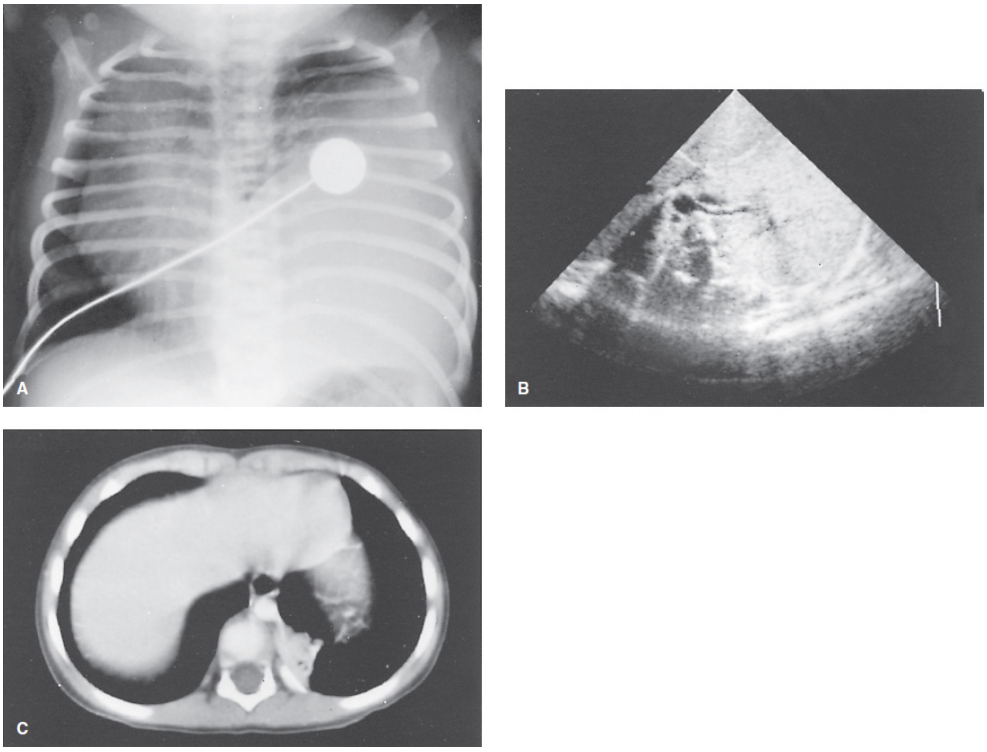


Figure 80.27 Abnormal radiograph of the chest of a newborn with respiratory distress (**A**). Ultrasound identified the anomalous vessel coursing through the diaphragm and entering the sequestration (**B**). This computed tomographic scan clearly demonstrates the anomalous artery arising from the thoracic aorta and entering the sequestered lung (**C**). (Reproduced with permission from Shields TW, ed. *General Thoracic Surgery*. 6th ed. 2005.)

Figure 80.28 Radiograph of a newborn with lobar emphysema involving the right middle lobe. Note the compressed right lower lobe and mediastinal shift. (Reproduced with permission from Shields TW, ed. *General Thoracic Surgery*. 6th ed. 2005.)

Pleural Disease

Pleural diseases include benign complications from systemic disease, postoperative infections, local infections, and cancers from primary and metastatic sites. Diseases involving the pleura can lead to limitations to respiration and symptoms of dyspnea. Surgical intervention may be indicated, and it is imperative for the surgeon to be able to recognize which disease processes require a surgical procedure. Pneumothoraces are discussed earlier in this chapter, and here we will cover pleural effusions, including empyemas, and malignant pleural mesotheliomas (MPMs).

Table 80.3 The Stocker Classification of CCAM

▪ Type I 75% of lesions Few large cysts Parenchymal compression
▪ Type II Numerous, <1 cm cysts Associated with other congenital anomalies Worse prognosis
▪ Type III Rarest type Cysts are solid and smaller (few mm in diameter)

Figure 80.29 Specimen removed from an infant with a cystic adenomatoid malformation. Microscopically, there was marked proliferation of terminal bronchioles, and cartilage was lacking. (Reproduced with permission from Shields TW, ed. *General Thoracic Surgery*. 6th ed. 2005.)

PLEURAL EFFUSIONS

Pleural effusions are a common condition that elicits a surgical consult for potential drainage and even thoracoscopic intervention to assist in the

diagnosis and treatment of the condition. The essential first step in the evaluation of a new effusion is to determine if it is a transudative or exudative process. A transudative fluid collection is the result of a poorly balanced hydrostatic and/or osmotic pressure across the pleural membrane resulting in increased serum leak across the pleural barrier. Exudative processes result from inflammation or neoplastic processes that cause increased capillary leak at the pleural membrane, which results in higher protein and lactate dehydrogenase (LDH) levels in the exudative fluid compared to the transudative fluid (**Table 80.4**).[53] The Light's criteria are commonly used to distinguish transudative and exudative effusions (**Table 80.5**). If one or more of the criteria are met, then the fluid is considered exudative.[54] Other tests have been evaluated, including measuring cholesterol ratios, albumin gradient, but Light's criteria are still the best overall test.[53]

Transudative effusions are most often caused by congestive heart failure. Even if a patient does not have other symptoms of heart failure, in the setting of a transudative effusion, a complete cardiac workup should be considered. The pleural fluid concentration of N-terminal pro–B-type natriuretic peptide can accurately identify effusions due to heart failure.[55] Other causes include cirrhosis which may or may not be associated with ascites. Isolated right- and left-sided effusions due to liver disease have been described. Effusions can be seen in more than 20% of patients with nephrotic syndrome, and so all patients with new effusions should be evaluated for the presence of proteinuria. Rarer causes include retroperitoneal urine leaks or cerebrospinal 6 fluid leaks.[56] Surgical interventions, such as chest tube placement, should be avoided in transudative disease settings, as patients will continue to drain fluid from their chest until the primary cause is treated. Aspiration of fluid may help temporarily while systemic treatment is instituted, but should only be done as part of a larger treatment plan.

Table 80.4 Differential Diagnosis of Pleural Effusions

Transudative Pleural Effusions

Congestive heart failure
Pericardial disease
Cirrhosis
Nephrotic syndrome
Peritoneal dialysis
Superior vena cava obstruction
Myxedema
Pulmonary emboli
Sarcoidosis
Urinothorax

Exudative Pleural Effusions

Neoplastic diseases
- Metastatic disease
- Mesothelioma

Infectious diseases
- Bacterial infections
- Tuberculosis
- Fungal infections
- Viral infections
- Parasitic infections
- Pulmonary embolization

Gastrointestinal disease
- Esophageal perforation
- Pancreatic disease
- Intra-abdominal abscess
- Diaphragmatic hernia
- Postabdominal surgery
- Endoscopic variceal sclerotherapy

Collagen vascular diseases
- Rheumatoid pleuritis
- Systemic lupus erythematosus
- Drug-induced lupus erythematosus
- Immunoblastic lymphadenopathy
- Sjögren syndrome

Wegener granulomatosis
Churg–Strauss syndrome
Postcardiac injury syndrome
Asbestos exposure
Sarcoidosis
Uremia
Meigs syndrome
Yellow nail syndrome
Drug-induced pleural disease
Nitrofurantoin
Dantrolene
Methysergide
Bromocriptine
Procarbazine
Amiodarone
Trapped lung
Radiotherapy
Electric burns
Urinary tract obstruction
Iatrogenic injury
Ovarian hyperstimulation syndrome
Chylothorax
Hemothorax

Table 80.5 Criteria for Exudative Effusions Based on Ratio of Pleural Fluid Protein and LDH Concentrations to Serum Concentration

Protein/serum protein >0.5
LDH/serum LDH >0.6
Pleural LDH 1.67 times normal serum LDH

LDH, lactate dehydrogenase.

Exudative effusions have a number of etiologies, but infections, typically pneumonia, are the most common cause.[54] Tuberculosis (TB) and fungal infections can also cause exudative effusions. Although rarer in the United States, TB is still a common etiology worldwide. If someone is suspected of having pleural TB, the pleural fluid should be evaluated for adenosine deaminase (ADA) and gamma-interferon levels, which if low will rule out the diagnosis of TB. If other infections are suspected, the pleural fluid should be cultured.

Malignancy is the next most common cause of exudative effusions.[54] Approximately a quarter of pleural effusions in a community hospital setting have been attributed to cancer. The malignancies that cause the effusions are, in order of decreasing frequency: lung cancer, breast cancer, and hematologic cancers such as lymphoma. Other malignancies can also cause effusions, such as ovarian cancer.[57] Pancreatitis may also cause an exudate, and elevated serum amylase levels will support the diagnosis. Autoimmune processes, such as rheumatoid disease and lupus, can also cause effusions. A chylothorax may present after problems with thoracic duct lymphatic drainage leading to an accumulation of lymphatic fluid, "chyle," in one or both thoraces. The thoracic duct collects lymph from the cysterna chyli, the plexus of lymphatics in the upper abdomen, and travels anterior to the spine and just posterolateral to the aorta. It follows behind the aorta and enters the left neck where it empties into the confluence of the left internal jugular and subclavian veins (**Fig. 80.30**). Chylous leaks are due primarily to thoracic duct injury from trauma or surgery or lymphomas resulting in obstructed lymphatics. Pleural triglyceride and cholesterol levels will be elevated and the fluid will have a milky color. Treatment for persistent chylothoraces includes thoracic duct ligation by surgery or by embolization of the site of leak in the interventional suite.[58]

The management of malignant pleural effusions includes a variety of options, but critical to the decision-making process is the knowledge of the median life expectancy in that patient due to the underlying malignancy. Chest tube drainage may be therapeutic and diagnostic, allowing fluid drainage and alleviation of symptoms of dyspnea. It will also allow determination of whether the underlying lung is able to expand. If not, it is described as a "trapped lung" and although the fluid may be gone, a persistent pneumothorax appears on chest x-rays as the lung cannot expand and fill the thorax. In these

settings, an indwelling pleural drainage catheter may be the best option to intermittently drain accumulating fluid. Decortication is not recommended, as most patients with malignancy in this setting have a limited life expectancy and the success rate is low compared to decortication in the setting of an empyema. VATS exploration may also be used to remove loculated fluid collections and to evaluate for lung reexpansion after the procedure. If the lung reexpands, further treatment includes pleurodesis, utilizing talc, doxycycline, or bleomycin. These medications will cause an inflammatory reaction between the parietal and visceral pleura resulting in the lung being "stuck" in an expanded state. Mechanical pleurodesis can also be performed by mechanical debridement of the pleura via VATS. Chemical pleurodesis may be performed via VATS or through an existing thoracostomy tube. The goal of treatment in the setting of a malignant pleural effusion is palliation.[57] Patients treated with indwelling pleural catheters may spend fewer days in the hospital at the end of life than patients treated with pleurodesis.[59]

THORACIC DUCT

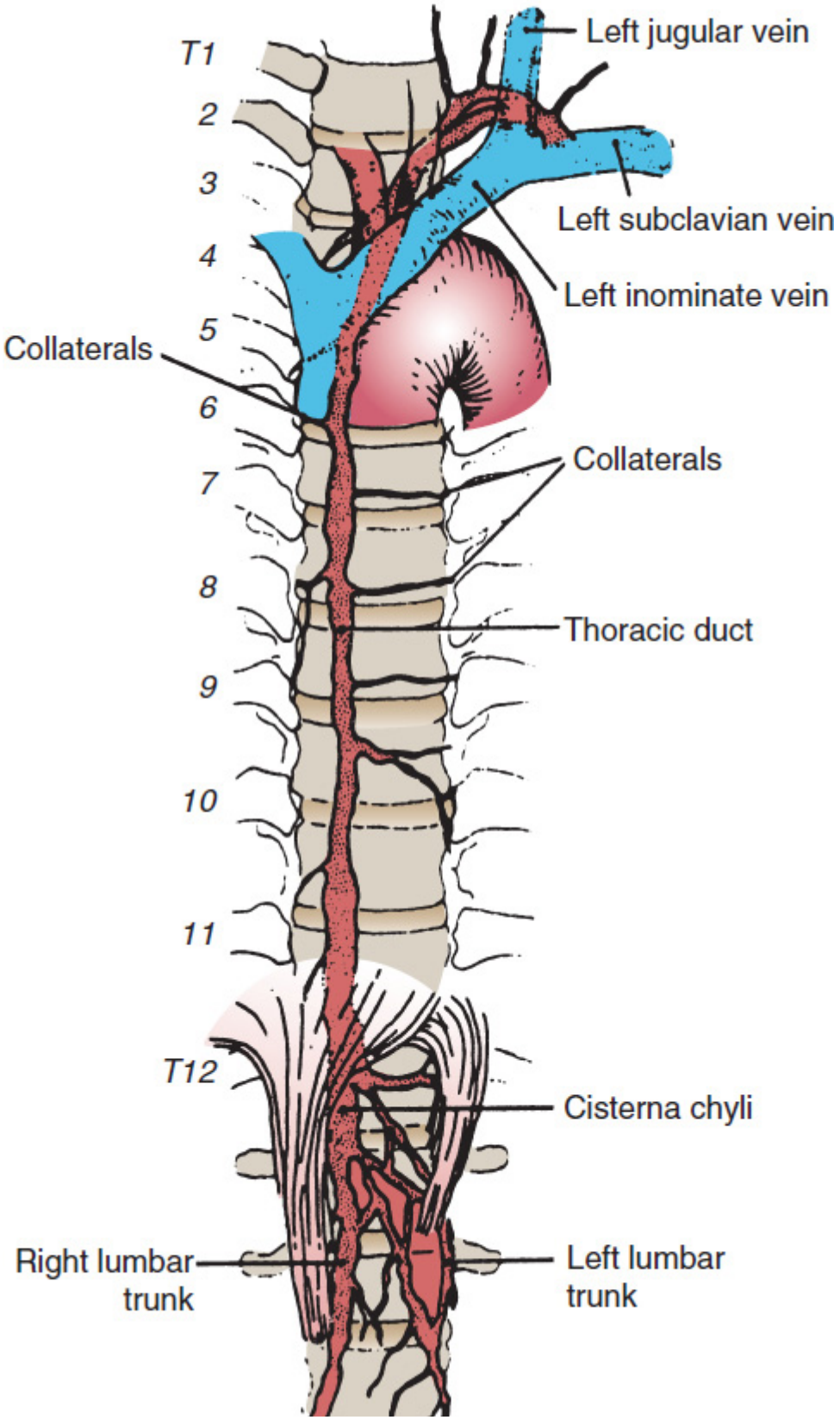


Figure 80.30 Schematic drawing of the most usual pattern and course of the thoracic duct. The single duct that enters the chest through the aortic hiatus between T12 and T10 is a relatively consistent finding and the usual site for surgical ligation.

Empyema

7 Empyemas are defined as frank pus in the thoracic cavity. This represents part of the continuum of disease that begins with simple parapneumonic effusion, where exudative fluid is not infected and not loculated. As the disease progresses, fluid becomes loculated with fibrinous septations and becomes infected, leading to pus and ultimately the development of a fibrinous peel. Up to half of pneumonias have an associated effusion, but less than 5% of cases lead to an empyema.[60] Other causes include surgical thoracotomies and/or other infections from nearby organs, such as esophageal injuries. Pleural infections have been categorized into three overlapping stages. The first is the exudative stage, where the fluid is thin, sterile, has a lower white blood cell (WBC) count and LDH levels, and the glucose level is still above 40 mg/dL (**Table 80.6**). Treatment usually involves addressing the underlying etiology, such as pneumonia. The second stage is the fibrinopurulent stage, where the fluid becomes infected and fibrin deposits accumulate on the pleura. The LDH and WBC count increases, the glucose and pH levels drop. The fluid becomes thick and purulent and the lung is often unable to expand. Chest tube drainage alone at this stage may not be effective to remove the fluid. The third stage is the organizing stage, and a thick pleural peel is created by migrating fibroblasts. At this point, a formal debridement and decortication are required to allow the lung to return to full function.[60]

Table 80.6 Diagnostic Criteria for Pleural Fluid in Empyema

Stage	Fluid/Peel	WBC	LDH (cells/mm^3)	pH (IU)	Bacteria
Exudative	Thin/elastic	<1,000	<500	>7.3	Absent
Fibrinopurulent	Purulent/ inelastic	>5,000	>1,000	<7.1	Present
Organizing	Thick/rigid peel	Varies	Varies	<7.1	Varies

Organisms causing empyemas have shifted from predominately *Streptococcus pneumoniae* in the preantibiotic era, to anaerobic organisms in up to three-quarters of empyemas in the current era. There is also a notable difference between community-acquired and hospital-acquired empyema, with a higher prevalence of *S. aureus* and *Klebsiella pneumoniae* in hospital-acquired empyemas.[61] Imaging to evaluate the presence of an empyema begins with a simple chest x-ray, but requires a chest CT to show potential loculations. After the institution of antibiotic therapy, surgical intervention depends on the stage of the disease, but may require a VATS exploration or even a thoracotomy to debride the thorax effectively and to decorticate the pleural peel off of the lung to allow reexpansion.[60] Postpneumonectomy empyemas are an especially difficult problem as there is no lung tissue to occupy the empty thorax. Risk factors in this setting include right pneumonectomies (vs. left), the need for postoperative ventilation, lower starting hematocrit levels, and poor preoperative pulmonary function test results.[62,63] Treatments of these empyemas are particularly difficult and may include an Eloessor flap or the Clagget procedure which allows for the creation of an open wound that allows for packing and granulation tissue to form in the empyema cavity.[64]

Mesothelioma

MPM is a cancer of the serosal pleura, related to the exposure to asbestos. Multiple hypotheses have been formed regarding how asbestos causes mesothelioma, and include the idea that asbestos fibers are inhaled deeply into the lung and penetrate the parenchymal surface, causing irritation of the pleura and repeated episodes of inflammation, ultimately leading to cancer. Other potential mechanisms include asbestos interfering with mitosis,

inducing free-radical production, and induction of proto-oncogene kinases by asbestos fibers.[65] Exposure to asbestos usually occurs decades prior to presentation with mesothelioma, and has been seen in miners exposed to asbestos dust, industrial workers such as plumbers and carpenters who used asbestos products, and even in 20% of patients with no known exposure but living in industrial countries. Mesothelioma is a relatively rare malignancy, with less than 5,000 cases in the United States per year.[66]

Patients with mesothelioma may present with dyspnea or chest pain. Often, patients are asymptomatic and the diagnosis is made after abnormalities are seen on a chest x-ray performed for another reason. Radiographs may show unilateral effusions and a loss of volume on the affected side, as the lung capacity is diminished due to disease. As the disease progresses, patients may have weight loss, worsening pain, and night sweats. Median survival may be as little as 1 year from the time of diagnosis.[67] Diagnostic studies include a chest CT scan or MRI to show the extent of pleural thickening as well as signs of local spread or metastasis (**Fig. 80.31**). The pathologic diagnosis almost always requires a tissue biopsy with a CT-guided biopsy, VATS, or thoracotomy approach. Cytologic examination of pleural fluid from a thoracentesis cannot differentiate between mesothelioma cells and other potential lung cancers. If the patient is being considered for surgical resection, a limited thoracotomy in the site of a potential later incision is optimal to limit seeding of the tumor.[67]

Mesotheliomas can be categorized into epithelial, sarcomatoid, and mixed histologies. Patients with epithelial histology have longer median survival than those with a sarcomatoid histology.[68] There are a variety of staging systems for mesothelioma, including the Butchart system, the revised Brigham and Women's Hospital system, and the TNM-based system by the International Mesothelioma Interest Group (IMIG) and International Association for the Study of Lung Cancer (IASLC) (**Table 80.7**).[69] The IMIG system allows for better reproducibility of the interpretation of local and regional lymph node spread. Laparoscopy may be useful to evaluate the patient for transdiaphragmatic spread of the tumor, differentiating between T3 and T4 tumors.[70]

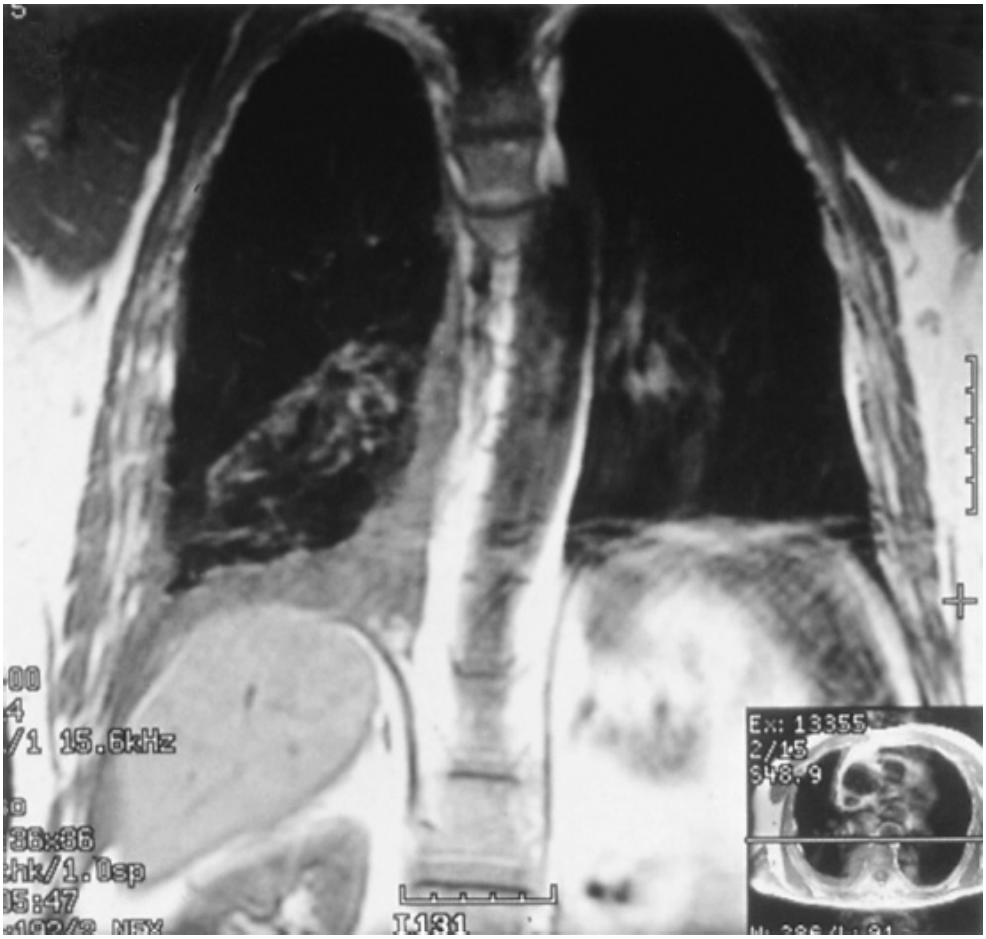


Figure 80.31 Magnetic resonance imaging of the patient in **Figure 80.25** shows a large amount of tumor within the pleural space and into the diaphragmatic sulcus with no evidence of extension outside the hemithorax. (Reproduced with permission from Flores RM, Sugarbaker DJ. Malignant mesothelioma of the pleural space. *Ann Thorac Surg* 2000;70:306.)

Table 80.7 The International Mesothelioma Interest Group (IMIG) and IASLC Staging System

T–Tumor	
T1	Tumor involving the ipsilateral parietal pleura (including mediastinal and diaphragmatic pleura) with or without involvement of visceral pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: Confluent visceral pleural tumor (including the fissures), involvement of diaphragmatic muscle, invasion of the lung parenchyma
T3	Locally advanced but potentially resectable tumor; tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic, and visceral pleura) with at least one of the following features: Involvement of the endothoracic fascia, extension into the mediastinal fat, solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall, nontransmural involvement of the pericardium
T4	Tumor involving all of the ipsilateral pleural surfaces with at least one of the following features: Diffuse multifocal invasion of soft tissues of the chest wall, any rib involvement, invasion of the peritoneum through the diaphragm, invasion of any mediastinal organ, direct extension to the contralateral pleura, invasion of the spine or brachial plexus, transmural invasion of the pericardium (with or without pericardial effusion) or myocardium invasion
N–Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases

N1	Metastases in the ipsilateral bronchopulmonary, hilar, or mediastinal lymph nodes (including the internal mammary, peridiaphragmatic, pericardial fat pad, or intercostal lymph nodes)
N2	Metastases in the contralateral bronchopulmonary, hilar, or mediastinal lymph nodes or ipsilateral or contralateral supraclavicular lymph nodes
M– Metastases	
MX	Presence of distant metastases cannot be assessed
M0	No evidence of distant metastases
M1	Evidence of distant metastases
Stage	**Description**
I	
Ia	T1N0M0
Ib	T2N0M0, T3N0M0
II	T1N1M0, T2N1M0
IIIa	T3N1M0
IIIb	T1N2M0, T2N2M0, T3NM0
IV	Any T4 Any M1

Adapted from Berzenji L, Van Schil P, Carp L. The eighth TNM classification for malignant pleural mesothelioma. *Transl Lung Cancer Res* 2018;7(5):543–549.

Treatment for mesothelioma may include chemotherapy, radiation therapy, and surgery. Surgical treatment ranges from a pleurodesis for palliation in the setting of effusions and unresectable disease, to pleurectomy/decortication for limited disease, and to the most aggressive treatment of an extrapleural pneumonectomy (EPP), with the goal of complete tumor resection. Less than a third of patients are candidates for any surgical intervention. Preoperative

workup for an EPP should include a cardiac evaluation, and optimal surgical candidates have pulmonary function tests with an FEV_1 of greater than 2 L/sec and an age under 70.[70] Surgery involves an en bloc removal of the lung, pleura, pericardium, and diaphragm with reconstruction of the pericardium and diaphragm. Pleurectomy and decortication are reserved for very early-stage disease and involves removal of the pleura only with preservation of the lung parenchyma. Multimodality approaches have shown better results, with neoadjuvant chemotherapy and adjuvant radiation therapy.[71] Chemotherapy for advanced disease includes pemetrexed and cisplatin or the combination of gemcitabine and cisplatin.[72] Both have shown similar levels of palliation. Radiotherapy may also be used, but is limited by the large field requiring treatment and the risks of pneumonitis and esophagitis.[65] It is best used in combination with EPP for local control after surgery, or to treat local painful areas.[70] Because of the rarity of surgical cases, most patients who are considered for surgery should be referred to high-volume centers where surgeons and other clinicians are comfortable treating this disease.

Trachea

The trachea is a well-known structure to the general surgeon who may perform tracheostomies and bronchoscopies as part of their clinical practice. A thorough knowledge of the anatomy and vascular supply is essential to minimize complications such as postintubation tracheal stenosis and tracheoinnominate fistulas after tracheostomies.

Anatomy

The trachea is the connection from the cricoid cartilage to the carina that allows ventilation and mucous clearance from the lungs. It is oval shaped, with C-shaped cartilaginous rings creating the anterior and lateral borders. A soft tissue membrane forms the posterior wall to complete the oval shape. In the average male, the anterior–posterior dimension is 1.8 cm, while the lateral aspect is 2.3 cm. Tracheal length reaches almost 12 cm with about 2 rings/cm. Tracheae in women are 10% to 20% smaller in size. In children, the shape is more circular, but becomes gradually more ovoid as people age.

There is a significant amount of flexibility in the normal trachea, and remodeling can occur in chronic disease states such as emphysema. The inner lining consists of ciliated pseudostratified columnar epithelium with goblet and mucous cells interspersed. At the carina, the right and left mainstem bronchi split off. The right side is characterized by the quick takeoff of the right upper lobe bronchus, with the bronchus intermedius continuing into the middle and lower lobe bronchi. The left side has a longer mainstem bronchus with a split into the upper and lower lobes.[73] The blood supply begins with the inferior thyroid artery supplying the cervical trachea through three tracheoesophageal branches. The lower trachea is supplied by bronchial arteries arising off the aorta. As the arteries approach the trachea, they further split to supply separate segments. Even within segments, it will branch into anterior and posterior transverse intercartilaginous arteries (**Fig. 80.32**). Because of this segmental blood supply, there should be minimal circumferential dissection around the trachea to limit impairment of the blood supply and healing in tracheal/bronchial surgery.

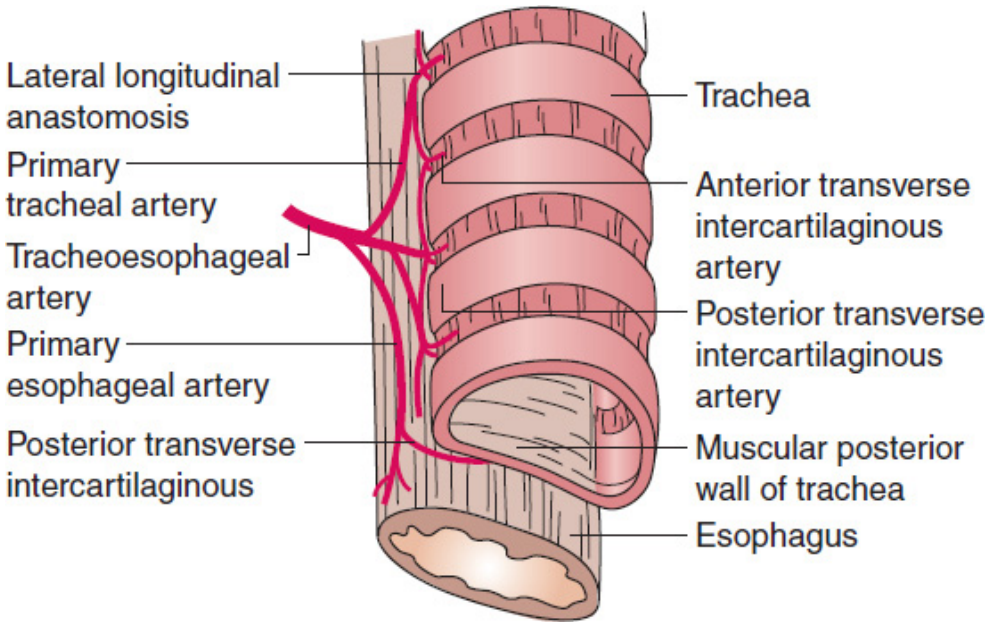


Figure 80.32 Semischematic view of the tracheal microscopical blood supply. Transverse intercartilaginous arteries derived from the lateral longitudinal anastomosis penetrate the soft tissues between each cartilage to supply a rich vascular network beneath the endotracheal mucosa.

Surgical Airways

The most common tracheal procedure is a tracheostomy. Over the last 20 years, there has been an increasing utilization of percutaneous tracheostomy. For patients who are intubated, the indication for and timing of tracheostomy depends on a multitude of factors, of which there is very little consensus in the medical literature. The goal of a tracheostomy is to limit the risk of laryngeal stenosis caused by prolonged endotracheal intubation, to improve pulmonary toilet, and to improve oral hygiene. Generally, tracheostomy should be considered after a patient has been intubated for more than 10 days, without clear expectation for immediate extubation.[74] Ideally, patients should be on minimal ventilator settings, but tracheostomy may be performed in patients with elevated oxygen (FiO_2 of up to 60%) and ventilatory (PEEP under 10) requirements. Patients requiring more support are at high risk of decompensating if they lose their airways, even if just for a moment, and the decision to perform a tracheostomy should be carefully considered in this setting (**Table 80.8**).[75]

Tracheostomies are performed with the neck extended. A 2- to 3-cm incision is made approximately 2 cm above the sternal notch. Dissection is carried down through the platysma, and the strap muscles are divided longitudinally. Exposure of the trachea and the 2nd and 3rd rings may require elevation of the thyroid. Lateral traction sutures may be placed around the 2nd or 3rd rings. A vertical incision is made between rings 2 and 4 and gradually dilated. A tracheostomy tube is placed under direct vision.[74,76] Percutaneous tracheostomy placement is based on the Seldinger technique. A needle is placed percutaneously into the trachea at the estimated level of the 2nd or 3rd rings with bronchoscopic visualization. A guidewire is placed into the airway, and serial dilations performed, until a tracheostomy tube is able to be advanced over the wire.[75] Cricothyroidotomy should only be performed in the emergent setting. The cricothyroid membrane is palpated below the superior thyroid notch. A transverse incision is made to the lateral borders of the thyroid cartilage. Rapid dilation is followed by tube insertion.

Complications can vary depending on the technique. Fistulas result from erosion of the tracheostomy tube into the innominate artery, with placement below the 3rd ring placing patients at higher 8 risk. A sentinel bleed may be the initial presentation. Pressure on the fistula with immediate repair or ligation of the vessel is required (**Fig. 80.33**).[77] Postintubation stenosis is

usually due to necrosis caused by high-pressure cuffs resulting in impaired blood flow to the segmental area of the trachea. This leads to the long-term loss of cartilage and narrowing of the airway. The use of low-pressure cuffs has reduced the incidence of this complication, but not eliminated it. Bronchoscopy and dilation may alleviate symptoms, but resection of the stenotic area may be needed (**Fig. 80.34**).[76]

Table 80.8 Tracheostomy Complications

Immediate Complications	Early Complications	Late Complications
Hemorrhage	Hemorrhage	Tracheal Stenosis
Structure damage to trachea	Tube displacement	Granulation tissue
Failure of procedure	Pneumothorax	Tracheomalacia
Aspiration event	Pneumomediastinum	Pneumonia
Air embolism	Subcutaneous emphysema	Aspiration event
Loss of airway	Stomal infection	Tracheoarterial fistula
Death	Stomal ulceration	Tracheoesophageal fistula
Hypoxemia, hypercarbia	Accidental decannulation Dysphagia	Accidental decannulation Dysphagia

Adapted from Cheung N, Napolitano LM. Tracheostomy: epidemiology, indications, timing, technique, and outcomes. *Respiratory Care* 2014;59(6):895–919.

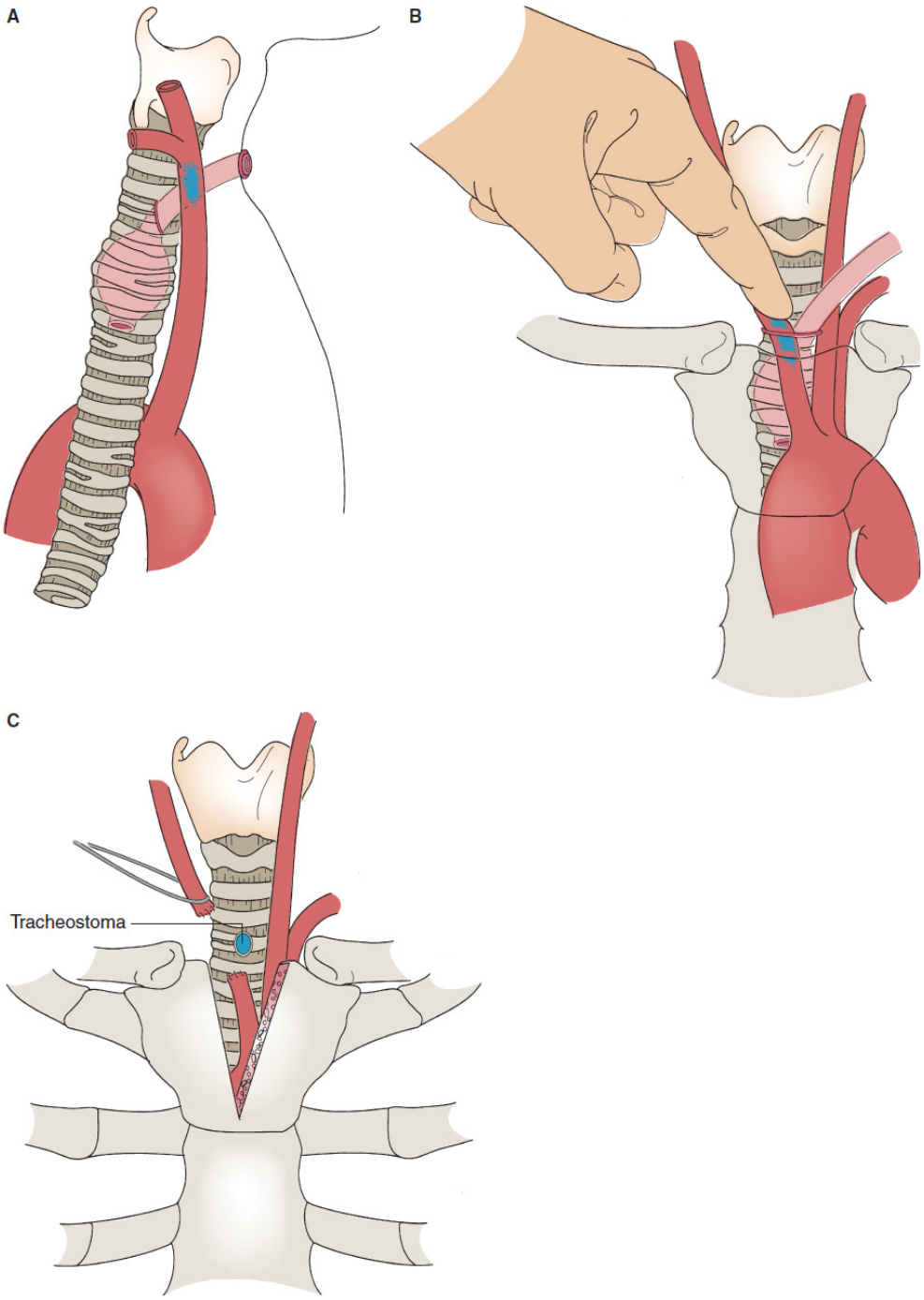


Figure 80.33 Management of tracheoinnominate artery fistula. **A:** Common mechanism of injury from erosion of innominate artery by adjacent tracheostomy tube. **B:** Emergency treatment of hemorrhage involves insertion of an endotracheal tube into the tracheostomy stoma, inflation of the cuff, and downward and outward pressure on the fistula by the finger inserted through the tracheostomy incision to further tamponade the bleeding. **C:** Through a partial upper sternal split, the segment of involved innominate artery is resected and the oversewn ends covered with adjacent mediastinal fat or muscle. Tracheal resection is usually not necessary. A new tracheostomy tube may have to be inserted higher in the trachea or, if

possible, the tracheostomy tube removed and the stoma covered with a sternohyoid muscle flap.

Tracheal Tumors

Benign lesions of the trachea are less common than malignant ones. They include papillomas, chondromas, hamartomas, fibromas, and hemangiomas. Papillomas are associated with the human papilloma virus and can degenerate into malignant lesions, thus requiring resection. Chondromas arise from the cartilage, and may recur after resection. Hamartomas are comprised of cartilage, epithelial, and lymphatic tissues. Recurrence is rare after resection. Fibromas can be resected via bronchoscopy. Hemangiomas are the most common pediatric tracheal mass. They may regress without treatment and can be observed if not causing obstructive symptoms. Biopsy is generally avoided due to bleeding risk. Surgery may be required if lesions persist.[78]

Although more common than benign lesions, malignant tracheal tumors are very rare with only 600 to 700 cases in the United States per year. Lesions may be primary tracheal lesions, tumors from adjacent organs growing into the trachea, or metastatic lesions.[79] Primary tumors are most commonly squamous cell carcinomas or adenoid cystic carcinomas in the trachea, followed by carcinoids in the bronchi.[79,80] Adjacent tumors may arise in the lung, esophagus, thyroid, or mediastinum. The most common cancers that cause tracheal metastases include renal cell cancers, sarcomas, breast cancers, and colon cancers.[79] Patients will present with stridor and wheezing, and have often been recently diagnosed with adult-onset asthma and treated with inhalers and even steroids without alleviation of symptoms. Hemoptysis may also occur, though it is more common in lung cancer than in tracheal disease.[80] Patients should undergo imaging such as a neck and chest CT scan to assist in making the proper diagnosis. Bronchoscopy with a flexible or rigid endoscope is essential to aid in the evaluation of the extent of disease and to control the airway if necessary. Treatment includes tracheal resection for primary tumors if possible. For metastatic disease, palliative treatment includes endoluminal resection and/or radiotherapy.[80] Endoluminal treatments include mechanical core-out, YAG-laser treatment, photodynamic therapy (PDT), cryotherapy, or brachytherapy. Stenting also may play a role

to maintain airway patency, either for a temporary period during radiation treatment, or in the setting of end-stage disease (**Algorithm 80.5**).[79]

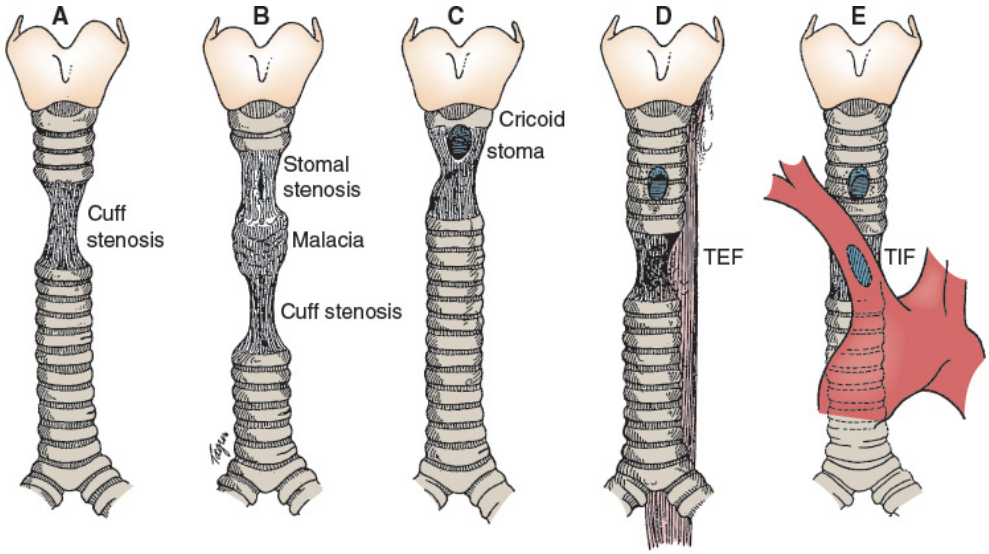
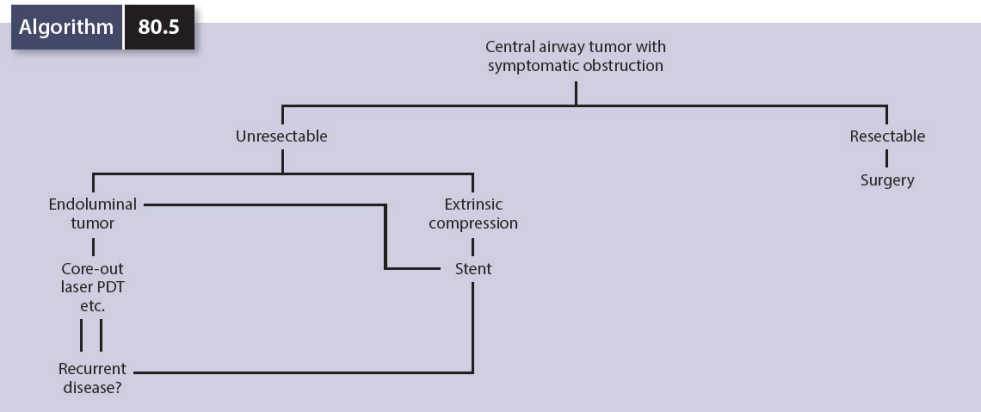


Figure 80.34 Diagrams of principal postintubation tracheal lesions. **A:** Cuff stenosis from the cuff of an endotracheal tube. **B:** Cuff stenosis from the cuff of a tracheostomy tube, usually lower in the trachea than that from an endotracheal tube. Stomal stenosis also occurs at the site of the tracheostomy itself. Malacia may occur either at the level of the cuff or in the segment between the stoma and the cuff stenosis. **C:** Cuff stenosis at the site of a high tracheostomy stoma, which has eroded into the lower margin of the cricoid cartilage. In older patients, this may erode back farther into the subglottic larynx, producing a laryngotracheal stenosis. A stoma placed in the cricothyroid membrane will, by definition, produce an intralaryngeal stenosis. **D:** Tracheoesophageal fistula (TEF) produced by pressure of the cuff against the "party wall," often abetted by an indwelling firm nasogastric tube. **E:** One type of tracheoinnominate fistula (TIF) as the result of a high-pressure cuff erosion. The more common type, but also rare, is that seen with a low-placed tracheostomy stoma, which rests against the innominate artery itself. (Reproduced with permission from Grillo HC. Surgical treatment of postintubation tracheal injuries. *J Thorac Cardiovasc Surg* 1979;78:860–875.)

Tracheomalacia and Airway Stents

Tracheomalacia occurs when the trachea loses its rigid form and the posterior membranous wall approaches the anterior wall, causing luminal narrowing and obstruction leading to dyspnea. Patients have a characteristic seal-like cough. Chest CT scans may demonstrate this condition, and pulmonary function testing in these patients will show reduced FEV_1, FVC, and peak expiratory flow rates. Bronchoscopy is the best diagnostic test and

reveals real-time airway collapse with expiration. Etiologies include congenital tracheomalacia, extrinsic compression, postintubation stenosis and inflammation, relapsing polychondritis, and COPD.[81] Surgical intervention may include resection for localized involvement, tracheoplasty, or stenting.[81,82] Airway stents can be divided into two groups, silicone and metal, with each type having distinct advantages (**Table 80.9**). Newer stents being developed include covered metal stents that prevent tumor in growth along the stent, but unfortunately still allow granulation tissue to grow in at the ends.[83] In addition to being useful in the setting of tracheal stenosis, they can also play an essential role in palliating posttransplant bronchial stenosis.[84]



Algorithm 80.5 Algorithm for management of tracheal masses. (Adapted from Wood DE. Management of malignant tracheobronchial obstruction. *Surg Clin North Am* 2002;82(3):621–642.)

Table 80.9 Classification of Airway Stents

- Silicone stents
  - Advantages
    - Adjustable
    - Removable
    - Minimal granulation
  - Disadvantages
    - Gen. anesthesia/rigid bronch to place
    - Migrates
    - Secretions adhere to stent
    - Interferes with ciliary clearance
    - Smaller inner diameter
- Metal stents
  - Advantages
    - Less migration
    - Larger inner diameter
    - Less ciliary interference
    - Flexible bronch to place
  - Disadvantages
    - May need balloon dilation
    - Difficult to remove
    - Granulation and tumor ingrowth in the stent
    - Radial force may lead to necrosis/fistula

Mediastinum

The mediastinum contains a number of important structures and may be involved in different disease processes. The mediastinum is divided into several compartments, including the superior, anterior, middle, and posterior regions. Sometimes the lower three compartments are extended superiorly and only three are described (**Fig. 80.35**). The anterior mediastinum includes the fat and lymph nodes posterior to the sternum, but anterior to the pericardium. The middle compartment includes the pericardium, heart, aorta, and trachea. The posterior compartment includes the esophagus, sympathetic

chain, and vertebral column (**Fig. 80.36**). Most lesions are found in asymptomatic patients, but presenting symptoms include dyspnea and chest pain. Symptoms may be local, related to compression on mediastinal structures, or systemic, caused by the release of cytokines or inflammatory factors, such as in lymphomas or thymomas with myasthenia gravis (MG). Imaging begins with plain radiographs, but CT scans are essential. MRI scans may be helpful to evaluate vascular or spinal involvement. PET scans are increasingly utilized as they may further aid in staging. Biopsy and/or surgical resection is required to confirm the diagnosis in almost all patients.[85]

Anterior Mediastinum

The anterior mediastinum can contain a variety of tumors (**Table 80.10**). Most common are thymomas, lymphomas, and germ cell tumors, in that order. Thymomas account for one-fifth of all anterior mediastinal masses in the adult population. They arise from the thymus gland and can be seen with autoimmune diseases such as MG and pure red cell aplasia. Tumors were previously classified by the Masaoka classification system which has now been supplanted by the IASLC TNM system (**Table 80.11**).[86] The World Health Organization (WHO) histologic criteria, which is based upon the morphology of the epithelial cells as well as the lymphocyte to epithelial cell ratio. Diagnosis is usually made by chest CT scan. Needle biopsy of a potential thymoma is not routinely recommended for fear of seeding the needle track. When thymomas are suspected, resection is the best option, via a midline sternotomy or thoracoscopic approaches (**Fig. 80.37**). During resection, one must take care to remove all of the tissue in the anterior compartment, including all fat and tissue around the innominate vein. Pleural seeding via drop metastases is a theoretical downside of thoracoscopic approaches compared to sternotomy.

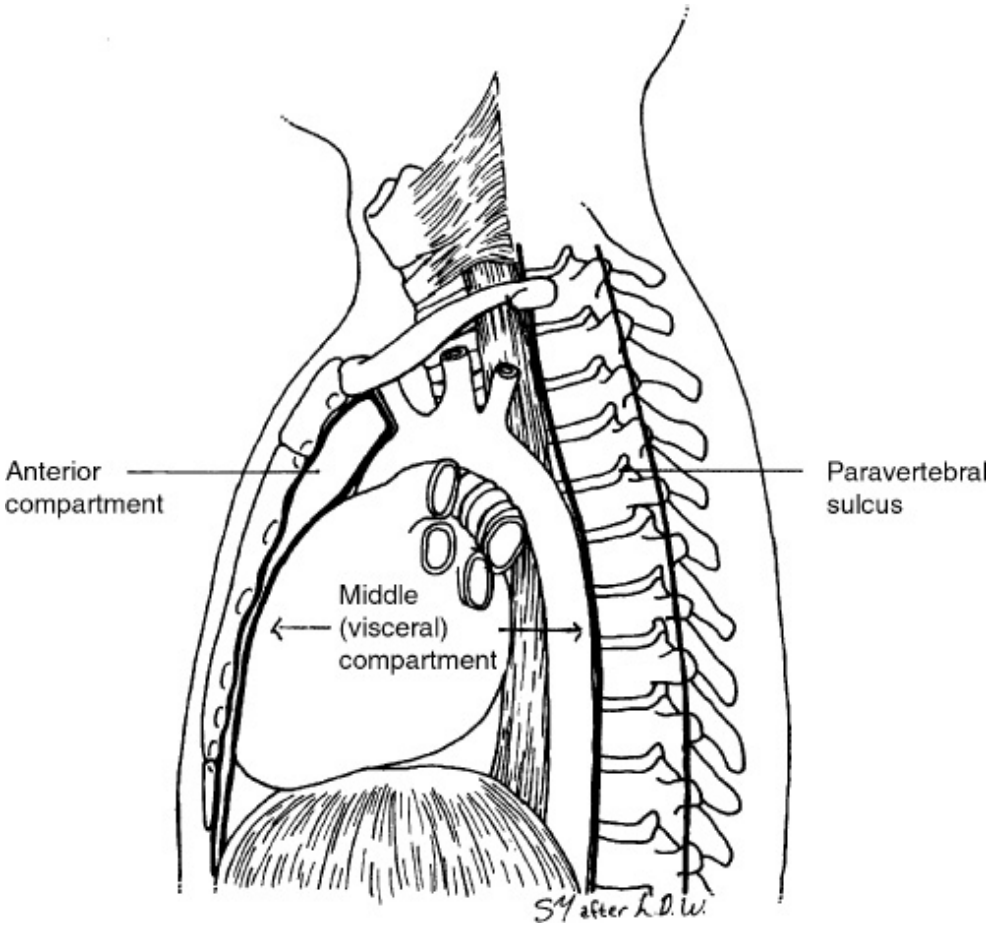


Figure 80.35 The mediastinal subdivisions. Note that the paravertebral sulcus encompasses the posterior compartment. (Reproduced with permission from Shields TW, ed. *General Thoracic Surgery*. 6th ed. 2005.)

Table 80.10 Location of Primary Mediastinal Masses in Adults and Children

Anterosuperior Mediastinum
Thymoma
Lymphoma
Germ cell tumor
Lymphangioma
Hemangioma
Lipoma
Carcinoma
Thyroid adenoma
Parathyroid adenoma
Middle Mediastinum
Pericardial cyst
Bronchogenic cyst
Lymphoma
Posterior Mediastinum
Neurogenic tumor
Enteric cyst

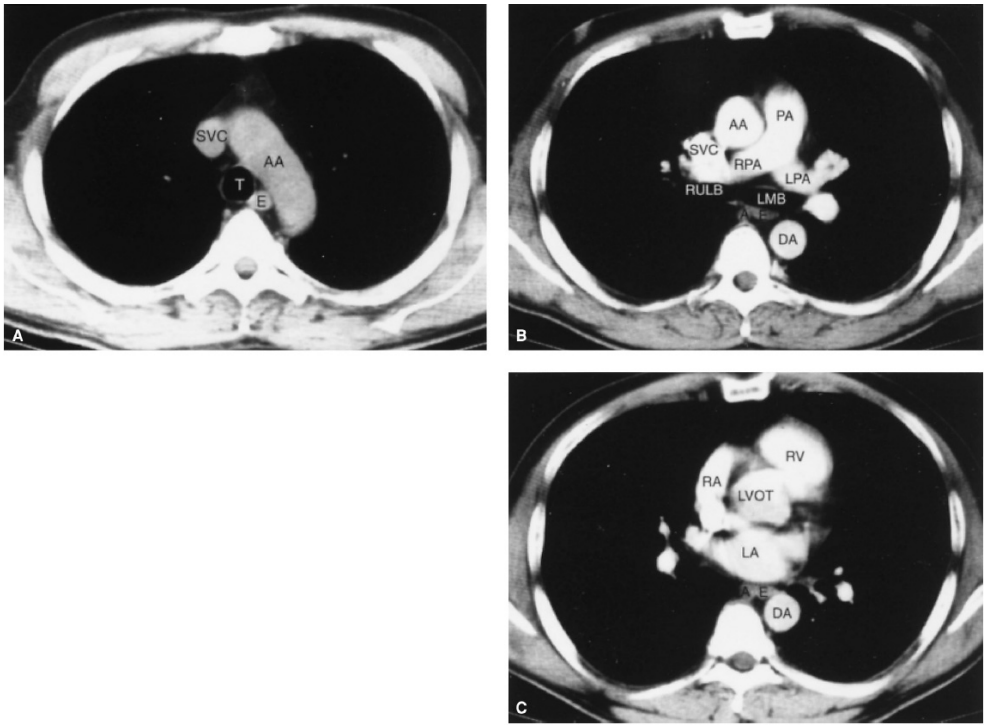


Figure 80.36 Normal mediastinal anatomy as shown with computed tomography scans. **A:** Scan at level of the aortic arch and midtrachea. T, trachea; E, esophagus; AA, aortic arch; SVC, superior vena cava. **B:** Scan at level of carina. RULB, right upper-lobe bronchus; LMB, left mainstem bronchus; AA, ascending aorta; DA, descending aorta; A, azygos vein; PA, main pulmonary artery; LPA and RPA, left and right pulmonary arteries. **C:** Scan at the level of the left atrium. LA, left atrium; RA, right atrium; LVOT, left ventricular outflow tract; RV, right ventricle.

Table 80.11 IASLC Staging System for Thymoma

T-Tumor	
T1a	Encapsulated or unencapsulated, with or without extension into mediastinal fat
T1b	Extension into mediastinal pleura
T2	Pericardium
T3	Lung, brachiocephalic vein, superior vena cava, chest wall, phrenic nerve, hilar (extrapericardial) pulmonary vessels
T4	Aorta, arch vessels, main pulmonary artery, myocardium, trachea, or esophagus
N–Lymph Nodes	
N0	No lymph node involvement
N1	Anterior (perithymic) nodes
N2	Deep intrathoracic or cervical nodes
M–Metastases	
M0	No metastatic pleural, pericardial, or distant sites
M1a	Separate pleural or pericardial nodule(s)
M1b	Pulmonary intraparenchymal nodule or distant organ metastasis
Stage	**Description**
I	T1N0M0
II	T2N0M0
IIIa	T3N0M0
IIIb	T4N0M0
IVa	T1-4N1M0, T1-4N0-1M1a
IVb	T1-4N2M0-1a, T1-4N0-2, M1b

Adapted from Detterbeck FC, Stratton K, Giroux D, et al. The IASLC/ITMIG thymic epithelial tumors staging project: proposal for an evidence-based stage classification system for the forthcoming (8th) edition of the TNM classification of malignant tumors. *J Thoracic Oncol* 2014;9(9):65–72.

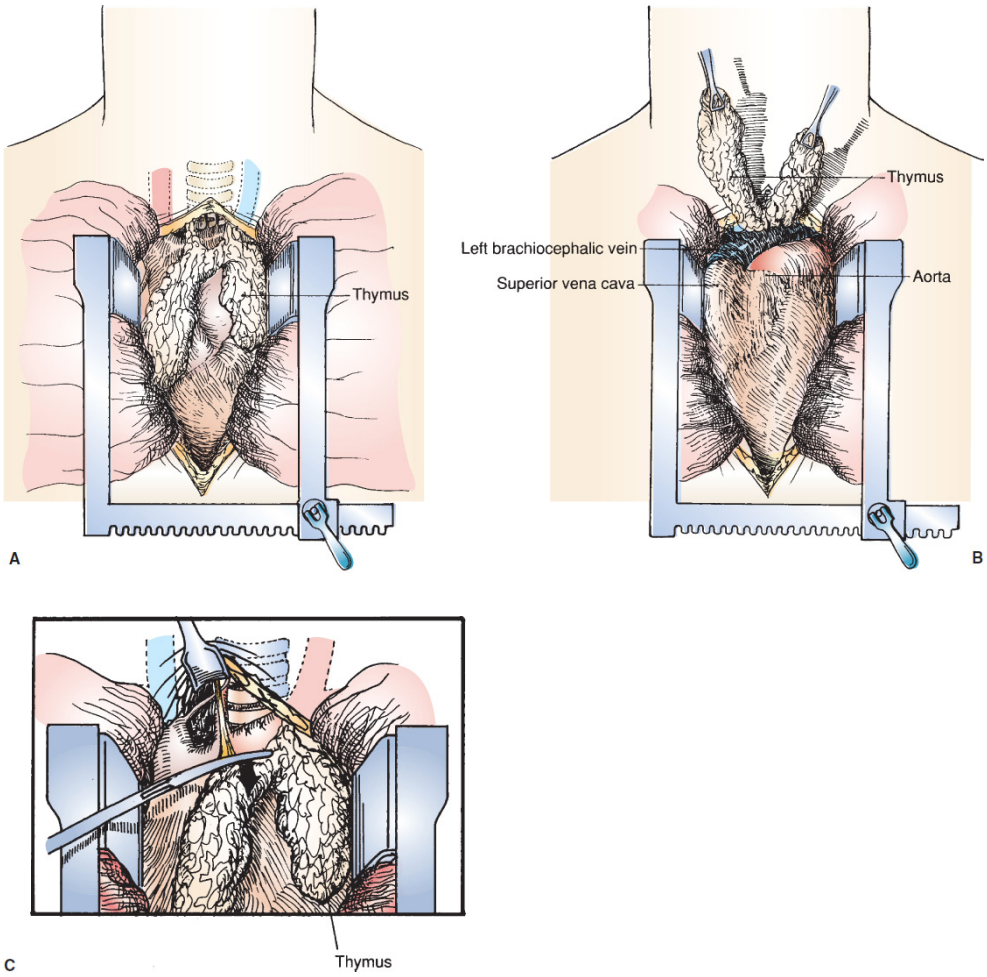


Figure 80.37 Thymic resection. **A:** Exposure of thymus via median sternotomy. **B:** Elevation of thymus completely off of the pericardium. **C:** Pulling the thymus inferiorly to resect the right superior horn (and later the left superior horn). (Reproduced with permission from Scott-Conner CE, Dawson DL, Shirazi MK, et al. *Operative Anatomy*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2013.)

Neoadjuvant chemotherapy and radiation may be used to downstage locally invasive tumors and allow for subsequent resection. Postoperative radiation is recommended for tumors that demonstrate capsular invasion or if residual disease is present. Platinum-based chemotherapy is typically utilized in the unresectable setting.[87] MG presents with diplopia, ptosis, fatigue, and weakness. One-third to one-half of patients with thymomas have

MG, but only 10% of patients with MG have thymomas. Antiacetylcholine receptor antibody levels may be measured to evaluate for MG in patients with suspected thymomas.[88] Thymic carcinomas and thymic carcinoids are other tumor types that can also arise from the thymus.

Germ cell tumors can present as benign teratomas, seminomas, and embryonal tumors, which include nonseminomatous germ cell tumors and malignant teratomas. Benign teratomas have a good prognosis and resection is the best treatment. Seminomas comprise up to half of mediastinal germ cell malignant tumors. Patients may have symptoms from local compression or systemic symptoms such as fever, weight loss, and even gynecomastia. These tumors are radiosensitive, but in locally advanced disease, chemotherapy with later surgical resection is the favored treatment. Nonseminomatous tumors include a wide variety of histologic malignancies. They usually occur in young men and are often symptomatic (**Fig. 80.38**). Elevated alpha-fetal protein (AFP) and beta-human chorionic gonadotropin (β-hCG) levels are seen with these tumors and should be measured. Chemotherapy is the best treatment, but patients have a poorer prognosis when compared to those with seminomas. Lymphomas in the mediastinum are usually part of a wider spectrum of disease. Two-thirds of cases are Hodgkin disease. Most patients present with symptoms of fevers, night sweats, and even weight loss. Treatment is always chemotherapy based, and surgery in the form of a biopsy is utilized only to help make the diagnosis.[88]

Middle and Posterior Mediastinum

Middle mediastinal masses include esophageal and bronchogenic cysts, pericardial cysts, lymphangiomas, and lymphomas (**Fig. 80.39**). For cystic lesions, surgical resection is the best treatment option. Posterior lesions include neurogenic tumors which may be benign or malignant. Almost 95% of tumors come from the sympathetic chain or intercostal nerve rami. Up to two-thirds of these tumors are benign nerve sheath tumors and are usually discovered incidentally. An MRI scan may be used to evaluate intraspinal extension.[88]

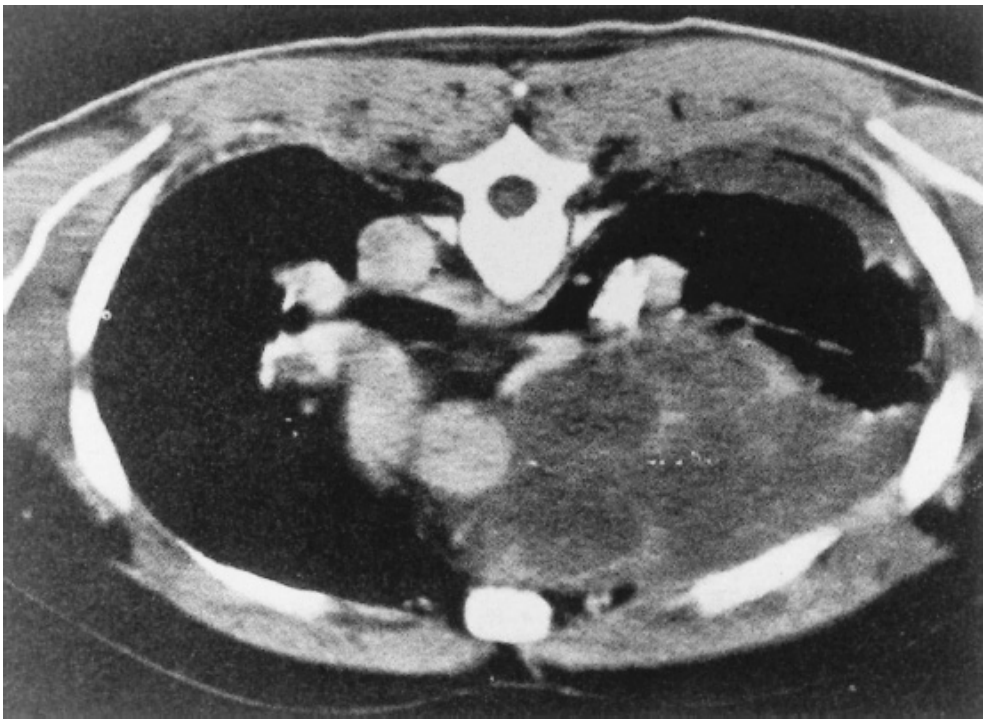


Figure 80.38 Computed tomography scan of a malignant nonseminomatous germ cell tumor of the anterior mediastinum reveals the inhomogeneous anterior mediastinal mass in contrast to the homogeneous density of a seminoma. Pleural effusion is also demonstrated in the right hemithorax. (Reproduced with permission from Shields TW. Primary lesions of the mediastinum and their investigation and treatment. In: Shields TW, ed. *General Thoracic Surgery*. Baltimore, MD: Williams & Wilkins; 1994:1724–1769.)

Pediatric Mediastinum

The presentation of mediastinal masses in the pediatric population varies from what is observed in adults. The rate of malignancy is slightly lower in children, and while thymomas are the most common adult masses seen, neurogenic tumors are more common in children (**Table 80.12**). Just over half of all mediastinal tumors arise in the posterior compartment.[89] Anterior masses may include the normal thymus in a young child. Teratomas are the most common germ cell tumor seen.[89] Vascular anomalies may be seen in children and include hemangiomas and cystic hygromas.[90] Middle compartment tumors are usually foregut cysts, as in the adult population. Posterior tumors are most often malignant neurogenic tumors, compared to more benign pathology in adults.[89]

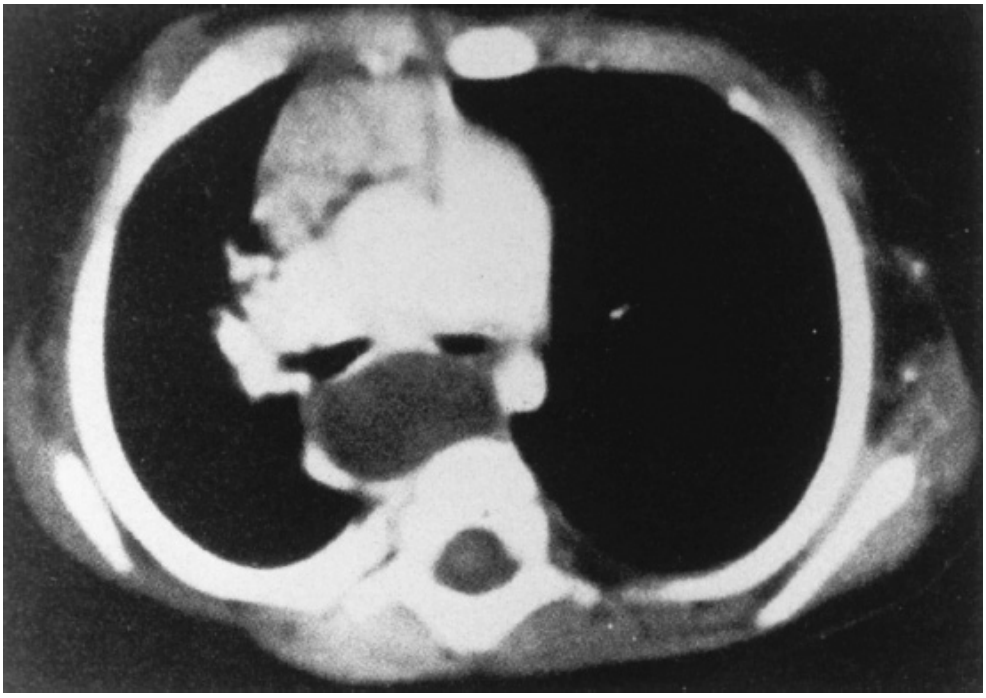


Figure 80.39 Computed tomography scan reveals a bronchogenic cyst located in the subcranial area with compression of the left mainstem bronchus with hyperinflation of the left lung and a mediastinal shift to the right. (Reproduced with permission from Shields TW. Primary lesions of the mediastinum and their investigation and treatment. In: Shields TW, ed. *General Thoracic Surgery*. Baltimore, MD: Williams & Wilkins; 1994:1764–1769.)

Table 80.12 Mediastinal Tumors in Children

Type of Tumor	Incidence Reported in Series (%)
Neurogenic	35
Lymphoma	25
Germ cell	11
Primary malignancy	2
Cysts	25

Adapted from Davis RD Jr, Oldham HN Jr, Sabiston DC Jr. The mediastinum. In: Sabiston DC Jr, Spencer FC, eds. *Surgery of the Chest*. 5th ed. Philadelphia, PA: WB Saunders; 1990:507.

Mediastinitis

Mediastinal inflammation can arise from different sources, but it is most often infectious in nature. Acute mediastinitis is life threatening and usually results from a perforated esophagus, postcardiac procedure, or trauma. Oral infections can also result in organisms traveling through the neck into the mediastinum along fascial planes. These infections can travel as quickly as necrotizing fasciitis does in other parts of the body and should be addressed immediately. A wide variety of organisms can cause mediastinitis. Patients will have chest pain, dyspnea, and fevers. Radiographic films may show pneumomediastinum or pneumothoraces. If an esophageal perforation is suspected, an esophagogram should be performed.[9] Treatment is broad-spectrum antibiotics and surgical drainage via a cervical incision and/or thoracotomy. Quick debridement and drainage are keys to patient survival. Minimally invasive approaches to the chest may be adequate, but surgeons should have a low threshold to perform a posterolateral thoracotomy, which may give the best exposure and opportunity to debride the chest. Sternal infections after cardiac surgery can also be a serious problem requiring drainage and debridement. Ultimate repair of the defect following debridement may involve muscle or omental flaps for sternal reconstruction.

Chronic mediastinitis is a separate entity from acute mediastinitis and may arise from infectious sources or autoimmune disorders. Patients may be asymptomatic until a mass effect is seen on their mediastinal organs. CT scans are the best imaging modality to diagnose this condition, and surgery is reserved only for diagnosis or in the end stages of the disease to relieve compression on other organs. Sclerosing mediastinitis may be seen in patients with retroperitoneal fibrosis.[91]

Superior Vena Cava Syndrome

Superior vena cava (SVC) syndrome is a rare condition seen when a mediastinal mass compresses the SVC resulting in facial and upper body edema. Only 15,000 cases per year are seen in the United States. Patients may present with cough, dyspnea, or even stridor from upper airway edema. When patients start to have symptoms, collateral venous drainage develops to drain into the azygos vein or inferior vena cava. This process usually takes

weeks. Malignant tumors are the most common cause, but venous thrombosis and nonmalignant lesions cause up to one-third of cases. CT scans are the best diagnostic test. Treatment is based on supportive care and addressing the underlying condition causing the obstruction. If a malignant tumor is causing the obstruction, chemotherapy or radiotherapy may shrink the tumor and lessen symptoms. Surgical resection with SVC reconstruction may be used in specific tumors such as locally advanced thymomas. Angioplasty and stenting may be of benefit but is usually palliative.[92] Although it is often felt to be an emergency, most cases of SVC syndrome have a slowly progressive course. When a patient develops symptoms, supportive care, including possible intubation, will allow time for collateral venous drainage to develop and symptoms to improve without other interventions. Although the median survival is typically 6 months or less in patients with SVC syndrome from malignant obstruction, some have seen long-term survivors when the primary tumors have responded to appropriate treatment.[93] When patients present with severe symptoms, it is a mistake to rush to surgical intervention without a long-term plan. Symptoms should be managed and the etiology discovered and treated appropriately.

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Section M: VASCULAR DISEASE

81

Congenital Heart Disease

Vikram Sood and Jennifer C. Romano

Key Points

1 An atrial septal defect (ASD) is a hole in the atrial septum. ASDs are the third most common congenital heart defect (CHD), occurring in 1–2 out of 1,000 live births and representing 1% of CHDs. ASDs cause right heart volume overload and can lead to pulmonary vascular obstructive disease (PVOD) later in life. The majority of ASDs are now closed with a device in the catheterization laboratory.

2 Ventricular septal defects (VSDs) are the most common CHD (with the exception of bicuspid aortic valve [BAV], which occurs in about 1.3% of the population). VSDs cause left heart volume overload.

3 Over 50% of children with trisomy 21 have a CHD. The most common heart defect in this population is an atrioventricular septal defect (AVSD). All infants with trisomy 21 should have an echocardiogram to rule out CHD.

4 Tetralogy of Fallot (TOF) is the most common cyanotic CHD. It occurs in 0.4 per 1,000 live births and has a prevalence of about 5% among all patients with congenital heart disease. The pathologic anatomy is frequently described as having four components: ventricular septal defect, overriding aorta, right ventricular outflow tract obstruction (RVOTO), and right ventricular hypertrophy.

5 Transposition of the great arteries (TGA) is the most common congenital heart defect presenting with cyanosis in the first week of life. In this lesion, the aorta arises from the right ventricle and the pulmonary artery originates from the left ventricle (ventriculoarterial discordance). This malformation accounts for approximately 10% of all congenital cardiovascular malformations in infants.

6 Upper extremity hypertension with diminished femoral pulses are hallmark clinical findings in patients with aortic coarctation.

7 The first successful treatment of a congenital lesion was the closure of a patent ductus arteriosus (PDA) by Gross and Hubbard in 1938. Prostaglandin inhibitors, such as ibuprofen, can be used to induce

closure of a PDA in the premature newborn with a success rate of 65%. When this is not successful, surgical closure or coil occlusion may be necessary.

INTRODUCTION

This chapter focuses on the major congenital cardiac lesions and their etiology, workup, indications for intervention, and treatment options. The aim is to provide the noncongenital heart surgeon with a basic survey of congenital heart disease and its surgical treatment.

HISTORY

Congenital cardiac surgery, as a specialty, is notable for rapid technical advances with marked improvement in survival and reduction in morbidity. Much of the original interest in cardiac surgery was focused on attempts to treat congenital heart defects associated with cyanosis and early mortality. The first successful treatment of a congenital lesion was the closure of a patent ductus arteriosus (PDA) by Gross and Hubbard in 1938.[1] The description of the subclavian artery-to-pulmonary artery (PA) shunt by Blalock, Taussig, and Thomas in 1945[2] introduced the palliation of many complex cyanotic lesions—most notably, tetralogy of Fallot (TOF). The 1950s represented the decade of greatest advances, which laid the foundation for the field of cardiac surgery. In 1952, Lewis and Taufic[3] performed the first open closure of an atrial septal defect (ASD) by using surface hypothermia and inflow occlusion. In 1953, Gibbon[4] performed the first ASD repair with the use of a pump oxygenator that became the model for modern cardiopulmonary bypass. Next, Warden et al.[5] used controlled cross-circulation with an adult as the oxygenator during intracardiac repairs. Building on the work of Gibbon, Kirklin et al.[6] published the first series of eight intracardiac operations performed at the Mayo Clinic with the use of cardiopulmonary bypass. With these landmark efforts focused on congenital heart disease, the field of cardiac surgery was established.

ATRIAL SEPTAL DEFECT

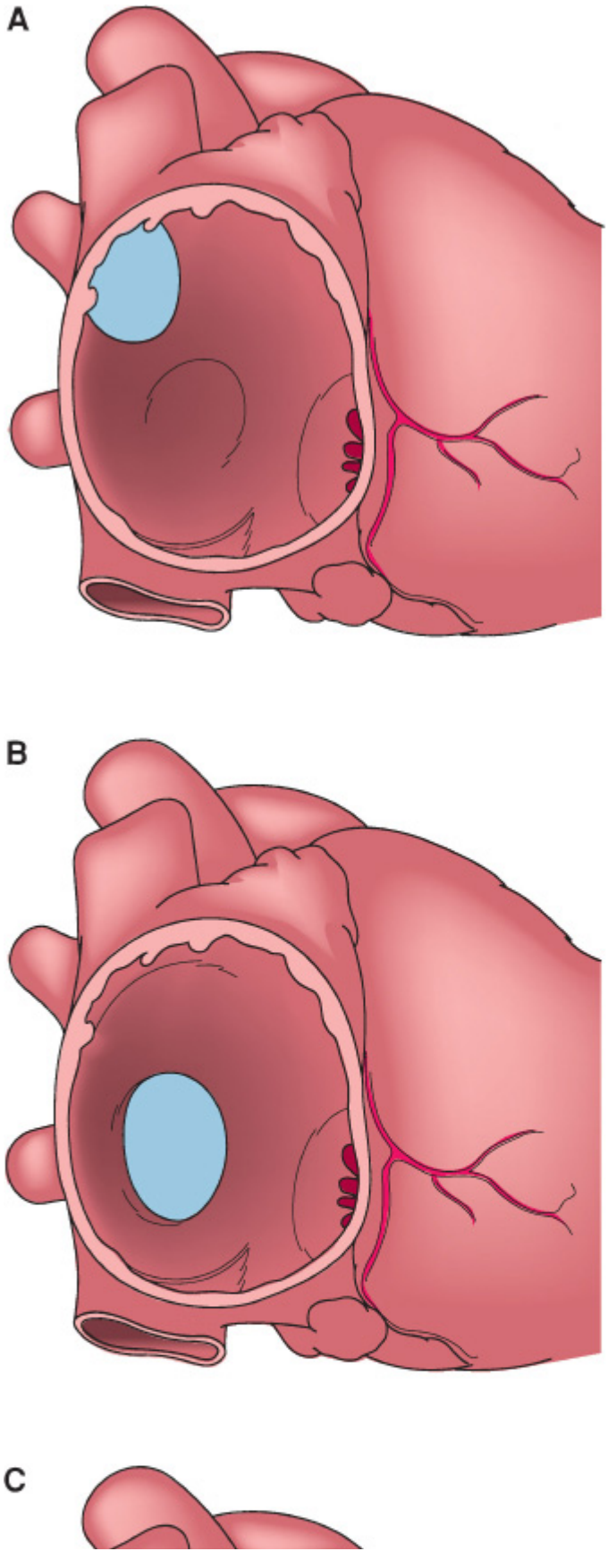
Embryology

Cardiac septation occurs between the third and sixth weeks of fetal development. The septum primum, which arises from the roof of the common atrium and descends inferiorly, initially divides the common atrium. The ostium primum is the opening below the inferior edge of the septum primum, which is obliterated as the septum primum fuses with the endocardial cushions. The ostium secundum forms in the midportion of the septum primum prior to closure of the ostium primum. The septum secundum arises from the roof of the atrium and descends along the right side of the septum primum and covers the ostium secundum. This creates a flap valve whereby blood from the inferior vena cava may preferentially stream beneath the edge of the septum secundum and through the ostium secundum into the left atrium. After birth, with increased pulmonary blood flow, the left atrial pressure increases and closes this pathway.

Anatomy and Pathophysiology

An ASD is a hole in the atrial septum (Fig. 81.1). ASDs are the third most common congenital heart defect, occurring in 1–2 out of 1,000 live births and representing 15% of congenital heart defects.[7] The most common ASD is the secundum defect, which occurs when there is excessive resorption of the septum primum or incomplete coverage of the ostium secundum by the septum secundum. Ostium secundum defects account for about 80% of ASDs. An ostium primum ASD, representing 10% of ASDs, occurs from failure of fusion of the septum primum with the endocardial cushions. Ostium primum defects are discussed later, in the section on atrioventricular septal defects (AVSDs). A third type of ASD is the sinus venosus defect, seen in about 10% of cases. Sinus venosus ASDs are caused by abnormal fusion of the venous pathways with the atrium and are characterized by defects high in the atrial septum near the orifice of the superior vena cava or, less commonly, low in the atrial septum near the inferior vena cava. Sinus venosus defects are frequently associated with partial anomalous pulmonary venous connection, usually with the right upper pulmonary vein draining into the superior vena

cava near the cavo–atrial junction. Finally, the rarest type of ASD is the unroofed coronary sinus septal defect. This occurs when there is loss of the common wall between the coronary sinus and the left atrium adjacent to the atrial septum. This unroofing of the coronary sinus leads to a communication between the right and left atria at the site of the coronary sinus.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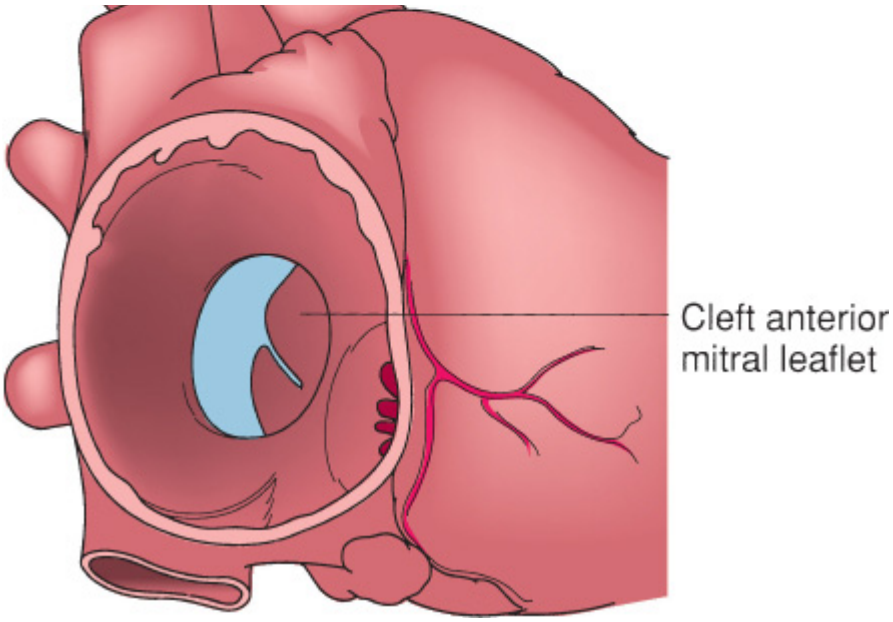

Figure 81.1 The anatomy of atrial septal defects. In the sinus venosus type (**A**), the right upper and middle pulmonary veins frequently drain to the superior vena cava or right atrium. **B:** Secundum defects generally occur as isolated lesions. **C:** Primum defects are part of a more complex lesion and are best considered as incomplete atrioventricular septal defects.

Patent foramen ovale (PFO) is extremely common in the general population, and autopsy studies have demonstrated a prevalence of 27%.[8] A PFO is generally considered distinct from other ASDs due to the absence of significant shunting. Failure of postnatal fusion of the septum secundum to the septum primum results in a persistent slit-like communication known as a PFO. Nevertheless, PFOs remain important clinically due to the potential for paradoxical embolization. A paradoxical embolus is a blood clot arising from a systemic vein that would normally pass to the lungs, but in the presence of a septal defect, may cross into the systemic circulation.

Increased pulmonary blood flow (PBF) results from ASDs secondary to left-to-right shunting. Shunting at the atrial level is determined by the size of the defect and by the relative ventricular compliance (i.e., blood preferentially fills the more compliant ventricle). At birth, both ventricles are equally compliant, but as pulmonary vascular resistance (PVR) falls, the right ventricle remodels and becomes more compliant. Shunting across the atrial septum causes a volume load on the right heart.

The volume overload from an ASD is usually well tolerated, and patients are frequently asymptomatic. Symptoms tend to develop when the ratio of

pulmonary to systemic blood flow (Q_p/Q_s) exceeds 2:1. The most common symptoms are fatigue, shortness of breath, exercise intolerance, and recurrent respiratory infections. Adults with untreated ASDs tend to develop atrial dysrhythmias (secondary to long-standing right atrial enlargement) and may develop congestive heart failure (CHF) and right ventricular dysfunction. Pulmonary vascular obstructive disease rarely occurs as a late complication of an untreated ASD. Paradoxical embolization, as described above, is also an important potential complication of an ASD.

Diagnostic Findings

The classic physical examination findings in patients with ASDs include fixed splitting of the second heart sound and a systolic ejection murmur at the left upper sternal border due to increased flow across a normal pulmonary valve. A diastolic flow murmur across the tricuspid valve is occasionally audible. A prominent right ventricular lift and increased intensity of the pulmonary component of the second heart sound may occur with pulmonary hypertension. Chest radiography shows cardiomegaly, with enlargement of the right atrium, right ventricle, and pulmonary artery. Electrocardiography (ECG) frequently demonstrates right axis deviation. Cardiac catheterization is important in selected cases to assess PVR in older patients, but it is used more frequently with therapeutic intent for device closure of ASDs.

Indications for Intervention and Treatment Options

Due to the long-term complications associated with ASDs, repair is recommended for all patients with symptomatic defects and in asymptomatic patients with a Q_p/Q_s is greater than 1.5 or signs of right heart enlargement. Repair is usually performed in children prior to school age (3 to 5 years), as it is anticipated that spontaneous closure is unlikely after this age. Closure of ASDs may be performed surgically or using a device deployed in the cardiac catheterization laboratory.

OPERATIVE STEPS

Table 81.1 Secundum ASD via Limited Sternotomy

CPB configuration	Bicaval cannulation, normothermia, and antegrade cardioplegic arrest
Exposure and intracardiac steps	Oblique right atriotomy, inspection of atrial septum/systemic venous return/pulmonary venous return, patch closure of ASD
Completion	De-airing of left heart, removal of cross clamp, primary closure of right atriotomy
Final steps	Wean off bypass, TEE, standard closure

CPB, cardiopulmonary bypass; ASD, atrial septal defect; TEE, transesophageal echocardiogram.

The operative steps are detailed in Table 81.1. Surgical repair is usually recommended for large, secundum defects that are not amenable to device closure and for all other types of ASDs. Small secundum defects or PFOs may sometimes be closed primarily by suturing the edge of the septum primum to the edge of the septum secundum. More commonly, larger defects are closed using a patch (polytetrafluoroethylene or autologous pericardium) and a running polypropylene suture. In sinus venosus defects, when anomalous pulmonary venous drainage is present, a baffle is created to redirect pulmonary venous return across the ASD. Surgical closure of an ASD can be accomplished with a mortality approaching zero and minimal morbidity.[9] Common postoperative complications include atrial arrhythmias and postpericardiotomy syndrome.

A number of devices are currently available for percutaneous closure of secundum ASDs with excellent efficacy.[10,11] The presence of a deficient rim is the most common reason for failed implantation.[11] Device closure has the advantages of fewer complications and a shorter hospitalization and recovery time.[12] 1 Device closure of small to moderate secundum ASDs and PFOs has now become the standard of care.

The long-term survival for patients undergoing ASD repair in childhood is equivalent to nonaffected patients.[13] The major long-term complication following closure of an ASD is the development of supraventricular arrhythmias, although the risk is lowered when it is closed in childhood.[13,14] Long-term follow-up of percutaneous device closure of secundum ASDs reveals excellent durability and safety.[15]

Occasionally, adults will present with a newly diagnosed ASD. Many studies have confirmed that ASD closure in adults over the age of 40 increases survival and limits the development of heart failure.[16] Nevertheless, when the Q_p/Q_s is less than 1.5, and the ratio of pulmonary to systemic vascular resistance (R_p/R_s) is greater than 0.7, significant PVOD is usually present. A PVR in excess of 10 to 12 Wood units/m^2 represents a contraindication to ASD closure.

VENTRICULAR SEPTAL DEFECT

Embryology

Ventricular septation is a complex process that requires accurate development and alignment of a number of structures including the muscular interventricular septum, the atrioventricular (AV) septum (arising from the endocardial cushions), and the infundibular septum (which divides the outflow tracts of the right and left ventricles). The membranous septum is a fibrous portion of the ventricular septum that is adjacent to the central fibrous body (where the mitral, tricuspid, and aortic valve annuli make contact). Septation is usually complete by the seventh week of gestation.

Anatomy and Pathophysiology

2 Ventricular septal defects (VSDs) are the most common congenital heart anomalies (with the exception of bicuspid aortic valve [BAV], which occurs in about 1.3% of the population). VSDs are present in about 2–3 of 1,000 live births and represent about 35% of congenital heart defects.[7] VSDs are classified based on their location in the ventricular septum (Fig. 81.2). The most common defects are perimembranous (80%), which are located in the

area of the membranous septum. Defects located high in the ventricular septum are termed outlet defects (10%) and are typically adjacent to the pulmonary and aortic valves. Outlet defects are more common in the Asian population. Inlet defects (5%) are located beneath the septal leaflet of the tricuspid valve and are sometimes called AV canal-type defects. Finally, muscular VSDs (5%) are completely bordered by muscle and often exist alongside perimembranous or outlet defects. The size of VSDs varies. By definition, a VSD is nonrestrictive when its size (or the cumulative size of multiple defects) is greater than or equal to the size of the aortic annulus.

A VSD causes increased PBF due to left-to-right shunting primarily during systole. This creates a volume load on the *left heart* (the left atrium and ventricle receive the increased venous return during diastole). The right ventricle is not volume loaded (blood is ejected from the left ventricle [LV], through the VSD, and directly into the pulmonary circulation during systole); however, the RV does experience a pressure load. The volume of shunt flow is determined by the size of the defect and by the ratio of pulmonary to systemic resistance.

Immediately after birth, the PVR is still high and shunting across a VSD may be minimal. Over the first several weeks of life, shunting tends to increase as the PVR falls. Therefore, a patient with a large VSD may be asymptomatic at birth and develop severe CHF symptoms over the first 6 weeks of life.

The natural history for patients with isolated VSDs is highly variable. Most VSDs are restrictive and tend to close spontaneously during the first year of life. Large VSDs are nonrestrictive, resulting in right ventricular and pulmonary pressures equal to systemic pressures, and high PBF with Q_p/Q_s ratios greater than 2.5 to 3. Moderate VSDs are restrictive, with pulmonary pressures that are one-half systemic (or less) and Q_p/Q_s ratios of 1.5 to 2.5. Small VSDs are highly restrictive, right ventricular pressures remain normal, and the Q_p/Q_s is less than 1.5.

Patients with large VSDs tend to develop symptoms of CHF by 2 months of age. Patients with smaller VSDs may remain asymptomatic. In patients with outlet VSDs, prolapse of the aortic valve into the defect with partial or complete closure of the defect may occur, producing aortic insufficiency. If left untreated, excessive PBF leads to PVOD by the second year of life.

Diagnostic Findings

Infants with large VSDs will have signs of CHF: tachypnea, hepatomegaly, poor feeding, and failure to thrive. On physical examination, there is a holosystolic murmur at the left sternal border. Usually, the murmur is louder with smaller defects. The precordium is active. The pulmonary component of the second heart sound is accentuated in the presence of pulmonary hypertension. Chest radiography shows increased pulmonary vascular markings and cardiomegaly. The ECG demonstrates right ventricular hypertrophy. Patients with small VSDs have little shunting and are usually asymptomatic, having only a pansystolic murmur. Patients with moderate VSDs manifest symptoms and signs that are proportional to the degree of shunting. In patients who have developed significant PVOD, the volume of left-to-right shunting is decreased, and the murmur may disappear. Eisenmenger physiology results when the shunt flow reverses to right to left (as a result of long-standing excessive PBF and resultant pulmonary HTN), creating cyanosis.

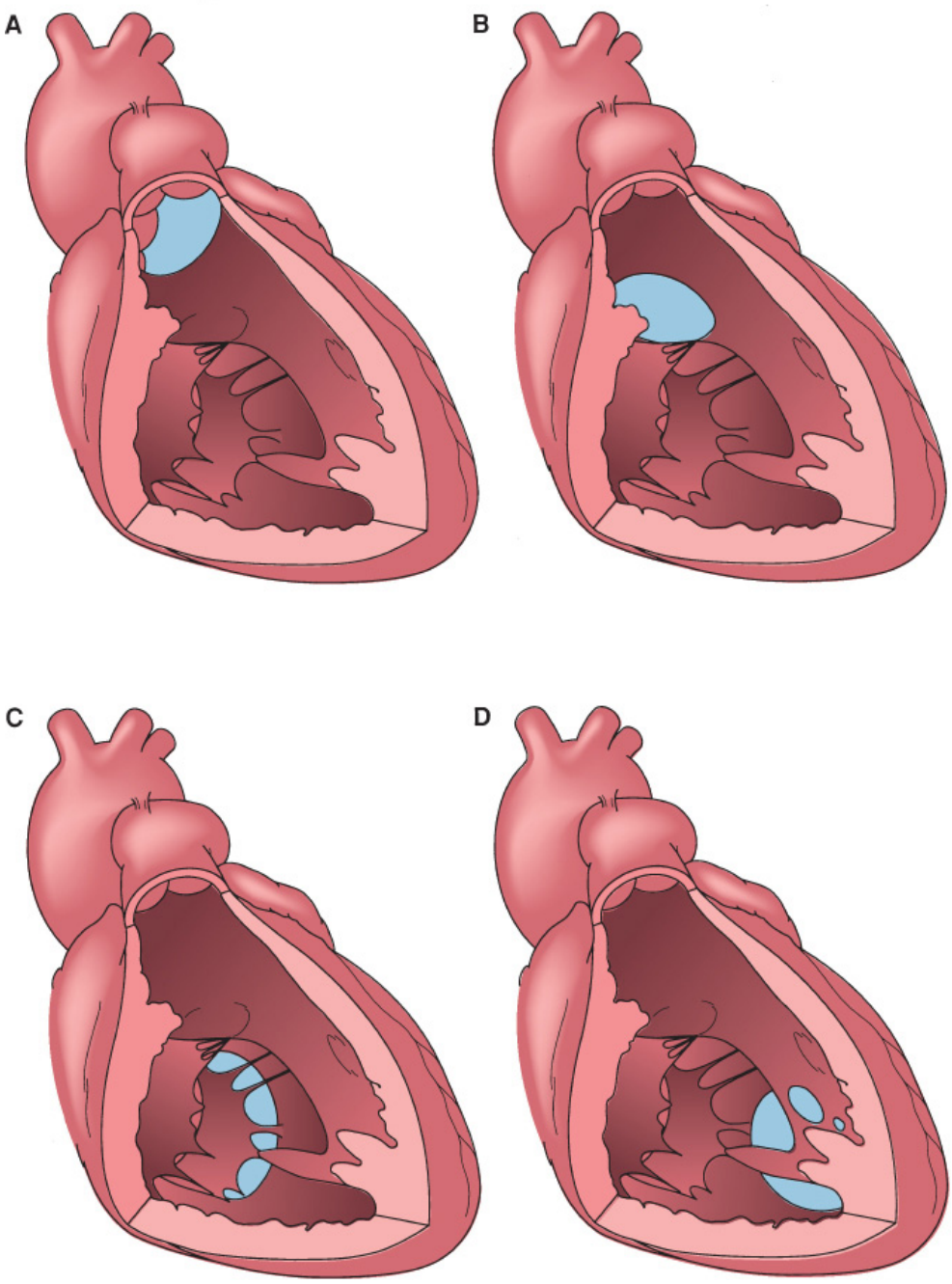

Figure 81.2 The anatomy of ventricular septal defects (VSDs) as seen through the right ventricle. **A:** Outlet, or subarterial, VSDs are generally bordered superiorly by the pulmonary valve annulus. **B:** Perimembranous VSDs are most common, extending from the membranous septum into the infundibular septum. **C:** Inlet defects are located predominantly beneath the septal leaflet of the tricuspid valve. **D:** Muscular VSDs are situated away from the valves, toward the cardiac apex.

The diagnosis of VSD is confirmed by echocardiography, which accurately defines the anatomy and excludes the presence of associated

defects. Cardiac catheterization is used selectively in older children and adults in whom elevated PVR is suspected. The PVR may be fixed or reactive, and, at the time of cardiac catheterization, response to nitric oxide or 100% fraction of inspired oxygen (FiO_2) may be assessed.

Indications for Intervention and Treatment Options

The management of a patient with a VSD depends on the size of the defect, the type of defect, the shunt volume, and the PVR. In general, patients with large defects who have intractable CHF or failure to thrive should undergo early surgical repair. If the CHF symptoms can be mitigated by medical therapy, then surgery may be deferred until 6 months of age.

Patients with small and moderate-sized VSDs may be safely followed out of infancy. If closure has not occurred by 2 years of age, then surgical closure is indicated if $Q_p/Q_s > 2:1$ or there is left-sided chamber enlargement. The majority of muscular defects close spontaneously and will not require intervention. There is a small long-term risk of endocarditis for these patients, though American Heart Association guidelines do not recommend the use of prophylactic antibiotics.[17] Patients with outlet VSDs have a risk of developing aortic insufficiency due to leaflet prolapse, and, therefore, all should undergo surgical closure if there is evidence of leaflet prolapse or aortic insufficiency.[18] Older children and adults must undergo cardiac catheterization to assess the pulmonary circulation. When there is a fixed PVR greater than 8 to 10 Wood units/m^2, surgery is contraindicated.

The operative steps are detailed in Table 81.2. Most perimembranous, inlet, and trabecular VSDs are exposed through the tricuspid valve via a right atriotomy, while outlet VSDs are frequently best exposed via a pulmonary arteriotomy. Trabecular VSDs located near the ventricular apex can be very difficult to expose, and an apical ventriculotomy may be necessary.

It is important to understand the anatomy of the conduction tissue when closing VSDs. The AV node is an atrial structure that lies at the apex of an anatomic triangle (known as the triangle of Koch) formed by the coronary sinus, the tendon of Todaro (a prominent band leading from the inferior vena cava and inserting in the atrial septum), and the septal attachment of the

tricuspid valve. The node gives rise to the bundle of His, which penetrates the AV junction beneath the membranous septum. The bundle of His then bifurcates into right and left bundle branches, which pass along either side of the muscular ventricular septum. In the presence of a perimembranous VSD, the bundle of His passes along the posterior and inferior rim of the defect, generally on the left ventricular side. In this critical area, sutures must be placed superficially on the right ventricular side a few millimeters from the edge of the defect. The bundle of His also tends to run along the posterior and inferior margin of inlet VSDs. The conduction tissue is usually remote from outlet and trabecular VSDs.

OPERATIVE STEPS

Table 81.2 VSD via Sternotomy

CPB configuration	Bicaval cannulation, mild hypothermia, antegrade cardioplegic arrest
Exposure and intracardiac steps	Oblique right atriotomy, retraction of anterior and septal leaflets of tricuspid valve, inspection of ventricular septal defect and nearby aortic valve, patch closure of VSD with running suture technique
Completion	De-airing of left heart, removal of cross clamp, primary closure of right atriotomy
Final steps	Wean off bypass, place temporary pacing wires, TEE, standard closure

CPB, cardiopulmonary bypass; VSD, ventricular septal defect; TEE, transesophageal echocardiogram.

Pulmonary artery banding is an alternative to primary surgical closure of a VSD. Pulmonary artery banding is a palliative maneuver that is used to protect the pulmonary circulation from excessive PBF while awaiting more optimal circumstances for VSD closure. A PA band increases the effective PVR, thereby reducing the shunt volume. This palliative procedure is

currently performed only in patients who are felt to be poor candidates for VSD closure, either due to associated illness or due to anatomic complexity, such as multiple trabecular VSDs ("Swiss cheese" septum).

Pulmonary artery banding is performed without the need for cardiopulmonary bypass. A band is placed around the main PA and tightened to achieve a distal PA pressure of about one-half systemic. The band is secured to the adventitia of the PA to prevent its migration. Later, when the patient is a candidate for VSD closure or when the muscular defects have spontaneously closed, the band must be removed. Repair of the main PA at the band site is usually necessary and can typically be accomplished by scar resection and patch repair.

Surgical closure of a VSD is associated with mortality less than 1%.[19] Potential complications include injury to the conduction tissue and injury to the tricuspid or aortic valves. Closure of perimembranous and inlet VSDs may result in distortion of the tricuspid valve and resultant regurgitation. Aortic valve injury may occur as a result of inaccurate suturing, especially in perimembranous and outlet defects. Transient heart block may result from tissue swelling or injury from retraction, but permanent heart block occurs in less than 1% of cases. When heart block develops after surgery, patients are usually observed for a period of 7 to 10 days prior to permanent pacemaker implantation. A residual VSD is seen in about 5% of cases, and reoperation is indicated when significant shunting persists (Q_p/Q_s ratio >1.5).

Transcatheter devices have been developed to allow closure of some VSDs in the cardiac catheterization laboratory or by periventricular deployment without the use of cardiopulmonary bypass. Device closure is optimal for large muscular defects with sufficient rims for securing the device. These defects are often difficult to visualize and close surgically. Periventricular closure allows the use of VSD device closure in smaller infants with symptomatic muscular VSDs with excellent results without the challenges of transvenous access.[20] The use of devices for perimembranous VSDs remains limited by the risk of damage to the conduction system or impingement on the function of the tricuspid or aortic valves.[21,22]

ATRIOVENTRICULAR SEPTAL DEFECT

Embryology

Defects in the embryologic development of the endocardial cushions may result in a variety of morphologic abnormalities in the AV valves and the atrial and ventricular septa. These anomalies range from ostium primum ASD to complete AVSD with a spectrum of intermediate forms.

Anatomy and Pathophysiology

Atrioventricular septal defects (AVSDs) are relatively uncommon forms of congenital heart disease, occurring in 0.3 per 1,000 live births, and making up approximately 4% of all CHDs.[7 3] There is a strong association between AVSDs and Down syndrome (trisomy 21); approximately 50% of patients with an AVSD have Down syndrome. Complete AVSD is an anomaly characterized by a common AV orifice rather than separate mitral and tricuspid orifices. There is a deficiency of endocardial cushion tissue, which results in a primum ASD and an inlet type of VSD. Complete AVSDs were subclassified by Rastelli et al.[23] into three types according to the morphology of the anterior leaflet of the common AV valve. Incomplete AVSDs are variants in which there is partial fusion of the AV valves, resulting in separate right and left AV valve orifices. The ostium primum ASD is a type of incomplete AVSD in which the VSD component is absent.

When both left and right AV valves equally share the common AV valve orifice, the AVSD is termed *balanced.* Occasionally, the orifice may favor the right AV valve (right dominance) or the left AV valve (left dominance). In marked right dominance, the left AV valve and LV are hypoplastic, and frequently coexist with other left-sided abnormalities, including aortic stenosis (AS), hypoplasia of the aorta, and coarctation. Conversely, marked left dominance results in a deficient right AV valve with associated hypoplasia of the right ventricle, PS or atresia, and TOF. Patients with severe imbalance require staged, single-ventricle palliation.

The conduction tissue is displaced in an AVSD and is at risk during surgical repair. The AV node is located posteriorly and inferiorly of its normal position toward the coronary sinus in what has been termed the *nodal triangle.* This triangle is bounded by the coronary sinus, the posterior attachment of the inferior bridging leaflet, and the rim of the ASD. The

bundle of His courses anteriorly and superiorly to run along the leftward aspect of the crest of the VSD, giving off the left bundle branch and continuing as the right bundle branch.

A number of other cardiac anomalies are associated with AVSDs including a PDA (10%) and TOF (10%).[24] Important, albeit rare, abnormalities of the left AV valve include single papillary muscle (parachute mitral valve) (2% to 6%) and double orifice mitral valve (8% to 14%).[24] A persistent left superior vena cava with or without an unroofed coronary sinus is encountered in 3% of patients with an AVSD. Left ventricular outflow tract obstruction (LVOTO) from subaortic stenosis or redundant AV valve tissue occurs in 3%.[24]

The pathophysiology of an AVSD is dependent on the sub-type. Complete AVSDs have excessive PBF due to shunting at the atrial and ventricular septal defects. As described in the section on ASDs and VSDs: an ASD leads to left-to-right shunting during diastole and a VSD leads to left-to-right shunting during systole. When left-sided AV valve regurgitation is present (10%) there is even more left-to-right shunting at the atrial septum. This exacerbates excessive PBF and places an additional volume load on the right ventricle.

Infants with complete AVSDs will develop heart failure symptoms within the first 2 months of life. Excessive PBF leads to PVOD and resultant pulmonary hypertension; this process is accelerated in patients with trisomy 21 for unknown reasons.

Incomplete AVSDs, which are associated with a cleft mitral valve and no VSD component, generally present in a similar fashion as a patient with a large secundum ASD. While there is a left-to-right shunt at the atrial septum, causing a volume load on the right ventricle, the degree of excessive PBF is far lower than in a complete AVSD. When there is a cleft mitral valve and resultant mitral regurgitation, there is increased left-to-right shunting at the ASD. Nevertheless, patients with incomplete AVSDs do not develop typically heart failure in infancy.

Diagnostic Findings

In patients with complete AVSD, on physical examination, the precordium is hyperactive, often with a prominent thrill. Auscultatory findings include a

systolic murmur along the left sternal border (VSD), a high-pitched murmur at the apex (left AV valve regurgitation), and a mid-diastolic flow murmur across the common AV valve. In the presence of elevated PVR, there may be a split first heart sound. Significant cardiomegaly and pulmonary over-circulation are found on the chest radiograph. The ECG reveals biventricular hypertrophy, atrial enlargement, prolonged PR interval, leftward axis, and counterclockwise frontal plane loop. Transthoracic echocardiography is diagnostic, defining the atrial and ventricular level shunting, valvular anatomy, and any associated anomalies.

Cardiac catheterization should be performed for patients older than 1 year of age, for patients with signs or symptoms of increased PVR. If the PVR is high, it is important to determine pulmonary vascular reactivity on 100% oxygen, with and without nitric oxide. If the pulmonary resistance falls, it implies that much of the elevated resistance is dynamic and can be managed in the perioperative period by ventilatory manipulation, supplemental oxygen, and nitric oxide. Later, these children can be transitioned to Sildenafil.[25] Markedly elevated pulmonary resistance (>10 Wood units/m^2) that does not respond to oxygen administration is generally considered a contraindication to repair of a complete AVSD.

Indications for Intervention and Treatment Options

In patients with complete AVSD, operative treatment should be performed prior to 6 months of age to prevent progressive PVOD. The majority of infants with symptoms can be medically managed to allow for repair between 3 and 6 months of age. Rarely, in patients refractory to medical management—often due to associated significant left AV valve insufficiency—surgical repair is needed earlier. Pulmonary artery banding, as described in the section on VSDs, permits delayed repair. This strategy is reserved for select cases such as extremely low–birth-weight infants, complex valvular anatomy, and infants in otherwise poor clinical condition.

The operative steps for repair of complete AVSD are listed in Table 81.3. Correcting AVSDs requires patch closure of both septal defects, with any necessary valve reconstruction. Separate atrial and ventricular patches or a

single patch for both chambers can be used.[26] During closure of the ventricular defect, the surgeon must be careful to avoid injury to the conduction system, which passes along the posterior and inferior rim of the ventricular septum.

Operative mortality for AVSDs varies with the sub-type, associated cardiac anomalies, and left AV valve regurgitation. Hospital mortality for repair of complete AVSD is 3%; weight (<3.5 kg) and age (<2.5 months) are associated with higher mortality.[27] Long-term survival is good after complete AVSD repair, though late reoperation occurs in approximately 20% of patients. The majority of reoperations are due to left AV valve regurgitation or subaortic stenosis.[28]

OPERATIVE STEPS

Table 81.3 Complete AVSD via Sternotomy

CPB configuration	Bicaval cannulation, mild hypothermia, antegrade cardioplegic arrest
Exposure and intracardiac steps	Oblique right atriotomy, patch closure of VSD, attachment of inferior aspect of ASD patch to superior aspect of VSD to partition the common AV valve in to right and left side components, closure of left AV valve cleft, and completion of patch closure of ostium primum ASD
Completion	De-airing of left heart, removal of cross clamp, primary closure of right atriotomy
Final steps	Wean off bypass, place temporary pacing wires, TEE, standard closure

CPB, cardiopulmonary bypass; AV, atrioventricular; VSD, ventricular septal defect; ASD, atrial septal defect; TEE, transesophageal echocardiogram.

Hospital mortality for repair of incomplete AVSDs is approximately 1%.[29,30] Long-term survival is excellent. As with complete AVSDs,

reoperation for left AV valve regurgitation or subaortic stenosis is the most common reason for late reintervention.[30]

TETRALOGY OF FALLOT

Embryology

The conotruncus usually divides into two equal-sized great vessels (aorta and pulmonary artery) during the fifth week of gestation. During normal development, the infundibular septum separates the primitive outflow tracts and fuses with the ventricular septum. In TOF, there is unequal division of the conotruncus which leads to narrowing of the pulmonary artery and anterior deviation of the infundibular septum. This results in an anterior, malaligned VSD with an overriding aorta and resultant variable RVOTO.[31] Neural crest-derived tissue is thought to play a central role in the development of TOF.

Anatomy and Pathophysiology

4 TOF is the most common cyanotic congenital heart defect. It occurs in 0.4 per 1,000 live births and has a prevalence of 5% among all patients with congenital heart disease.[7] The pathologic anatomy is frequently described as having four components: anterior malaligned VSD, overriding aorta, pulmonary stenosis (PS), and right ventricular (RV) hypertrophy (Fig. 81.3).

Infundibular malalignment crowds the right ventricular outflow tract, causing PS. Prominent muscle bands also extend from the septal insertion of the infundibular septum to the right ventricular free wall and contribute to RVOTO. The pulmonary valve is usually stenotic and is bicuspid in approximately 60% of cases. Right ventricular hypertrophy is thought to be a down-stream sequela of PS and RVOTO.

There are many associated cardiac lesions with TOF.[32] Pulmonary atresia —no communication between the right ventricle and main PA—is an uncommon variant of TOF (7%). The branch pulmonary arteries in TOF may exhibit mild, diffuse hypoplasia or discrete stenosis (most frequently of the left PA at the site of ductal insertion). Coronary artery anomalies are frequently present. The origin of the left anterior descending from the right

coronary artery, which occurs in 10% of cases, is clinically important because the vessel crosses the right ventricular infundibulum and is vulnerable to injury at the time of surgery. A right aortic arch is present in 25% of patients with TOF. Additional associated defects include ASD, complete AVSD, PDA, or multiple VSDs.

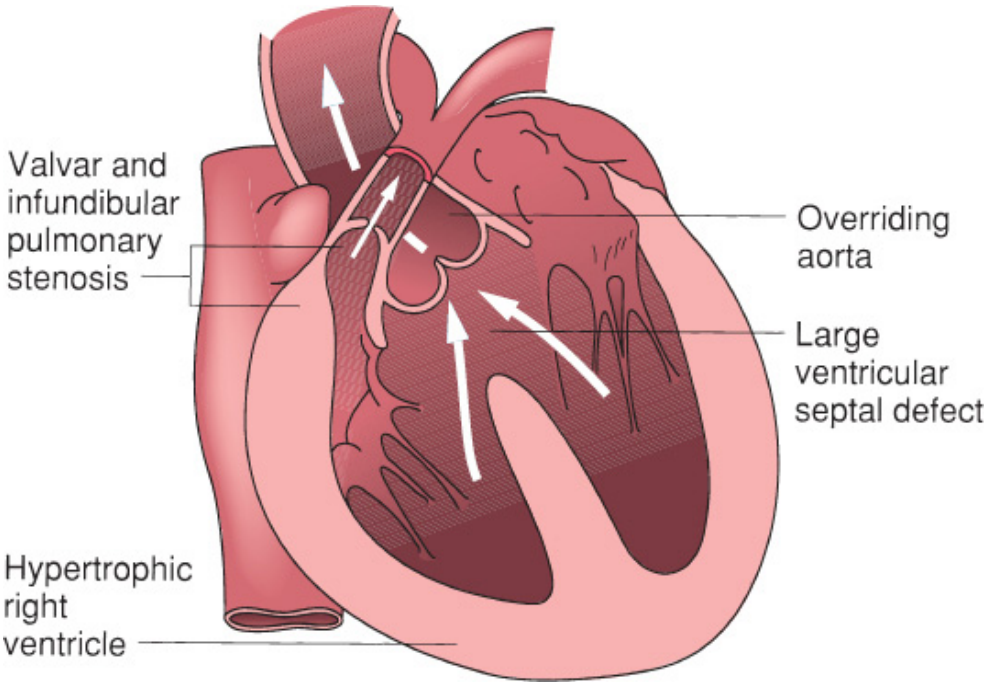

Figure 81.3 The four anatomic features of tetralogy of Fallot. The primary morphologic abnormality, anterior and superior displacement of the infundibular septum, results in a malalignment ventricular septal defect, overriding of the aortic valve, and obstruction of the right ventricular outflow. Right ventricular hypertrophy is a secondary occurrence.

Patients with TOF develop cyanosis due to *right-to-left* shunting across the VSD. The shunt is right to left because the effective PVR (obstructing muscle bundles, valvar PS, and hypoplastic MPA) is greater than the SVR. The degree of cyanosis depends on the severity of RVOTO. Neonates with severe infundibular obstruction or pulmonary atresia will require a prostaglandin infusion to maintain ductal patency to ensure adequate PBF and will ultimately require either a systemic to pulmonary artery shunt or ductal stent. In most infants though, there is adequate antegrade PBF in the neonatal period, and infants may be discharged with instructions of how parents may determine worrisome cyanosis. Of note, there are some patients with TOF

who have very mild RVOTO. In these patients, the predominant physiology is that of a large VSD with left-to-right shunting and CHF. These patients present similarly to patients with isolated VSDs (and are not cyanotic).

The occurrence of intermittent hypercyanotic spells is a well-known feature of TOF. The etiology of spelling is related to a transient imbalance between pulmonary and systemic blood flow. A spell may be triggered by hypovolemia or peripheral vasodilation (e.g., after a bath or vigorous physical exertion). Spells may occur in neonates but are most frequently reported in infants between the ages of 3 and 18 months. Most spells resolve spontaneously within a few minutes, but spells can be fatal. Older children have been observed to spontaneously squat to terminate spells. The squatting position increases SVR, which thereby favors PBF.

Diagnostic Findings

Cyanosis is the most frequent physical finding in TOF. Auscultation reveals a normal first heart sound and a single second heart sound. A systolic ejection murmur is present at the left upper sternal border. Older children may develop clubbing of the fingers and toes from long-standing cyanosis, but this is rare in the current era. Chest radiography typically demonstrates a boot-shaped heart due to elevation of the cardiac apex from right ventricular hypertrophy. Pulmonary vascular markings are usually reduced. A right aortic arch may be present. An ECG shows right ventricular hypertrophy. Echocardiography is definitive, and catheterization is not necessary in most cases.

Indications for Intervention and Treatment Options

While all patients with TOF should undergo surgical repair, most will not require palliation or complete repair at birth. Early repair is indicated for neonates with severe cyanosis and for infants who have had a documented spell or worsening cyanosis.

Medical management of TOF is directed toward the treatment and prevention of cyanotic spells. Transfusion is indicated for anemic infants.

Some centers have used beta-blockers as a form of long-term therapy to suppress the incidence of spells. In the appropriate setting, the immediate treatment of the spelling patient includes administration of oxygen, narcotics for sedation, and correction of acidosis. Alpha-agonists are useful for increasing systemic vascular resistance (which favors PBF) during a refractory spell.

In the current era, single-stage repair of TOF is preferred by most centers between 4 and 6 months of age. Initial palliation with a systemic to pulmonary artery shunt, usually modified Blalock–Taussig–Thompson, which is a polytetrafluoroethylene graft from the innominate artery to the ipsilateral PA, is still indicated for some patients who are at high risk for early complete repair. For example, patients with multiple congenital anomalies, severe concurrent illness, intracranial hemorrhage, an anomalous coronary artery crossing a hypoplastic infundibulum, or those presenting with prohibitive cyanosis as a newborn may benefit from shunt palliation prior to complete repair. In the absence of these risk factors, complete repair in the symptomatic neonate can be performed with lower mortality and reoperation rate compared to staged palliation.[33,34] Complete repair of TOF is described in Table 81.4.

When the pulmonary valve annulus or infundibulum is severely hypoplastic, a transannular outflow tract patch may be necessary to relieve the obstruction. In this setting, the pulmonary valve is typically excised. When an anomalous coronary artery crosses the infundibulum, a transannular incision may be contraindicated. In these cases, and in patients with pulmonary atresia, placement of a conduit (cryopreserved homograft, valved xenograft, or bioprosthetic heterograft) between the right ventricle (via a separate ventriculotomy) and main PA will be necessary.

OPERATIVE STEPS

Table 81.4 Complete Repair of TOF via Sternotomy

CPB configuration	Bicaval cannulation, mild hypothermia, antegrade cardioplegic arrest
Exposure and intracardiac steps	Oblique right atriotomy, retraction of septal and anterior leaflets of tricuspid valve, division of obstructing RV muscle bundles, patch closure of VSD, closure of ASD, pulmonary valvotomy or transannular patch placement as needed
Completion	De-airing of left heart, removal of cross clamp, primary closure of right atriotomy
Final steps	Wean off bypass, place temporary pacing wires, TEE, standard closure

CPB, cardiopulmonary bypass; RV, right ventricle; VSD, ventricular septal defect; ASD, atrial septal defect; TEE, transesophageal echocardiogram.

Patients who have a transannular patch develop pulmonary insufficiency as a consequence. This is well tolerated in most infants and children, as long as the tricuspid valve is competent. As these patients grow older, all will develop progressive dilation of their RV due to chronic pulmonary insufficiency, with the risk of progressing to ventricular failure over the long term. Pulmonary valve implantation is ultimately required to prevent this chronic volume overload, but this can usually be deferred until somatic growth is complete, often into the second or third decade of life.[35]

The early mortality following complete repair of TOF is approximately 1%.[36] Notable long-term complications include recurrent obstruction of the right ventricular outflow tract, development of right ventricular dysfunction due to chronic pulmonary insufficiency, aortic root dilation, and atrial arrhythmias. Actuarial survival at 20 years is 86% with excellent functional status.[37]

TRANSPOSITION OF THE GREAT ARTERIES

Embryology

There is not a unified theory defining the morphogenesis of transposition of the great arteries (TGA). In normal development, the subaortic conus is resorbed by the fifth week of gestation and allows for the usual mitral and aortic valve fibrous continuity. In dextro-TGA (d-TGA), Van Praagh postulates that the sub-pulmonary conus is resorbed, leading to fibrous continuity between the pulmonary and mitral valve.[38] As a result, the pulmonary valve (and PA) becomes continuous with the LV, and the aortic valve (and aorta) becomes continuous with the RV (ventriculoarterial discordance).

Looping refers to the right or left looping of the primitive heart tube during fetal development, which determines whether the atria and ventricles are concordant (right atrium attaches to RV and left atrium attaches to LV) or discordant. Levo-TGA (l-TGA) is associated with AV discordance (right atrium attaches to LV and left atrium attaches to right ventricle) along with ventriculoarterial discordance. This is also referred to as *congenitally corrected* TGA. Levo-TGA is a rare variant of TGA and is beyond the scope of this chapter, which will focus on d-TGA.

Anatomy and Pathophysiology

5 TGA is the most common form of congenital heart disease presenting as cyanosis in the first week of life. The malformation occurs in 0.3 of every 1,000 live births and accounts for approximately 4% of all CHDs.[7] TGA can be subdivided into d-TGA with intact ventricular septum (IVS) (55% to 60%) and d-TGA with VSD (40% to 45%), with one-third of the VSDs being hemodynamically insignificant. Pulmonary stenosis, causing significant LVOTO, occurs rarely with d-TGA/IVS and in approximately 10% of d-TGA/VSD.

The degree of cyanosis depends on the amount of mixing between the pulmonary and systemic circulations. 5 In d-TGA, oxygenated pulmonary venous blood is delivered to the lungs, while desaturated systemic blood is delivered to the body (Fig. 81.4). Because the two circulations exist in

parallel, some mixing between them must occur to allow oxygenated blood to reach the systemic circulation and the desaturated blood to reach the lungs. Mixing may occur at a number of levels, most commonly at the atrial level through an ASD or a PFO. Generally, two levels of mixing are necessary to maintain adequate systemic oxygen delivery, with a VSD or PDA serving as an additional site for cardiac mixing. Atrial level mixing is almost always required for adequate systemic oxygen delivery.

Clinical characteristics are dependent on the degree of mixing and the amount of PBF. These factors relate to the specific anatomic subtype of d-TGA. Neonates with d-TGA with IVS (or small VSD) have mixing limited to the atrial level and PDA. The ASD may be restrictive and the PDA generally will close over the first days to week of life (in the absence of PGE). As the degree of mixing decreases, the patient becomes increasingly cyanotic and will eventually suffer cardiovascular collapse within the first weeks of life. In d-TGA with a large VSD, there is additional opportunity for mixing and increased PBF. The neonate with d-TGA/VSD may only manifest mild cyanosis, which may be initially overlooked. Generally, within 2 to 6 weeks, tachypnea and tachycardia become prominent, whereas cyanosis may remain mild.

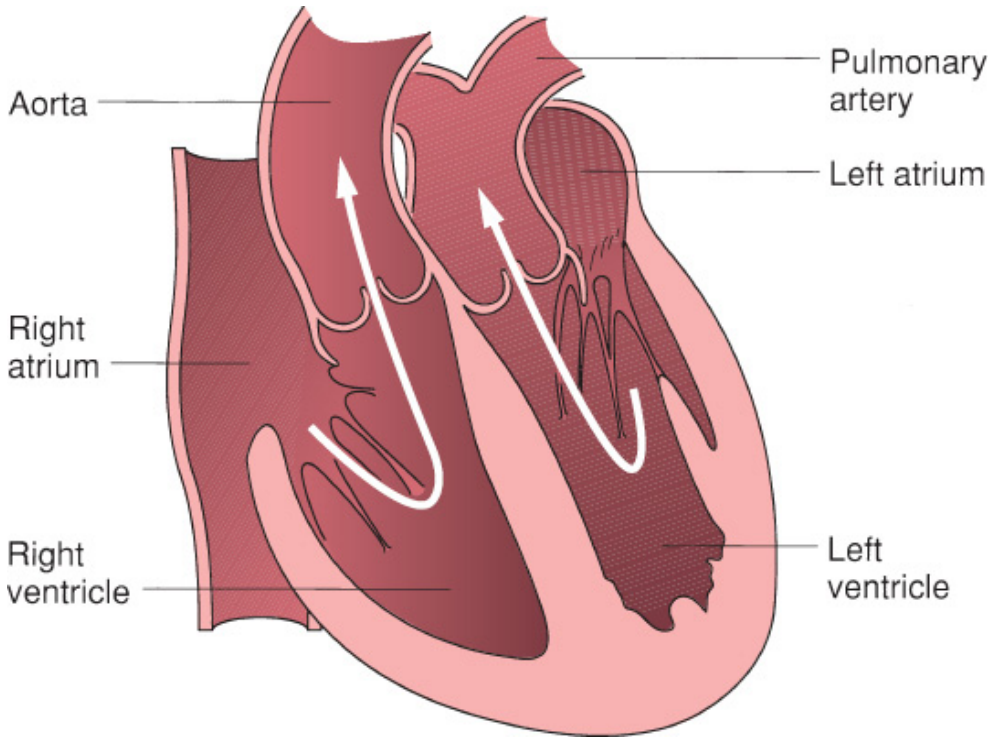

Figure 81.4 Anatomy of the most common type of transposition of the great arteries. The location of the ascending aorta is usually anterior and to the right of the pulmonary artery.

Auscultatory findings are consistent with CHF with increased PBF, including a pansystolic murmur, third heart sound, mid-diastolic rumble, gallop, and narrowly split second heart sound with increased pulmonary component. Neonates with d-TGA and significant PS present with severe cyanosis at birth. Lesser degrees of PS will result in varying levels of cyanosis. The ECG is normal at birth, demonstrating the typical pattern of right ventricular dominance. Although the classic chest radiographic appearance of an egg-shaped heart with a narrow superior mediastinum may be seen, this finding is often obscured by an enlarged thymic shadow. Echocardiography is diagnostic, demonstrating that the posterior great vessel arising from the LV is a PA that bifurcates soon after its origin. The anterior great vessel is the aorta and arises from the right ventricle. Associated lesions, including VSD, LVOTO, and coarctation, may also be diagnosed.

While diagnostic catheterization is not required, interventional catheterization to improve cardiac mixing by means of balloon atrial septostomy is frequently employed. The infant with d-TGA and severe cyanosis requires prompt diagnosis and treatment to improve mixing and

increase the arterial oxygen saturation. The first intervention to improve mixing in a cyanotic newborn suspected of having d-TGA is to ensure ductal patency by beginning an infusion of prostaglandin E_1 (PGE_1). In the presence of a restrictive ASD, a balloon atrial septostomy, a technique developed by William Rashkind in 1966, is performed. The procedure involves inserting a balloon-tipped catheter across the foramen ovale into the left atrium. Inflation and forcible withdrawal of the catheter tears the septum primum and enlarges the ASD. Mixing generally increases immediately, with a substantial improvement in arterial oxygen saturation.

Indications for Intervention and Treatment Options

Without intervention, d-TGA is universally fatal. Historically, definitive repair was achieved by redirecting venous inflow at the atrial level and allowing for persistent ventriculoarterial discordance thereby leaving the RV as the systemic ventricle. First successfully performed by Senning in 1959; the operation was further modified by Mustard in 1964. Although physiologic repair at the atrial level is associated with a low operative mortality rate (<5%), a number of late problems have occurred. The most serious long-term complication of repair by either the Senning or Mustard technique has been right ventricular dysfunction.[39] Right ventricular failure with an enlarged, poorly contractile chamber and secondary tricuspid regurgitation has been found in a significant number of these patients in long-term follow-up studies.[40]

OPERATIVE STEPS

Table 81.5 Arterial Switch Operation via Sternotomy

CPB configuration	Bicaval cannulation, mild hypothermia, antegrade cardioplegic arrest
Exposure and intracardiac steps	Division of aorta and PA, harvesting of coronary buttons, LeCompte maneuver, reconstruction of neo-aorta and positioning of coronary buttons, oblique right-atriotomy and patch closure of ASD
Completion	De-airing of left heart, removal of cross clamp, primary closure of right atriotomy, completion of neo-pulmonary root reconstruction and reanastomosis with branch PAs
Final steps	Wean off bypass, place temporary pacing wires, TEE, standard closure

CPB, cardiopulmonary bypass; PA, pulmonary artery; ASD, atrial septal defect; TEE, transesophageal echocardiogram.

The long-term complications of atrial repair prompted a reexamination of direct arterial repair for d-TGA. The "arterial switch" operation (ASO), first successfully performed by Jatene in 1975, has become the standard surgical procedure for neonates with this condition.[41] The operative technique is described in Table 81.5. Chiefly, the procedure reestablishes ventriculoarterial concordance (Fig. 81.5). The extensive experience gained with this procedure has confirmed that any variant of coronary artery anatomy can be successfully repaired. Certain coronary anatomy variants were previously felt to be associated with higher risk; however, this concern has been neutralized in recent series.[42,43]

Many patients with d-TGA have an IVS, and left ventricular pressure falls early in life as PVR decreases. In this situation, it is essential that the arterial

repair be performed within the first week of life, while the LV is still able to meet systemic workloads. In patients presenting later, the LV can be retrained with a preliminary PA band and a systemic-PA shunt, if necessary, followed by the definitive arterial repair. Patients with large VSDs do not require early repair because they maintain systemic left ventricular pressures. Nevertheless, experience has indicated that even in this subgroup, the operation is best performed within the first 1 to 2 weeks of life, before secondary complications such as pulmonary hypertension, CHF, or infection develop.

Patients with fixed LVOTO are not candidates for the arterial switch operation because correction would result in systemic ventricular outflow tract obstruction. Most of these patients also have large VSDs. Palliation early in life with systemic-to-PA shunting is an option, with definitive repair postponed until somatic growth results in cyanosis as the shunt is outgrown. At that time, the Rastelli procedure is performed, in which left ventricular blood is redirected through the VSD and to the anterior aorta by placement of an intraventricular patch along with the placement of a conduit between the RV and the PA (Fig. 81.6). An increasing number of experienced centers currently recommend early complete repair in the neonatal period using a Rastelli procedure. Early repair eliminates the interim morbidity and mortality associated with a systemic-to-PA shunt and chronic cyanosis however at the expense of usually a more complex neonatal postoperative course and the placement of a smaller initial conduit.

Current hospital mortality for the arterial switch operation is 2.2% (d-TGA/IVS) and 4.6% (d-TGA/VSD).[36] Prematurity, low birth weight, and complex d-TGA including d-TGA/VSD/PS and d-TGA/VSD with aortic arch hypoplasia are independent predictors of increased operative complexity and mortality.[42,44] Coronary artery anatomy does not affect mortality.[42] The most common cause for reintervention is supravalvar PS (15% to 20%).[45] Long-term survival among perioperative survivors is excellent (approximately 97% at 25 years).[46] Nevertheless, late follow-up of arterial switch operation patients has led to increased concern regarding late coronary artery patency and neoaortic root dilation with subsequent aortic insufficiency.[47]

TRUNCUS ARTERIOSUS

Embryology

In normal development, the conotruncal septum divides the truncal root into the main PA and aorta by the fifth week of gestation. Abnormal development of the conotruncal septum results in truncus arteriosus (TA). The lack of a division between the aorta and PA results in a single truncal valve. Normal septation leads to the development of both pulmonary and systemic outflow tracts, division of the semilunar valves, and formation of the aorta and pulmonary arteries. Failure of septation results in a VSD (absence of the infundibular septum), a single semilunar valve, and a single arterial trunk. Neural crest cell–derived tissue is thought to play a critical role in the development of this lesion.

Anatomy and Pathophysiology

Truncus arteriosus is a rare anomaly. The lesion accounts for 1% of cyanotic congenital heart disease.[7] Truncus arteriosus is defined by a single arterial vessel arising from the heart, overriding the ventricular septum and giving rise to the systemic, coronary, and pulmonary circulations. Two classification schemes have been proposed: one by Collett and Edwards[48] in 1949 and the other by Van Praagh and Van Praagh[49] in 1965 (Fig. 81.7). The Collett and Edwards classification, the most widely used, focuses on the origin of the pulmonary arteries from the common arterial trunk (Table 81.6).

The truncal valve leaflets are generally dysmorphic, and their motion may be restricted. Leaflet number is highly variable, with 70% tricuspid, 20% quadricuspid, 10% bicuspid, and rarely unicuspid or pentacuspid. As a result of these abnormally developed valve leaflets, a moderate or greater degree of truncal insufficiency is present in approximately 25% of patients. Mild stenosis is common; however, significant stenosis is rare. Significant obstruction is predicted by gradients of more than 30 mm Hg in the presence of a normal cardiac output following complete repair. The PAs are of normal size and most often arise from the left posterolateral aspect of the truncal artery, often in close proximity to the truncal valve and ostium of the left coronary artery.

Other cardiac anomalies are common in TA, with a PFO usually present. An interrupted aortic arch is associated with TA in approximately 10% to 20%.[50] The arch is rightward in 25% to 35%. Coronary ostial abnormalities are of particular surgical significance and occur in approximately 35% to 50% of cases. The left coronary artery is frequently noted to have a high origin, not uncommonly near the takeoff of the pulmonary arteries. Rarely, the left coronary can originate from the main pulmonary trunk or a branch PA.

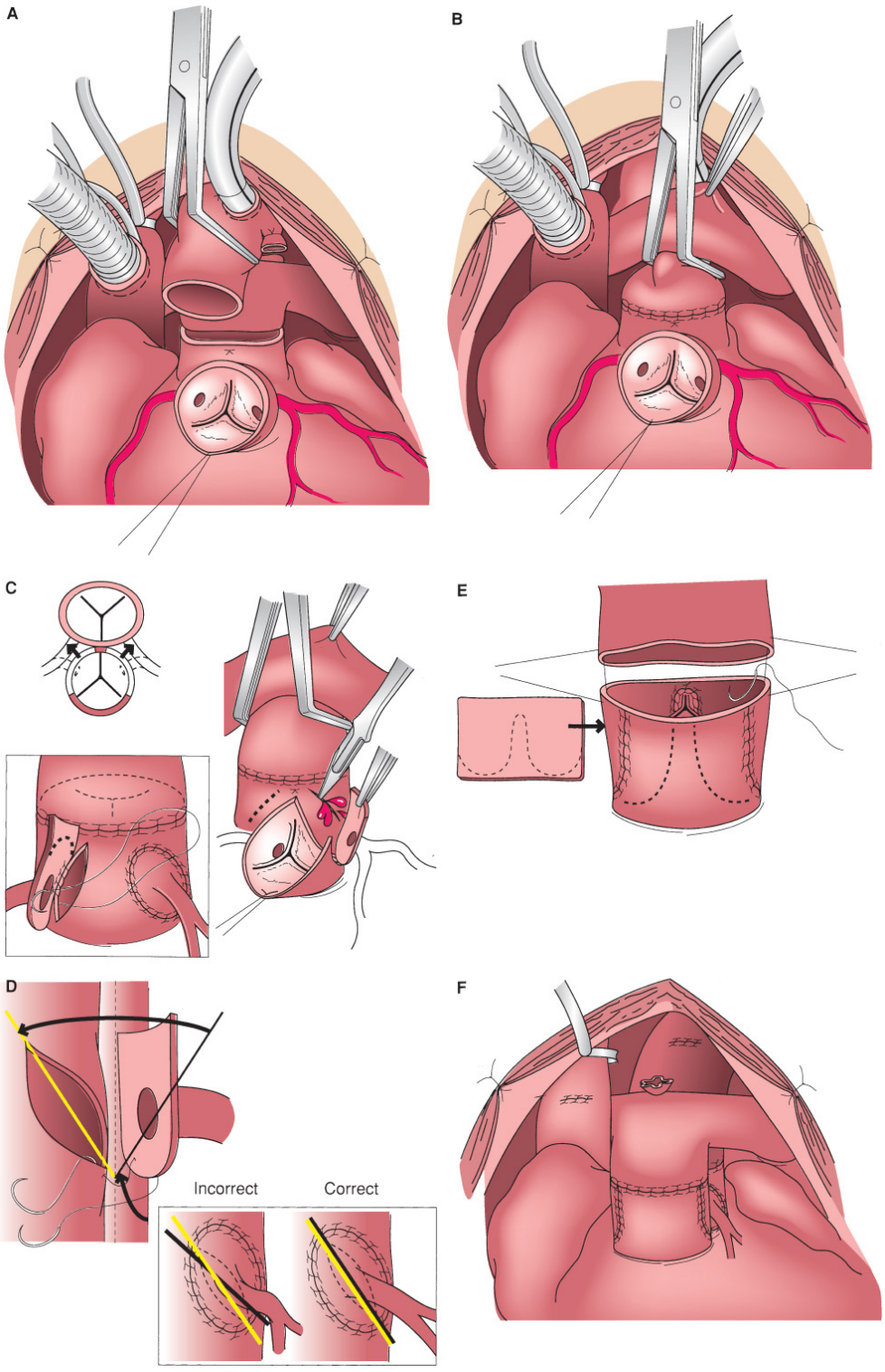

Figure 81.5 Arterial switch procedure for transposition of the great arteries. **A:** Division of aorta and pulmonary artery. **B:** LeCompte maneuver; anterior translocation of the pulmonary arteries. **C:** Mobilization of the coronary arteries. **D:** Correct orientation for coronary re-implantation. **E:** Placement of a pantaloon-

shaped pericardial patch to reconstruct the neo-pulmonary artery. **F:** Completed repair.

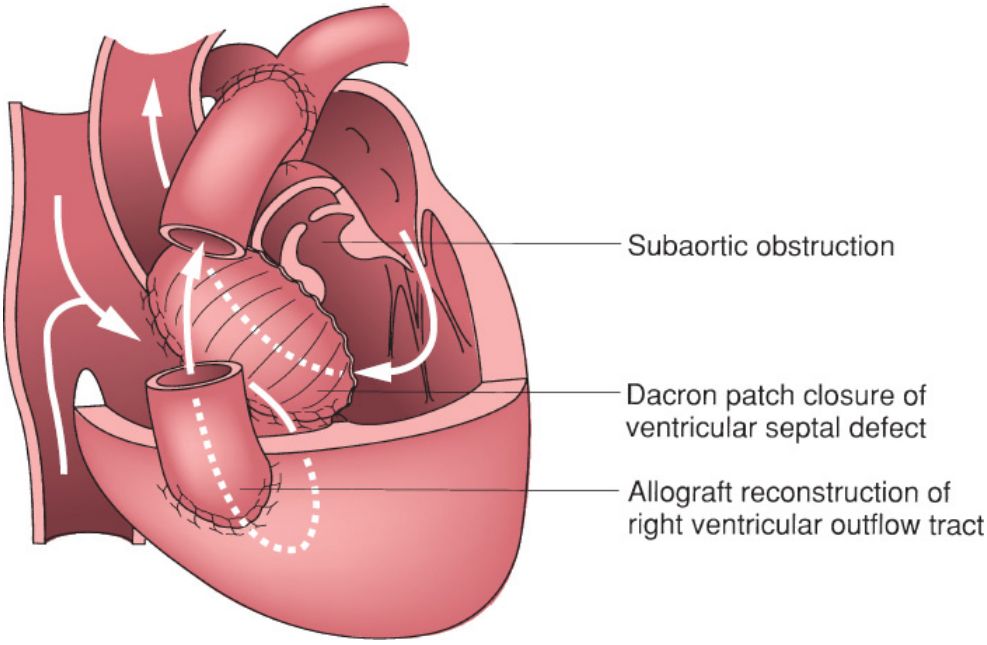

Figure 81.6 The Rastelli procedure for transposition of the great arteries with ventricular septal defect and pulmonary stenosis. A prosthetic patch placed within the right ventricle directs left ventricular blood through the defect to the aorta. The main pulmonary artery is ligated, and right ventricular blood then passes through a conduit to the distal pulmonary arteries.

Extracardiac anomalies are reported in approximately 40% of patients.[51] Described abnormalities include skeletal, genitourinary, and gastrointestinal deformities. Monoallelic microdeletion of chromosome 22q11 occurs in 40% of patients.[52]

The anatomy of TA results in the obligatory mixing of systemic and pulmonary venous blood at the level of the VSD and truncal valve, which produces arterial saturations of 85% to 90%. The systemic arterial saturation depends on the volume of PBF, which in turn is determined by the PVR. As the PVR begins to fall, excessive pulmonary circulation ensues and leads to pulmonary congestion and signs and symptoms of CHF. This nonrestrictive left-to-right shunt may cause early development of irreversible PVOD.

Truncal valve abnormalities add further hemodynamic burden. Truncal valve regurgitation leads to ventricular dilatation and low diastolic coronary perfusion pressures that can result in myocardial ischemia. Truncal valve

stenosis promotes ventricular hypertrophy, increases myocardial oxygen demand, and limits coronary and systemic perfusion.

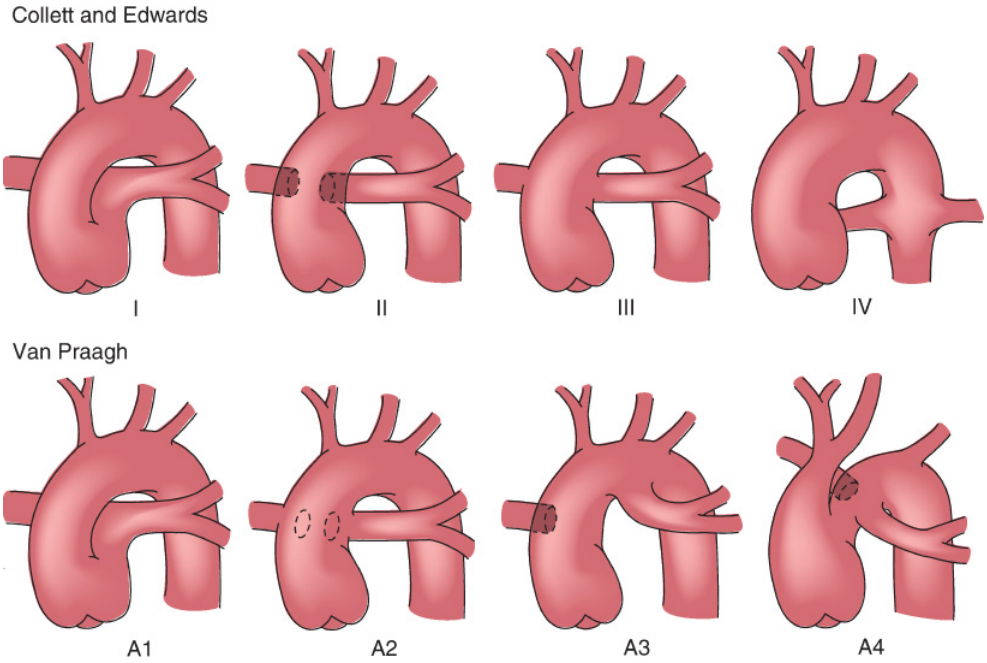

Figure 81.7 Truncus arteriosus: classification schemes as described by Collett and Edwards[48] and by Van Praagh and Van Praagh.[49] (Adapted from Hernanz-Schulman M, Fellows KE. Persistent truncus arteriosus: pathologic, diagnostic, and therapeutic considerations. *Semin Roentgenol* 1985;20:121.)

Table 81.6 Collett and Edwards Classification of Truncus Arteriosus

Type	Description
I	Common arterial trunk gives rise to a main pulmonary artery and the aorta.
II	Right and left pulmonary arteries arise directly and in close proximity from the posterior wall of the truncus.
III	Right and left pulmonary arteries arise from more widely separated orifices on the posterior truncal wall.
IV	Branch pulmonary arteries are absent. Pulmonary blood flow is derived from aorticopulmonary collaterals.

OPERATIVE STEPS

Table 81.7 Repair of Truncus Arteriosus via Sternotomy

CPB configuration	Bicaval cannulation, snare PAs immediately upon commencement of CPB, mild hypothermia, antegrade cardioplegic arrest
Exposure and intracardiac steps	Division of truncal vessel and removal of PAs, repair of defect within aorta, patch closure of VSD via ventriculotomy, oblique right atriotomy and closure of ASD, restoration of continuity between RV and branch PAs with extracardiac conduit
Completion	De-airing of left heart, removal of cross clamp, and primary closure of right atriotomy
Final steps	Wean off bypass, place temporary pacing wires, TEE, standard closure

CPB, cardiopulmonary bypass; PA, pulmonary artery; VSD, ventricular septal defect; ASD, atrial septal defect; RV, right ventricle; TEE, transesophageal echocardiogram.

Diagnostic Findings

Neonates with TA present with signs of CHF and diminished peripheral pulses. Chest radiography shows marked cardiomegaly; pulmonary plethora, often with minimal thymic shadow; and a right aortic arch (when present). The ECG most often depicts biventricular hypertrophy. Echocardiography is the diagnostic procedure of choice and can demonstrate the truncal vessel, the structure and function of the truncal valve, associated lesions such as interrupted aortic arch, and the PA anatomy. Cardiac catheterization is not performed unless the status of the pulmonary vasculature is unclear (i.e., infants older than 3 months at diagnosis).

Indications for Intervention and Treatment Options

The natural history of patients born with TA is early demise secondary to CHF. Survivors may do well for a period of time until the development of PVOD and Eisenmenger syndrome.

The standard treatment of TA is surgical correction in the neonatal period. Complete repair is detailed in Table 81.7. Severe truncal valve regurgitation requires truncal valve repair[53] or replacement, which is best done with a cryopreserved allograft. An associated interrupted aortic arch is repaired by constructing a primary end-to-end anastomosis with proximal augmentation if necessary.

The results of TA repair have improved greatly during the last two decades. Current hospital mortality for the neonatal repair of TA is 9.5%.[36] Severe truncal valve regurgitation increases the risk of perioperative mortality.[53] Risk factors for poor outcome identified in various studies include significant truncal regurgitation, need for truncal valve replacement, birth weight less than 2.5 kg, coronary artery anomalies, pulmonary reconstruction with a technique other than valved heterograft or allograft, and age older than 100 days.[53,54]

HYPOPLASTIC LEFT HEART SYNDROME

Embryology

Hypoplastic left heart syndrome (HLHS) refers to a constellation of congenital cardiac anomalies characterized by marked hypoplasia of left-sided heart structures. While there is growing evidence of genetics playing a role in the development of HLHS,[55] the most commonly cited theory centers upon altered blood flow through the left side of the heart in utero.[56] Advanced animal models have demonstrated the complex interaction between intracardiac hemodynamics and embryonic cardiogenesis.[57]

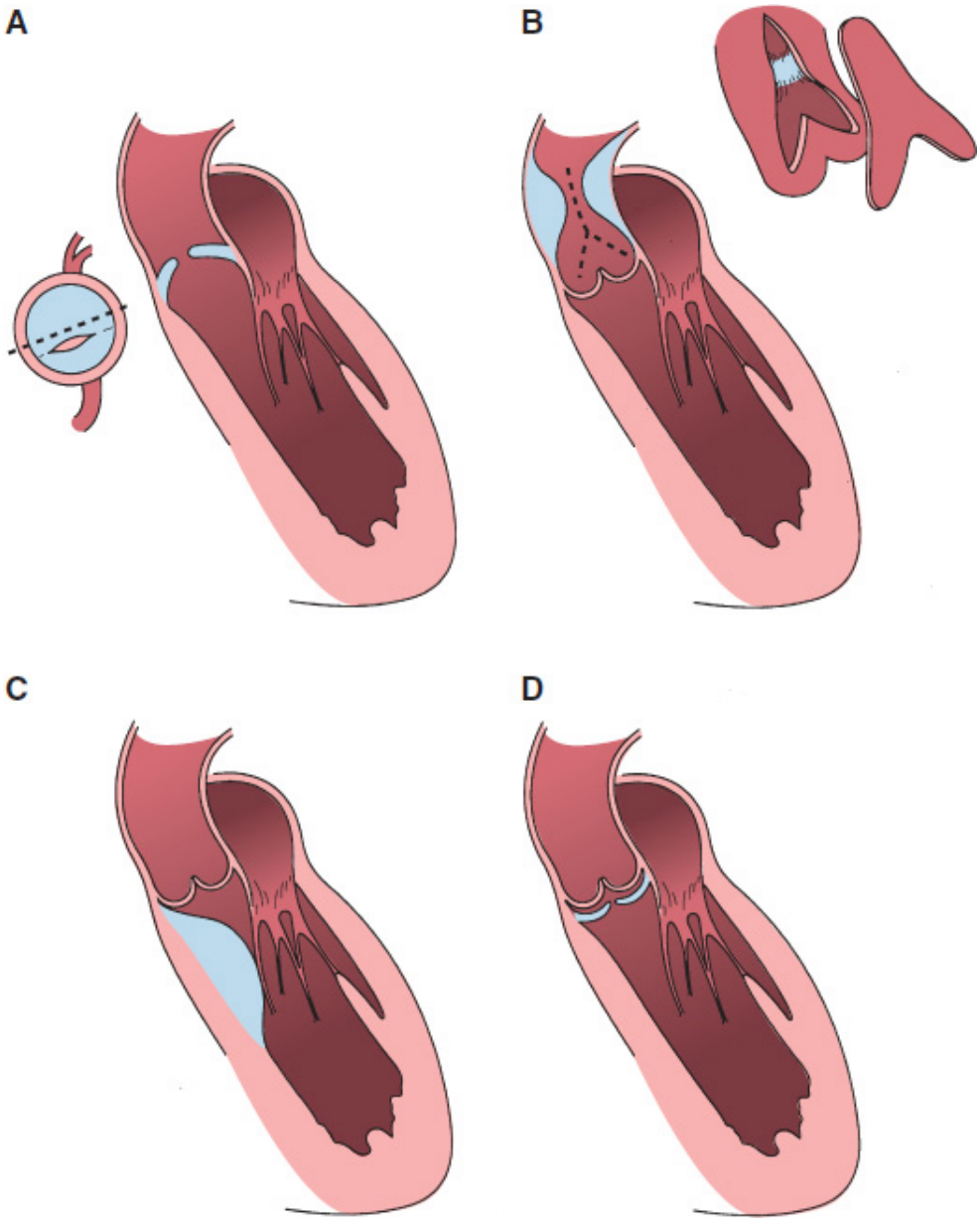

Figure 81.8 Anatomy of the types of congenital aortic stenosis. **A:** Valvar aortic stenosis. **B:** Supravalvar aortic stenosis and its repair (*inset*). **C:** Diffuse (tunnel) subvalvar aortic stenosis. **D:** Discrete subvalvar aortic stenosis.

Anatomy and Pathophysiology

HLHS accounts for 2% to 3% of CHD and is found in 0.2 per 1,000 live births.[7] While there is a spectrum of anatomic variants, HLHS is defined by underdevelopment of left-sided structures (mitral valve, aortic valve, left ventricle, ascending aorta, and aortic arch). Survival is dependent on a

nonrestrictive ASD with obligatory mixing of pulmonary and systemic venous blood in the right atrium and maintenance of ductal patency to maintain systemic output via the right ventricle.

Infants born with HLHS may initially have balanced circulation owing to relatively high PVR. However, in the absence of PGE to maintain ductal patency and with decreasing PVR, the infant will develop shock and intractable hemodynamic instability. If left untreated, HLHS is uniformly fatal within the first few days to weeks of life.

Diagnostic Findings

The diagnosis of HLHS is often made prenatally on ultrasound. In patients without a prenatal diagnosis, tachypnea and cyanosis with cardiovascular collapse within 24 to 48 hours of birth often lead to confirmatory studies. If the ductus is closing, diminished pulses within the lower extremities may be palpated. Auscultation will reveal a single second heart sound, and a nonspecific, soft, systolic murmur at the left sternal border. The ECG demonstrates right atrial enlargement and RV hypertrophy. Chest radiograph demonstrates cardiomegaly and increased pulmonary vascular markings. Transthoracic echocardiogram is diagnostic. Catheterization is rarely utilized for diagnostic benefit but may be employed to enlarge the ASD if it is restrictive.[58]

Indications for Intervention and Treatment Options

All patients with HLHS should be considered for staged palliation or evaluation for orthotopic heart transplant. In some variants of HLHS that portend a very poor prognosis, consultation with the family regarding palliative options is critically important. The initial management of HLHS includes a PGE_1 infusion to maintain ductal patency and correction of metabolic acidosis. The patient may require intubation and ventilator adjustment to reduce supplemental oxygen and maintain a partial pressure of carbon dioxide (PCO_2) of about 40 mm Hg to avoid excessive pulmonary flow.

Treatment options for this lesion include staged reconstructive surgery and cardiac transplantation. In the context of improving results for staged reconstruction, risks of immunosuppression, and limited donor availability, competing risk analysis favors staged repair, and most centers pursue this option as primary therapy for HLHS.[59,60] Transplantation is generally reserved for very high-risk patients, such as those with depressed right ventricular function or severe tricuspid regurgitation. Results of transplantation in neonates have been excellent in centers with extensive experience in this area, and a 2-year survival as high as 70% has been reported.[61]

The first successful palliation of HLHS was reported by Norwood et al. on a series of infants operated on between 1979 and 1981.[62] This procedure has been technically refined over the years, but three essential components remain: atrial septectomy, anastomosis of the proximal PA to the aorta with homograft augmentation of the aortic arch, and aortopulmonary shunt or RV–PA conduit. With the advance of transcatheter techniques, hybrid stage 1 palliation (HS1P) has developed into a viable and important technique. In the HS1P, bilateral pulmonary artery bands are placed to restrict pulmonary blood flow, and the ductus is stented to preserve unobstructed outflow to the systemic circulation. While HS1P has gained traction, it accounts for a minority of stage 1 palliation patients.[63]

At the second stage, a hemi-Fontan procedure or bidirectional Glenn anastomosis is performed. Stage 2 is usually performed at 4 to 6 months of age. The original shunt is removed, and superior vena cava blood flow is directed to the pulmonary artery. Principally, the hemi-Fontan and bidirectional Glenn procedures achieve the same goals, however there is evidence of improved fluid dynamics with the hemi-Fontan procedure.[64,65]

At the third stage, the Fontan procedure, is performed at about 18 to 24 months. The inferior vena caval flow is directed to the PA with an intra-atrial baffle (lateral tunnel technique, or an extracardiac conduit). All oxygenated pulmonary venous flow now empties into the ventricular chamber through the AV valves to be ejected to the systemic circulation, while superior and inferior vena caval blood flows passively to the lungs to acquire oxygen prior to returning to the heart. For the Fontan procedure to be performed with a low operative mortality and an acceptable functional result, certain criteria must be met. Normal PA pressure (<20 mm Hg) and PVR (<2 Wood units/m^2)

are the most important prerequisites. Additionally, it is essential that ventricular function and AV valve function be normal. Although the Fontan procedure cannot be considered a truly corrective operation, it offers benefits that cannot be equaled by any of the other palliative procedures. The major advantages include restoration of normal systemic oxygen saturation and reduction of ventricular volume overload.

Universally fatal only four decades ago, tremendous strides have been made in improving the outcomes for patients with HLHS. Of the three stages, the highest-risk stage of the repair remains the Norwood operation. Currently, select centers have reported hospital survivals of 90% or greater.[65,66] Reported survivals for the hemi-Fontan and Fontan procedures have also been excellent at 98% for both operations.[67–71]

While major advancements have been made in the outcomes of patients with HLHS, a vast spectrum of techniques and corresponding results exists. In 2005, a prospective, randomized clinical trial was initiated in order to determine the impact of shunt type at the Norwood procedure. This trial, termed the Single Ventricle Reconstruction trial, has had a significant impact on the treatment of HLHS. In addition to demonstrating early superiority of an RV to PA shunt, this study revealed sobering 1-year mortality of 30%.[72,73] The risk factors for mortality included low gestational age, weight <2.5 kg, and noncardiac abnormalities.[74,75]

AORTIC STENOSIS

Embryology

Left ventricular outflow tract development is related to appropriate development of the aorticopulmonary septum and conotruncal septum. The aortic valve leaflets develop as subendothelial swellings within the developing aorta. Inappropriate development of the aorticopulmonary septum, conotruncal septum, or of the endocardial cushions can be related to LVOTO.

AS broadly refers to a form of LVOTO that may occur at the valvar (71%), subvalvar (14%), or supravalvar (8%) level (Fig. 81.8). AS occurs in about 2.5% of patients with congenital heart disease.[7] BAV is the most common

congenital heart lesion—though many individuals with BAV without stenosis or insufficiency are never diagnosed and do not require any intervention.

Anatomy and Pathophysiology of Valvar Aortic Stenosis

Valvar AS occurs secondary to maldevelopment of the aortic valve. Most commonly, a bicuspid valve is present, although tricuspid and unicuspid valves may also produce AS. In valvar AS, the leaflets are thickened and frequently dysmorphic, and there is a variable degree of leaflet fusion along the commissures. The aortic annulus may be hypoplastic. In 20% of cases, valvar AS is associated with other cardiac defects, most commonly coarctation of the aorta, PDA, VSD, or mitral stenosis.

There is a wide spectrum of clinical presentation for valvar AS, but patients tend to present in one of two groups: younger patients (neonates and infants) with severe AS who develop symptoms of rapidly progressive CHF, whereas older patients, with less severe obstruction at birth, have a more indolent course. Older patients will be discussed later in this section.

Severe valvar AS is usually well tolerated during fetal development. While left ventricular output and antegrade flow across the aortic valve are decreased, the right ventricle compensates with increased output, and systemic perfusion is maintained by flow across the ductus. After birth, there is increased venous return to the left heart, and this exacerbates the pressure load created by the stenotic aortic valve, leading to left ventricular dysfunction. As the ductus closes during postnatal life, systemic malperfusion may develop with resulting hypotension, acidosis, and oliguria. Coronary perfusion is also impaired due to the combination of systemic hypotension and elevated left ventricular end-diastolic pressure.

Diagnostic Findings of Valvar AS in the Neonate or Infant

Infants with critical valvar AS typically exhibit severe left ventricular dysfunction. These patients show signs of distress soon after birth. On examination, there is impaired distal perfusion with poor capillary refill and

diminished pulses. A systolic ejection murmur may be absent if the cardiac output is severely diminished. Differential cyanosis may be observed due to perfusion of the lower body with desaturated blood shunting through the ductus. The ECG shows left ventricular hypertrophy, and the chest radiograph displays cardiomegaly and pulmonary congestion. Echocardiography establishes the diagnosis. The severity of valvar AS may be graded by echocardiography or catheterization. Classification by echocardiography peak instantaneous pressure gradient is mild (<40 mm Hg), moderate (40 to 70 mm Hg), and severe (>70 mm Hg). Classification by catheterization peak-to-peak pressure gradient is mild (<30 mm Hg), moderate (30 to 50 mm Hg), and severe (>50 mm Hg).

Fetal echocardiography has allowed for early diagnosis of critical valvar AS. For some, this may predict the progression to HLHS or irreversible left ventricular dysfunction.

Indications for Intervention and Treatment Options for Valvar AS in the Neonate or Infant

The neonate or infant with severe or critical valvar AS represents a true emergency. Endotracheal intubation and inotropic support are routine. Ductal patency is maintained with prostaglandins, and acidosis is corrected. All patients with critical valvar AS require some form of urgent intervention. The approach is determined by the valve morphology and by the presence of associated defects.

In its most extreme form, critical AS may be associated with underdeveloped left-sided cardiac chambers and therefore may represent a form of HLHS. In these cases, single-ventricle palliation must be undertaken.

For patients with adequate left-sided chambers, relief of valvar AS may be achieved by one of the following three approaches: percutaneous balloon valvuloplasty, surgical valvotomy, or aortic valve replacement. Balloon valvuloplasty is generally considered the procedure of choice when the aortic valve annulus is adequate and there are no associated cardiac defects. Alternatively, surgical valvotomy may be accomplished by closed or open techniques. The closed approach is performed using cardiopulmonary bypass, but without aortic cross-clamping. Dilators of increasing size are

passed through a ventriculotomy in the left ventricular apex and advanced across the aortic valve. Alternatively, some centers prefer open surgical valvotomy, which allows a precise valvotomy under direct vision. Surgical valvotomy has been demonstrated to have improved reduction in aortic valve gradient, less postprocedural aortic insufficiency, and excellent freedom from reintervention (72% at 10 years).[75] In all cases, the goal of therapy is to relieve stenosis without creating excessive aortic insufficiency. Dramatic clinical improvement is expected following balloon or surgical valvotomy, and early survivals of greater than 80% have been reported regardless of approach.[76] The incidence of aortic insufficiency is slightly higher following balloon valvotomy.[75,76] In most cases stenosis will recur and repeat valvotomy or aortic valve replacement will eventually be required.

Aortic valve replacement is problematic in the neonate due to small patient size. In these cases, many consider the best valve replacement to be a pulmonary autograft (Ross procedure)[77] with enlargement of the aortic annulus (Konno aortoventriculoplasty).[78] The Ross–Konno procedure has been used successfully for neonates with critical AS in whom the aortic annulus is hypoplastic and for selected patients in whom valvuloplasty was unsuccessful. Survival following the Ross–Konno procedure in infants has been shown to be excellent.[79] Growth of the pulmonary autograft has been documented, thereby making it an ideal valve replacement for children. Unfortunately, as part of the Ross procedure, the pulmonary valve must be replaced using a cryopreserved homograft that does not grow, and homograft replacement must be anticipated at intervals as the patient grows.

Notably, select centers have been able to successfully balloon dilate the aortic valve in utero to promote left ventricular growth and preserve function in select cases.[80–82] This therapy is more often utilized as a measure to prevent the development of HLHS rather than treatment of simple, valvar AS.

Diagnostic Findings of Valvar AS in the Older Child

In contrast to infants with critical AS, older children with valvar AS usually present with less severe stenosis (mild or moderate) and most are asymptomatic. Symptoms of angina, syncope, and CHF are not commonly

reported. Congenital valvar AS is a progressive lesion, however, and survival is dependent on the severity of stenosis and the rate of its progression. Sudden cardiac death is the most common cause of mortality. Endocarditis occurs in less than 1% of patients.

The diagnosis of valvar AS in older children is usually made on physical examination. There is a classic systolic crescendo–decrescendo murmur at the upper sternal border, which radiates to the neck. An ejection click is often present. A visible apical impulse is suggestive of significant left ventricular hypertrophy. In severe cases, the pulse may be weak and delayed (*pulsus tardus et parvus*). The ECG shows left ventricular hypertrophy. The chest radiograph is usually normal. Echocardiography accurately defines the level of stenosis and its severity. Using Doppler techniques, the pressure gradient across the stenotic valve may be estimated using a simplified form of Bernoulli's equation, $P = 4V^2$, where P is the pressure gradient and V is the peak flow velocity. Cardiac catheterization is generally reserved for therapeutic intervention.

Indications for Intervention and Treatment Options for Valvar AS in the Older Patient

All patients with severe valvar AS should undergo intervention, as should all symptomatic patients with moderate stenosis. Asymptomatic patients with mild or moderate stenosis are generally observed. As described previously for critical valvar AS in the neonate, the techniques used to relieve AS in older patients include percutaneous balloon valvuloplasty, surgical valvulotomy, and valve replacement. In older patients, balloon valvuloplasty is usually performed as the primary intervention, with comparable rates of efficacy, safety, and reintervention as surgical valvotomy.[83]

For valves that are severely dysplastic, develop restenosis after intervention, or become insufficient as a result of prior intervention, valve replacement may be necessary. For older children, there are more options for valve replacement. The choices include mechanical prostheses, bioprosthetic valves, cryopreserved human allografts, and pulmonary autografts (Ross procedure). Mechanical valves are the most durable but require chronic anticoagulation. Bioprosthetic valves do not require long-term

anticoagulation but tend to deteriorate over time (with the exception of the pulmonary autograft). The pulmonary autograft has the potential advantage of growth, but the homograft used to replace the pulmonary valve will require replacement. Selection of the appropriate replacement valve is a complex decision that requires input from all involved parties.

Anatomy and Pathophysiology of Subvalvar Aortic Stenosis

Subvalvar AS occurs below the level of the aortic valve and may be discrete (80%) or diffuse (20%). Discrete (or membranous) subaortic stenosis is rarely seen in infants and tends to progress over time. This lesion consists of a crescentic or circumferential fibrous or fibromuscular membrane that protrudes into the left ventricular outflow tract. The pathogenesis of discrete subaortic stenosis is unknown, but it is thought to be an acquired lesion that develops secondary to a congenital abnormality of the left ventricular outflow tract in which abnormal flow patterns lead to endocardial injury with resultant fibrosis. Although the aortic valve leaflets are usually normal in discrete subaortic stenosis, the turbulent flow created by the obstruction can cause leaflet thickening and progressive aortic insufficiency. Diffuse subaortic stenosis is a more severe form that creates a long, tunnel-like obstruction. Diffuse subaortic stenosis should be distinguished from hypertrophic cardiomyopathy. Both forms of subaortic stenosis (discrete and diffuse) are associated with a higher risk of endocarditis.

Diagnostic Findings of Subvalvar AS

The clinical findings in subvalvar AS are similar to those for valvar stenosis. With a Valsalva maneuver, the intensity of the systolic murmur typically decreases in subvalvar AS. Echocardiogram remains the gold standard for evaluating the LVOT and any associated lesions.

Indications for Intervention and Treatment Options for Subvalvar AS

Intervention for *discrete* subvalvar stenosis is usually undertaken when the gradient exceeds 30 to 50 mm Hg or when aortic insufficiency is present. In these patients, resection of the membrane is easily performed by a transaortic approach and is durable. To reduce the incidence of restenosis, we advocate concurrent performance of a septal myomectomy to alter the geometry of the left ventricular outflow tract. Operative mortality ranges from 0% to 3%.[84] The reoperation rate for discrete stenosis following membrane resection and myomectomy has been reported to be 2% per year.[84] Complications associated with membrane resection can include heart block, iatrogenic VSD, or damage to the aortic or mitral valve leaflets.

The indications for operative intervention in *diffuse* subaortic stenosis are similar to those for valvar stenosis. When diffuse subaortic stenosis is associated with hypoplasia of the aortic annulus, repair is best achieved with a Konno aortoventriculoplasty, whereby an incision is carried across the aortic annulus and subjacent ventricular septum, the opening patched, and an aortic valve implanted. Patients with an adequate aortic annulus may undergo a septoplasty (modified Konno),[85] in which the septal incision is confined to the immediate subvalvar area and a patch is used to widen the left ventricular outflow tract without replacing the aortic valve. Despite the technical complexity of repair for diffuse subaortic stenosis, excellent results have been reported with high survival and freedom from reoperation.[85]

Anatomy and Pathophysiology of Supravalvar Aortic Stenosis

Supravalvar AS is characterized by thickening of the wall of the ascending aorta. The lesion may be localized (80%) to the region of the sinotubular ridge (at the level of the valve commissures), creating an hourglass deformity, or it may be more diffuse (20%), extending into the aortic arch and its branches.[86] In both varieties, the aortic valve leaflets may be abnormal. The free edges of the aortic valve leaflets may adhere to the aortic wall in the region of intraluminal thickening, and this may lead to reduced coronary blood flow during diastole. Aortic wall thickening may also extend into the coronary ostia and further impair coronary blood flow.

Associated cardiac lesions are common, particularly branch PA stenoses. A genetic basis for supravalvar AS has been established. Supravalvar AS is associated with Williams syndrome, in which a partial deletion of chromosome 7 (including the elastin gene) leads to the triad of supravalvar stenosis, mental retardation, and characteristic "elfin" facies.[87] Isolated mutations in the elastin gene have also been shown to produce familial supravalvar AS with an autosomal dominant pattern of transmission. There is a significant incidence of endocarditis in patients with supravalvar AS. Sudden death is frequently reported and is probably related to coronary obstruction.

Diagnostic Findings of Supravalvar AS

The signs and symptoms of supravalvar AS are similar to those in other forms of LVOTO. The diagnosis is made by echocardiography. Cross-sectional imaging with MRI or computed tomography (CT) scan has become essential to define the aortic, coronary, and pulmonary arterial anatomy prior to surgical intervention.

Indications for Intervention and Treatment Options for Supravalvar AS

Operative intervention is indicated for patients with supravalvar AS in whom the gradient exceeds 50 mm Hg. A number of operations have been proposed for the treatment of localized supravalvar stenosis. The classic repair involves a longitudinal incision across the obstruction in the ascending aorta, which is extended into the noncoronary sinus. The thickened, hypertrophic ridge is resected by endarterectomy and the aortotomy is augmented with an elliptical patch. A variation of this repair involves creation of an inverted-Y aortotomy with one limb of the Y extended into the noncoronary sinus and the other into the right coronary sinus. A Y-shaped patch is then used to augment the aortotomy. Finally, the Brom repair is performed by transection of the ascending aorta beyond the supravalvar ridge. Separate incisions are then made through the supravalvar ridge into each sinus of Valsalva. Triangular patches are placed to augment each of

these incisions, thereby relieving the supravalvar obstruction. Reconnection of the aortic root to the ascending aorta completes the repair.

The repair of the diffuse type of supravalvar stenosis is performed under circulatory arrest with extensive patching of the ascending aorta, transverse arch, and involved arch arteries.

The results of surgery for localized supravalvar AS are generally good with low operative mortality and excellent long-term survival.[88–90] The diffuse form is more difficult to treat, and recurrence is more likely.[90]

COARCTATION OF THE AORTA

Embryology

Coarctation of the aorta is thought to occur as a result of ectopic tissue from the ductus arteriosus which migrates into the wall of the adjacent aorta. After birth, as the ductus closes, the ectopic tissue in the aorta also constricts. Frequently, a posterior shelf of tissue is present within the aorta at the point of most severe obstruction.

Anatomy and Pathophysiology

Coarctation of the aorta is a narrowing of the proximal descending thoracic aorta distal to the origin of the left subclavian artery, near the insertion of the ductus arteriosus (or ligamentum arteriosum). The severity of luminal narrowing and the length of the aorta affected are variable. The aortic obstruction caused by coarctation creates a pressure load on the LV.

The incidence of coarctation is about 0.3 per 1,000 live births, and it accounts for 3% to 4% of congenital heart defects.[7] Coarctation is commonly associated with other heart defects including BAV (in more than 50% of cases), PDA, and VSD. Other left-sided obstructive lesions may also be present, such as aortic arch hypoplasia, valvar AS, mitral stenosis, and left ventricular hypoplasia. Turner syndrome (XO) has been associated with a higher incidence of coarctation.[91]

Diagnostic Findings

6 Patients with severe coarctation present in the newborn period. Aortic obstruction is so significant that perfusion of the lower body is dependent on flow from the RV through the ductus arteriosus. Spontaneous ductal closure typically worsens the aortic obstruction and may lead to malperfusion distal to the coarctation. The pressure load on the LV may precipitate CHF. Infants may develop shock with severe acidosis, oliguria, and diminished distal pulses.

Unlike infants, older children with coarctation are usually asymptomatic. The diagnosis is commonly made on the basis of hypertension in the upper extremities with decreased pulses in the lower extremities. Noninvasive blood pressure measurements in all four extremities help to quantify the severity of aortic obstruction. Notably, older patients tend to develop extensive collateral arteries that bypass the obstruction.

The diagnosis of coarctation in the neonate can usually be made clinically. The infant with significant coarctation is frequently asymptomatic at birth. Following closure of the ductus, though, the infant will develop signs of heart failure, such as irritability, tachypnea, and poor feeding. Lower extremity pulses are absent, and upper extremity pulses may be weak. Chest radiography shows cardiomegaly and pulmonary venous congestion. There is a left ventricular strain pattern on the ECG. Echocardiography is usually diagnostic, demonstrating narrowing of the aorta at the coarctation site with loss of pulsatile blood flow in the descending aorta.

In older children and adults with coarctation, the diagnosis is usually made after workup of a pressure gradient between the arms and legs. On chest radiography, rib notching may be evident, secondary to erosion of the inferior rib borders from the development of large intercostal collateral vessels. Echocardiography usually confirms the diagnosis. Anatomic details may also be clarified with CT and MRI. Cardiac catheterization is usually not necessary unless balloon angioplasty or aortic stent placement is being considered.

Indications for Intervention and Treatment Options

Generally, all patients with a coarctation gradient >20 mm Hg should undergo surgical repair. For neonates, the acute medical management includes initiation of PGE_1 for the purpose of reopening the ductus; this maneuver partially relieves the aortic obstruction and augments perfusion of the lower body due to improved antegrade flow across the arch, as well as right-to-left flow across the ductus. Prostaglandins are usually effective for reopening the ductus when initiated within 7 to 10 days of life but are less successful thereafter. There is no role for PGE_1 in the older patient.

Surgical repair of coarctation is described in Table 81.8. Neonates with an associated hypoplastic aortic arch may require sternotomy for extended arch augmentation with either primary extended end-to-end repair or patch augmentation. The preferred surgical approach to isolated coarctation in infants and children is a resection with end-to-end anastomosis or extended end-to-end repair if there is associated mild distal arch hypoplasia.[92]

In older children and adults, it may not be possible to perform a resection with primary repair without creating excessive tension on the anastomosis, which may lead to hemorrhage or scarring with recurrent coarctation. An alternative strategy is necessary in these cases. Patch aortoplasty may be performed in children in whom further growth is anticipated. The subclavian flap repair augments the narrowed aorta using native arterial tissue. Blood flow to the left arm is maintained by collateral vessels, although long-term studies have demonstrated a slight discrepancy in limb length in some patients. Prosthetic patch material may also be used.

OPERATIVE STEPS

Table 81.8 Repair of Coarctation of the Aorta in the Infant

Incision and exposure	Right lateral decubitus position, left third intercostal space posterolateral thoracotomy, retraction of lung anteriorly, and opening of posterior pleura
Critical steps	Exposure of left subclavian artery, aortic arch, descending thoracic aorta, and ductus; division of ductus; placement of proximal and distal clamps, excision of coarctation segment, extended end-to-end anastomosis
Completion	De-airing of anastomosis, removal of vascular clamps, assessment of pressure gradient
Final steps	Intercostal nerve block, closure of overlying pleura, and standard closure

By avoiding circumferential prosthetic material, growth potential of the native aorta is preserved. The disadvantage of patch repair is a high risk of aneurysm formation. In adults in whom growth is no longer a concern, resection of the coarctation may be performed with subsequent placement of a prosthetic interposition graft (either Dacron or polytetrafluoroethylene).

One of the principal concerns during coarctation repair is interruption of distal aortic blood flow, especially to the spinal cord. The anterior spinal artery is fed by major radicular branches from intercostal arteries. In patients without well-formed collaterals, ischemia of the spinal cord may be precipitated by aortic cross-clamping, and paraplegia may result. Protective measures include induction of mild hypothermia, maintenance of a high proximal aortic pressure, and minimization of cross-clamp time. In older patients, distal aortic perfusion may be maintained by the technique of left heart bypass, in which oxygenated blood is taken from the left atrium and delivered to the femoral artery or distal aorta using a centrifugal pump.[93]

This is usually not necessary due to the presence of significant collaterals in older children. Overall, the incidence of paraplegia following coarctation repair is less than 1%.

Following repair, patients may develop severe hypertension. This can be managed using intravenous beta blockers (e.g., esmolol). Uncontrolled hypertension can lead to of mesenteric arteritis with resultant gut ischemia. Hypertension usually resolves within days to weeks after repair, although older children and adults may require lifelong antihypertensive therapy. Repair of coarctation during infancy is thought to minimize the risk of late hypertension.

Transcatheter interventions (balloon angioplasty [BA] or stenting) are not recommended for infants due to poor rates of success. Transcatheter intervention for primary therapy of discrete coarctation in young children and adolescents remains controversial. In older patients, BA is effective and safe, with similar short-term results to surgery.[94] Nevertheless, long-term follow-up after BA reveals increased incidence of short-term recoarctation[94] and higher incidence of aneurysm formation and iliofemoral artery injury.[95] Stent placement in older children and adolescents was studied by the Multicenter Coarctation of the Aorta Stent Trial (COAST). The COAST trial demonstrated excellent safety (no procedural deaths) and immediate and sustained reduction in pressure gradient.[96] Nevertheless, reintervention to re-expand the stent or to treat aortic wall injury was common.[96] Notably, balloon angioplasty is widely accepted for the treatment of recurrent coarctation following surgery, in which the success rate is on the order of 90% with low recurrence rates.[97–99]

Early mortality following surgical repair of coarctation in neonates and children approaches 0%.[92,100] The incidence of recurrent coarctation following resection and end-to-end repair is 2% to 5%.[92,100] Importantly, while long-term survival following repair of coarctation is excellent, many patients will require reintervention and survival is reduced compared to age- and sex-matched population which may be related to persistent hypertension.[101]

PATENT DUCTUS ARTERIOSUS

Embryology

The ductus arteriosus is a normal fetal vascular structure that allows blood from the right ventricle to bypass the high-resistance pulmonary vascular bed and pass directly to the systemic circulation. The ductus communicates between the main PA (or proximal left PA) and the proximal descending thoracic aorta. During fetal development, low oxygen tension and high levels of circulating prostaglandin maintain ductal patency. During the final trimester, the ductus becomes less sensitive to prostaglandins and more sensitive to the effects of oxygen tension. Following birth, the rise in oxygen tension and a fall in prostaglandins (which were previously supplied principally by the placenta) lead to ductal closure, which is usually complete by 12 to 24 hours. After closure, the ductus becomes a fibrous cord known as the ligamentum arteriosum. Failure of closure of the ductus leads to the condition called PDA.

Anatomy and Pathophysiology

Patent ductus arteriosus occurs in about 1 out of 10,000 live births and accounts for 10% of congenital heart defects.[7] The incidence is much higher in premature infants (>20%).[102] This elevated incidence is thought to be related to immaturity of the ductal wall, resulting in impaired sensitivity to oxygen tension.

Patent ductus arteriosus may occur as an isolated defect or in association with a number of other anomalies. Patency of the ductus arteriosus is desirable in a number of defects in which there is either inadequate PBF (such as pulmonary atresia) or inadequate systemic blood flow (as in severe coarctation of the aorta). The discovery that extrinsic delivery of prostaglandins can maintain ductal patency has played a critical role in improving the survival of these patients.[103]

The physiologic manifestation of PDA is shunting of blood across the ductus. The shunt volume is determined by the size of the ductus and by the ratio of pulmonary to systemic vascular resistance. At birth, the PVR drops dramatically and continues to decline over the first several weeks of life. As a result, shunting across a PDA is from left to right. Excessive PBF can lead to CHF. In extreme cases, hypotension and systemic malperfusion may result.

Patients with a large PDA who survive infancy tend to develop PVOD. Eisenmenger physiology results when the PVR exceeds the systemic vascular resistance, producing a reversal of shunting across the ductus to right to left. This leads to cyanosis and, eventually, right ventricular failure. Small PDAs may persist to adulthood without producing any symptoms or physiologic derangement. Endocarditis and endarteritis have been reported as long-term (but quite rare) complications of PDA.[104,105]

Diagnostic Findings

In patients with PDA, symptoms are proportional to the shunt volume and the presence of associated defects. Left-to-right shunting across the PDA produces volume overload of the left heart. Infants with CHF demonstrate symptoms of tachypnea, tachycardia, and poor feeding. Older children may present with recurrent respiratory infections, fatigue, and failure to thrive. Physical examination findings include a widened pulse pressure and a continuous "machinery" murmur heard best along the left upper sternal border. Chest radiography shows increased pulmonary vascular markings and left heart enlargement. Left ventricular hypertrophy and left atrial enlargement may be evident on the ECG. Echocardiography is the diagnostic method of choice. Cardiac catheterization is performed in older patients with suspected pulmonary hypertension to evaluate for PVOD or for transcatheter occlusion of the ductus.

Indications for Intervention and Treatment Options

Closure of PDA is performed for all symptomatic patients. Closure is also recommended for asymptomatic patients due to the risk of heart failure, pulmonary hypertension, and endocarditis. Closure of the ductus may be accomplished by one of three approaches: pharmacologic, surgical, and endovascular.

Pharmacologic closure of PDA in premature infants is accomplished by indomethacin and ibuprofen, which are cyclooxygenase inhibitors.[106,107] Due to improved side-effect profile of gastrointestinal bleeding and renal

dysfunction, ibuprofen is the current drug of choice.[108] 7 Pharmacologic closure is effective in about 65% of premature infants.[109] Due to their side effects, indomethacin and ibuprofen are contraindicated in patients with sepsis, renal insufficiency, intracranial hemorrhage, or bleeding disorders. Failure of ibuprofen after three complete courses results in referral for endovascular or surgical closure.

The surgical approach to PDA is accomplished via a left, third intercostal space, posterolateral thoracotomy, with exposure of the transverse aortic arch and descending thoracic aorta, along with circumferential control of the PDA. In many cases, the ductus is the largest vascular structure present, and it must not be confused with the aorta. Ductal tissue is extremely friable, so direct manipulation is minimized. In premature infants, the ductus is controlled with a single surgical clip; this procedure is commonly performed in the neonatal intensive care unit, thereby avoiding problems associated with patient transfer.[110,111] In older patients, occlusion of the ductus is achieved with simple silk ligature, or, preferably, by division between ligatures to minimize recurrence.

Thoracoscopic techniques can be employed to perform PDA ligation.[112,113] This approach has the potential benefits of decreased pain and quicker recovery. Disadvantages include a substantial learning curve and increased operating time.

A number of endovascular devices have been developed for the purpose of transcatheter occlusion of the PDA.[114] This approach is very successful in older infants, children, and adults with small and moderate-sized PDAs and has become the treatment of choice.[115,116] A new device, the Amplatzer Piccolo Occluder (Abbott Laboratories, Abbott Park, IL), was recently granted FDA approval for endovascular PDA occlusion in infants less than 2 kg. The device has demonstrated excellent safety (3% procedural mortality) and efficacy (>90% with complete ductal closure).[117] As a result of the major advancements in device technology, surgical closure is rarely needed and is reserved for PDAs having a large diameter or very short length.

Rarely, an adult will present with a significant PDA. These patients must be carefully evaluated for the presence of PVOD prior to ductal closure. If the patient is not a candidate for device closure, surgical closure can be problematic. Calcification of the ductal wall is common in adults, making

ligation hazardous. In some cases, cardiopulmonary bypass may be required with closure of the ductus from within the PA.[118,119]

Closure of the ductus by surgical or transcatheter techniques is achieved with a periprocedural mortality that approaches zero.[120] Potential complications of surgery include pneumothorax, recurrent laryngeal nerve injury, phrenic nerve injury, and chylothorax (from injury to the thoracic duct). Long-term survival should be normal following PDA ligation in most patients. Survival in premature infants depends primarily on the extent of prematurity with its attendant complications.

VASCULAR RINGS

Embryology

By the end of the fourth week of embryonic development, the six aortic or branchial arches have formed between the dorsal aortae and ventral roots. Subsequent involution and migration of the arches result in the anatomically normal or abnormal development of the aorta and its branches. The majority of the first, second, and fifth arches regress. The third arch forms the common carotid artery and proximal internal carotid artery. The right fourth arch forms the proximal right subclavian artery. The left fourth arch contributes to the portion of the aortic arch from the left carotid to left subclavian arteries. The proximal portion of the right sixth arch becomes the proximal portion of the right pulmonary artery, while the distal segment involutes. Similarly, the proximal left sixth arch contributes to the proximal left pulmonary artery (LPA), and the distal sixth arch becomes the ductus arteriosus.

Anatomy and Pathophysiology

Vascular rings comprise a spectrum of vascular anomalies of the aortic arch, pulmonary artery, and brachiocephalic vessels. The clinically significant manifestation of these lesions is a varying degree of tracheoesophageal compression. These vascular anomalies can be divided into *complete* vascular rings and *partial* vascular rings. Partial vascular rings include aberrant right subclavian artery, innominate artery compression, and

pulmonary artery sling. Complete rings include double aortic arch and right aortic arch with mirror image branching or retroesophageal left subclavian artery (and leftward ligamentum). The incidence of clinically significant vascular rings is 1% to 2% of all congenital heart defects.[121]

Vascular rings and pulmonary slings have been described in conjunction with other cardiac defects, including TOF, ASD, branch pulmonary artery stenosis, coarctation, AVSD, VSD, interrupted aortic arch, and aortopulmonary window. Significant associated cardiac anomalies occur in 12% to 30% of patients with a vascular ring.[122,23] A right aortic arch is generally associated with a greater incidence of coexisting anomalies.

Complete Rings

A double aortic arch occurs when the distal portion of the right dorsal aorta fails to regress. The two arches form a complete ring, encircling the trachea and esophagus. The right arch is dominant in the majority of the cases, followed by left dominance, with codominant arches being the least common. The left and right carotid and subclavian arteries generally arise from their respective arches. The ligamentum arteriosum and descending aorta usually remain on the left.

A right aortic arch occurs if the left fourth arch involutes; the apex of the arch is to the right of the trachea. The two most common variants of a right arch are: mirror image arch branching, and an aberrant, retroesophageal left subclavian artery.[121] When the ligamentum arises from the descending thoracic aorta, a complete ring is formed.

Partial Rings

In innominate artery compression syndrome, the aortic arch and ligamentum are in their normal, leftward position. However, the innominate artery arises partially or totally to the left of midline. As the artery courses from left to right, anterior to the trachea, it causes tracheal compression.

An aberrant right subclavian artery, arising from the descending thoracic aorta and coursing posteriorly across the mediastinum can compress the esophagus posteriorly. An indentation can be seen on the esophagus, though this is not a complete ring. Aberrant right subclavian artery is the most common arch anomaly, occurring in approximately 0.5% to 1% of the population.

Pulmonary artery sling is thought to develop when the left lung inappropriately captures its arterial supply from the right sixth arch *below* the tracheobronchial tree. The LPA branches from the RPA rather than the main PA, passes behind the right main bronchus, and travels between the trachea and esophagus (causing compression to the tracheobronchial tree).[121]

Diagnostic Findings

Children with a *complete* vascular ring generally present within the first weeks to months of life. Typically, children with a double aortic arch present earlier in life than those with a right arch and retroesophageal left ligamentum. In the younger age group, respiratory symptoms predominate, as liquids are generally well tolerated. Respiratory symptoms may include stridor, nonproductive cough, apnea, or frequent respiratory infections. The cough is classically described as a "seal bark" or "brassy." These symptoms may mimic asthma, respiratory infection, or reflux, and children with vascular rings are often initially misdiagnosed. With the transition to solid food, dysphagia becomes more apparent.

The presentation of a patient with a *partial* vascular ring is variable. Children with innominate artery compression usually present within the first 1 to 2 years of life with respiratory symptoms. Aberrant right subclavian artery does not cause significant tracheoesophageal compression and is therefore usually asymptomatic. Classically, when symptoms do occur, they present in the seventh and eighth decades, as the aberrant vessel becomes ectatic and calcified, causing *dysphagia lusoria* due to impingement of the artery on the posterior esophagus.

Children with pulmonary artery slings generally present with respiratory symptoms within the first few weeks to months of life. As with complete vascular rings, respiratory symptoms may include stridor, nonproductive cough, apnea, or frequent respiratory infections and may mimic other conditions, leading to misdiagnosis. Pulmonary artery slings are associated with complete tracheal rings in 30% to 40% of patients, leading to focal or diffuse tracheal stenosis which is the primary cause of the respiratory symptoms.

The methods for diagnosing a vascular ring are nonuniform due to the variability in presentation and the spectrum of diagnostic tests available. A

child with a presumptive diagnosis of asthma or tracheomalacia may be referred to a pulmonologist and a diagnosis of vascular ring made or suspected initially by chest radiograph and bronchoscopy. In some situations, the diagnosis is made by echocardiography during evaluation for concurrent cardiac defects. Regardless, the diagnosis generally begins with a chest radiograph. Complementary studies may include barium esophagogram, CT, MRI, and bronchoscopy. CT, MRI, and bronchoscopy are important modalities to define the tracheal anatomy in a patient with a pulmonary artery sling. Echocardiography may be diagnostic and may be used to rule out other cardiac anomalies.

Indications for Intervention and Treatment Options

Complete Rings

Patients with symptoms secondary to complete vascular rings should undergo surgical correction. Repair of a double aortic arch is accomplished via a left, third intercostal space posterolateral thoracotomy; exposure of the left subclavian artery, left and right aortic arches, descending thoracic aorta; ligation and division of the ductus; and ligation and division of the atretic segment of the nondominant arch. If there is concern regarding the location for division, the arches can be temporarily occluded at various points while monitoring pulse and blood pressure in each limb. Dissection around the esophagus and trachea in the regions of the ligamentum/ductus and nondominant arch allows for retraction of the vascular structures and lysis of any residual obstructing adhesions.

The surgical approach for a right aortic arch with retroesophageal left ligamentum arteriosum is the same as for a double arch. The ligamentum is divided and any adhesions around the esophagus and trachea are lysed. Rarely, the Kommerell diverticulum has been reported to cause compression even after division of the ligamentum. As such, it may be prudent to resect or suspend the diverticulum posteriorly.

Partial Rings

Similar to patients with complete rings, individuals with partial rings and symptoms should undergo surgical correction. The symptoms of innominate artery compression may be mild to severe. With mild symptoms and minimal tracheal compression on bronchoscopy, children can be observed expectantly as the symptoms may resolve with growth. Indications for surgery include apnea, severe respiratory distress, significant stridor, and recurrent respiratory tract infection. Several approaches for the correction of innominate artery compression syndrome have been described. These include simple division, division with reimplantation into the right side of the ascending aorta, and suspension to the overlying sternum.

An aberrant right subclavian artery can compress the esophagus posteriorly, though it is rarely the cause of symptoms in children. Surgical treatment involves simple division via a left posterolateral thoracotomy. Rarely, reimplantation or grafting from the right carotid or aortic arch may be necessary.

Patients with PA sling, compression of the tracheobronchial tree, and associated respiratory symptoms should undergo surgical correction. Evaluation of the trachea must be undertaken in order to determine if complete tracheal rings are present (absence of the membranous portion of the trachea).

Initial attempts at the repair of a pulmonary artery sling involved reimplantation after division of the LPA and translocation of the trachea without cardiopulmonary bypass. These early reports had a high incidence of LPA thrombosis. This has led some authors to advocate for division of the trachea and translocation of the LPA. This approach would seem sensible if the trachea were being divided in the course of tracheal reconstruction. However, currently, most authors advocate the reimplantation of the LPA, which has resulted in excellent results. The procedure is done via a median sternotomy on cardiopulmonary bypass to ensure optimal visualization of the repair. Aortic cross-clamping is not necessary. The LPA is divided off of the right pulmonary artery, translocated anterior to the trachea, and reimplanted into the main pulmonary artery. Any necessary reconstruction of the trachea is done concurrently with bronchoscopic assistance if complete tracheal rings are present. Many techniques for tracheal reconstruction have been described, the most common of which are resection with primary reanastomosis and sliding tracheoplasty for long-segment stenosis.[124]

Outcomes

Over 95% of vascular rings without concurrent cardiac defects can be performed through a left thoracotomy. A right thoracotomy is indicated for the rare cases where there is a right ligamentum arteriosum. In addition, a double aortic arch with an atretic segment proximal to the right carotid artery is more easily divided through a right thoracotomy. The approach to these anomalies is the same as for a left-sided ring division, with the caveat that the right recurrent laryngeal nerve will loop around the right ligamentum.

Repair of vascular rings has been described using video-assisted thoracoscopic surgery (VATS) both with and without robotic assistance. Candidates for thoracoscopic division are limited to those patients requiring only the division of nonpatent vascular structures. In general, VATS is used for patients greater than 15 kg due to current size limitations of the instruments.[125]

Mortality for the repair of a vascular ring is 0% to 4%, with improved survival occurring in more recent series.[123,126,127] The majority of deaths are related to other cardiac defects or respiratory infection and failure. Backer et al. reported a series of 34 patients repaired utilizing LPA division and reimplantation for pulmonary artery sling, many whom also required tracheal reconstruction. There were no operative mortalities and four late deaths.[124] The major source of morbidity, as well as mortality, in this and other series is related to the tracheal reconstruction.

CORONARY ARTERY ANOMALIES

Embryology

The embryology of congenital coronary artery anomalies is not fully understood. Complex theories have been postulated that suggest the importance of in utero wall tension within the right and left coronary sinuses of the aorta to go on to have normal coronary development.[128] Controversy still exists, however, on whether the coronary arteries grow outward from the aortic root or originate on the epicardium and grow inward toward the aortic root.[129]

Of note, this section is structured differently: each lesion's anatomy, pathophysiology, diagnostic findings, and potential treatment are discussed independently of one another.

Background

Coronary artery anomalies occur in 0.3% to 1.3% of the population.[130,131] They can be classified as minor, secondary, or major based on their clinical significance.[132] Minor defects have no functional significance and are usually detected as incidental findings at cardiac catheterization. Secondary defects have no intrinsic significance but alter surgical management when they are present. An example of a secondary defect is an anomalous origin of the left anterior descending artery from the right coronary artery that crosses the hypoplastic infundibulum in a patient with TOF. The presence of this vessel may prevent the safe performance of a transannular incision and thereby mandate the use of a conduit. Major defects are the most important form of coronary anomaly, because they exert an intrinsically adverse effect on the myocardium. Major anomalies can be subdivided based on anatomy: coronary arteriovenous fistula, anomalous pulmonary origin of a coronary artery, anomalous aortic origin of a coronary artery, myocardial bridging, and coronary artery aneurysm.

Coronary Arteriovenous Fistula

Coronary arteriovenous fistula is the most common major coronary anomaly. An abnormal connection exists between a coronary artery (usually the right) and another vascular structure (usually one of the right heart chambers). Most fistulae are isolated and solitary. The fistula leads to left-to-right shunting, which can produce CHF. Other symptoms include angina, endocarditis, myocardial infarction, arrhythmia, and sudden death. The diagnosis is suggested by echocardiography and confirmed by catheterization. All symptomatic fistulas should be occluded, either surgically or by transcatheter techniques.[133] In some cases, coronary bypass grafting may be necessary when distal flow is compromised by fistula occlusion. Treatment of asymptomatic fistulae is controversial, but occlusion should probably be undertaken when significant left-to-right shunting is present.[133] Coronary

artery fistulae can be surgically corrected with minimal mortality and morbidity.[134] Alternatively, transcatheter closure, when technically feasible, can be utilized with similar results.[135]

Coronary Artery Origin from the Pulmonary Artery

The second most common major coronary anomaly is origin of a coronary artery from the PA. The most common manifestation is anomalous left coronary artery arising from the pulmonary artery (ALCAPA). The right coronary (or both coronaries) may also arise anomalously from the PA, but only in very rare cases. Anomalous left coronary artery arising from the pulmonary artery is usually well tolerated during fetal development, but after birth, the pulmonary systolic pressure usually drops (following ductal closure and decline in PVR) and the anomalous coronary is perfused with desaturated blood at low pressure. Collateral vessels develop between the normal right coronary artery and the abnormal left coronary, but the benefit is negated due to the development of coronary steal, whereby the collateral blood shunts left to right by retrograde flow in the anomalous coronary into the low-pressure PA.

Most patients will present between 6 weeks and 3 months of life. Typical symptoms include irritability, difficulty in feeding, and other signs of CHF. Untreated, ALCAPA is nearly always fatal. Rarely, patients will survive to adulthood and present with symptoms of angina or sudden death. On examination, patients with ALCAPA frequently have a holosystolic murmur of ischemic mitral regurgitation. The pulmonary component of the second heart sound may be pronounced due to pulmonary hypertension. Chest radiography is significant for cardiomegaly and pulmonary edema. Electrocardiographic evidence of ischemia and infarction is usually present. Echocardiography is usually diagnostic and is useful for assessing the severity of left ventricular dysfunction and ischemic mitral regurgitation, which are commonly present. Catheterization is occasionally necessary to clarify the anatomy, but this technique is used less frequently due to the risk of inducing life-threatening arrhythmias.

Surgical repair is indicated for all patients with ALCAPA. Historically, the initial surgical approach involved ligation of the proximal left coronary artery. This served to eliminate coronary steal and allow perfusion of the left coronary system by collaterals from the right. Despite the ease of simple ligation, most centers have abandoned this approach in favor of establishment of a two-coronary system, which offers better long-term freedom from ischemia. Most commonly, this can be achieved by removing the origin of the left coronary artery (along with a button of adjacent PA) and reimplanting the vessel directly into the side of the aorta. Another approach involves creation of a side-to-side connection between the aorta and PA with placement of an intrapulmonary baffle to direct flow from this connection to the anomalous left coronary ostium. With improved coronary transfer techniques learned from the arterial switch operation, direct reimplantation of the anomalous coronary artery is always feasible and preferred. Survival following surgical repair of ALCAPA has improved over the years.[136] Recent reports have suggested an operative mortality of 6% or less.[136] Ventricular function tends to normalize after surgery.[137] In most patients, mitral valve function also improves. Nevertheless, for patients with severe mitral regurgitation, concurrent mitral valve repair may rarely be indicated.[137] These patients should be followed for life with serial imaging due to rare but potentially lethal LV scarring and subsequent failure.[138]

Anomalous Aortic Origin of Coronary Artery

Most anomalous aortic origin of the coronary arteries (AAOCA) are usually minor defects, but AAOCA can be a major coronary anomaly when the left main coronary artery arises from the right coronary sinus and passes between the PA and aorta. This defect has been associated with cardiac symptoms and sudden death, as has the origin of the right coronary artery from the left coronary sinus (usually when the right coronary is dominant).[139,140] The etiology of ischemia in both defects is thought to be related to the acute angle of origin and slit-like orifice of the anomalous vessel often with an intramural course. These defects usually present in older patients. Symptomatic patients are treated surgically by unroofing the coronary ostia into the aorta or, rarely, by coronary artery bypass. Because of highly variable practice patterns, an expert consensus guideline was recently

published detailing the management of AAOCA.[141] Surgical correction of AAOCA has been demonstrated to be very safe and efficacious in select patients.[142]

Myocardial Bridging

Myocardial bridging occurs when a segment of an epicardial coronary artery (usually the left anterior descending) takes an intramyocardial course over a short segment. Although this is a common incidental finding at cardiac catheterization, this defect has been associated in some cases with myocardial ischemia.[143] Treatment involves dividing the muscle bridge to free the coronary, coronary bypass beyond the bridge, or transcatheter stenting.

Coronary Artery Aneurysms

Coronary aneurysms are rare and usually occur in conjunction with an inflammatory condition, such as Kawasaki syndrome, polyarteritis nodosa, Takayasu arteritis, or syphilis. Coronary aneurysms may thrombose or lead to distal coronary stenosis or embolization. Rupture occurs uncommonly. Treatment ranges from antiplatelet therapy to coronary bypass grafting.

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82

Valvular Heart Disease

Daniel J. P. Burns, Per Wierup, and A. Marc Gillinov

Key Points

1. The most common cause of aortic stenosis (AS) is degenerative calcific disease, followed by congenital AS due to bicuspid valve anatomy.
2. Two-dimensional (2D) echocardiography with Doppler allows precise real-time analysis of valvular anatomy and function and is the study of choice for the diagnosis and management of valvular lesions.
3. The current indication for cardiac catheterization in patients with valvular heart disease is limited to preoperative evaluation of coronary artery disease.
4. There is no effective medical therapy for patients with severe AS. Mechanical relief of the obstruction to blood flow is the only effective treatment.
5. The most common causes of aortic regurgitation (AR) include bicuspid valve disease, rheumatic fever, and endocarditis.
6. Mitral stenosis (MS) is almost exclusively caused by rheumatic fever.
7. The most common cause of mitral regurgitation is degenerative mitral valve disease. Other causes include rheumatic valve disease, endocarditis, certain drugs, and collagen vascular diseases.

VALVULAR ANATOMY

The basic structural framework of all heart valves is provided by the fibrous cardiac skeleton (Fig. 82.1). The skeleton is a collection of dense connective tissue in the shape of four interconnected rings in the plane between the atria and the ventricles. The interconnecting areas include the right fibrous trigone, which is between the aortic and tricuspid rings and contiguous with the membranous septum, and the left trigone and intervalvular fibrosa, which are between the aortic and mitral rings and form the posterior wall of the left ventricular (LV) outflow tract. The cardiac skeleton maintains the integrity of

the valve orifices and provides points of attachment for the valve leaflets. It also serves as a partition by electrically isolating the atria and ventricles except at the atrioventricular bundle, which passes through the right fibrous trigone near the septal leaflet of the tricuspid valve (TV).

The normal aortic valve (AV) consists of three semilunar cusps projecting outward and upward into the lumen of the ascending aorta (Fig. 82.2). The space between the free edge of each cusp and the points of attachment to the aorta comprises the sinuses of Valsalva. Since the coronary arteries arise from two of the three sinuses, the sinuses and the respective cusps are named the right coronary, left coronary, and noncoronary (or posterior) sinuses and cusps.

The properties of the AV ensure minimal obstruction to flow when open and minimal flow reversal when closed. The valve function is passive, as it functions only in response to pressure differences between the left ventricle and aorta during the cardiac cycle. The pressure generated from ventricular contraction forces the valve open, and the subsequent recoil of blood from the aorta fills the sinuses of Valsalva and forces the leaflets closed.

There are two structures in close proximity to the AV susceptible to injury during AV surgery (Fig. 82.2). The anterior leaflet of the mitral valve (MV) is positioned under the commissure between the left and noncoronary cusps. The left bundle of His is positioned under the commissure between the right and noncoronary cusps, in the area of the membranous septum.

The anatomy and active valve mechanics of the MV are more complex. Indeed, proper functioning of the MV depends on the organized interaction of all components of the MV apparatus, which consists of the leaflets, annulus, LV papillary muscles, and chordae tendineae.

The normal MV consists of two leaflets: the anterior and posterior leaflets. The anterior leaflet is semicircular, extends from the anteromedial aspect of the mitral annulus, and encompasses approximately one-third of the annular circumference. The posterior leaflet is rectangular, extends from the posterolateral aspect of the mitral annulus, and encompasses approximately two-thirds of the annular circumference. The leaflets are separated from one another at the annulus by the posteromedial and anterolateral commissures. Indentations subdivide the posterior leaflet into three scallops, namely, laterally to medially, P1, P2, and P3. Corresponding regions of the anterior leaflet are analogously referred to as A1, A2, and A3. Together these

comprise an average cross-sectional area of 5 to 11 cm^2. The mitral annulus is formed anteriorly by the confluence of the right and left fibrous trigones and the intervalvular fibrosa and posteriorly by a less well-developed fibrous band. Due to the trigones and intervalvular fibrosa, the anterior mitral annulus has limited flexibility. Conversely, the posterior aspect of the annulus, which is not surrounded by any rigid structures, has more flexibility. In systole, the mitral annulus contracts (primarily the posterior aspect) and adopts an elliptical shape (shortening occurs perpendicular to the line of leaflet coaptation), and in diastole, it relaxes and adopts a circular shape.[1,2] This dynamic motion of the annulus provides increased leaflet coaptation during systole and increased orifice area during diastole.

Two papillary muscles arise directly from the ventricular wall: the anterolateral and posteromedial papillary muscles. Importantly, the anterolateral papillary muscle usually is supplied by two coronary arteries, the left anterior descending artery and branches of the circumflex artery. The posteromedial papillary muscle is usually supplied by a single coronary artery, either from the right coronary artery or from the circumflex artery, which makes it more susceptible to rupture as a complication of myocardial infarction. The papillary muscles play an important role in the proper function of the MV, as closure and appropriate leaflet coaptation are permitted by end-diastolic and early systolic lengthening of the papillary muscles.[3]

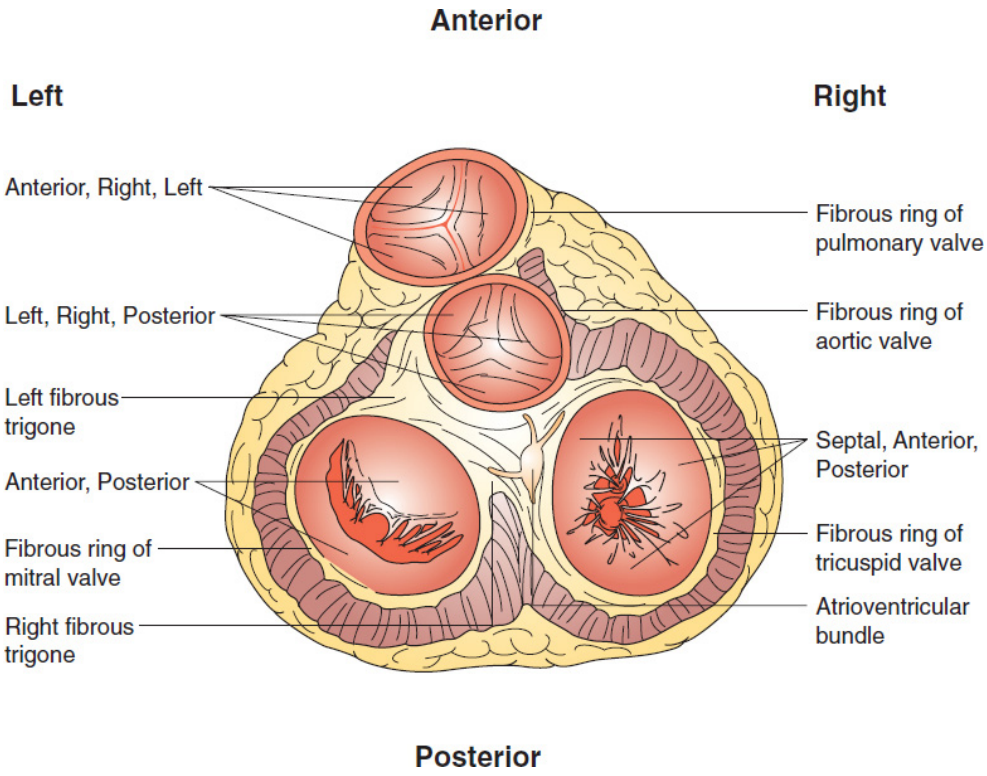

Figure 82.1 Schematic diagram of the fibrous cardiac skeleton.

Chordae tendineae attach the leaflets to either the papillary muscles or the ventricular wall and can be categorized by the attachments. Primary chordae extend from the papillary muscle and attach to the leaflets at the free edge, ensuring proper coaptation without prolapse or flail. Secondary chordae attach to the ventricular side of the leaflets, along the line of coaptation, and are more prominent on the anterior leaflet. Tertiary chordae can arise from the papillary muscle or directly from the ventricular wall and attach to the base of the posterior leaflet. Fan-like commissural chordae attach to both leaflets and arise from either papillary muscle.

The structures in close proximity to the MV susceptible to injury during MV surgery include the AV, the atrioventricular node, and the circumflex coronary artery (Fig. 82.3).

AORTIC STENOSIS

Prevalence and Etiology

Aortic stenosis (AS)[1] is the most prevalent valvular heart disease in developed countries. The most common cause of AS is degenerative calcific disease, followed by congenital AS due to bicuspid valve anatomy. Rheumatic AS is becoming exceedingly uncommon in developed countries due to efficient prevention of rheumatic heart disease.

Degenerative Calcific Aortic Stenosis

The most frequent cause of AS is degenerative calcification of the AV. The prevalence of degenerative AS in persons older than 65 years, which is the most commonly affected age group, is 2%.[4] The degenerative process that leads to stiffening of the aortic leaflets is the result of proliferative and inflammatory changes with lipid accumulation and infiltration of macrophages and T lymphocytes.[4–9] Fibrosis and calcification initially affect the base of the leaflets but ultimately progress to immobilization of the leaflets due to large calcific deposits that can extend deep into the annulus. These deposits may also extend onto the ventricular surface of the anterior leaflet of the MV, as well as into the wall of the ascending aorta. The risk factors for the development of calcific AS are similar to those for atherosclerosis and include elevated serum levels of low-density lipoprotein (LDL) cholesterol, diabetes, smoking, and hypertension.[10,11]

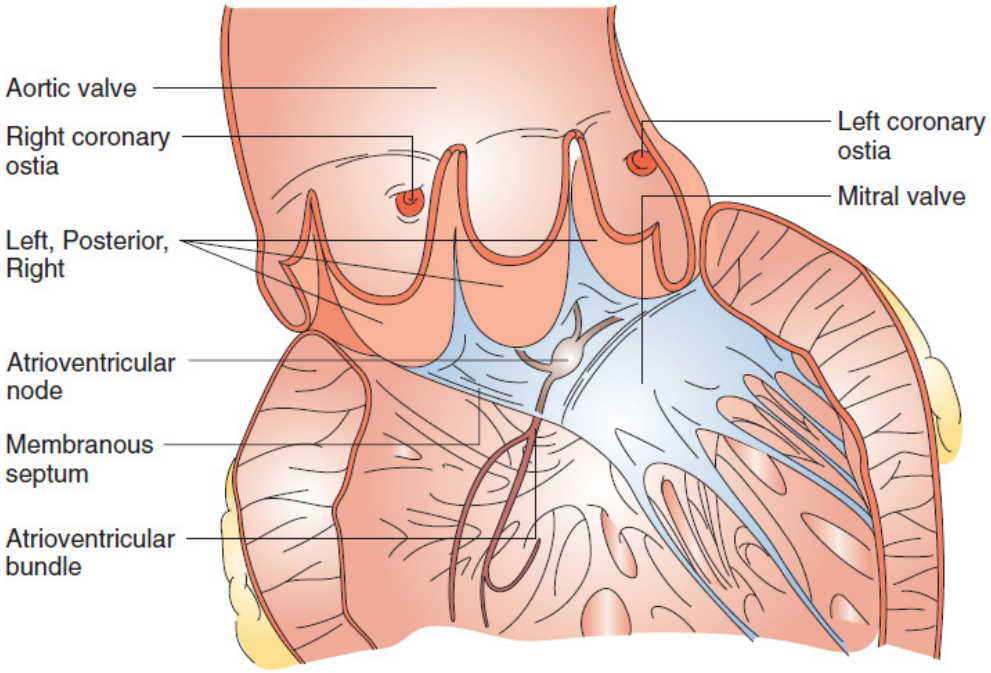

Figure 82.2 Schematic diagram of the relationship of the aortic valve to the underlying structures.

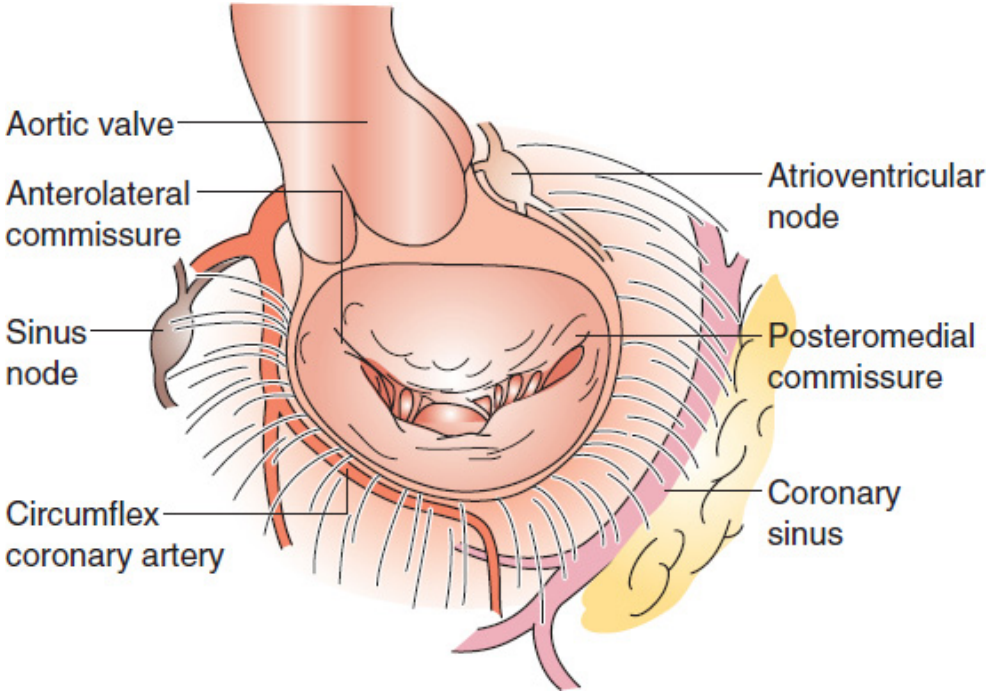

Figure 82.3 Schematic diagram of the relationship of the mitral valve to the underlying structures.

Bicuspid Aortic Stenosis

Bicuspid AVs are present in approximately 2% of the population. Degeneration of bicuspid AVs represents the most common form of congenital AS. Most commonly, the left and right coronary cusps are fused at a rudimentary commissure known as a raphe, while the noncoronary cusp is freestanding. Gradual calcification of the bicuspid valve results in AS, with typical onset of symptoms in the fifth or sixth decades of life, in contrast to degenerative AS, which causes symptoms in elderly individuals. Bicuspid AS is frequently associated with degenerative changes in the wall of the ascending aorta with resultant dilation or aneurysm formation.

Rheumatic Aortic Stenosis

Introduction of effective antibiotic therapy has resulted in a decline in the prevalence of rheumatic fever and rheumatic valve disease. Rheumatic AS is caused by inflammation and thickening of the AV leaflets, producing a mixture of AS and regurgitation. Rheumatic AS is rarely an isolated disease and usually occurs in conjunction with MV stenosis.[12]

Pathophysiology

Regardless of the etiology of AS, the pathophysiologic consequences are similar. Narrowing of the AV to a quarter of its normal area of 3 to 4 cm^2 produces a significant pressure gradient between the LV and the aorta. There is a resultant increase in LV workload and compensatory LV hypertrophy.

Even though this hypertrophy is an appropriate response to the increased afterload, there are numerous harmful effects. The increased wall thickness makes the ventricle stiff and less compliant. This leads to diastolic dysfunction and increased wall tension. Systolic dysfunction can develop from chronic ischemia. All of the following contribute to increased myocardial oxygen demand: increased LV muscle mass, increased wall tension, increased systolic ventricular pressure, and increased systolic ejection time. There is also decreased coronary artery perfusion, which occurs during diastole, due to increased wall tension, increased diastolic ventricular pressure, and decreased diastolic aortic pressure.[13,14] Subsequent ischemia of the subendocardium due to increased oxygen demand and decreased perfusion leads to cell death and fibrosis.

Diagnosis

Symptoms

The most common symptoms of AS are angina pectoris, syncope, and heart failure.[15] Angina pectoris occurs in 30% to 50% of patients with severe AS. It reflects myocardial ischemia caused by increased metabolic demands and decreased coronary perfusion. Coronary artery disease, which affects >70% of elderly patients with degenerative AV disease, further decreases myocardial perfusion, lowering the threshold for angina.

Syncope is most commonly due to reduced cerebral perfusion that occurs during exertion. Reduced cerebral perfusion is a result of decreased mean arterial pressure from peripheral vasodilation in the presence of a fixed cardiac output. Approximately 15% of patients present with syncope and only 50% of these survive for 3 years.

Congestive heart failure in patients with severe AS is typically a sign of advanced and long-standing disease. It is marked by dyspnea on exertion, fatigue, and/or peripheral edema resulting from ongoing LV outflow obstruction. Heart failure is a consequence of the aforementioned diastolic and systolic dysfunction from decreased compliance and ischemia, respectively. As the left ventricle becomes less compliant, atrial systole becomes more important for maintaining cardiac output, and the onset of atrial fibrillation may result in worsening congestive heart failure.

Some patients with severe AS may develop serious gastrointestinal bleeding secondary to angiodysplasia occurring predominantly not only in the right colon but also in the small bowel and stomach (Heyde syndrome). This is due to shear stress–induced platelet aggregation with reduction in high-molecular-weight multimers of von Willebrand factor.

Signs

Signs of AS include a loud systolic ejection murmur that radiates to the neck and may be accompanied by a thrill. “Pulsus parvus et tardus” describes a weak and prolonged arterial pulse characteristic of advanced AS. The weak pulse reflects a narrowed pulse pressure, while the slow rise in pulse reflects a prolonged ejection of blood volume through a stenotic valve.[16]

Electrocardiogram and Imaging

The electrocardiogram typically shows signs of LV hypertrophy, which is found in the majority of patients with AS. Echocardiography represents the gold standard modality for the diagnosis of AS.[2] Two-dimensional (2D) echocardiography with Doppler allows precise noninvasive real-time analysis of the anatomy and function of both the valve and the ventricle. The most important objective is the correct assessment of AS severity, calculating jet velocity, mean transvalvular pressure gradient, and valve orifice area (Table 82.1). It is also used to assess valve thickening and calcification, leaflet motion, and the presence of any concomitant aortic insufficiency. The echocardiogram is often able to distinguish between bicuspid and tricuspid AVs, particularly with less severe calcification.

2 2D echocardiography is also used to detect disease in additional valves, as well as assess LV hypertrophy and systolic/diastolic function. Ejection fraction is used to measure LV systolic function. However, a decreased ejection fraction can falsely lower estimates of AS severity due to the inability of the LV to generate the expected pressure gradients. This is known as low-flow low-gradient AS. Stress echocardiography with dobutamine administration may be required to properly assess the severity of valvular disease and to distinguish it from primary contractile dysfunction.[17]

Table 82.1 Classification of Aortic Stenosis Severity

Indicator	Mild	Moderate	Severe
Jet velocity (m/sec)	2.0–2.9	3.0–4.9	≥4.0
Mean gradient (mm Hg)	<20	20–39	≥40
Valve area (cm^2)	>1.5	1.0–1.5	<1.0
Valve area index (cm^2/m^2)			<0.6

Adapted from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(23):2440–2492.

Invasive cardiac catheterization with direct measurement of the pressure gradients across the AV has been replaced by echocardiography. 3 The current indication for cardiac catheterization is limited to preoperative evaluation of coronary artery disease.

Natural History

The natural history of AS is marked by a prolonged latent period with few symptoms and minimal morbidity. Even patients with moderately severe AS have a slow decrease in AV area, generally by approximately 0.1 cm^2 per year.[18,19] The natural history of severe AS correlates well with the onset and severity of symptoms. The average life expectancy of patients with symptomatic, severe, and untreated AS is 5, 3, and 2 years for patients with angina, syncope, and heart failure, respectively (Fig. 82.4).[20]

Treatment

There is no effective medical therapy 4 for patients with severe AS. Diuretics and digitalis may alleviate the symptoms of congestive heart failure. Mechanical relief of AS is accomplished by surgical AV replacement (SAVR), transcatheter AV replacement (TAVR), or percutaneous balloon aortic valvuloplasty (PBAV).

Surgical Aortic Valve Replacement

The primary indication for surgery is the presence of symptoms in patients with severe AS. AV replacement (AVR) is also indicated in patients with severe AS and reduced LV function and in patients with moderate AS requiring cardiac surgery for other indications.[17] AVR may also be beneficial in patients with asymptomatic severe AS and severe LV hypertrophy.[21]

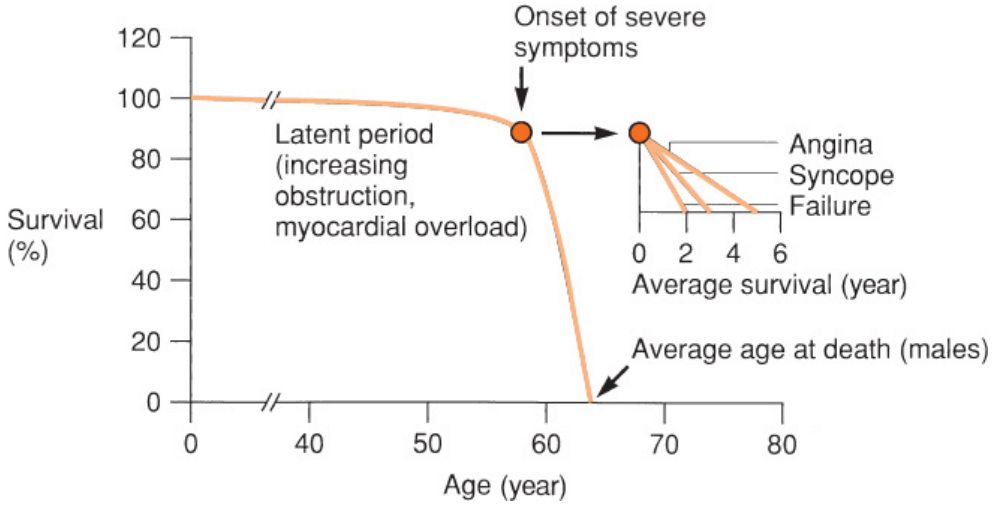

Figure 82.4 Natural history of aortic stenosis without operative treatment. Onset of symptoms identifies patients at high risk of death over the next 2 to 5 years.

Figure 82.5 St. Jude Medical Regent Valve.

Choice of valve prosthesis for AVR is primarily influenced by the patient's age.[22] Mechanical prostheses are made of carbon, require lifelong anticoagulation, and are very durable (Fig. 82.5). Mechanical prostheses are therefore indicated in patients younger than 50 years. Stented biologic prostheses are most commonly made of bovine pericardium or porcine valve leaflets, do not require anticoagulation, and have a limited durability of approximately 15 years (Fig. 82.6). Biologic prostheses are used in elderly patients (>70 years) and in younger patients in whom long-term anticoagulation is contraindicated (bleeding diathesis, peptic ulcer disease, etc.).

Transcatheter Aortic Valve Replacement

TAVR utilizes a bioprosthesis mounted on a balloon or self-expandable stainless steel or nitinol stent (Fig. 82.7). The prosthesis is introduced through the femoral artery retrogradely into the aorta and placed at the mid-part of the native stenotic AV. The radial forces of the stent push the native AV aside to increase the valve orifice area. In cases where the femoral artery is not usable due to artery size or vascular disease considerations,

alternative access may be utilized. These approaches include subclavian, carotid, direct aortic, caval, and apical. The transapical approach via the LV apex, accessed by a left anterior mini-thoracotomy, was the initial alternative access of choice. However, in recent years, this has fallen out of favor relative to the other access routes.

TAVR is an actively evolving therapy for patients with surgical AV disease. Previously, this therapy was limited to patients deemed at high or prohibitive risk for SAVR, though TAVR has now expanded into intermediate- and low-risk cohorts following encouraging results from recent randomized trials in these lower-risk populations, with TAVR being not worse than SAVR.[17,23–26] In low-risk patients at 1 year, TAVR has also been shown to be superior to SAVR when considering the composite outcome of death, stroke, or rehospitalization, with a demonstrated hazard ratio for TAVR of 0.54 (0.37 to 0.79) 95% CI.[27] Although recent results are encouraging, it must be remembered that data are limited to 1 to 5 years and in active evolution.

Figure 82.6 St. Jude Medical Epic Valve.

Percutaneous Balloon Aortic Valvuloplasty

PBAV is a procedure in which a balloon is placed across a stenotic AV and inflated in order to decrease the degree of valve narrowing. This procedure

is a valuable tool for treatment of AS in children and young adults. Rapid development of restenosis and clinical deterioration limits its application in the treatment of adults to those who require a bridge to definitive management or who are otherwise not SAVR or TAVR candidates.

AORTIC REGURGITATION

Prevalence and Etiology

AR results from the improper coaptation of the AV leaflets due to either intrinsic leaflet abnormalities or aortic root distortion. 5 The most common causes of aortic regurgitation (AR) include bicuspid valve disease, rheumatic fever, and endocarditis. Regurgitant bicuspid AVs are often partly calcified, which results in limited opening and closing of the valve and a mixture of AR and AS. Rheumatic fever causes inflammation and fibrosis of the leaflets, while endocarditis causes destruction of leaflets. In addition, AR can occur as a secondary phenomenon of aortic root enlargement due to connective tissue disorders, annuloaortic ectasia, or aortic dissection. Most of these causes produce chronic AR with a slow increase in LV size. Some lesions, in particular acute aortic dissection and endocarditis, cause acute AR with a sudden decrease in cardiac output.

Pathophysiology

In patients with AR, inappropriate coaptation of the aortic leaflets causes diastolic reflux of blood from the aorta into the LV with a consequent increase in LV end-diastolic volume and pressure. In chronic AR, compensatory mechanisms of the LV result in dilation and hypertrophy. Over time, these measures decompensate and ultimately result in decreased LV function and heart failure.

Diagnosis

Symptoms

Chronic AR is usually well-tolerated, and patients with even severe AR often remain asymptomatic for years. Initial symptoms of severe AR include fatigue, shortness of breath, and dyspnea on exertion. Advanced AR is marked by the onset of congestive heart failure, syncope, and angina. Acute onset of severe AR, such as in cases of aortic dissection or endocarditis-induced valve destruction, causes a sudden increase in LV end-diastolic volume and pressure with subsequent cardiogenic shock and pulmonary edema.

Signs

Lateral displacement of the point of maximum impulse is seen in chronic AR due to LV dilation and hypertrophy. The classic auscultatory findings of AR are best heard at the right sternal border of the second intercostal space and include a high-pitched, blowing holodiastolic decrescendo murmur, an S_3 heart sound, and a systolic ejection murmur.

The widened pulse pressure leads to a number of interesting findings, such as bounding pulses (water hammer pulse), Quincke pulse (pulse in fingernail bed), De Musset sign (rhythmic bobbing of the head), Duroziez sign (systolic and diastolic murmurs heard over the femoral artery when it is gradually compressed), and Müller sign (pulsations of the uvula).[16]

Imaging

Echocardiography represents the diagnostic gold standard for patients with AR. It allows assessment of the valvular and aortic anatomy, the severity of regurgitation, and ventricular size and function. Assessment of the severity of AR is determined by color Doppler jet width, regurgitant volume, regurgitant fraction, and regurgitant orifice area (Table 82.2). The role of coronary angiography is limited to the preoperative diagnosis of coronary artery disease.

Natural History

The natural history of AR is strongly dependent on the presence of symptoms and LV dysfunction at the time of presentation. Asymptomatic patients with

normal LV function develop symptoms and/or LV dysfunction at a rate of 6% per year. Asymptomatic patients with LV dysfunction at presentation develop cardiac symptoms at a rate of 25% per year. Finally, the mortality rate of symptomatic patients is 10% per year.[17]

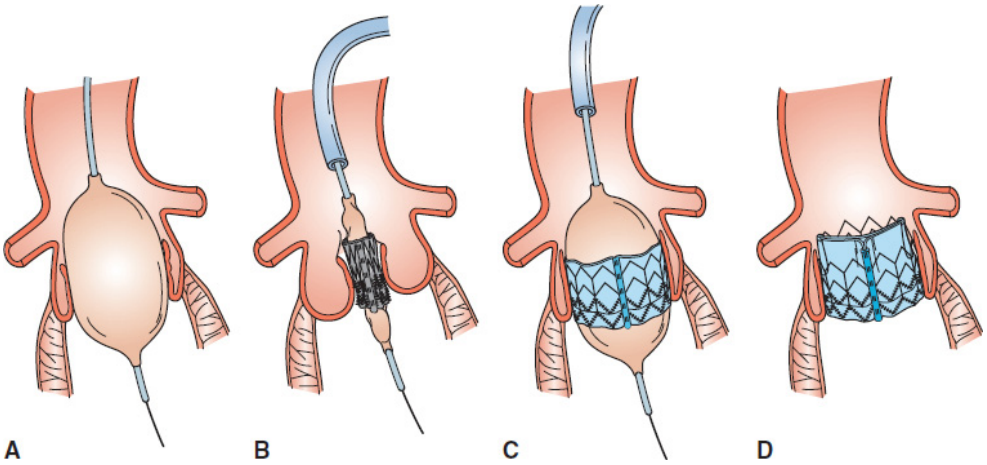

Figure 82.7 Schematic diagram of percutaneous aortic valve replacement. **A:** Balloon valvuloplasty. **B:** Balloon catheter with valve in the native diseased valve. **C:** Balloon inflation to secure the valve. **D:** Valve in place.

Table 82.2 Classification of Aortic Regurgitation Severity

Indicator	Mild	Moderate	Severe
Angiographic grade	1+	2+	3–4+
Doppler jet width	<25% LVOT	25–64% LVOT	≥65% LVOT
Regurgitant volume (mL/beat)	<30	30–59	≥60
Regurgitant fraction (%)	<30	30–49	≥50
Effective regurgitant orifice (cm^2)	<0.10	0.10–0.29	≥0.30
Vena contracta (cm)	<0.3	0.3–0.6	>0.6

LVOT, left ventricular outflow tract.

Adapted from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(23):2440–2492.

Treatment

Management of patients with AR depends on the severity of symptoms and the size and function of the left ventricle. Asymptomatic patients with chronic severe AR and preserved LV size and function are treated with vasodilator medical therapy, which reduces afterload and improves forward flow.

Surgery is indicated in symptomatic patients with chronic severe AR and in asymptomatic patients with severe AR and evidence of LV dilation (end-

systolic LV diameter >55 mm) or dysfunction (ejection fraction <50%). Additionally, acute severe AR with consequent pulmonary edema and shock caused by endocarditis or aortic dissection is a surgical emergency.

AVR should be performed before irreversible changes in LV function occur. Considerations for prosthetic valve choice in replacement are identical to those discussed previously. AV repair can often be performed in patients with severe AR caused by bicuspid valve disease or connective tissue disorders. Traditionally, patients with proximal aortic root pathology, including dissection and aneurysms with secondary AR, underwent aortic root replacement with a mechanical valve. The valve-sparing root replacement (the David procedure) has been shown to have similar morbidity and mortality with minimal risk of thromboembolism or endocarditis. Additionally, it precludes the need for anticoagulation and has an acceptably low reoperation rate. This makes it ideal for young patients, especially those with connective tissue disorders.[28–31]

MITRAL STENOSIS

Prevalence and Etiology

6 Mitral stenosis (MS) is predominantly caused by rheumatic fever. The steady rate of decline of rheumatic fever in developed countries has resulted in a similar decline in the prevalence of MS. Less common causes of MS include severe annular and leaflet calcification, congenital malformations, malignant carcinoid, left atrial myxoma, left atrial thrombus, and endocarditis. A definitive history of rheumatic fever can only be obtained in 50% to 60% of cases, and women are affected more often than men by a 2:1 ratio.[32,33] Rheumatic fever commonly occurs in childhood or adolescence and can lead to a postinfective pancarditis, affecting to various degrees the valves, endocardium, myocardium, and pericardium. In MS due to rheumatic fever, there is leaflet thickening and calcification, chordal shortening and fusion, and commissural fusion, which all lead to a smaller, funnel-shaped mitral orifice. This deformation can also prevent complete closure of the valve, which is evidenced by concomitant regurgitation in about half of patients with MS.

Pathophysiology

The cross-sectional area of the normal MV is 4 to 6 cm^2. Normally, there is a trivial diastolic pressure gradient present to move blood across the MV from the left atrium into the left ventricle. An increasing gradient is required as the MV becomes more narrowed, and a significant transvalvular gradient first develops when there is reduction of the mitral orifice to <2.5 cm^2. Increasing atrial pressure leads to left atrial enlargement, and the pressure is subsequently transmitted retrograde into the pulmonary veins, capillaries, and arteries. The determinants of the transvalvular gradient and left atrial pressure are atrial contractility, cardiac output, and heart rate. Consequently, the gradient and atrial pressure are increased if atrial kick is lost (decreased atrial contractility), flow rate across the valve increases (increased cardiac output), or transit time across the valve is shortened (increased heart rate).

Diagnosis

Symptoms

Symptoms of left-sided heart failure, such as dyspnea, orthopnea, and paroxysmal nocturnal dyspnea, are the primary indicators of MS and are typically triggered by exertion, stress, infection, pregnancy, or the abrupt onset of atrial fibrillation. The increased heart rate and cardiac output that can occur under these circumstances, and the mechanical obstruction inherent to MS, lead to an increased transvalvular gradient and left atrial pressure. The ensuing pulmonary congestion results in dyspnea. Likewise, the loss of atrial kick with atrial fibrillation increases the gradient and atrial pressure and may be poorly tolerated. Patients with atrial fibrillation may also present with palpitations or systemic embolization.

Patients infrequently present with hoarseness, dysphagia, hemoptysis, and symptoms of right-sided heart failure. Hoarseness and dysphagia may result if left atrial enlargement is sufficient to compress surrounding structures. Hemoptysis may occur from significant pulmonary venous hypertension. Symptoms of right-sided heart failure arise when right ventricular function is impaired due to an increased afterload from the stenotic MV and secondary

pulmonary hypertension. Patients may present without symptoms but have an abnormal physical examination.

Signs

The left ventricle is typically not enlarged, and the point of maximum impulse is not displaced. The typical auscultatory findings of MS are best heard at the apex and include a low-pitched, rumbling mid-diastolic murmur; an accentuated first heart sound; and an opening snap. These findings may be absent with a heavily calcified immobile valve, severe pulmonary hypertension, or low cardiac output. Physical findings of pulmonary hypertension, such as a loud pulmonic component of the second heart sound (P_2), a right ventricular heave, distended neck veins, hepatomegaly, ascites, and peripheral edema, can also be observed with MS.[16]

DIAGNOSIS

Table 82.3 Classification of Mitral Stenosis Severity

Indicator	Progressive	Severe
Mean gradient (mm Hg)		>5–10
Diastolic pressure half-time (msec)	<150	≥150 ≥220 (very severe)
Valve area (cm^2)	>1.5	≤1.5 ≤1.0 (very severe)

Adapted from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(23):2440–2492.

Imaging

Echocardiography is the principal tool used in the diagnosis of MS. It is used to assess the morphologic characteristics of the valve apparatus: leaflet mobility, leaflet flexibility, leaflet thickness, presence of calcifications, subvalvular fusion, and appearance of the commissures. Doppler echocardiography is utilized to determine the hemodynamic severity by measurement of the mean transvalvular pressure gradient, pulmonary artery systolic pressure, diastolic pressure halftime, and valve area (Table 82.3). This morphology and severity information is fundamental in determining the timing and type of intervention to be used.[17]

The enlarged left atrium gives rise to characteristic findings on the chest radiograph, which includes displacement of the left main-stem bronchus superiorly and displacement of the esophagus posteriorly. Additionally, calcification of the mitral leaflets and enlarged pulmonary arteries with cephalization of pulmonary blood flow can be seen.

Similar to the diagnosis of other valvular heart disease, cardiac catheterization with direct pressure measurement has largely been replaced by echocardiography.

Natural History

The natural history of MS is that of a continuous decline usually consisting of a slow, stable course, followed by a progressive acceleration. The latent period from rheumatic fever to the onset of symptoms is typically 20 to 40 years, with another decade before symptoms become disabling. Depending on the symptoms at presentation, the overall 10-year survival rate of untreated patients presenting with MS is 50% to 60%. Once disabling symptoms occur, the 10-year survival rate is a bleak 0% to 15%.[32–35] Mortality in untreated patients is due to pulmonary and systemic congestion, systemic embolism, pulmonary embolism, and infection.[34,36]

Treatment

For the asymptomatic patient with mild MS in sinus rhythm, prophylaxis against rheumatic fever is the only therapy indicated. A yearly history, physical examination, chest radiograph, and electrocardiogram should be

obtained; serial echocardiograms are only warranted in patients with severe MS or when there is a change in symptoms.[17]

Mechanical relief is considered in symptomatic patients with moderate to severe MS. In symptomatic patients with mild MS, further exercise testing or dobutamine stress testing is useful to determine whether or not mechanical relief is warranted. Patients with a significant elevation in mean transmitral gradient (>15 mm Hg), pulmonary artery systolic pressure (>60 mm Hg), or pulmonary artery wedge pressure (>25 mm Hg) during provocative testing have hemodynamically significant MS and should be considered for mechanical relief.[17] The options for mechanical relief of MS include percutaneous balloon mitral valvuloplasty (PBMV), open mitral commissurotomy (OMC), and MV replacement.

Percutaneous Balloon Mitral Valvuloplasty

PBMV requires a balloon-tipped catheter to be introduced into the right atrium via a transseptal approach and inflated across the diseased valve.[37] This has become the standard of care for select MS patients.[17] Scoring systems have been developed to aid in patient selection. Leaflet thickness, pliability, and degree of calcification of the valves and the subvalvular apparatus are central in these scoring systems. Lower scores (e.g., <8 in the Wilkins score) correlate with improved outcomes.[38] Contraindications include the presence of a left atrial thrombus, moderate to severe MR, heavy annular or leaflet calcification, and severe subvalvular distortion.

Procedural mortality of PBMV is 1% to 2% in large series. Rare risks of the procedure include MR, iatrogenic creation of an atrial septal defect, perforation of the left ventricle, embolic events, and myocardial infarction.[39–43]

Success of PBMV can be measured by the increase in mitral valve area (MVA), restenosis at long-term follow-up, and event-free survival (death, repeat procedure or surgery, NYHA III or IV). Overall, significant (MVA $\geq$1.5 cm^2) increases in MVA are obtained in over 80% of patients,[44] with a 10-year event-free survival rate of 80% and 10-year freedom from restenosis of 70%.[45,46]

Open Mitral Commissurotomy

OMC permits direct inspection of the MV apparatus and allows debridement of calcium deposits, division of the commissures, and splitting of fused chordae tendineae under direct vision. Additionally, the left atrial appendage can be surgically excluded, reducing the risk of postoperative embolization. The contraindications to OMC are similar to those of PBMV.

The operative mortality of OMC is <2%,[47,48] and complication rates are similar to those of PBMV.[49,50] Short- and long-term hemodynamic results and symptomatic results are similar between PBMV and OMC in younger patients with less severe valve pathology.[49] More favorable results are seen with OMC in older patients with subvalvular fusion, leaflet calcification, and less valve flexibility.[50]

Mitral Valve Replacement

MV replacement is necessary in symptomatic patients with moderate to severe MS when there is a significant amount of calcification or subvalvular fusion, since PBMV and OMC are less likely to be successful. MV replacement is also necessary in symptomatic patients with moderate to severe MS and concomitant moderate to severe MR.[17] The choice of valve prosthesis for MV replacement is determined similarly to choosing the prosthesis for AVR.[22] Regardless of the prosthesis used, it is well established that preservation of the papillary muscle attachments to the annulus plays an important role in the maintenance of LV function.[51–55] The operative mortality rate of MV replacement is 5% to 6% and freedom from reoperation at 15 years is 50% to 75%.[56]

MITRAL REGURGITATION

Prevalence and Etiology

Competency of the MV is dependent on the entire MV apparatus; dysfunction of any one of the components can 7 lead to mitral regurgitation (MR). The most common overall cause of MR is degenerative MV disease. Other causes of MR include rheumatic valve disease, endocarditis, certain drugs, and collagen vascular disease. In some cases, functional MR develops as a result of dilation of the LV from cardiomyopathy or severe ischemic heart disease.

Rupture of a papillary muscle from myocardial infarction or endocarditis, or rupture of a chord, can lead to the onset of acute, severe MR.

Pathophysiology

Myxomatous degeneration of the valve leaflets leads to leaflet thickening, leaflet redundancy, and chordal elongation. Annular dilation is also present to varying degrees. This ultimately leads to leaflet malcoaptation and/or chordal rupture, leading to regurgitation: blood flow from the left ventricle into the left atrium during systole. Regardless of etiology, the pathophysiology of chronic MR is similar. MR results in gradual enlargement of the left atrium as a result of volume overload. Decrease in the functional stroke volume causes an increase in LV size with a subsequent decrease in LV function.

The pathologic process that takes place in acute MR is quite different. Sudden volume overload results in an increase in LV preload and a decrease in forward stroke volume, since compensatory LV eccentric hypertrophy has not had time to develop. Similarly, acute volume overload of the left atrium results in an increase in left atrial pressure and pulmonary congestion.

Diagnosis

Symptoms

Symptoms of chronic MR include fatigue, dyspnea on exertion, and shortness of breath. More advanced stages of disease are characterized by the development of heart failure. Acute, severe MR is characterized by acute pulmonary edema and cardiogenic shock.

Signs

The point of maximum impulse is typically laterally displaced. The classic auscultatory findings of MR are best heard at the apex and include a high-pitched, blowing, holosystolic murmur radiating to the axilla; a diminished S_1; and an S_3.

Imaging

Echocardiography is used to assess the severity of MR, morphology of the MV, and size and function of the LV and atrium. Assessment of the severity of MR is determined by the jet area/left atrial area, regurgitant volume, regurgitant fraction, and regurgitant orifice area (Table 82.4). Additionally, magnetic resonance imaging (MRI) allows accurate measurements of the severity of regurgitation and quantification of regurgitant volumes, along with assessment of LV size and function.

Natural History

Patients with mild to moderate MR usually remain asymptomatic with little or no hemodynamic compromise for many years. In patients with severe MR caused by flail leaflets, the mortality rate is 6% to 7% per year, and 90% of patients die or require an MV operation within 10 years.[57]

Treatment

Surgery should be performed early, before the onset of LV dysfunction. Even asymptomatic patients with severe MR should be offered surgery if there is a high probability of successful repair and low mortality risk.[22,58] MV repair is the preferred surgical therapy for most patients, since it preserves the native valve and avoids the need for anticoagulation, which is required in many patients who undergo MV replacement.[59] Preservation of the MV and chordae preserves LV function and improves survival. Success rates of MV repair depend on the etiology of regurgitation. Durable MV repair can be accomplished in >90% of patients with degenerative MV disease. Techniques for MV repair include resection of the prolapsed portion of the MV leaflet with leaflet reconstruction or remodeling the zone of coaptation by creating artificial chordae (Fig. 82.8). Whichever repair technique is used, it must be supplemented by the placement of a prosthetic annuloplasty ring or band.

Table 82.4 Classification of Primary Mitral Regurgitation Severity

Indicator	Progressive	Severe
Angiographic grade	1–2+	3–4+
Jet size	Central jet 20–40% of LA or Late systolic eccentric jet	Central jet >40% of LA or Holosystolic eccentric jet
Vena contracta (cm)	<0.7	≥0.7
Regurgitant volume (mL/beat)	<60	≥60
Regurgitant fraction (%)	<50	≥50
Effective regurgitant orifice (cm^2)	<40	≥0.40

Adapted from Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: executive summary a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014;129(23):2440–2492.

Mortality of isolated MV repair is <1%, with >90% freedom from reoperation at 10 years. Functional MR is usually repaired with the use of an undersized annuloplasty ring to reduce the diameter of the mitral annulus and restore valve competency. MV repair, if possible, is also the preferred surgical therapy in patients with MV endocarditis. Resection of all infected valve tissue is the mainstay of valvular reconstruction in patients with

endocarditis. This is followed by leaflet reconstruction, commonly with the use of an autologous pericardial patch and an annuloplasty (Fig. 82.9).

MV replacement is indicated when adequate MV repair cannot be accomplished. Mechanical valve replacements are indicated in patients younger than 50 years and stented bioprostheses are indicated in elderly patients (>70 years).[22]

Isolated MV surgery is traditionally performed through a full sternotomy. Minimally invasive approaches, which include partial upper and lower sternotomy and right mini anterolateral thoracotomy, decrease the degree of surgical trauma and blood loss and allow faster recovery with less postoperative pain and sternal wound complications and better cosmetic result.[60–62] Robotically assisted MV repair, which is performed through small port-like incisions, is the least invasive surgical approach that eliminates the need for sternotomy or thoracotomy and as such provides faster postoperative recovery in hospital as well as after discharge (Fig. 82.10).[63–66]

In patients with severe MR who are determined to be at prohibitive risk for surgery, given existing comorbidities, an alternative treatment option is percutaneous MV repair. The MitraClip system (Abbott, Abbott Park, Illinois, USA) is a percutaneously delivered device that offers similar mortality and symptomatic improvement. However, due to the higher rate of MR requiring repeat procedures, and less improvement in LV dimensions as compared to surgery, surgical repair remains the standard of care for treatment of MR among eligible patients.[67]

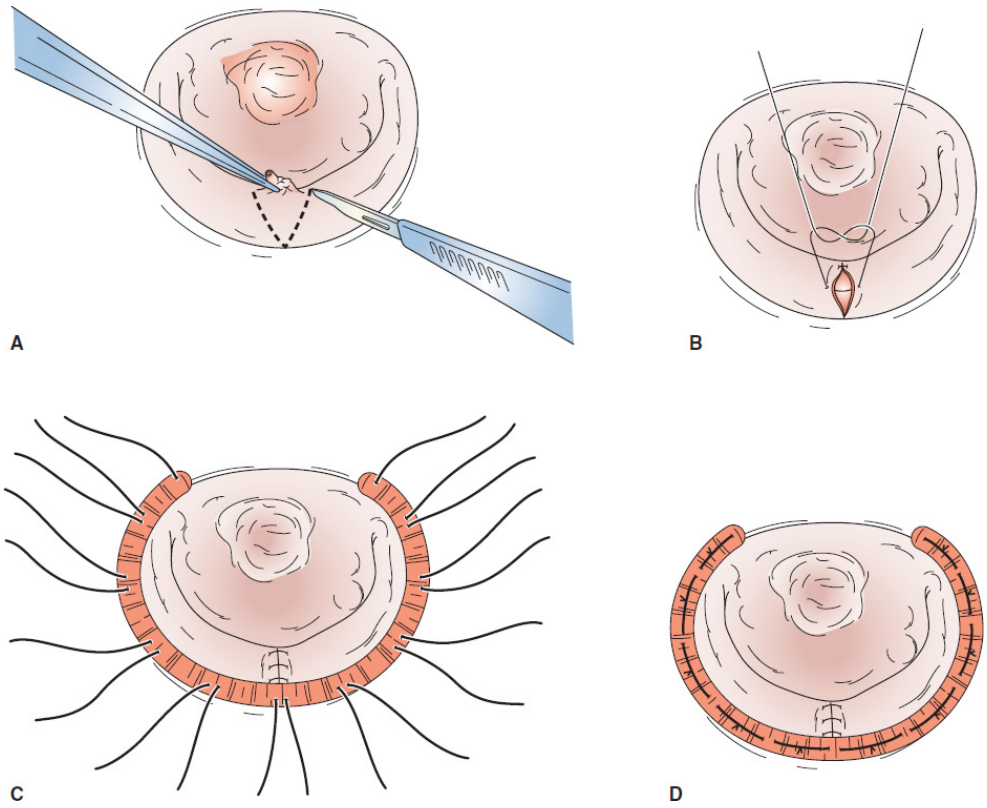

Figure 82.8 Schematic diagram of posterior mitral valve repair and insertion of annuloplasty ring. **A:** Resection of prolapsing segment. P2 triangular section. **B:** Suture reconstruction of P2 scallop. **C:** Posterior annular sutures placed through annuloplasty band. **D:** completed mitral valve repair.

TRICUSPID VALVE DISEASE

TV disease is less common than AV and MV disease. Tricuspid regurgitation (TR), the most common form of TV dysfunction, can occur with anatomically normal or abnormal valves. Functional TR is caused by right ventricular dilation and consequent leaflet malcoaptation in an otherwise anatomically normal valve. Right ventricular enlargement occurs in patients with pulmonary hypertension, most commonly caused by long-standing MV dysfunction. TV endocarditis most commonly occurs in intravenous drug users and causes TR by destruction of the leaflets.

Echocardiography is used to assess the degree of TR, anatomy of the TV, right ventricular function, and pulmonary pressures.

Mild to moderate degrees of TR often resolve due to remodeling after the correction of MV disease causing pulmonary hypertension. Severe functional

TR is corrected by reduction in the diameter of the tricuspid annulus using an annuloplasty band. Severe endocarditis requires complete resection of infected valve tissue, followed by TV reconstruction with pericardium or replacement with a bioprosthesis. In active drug users, insertion of a valve prosthesis may be delayed by several months to decrease the risk of recurrent endocarditis.

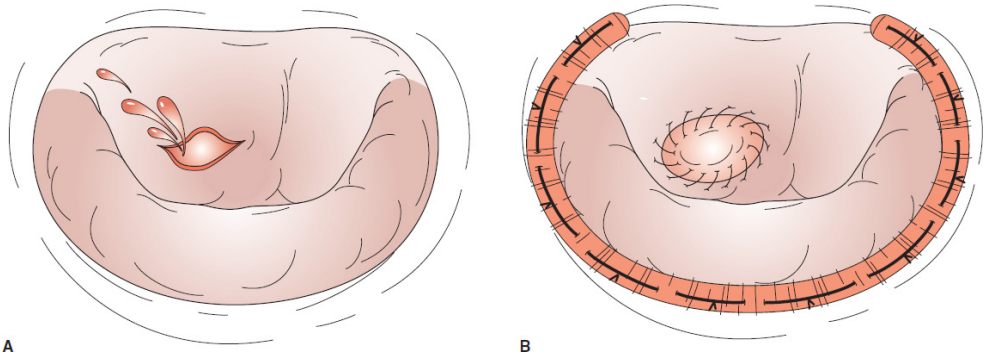

Figure 82.9 Schematic diagram of mitral valve repair with autologous pericardial patch and insertion of an annuloplasty ring. **A:** Defect in anterior mitral leaflet following resection of vegetation. **B:** Completed mitral valve repair after pericardial path and posterior annuloplasty.

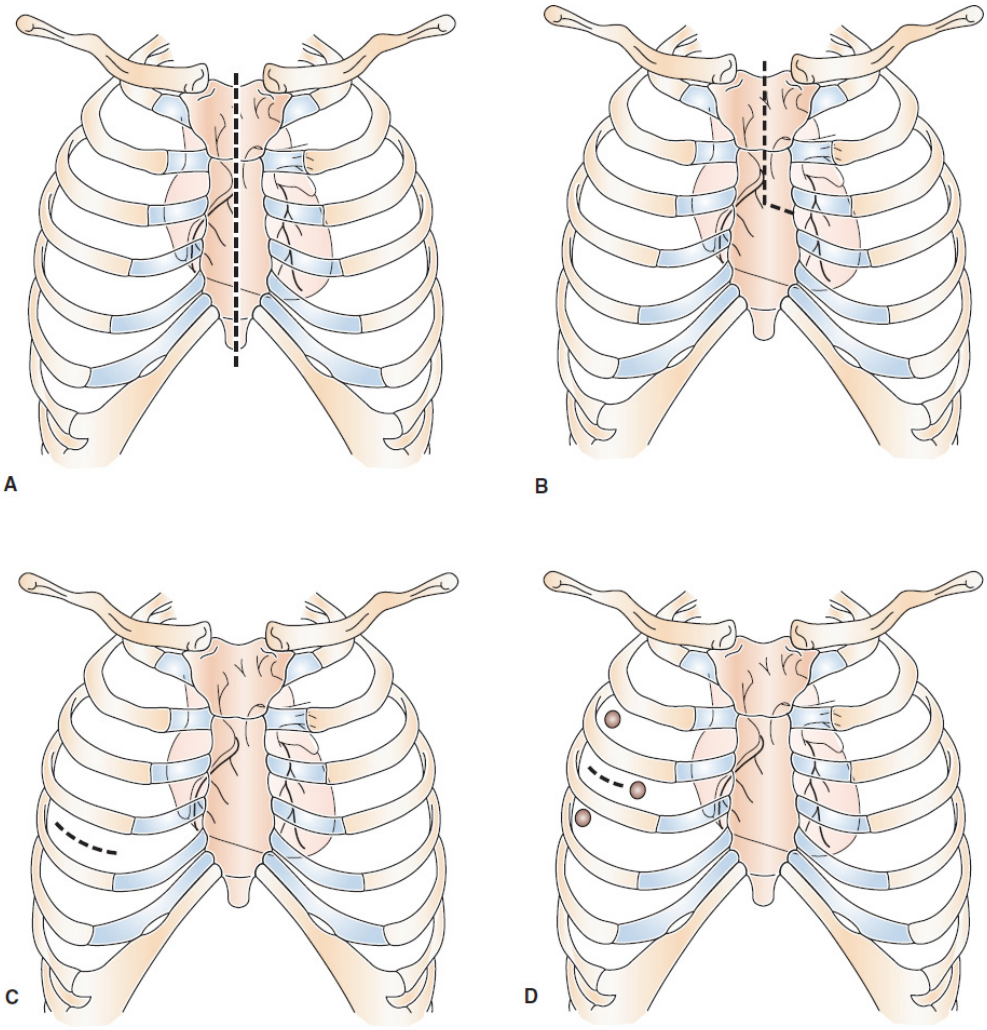

Figure 82.10 Surgical approaches to the mitral valve. **A:** Full sternotomy. **B:** Partial sternotomy. **C:** Limited right anterolateral mini-thoracotomy. **D:** Robotically assisted.

Valve Prostheses

Numerous types of valve prostheses are currently available for clinical use. All differ in design, biocompatibility, and hemodynamic characteristics. They are broadly classified into mechanical and bioprosthetic.

Contemporary mechanical valves are bileaflet valves composed of carbon material that is mounted on a sewing ring (Fig. 82.5). Mechanical valve prostheses are durable and have excellent hemodynamic performance. Patients with mechanical prostheses require lifelong anticoagulation with warfarin, which results in a 1% to 3% risk of bleeding per year. These

characteristics make mechanical valves the prosthesis of choice for younger patients with no contraindications to long-term anticoagulation.[22]

Biologic prostheses are composed of valve leaflets created from bovine pericardium, or a porcine heart valve xenograft, each mounted on a stented sewing ring (Fig. 82.6). Biologic prostheses have slightly inferior hemodynamic characteristics when compared with mechanical prostheses and a limited durability of 10 to 15 years. Bioprostheses are not thrombogenic and therefore do not require anticoagulation. Bioprostheses are generally indicated in older individuals and younger patients who have contraindications to long-term anticoagulation.

There has been an increased use of bioprostheses in younger individuals due to recent improvements in design of the prostheses, expected increases in valve durability, decreased risk of reoperations, and the ability to perform valve-in-valve TAVR.

Aortic homografts are cryopreserved cadaveric allografts. These consist of the entire aortic root (including the AV, surrounding ventricular myocardium, intervalvular fibrosa, and anterior MV leaflet) and the ascending aorta. Homografts are not thrombogenic, have excellent hemodynamic characteristics, and have high resistance to infection. Homografts are indicated in patients with AV endocarditis. Their use for primary AVR is limited due to the complexity of the operation and limited durability (10 years).

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83

Mechanical Circulatory Support

Eric I. Jeng

Key Points

1. The term mechanical circulatory support (MCS) refers to a broad array of cardiac support devices distinguished by the following important features: location of the pumping chamber of the device, ventricle being supported, and pumping mechanism.
2. Indications for MCS include bridge to recovery, bridge to transplantation, and destination therapy.
3. Durable devices utilized for bridge to transplantation or destination therapy require major operative implantation that facilitates patient discharge from the hospital.
4. Delay in establishing any type of MCS results in a greater acuity and severity of illness delay in establishing any type of MCS results in a greater acuity and severity of illness, decreasing survival secondary to a greater degree of organ failure present at the time of implantation survival secondary to a greater degree of organ failure present at implant.
5. Patient selection is the most important factor in determining outcome of patients who receive MCS.
6. Major adverse events following initiation of MCS are those related to anticoagulation therapy necessary during MCS, infection, right-sided heart failure, and malfunction of the device.
7. The Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) is a National Institutes of Health-funded data registry designed to study outcomes for patients with durable, long-term implantable MCS devices.
8. Major technologic advances in device designs for temporary and durable devices have incorporated continuous-flow rotary pumps.

INTRODUCTION

The term mechanical circulatory support (MCS) refers to a broad 1 array of cardiac support devices. These devices are distinguished by the following important features: (1) location of the pumping chamber of the device (extracorporeal vs. intracorporeal or "implantable"); (**Fig. 83.1**) (2) ventricle being supported (left ventricular assist device [LVAD] vs. right ventricular assist device [RVAD] vs. biventricular assist device [BiVAD] vs. total artificial heart [TAH]); (**Fig. 83.2**) and (3) pumping mechanism (pulsatile, volume displacement device vs. continuous-flow rotary device with axial or centrifugal design) (**Fig. 83.3**). Generally, the pumping chamber of short-term support devices is extracorporeal or paracorporeal in location, while durable systems are intracorporeal.

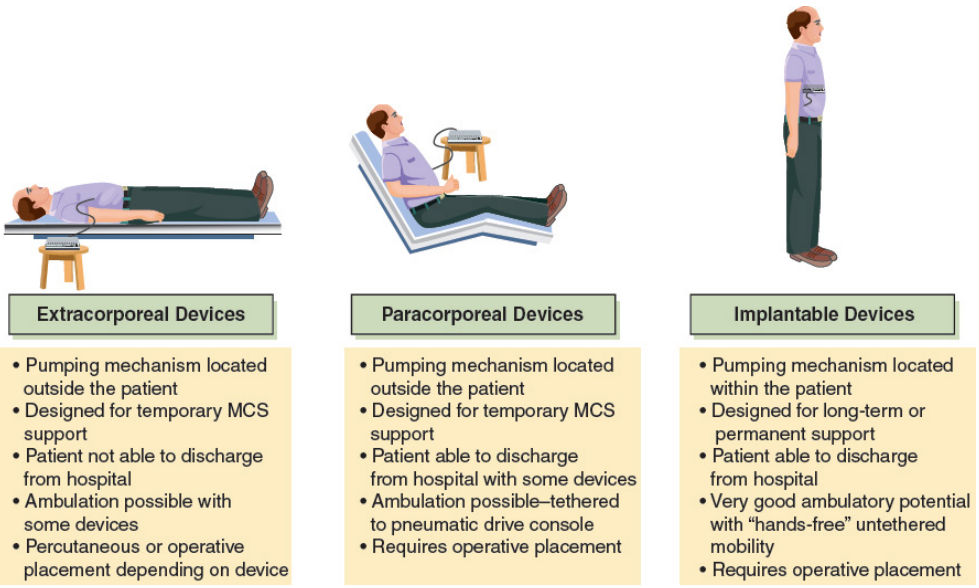


Figure 83.1 Classification of mechanical circulatory support devices by location of the pumping mechanism (extracorporeal, paracorporeal, and implantable).

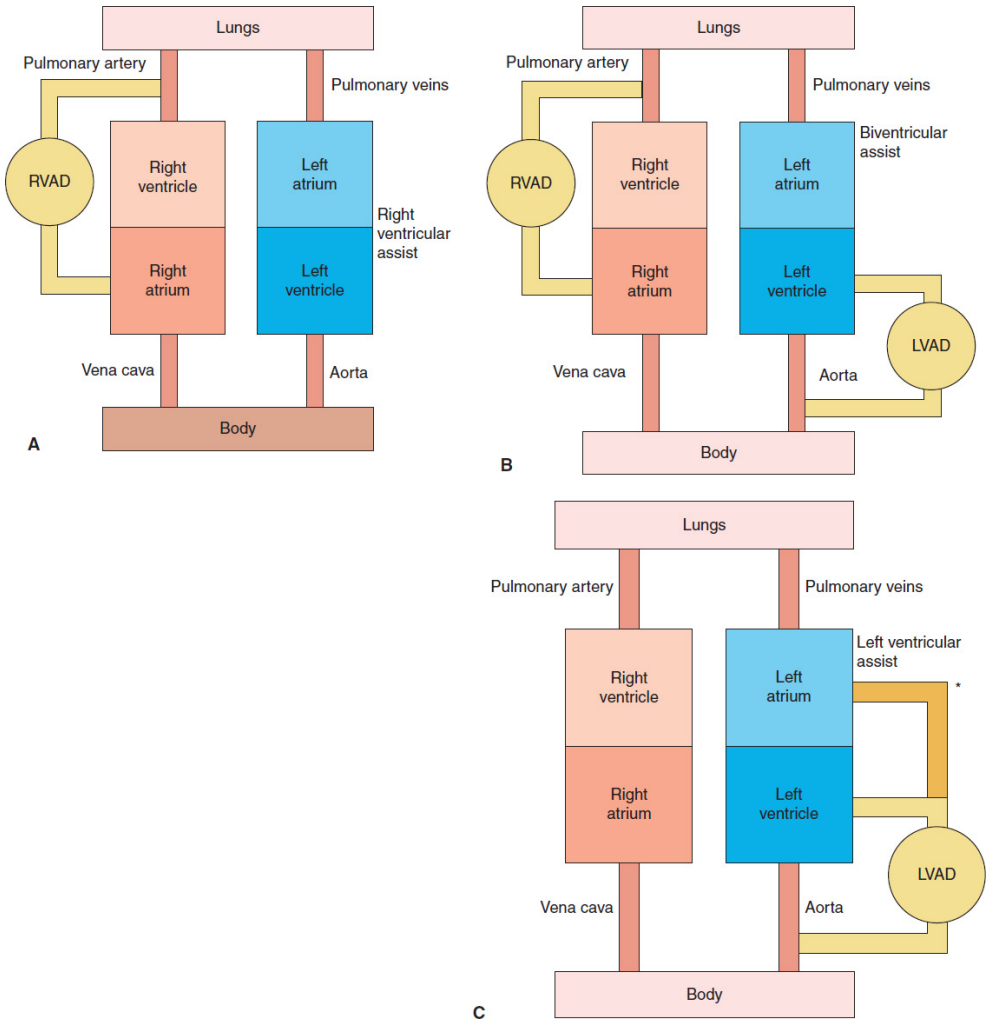


Figure 83.2 Classification of mechanical circulatory support devices by the ventricle being assisted. **A**: right ventricular assist. **B**: biventricular assist. **C**: left ventricular assist.

INDICATIONS FOR MCS

The spectrum of MCS therapy encompasses several indications for 2 use and a broad range of MCS device designs. Currently, there are three accepted indications for MCS based upon regulatory oversight by the U.S. Food and Drug Administration (FDA) and reimbursement criteria set by the Centers for Medicare & Medicaid Services, bridge to recovery (BTR), bridge to transplant (BTT), and destination therapy (DT).

BTR refers to the use of MCS in patients who are presenting with acute cardiogenic shock and/or decompensated heart failure, where the optimal

medical therapy (OMT), including intravenous inotropes and/or vasoconstrictors, has failed. These patients are thought to have an expectation of myocardial recovery following a short period (days to weeks) of temporary MCS. The short-term utilization of MCS for BTR is the most common application of MCS in the United States.[1] Examples of reversible forms of myocardial injury include acute myocardial infarction, viral myocarditis, or postcardiotomy cardiogenic shock with failure to separate from cardiopulmonary bypass (CPB) following various cardiac surgical procedures. Several types of devices can provide temporary MCS in these circumstances and include an intra-aortic balloon pump (IABP), extracorporeal ventricular assist device (VAD), or extracorporeal membrane oxygenation (ECMO)/extracorporeal life support (ECLS).[1] Typically, temporary MCS devices are implanted percutaneously allowing for rapid initiation of support and facilitating removal once cardiac function returns.[1] Certain types of extracorporeal VAD systems require major operative procedures via sternotomy and/or thoracotomy for insertion. These types of systems are utilized for postcardiotomy support where access to the mediastinum is facilitated by prior sternotomy and/or thoracotomy performed initially for the open-heart operation.

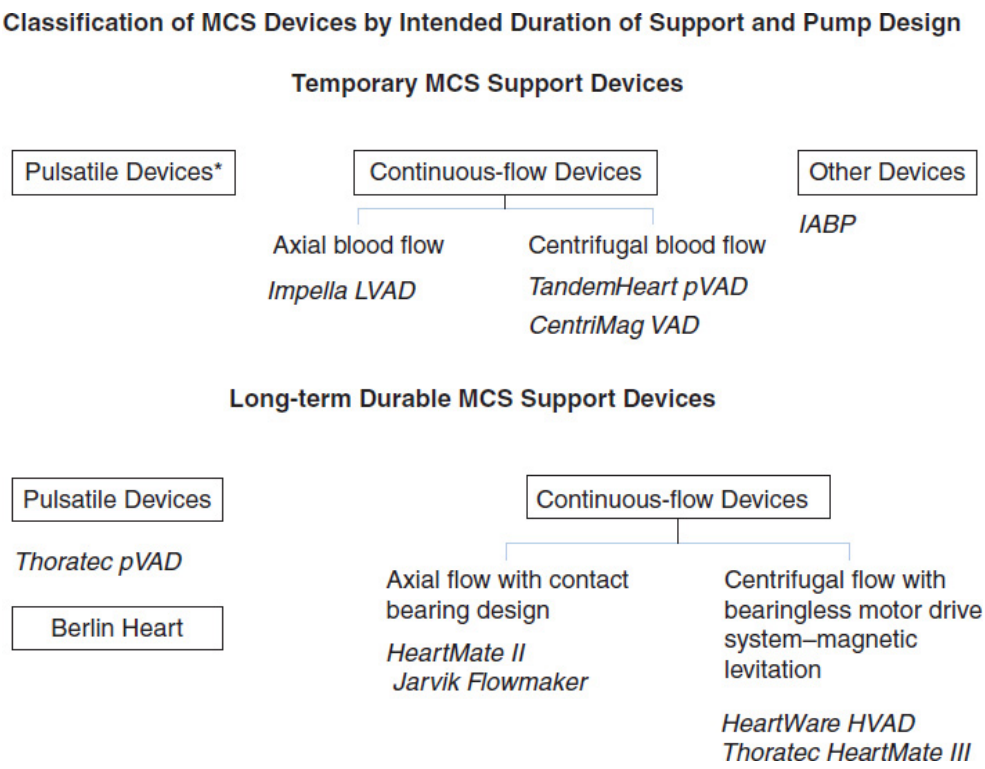


Figure 83.3 Classification of mechanical circulatory support devices by intended duration of support and pumping mechanism (pulsatile, volume displacement, or continuous-flow rotary pumps). (Impella, Abiomed Corporation, Danvers, MA; pVAD, HeartMate II, HeartMate III, Abbot Laboratories, Chicago, IL; CardioWest TAH, Syncardia Systems, Tucson, AZ; TandemHeart pVAD, CardiacAssist Corporation, Pittsburgh, PA; CentriMag VAD, Levitronix LLC, Waltham, MA; Jarvik LVAD, *Jarvik Heart Corporation*, New York, NY; HVAD, Berlin Heart, The Woodlands, Tx; LVAD, HeartWare Medtronic, Minneapolis, MN.)

BTT applies to patients presenting in cardiogenic shock and/or 3 decompensated heart failure refractory to OMT where myocardial function is unlikely to recover and the patient is considered a candidate for heart transplantation. Durable MCS devices designed for long-term support as a BTT and permit discharge from the hospital. Implantation of these types of MCS devices requires a major operative procedure usually including CPB and is ideal for patients who are hemodynamically stable with advanced symptoms and/or inotrope dependence in the absence of significant end-organ dysfunction or cardiogenic shock.

DT applies to hemodynamically stable patients with chronic refractory symptoms of advanced heart failure due to irreversible forms of cardiomyopathy, but who are not eligible for heart transplantation. These patients require long-term, durable, and reliable MCS devices permitting

patient mobility and discharge home.[2] Long-term, durable MCS devices are implantable and are ideally placed in patients with significant symptoms of advanced heart failure refractory to OMT but with stable hemodynamics. The survival, functional, and quality-of-life benefit of MCS for DT for the treatment of chronic advanced heart failure was established in a prospective, randomized trial known as the REMATCH Trial (Randomized Evaluation of Mechanical Assistance in the Treatment of Congestive Heart Failure).[2] This prospective, randomized trial evaluated the use of an implantable LVAD compared with OMT for refractory chronic advanced heart failure. LVAD therapy significantly reduced (relative risk, 0.52; 95% confidence limit, 0.34–0.78 at 1 year) the mortality seen in the control population treated with OMT at both 1-year and 2-year follow-up. Despite serious adverse events attributable to MCS from infection, bleeding, and device malfunction, LVAD recipients had an improved survival rate and experienced a superior quality of life compared to the medical therapy group. Currently, patients evaluated for DT must meet the following specific criteria: (1) New York Heart Association Class IV or American Heart Association Stage D heart failure symptoms; (2) a left ventricular ejection fraction of <25%; (3) a peak exercise oxygen consumption of <14 mL/kg/min (if unable to exercise be dependent on intravenous inotropes for 14 days or intra-aortic balloon pump therapy for 7 days); and (4) significant functional limitations despite the use of maximally tolerated doses of drugs outlined in the recent guidelines for heart failure treatment for at least 45 of the last 60 days.[3] The intended use and indication for MCS significantly influence MCS device selection and use and must be individualized.

TIMING OF MCS INTERVENTION

Cardiogenic Shock and Acute Heart Failure

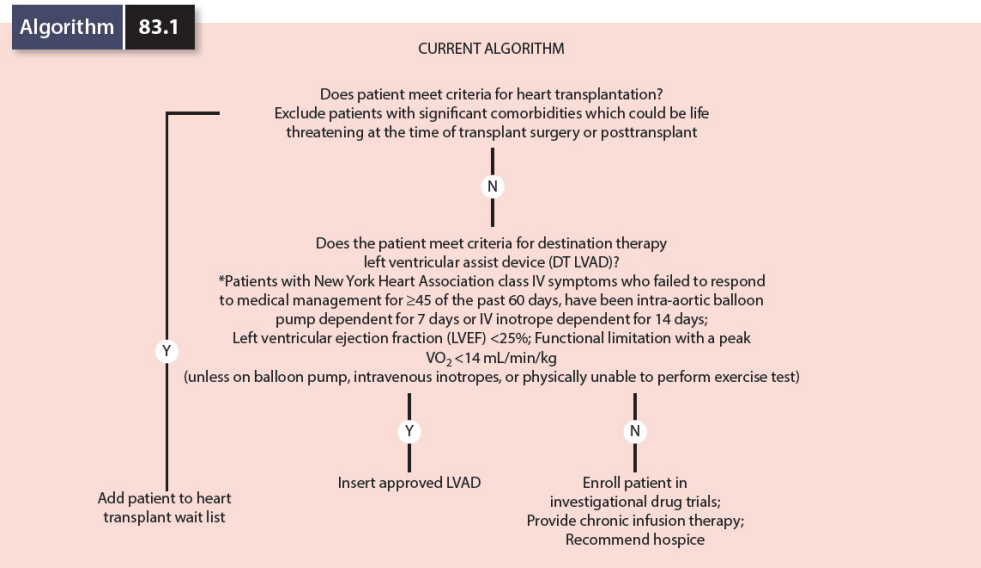
Criteria for initiation of MCS vary widely in clinical practice,[1] and the timing of implant is paramount and directly affects outcomes. Generally, patients presenting with acute forms of myocardial injury have recognizable hemodynamic changes—a cardiac index of less than 2.2 L/min/m^2, systolic blood pressure less than 90 mm Hg, pulmonary capillary wedge pressure

higher than 20 mm Hg, right atrial pressure higher than 18 mm Hg, and evidence of tissue malperfusion and multiorgan dysfunction, despite OMT. Patient history and overall clinical setting need to be considered in the decision to initiate MCS. When patients reach this degree of hemodynamic compromise, the mortality risk is substantial and frequently exceeds 50% at 30 days despite the availability of OMT, invasive circulatory monitoring, thrombolysis, and IABP support.[4,5] Data from the Abiomed BVS 5000 registry demonstrated that delay in initiating temporary MCS for more than 6 hours in the context of postcardiotomy shock or after failure to separate from CPB is associated with a significant decrease in survival rate; 44% versus 14%.[6] Delay in instituting any type of MCS with rapid progression of multiorgan failure increases the need for biventricular4 support as opposed to LVAD support alone.[7–11] Similarly, an episode of cardiac arrest prior to the initiation of MCS significantly impacts survival rate, decreasing it from 47% to only 7%.[6]

Chronic Heart Failure

Patients with chronic advanced heart failure are evaluated for BTT or DT MCS when they experience dyspnea at rest and/or with any effort and accompanied by resting tachycardia, progressive organ dysfunction (reflected in worsening renal or hepatic parameters), limited functional capacity, and poor quality of life despite OMT with or without inotrope therapy. Deterioration in end-organ function or progressive decline in functional performance may occur in the absence of a significant change in hemodynamic parameters due to chronic adaptation to low cardiac output. In addition, patients who experience renal insufficiency or hypotension in the setting of optimal doses of ACE inhibitors or beta blockers, as well as those who do not tolerate inotrope therapy due to refractory ventricular arrhythmias or have life-threatening coronary disease may benefit from MCS therapy (Algorithm 83.1). Dependence on intravenous inotropes has traditionally been considered the threshold that prompts consideration of MCS[12–14] (Fig. 83.4). However, patients with advanced systolic heart failure are currently eligible for DT therapy even if they are not dependent on inotropes, provided they meet indications for DT therapy. Only 18% of durable adult LVADs are currently implanted in patients not yet dependent on

intravenous inotropes.[12,13] Low implant rates in ambulatory advanced heart failure (noninotrope dependent) may reflect reluctance of both physicians and patients.[15] Ambulatory patients with advanced heart failure should have ongoing discussions about the trade-offs of living with heart failure in comparison with undergoing LVAD implantation to identify preferences and thresholds for considering elective LVAD therapy. Evidence to guide LVAD use before inotrope dependence is growing.[16]



Algorithm 83.1 Current algorithm for assessing patients with advanced heart failure for heart transplantation and mechanical circulatory support. Transplant status is initially assessed to determine appropriate indication for MCS use; BTT versus DT. (Adapted from Mancini D, Colombo PC. *J Am Coll Cardiol* 2015;65(23):2542–2555, with permission.)

PATIENT SELECTION AND INFLUENCE OF COMORBIDITIES ON OUTCOMES

Patient selection is paramount in determining outcome in patients requiring MCS. Relative contraindications to MCS include irreversible renal, hepatic or respiratory failure, sepsis, and/or a significant cognitive deficit.

Renal Function

MCS in the setting of renal dysfunction has consistently been associated with increased morbidity and mortality rates.[17,18] The patient's baseline renal function and the duration and chronicity of cardiogenic shock play an important role in predicting the probability of recovery of renal function. In some instances, reestablishing normal hemodynamics with short-term MCS facilitates resolution of the acute renal failure. Clinically, this may guide decisions for durable MCS options.

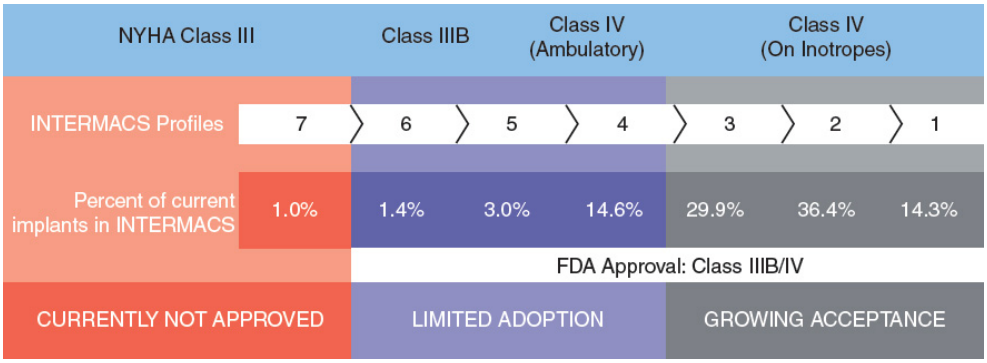


Figure 83.4 INTERMACS scale for classifying patients with advanced heart failure. Percent of implants by INTERMACS profile. Current U.S. Food and Drug Administration (FDA) approval status and acceptance in the medical community. (Adapted from Mancini D, Colombo PC. Left ventricular assist devices: a rapidly evolving alternative to transplant. *J Am Coll Cardiol* 2015;65(23):2542–2555, with permission.)

Pulmonary Function

Patients with a history of smoking and/or intrinsic lung disease identified by abnormalities on pulmonary function testing warrant high-resolution computed tomography (CT) to characterize the lung disease. Perioperative hypoxia related to lung disease may contribute to pulmonary vasoconstriction and worsening of right heart function. Moderate elevations of pulmonary vascular resistance encountered in patients with cardiogenic shock do not preclude the successful use of MCS if reversibility of the pulmonary vascular resistance can be achieved with inotropes or pulmonary vasodilators. Patients with severe pulmonary disease may have fixed high pulmonary vascular resistance (>8 Wood units), which represents an absolute contraindication to heart transplantation.

Liver Function

Total bilirubin and hepatic cellular enzyme levels more than three times normal are independent risk factors for adverse outcomes.[18,19] The etiology of the hyperbilirubinemia may be multifactorial, resulting from any combination of congestive hepatopathy, cholestasis, primary biliary, or infectious or parenchymal disease. Attempts should be made to normalize the liver function prior to initiation of durable MCS, as abnormal liver function often results in low serum albumin and abnormal coagulation. In our potential MCS patients we review for significant alcohol and drug use, and test for presence of hepatitis A, B, or C or other viruses. We obtain a CT of the chest, abdomen, and pelvis for surgical planning. If the liver is abnormal on CT, we utilize liver ultrasonography and/or magnetic resonance imaging to rule out infiltrative disease, mass or other pathology that may warrant biopsy. While permanent liver dysfunction may rule out durable MCS options, these same patients may in fact be candidates for multi-organ heart-liver transplantation.

Right Ventricular Heart Failure

Right ventricular (RV) heart failure presents as signs of renal, pulmonary, and hepatic dysfunction following LVAD implantation. It is a significant cause of mortality and morbidity, and often necessitates initiation of BiVAD support.[7–11,20–22] BiVAD support is associated with lower survival during both short- and long-term MCS. Thus, preoperative optimization of RV function with 5 a goal of lowering the right atrial pressure lower than 15 mm Hg is important in reducing the need for postoperative RVAD support. Patient selection is the most important factor in determining outcomes of those receiving MCS therapy.

Nutrition

Malnutrition is an important contributor to morbidity among patients on MCS. A serum albumin lower than 3.3 mg/dL appears to increase the mortality rate 6.6 times in the DT population of LVAD patients.[23,24] Significant nutritional deficiency is often associated with poor wound

healing, an increased risk of infection. Patients whose body mass index is either less than 22 or more than 36 are at risk for perioperative complications. In morbidly obese patients, some have described bariatric surgery as a means for weight reduction to bridge to transplantation.[25]

OTHER IMPORTANT MEDICAL CONSIDERATIONS WHEN INITIATING MCS

Valvular Heart Disease

Valvular heart disease can have important consequences in patients considered for MCS. In the aortic position, preexisting stenosis mild, moderate, and severe can left alone as it does not affect LVAD function. Severe aortic stenosis should be addressed if recovery is an option.[26] The presence of greater than mild aortic insufficiency can have a significant impact on the effectiveness of MCS therapy as it leads to recirculation, LV distention, decrease in subendocardial blood flow, and potentially decreased systemic forward flow and end-organ perfusion. The presence of aortic insufficiency can be confirmed by perioperative echocardiography and addressed by either AV replacement with a bioprosthesis, repair via a Park's Stitch, and/or complete closure.[27] Patients with a mechanical valve prosthesis in the aortic valve position should have the mechanical valve replaced with a bioprosthetic valve prior to institution of LV assistance. During unloading of the LV by an LVAD, the aortic valve may not open and a mechanical valve may be prone to thrombosis, potentially propagating clot in the aortic root, the coronaries, and potentially act as a nidus for stroke. Development of aortic insufficiency after LVAD implantation may be addressed at later date with aortic valve replacement, via either open surgical or transcatheter aortic valve replacement.[28,29]

Patients with significant mitral stenosis at the time of initiation of device support may require correction of the valvular problem before implantation, as LV filling is impaired which limits device filling. Mitral regurgitation likely does not have an impact on the filling of a VAD, and we do not routinely repair or replace the mitral valve in the setting of regurgitation. Multiples studies have shown that mitral valve intervention does not change

mortality, rates of right heart failure, and readmission rates.[30,31] Tricuspid regurgitation and RV dilatation contribute to elevated central venous pressure, hepatic congestion, and renal dysfunction.[20–22,32–34] Significant degrees of tricuspid regurgitation can impair the flow of blood from the RV through the pulmonary circuit. Studies that while CPB times were longer, there were no significant differences in early mortality and late mortality, early RV failure and late RV failure, acute kidney failure, early RV assist device implantation or length of hospital stay in patients undergoing LVAD + tricuspid valve surgery versus LVAD alone.[34] With that said, it is our practice to evaluate the tricuspid annular dimensions and perform an annuloplasty for moderate or more degrees of tricuspid regurgitation.

Coronary Artery Disease

The presence of coronary disease may contribute to ongoing myocardial ischemia and increase the risk of ventricular arrhythmias for patients supported with temporary or durable MCS. Perioperative ischemia of the RV may be of hemodynamic significance during initiation of LVAD support. In patients who have had coronary bypass surgery and are candidates for MCS, patent bypass grafts, particularly to the right coronary artery or left anterior descending coronary artery should be preserved to reduce the risk of perioperative RV failure and arrhythmias. In highly selected situations, it may be important to perform a coronary artery bypass to the right coronary artery or left anterior descending coronary artery systems to optimize RV or septal function in the perioperative period.

Arrhythmias

Atrial and ventricular arrhythmias are common in patients with cardiogenic shock and underlying cardiomyopathies. Early perioperative period, some patients with refractory ventricular arrhythmias may require biventricular support. In situations where weaning from MCS is feasible or planned, elimination of the ventricular arrhythmias with antiarrhythmic therapy is essential. The majority of patients undergoing implantation of a durable VAD have an implantable cardiac defibrillator (ICD) in place as part of their care for advanced heart failure. Currently, for those patients who do not have an

ICD at the time of VAD implant, the International Society for Heart and Lung Transplantation (ISHLT) guidelines recommend routine evaluation for ICD therapy.[35,36]

Intracardiac Shunts

Intracardiac shunts (atrial or ventricular septal defects) identified by transesophageal echocardiography prior to surgery should be closed at the time of implantation of a VAD to prevent right-to-left shunting.[37] As LV assistance is initiated, left atrial pressure can be reduced compared with right atrial pressures causing shunting of deoxygenated blood from the right atrium into the left resulting in systemic hypoxemia.

PATIENT OUTCOMES AND MAJOR ADVERSE EVENTS FOLLOWING INITIATION OF MCS

6 Bleeding, stroke and thromboembolism, infection, and RV failure are the most frequent complications that occur following initiation of MCS.

Bleeding

Bleeding is a frequent complication in patients supported by MCS. Risk factors for early bleeding include preoperative hepatic congestion and failure, poor preoperative nutritional status, prolonged CPB times, extensive surgical dissection, reoperative surgery, multiple cannulation sites, and decreased platelet function. Nonsurgical sources of bleeding are epistaxis, GI tract bleeding, bleeding of the mediastinum and thorax, and intracranial hemorrhage.[38–43] Some data demonstrate patients supported with long-term durable MCS have acquired von Willebrand disease caused by high shear stresses within continuous-flow rotary pumps.[41–42] These bleeding episodes manifest at mucosal sites including gastrointestinal bleeding and epistaxis and appears to accentuate previous subclinical arteriovenous malformations.[44,45]

RV Failure

RV failure occurs in approximately 3% to 30% of patients supported by LVAD support alone. The large variation in occurrence of RV failure is dependent on various patient factors including severity of illness and timing of intervention. The etiology of RV failure is multifactorial and includes pathologies within the pulmonary vascular bed and/or RV. Factors contributing to RV failure include impaired RV function as a result of intraoperative air embolism, myocardial stunning due to poor intraoperative myocardial protection, ischemia secondary to coronary artery disease, arrhythmias, volume loading, and alteration of RV septal geometry induced by LV unloading. Several studies have demonstrated that factors such as elevated central venous pressure, reduced RV stroke work index, low preoperative pulmonary artery pressures, increased transpulmonary gradient greater than 16 mm Hg, acute decrease in pulmonary artery pressures equal to or greater than 10 mm Hg at the onset of LVAD support, degree of preoperative pulmonary edema, increased need for perioperative transfusions, increasing degree of renal and hepatic dysfunction, female gender, nonischemic etiology, and preoperative temporary MCS support, all increase the need for RV MCS following LVAD implantation.[7–11,20–22] Data analysis revealed that a central venous pressure/pulmonary capillary wedge pressure ratio greater than 0.63, need for preoperative ventilator support, and blood urea nitrogen level higher than 39 mg/dL were independent predictors of right-sided heart failure after LVAD implantation.[20] Acute unloading of the LV by MCS may cause the septum to shift leftward, increasing RV volume loading and reducing its function.[21,22,46] The negative consequences of this phenomenon may be offset by the reduction in pulmonary artery pressures and RV afterload caused by device-mediated LV decompression.[21,22,46] Hemodynamic stability can be attained with isolated mechanical LV support in the overwhelming majority of patients, even in those patients with substantial RV dysfunction, if there is effective replacement of left-sided heart function and aggressive treatment of pulmonary hypertension. More recently, the improved perioperative management of elevated pulmonary vascular resistance including the use of inhaled nitric oxide and/or flolan, in combination with milrinone, isoproterenol, or dobutamine has significantly reduced the need for placement of an RVAD.[46] In patients with marked

elevation of central venous pressure, multiorgan failure, and severe RV dysfunction with low pulmonary artery pressures, early biventricular support may be indicated.[46]

Intracranial Bleeding and Thromboembolism

Cerebral vascular accidents are one of the most feared complications of MCS. The reported rates of hemorrhagic stroke range from 0.01 to 0.08 events per patient-year.[45] The occurrence of thromboembolic events following MCS is variable and depends on a number of factors including the type of device, duration of support, location and number of cannulation sites, and the presence of prosthetic valves within the heart. Approximately 10% of patients receiving MCS with implantable devices will experience a thromboembolic event or stroke.[23,45,47] This rate is in the range of 20% for patients on short-term extracorporeal MCS devices.[1] Hemorrhagic stroke rates have been improved with guided blood pressure control protocols[48] Improvement in the rate of thromboembolic events has come from more aggressive antiplatelet therapy in conjunction with warfarin, in addition to improved device design. In MOMENTUM 3, where patients with axial and centrifugal continuous-flow devices were prospectively compared, the numbers of events per patient-year for stroke of any severity, major bleeding, and gastrointestinal hemorrhage were lower in the centrifugal-flow pump group than in the axial-flow pump group.[49]

Infection

Infections can be device-related (i.e., device endocarditis, percutaneous lead or cannula site infection, pocket infection [infection external to an implanted device]) or non–device-related (i.e., pneumonia and urinary tract infection). The incidence of early nosocomial device-related infections in patients undergoing MCS is approximately 30% in many series and is related to the acuity of illness in this population of patients.[50–55] Patients with persistent or recurrent sepsis, and those patients with device-related infections, tend to have a higher mortality rate than patients without these complications.[55] In patients on long-term MCS, infection remains an important obstacle to successful outcome.[55] Most of these late infections begin in the percutaneous

driveline tract and pocket of the device. However, clinical experience has revealed that VAD infection rates can be minimized with attention to infection control guidelines, optimal implantation techniques, meticulous wound care, and the utilization of new continuous-flow rotary pump technology.[55] The risk factors for development of infection include preoperative infection at remote sites (not in the area of implantation), malnutrition, prolonged hospitalization, immobilization, broad-spectrum antibiotic therapy, immunosuppressive medications, mechanical ventilation, and the presence of central venous catheters. Device-related infections can sometimes be successfully treated with antibiotic suppression and device exchange or removal. Patients who are device-dependent and awaiting transplantation generally cannot tolerate device removal as a therapeutic option to eradicate the infection. Antibiotic suppression and transplantation remain the only chance for cure of device-related infections in these instances.

Device Malfunction and Thrombosis

The types and severity of device malfunctions vary with each MCS device. Many devices have built-in backup systems that, in the event of catastrophic device failure, provide some support to the patient. In some instances, patients supported by an LVAD have enough residual LV function remaining to help sustain them until corrective measures can be taken in the event of complete device failure. Fortunately, the reported frequency of this event is low.[23] Device malfunctions in TAHs are more problematic as there is no native heart to provide hemodynamic support in the event of a total device failure.

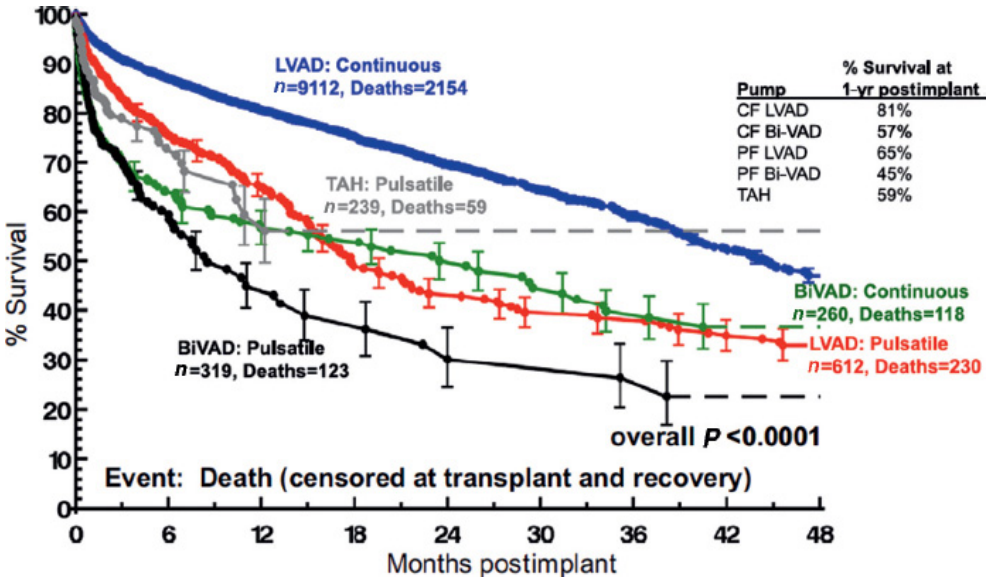


Figure 83.5 Actuarial survival for primary device implant, stratified by device type. Error bars indicate ± 1 SE. Patients are censored at transplant and recovery. CF, continuous flow; LVAD, left ventricular assist device; PF, pulsatile flow; TAH, total artificial heart. (From Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: a 10,000-patient database. *J Heart Lung Transplant* 2014;33:1304–1311, with permission.)

Pump thrombosis is potentially a catastrophic complication of VAD therapy. The variability in clinical presentation makes it a challenging diagnosis. It occurs both early and late after VAD implantation and may manifest itself with increased pump power, decreased device flow with heart failure, and hemolysis with hemoglobinuria or with embolic event. Serum lactate dehydrogenase level is as the primary biochemical marker of hemolysis in this clinical context. Clinically suspected thrombosis can be managed medically by intravenous anticoagulation, antiplatelet agents, or thrombolytics in some cases. Surgical treatment by pump explantation and pump replacement and/or urgent heart transplantation is generally indicated.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Database

7 The INTERMACS registry represents one of the largest available data repositories for the study of durable MCS device outcomes. The most recent INTERMACS database annual report summarizes outcomes in patients (≥19 years of age) who underwent durable MCS implant between June 23, 2006, and December 31, 2017. There were 25,145 adult patients with MCS

reported, of whom 18,539 (74%) received CF LVADs, 667 (2.6%) had an RVAD with CF LVAD, 339 received a total artificial heart (1.3%), and 20 (0.07%) received an isolated RVAD. CF LVADs included 14,527 axial flow (78%) and 4,012 centrifugal flow (22%) devices. Mean CF LVAD support duration was 20 months (31,563 patient-years). One-year survival for isolated CF LVADs was 83% and 5-year survival was 46%. One-year survivals for centrifugal versus axial flow devices were 85% and 84%, respectively. Patients who required concomitant RVAD support had 1- and 5-year survivals of 58% and 28%, respectively.[12,13,56] The actuarial survival for primary device implant as stratified by device type is summarized in Figure 83.5. Figure 83.6 displays the actuarial survival for primary continuous-flow devices as stratified by strategy at implant. The survival analysis for patients on mechanical circulatory support stratified by INTERMACS profile is presented in Figure 83.7. On January 1, 2018, the INTERMACS Database became part of The Society of Thoracic Surgeons National Database.[13] Table 83.1 exhibits MCS device implants by implant era and indication for implantation.

WEANING PATIENTS FROM MCS

Weaning Short-Term MCS

A number of factors are considered when weaning patients from MCS. Optimization of volume status, afterload, cardiac rhythm, and degree of inotropic support as well as exclusion of obvious surgical pathology, such as tamponade, is paramount before attempting separation from MCS. In addition, extracardiac causes, such as pulmonary edema, elevated pulmonary vascular resistance, acute respiratory distress syndrome, and pneumonia, may worsen RV function and prevent successful weaning from MCS. Once a patient's status has been optimized, weaning from MCS aided with echocardiographic monitoring is preferred. As device flows are reduced, echocardiogram provides information on ventricular filling and performance and valve function. If patients maintain satisfactory hemodynamics with reduction of pump flow, they can be considered for weaning. In the setting of biventricular support, it is important that device flows on the right side be

reduced before lowering left-sided device flows. This prevents pulmonary edema in the event of inadequate LV function. As device flows are reduced, native heart function begins to support the circulation. When weaning from MCS is not possible, patients should be evaluated for heart transplantation and/or bridged to a durable MCS device.

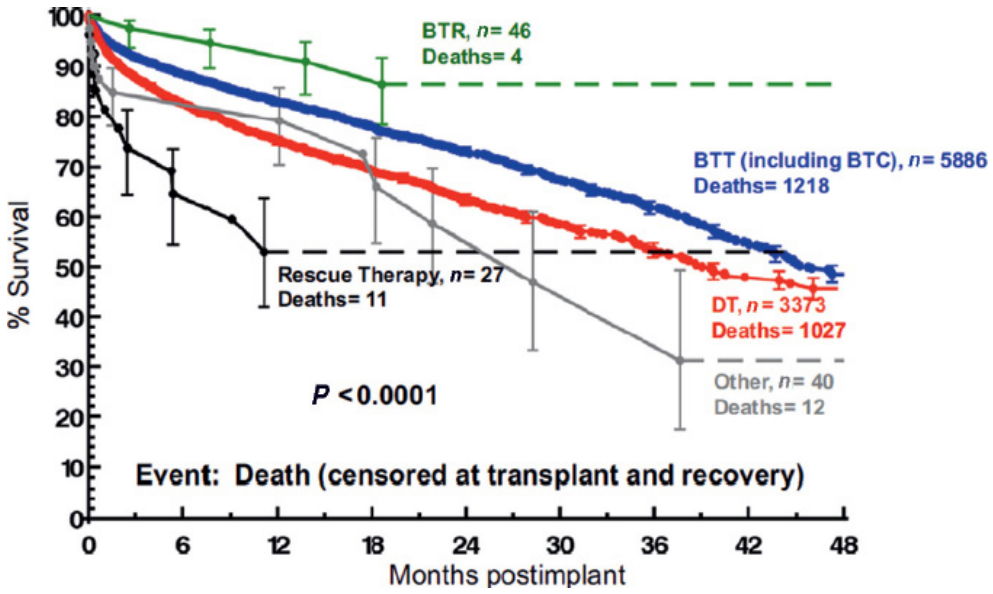


Figure 83.6 Actuarial survival for primary continuous-flow devices, stratified by strategy at implant: BTR, bridge to recovery; DT, destination therapy; BTT, bridge to transplant; BTC, bridge to candidacy. Error bars indicate ± 1 SE. (From Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: a 10,000-patient database. *J Heart Lung Transplant* 2014;33:1304–1311, with permission.)

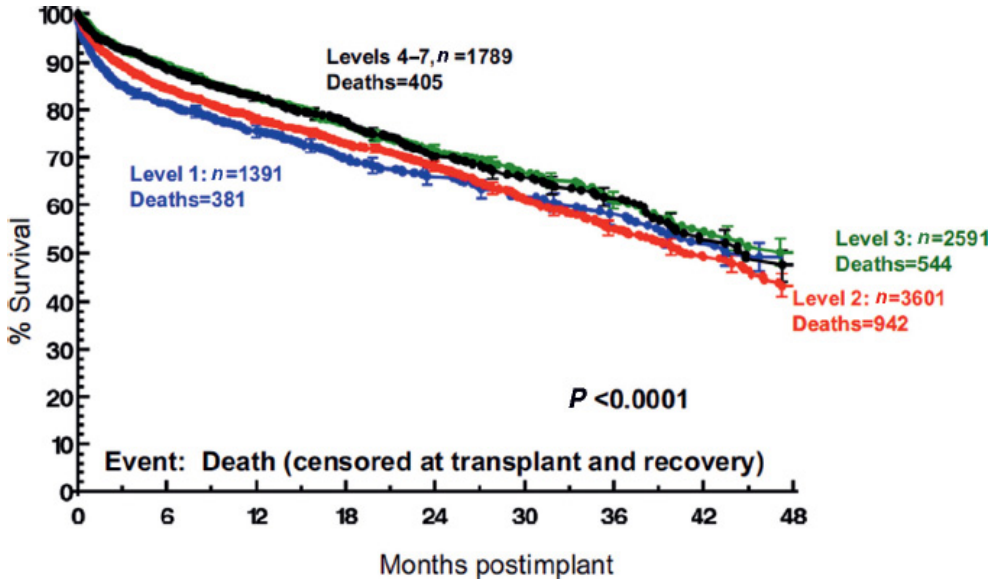


Figure 83.7 Survival analysis for patients on mechanical circulatory support by INTERMACS Profile. Error bars indicate ± 1 SE. See Table 84.2 (from previous edition) for a description of INTERMACS Profiles. (From Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: a 10,000-patient database. *J Heart Lung Transplant* 2014;33:1304–1311, with permission.)

Weaning Long-Term MCS

Observations from the cumulative experience with long-term MCS for BTT and recent small clinical studies have demonstrated that long-term MCS, associated with sustained mechanical unloading of the LV, can improve myocardial function even in those patients initially thought to have irreversible, dilated cardiomyopathies.[57–59] Several studies have demonstrated that long-term MCS can restore ventricular geometry, improve myocyte function, orientation, and size, reduce myocyte apoptosis, reduce myocardial cytokine gene and protein expression, reverse abnormal neurohormonal patterns associated with advanced heart failure, and improve myocardial mitochondrial function.[57–59]

MCS DEVICES

The devices currently approved by the FDA are broadly grouped into two categories based on durability and the intended length of support and use.

Devices Intended for Short-Term MCS (Temporary Devices)

IABP

Since its first reported clinical use by Kantrowitz in 1968, the IABP has become the most frequently utilized MCS device (Fig. 83.8).[60] The IABP is positioned within the descending thoracic aorta, augmenting ventricular performance and cardiac output increasing diastolic coronary blood flow, decreasing myocardial oxygen consumption, and reducing left ventricular afterload. Inflation of the balloon during diastole increases diastolic pressure and coronary blood flow and deflation of the balloon during systole reduces arterial afterload facilitating LV ejection. Although the IABP has been the mainstay of circulatory support for decades, the utility of IABP in cardiogenic shock complicating acute myocardial infarction was recently challenged by the results of the SHOCK-IABP Trial, and SHOCK-IABP II Trial.[61–63] These prospective studies randomized patients to IABP counterpulsation or no IABP counterpulsation in addition to revascularization and OMT. Both studies revealed no difference in 30-day mortality, length of stay in the intensive care unit, serum lactate level, incidence of renal failure, or duration of catecholamine therapy.[61–63] In the long-term follow-up, IABP has no effect on all-cause mortality at 6-year long-term follow-up. Mortality is still very high, with two-thirds of patients with cardiogenic shock dying despite contemporary treatment with revascularization therapy.[63] Complications from the use of the IABP include leg ischemia, balloon rupture, infection, bleeding, false aneurysm formation, femoral neuropathy, vessel perforation with hemorrhage, and aortic dissection. Female gender, peripheral vascular disease, diabetes, smoking, advanced age, obesity, and cardiogenic shock are predisposing factors for tissue malperfusion and limb ischemia.

Table 83.1 MCS Device Implants by Implant Era and Indications for MCS Device Implantation in the INTERMACS Registry

Device Strategy at the Time of Implant	Implant Date Era							
	2006–2007		2008–2010		2011–2013		Total	
	n	%	*n*	%	*n*	%	*n*	%
BTT listed	185	42.4	1,335	39.2	1,453	21.7	2,973	28.2
BTT likely	85	19.5	884	26.0	1,474	22.0	2,443	23.2
BTT moderate	49	11.2	337	9.9	677	10.1	1,063	10.1
BTT unlikely	28	6.4	104	3.1	222	3.3	354	3.4
DT	64	14.7	666	19.6	2,786	41.6	3,516	33.4
BTR	17	3.9	38	1.1	38	1.0	93	0.9
Rescue therapy	8	1.8	24	1.0	28	0.4	60	0.6
Other	0	0.0	14	0.4	26	0.4	40	0.4
Total	436	100.0	3,402	100.0	6,704	100.0	10,542	100.0

Adapted from Kirklin JK, Naftel DC, Pagani FD, et al. Sixth INTERMACS annual report: A 10,000-patient database. *J Heart Lung Transplant* 2014;33:1304–1311.

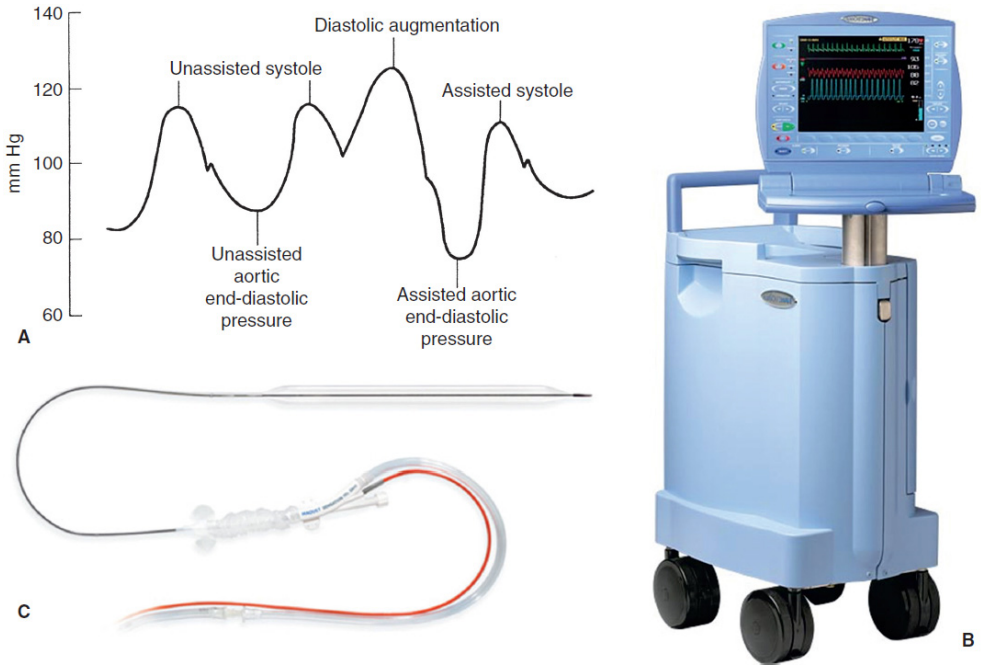


Figure 83.8 Intra-aortic balloon pump. **A:** Aortic pressure tracing during intra-aortic balloon pump support. Balloon counterpulsation is occurring after every other heartbeat (1:2 counterpulsation). With correct timing, balloon inflation (IP) begins immediately after aortic valve closure, signaled by the dicrotic notch of the arterial waveform. Compared with unassisted ejection, the pump augments diastolic blood flow by increasing peak aortic pressure during diastole. Balloon deflation before systole decreases ventricular afterload, with lower aortic end-diastolic pressure and lower peak systolic pressure. **B:** Console for the intra-aortic balloon pump. **C:** Catheter-mounted balloon is positioned within the thoracic aorta through a percutaneous or surgical approach via the femoral artery. (Photo courtesy of Maquet Cardiac Assist, Fairfield, NJ.)

Impella

Impella (Abiomed Corporation, Danvers, MA) is a continuous-flow rotary pump with axial design that propels blood from the LV across the aortic valve and into the ascending aorta[64,65] (Fig. 83.10). It is available in four delivery platforms for LV support including Impella LP 2.5, Impella CP, Impella LP 5.0, and Impella 5.5 with smart assist system and the Impella RP, a system uniquely designed for RV support. The LVAD is positioned across the aortic valve with the inlet port below and outlet above the aortic valve. The hemodynamic effects of Impella devices are based on LV unloading and augmentation of forward flow. This reduces myocardial oxygen consumption, improves mean arterial blood pressure, and reduces pulmonary capillary wedge pressure.[66] In a prospective, randomized clinical trial comparing the

Impella LP2.5 to IABP, cardiac index was significantly increased in patients with the LP2.5 compared with patients supported with an IABP. Overall mortality rate at 30 days 8 was similar in both groups.[64] The Impella RP (Fig. 83.9) is a novel RVAD designed using the Impella system but adapted for RV support. The major technologic advances in device designs for temporary and durable MCS devices have incorporated continuous-flow rotary pumps.

Tandem Heart

The Tandem Heart/Life Sparc (LivaNova, London, England) is a low-speed continuous-flow, centrifugal device MCS. With its most recent hardware upgrade in the LifeSparc design, the pump can now flow up to 8 L/min. The percutaneous cannulation strategy originated as a transseptal approach for left atrial-to-femoral artery VAD[67] (Fig. 83.10). Hemodynamic effects of this device are based on the parallel flow contribution to the aorta of both the device and the LV itself. This results in reduction of LV preload, myocardial oxygen consumption, filling pressures, and ventricular wall stress.[68] Protek Duo is a multilumen cannula that has been utilized as an RVAD. It is usually inserted through the right internal jugular vein or the left subclavian vein, with proximal ports in the right atrial and distal port in the distal main pulmonary artery. More recently, some groups[69] have described utilization of the Protek Duo Rapid Deployment in left apical cannulation to function as temporary LVAD.

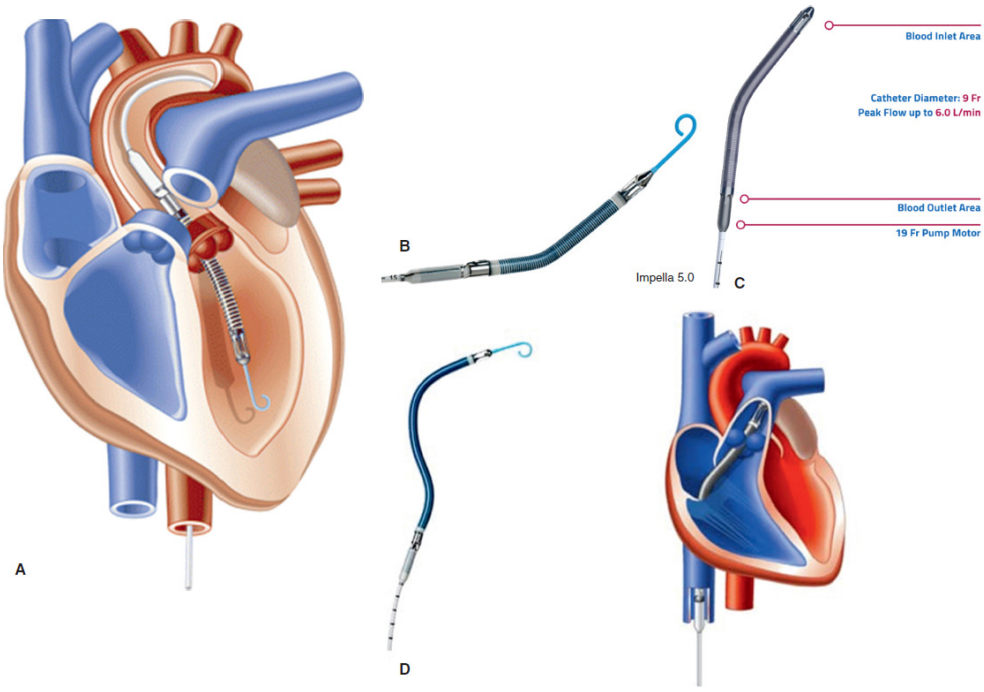


Figure 83.9 The Impella left ventricular assist device (Abiomed Inc., Danvers, MA). **A:** Diagram demonstrating positioning of the device across the aortic valve. Device inflow is within the left ventricle and device outflow is above the aortic valve. **B:** Impella 5.0. **C:** Impella 5.5. **D:** Impella RP. (Photographs courtesy of Abiomed Inc., Danvers, MA.)

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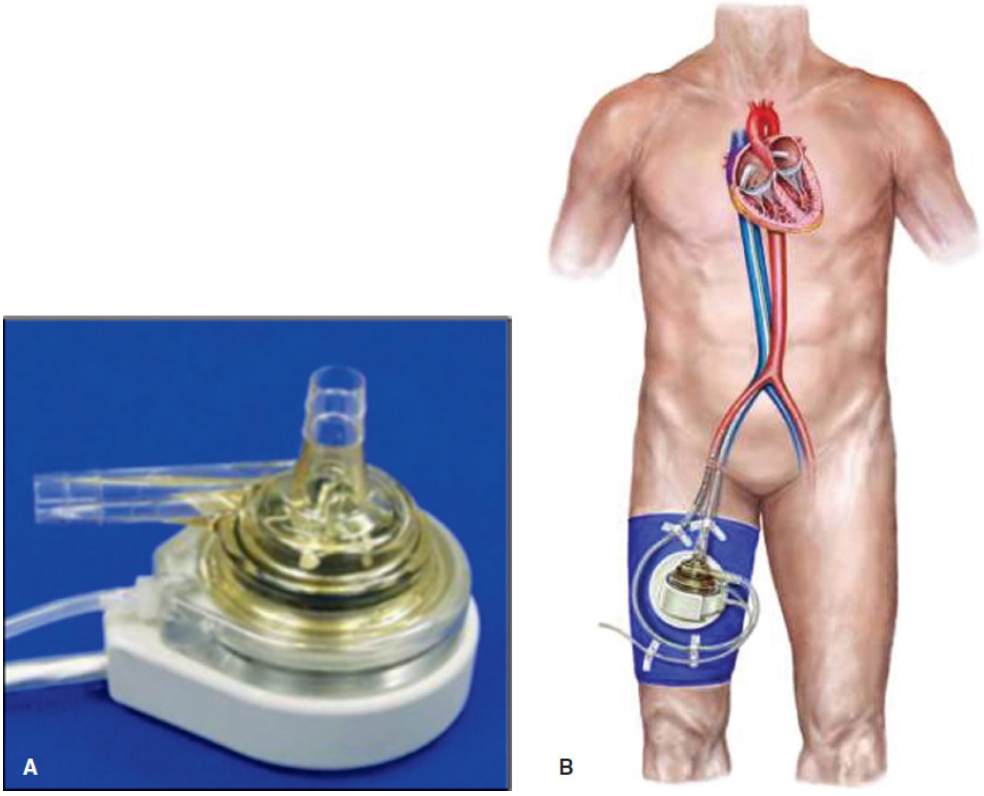

Figure 83.10 **A:** The Tandem Heart pVAD centrifugal pump (CardiacAssist Corporation, Pittsburgh, PA). The TandemHeart pVAD is an extracorporeal, continuous-flow rotary pump with centrifugal design providing temporary mechanical circulatory support to the left ventricle (left atrium to femoral artery). The TandemHeart pVAD utilizes a bearing design in the pump for impeller positioning and rotation. **B:** Schematic representation of the cannulation of the femoral artery and femoral vein with the transseptal placement of the inflow catheter within the left atrium from the femoral vein. The centrifugal pump of the Tandem Heart pVAD is secured to the patient's right thigh. (Photographs courtesy of CardiacAssist Corporation, Pittsburgh, PA.)

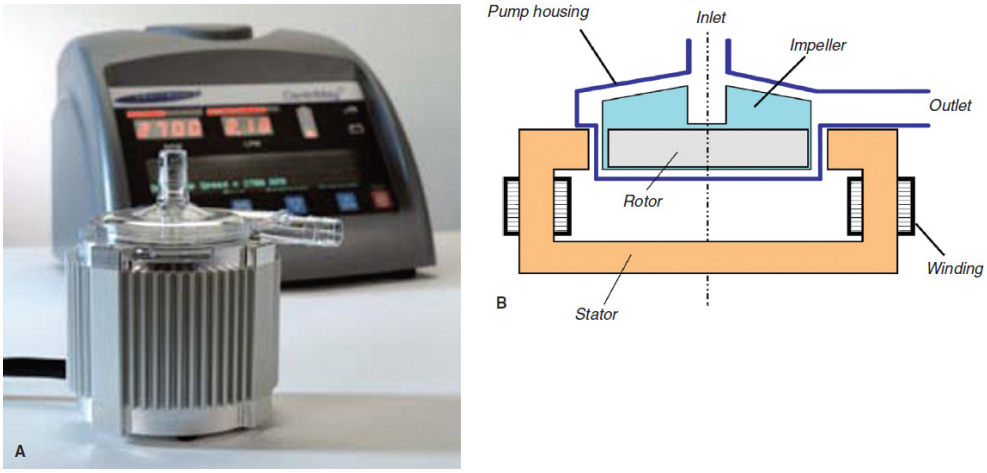

Figure 83.11 The CentriMag VAD. The CentriMag VAD is an extracorporeal, continuous-flow rotary pump with centrifugal design utilized for temporary mechanical circulatory support. The CentriMag can provide univentricular or biventricular support. **A:** The CentriMag console (background) and pump/motor (foreground). **B:** Schematic representation of the CentriMag pump. The rotor located within the upper pump housing is magnetically coupled to the lower motor housing to produce rotor levitation and spin. (Photograph courtesy of Levitronix LLC, Waltham, MA.)

CentriMag

The CentriMag (Abbot Laboratories, Chicago, IL) is an extracorporeal, continuous-flow centrifugal pump[70,71] (Fig. 83.11) based on a magnetically levitated "bearingless motor" design. This device can produce flows of up to 10 L/min under normal physiologic conditions, and can used as the pump with various cannulation strategies to support the left, or right ventricle.

Extracorporeal Life Support

Extracorporeal life support, or extracorporeal membrane oxygenation, is a temporary form of MCS similar to CPB that provides circulatory assistance while allowing for both oxygenation and carbon dioxide removal from blood.[72–79] ECLS has been used in a variety of both pediatric and adult clinical settings, including respiratory support, postcardiotomy support, and as a bridge to an LVAD or heart and/or lung transplantation.[76]

In venoarterial ECLS, the blood is drained from the venous circulation, oxygenated, and returned to the arterial circulation. Although it does reduce LV preload by decreasing the pulmonary venous return, ECLS does not directly unload the LV. In patients with severe LV dysfunction, the use of an

IABP and catecholamines helps reduce LV afterload and improves myocardial contractility, thus preventing blood stasis and thrombus formation within the LV. If LV function is so severely reduced that there is essentially no ejection, an atrial septostomy or insertion of a left ventricular vent can be inserted to relieve LV distention, a potential cause of pulmonary edema.

Venovenous ECLS, unlike venoarterial ECLS, maintains flow through the heart and is used solely for oxygenation and ventilation pulmonary support. Current ECLS circuits are typically composed of a centrifugal pump with membrane oxygenator, oxygen blender, pump console, heat exchanger, and pump cart. The CardioHelp (Maquet Cardiopulmonary GmbH, Rastatt, Germany) is a compact, portable unit useful due to the relative ease of transport and initiation. Gray and colleagues[76] at the University of Michigan reported on the outcome of 2,000 patients supported with ECLS from 1973 through 2010. Of the 2,000 patients, 74% were weaned from ECLS and 64% survived to hospital discharge. In patients with respiratory failure, survival to hospital discharge was 84% in 799 neonates, 76% in 239 children, and 50% in 353 adults. Survival in patients with cardiac failure was 45% in 361 children and 38% in 119 adults. ECLS during extracorporeal cardiopulmonary resuscitation was performed in 129 patients, with 41% surviving to discharge.

Implantable Devices Intended for Durable MCS

Historical Perspective

The majority of patients receiving long-term MCS in the 1990s and early 2000s were supported by devices engineered with pulsatile, volume displacement designs. A critical limitation of these devices were the large pump size restricting mobility, and the requirement for extensive surgical dissection for implant leading to bleeding and infection complications, both of which contributed to the high incidence of device malfunction.[80] These first-generation devices, now obsolete in clinical practice in favor of smaller, continuous-centrifugal-flow MCS device designs.

Implantable, Axial, Continuous-Flow MCS Devices

Implantable, continuous-flow, rotary pumps with axial or centrifugal blood flow design represent a new generation of implantable VAD technology that have now completely replaced pulsatile devices for long-term MCS indications.[23,47–49,81,82]

HeartMate II

The HeartMate II LVAD (Abbot Laboratories, Chicago, IL)[23,47–49,81] (Fig. 83.12) is a continuous-flow rotary pump with axial design and mechanical bearing support of the internal impeller. The sealed inflow conduit of the pump is attached to the apex of the LV and the pump-sealed outflow graft is connected to the ascending aorta, creating a circuit parallel to the native circulation. The percutaneous driveline transmits commands and power from the external System Controller and power source to the LVAD itself. The HeartMate II was approved for BTT therapy in 2008 and for DT in 2010. In a prospective, multicenter, controlled study of HeartMate II as BTT the overall survival rate for the patients who continued on LVAD support was 82% (95% confidence interval [CI]: 77% to 87%) at 6 months, 73% (95% CI: 66% to 80%) at 1 year, and 72% (95% CI: 65% to 79%) at 18 months. The most common adverse effects were bleeding, stroke, infection, and neurocognitive dysfunction, while sepsis and stroke were the primary causes of mortality. The randomized, prospective, multicenter HeartMate II Pivotal Trial for DT followed patients implanted with HeartMate II or HeartMate XVE. The primary composite end-point was reached in more patients in the study group than in the control group (46% vs. 11%; hazard ratio, 0.38; 95% CI, 0.27 to 0.54; p <0.001).[23,47,81] The HeartMate II population experienced higher actuarial survival rates and lower rates of pump replacement for malfunction and thrombosis, infection, renal failure, RV failure, respiratory failure, and arrhythmias. Both groups experienced significant improvement in functional capacity and overall quality of life.[83]

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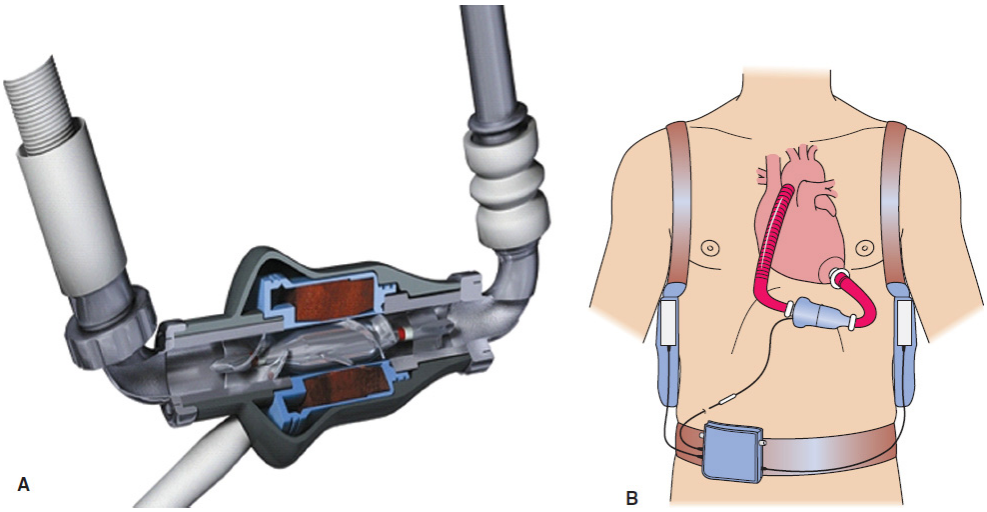

Figure 83.12 **A:** The HeartMate II LVAD (Thoratec Corporation, Pleasanton, CA) is an implantable, continuous-flow rotary left ventricular assist device with axial design intended for long-term mechanical circulatory support for bridge to transplantation or destination therapy. Schematic drawing showing internal rotor, stators, and bearings and external motor coils. (Drawing courtesy of Thoratec Corporation, Pleasantan, CA.) **B:** Schematic representation of the HeartMate II in the preperitoneal position with associated percutaneous lead, external controller, and power source (batteries).

Implantable, Centrifugal, Continuous-Flow MCS Devices

Although significant improvements in pump design have occurred with continuous-flow rotary pumps, the use of a mechanical bearing support for the internal impeller, typical of most axial designs, has potential limitations. The presence of motor-suspending contact bearings in the blood path represents a potential point of frictional wear that can result in device failure and subsequent need for device exchange.[82,84,85] Rotary pumps with axial design with bearing support still demonstrate the potential for thrombus formation on the device rotor and bearing interface due to the presence of stasis and incomplete "wash" of the bearings and formation of heat from frictional at the bearing surfaces.[86,87] The major feature of current designs are the impeller rotation and levitation with magnetic and/or hydrodynamic forces, which eliminate the need for bearings and the subsequent bearing

associated problems, enabling the potential for very long term durability[81,83,84,88,90] (Fig. 83.13).

HVAD

The HVAD (Medtronic, Minneapolis, Minnesota) is a small continuous-flow rotary pump with centrifugal and noncontact bearing design. The unique feature of the HVAD is its small design size[81,90,91] (Fig. 83.14). It has a flow capacity of up to 10 L/min, and is designed for intrapericardial placement. The HVAD is approved for use in the United States for BTT and DT indications. The ADVANCE trial was a prospective, evaluation of the HVAD for BTT indication in the United States.[90] The success primary outcome, was defined as survival on the originally implanted device, transplantation, or explantation for ventricular recovery at 180 days. Secondary outcomes included a comparison of survival between groups and functional and quality-of-life outcomes and adverse events in the investigational device group. Success occurred in 90.7% of investigational pump patients and 90.1% of controls, establishing the noninferiority of the investigational pump ($p < 0.001$; 15% noninferiority margin). Kaplan–Meier survival estimates at 30, 60, 180, and 360 days were 99%, 96%, 94%, and 86%, respectively, for the investigational device group and 97%, 95%, 90%, and 85%, respectively, for the INTERMACS control group. Bleeding, infections, and perioperative right-sided heart failure were the most frequent complications. Inotropic support for greater than 14 days was required by 16.4% of patients. Driveline exit site infections and sepsis occurred in 12.1% and 11.4% of recipients, respectively. The ENDURANCE Trial prospectively compared DT LVAD patients and found centrifugal-flow LVAD was noninferior to an axial-flow LVAD with respect to survival free from disabling stroke or device removal for malfunction or failure.[91] Subsequently, the ENDURANCE Supplemental Trial followed to evaluate the primary end-point of 12-month incidence of transient ischemic attack or stroke with residual deficit 24 weeks post-event. While enhanced blood pressure protocol significantly reduced mean arterial blood pressure, the primary endpoint was not achieved (14.7% with HVAD vs. 12.1% with control, noninferiority [margin 6%], $p = 0.14$).[48]

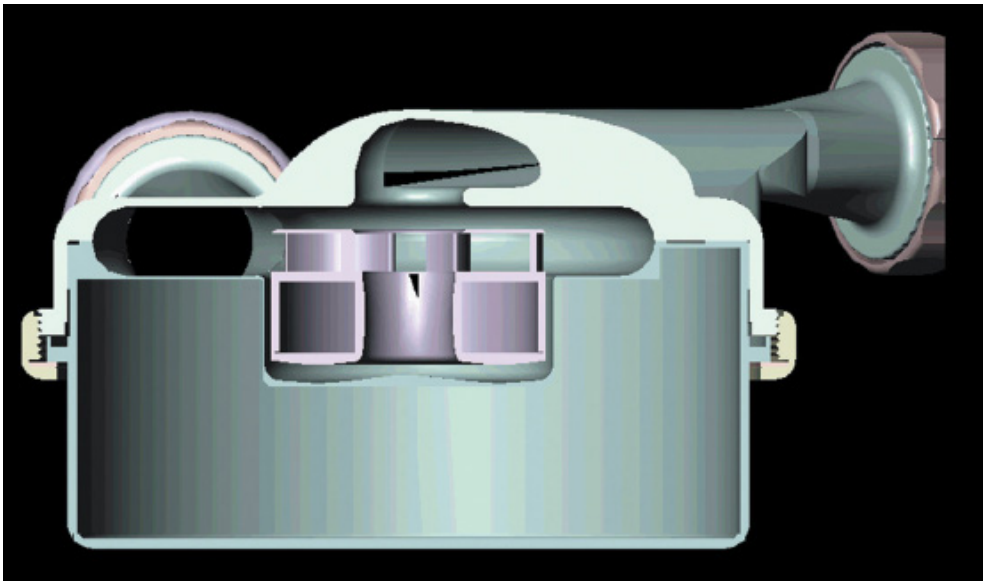

Figure 83.13 Schematic representation of a continuous-flow rotary pump utilizing magnetic coupling of the internal impeller for levitation and rotation that obviates the need for bearings in the blood flow path.

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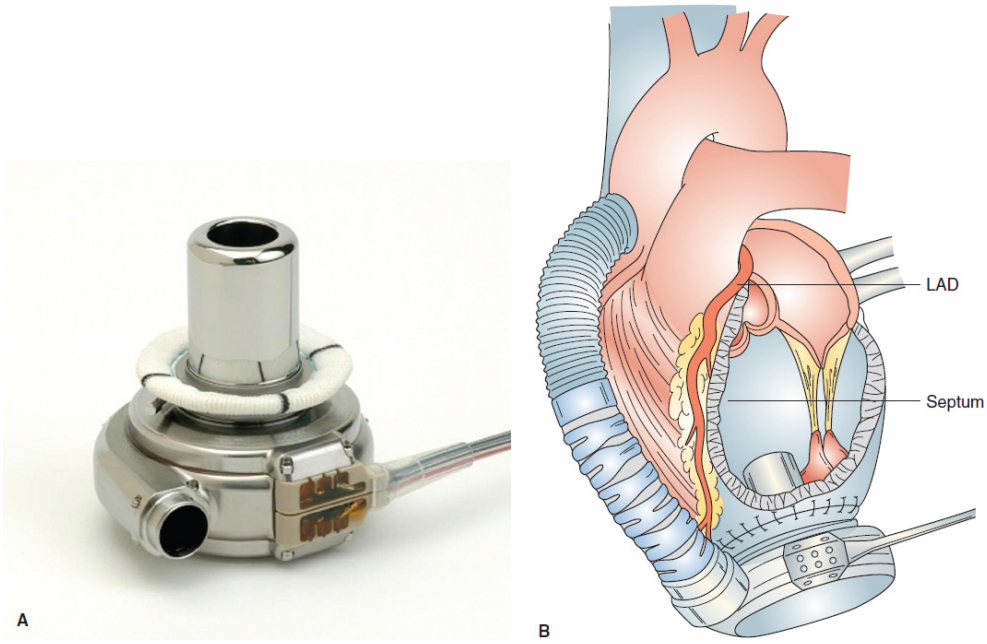

Figure 83.14 **A:** The HVAD LVAD (Medtronic, Minneapolis, MN) is an implantable, continuous-flow rotary pump with centrifugal design. The device incorporates passive magnetic and hydrodynamic forces for impeller levitation and rotation. **B:** Schematic representation of the HVAD with the inlet cannula inserted into the apex of the left ventricle. The outflow cannulae and graft are anastomosed to the ascending aorta. (Photograph courtesy of Medtronic, Minneapolis, MN.)

HeartMate III

The HeartMate III LVAD (Abbot Laboratories, Chicago, IL) is intrapericardial-positioned continuous-flow rotary pump with centrifugal design[88] (Fig. 83.15). The unique feature of the HeartMate III is the full magnetic levitation of the internal rotor. The design differs from currently used devices due to active control of rotation and levitation of the rotor that permits impellor movement further away from the outer housing creating larger gaps for blood flow within the device. The larger gaps may reduce blood component trauma and improve biocompatibility. MOMENTUM 3 was a prospective randomized trial comparing axial continuous-flow LVAD to centrifugal-continuous-flow LVAD. The final analysis of 1,028 patients, the primary end-point (alive and free of disabling stroke or reoperation to replace or remove a malfunctioning device at 2 years) was 64.8% in the axial-flow pump group as compared to 76.9% in the centrifugal-flow pump group, demonstrating superiority ($p < 0.001$). Furthermore, the numbers of events per patient-year for stroke of any severity, major bleeding, and gastrointestinal hemorrhage were lower in the centrifugal-flow pump group than in the axial-flow pump group.[49]

MVAD

The MVAD (Medtronic, Minneapolis, MN) is a novel continuous-axial-flow pump, approximately one-third the size of the HVAD (Fig. 83.16).[92] The contactless impeller suspension technology has a single moving part—the rotor, secured in place by a combination of passive-magnetic and hydrodynamic forces. Urban and colleagues highlighted the first-in-man implantation of a HeartWare MVAD and reported excellent results after more than 2 years of support. The European MVAD clinical trial for MVAD enrolled 11 patients beginning in July 2015, but was stopped in August 2016 due to controller issues. During that stoppage there were 4 pump thrombus events, but no patient has had a neurologic event. Currently, 5 patients have undergone successful transplantation, 3 remain on MVAD support at 27 to 28 months, 2 underwent exchange to an HVAD system, and 1 died. Since cessation of the clinical trial, improvements to the original MVAD system have been identified and will be reintroduced in the future.[93]

Total Artificial Heart

Syncardia Total Artificial Heart

The Syncardia TAH-t (SynCardia Systems Corporation, Tucson, AZ) is a pulsatile, volume displacement, TAH[94–98] (Fig. 83.17). The rigid polyurethane pump contains a flexible polyurethane diaphragm that separates blood and air chambers. Two mechanical valves located at the inflow and outflow orifices ensure unidirectional blood flow. Compressed air from the external drive console moves the diaphragm upward, pressurizing the blood chamber and causing ejection of blood. The pump has a maximum stroke volume of 70 mL and a maximum flow rate of 15 L/min, although the average flow rate is <8 L/min. Pump rate, duration of systole, and driving pressure can be adjusted to achieve optimal flow conditions. The TAH is surgically implanted in the mediastinal space after the ventricles have been excised, while the atrial cuffs are retained. The pneumatic drivelines are externalized percutaneously and attached to the drive console. Ambulation is facilitated by small portable drive systems and consoles. The Syncardia TAH-t is approved by the FDA for bridge to heart transplant indication. Copeland and colleagues reported a survival rate of 79% to heart transplantation compared with 46% for the observational arm, with one-year posttransplant survival rate was 86%.[95] The SynCardia TAH-t has now been implanted in more than 1,100 patients in approximately 100 centers in North America, Western Europe, Russia, Turkey, Israel, and Australia. To date, the longest duration of support has been 3.75 years, in a man who has since survived after transplantation. More than 47 patients have survived for longer than 1 year of support, and 72% of those underwent transplantation.[98]

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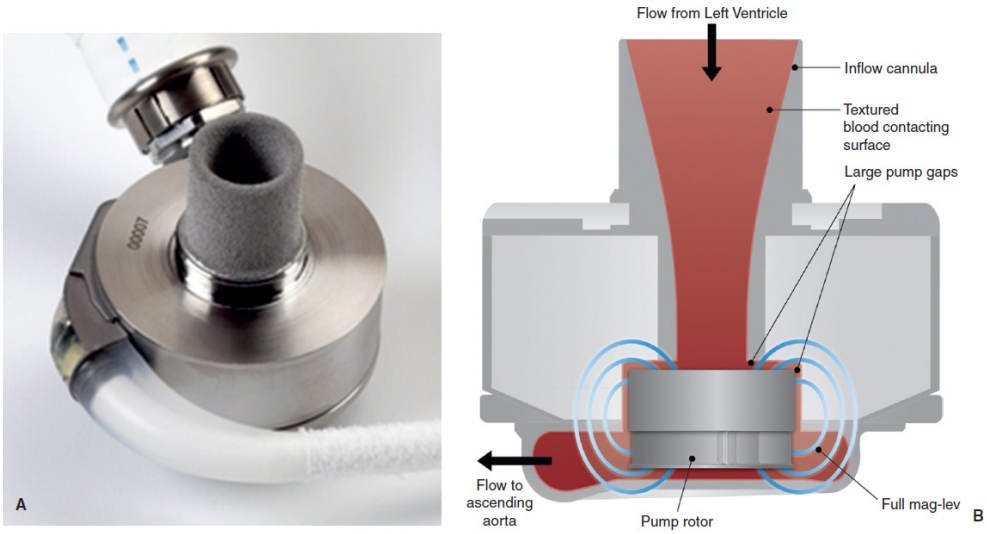

Figure 83.15 **A:** The Thoratec HeartMate III (Thoratec Corp., Pleasanton, CA) is an implantable, continuous-flow rotary pump with centrifugal design. The device incorporates complete magnetic levitation for both impeller levitation and rotation. **B:** Schematic representation of the HeartMate III showing the blood path, internal rotor, and magnetic fields that achieve levitation and rotation of the internal rotor. (From Schmitto JD, Hanke JS, Rojas SV, et al. First implantation in man of a new magnetically levitated left ventricular assist device (HeartMate III). *J Heart Lung Transplant* 2015;34:858–860.)

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Figure 83.16 **A:** The HeartWare MVAD (HeartWare Inc., Miami, FL) is an implantable, continuous-flow rotary pump with axial design. The device incorporates hydrodynamic levitation (fluid forces) for radial stability and magnetic levitation for axial stability. **B:** Schematic representation of the MVAD demonstrating the blood path and internal rotor. (Photo courtesy of HeartWare, Inc., Miami, FL.)

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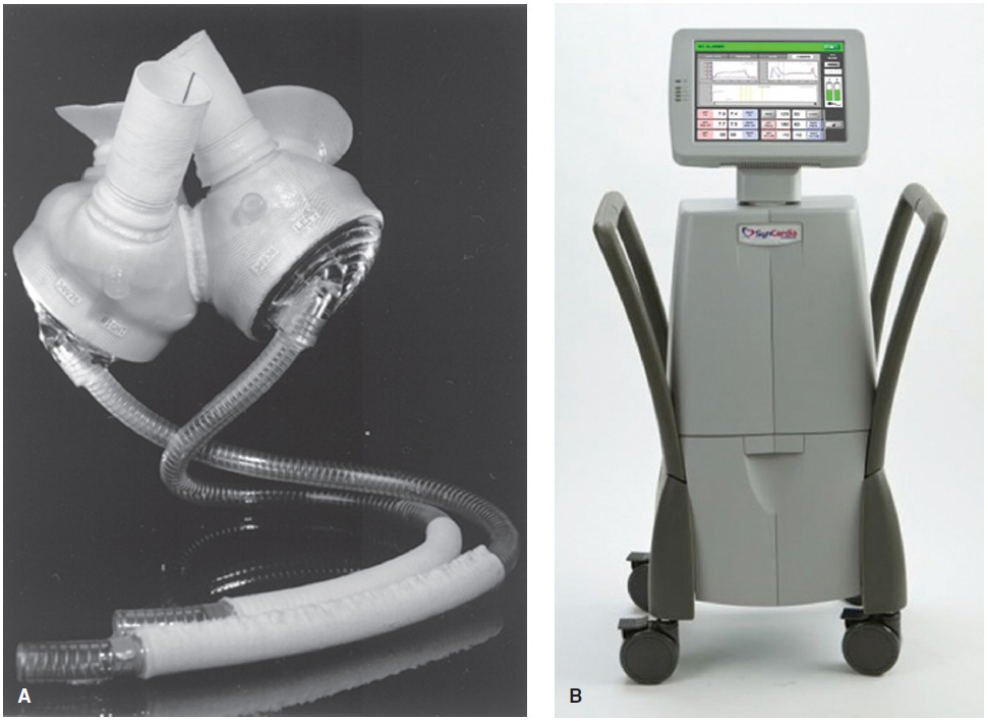

Figure 83.17 **A:** The CardioWest total artificial heart (Syncardia Systems Corporation, Tucson, AZ) is a pneumatically driven, pulsatile, volume displacement device. **B:** The device is positioned orthotopically as a complete replacement of the native heart. The device is powered by drivelines that exit the anterior abdominal wall and connect to a pneumatic drive console. (Photos courtesy of Syncardia, Inc., Tucson, AZ.)

FUTURE DIRECTIONS

Recent rapid technologic advancements and successful clinical applications of MCS have made the future of this field optimistic, but uncertain. Areas of continued research include the use of wireless energy transfer to facilitate complete internalization of MCS devices, application of less invasive surgical techniques for device implantation, application of MCS devices for the pediatric population, partial support devices and device designs, and new materials to improve compatibility of the blood–device interface to reduce thromboembolic complications and need for anticoagulation. It is possible that long-term MCS will provide a viable alternative to heart transplantation and medical therapy for patients with advanced heart failure.

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84

Pericardium

Jules Lin

Key Points

1. Prompt recognition and treatment of cardiac tamponade can be lifesaving.
2. The echocardiogram is the most useful noninvasive test in evaluating pericardial disease.
3. The electrocardiogram is important in the diagnosis of acute pericarditis and classically shows diffuse ST elevations.
4. The hemodynamic significance of a pericardial effusion depends on the volume and the rate of accumulation.
5. Postoperative tamponade should always be in the differential diagnosis with low cardiac output after cardiac surgery.
6. Distinguishing constrictive pericarditis from restrictive cardiomyopathy can be difficult but is important since the treatment is significantly different.
7. Metastatic disease is the most common cause of pericardial effusion.
8. Reconstruction of the pericardium should be considered to reduce adhesions in cases where a future redo sternotomy is likely and is important when there is a risk of cardiac herniation after an intrapericardial pneumonectomy.

INTRODUCTION

The pericardium supports and protects the heart. The smooth pericardial surface and the small amount of normal pericardial fluid provide a frictionless chamber improving cardiac efficiency as well as serving as a barrier to infection. The pericardium can be susceptible to a variety of disease processes including inflammation, infection, malignancy, and trauma. Changes in compliance and the accumulation of 1 pericardial fluid can impair cardiac function, and the prompt recognition and treatment of cardiac tamponade can be lifesaving.

HISTORY

Hippocrates first described the pericardium in 460 BC. Three hundred years later, Galen described a pericardial effusion and the inflammatory changes associated with pericarditis. Lower first reported pericardial tamponade in humans in 1669. Lancisi and Morgagni described constrictive pericarditis, and Laennec wrote of the "bread-and-butter" appearance of acute pericarditis in 1819.[1] Kussmaul described the hemodynamic changes known as pulsus parodoxus, and Beck and Griswald performed experimental studies in the 1930s leading to a better understanding of the pathophysiology of pericardial effusion.[2,3] Karaeneff first described relieving the symptoms of tamponade using pericardiocentesis in 1840.[4] Rehn reported methods to resect the pericardium in 1913.[5]

EMBRYOLOGY AND ANATOMY

The pleuropericardial membranes fuse during the fifth week of gestation dividing the thoracic cavity into pleural and pericardial spaces and forming the fibrous pericardium.[6] The serous pericardium is a single layer of mesothelial cells that produce and reabsorb pericardial fluid. The serous and fibrous pericardium form the parietal pericardium which is normally 2 mm in thickness. The visceral pericardium covers the heart and the intrapericardial great vessels. The phrenic nerves are contained in the parietal pericardium, and there is a risk of diaphragmatic paralysis with any operation on the pericardium. The pericardial folds form the oblique sinus, a blind cul-de-sac behind the left atrium, and the transverse sinus between the aorta and pulmonary artery superiorly and the left and right atrium inferiorly (**Fig. 84.1**). Lymphatic drainage is to the bronchial and tracheal lymph nodes and the thoracic duct. The pericardium normally produces 15 to 50 mL of serous fluid with a protein level lower than plasma.[7]

NORMAL PHYSIOLOGY

Although there are no significant consequences of the congenital absence or surgical resection of the pericardium as long as the defect does not lead to cardiac herniation, the pericardium has some function in the normal patient. The pericardium anchors the heart and prevents torsion and acute distension.[8] The pericardium contributes to the diastolic coupling of the ventricles along the Starling curve. Mechanoreceptors in the pericardium may also regulate blood pressure and heart rate. The pericardium stretches up to 20% with small changes in pressure but becomes abruptly stiff and resistant with larger volumes. Compliance depends on the rate of fluid accumulation, and the hemodynamic response is also partially dependent on intravascular volume status.

The normal pericardial pressure is less than the atmospheric pressure and is the same as the intrapleural pressure. With inspiration, right-sided venous return and preload increases. Blood pools in the lungs and decreases left-sided venous return and aortic blood flow. The arterial pressure normally decreases less than 10 mm Hg with inspiration. The normal jugular waveforms are shown in **Figure 84.2**. The a wave is the normal atrial contraction. The c wave reflects the bulging of the atrioventricular valve into the atrium during isovolumic ventricular systole. The v wave represents passive atrial filling from the vena cava. The x descent occurs with systolic collapse during ventricular systole and atrial relaxation. The y descent reflects diastolic collapse with opening of the atrioventricular valve and passive ventricular filling. Inspiration decreases intrathoracic pressure and leads to a lower x descent compared to the y descent.

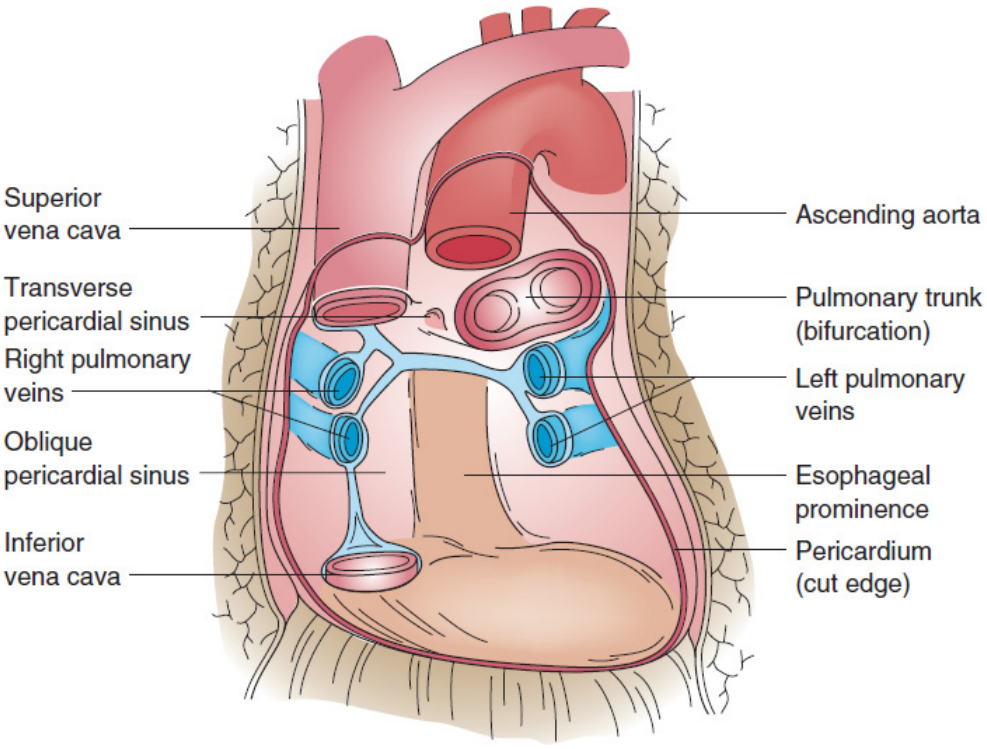


Figure 84.1 This drawing illustrates the pericardial attachments of the great vessels and pulmonary veins. The oblique sinus forms a blind cul-de-sac behind the left atrium, and the transverse sinus is a space between the aorta and pulmonary artery superiorly and the left and right atrium inferiorly.

DIAGNOSTIC STUDIES

While the electrocardiogram (EKG) is nonspecific, it can be helpful in suggesting the diagnosis. In acute pericarditis, the EKG classically shows diffuse ST elevations, and a low-voltage QRS is seen with a large pericardial effusion. The chest radiograph in a patient with a pericardial effusion shows an enlarged cardiac silhouette described as a water bottle. Pericardial calcification can be seen in chronic constrictive pericarditis secondary to tuberculosis.

2 The echocardiogram is the most useful noninvasive test in evaluating pericardial disease. The echocardiogram can identify an effusion, pericardial thickening, or masses. By using Doppler and assessing changes in chamber size, echocardiography is useful in assessing hemodynamics and can help differentiate tamponade, constriction, and restriction. It can also be used to help guide procedures like pericardiocentesis. Computed tomography (CT)

and magnetic resonance imaging (MRI) can identify pericardial masses and pericardial thickening or calcification.[9] Cardiac catheterization provides pressure tracings that help to distinguish cardiac tamponade, constriction, and restriction. Endomyocardial biopsy can also be useful in diagnosing restrictive cardiomyopathy.

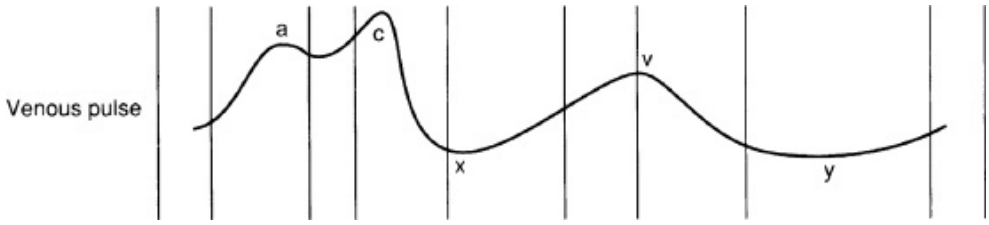


Figure 84.2 The jugular venous pulse waveform.

CONGENITAL ABNORMALITIES

Congenital absence of the pericardium is usually partial but can be complete. It is most common on the left side and is more frequent in males. Associated congenital cardiac defects include atrial septal defect, a bicuspid aortic valve, and pulmonary malformations. Defects on the right side can lead to cardiac herniation. Patients can present with chest pain, syncope, or death. The EKG can show a right bundle branch block. The pericardial defect can be appreciated on CT or MRI. The treatment of a partial defect is total pericardiectomy or patch closure with PTFE or bovine pericardium. Total pericardial absence is usually asymptomatic and is found incidentally.

Pericardial cysts are rare benign cysts that generally measure 1 to 15 cm in size. They are most commonly found at the right cardiophrenic angle and are asymptomatic. Patients may present with mediastinal compression and respiratory symptoms. The differential diagnosis includes a Morgagni hernia, lipoma, mediastinal tumor, or bronchogenic cyst. CT scans are used to confirm the location and relationship to surrounding structures. The cyst is excised if the patient is symptomatic, or the diagnosis is unclear.

ACUTE PERICARDITIS

Acute pericarditis is an inflammatory process that has involved the pericardium for less than 2 weeks (**Table 84.1**). Patients often present with a 3- to 7-day prodrome of low-grade fevers, malaise, and muscle aches. Acute pericarditis occurs in 5% of those who present to the emergency department with nonischemic chest pain[10] and in 1% of those with ST elevation.[11] It is important to distinguish pericarditis from the chest pain of an acute myocardial infarction. Acute pericarditis usually causes sharp, pleuritic pain that can last several days. The pain most commonly radiates to the trapezius ridge and is improved by leaning forward. Patients can present with shortness of breath, a nonproductive cough, and clear lung fields. The differential diagnosis also includes aortic dissection and pneumothorax. On physical examination, a friction rub may be heard and is sometimes intermittent. The classic friction rub has three components during systole, early diastolic filling, and atrial contraction.

3 The EKG is important in the diagnosis and classically shows diffuse ST elevations without Q waves or T-wave inversion. PR depression can also be seen. There is a four-stage progression in the changes seen on EKG with diffuse ST elevations followed by normalization of ST segments with flattening of T waves. The EKG then evolves with T-wave inversions prior to normalization of the EKG. Pericarditis and associated myocarditis can cause elevations in creatinine kinase and troponin I.[12] The minimal workup should include an EKG, complete blood count, cultures, chemistry profile, C-reactive protein, and antibody titers for collagen diseases.

ETIOLOGY

Table 84.1 Causes of Pericarditis
Idiopathic
Infectious
Neoplastic
Hemopericardium Blunt and penetrating trauma Postcardiac surgery Aortic dissection
Autoimmune and inflammatory Connective tissue disorders Postmyocardial infarction Medication induced
Miscellaneous Radiation induced Hypothyroidism Uremic

Idiopathic and Viral Pericarditis

Idiopathic causes of pericarditis are the second most common after neoplastic disease. The majority are likely viral although routine testing is not usually performed. A virus is only identified in 15% to 20% of cases with the most common being Coxsackievirus, echovirus, adenovirus, influenza, and cytomegalovirus. Patients present with chest pain, malaise, and fever, and often have an elevated erythrocyte sedimentation rate. The episode is self-limited in 70% to 90% of cases.[10] A systematic review of 30 studies showed that fever, a large effusion or tamponade, failure of nonsteroidal anti-inflammatory drugs (NSAIDs), and a subacute course were associated with a worse prognosis and the need for hospital admission.[13]

Initial treatment was traditionally NSAIDs with a 15% to 30% relapse rate.[10] However, a multicenter randomized trial showed that the addition of colchicine during initial treatment reduced the rate of persistent or recurrent pericarditis by approximately 50%.[14] Colchicine is now included as a class I recommendation in the European Society of Cardiology Guidelines for the diagnosis and management of pericardial diseases as first-line therapy for acute pericarditis combined with NSAIDs.[15] Recurrent pericarditis can be treated with a repeat course of NSAIDs, colchicine, or steroids, and specific causes such as autoimmune disorders should be investigated. There is also growing evidence including the randomized controlled Anakinra-Treatment of Recurrent Idiopathic Pericarditis, or AIRTRIP, trial supporting the use of IL-1 blockade in the treatment of recurrent pericarditis.[16] Pericardiectomy is recommended if the patient is unresponsive to medical treatment or constriction develops.

Acquired Immunodeficiency Syndrome

A pericardial effusion develops in up to 20% of patients with HIV and is usually a poor prognostic sign.[17] This may be partly due to a generalized capillary leak syndrome as well as increased cytokine expression seen in the more advanced stages of HIV. Other contributing factors include tubercular and mycobacterial infections, lymphoma, Kaposi's, or congestive heart failure. The majority are idiopathic and do not require further therapy if asymptomatic. Symptomatic effusions are drained.

Tuberculous Pericarditis

Tuberculous pericarditis occurs in 1% to 8% of patients.[18] In immunocompromised patients, infection by *Mycobacterium avium* or *Mycobacterium intracellulare* can lead to pericarditis. The incidence of tuberculous pericarditis has decreased although it continues to be a significant issue in immunocompromised patients, particularly HIV patients in Africa. Patients present with fever, night sweats, cough, dyspnea, and weight loss. While infection usually results from hematogenous spread, it can also extend directly from lymph nodes or through lymphatics. Pericardial changes occur in four stages including fibrinous, effusive, fibrous, and

constrictive fibrous stages. Making the diagnosis from pericardial fluid alone is rare. Pericardial biopsy with acid-fast staining provides the diagnosis 80% to 90% of the time. Treatment includes multidrug antitubercular therapy and pericardiocentesis. Steroids have not been shown to be beneficial for mortality or progression to constriction but leads to a faster resolution of symptoms and reaccumulation.[19] If patients present with late constriction, pericardiectomy may be required.

Purulent Pericarditis

Bacteria can be introduced into the pericardial space by direct injury, pneumonia, extension from head and neck infections, or hematogenous and lymphatic spread. Patients present with chest pain, fever, and leukocytosis. The most common organisms in adults are staphylococcus, pneumococcus, and streptococcus. Purulent pericarditis can evolve rapidly into tamponade and can be confused with septic shock. Fungal infections are less common, but immunocompromised patients and drug addicts are at greater risk. Pericardial fluid in purulent pericarditis has low glucose, high protein, and elevated LDH and neutrophils. An air–fluid level may be seen on chest radiograph with gas-producing organisms. Treatment includes antibiotics and drainage. Surgical drainage may be needed for thick fluid or refractory effusions. The prognosis for purulent pericarditis is poor with a survival of 30%.[10,20]

Uremic Pericarditis

Fifty percent of patients with untreated renal disease develop pericarditis. The incidence is decreased to approximately 20% in patients on hemodialysis. The exact cause is unknown but is not directly related to the BUN or creatinine. Other possible etiologies include hypercalcemia, viral infection, and autoimmune disease. Chest pain is usually less common, and the large effusions accumulate gradually. Treatment includes more intensive dialysis, NSAIDs, and steroids. The fluid is generally bloody and care should be taken in heparinizing these patients for dialysis. If patients develop tamponade or the effusion is unresponsive, pericardiocentesis or surgical drainage is performed.

Vasculitis, Connective Tissue Disease, and Drugs

Pericarditis can result from a variety of vasculitic and connective tissue diseases including rheumatoid arthritis, Wegener's granulomatosis, rheumatic fever, lupus, scleroderma, Reiter's syndrome, Behçet's disease, dermatomyositis, polyarteritis nodosa, dermatomyositis, sarcoidosis, and amyloidosis. Treatment includes management of the underlying disease process and NSAIDs. Pericardiocentesis is performed if necessary. Several medications can also lead to pericarditis including warfarin, hydralazine, isoniazid, procainamide, phenytoin, dantrolene, cromolyn, and methysergide.

Dressler and Postpericardiotomy Syndrome

Pericarditis can occur following acute myocardial infarction in 3% to 5% of patients.[21] Pericarditis can develop early in the first 1 to 3 days particularly with transmural infarction. Forty percent of large Q-wave infarctions cause pericardial inflammation although the incidence is decreasing with the use of thrombolytics and early revascularization. Patients are usually asymptomatic and are found to have a pericardial rub on examination although they can present with pleuritic chest pain. Treatment is usually with NSAIDs. Steroids can prevent conversion of infarcted myocardium to scar leading to greater thinning and risk of rupture.[22]

Patients can also present with pericarditis 1 week to a few months after a myocardial infarction with a friction rub, typical EKG changes, and chest pain although the incidence has decreased with increased revascularization. Pericardial inflammation is thought to be from an autoimmune reaction to myocardial cells. Similar symptoms can also occur after cardiac surgery, blunt trauma, and pacemaker placement. Patients can develop a pericardial effusion and even tamponade. Treatment includes NSAIDs and colchicine for 2 to 3 weeks and occasionally steroids. The syndrome is usually self-limited.

Radiation-Induced Pericarditis

Pericarditis can result from mediastinal and thoracic radiation for cancer including lymphoma and breast carcinoma, and is related to the dosage

delivered. With modern techniques, the incidence is 2% but can be as high as 20% if the entire pericardium is treated. Patients may develop chest pain and fever.[15] Symptoms are usually self-limited, and tamponade is rare. Delayed symptoms can develop years later and can result in pericardial constriction. Due to the history of malignancy, the etiology can be confused with a malignant effusion. If pericardial constriction develops, the treatment is pericardiectomy although the mortality is higher than for other etiologies.

PERICARDIAL EFFUSION AND TAMPONADE

Any of the etiologies mentioned above for pericarditis can also lead to a pericardial effusion. Other causes include blunt or penetrating trauma, retrograde bleeding from an aortic dissection, and a transudative effusion from congestive heart failure. Effusions due to a bacterial or fungal infection, HIV, or malignancy have a higher incidence of progressing to tamponade. Twenty percent of large symptomatic effusions of unknown cause are due to an undiagnosed cancer.[23]

Normally there is only a small reserve volume before pericardial fluid causes significant cardiac compression and prevents adequate 4 cardiac filling. The hemodynamic significance of a pericardial effusion depends on the volume and the rate of accumulation. The compensatory adrenergic response to a pericardial effusion leads to tachycardia and increased contractility, and patients on beta blockers are less likely to compensate. Tamponade usually occurs when filling pressures reach 15 to 20 mm Hg although tamponade can occur at lower pressures in conditions where blood volume is reduced including dialysis, with diuretic therapy, and bleeding. Cardiac pressures become elevated and are most closely equalized during inspiration. Tamponade generally affects right heart filling first which then leads to underfilling of the left heart.[24]

Patients may present with dyspnea, tachycardia, and diaphoresis. The three classic signs of Beck's triad are hypotension, jugular venous distension, and muffled heart sounds although each may be absent in patients with tamponade.[25] Symptoms can be confused with right heart failure and pulmonary embolus. The jugular waveform changes characteristically with loss of the y descent.[26] Since the total heart volume is fixed in tamponade,

blood only enters the heart when blood leaves. The y descent represents opening of the tricuspid valve and is lost since no blood is ejected from the heart. Pulsus paradoxus is also noted with a fall in the systolic blood pressure of greater than 10 mm Hg with inspiration. Pulsus paradoxus is absent in left ventricular dysfunction, atrial septal defect, positive-pressure ventilation, aortic insufficiency, and regional tamponade. The EKG shows variation in the morphology of every other QRS complex, or electrical alternans, due to swinging of the heart in the pericardial effusion (**Fig. 84.3**). Chest radiograph shows an enlarged, rounded cardiac silhouette, and the pericardial fat pad sign is seen when the pericardial fat is separated from the heart by the effusion.

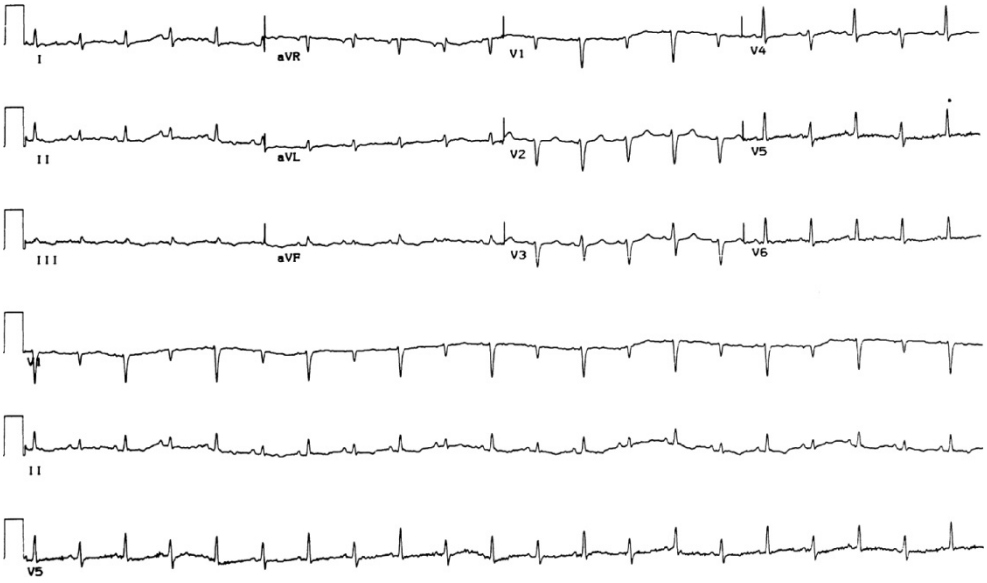


Figure 84.3 The 12-lead EKG shows electrical alternans with variation in the morphology of every other QRS complex in a patient with a large pericardial effusion. (From Joffe II, Jacobs LE, Kotler MN. Pericardial tamponade. *Circulation* 1996;94:2667, with permission.)

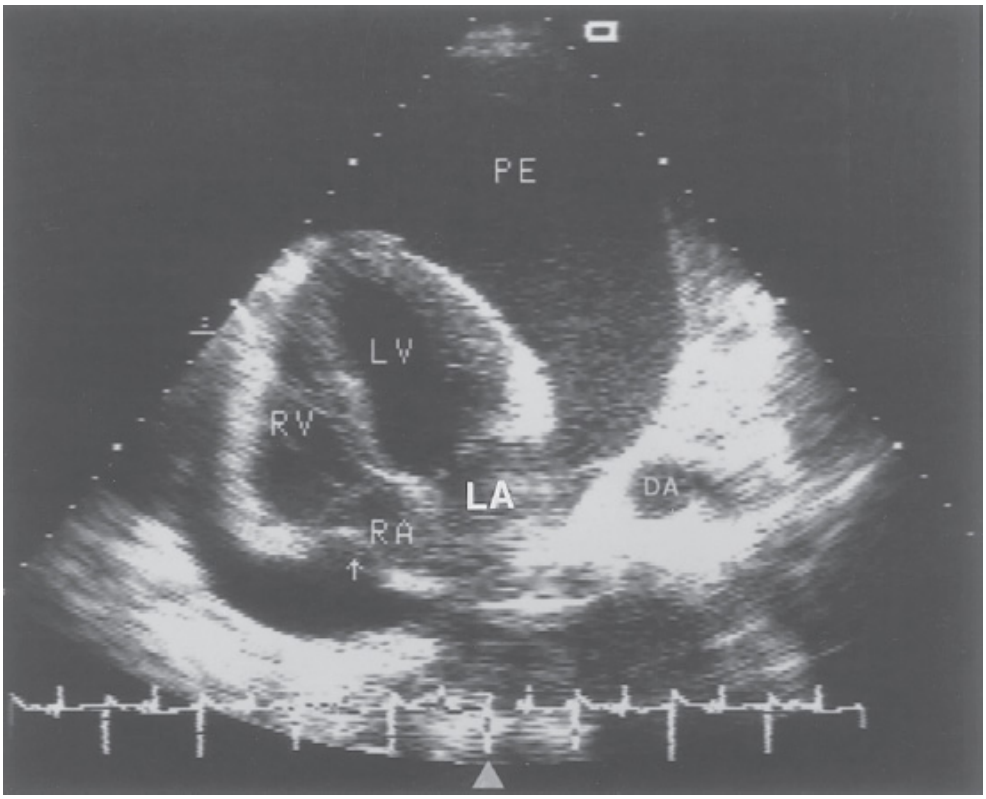


Figure 84.4 The echocardiogram shows a large pericardial effusion with diastolic right atrial collapse (*arrow*). (From Joffe II, Jacobs LE, Kotler MN. Pericardial tamponade. *Circulation* 1996;94:2667, with permission.)

Echocardiography is the most useful test in diagnosing pericardial effusion and tamponade. Signs of tamponade include early diastolic right ventricular and right atrial collapse (**Fig. 84.4**) and distension of the cava that does not diminish with inspiration. Doppler is useful in evaluating blood flow and shows exaggerated respiratory variation with an increase with inspiration on the right and decrease on the left side of the heart. Echocardiography is also useful in identifying localized atrial compression which can lead to tamponade with the other changes described above.

If there are significant hemodynamic changes, emergent pericardiocentesis should be performed. Intravenous fluid and inotropes can temporize the hypotension but should not delay pericardiocentesis. If the effusion is loculated or contains blood clots, open drainage may be necessary. There should be a higher suspicion for tamponade in situations involving bleeding, bacterial or tuberculous pericarditis, or an acute or increasing moderate-to-

large effusion. The approach to a patient with a large pericardial effusion is outlined in **Algorithm 84.1**.

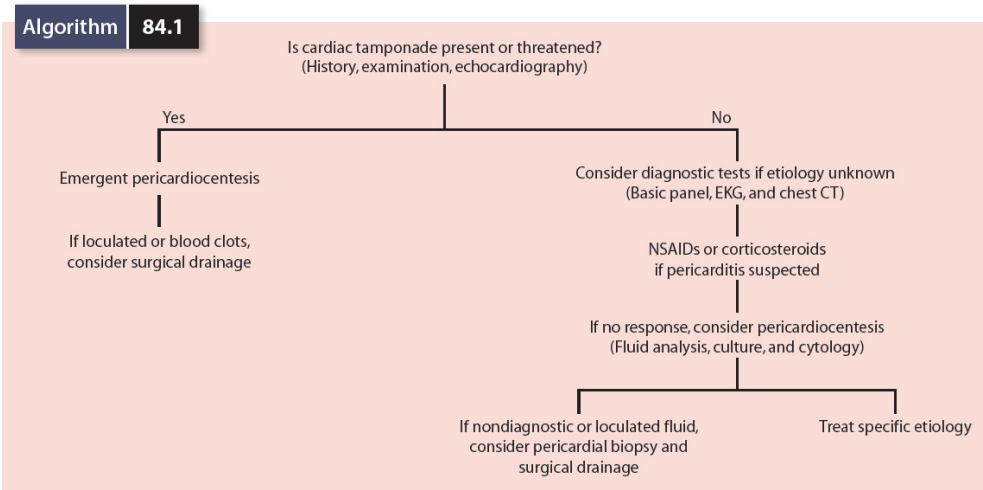
Postoperative Cardiac Tamponade

5 Postoperative tamponade should always be in the differential diagnosis with low cardiac output after cardiac surgery. Patients may have rising filling pressures, hypotension, and decreased urine and cardiac output. Mediastinal chest tube output may increase or abruptly stop. Hypovolemia during the postoperative period can limit the increase in filling pressures. Pulsus paradoxus may also be masked by positive-pressure ventilation. On chest radiograph, the cardiac silhouette is enlarged. In the postoperative cardiac patient, the epicardial pacing wires may move farther from the pericardium with increasing tamponade on chest films. Tamponade can result from relatively small amounts of blood with localized atrial compression from blood clots. There should be a low threshold for reexploration which also provides a definitive diagnosis. Patients can also present with delayed tamponade after being started on anticoagulants.

PERICARDIAL CONSTRICTION

Constriction develops when the heart becomes constrained by a fibrotic pericardium. The process can progress over years, and the most common causes in the developed world are radiation treatment, postsurgical changes, and idiopathic. Tuberculosis was the most common cause before antitubercular drug therapy. Other causes include amyloidosis, scleroderma, sarcoidosis, hemochromatosis, and malignant disease. Patients develop signs and symptoms of right heart failure due to obstruction of the right ventricular outflow tract including hepatomegaly, ascites, and peripheral edema. Patients can also have dyspnea, pleural effusions, fatigue, and weight loss. On physical examination, a pericardial knock, or a loud third heart sound, can be heard which corresponds to the abrupt cessation of diastolic filling. Kussmaul's sign is increased jugular venous distension with inspiration. Atrial fibrillation or flutter is present in up to 25% of patients, and tricuspid regurgitation is also common.

Pericardial calcification is pathognomonic but is only seen in 40% of cases. Thickened pericardium can be seen on CT or MRI (**Fig. 84.5**) although the pericardium was normal in thickness in 18% of patients in one series.[27] The normal pericardial thickness is 2 mm on CT and 4 mm on MRI. Echocardiography shows a thickened pericardium and a septal bounce due to the abrupt displacement of the septum during early diastole. The ventricles are small with good function. Ventricular filling halts abruptly in diastole due to the limits of the stiff, fibrotic pericardium. There are signs of systemic venous congestion with a distended inferior vena cava. In contrast to tamponade, there is no decrease in early diastolic filling but a sudden decrease in late diastole (**Table 84.2**).[26] When the myocardium is involved by fibrosis, ventricular dysfunction is present which is associated with a poorer response to pericardiectomy.



Algorithm 84.1 The algorithm outlines the initial approach to a patient with a large pericardial effusion.

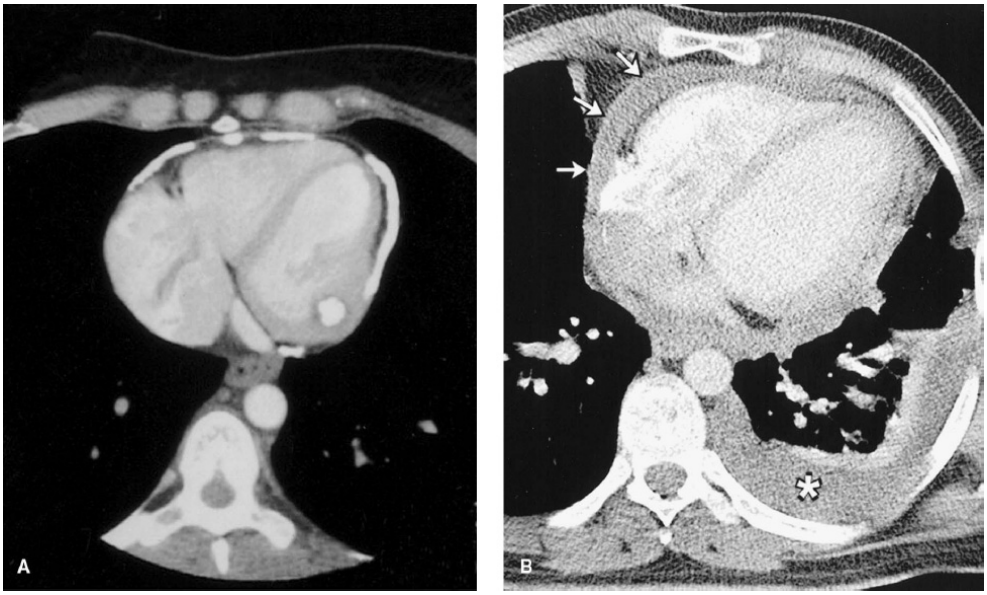


Figure 84.5 **A:** Chest CT shows extensive pericardial calcification. (From Cavendish JJ, Linz PE. Constrictive pericarditis from a severely calcified pericardium. Circulation 2005;112(11):e137–e139, with permission.) **B:** Chest CT shows thickening of the pericardium in a patient with constrictive pericarditis. (From Tom CW, Oh JK. Images in cardiovascular medicine. A case of transient constrictive pericarditis. *Circulation* 2005;111:e364, with permission.)

On right heart catheterization, the y descent is deeper and more rapid than normal. The right atrial waveform is M or W shaped. The right ventricular tracing is described as the square root sign with an early diastolic decrease with a rapid increase and plateau (**Fig. 84.6**). Pulmonary artery and right ventricular pressures can be moderately elevated, but more severe pulmonary hypertension suggests a different disease process. In addition, hypovolemia can mask these findings, and patients may need to be volume-challenged to see the diagnostic changes.[28]

6 Distinguishing constrictive pericarditis from restrictive cardiomyopathy can be difficult but is important since the treatment is significantly different (**Table 84.3**). In restrictive cardiomyopathy, there is no pericardial thickening. Decreased systolic function, mitral regurgitation, and left heart pressures greater than right are more common in restrictive cardiomyopathy. Early diastolic filling is slower. In addition, left and right ventricular pressures move in the same direction on inspiration rather than opposite directions.[29]

Constrictive pericarditis is generally progressive although it can be transient after cardiac surgery and should be observed for several months. Diuretics with fluid and salt restriction may help initially. Pericardial enhancement on cardiac MRI may be able to identify early forms of reversible constrictive pericarditis, and a trial of anti-inflammatory medical therapy may be beneficial.[30] However, pericardiectomy is the definitive treatment when symptoms progress. Tachycardia is a compensatory response, and beta and calcium channel blockers should be avoided.

NEOPLASTIC PERICARDIAL DISEASE

Primary tumors of the pericardium are rare and include benign fibromas, hemangiomas, lipomas, lymphangiomas, leiomyomas, and neurofibromas. Malignant pleural tumors include mesothelioma, teratoma, and fibrosarcoma. Surgical resection is therapeutic and diagnostic.

Table 84.2 Distinguishing Cardiac Tamponade and Constrictive Pericarditis

	Tamponade	Constriction
Pulsus paradoxus	Usually present	Present in one-third of cases
Jugular venous waveform	Absent y descent	Prominent y descent (M or W)
Inspiratory changes in venous pressure	Decrease	Increase (Kussmaul's sign)
Equal right and left pressures	Present	Present
"Square root" sign ventricular pressure	Absent	Present

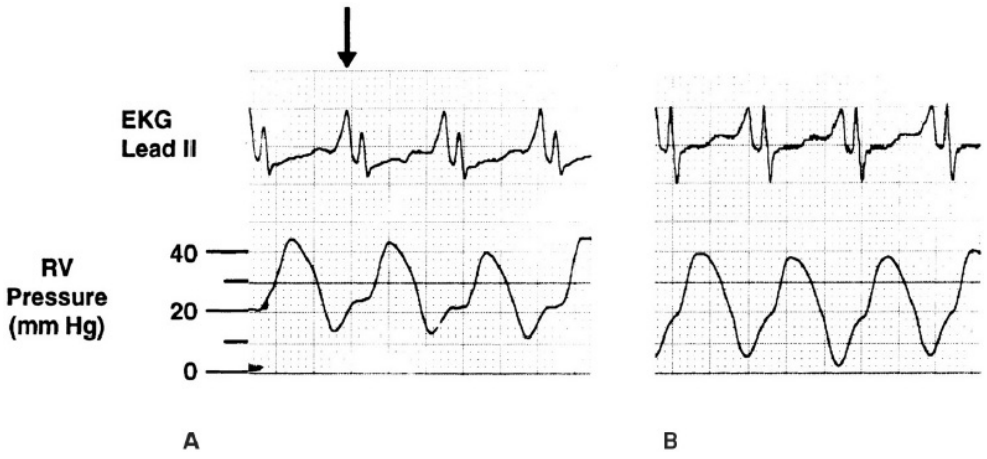


Figure 84.6 Pericardial constriction. **A:** The right ventricular (RV) pressure tracing shows elevated RV diastolic pressure with the dip-and-plateau waveform known as the "square root sign." The EKG tracing shows a large P wave indicative of atrial enlargement. **B:** The postoperative RV tracing shows normalization of the RV waveform. (From Correa SD, Amsterdam EA. Constrictive pericarditis. *Circulation* 1998;97:806, with permission.)

Malignancies can also extend directly from the mediastinum, esophagus [7], and lung. Metastatic disease is the most common cause of pericardial effusion. Cardiac involvement is found in 5% to 10% of patients dying of cancer with 85% of those having pericardial involvement. The most common cancers are lung and breast carcinoma, lymphoma, melanoma, and leukemia. Patients often present with tamponade. The diagnosis is made on echocardiography or CT. Cytology of pericardial fluid is negative in 20% to 50% of cases, and pericardial biopsy may be helpful. Palliation includes sclerosing agents such as tetracycline, radiotherapy, intrapericardial chemotherapy, catheter drainage, and pericardial window.

Table 84.3 Distinguishing Constrictive Pericarditis from Restrictive Cardiomyopathy

	Restriction	Constriction
Pericardial knock	Absent	Present
Pulsus paradoxus	Absent	Present in one-third of cases
Thickened pericardium	Absent	Present
Atrial enlargement	Severe biatrial	Possibly left atrial
Septal bounce	Absent	Present
Equal right and left pressures	Left 3–5 mm Hg > Right	Present
Filling pressures >25 mm Hg	Present	Uncommon
Pulmonary artery SBP >60 mm Hg	Present	Absent
"Square root" sign ventricular pressure	Variable	Present
Prominent y descent	Variable	Present

SBP, systolic blood pressure.

PERICARDIOCENTESIS

Pericardiocentesis can be diagnostic and therapeutic. Ideally, it should be performed in the catheterization laboratory so the hemodynamic response can be monitored. Normal pericardial fluid is an ultrafiltrate with an LDH 2.4

times serum and protein 0.6 times.[31] Uremic fluid is bloody. Rheumatic effusions are high in protein and leukocytes and low in glucose. Cholesterol crystals are seen with myxedema, tuberculosis, and rheumatoid arthritis.

Generally, a 16- to 22-gauge needle is inserted to the left of the xiphoid. The needle is angled at a 45-degree angle toward the left shoulder (**Fig. 84.7**). An EKG lead may also be attached to the needle to monitor for an injury current although echocardiography is more commonly used for guidance. There is a 97% success rate with a complication rate of 4.7% (**Table 84.4**).[32] If the effusion is anterior, a parasternal approach is used 1 to 2 cm to the left of the sternum in the fourth or fifth intercostal space. The removal of even a small amount of fluid can lead to significant hemodynamic improvement. For longer-term drainage, a catheter can be placed over a guidewire. Pericardiocentesis may not be effective for purulent or bloody effusions that may require open drainage.

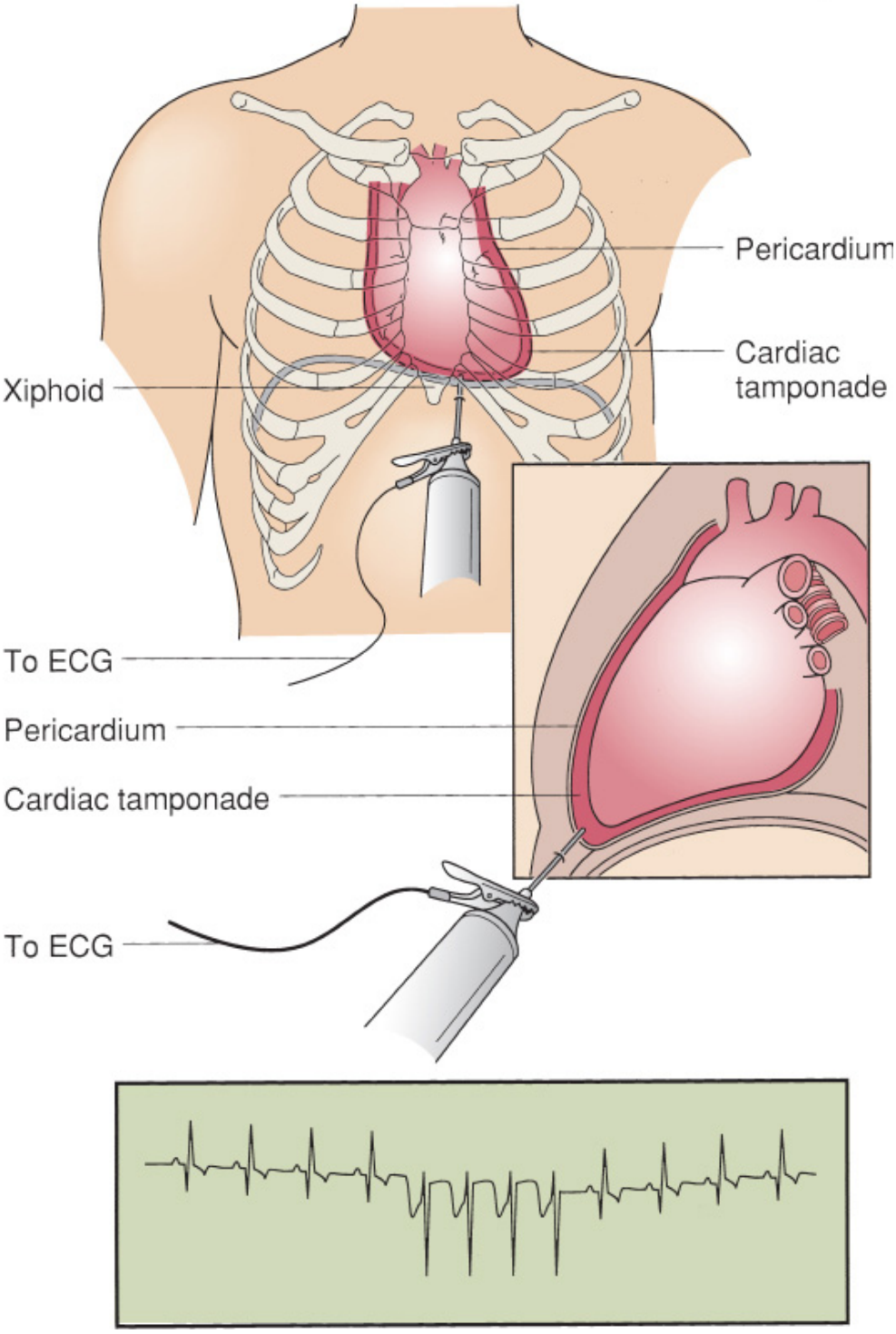


Figure 84.7 Pericardiocentesis is performed by inserting a needle to the left of the xiphoid and toward the left shoulder at a 45-degree angle. An EKG lead may be attached to the needle to monitor for Q waves indicating contact with the epicardium.

COMPLICATIONS

Table 84.4 Potential Complications from Pericardiocentesis
Injury to surrounding organs Liver laceration Lung (pneumothorax) Coronary arteries Myocardium
Arrhythmias
Pulmonary edema from acute left ventricular failure
Recurrence

PERICARDIAL BIOPSY AND SURGICAL DRAINAGE

Pericardial biopsy is useful when pericardiocentesis is nondiagnostic, which is not uncommon in neoplastic and tubercular effusions. This can be approached through a subxiphoid incision, anterior thoracotomy, or thoracoscopically (**Fig. 84.8**). Open drainage may be useful if the fluid is viscous, including bloody or purulent effusions, or in patients who have recurrent effusions. Loculated effusions may also require open drainage. The subxiphoid approach is better for purulent effusions to prevent contamination of the pleural space. Chronic or malignant effusions can be drained through a pericardial window into the left pleura. Preinduction pericardiocentesis or intravenous fluids may be necessary for patients to tolerate general anesthesia.

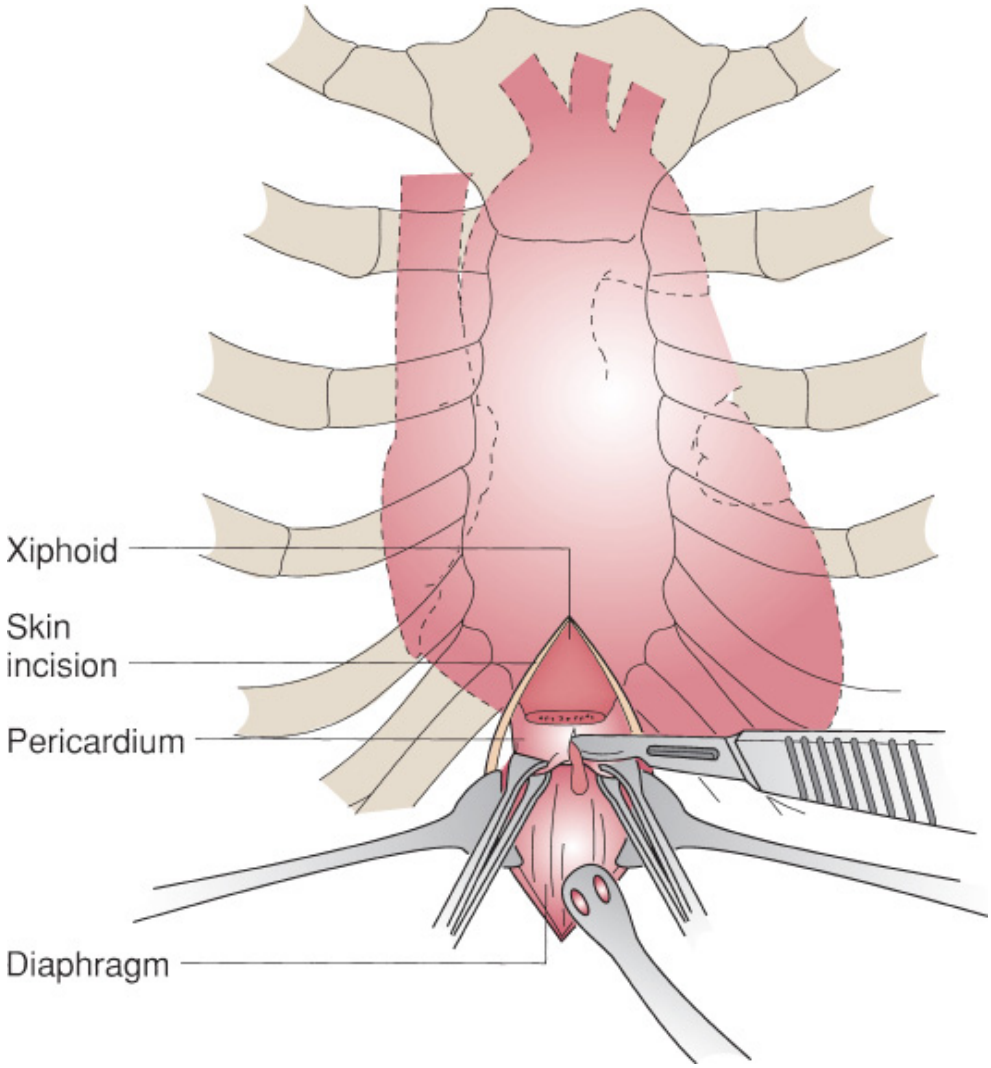


Figure 84.8 Open pericardial biopsy or drainage is performed through an upper midline incision. The xiphoid is retracted or removed providing exposure to the pericardium.

RECONSTRUCTION OF THE PERICARDIUM

Generally, the pericardium does not need to be reconstructed after routine opening of the pericardium during cardiac surgery or when resecting portions of the pericardium for adjacent tumors such as a thymoma. Primary pericardial closure is often avoided due to concerns for hemodynamic compromise and perioperative tamponade. Dantas et al. found a temporary, but clinically insignificant, decrease in hemodynamics in a study of 48 patients with primary closure of the pericardium after open heart surgery.[33]

Reconstruction 8 of the pericardium should be considered in cases where a future redo sternotomy is likely such as a bioprosthetic valve that will need to be replaced or a left ventricular assist device that will be removed at the time of transplant. To prevent hemodynamic compromise, the closure should be performed without tension. A biologic mesh implant made of porcine extracellular matrix has been used to prevent adhesions and protect the right ventricle, aorta, and coronary bypass grafts. Reconstruction of the pericardium was also reported in a retrospective study of 222 patients to decrease the incidence of atrial fibrillation.[34] The results of a randomized trial evaluating new-onset postoperative atrial fibrillation after pericardial reconstruction using extracellular matrix (NCT01247974) have not been published, but the rate of serious adverse events listed on clinicaltrials.gov was higher in the extracellular matrix group (36.54% vs. 24.55%), and the rate of atrial fibrillation was similar (5.77% vs. 5.00%).

Reconstruction of the pericardium is important when there is a risk of cardiac herniation. When resection of the pericardium is required during pneumonectomy due to a central lung tumor or an extrapleural pneumonectomy for mesothelioma, the pericardium should be reconstructed to prevent herniation into the empty hemithorax.[35] Cardiac herniation must be quickly recognized if the patient becomes hypotensive postoperatively. The pericardial defect is reconstructed with a 0.1-mm Gore-Tex mesh. The mesh should be fenestrated with small incisions to allow fluid to escape decreasing the risk of tamponade. Reconstruction of the pericardium may also help to prevent inflammatory epicarditis which can lead to constrictive physiology after extrapleural pneumonectomy.[36]

PERICARDIECTOMY

Pericardiectomy is most commonly performed for constrictive pericarditis. It can be performed through a median sternotomy or a left anterior thoracotomy in the fifth intercostal space. Anterior thoracotomy allows removal of the pericardium over the left ventricle with minimal manipulation. Median sternotomy is the most common approach (**Fig. 84.9**). Cardiopulmonary bypass increases the risk of bleeding and is used when significant cardiac manipulation is needed or the dissection is difficult. Femoral cannulation is

used if bypass is necessary. The pericardium over the left ventricle is resected first to avoid pulmonary edema from the right ventricle ejecting against a constricted left ventricle. The pericardium is removed from phrenic nerve to phrenic nerve. Some patients have an immediate improvement in hemodynamics and symptoms while others do not improve until weeks or months later. A delayed or partial response is thought to be due to incomplete resection of the visceral pericardium or myocardial atrophy and fibrosis. Left ventricular function returns to normal in 40% of patients.

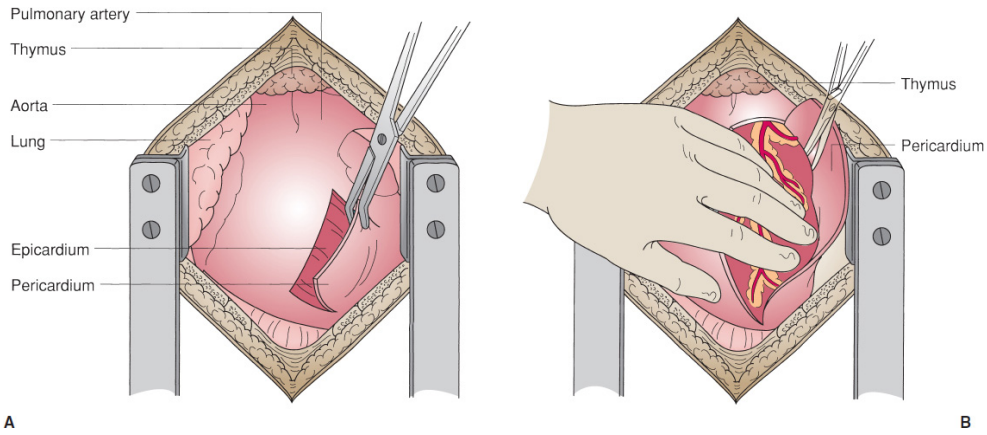


Figure 84.9 Pericardiectomy is most commonly approached through a median sternotomy. **A:** The pericardium is incised, and the fibrous pericardium dissected from the left ventricle. **B:** The heart is retracted to the right so that the pericardium can be resected from phrenic nerve to phrenic nerve.

Perioperative mortality has been reported between 5% and 15% and is due to low cardiac output, sepsis, bleeding, and renal or respiratory failure.[37] Seventy percent of mortality is due to low cardiac output. Mortality is directly related to the patient's preoperative status[38] and is 1% for New York Heart Association class I to II, 10% for class III, and 46% for class IV.[39] Five-year survival is 84%, and 99% of late survivors were class I or II. Patients with constriction due to radiotherapy have a higher mortality which may be due to radiation-induced myocardial injury. Other poor prognostic factors are renal failure, advanced age, pulmonary hypertension, hyponatremia, and reduced cardiac output.[37,40]

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85

Vascular Diagnostics: The Noninvasive Vascular Laboratory

Gregory L. Moneta

Key Points

1 Duplex ultrasound consists of a combination of grayscale imaging and pulse Doppler. Because the speed of sound is relatively constant in tissue, with a pulse Doppler it can be determined when an echo is generated and when it is received. This provides range resolution enabling the operator of the duplex machine to precisely sample and interrogate blood flow at a known location.

2 When a sound wave encounters moving reflectors, such as red blood cells, the frequency of the reflected wave changes from that of the original wave generated by the transducer. This relationship is reflected in the Doppler equation: $f_r - f_o = [(2f_o v)/c] \cos \theta$, where f_r is the received frequency, f_o is the originating frequency, v is the velocity of the reflector, c is the speed of sound in tissue, and θ is the angle of the incident sound beam with the moving reflectors, the so-called Doppler angle.

3 Arterial Doppler waveforms reflect the resistance of the circulation supplied by the artery being examined. Low-resistance circulations such as cerebral and renal circulations have relatively high amounts of diastolic flow whereas high-resistance circulations, such as extremity arteries have little flow at the end of diastole.

4 Carotid stenosis is determined primarily from measurement of peak systolic velocity (PSV) and end-diastolic velocity (EDV) from pulse Doppler waveforms using criteria agreed upon in a national consensus conference.

5 Air plethysmography (APG) can be used to display pulse volume waveforms. Pulse volume recordings (PVRs) are obtained with partially inflated blood pressure cuffs that detect volume changes sequentially down a limb. Volume changes beneath the cuffs resulting from the pulse wave result in small pressure changes within the cuffs. These changes are displayed as arterial waveforms with the use of appropriate transducers and provide an overall measure of the arterial circulation in an extremity.

6 The ankle brachial index (ABI) is determined by dividing the higher ipsilateral dorsal pedal or posterior tibial artery pressure by the higher of the two brachial artery systolic pressures and is highly sensitive and specific for documenting the presence or absence of lower extremity arterial occlusive disease.

7 Measurement of ankle pressures after exercise can be used to confirm arterial disease as an etiology for exercise-associated leg pain. Failure of the ankle pressure to drop with exercise along with failure of the ABI to decrease 20% with exercise, combined with a normal resting ABI, substantially rules out arterial insufficiency as an etiology of exercise-induced complaints of leg pain.

8 Duplex ultrasound can detect hemodynamically significant stenosis in abdominal arteries: a PSV in the superior mesenteric artery (SMA) of 275 cm/s or more indicates a ≥70% SMA stenosis, a celiac artery PSV of ≥200 cm/s indicates a ≥70% celiac artery stenosis whereas a ratio of the PSV in a renal artery to that in the aorta (renal–aortic ratio, RAR) of ≥3.5 indicates a ≥60% diameter-reducing renal artery stenosis.

9 The primary ultrasound diagnostic criterion for diagnosis of venous thrombosis is failure of the vein to collapse with application of pressure with the ultrasound probe.

10 In the upright position, venous reflux stimulated by cuff deflation that lasts >0.5 to 1 second is indicative of pathologic venous reflux.

INTRODUCTION

The noninvasive vascular laboratory provides accurate, safe, and objective evidence of the presence and physiologic significance of vascular disease throughout the body. Two broad categories of testing are available in the noninvasive vascular laboratory; those based on plethysmographic techniques, and those based on ultrasound-based techniques.

PLETHYSMOGRAPHY

Plethysmographic techniques detect volume changes in limbs that occur in response to arterial and venous disease. The technology can be modified to determine digital pressures and produce pulse waveforms. Examples of plethysmographic techniques include mercury strain gauge plethysmography, air plethysmography (APG) (pulse volume recordings [PVRs]), and photoplethysmography (PPG).

ULTRASOUND

Ultrasound techniques, in particular duplex ultrasound-based technique, have largely eclipsed plethysmographic techniques. Duplex ultrasound, introduced in 1974, was first applied to carotid arteries. The technique combines information from ultrasound-generated images (B-mode) and Doppler analysis of blood flow direction and velocity, hence the term "duplex." Duplex ultrasound is currently extensively employed for evaluation of carotid arteries, intra-abdominal arteries and veins, and upper and lower extremity arteries and veins. Since inception duplex ultrasound has advanced through: (1) improved B-mode imaging, (2) better low-frequency scan heads permitting deeper penetration of the ultrasound beam from the skin surface, (3) improvements in online computer-based microprocessor software, and (4) perhaps, most importantly, the addition of color flow to the B-mode image.

Color flow superimposes a real-time color image of blood flow onto a standard gray-scale B-mode picture. Returning echoes from stationary tissues generate the B-mode image, whereas those interacting with moving substances (blood) generate a significant enough phase shift that they can be processed separately and color coded by operator selection to give information on direction and velocity of blood flow according to the magnitude and direction of the Doppler frequency shift. It is color flow, combined with the ability of the current generation of duplex scanners to detect very low blood flow velocities (<5 cm/s), which makes duplex scanning practical on a routine basis throughout the body. Color flow permits

more rapid identification of vessels to be examined and is essential for duplex examination of some vessels such as tibial arteries and veins.

BASICS OF DUPLEX ULTRASOUND

An ultrasonic wave is produced in tissue by placing a vibrating source in contact with the tissue. In medical ultrasound the vibrating source is the ultrasound *transducer* contained within the ultrasound *scan head.* The scan head steers and focuses the sound beam arising from the transducer, functions crucial in deriving an ultrasound image from returning echoes.

Ultrasound transducers convert electrical energy into vibrational energy and, conversely, turn vibrational energy of returning echoes into electrical signals that can be analyzed by the software of the duplex machine. The design of the transducer determines the frequency of the vibrations which in turn determines the wavelength of the sound wave produced. The relationship between frequency and wavelength is expressed mathematically as follows:

$$\lambda = c/f \qquad (85.1)$$

where λ is the wavelength, c is the speed of sound in tissue and f is the incident frequency.

The speed of sound in soft tissues averages 1,540 m/s and varies only minimally from this average in soft tissues insonated in clinical applications of duplex ultrasound. The wavelength of the sound beam is the primary determinant of how well the ultrasound beam penetrates the tissue. Because the speed of sound within the tissue is, for all practical purposes, constant (1,540 m/s), the ability of ultrasound to penetrate tissue depends on the frequency of the vibrating source (transducer). As noted above, transducer frequency is determined by the design of the transducer and is thus controlled by the manufacturer of the duplex device. For examination of the carotid artery, transducer frequencies of 5 to 7.5 MHz provide optimal tissue penetration for clinical purposes.

As noted above the term duplex refers to the combination of Doppler and B-mode ("B" stands for "brightness") ultrasound in the same device. Both types of ultrasound require analysis of reflected echoes of the original sound beam initially created by placing the ultrasound transducer in contact with the

tissue. The B-mode component of the duplex machine analyzes the *strength* (intensity) and *origin* of the reflected echo. The Doppler component analyzes *shifts* in frequency of the original sound wave produced by the transducer that result when the ultrasonic wave encounters moving reflectors.

B-Mode Ultrasound

As a sound wave passes through tissue, its strength moving away from the transducer depends upon the degree to which the beam is attenuated, scattered, and reflected. The strength of the reflected echo depends in part, upon relative differences in acoustic impedance between two different media. Major differences in acoustic impedance result in reflection of a large proportion of the sound beam back to the transducer, whereas small differences result in comparatively little reflection and continued propagation of the beam through the tissue.

In B-mode ultrasound, the strength of the returning echo is reflected in the brightness of the individual pixels comprising the ultrasound image. This is the ultrasound *grayscale* and the resulting image is termed a *grayscale image*. (As we will in the chapter, the primary purpose of the grayscale image in duplex ultrasonography is to aid in properly positioning the Doppler sample volume.)

Very bright pixels represent sites of large differences in acoustic impedance between media, whereas less dramatic differences are represented by proportionally less bright pixels on the B-mode image. Thus gallstones, which differ dramatically in acoustic properties from soft tissue, result in strong echoes and proportionally brighter pixels on an ultrasound image, whereas blood, which differs little from soft tissue in acoustic characteristics, frequently cannot be distinguished from soft tissue in a grayscale image.

The strength of the reflected echo will also be dependent upon the strength of the sound beam at the point of its reflection. Grayscale images do not show the percentage of the beam reflected, but rather represent the absolute strength of the reflected echo arriving back at the transducer. Thus if the sound beam is very weak at the site of its reflection, even areas of significant differences in acoustic impedance will not result in a bright pixel on the ultrasound image.

The strength of the ultrasound beam at any point also depends on the degree to which the beam has been attenuated as it passes through the tissue. Attenuation of a sound wave as it traverses tissue weakens the wave and depends upon the tissue traversed and the frequency of the wave. The frequency of the wave depends upon the frequency of the transducer used to generate the wave (see discussion above and Equation 85.1). Sound waves resulting from higher-frequency transducers are attenuated more rapidly than those produced with lower-frequency transducers. Higher-frequency transducers therefore provide relatively weak echoes to be reflected from a deep structure and thus a comparatively poor B-mode image compared to a lower frequency transducer.

The linear resolution of an ultrasound image depends upon the ability to focus the beam. Sound beams emanating from high-frequency transducers can be more precisely focused than those from low-frequency transducers and thus provide clearer B-mode images of more superficial structures. Because the carotid artery is superficial, higher-frequency transducers can be used to provide much clearer B-mode images than is possible with deeper vessels such as the aorta, renal, or iliac arteries.

Doppler Ultrasound

In a continuous wave Doppler, a transducer continually emits vibrations into the tissue. Echoes are therefore continually reflected back to the transducer. A transducer cannot, however, simultaneously generate and receive an echo. Continuous wave Doppler therefore must have separate transmitters and receivers to both generate and receive echoes.

Duplex 1 devices utilize pulse Doppler. A pulse Doppler uses the same transducer to generate and receive echoes. Because the speed of sound is relatively constant in tissue, with a pulse Doppler it can be determined when an echo is generated and when it is received and therefore it is possible to calculate the depth in the tissue where a reflected echo originated. The *sample volume* of the duplex device is thus determined by specifying from what depth one wishes the pulse Doppler to receive reflected echoes.

The transducer is *gated,* based on the total time from original sound-wave generation to arrival of the reflected echo back at the transducer, to only receive echoes from the specified depth of the sample volume. The desired

"position" of the sample volume is determined by the operator of the duplex device from the B-mode image, and in duplex examination of arterial and venous flow corresponds to particular points within the lumen of the vessel examined. Because B-mode images and Doppler waveforms cannot be generated simultaneously, the technologist must continually update the B-mode image during the course of the examination to insure proper placement of the sample volume.

2 When a sound wave encounters moving reflectors, such as red blood cells, so-called Rayleigh scatters, within the lumen of an artery or vein, the frequency of the reflected wave changes from that of the original wave generated by the transducer. Velocity is a vector with both speed and direction therefore, the magnitude of the frequency shift depends upon the velocity of the moving reflectors and their angle with the incident sound beam. Because the frequency of the original sound wave is known, and the frequency of the received echo can be determined by the software of the duplex machine, the velocity of the moving reflectors (red blood cells) can be calculated provided the angle of the incident sound beam with the moving reflectors is also known. This relationship is reflected in the *Doppler equation:*

$$f_r - f_o = [2f_o v/c] \cos \theta \qquad (85.2)$$

where f_r is the received frequency, f_o is the originating frequency, v is the velocity of the reflector, c is the speed of sound in tissue, and θ is the angle of the incident sound beam with the moving reflectors, the so-called *Doppler angle.*

A Doppler angle of 0 degrees is ideal for velocity calculations as the cosine of 0 is 1 and measured reflected velocity changes are therefore 100% of what actually occurred. However 0-degree Doppler angles are difficult to obtain as it is not generally possible to look directly down the lumen of a vessel from a percutaneous approach. Therefore to solve the Doppler equation for the velocity of the moving reflectors, the Doppler angle must be known. To standardize the results of duplex scanning, it has been traditionally recommended that examinations be conducted as close as possible to a Doppler angle of 60 degrees. The cosine of 60 is 0.5, therefore at this angle the measured reflected velocity is half the actual reflected

velocity. Errors in velocity calculations secondary to misreading of the Doppler angle are small as a percentage of the true velocity at ≤60 degrees as cosine vary comparatively little with incremental changes in angle below 60 degrees. When the Doppler angle approaches 70 degrees, changes in the cosine of the angle become more pronounced with incremental increases in angle, and errors in velocity calculations secondary to improper angle measurement become much more significant. Small errors in determining the Doppler angle when the angle of insonation is <60 degrees have little overall impact on the calculation of the velocity of the moving red cells. Indeed, Doppler angles from 45 to 60 degrees are acceptable for most clinical studies. Most often an angle of 60 degrees can be easily obtained in carotid artery and extremity artery duplex examinations and, in line with traditional teaching, 60 degrees is chosen whenever possible as the Doppler angle in such studies. In examination of intra-abdominal vessels it may be much more difficult to adhere to a 60-degree angle.

As noted above, pulse Doppler both transmits and receives echoes with the same transducer. This dual function places limits on the frequencies that can be displayed in the spectral waveform. The maximum frequency that can be displayed is half the pulse-transmitting frequency or pulse-repetition frequency (PRF), and is known as the *Nyquist limit*. If frequencies are encountered that exceed the Nyquist limit, they are flipped and appear on the reverse-flow side of the spectrum. This is termed *aliasing*. If aliasing is encountered, the PRF should be increased to increase the Nyquist limit. The PRF can be adjusted by changing the scale displayed on the right side of the spectral waveform or by adjusting the baseline. If aliasing still occurs, the operator should consider switching to a lower frequency transducer or to the use of a continuous-wave Doppler. A continuous-wave Doppler is not affected by aliasing.

Color Flow

A color flow image is produced by assigning color to Doppler shifts. Returning echoes that are not Doppler shifted are shown in grayscale. The net result is what appears to be color pasted or superimposed on a grayscale image. This pasting process can in effect obscure the edges of the grayscale image resulting in obfuscation of the true lumen of the grayscale image

limiting somewhat the accuracy of color images to define stenosis. The hue and intensity of the color are determined by the direction and magnitude of the Doppler shifts. The technologist can adjust the color settings as desired. Varying shades of red and blue are generally used to distinguish flow toward or away from the transducer. By convention, red is most often assigned to arterial flow and blue to venous flow.

When the Doppler angle is 90 degrees, there is no Doppler shift. When this occurs, the assigned color is black and corresponds to the horizontal black bar serving as the baseline on the color scale that appears on the right side of a color flow image (Fig. 85.1). Aliasing can be readily recognized on a color flow image as a mosaic pattern or as a transition from red-to-blue or blue-to-red without an intervening black line. In areas of actual reverse flow, the blue and red colors are separated by a black border. Just as with pulsed Doppler, color aliasing can be reduced by increasing the PRF. This is often quite important, as an extensive mosaic pattern can obscure clear visualization of a stenotic site.

Power Doppler is a variant of color Doppler. Power Doppler, however, assigns no direction of flow to the color image and velocity information is not calculated. Any detected Doppler shift is colorized without consideration of the direction of the Doppler shift or the magnitude of the Doppler shift. It is therefore not subject to aliasing or affected by Doppler angle. Its principal utility lies in the ability to detect blood moving at very low velocity and in outlining the course of tortuous vessels. It can be quite useful in detecting flow in small distal veins and flow in arteries distal to a very high-grade stenosis.

It is tempting to try a direct estimate of the severity of a stenosis from the color flow image. However as discussed above such estimates are probably less accurate than measurements of stenosis derived from spectral analysis. Color serves primarily as a guide in locating the vessels and selecting specific sites for examination with the pulse Doppler. The absence of color can indicate extensive mural calcification and difficulty in obtaining a pulse Doppler waveform.

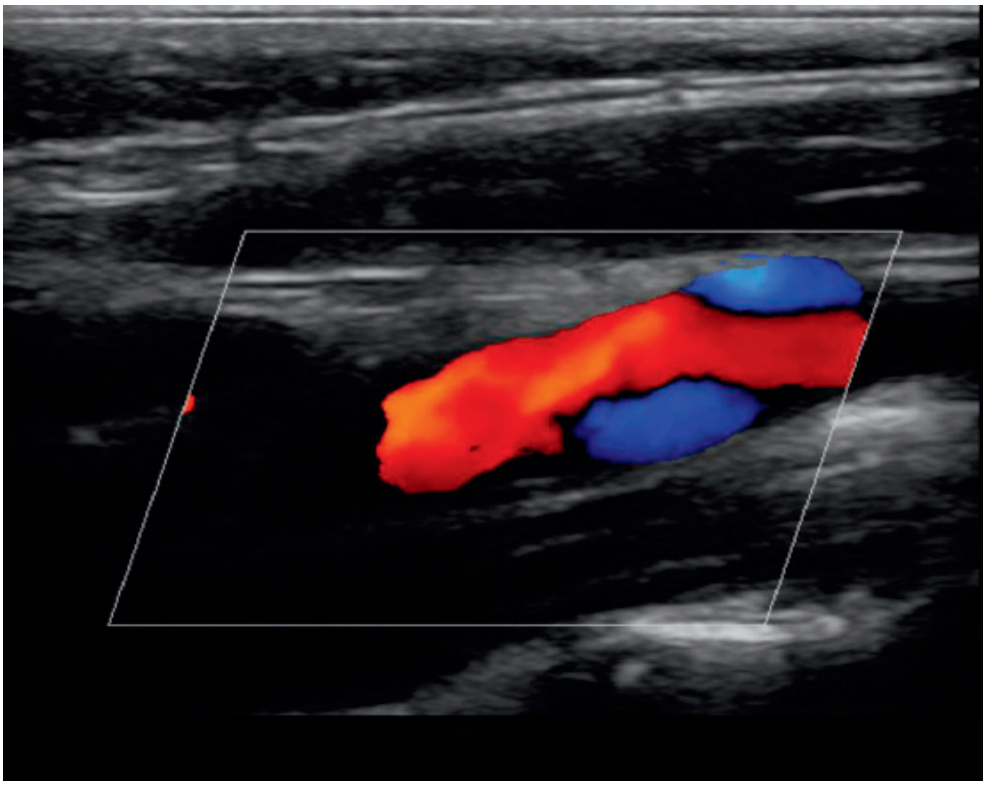

Figure 85.1 Flow separation with reverse flow along the wall of the carotid bulb as indicated by direct transition from *blue* to *red* with an intervening black line is a normal finding and indicates an artery without significant plaque.

Carotid and Vertebral Arteries

The vascular laboratory began with assessing internal carotid artery (ICA) stenosis. Doppler diagnosis of ICA stenosis, and arterial stenosis in general is based on duplex ultrasound and focuses on three areas, the prestenotic region, the stenosis itself, and the poststenotic region. Detecting carotid stenosis involves a combination of spectral analysis, color and grayscale imaging and, in selected cases, power Doppler. The primary interest is in the detection of increased flow velocities within the area of suspected stenosis and therefore in most cases spectral analysis dominates in the detection of carotid stenosis. The exception is in distinguishing ICA occlusion from a very high-grade stenosis where color flow or power Doppler flow can identify very low flow in the area of the stenosis or distal to the stenosis that may not be detected by pulse Doppler.

In all cases, the pulsed Doppler and color flow findings should be crosschecked for concordance. If there is disagreement between the

impression obtained with color and pulsed Doppler examinations (i.e., color Doppler suggests high-grade stenosis but velocities are only moderately elevated), the findings of both should be reviewed to resolve the discrepancy.

Common Carotid Artery Waveforms

In the majority of cases, carotid stenosis or occlusion occurs in the proximal ICA at or just beyond the carotid bifurcation. A normal ICA waveform reflects the low resistance of the cerebral circulation with high flow at the end of the diastolic component of the waveform. In the presence of a distal ICA occlusion resistance to flow increases and there is decreased flow in diastole (Fig. 85.2**A,B**). The external carotid artery (ECA) supplies the relatively higher-resistance circulation of the scalp and face and therefore has a low-end diastolic flow component (Fig. 85.2**C**). The common carotid artery (CCA) waveform reflects the fact that normally 80% of CCA flow is directed to the ICA. CCA end-diastolic flow is therefore generally well above baseline and exceeds ECA diastolic flow (Fig. 85.2**D**). In the presence of a very high-grade ICA stenosis or ICA occlusion, outflow is primarily through the higher-resistance external carotid 3 circulation. The CCA waveform then takes on the high-flow resistance characteristics of an ECA, with flow to zero, or nearly zero, in end diastole (Fig. 85.3).[1] In addition, the PSV and the overall flow velocity may be substantially lower than normal because of reduced carotid artery flow. By observing these changes in the CCA, one can reliably predict the presence of high-grade stenosis or occlusion of the ICA.

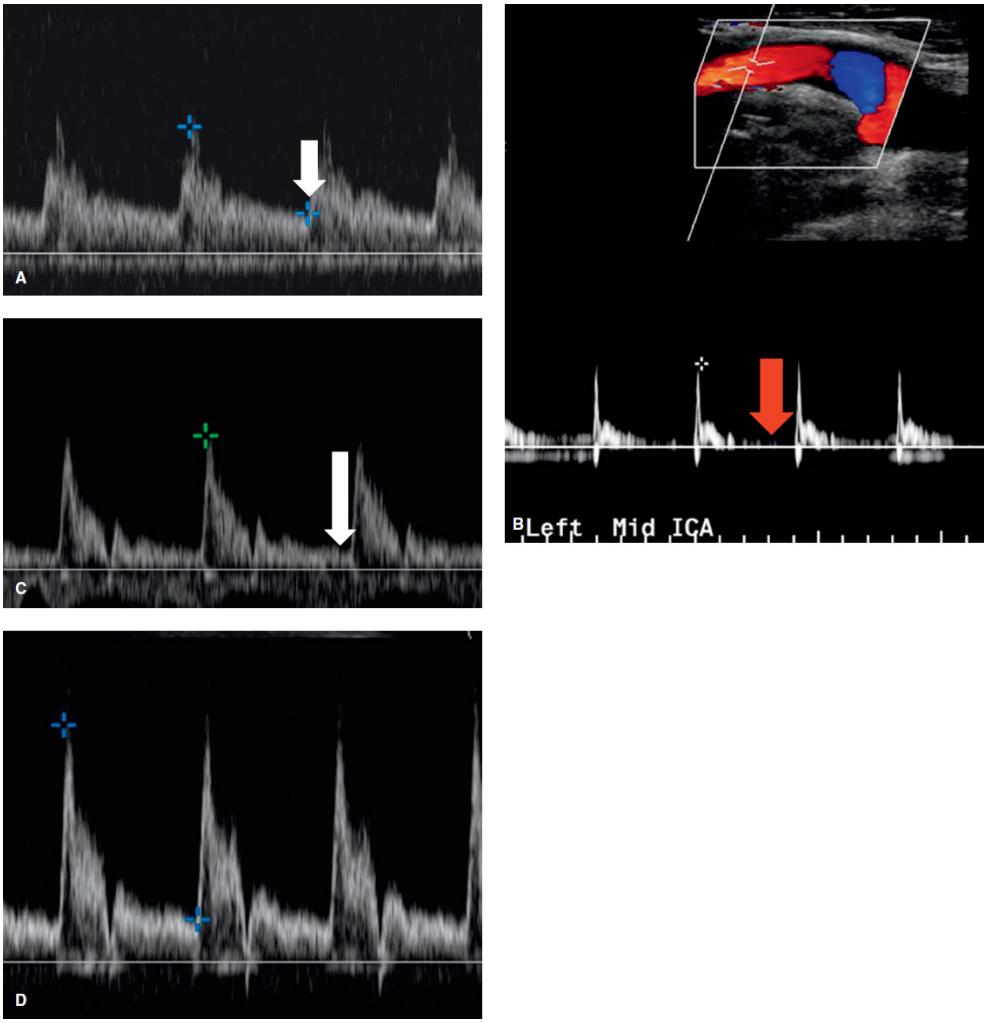

Figure 85.2 **A:** A normal internal carotid artery (ICA) waveform with high diastolic flow (*white arrow*) reflecting the low resistance of the cerebral circulation. **B:** Absence of ICA diastolic flow (*red arrow*) indicates more distal occlusion or severe stenosis of the extracranial or intracranial ICA. **C:** Normal external carotid artery waveform. The external carotid artery has low diastolic flow reflecting the high-resistance circulation of the scalp and face. **D:** Normal common carotid artery waveform. The common carotid artery waveform has diastolic flow well above the baseline as the majority of flow is directed to the low-resistance internal carotid artery circulation.

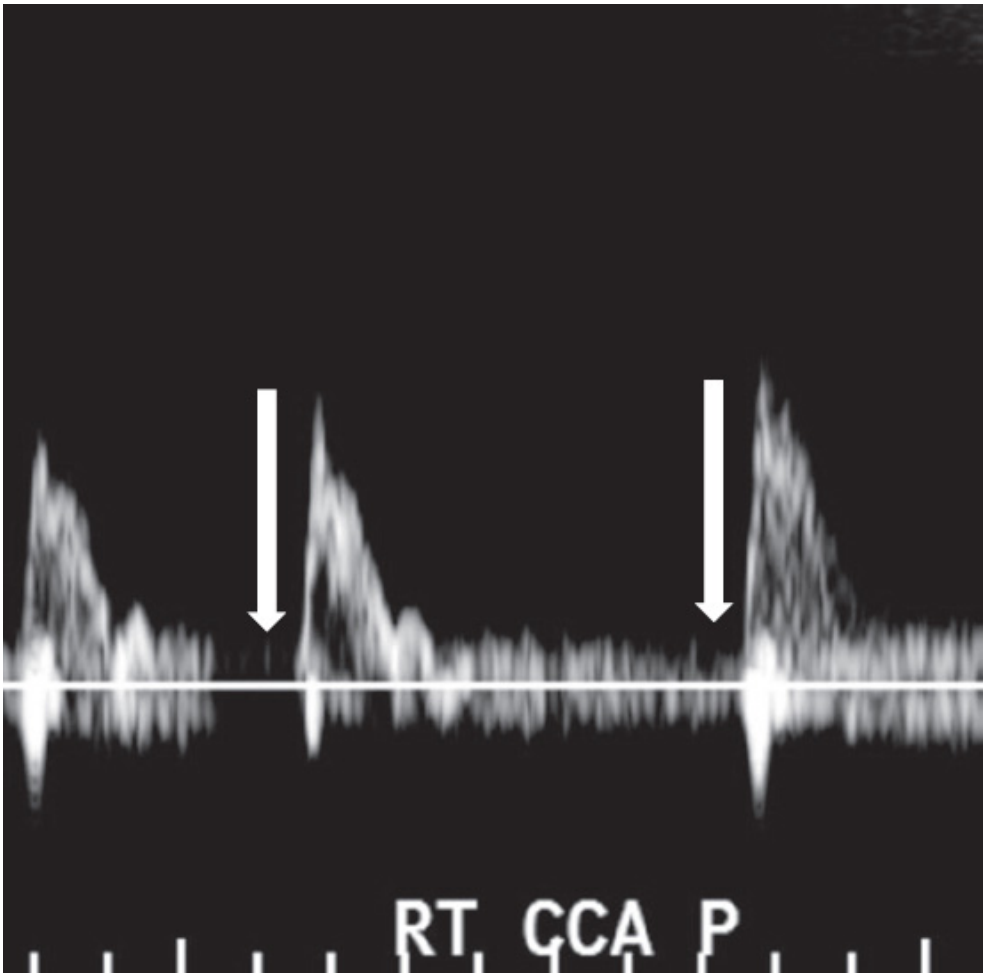

Figure 85.3 In a patient with internal carotid occlusion common carotid artery (CCA) diastolic flow approaches 0 (*arrows*) as CCA flow is now routed to the high-resistance external carotid circulation.

The CCA *contralateral* to an ICA stenosis or occlusion may demonstrate an increased flow velocity with particular elevation of the velocity at the end of diastole; the so-called end-diastolic velocity (EDV). These changes represent a compensatory increase in blood flow volume in the nonobstructed ICA in response to reduced contribution to cerebral perfusion from the opposite high-grade stenotic or occluded ICA. This compensatory hemodynamic change can be substantial and flow velocities may be artificially elevated on the side with compensatory high-volume flow giving a false impression of the presence of a stenosis or a higher degree of stenosis than is actually present.[2]

In the presence of a significant stenosis at the origin of a CCA or the innominate artery, the ipsilateral CCA waveform may be dampened, with

low overall peak systolic velocities (PSVs) and EDVs and a slower rise to peak systole when compared with the contralateral CCA waveform and potentially reverse flow in the ICA (Fig. 85.4**A,B**). The CCA flow changes seen with proximal stenosis are also important in the diagnosis of ICA stenosis because the overall reduction in flow velocity may artificially lower velocities in an ipsilateral ICA stenosis, leading to underestimation of the severity of ICA stenosis. In some cases of proximal CCA or innominate artery stenosis, the stenotic lesion may not be accessible to direct insonation by the duplex scanner. In such cases, a stenotic lesion can be suspected as the ipsilateral CCA waveform will often exhibit poststenotic turbulence low in the neck, reflecting disturbed flow distal to the more proximal stenosis.

ICA Waveforms

As noted above, the normal ICA spectral waveform is indicative of high flow in a low-resistant circulation. The systolic upstroke is rapid, PSV is <125 cm/s, and flow is maintained throughout diastole (Fig. 85.2**A**).[3] In the absence of plaque there is generally a clear spectral window under the outline of the spectral waveform as there is little turbulent flow. The presence of color shifts, indicating high-velocity flow, and color mosaics, indicating poststenotic turbulence, aids in selecting potential areas for examination with the pulsed Doppler.

Hemodynamic quantification of the severity of ICA stenosis is primarily achieved by analysis of Doppler spectral waveforms and measurements of peak systolic and EDV or comparison of PSVs in the ICA to those in the CCA just proximal to the carotid bifurcation, ICA/CCA ratio. As a stenosis develops, the PSV first becomes elevated. PSV is the primary measure of stenosis severity. EDV lags behind, relatively speaking, as stenosis severity progresses but rises rapidly as the stenosis becomes severe (diameter reductions of ≥60%). Thus, elevation of EDV is a good marker for high-grade stenosis (Fig. 85.5).[4] The ICA/CCA ratio is also a very important measure of stenosis severity.[5] Because it is a ratio, it compensates for abnormally high- and low-flow states that may skew the PSV and EDV upward or downward.

To accurately measure flow velocity, the sample volume must be placed within the area of greatest stenosis. Color flow imaging has demonstrated

that the orientation of the stenotic jet within a stenosis is frequently not along the longitudinal axis of the vessel. This finding has resulted in controversy with regard to the proper technique of obtaining velocity waveforms at sites of stenosis. In areas of mild to moderate stenosis, use of a Doppler angle of 60 degrees to the long axis of the vessel is recommended. However, in areas of more severe stenosis and/or wall abnormalities, the Doppler angle of 60 degrees should be defined by the long axis of the stenotic flow jet, as demonstrated by color flow.

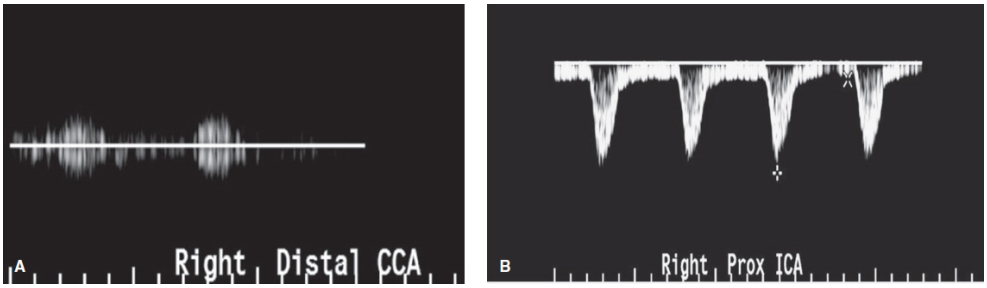

Figure 85.4 **A and B:** In the presence of innominate artery very high–grade stenosis or occlusion the common carotid artery (CCA) waveform will be blunted with a decreased amplitude and slowed upstroke **(A),** and there can be actually reverse flow **(B)** in the ipsilateral internal carotid artery (ICA).

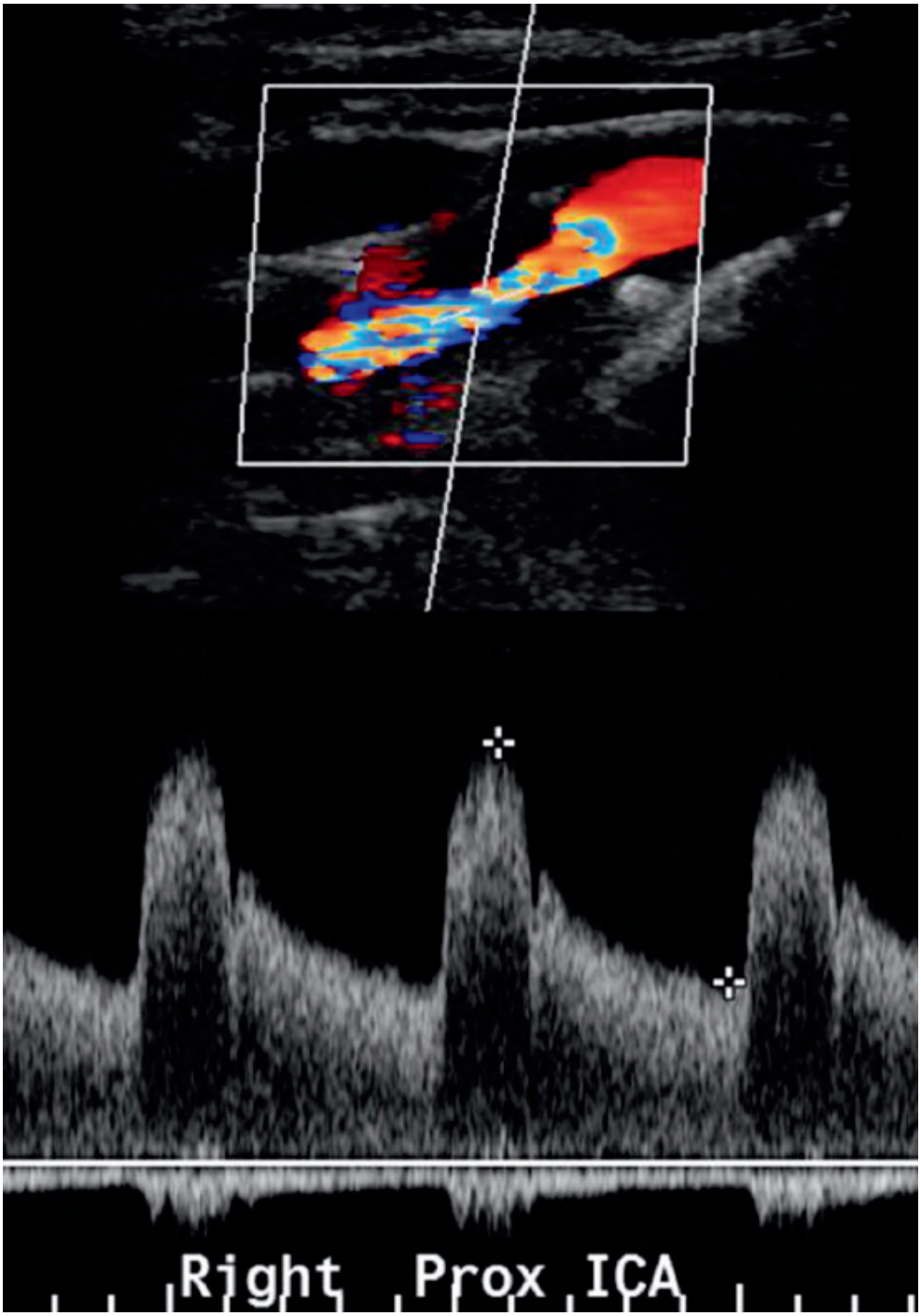

Figure 85.5 Internal carotid artery (ICA) waveform from the site of a >80% ICA stenosis. Both peak systolic and end-diastolic velocities are very elevated.

The sample volume size should be kept as small as possible, usually 1.5 mm, to detect discrete changes in flow velocity. This is important as the highest velocities may be localized to a small area in the flow stream that

emanates from the stenosis. A large sample volume that incorporates flow from many points within the vessel in the generation of the spectral waveform may give the false impression of disturbed flow, potentially leading to the misdiagnosis of moderate disease in an otherwise normal vessel. In practice, the sonographer, having identified the stenosis, gently moves a small sample volume around until the point of highest velocity is found.

Damping of spectral Doppler waveforms may be seen in the region distal to the carotid stenosis when the lesion is severe enough to be flow reducing. The most common abnormality seen distal to a carotid stenosis is spectral broadening caused by disturbed blood flow or turbulence. At best, poststenotic flow disturbance is a qualitative measure of arterial stenosis; nevertheless, its detection is important. With proper gain settings, "fill-in" of the Doppler spectral waveform generally indicates the presence of carotid stenosis with diameter reduction of at least 50%. However, this level of disturbed flow occasionally can be seen with nonstenotic disease. Diagnostically, the most significant poststenotic flow disturbance produces a simultaneous forward and reverse spectral Doppler signal, accompanied by poor definition of the upper spectral border. Such disturbed flow implies the presence of severe carotid stenosis. Severely disturbed flow distal to a highly calcified plaque may be the only substantial evidence for the presence of clinically significant stenosis if calcification prevents direct insonation of the stenosis.

Vertebral Artery

On rare occasions, a stenosis may be found in the cervical portion of the vertebral artery associated with cervical osteoarthritis. However, the origin of the vertebral artery from the subclavian artery is by far the most common site of disease in the vertebral artery. The vertebral artery origin lies deep in the base of the neck and may be difficult to access with ultrasound. Mean vertebral artery diameter is about 4 mm but the vertebral arteries are frequently asymmetric in size with one, most commonly the left, being larger than the right.

The vertebral artery is most commonly interrogated with ultrasound further distally in the neck, from an anteroposterior window, as it threads through the

transverse processes of the cervical spine. The vertebral bodies serve as a reference to insure the vertebral artery is actually under examination (Fig. 85.6). The artery is usually seen deeper but adjacent to the vertebral vein. Color Doppler is helpful to locate the vessel. A spectral waveform from the vertebral artery in the mid-neck provides information about direction of flow, waveform shape, and velocity but does not rule out disease at the origin. The normal vertebral artery waveform is similar to that of the ICA with normal PSVs reported to be 20 to 40 cm/s.[6] Velocities up to 80 cm/s are, however, frequently seen without apparent clinical importance and may represent collateral flow through a dominant vertebral artery, or a small but disease-free, vertebral artery. Evaluation of disturbed flow distally may help determine which elevated velocities are associated with a vertebral artery stenosis and which are not. Velocity patterns are usually similar in the two vertebral arteries but systolic and diastolic velocities may differ if vertebral artery diameters are asymmetric. For this reason if there is concern for stenosis based on an elevated peak systolic velocity (PSV) in a vertebral artery, recording of vertebral artery diameters is important.

Flow in the vertebral artery is normally antegrade with a rapid upstroke and continuous diastolic flow. In cases of anatomic subclavian steal, color flow provides an important initial clue to the diagnosis as flow in the artery will be retrograde in the same direction as the vein. Spectral Doppler must still be used to verify arterial flow and will demonstrate reverse or bidirectional flow in cases of subclavian steal. Depending on the degree of subclavian stenosis the vertebral artery flow may be reversed or biphasic, with flow above and below the baseline (Fig. 85.7**A,B**). End-diastolic flow will be zero or near zero reflecting the high resistance of the peripheral arm circulation rather than low-resistance cerebral circulation. High-resistance vertebral artery flow may also be seen with antegrade flow and like the situation for the ICA may represent distal stenosis or occlusion of the vertebral artery or an atretic or hypoplastic distal vessel.

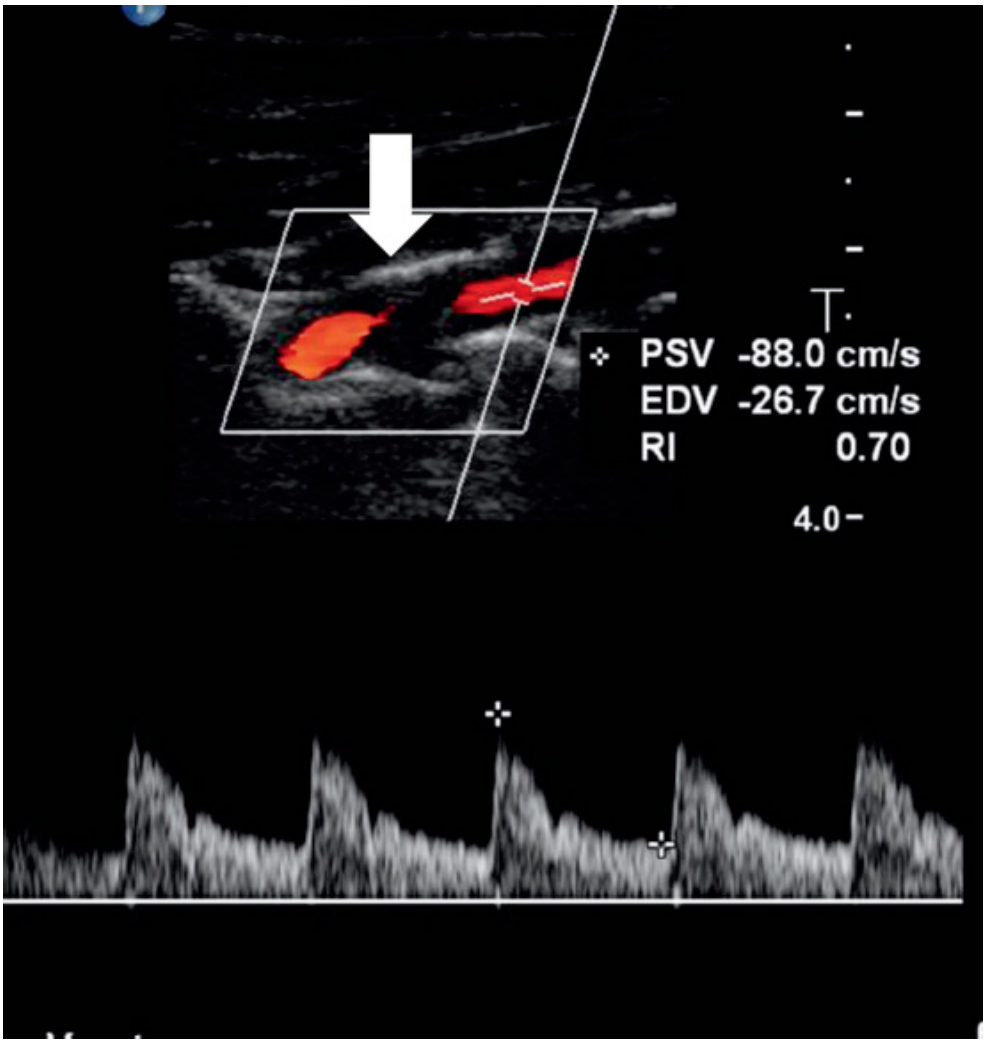

Figure 85.6 Bony landmarks of the vertebral bodies (*arrow*) mark the course of the vertebral artery.

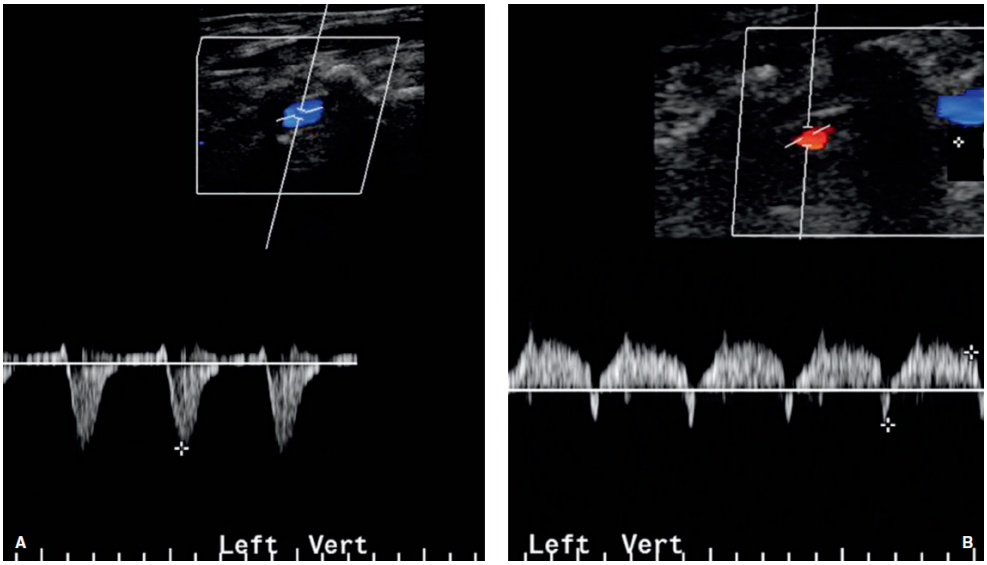

Figure 85.7 **A and B:** Both reverse vertebral artery flow **(A),** and vertebral flow both above and below the baseline **(B)** indicate a proximal innominate or subclavian artery stenosis.

External Carotid Artery

The ECA is smaller in diameter than the ICA at the level of the carotid bulb but similar in diameter beyond the bulb. It has little clinical significance in most cases but can serve as an important source of collateral flow to the brain in cases of ICA very high-grade stenosis, or occlusion. The ECA may also serve in such cases as a conduit for emboli to the brain; the so-called carotid stump syndrome.[7]

The ECA waveform has a sharp upstroke, a prominent dichroitic wave in late systole or early diastole, and velocity that is near or at the zero base line in end-diastole. The PSV of the ECA is normally higher than the ICA. The ECA may adopt the characteristics of the ICA in end-diastole as the resistance in the face and scalp decreases with temperature change and/or in the presence of disease. In cases of common carotid occlusion with preservation of patency of the carotid bulb, reverse flow in the ECA can provide antegrade flow in the ICA maintaining patency of the ICA even with CCA occlusion.

Classifying Carotid Stenosis

Duplex criteria for quantifying carotid artery stenosis were developed by comparing duplex-derived spectral waveforms and contrast arteriograms. Duplex-derived *categories* of stenosis are relatively broad. Sensitivities and specificities for spectral analysis of duplex-derived waveforms for detecting an ICA stenosis of >50% to 99% are between 90% and 95%. There are numerous spectral criteria for classifying ICA stenosis. Some focus on *categories* of stenosis, whereas others focus on *threshold levels* of stenosis.

One of the most widely accepted classification schemes for categories for ICA stenosis was developed at the University of Washington under the direction of Dr. Eugene Strandness. These criteria were useful in the study of the natural history of carotid atherosclerosis and in clinical practice. In the University of Washington system, velocity waveform analysis and spectral criteria were used to classify ICA angiographic stenosis as normal, 1% to 15%, 16% to 49%, 50% to 79%, and 80% to 99% stenosis and occlusion. Prospective validation of these criteria has demonstrated an overall agreement of 82% with contrast angiography. The ability of the criteria to detect carotid disease is 99% sensitive and the ability of the criteria to recognize normal arteries is 84% specific.[3]

Criteria for detecting carotid artery stenosis scanning have undergone reevaluation to remain relevant to current clinical practice. This reevaluation was stimulated by the randomized trials testing the efficacy of carotid endarterectomy (CEA) that took place over the last two decades (Table 85.1).[8–12] The trials had a profound impact on validating the indications for CEA in patients with carotid bifurcation atherosclerosis. The trials identified significant benefit, in terms of stroke reduction, for CEA in patients with specific levels of ICA stenosis. In particular, patients with symptomatic ICA stenosis >70% to 99% had dramatic benefit from CEA, whereas patients with symptomatic ICA stenosis between 50% and 69% and patients with asymptomatic ICA stenosis between 60% and 99% also benefited, albeit to a lesser extent, from CEA.

In the North American trials of CEA, ICA stenosis was calculated from arteriograms by comparing the diameter of the minimal residual lumen to the diameter of the distal cervical ICA.[13] The University of Washington duplex criteria for categories of stenosis pre-dated the endarterectomy trials. These criteria compared the diameter of the residual ICA lumen at its narrowest point with an estimate of the ICA bulb diameter assuming it free of

atherosclerotic plaque. Because the bulb has a greater diameter than the distal ICA, the two methods of measurement do not give the same calculated percentage of angiographic stenosis for the same lesion. Calculations of angiographic stenosis using the distal ICA as the reference vessel result in lower calculated stenosis percentages than calculations using the bulb as the reference site. This effect is particularly striking for modest lesions.

Table 85.1 Major Randomized Trials Assessing Efficacy of Carotid Endarterectomy

Symptomatic Stenosis
North American Symptomatic Carotid Endarterectomy Trial (NASCET)[8]
European Carotid Surgery Trial (ECST)[9]
VA Cooperative Study # 309[10]
Asymptomatic Stenosis
Asymptomatic Carotid Atherosclerosis Study (ACAS)[11]
Asymptomatic Carotid Surgery Trial (ACST)[12]

In a review of 1,001 internal carotid angiograms, 34% of the ICAs were classified as stenosis of 70% to 99% using the ICA bulb as the reference vessel. In contrast, when the distal cervical ICA was used as the reference site, only 16% of the ICAs were classified as 70% to 99% stenosis.[14] More than 99% of the distal ICA-based calculations of stenosis were less than bulb-based calculations. Thus, the duplex stenosis criteria using the bulb as the reference vessel are not and were not directly applicable to the results of the clinical trials.

Current Criteria for ICA Stenosis

Since the randomized CEA trials were completed, additional duplex criteria were developed comparing duplex scans to angiographic ICA stenosis using the distal ICA as the reference vessel in calculating angiographic stenosis. Such criteria are considered more useful by many in selection of patients for carotid intervention because they are directly applicable to the threshold levels of carotid stenosis addressed in the CEA trials.

The initial studies addressing the issue of duplex criteria relevant to the CEA trials were performed at the Oregon Health & Science University (OHSU)[5,15] with subsequent publications from many different institutions, with many different proposed criteria for identification of clinically relevant threshold levels of ICA stenosis.[16–21]

Recognizing that duplex criteria from different centers differed for the threshold levels of angiographic stenosis determined by the CEA trials, a panel of authorities from a variety of medical specialties assembled to review the carotid ultrasound literature. The panel developed a consensus regarding the key components of the carotid ultrasound examination and reasonable criteria for stratification of ICA stenosis.[22]

The consensus committee recommended that all carotid examinations be performed with grayscale imaging, color Doppler, and spectral Doppler. Examinations should be performed by a credentialed vascular technologist in accordance with the standards of an accrediting body. Doppler waveforms should be measured with an insonation angle as close to 60 degrees as possible but not exceeding 60 degrees, and the sample volumes should be placed within the area of maximal stenosis. The panelists recommended the consistent use of relatively broad diagnostic strata to estimate the degree of ICA stenosis. The panel also concluded that Doppler is relatively inaccurate for subcategorizing ICA stenosis <50%, and recommended that these lesions be reported under a single category as <50% stenosis, and that subcategories for minor degrees of stenosis not be used.

Table 85.2 Consensus Panel Recommendations for Classification of Internal Carotid Artery Stenosis[22]

Normal	The ICA PSV is less than 125 cm/s and there is no visible plaque or intimal thickening. Normal arteries should also have an ICA/CCA ratio of less than 2.0 and ICA EDV of less than 40 cm/s.
ICA stenosis <50%	is present when the ICA PSV is less than 125 cm/s and there is visible plaque or intimal thickening. Such arteries should also have an ICA/CCA PSV ratio of less than 2.0 and an ICA EDV of less than 40 cm/s.
ICA stenosis of 50–69%	is present when the ICA PSV is 125 cm/s to 230 cm/s and there is visible plaque. Such arteries should also have an ICA/CCA PSV ratio of 2.0 to 4.0 and an ICA EDV of 40 cm/s to 100 cm/s.
ICA stenosis ≥70–99%	but less than near occlusion is present when the ICA PSV is more than 230 cm/s and there is visible plaque with lumen narrowing on grayscale and color Doppler imaging. The higher the PSV, the more likely (higher positive predictive value) it is to have severe disease. Such stenosis should also have an ICA/CCA ratio of more than 4.0 and an ICA EDV of more than 100 cm/s.
Near occlusion of the ICA	The velocity parameters may not apply. "Preocclusive" lesions may be associated with high, low, or undetectable velocity measurements. The diagnosis of near occlusion is therefore established primarily by demonstration of a markedly narrowed lumen with color Doppler. In some near occlusive lesions, color Doppler can distinguish between near occlusion and occlusion by demonstrating a thin wisp of color traversing the lesion.
Occlusion	There is no detectable patent lumen on grayscale imaging and no flow with spectral, color, and power Doppler. Near occlusive lesions may be misdiagnosed as occlusions when only grayscale ultrasound and spectral Doppler are used.

ICA, internal carotid artery; PSV, peak systolic velocity; EDV, end diastolic velocity; CCA, common carotid artery.

The consensus panel noted that PSV is easy to obtain. However, data suggest reproducibility of PSV, even among experienced vascular

technologists, has sufficient problems that PSVs should not be used as a continuous variable in clinical carotid duplex scanning. Even so, the degree of stenosis estimated by ICA PSV and the degree of narrowing of the ICA lumen seen on grayscale and color Doppler should correlate with PSV as the primary parameters for determining ICA stenosis. Additional parameters such as ICA/CCA PSV ratio and ICA EDV are secondary parameters and should be employed as internal checks. They are especially useful when ICA PSV may not be representative of the extent of disease. After their discussions the consensus panel recommended criteria, stratifying ICA stenosis into specific categories relevant to the 4 CEA trials (Table 85.2). These criteria have not been subjected to widespread retrospective or prospective evaluation and do not represent the results of any one laboratory or study. They are not meant to serve as a substitute for continuous quality assurance in individual laboratories.

BILATERAL HIGH-GRADE ICA STENOSIS

Doppler-derived flow velocities from the ICA opposite an ICA occlusion or high-grade stenosis may suggest a higher degree of narrowing than is observed angiographically.[2] This likely is because of compensatory flow. Duplex scan overestimation of stenosis is more common in less-severe categories of stenosis than in higher-severity categories.[23]

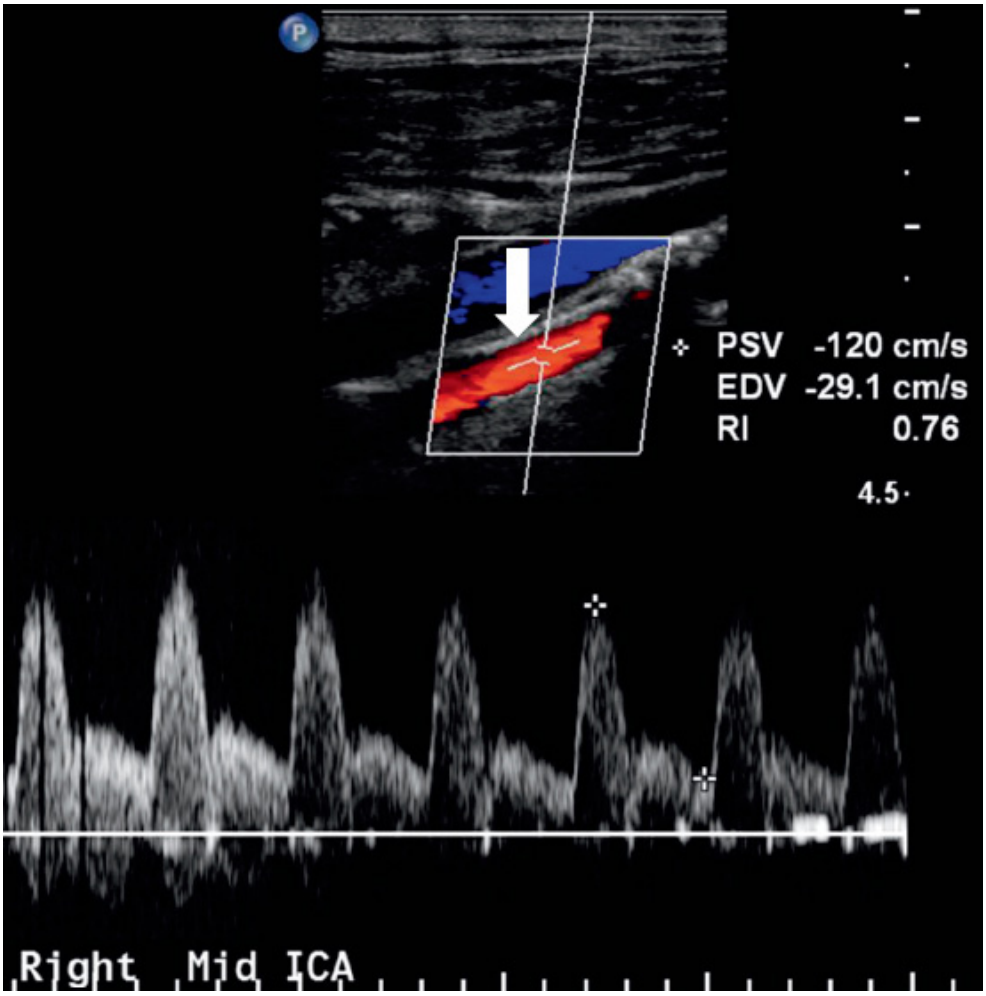

Figure 85.8 Color flow image and velocity waveforms from a stented internal carotid artery. A peak systolic velocity of 120 cm/s indicates the stent is widely patent. The stent itself is easily recognized as a hyperechoic stripe (*arrow*) parallel to the vessel wall.

Stented Carotid Arteries

Carotid artery stenosis may be selectively treated with an intraluminal stent. However, ultrasound criteria developed for native ICAs are likely not applicable to stented carotid arteries, especially to more modest lesions in the stented arteries. With rare exceptions the number of patients in studies of stented carotid arteries that have actually had severe in-stent restenosis is small. No study has correlated the degree of stenosis or increase in ICA velocities within a stented carotid artery with clinical symptoms or outcomes. Studies have also not evaluated the effect of the stented carotid

artery on the opposite nonstented artery. It is generally agreed that PSVs >125 cm/s, will be needed to identify a >50% stenosis in a stented ICA. Criteria to detect high-grade stenosis in native ICAs still work reasonably well to identify high-grade stenosis in stented ICAs (Fig. 85.8).[24,25]

CCA and ECA Stenosis

Criteria used for classifying disease in the ICA have not been prospectively tested for application to the ECA or the CCA. However, as with the ICA, relative degrees of stenosis may be determined by the presence of plaque with B-mode imaging, aberration in color flow on duplex examination, spectral broadening, and increases in PSV. Greater than 50% stenosis can be inferred by the presence of a focally increased PSV followed by poststenotic turbulence. As noted above, the CCA waveform normally has attributes of the ICA and ECA. The CCA will take on the quality of the "normal" vessel (ICA or ECA) when the other is occluded. If there is a proximal CCA (or innominate artery) high-grade stenosis or occlusion, the ipsilateral CCA Doppler flow quality will be dampened with low PSVs and delayed upstroke of the waveform compared with the nonstenotic contralateral side. Poststenotic turbulence also may be seen. There are no widely employed validated criteria to give a diameter reduction for stenosis in the CCA or ECA. Greater than 50% stenosis in the ECA is often inferred by PSV >125 cm/s associated with poststenotic turbulence whereas a PSV >200 cm/s may be an appropriate threshold for >50% stenosis in the CCA.[26]

LOWER EXTREMITY ARTERIAL DISEASE

The noninvasive vascular laboratory, in combination with the history and physical examination, has a critical role in providing objective diagnosis of lower extremity arterial occlusive disease in asymptomatic patients, those with intermittent claudication (IC), and in those with critical arterial insufficiency. Both plethysmographic and ultrasound techniques are used in the evaluation of peripheral arterial disease (PAD).

In many patients the clinical history and physical examination are all that is necessary to establish a diagnosis of IC. Almost all patients with IC have

diminished or absent lower extremity pulses. However, palpation of pulses is subjective and poorly reproducible. Therefore, the pulse examination in a patient suspected of having arterial disease should be supplemented with objective testing in the noninvasive vascular laboratory. On occasion a patient will give a history suggesting IC, yet have what appear to be normal resting lower extremity pulses. In such cases, exercise testing with postexercise Doppler-measured ankle pressures and ankle–brachial systolic blood pressure ratios is crucial to confirm the diagnosis of IC secondary to arterial stenosis or occlusion.

Many patients with PAD have atypical leg symptoms or are asymptomatic. Such patients have a similar increased risk of cardiovascular death as patients with typical IC symptoms, leading some to advocate for screening for PAD in patients with atypical leg symptoms or atherosclerotic risk factors.

Patients with exercise-induced lower extremity and/or buttock pain should be asked about the location of their pain, its relationship to walking, severity and duration of symptoms, and symptom progression over time. Only exercise-induced muscular pain of the calf, thigh, or buttock, relieved within a few minutes of rest and reproduced by additional walking, can be predictably improved by lower extremity arterial revascularization. There are no data on the response of atypical leg symptoms to revascularization in patients with evidence of PAD.

Ischemic pain at rest is a clinical diagnosis. It is suspected when a patient complains of pain and/or numbness in the forefoot, toes, or instep at rest. In such patients the vascular laboratory can objectively confirm and quantify the magnitude of arterial insufficiency. Ischemic pain is generally associated with an ankle pressure <50 mm Hg and an ankle brachial index (ABI) ≤0.4.

PLETHYSMOGRAPHIC TECHNIQUES

Volume Flow

Calf or foot blood flow can be recorded with a mercury-in-silastic strain gauge. Electrical resistance of the mercury column depends on the length of the column. Changes in electrical resistance, reflect changes in the volume of

the extremity, and are based on detection of minute changes in the length of the column. However, neither calf nor foot blood flow at rest differ between normal subjects and patients with even rather severe IC.[27] Hyperemic volume flow is often lower in patients with occlusive disease but such testing can be quite painful for the patient. Measurements of volume flow therefore are not very useful in the evaluation of lower extremity ischemia.

Pulse Volume Recordings

5 APG can be used to display pulse volume waveforms. PVRs are obtained with partially inflated blood pressure cuffs that detect volume changes sequentially down a limb. Volume changes beneath the cuffs resulting from the pulse wave result in small pressure changes within the cuffs. These changes are displayed as arterial waveforms with the use of appropriate transducers. A normal pulse volume waveform has a sharp systolic upstroke and peak, as well as a prominent dichroic notch on the downward portion of the curve. With increasing proximal arterial occlusion, the dichroitic notch is lost and the waveform bows out on the down portion of the systolic portion of the curve. The peak of the pulse wave also becomes rounded and there is loss of amplitude of the wave as disease is more severe. With even more severe disease there are nearly equal upstroke and downstroke times and in very severe proximal disease the pulse wave is absent (Fig. 85.9).[28,29] An absence of quantitative data limits the utility of PVRs. More quantitative data for the evaluation of lower extremity arterial disease are available using ultrasound-based techniques.

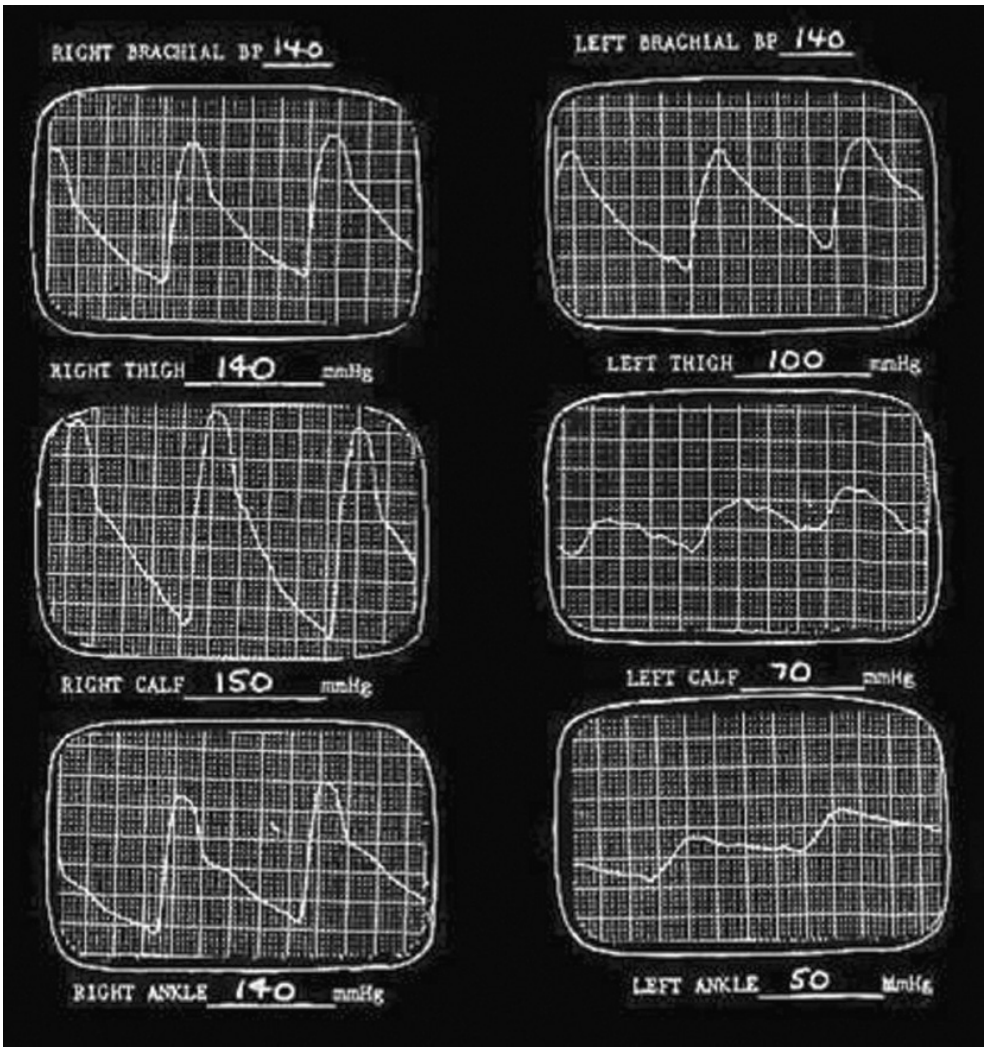

Figure 85.9 Pulse volume recordings. The plethysmographic waveforms are normal on the right and severely abnormal in the left leg with loss of amplitude of the waveform, slowing of the upstroke of the waveform, and outward bowing of the downstroke of the waveform.

ULTRASOUND TECHNIQUES

Ankle–Brachial Index

6 ABI is a very useful measure of overall lower extremity perfusion. The test is performed with the patient supine and having rested for a few minutes. A pneumatic pressure cuff is placed just above the ankle and inflated to supra systolic levels. A continuous wave Doppler probe is positioned over the posterior tibial or dorsalis pedal artery distal to the cuff. The cuff is deflated

and the pressure reading when the Doppler signal returns is recorded. The sequence is repeated for the other ankle artery and the values compared with the highest brachial artery systolic pressure also obtained with the Doppler. For clinical purposes, the higher ipsilateral dorsal pedal or posterior tibial pressure is divided by the higher brachial artery systolic pressure, yielding an ABI for that lower extremity. The use of a ratio makes the test relatively independent of day-to-day variations in arterial blood pressure.

A normal ABI is 1.0 to 1.2, with progressively lower values corresponding to worsening arterial disease (Table 85.3). ABIs below normal indicate relative lower extremity arterial insufficiency and increased risk of cardiovascular death with the risk increasing with the magnitude of depression of the ABI. This test has several limitations. Significant bilateral subclavian or axillary artery occlusive disease results in a falsely elevated ABI. Calcified tibial arteries that can frequently occur with diabetes or renal failure may be inadequately compressed by the pressure cuff. This also results in a falsely elevated (suprasystolic) ankle pressure. An ABI >1.4 should therefore also be considered abnormal. Such patients often have severe arterial disease and are also at increased risk of cardiovascular death. When the ABI may be falsely elevated, qualitative analysis of Doppler-derived analog or plethysmographic waveforms or measurement of digital systolic pressures is a more appropriate indicator of the arterial status of the lower extremity. Other problems with ABI include confusion with venous signals when the ankle arterial pressure is low or unmeasurable and relative insensitivity to certain patterns of progression of arterial disease. A tibial artery can occlude without a change in ABI if the remaining tibial vessels remain patent. High-grade stenosis may also progress to occlusion without a change in ABI.

Table 85.3 Correlation between Ankle Brachial Index (ABI) and Clinical Severity of Lower Extremity Arterial Ischemia

ABI	Clinical Status
>1.3	Abnormal, significant arterial wall calcification
1.1 ± 0.1	Normal
0.6 ± 0.2	Intermittent claudication
0.3 ± 0.1	Ischemic rest pain
0.1 ± 0.1	Impending tissue necrosis

Segmental Limb Pressures

Multiple pneumatic cuffs may be used along the lower extremity to determine the arterial blood pressure at specified levels. These "segmental leg pressures" are compared with the higher brachial artery systolic pressure, with other locations in the ipsilateral leg and with the corresponding levels in the contralateral extremity. Three or four cuffs may be used. In the four-cuff technique cuffs are placed: (1) as far proximal on the thigh as possible; (2) immediately above the knee; (3) just below the knee; and (4) just proximal to the ankle. Each cuff width should be 20% greater than the diameter of the limb at the point of application to avoid falsely elevated pressure readings induced by too narrow a cuff.[30] For the thigh, this generally necessitates a single, wide, thigh cuff. Use of two cuffs above the knee, however, can permit assessment of inflow at or proximal to the common femoral artery with the proximal cuff, and permit evaluation for the presence of superficial femoral artery disease by the distal thigh cuff. With two thigh cuffs the most proximal thigh cuff is often too narrow. An artificially elevated pressure in the proximal thigh is then expected. Therefore the high-thigh index, comparing the proximal thigh pressure to the brachial pressure, is normally about 1.4 with the four-cuff technique and 1.0 to 1.1 with the three-cuff technique (Fig. 85.10).

A hand-held Doppler is used to detect the most prominent Doppler signal at the ankle. Examination proceeds proximal to distal. First the high-thigh

cuff is inflated until the ankle Doppler signal is no longer audible. The cuff is then deflated and the pressure where there is return of the Doppler signal at the ankle is the high-thigh pressure. The above-knee, below-knee, and ankle pressures are similarly determined. If there is no audible ankle Doppler signal, the popliteal artery is insonated with the Doppler to determine high-thigh and above-knee pressures. Comparison of the pressures measured at each location permits an estimation of the location of occlusive lesions (Fig. 85.11).

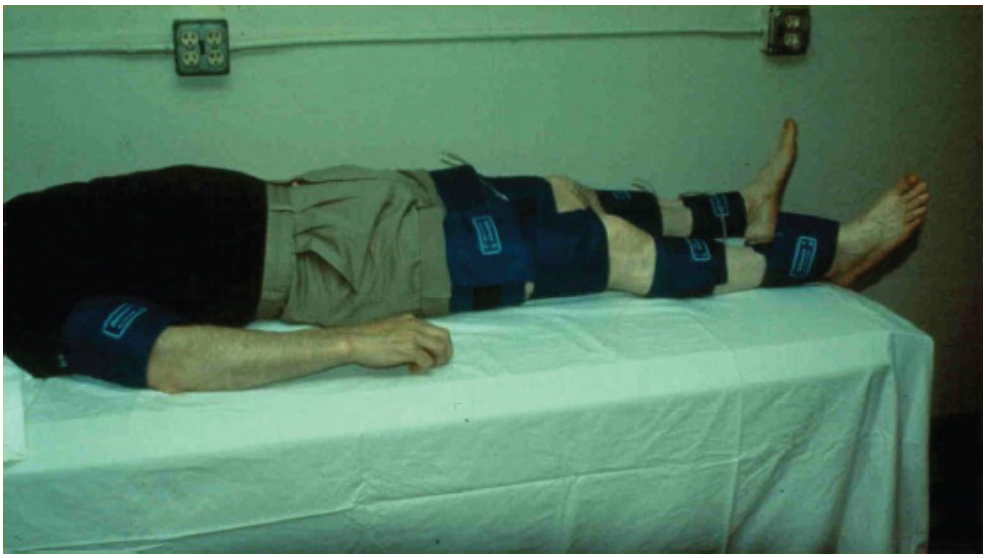

Figure 85.10 Segmental pressures multiple pneumatic cuffs may be used along the lower extremity to determine the arterial blood pressure at each level. Comparison of the pressures measured at each location permits an estimation of the location of occlusive lesions. Use of two cuffs above the knee can permit assessment of inflow at or proximal to the common femoral artery with the proximal cuff, and permit evaluation for the presence of superficial femoral artery disease by the distal thigh cuff. In many patients, however, the high-thigh cuff is relatively narrow compared to the diameter of the thigh resulting in an artificial elevation of the high-thigh pressure so that with use of four cuffs the high-thigh pressure will be 30 to 40 mm Hg higher than the highest brachial pressure.

There are multiple limitations in the interpretation of segmental limb pressures. The high-thigh pressure is subject to particular interpretation difficulties. A diminished high-thigh pressure can reflect an occlusive lesion anywhere at or proximal to the common femoral artery bifurcation. Low high-thigh pressures therefore may reflect a pressure-reducing stenosis in the ipsilateral common or external iliac artery, a common femoral artery lesion

or tandem pressure-reducing lesions in the profunda femoris, and the proximal superficial femoral artery or any combination of such lesions. The accuracy of segmental pressures may be affected by mural calcification resulting in artificially elevated pressures. Diminished proximal pressures may also mask gradients that exist further down the leg. Segmental pressures also do not allow differentiation between short- and long-segment occlusions, or between occluded and patent, but highly stenotic arteries.

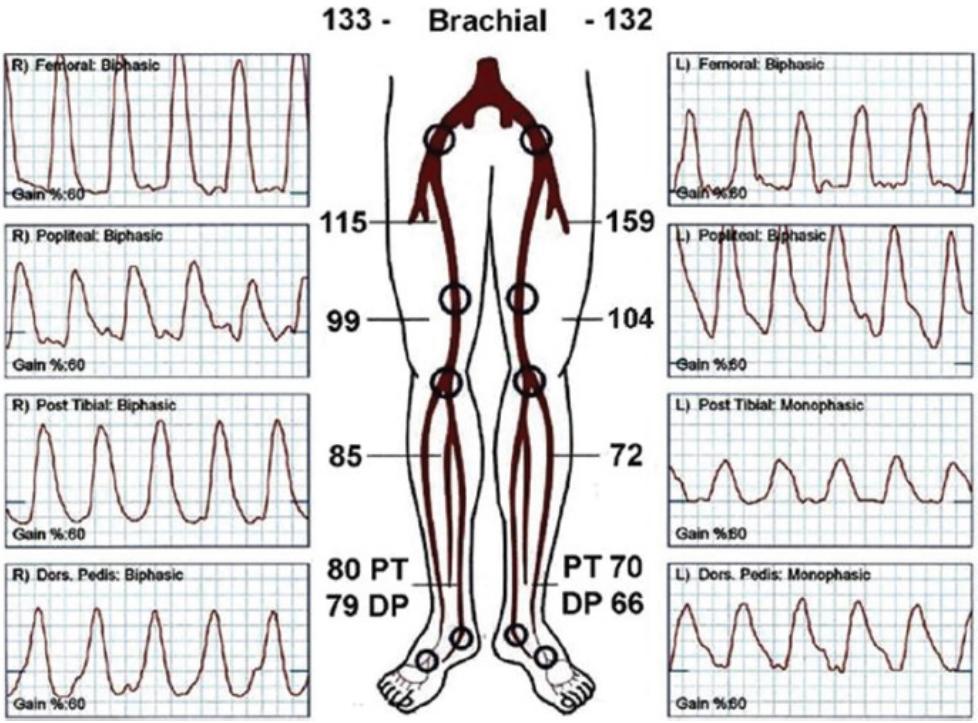

Figure 85.11 Segmental pressure examination with use of thigh, calf, and ankle cuffs. A drop in pressure of 30 mm Hg between levels indicates a hemodynamically significant stenosis between the two adjacent cuffs. This study therefore indicates a flow-reducing lesion somewhere at or proximal to the common femoral artery bifurcation on the *right side* and likely superficial femoral artery/popliteal artery occlusive disease on the *left*.

Exercise Testing

Doppler-determined pressures can be combined with treadmill exercise testing in patients without a contraindication to exercise. After determination of resting supine ankle pressures and ABIs, the patient walks on a treadmill with a predetermined incline at a predetermined rate. The test continues for 5 minutes or until the patient is forced to stop. The type, time-to-onset, and

location of symptoms are recorded. At completion of the test, the patient is immediately placed supine and absolute ankle pressures and ABIs determined.

In most patients exercise testing serves only to confirm a diagnosis of claudication. It is not required in a patient with classic symptoms of claudication, absent peripheral pulses and a diminished ABI. In some cases exercise testing can document a physiologic response to revascularization or provide an objective assessment of the potential postoperative physiologic benefit.

Exercise testing is particularly useful in the infrequent patient with symptoms of claudication and who has palpable pedal pulses and/or a normal ABI. Patients with exercise-induced leg pain occurring on the basis of arterial insufficiency will show a decrease in the postexercise ankle pressures and ABI. Exercise testing can also be used to document an ischemic response to exercise in a patient with PAD and other conditions that may limit their ability to walk. Patients with COPD, arthritis, venous disease, and PAD are often more limited in their walking ability by these coexisting conditions than by their PAD. If the patients cannot complete a treadmill examination, and no ischemic pressure response to exercise occurs, it is highly unlikely their walking ability would be improved by a revascularization procedure.

The precise endpoints and techniques of exercise testing are controversial. Some laboratories exercise patients at low speeds with no inclination of the treadmill whereas others utilize various inclines and graded increases in treadmill speed. Both initial and absolute claudication distances can be determined. Initial claudication distance is the point where the patient initially experiences claudication-type pain. The absolute claudication distance is where the patient can no longer continue to walk on the treadmill.

Criteria for a positive exercise test include a decrease in the ankle pressure of 20 mm Hg or 20%, a decrease in the ABI of 0.2 in the symptomatic extremity, or failure of the ankle pressure to return to baseline within 3 minutes of completing the treadmill portion of the examination. Because systemic pressure and therefore arm pressures, depending on work load, will increase with exercise, use of the ABI alone to indicate a positive exercise test is incorrect. The ABI decrease should be accompanied by an absolute pressure drop at the ankle.

7 Failure of the ankle pressure to drop with exercise along with failure of the ABI to decrease 20% with exercise, combined with a normal resting ABI, substantially rules out arterial insufficiency as the etiology of the patient's exercise-induced complaints of leg pain. An exception is the rare patient with buttock claudication secondary to isolated internal iliac disease.

Neurogenic claudication may be confused with arterial ischemia. Patients present with symptoms of exercise-induced leg or calf pain. Careful questioning, however, reveals atypical characteristics for vascular-induced exercise-associated pain. Such characteristics include occurrence of pain with standing, pain relief when leaning forward, worsening with coughing, and prolonged time for pain to resolve following exercise. These patients often have normal ankle pressures at rest that do not decrease with exercise despite onset of symptoms. Failure of the ankle pressures to decrease with exercise may also be a clue to the presence of other uncommon conditions, such as venous claudication and chronic exercise-induced compartment syndromes.

Doppler Analog Waveform Analysis

Similar to plethysmographic waveforms, continuous-wave Doppler waveforms may also be analyzed qualitatively. Normal lower extremity Doppler waveforms are described as triphasic with a sharp systolic upstroke, an end-systolic reverse flow component followed by low forward flow through diastole. The shape of the waveform changes with increasing severity of proximal obstruction. Initially, the reverse-flow component is lost. As proximal stenosis increases, the rate of rise of the systolic upstroke is decreased, the amplitude of the waveform is diminished, and diastolic flow increases relative to systolic flow.

Continuous-wave Doppler waveforms are generally used in conjunction with measurement of segmental Doppler pressures similar to the use of PVRs. Doppler waveform analysis can also be used to assess iliac artery inflow to the common femoral artery. An attenuated common femoral artery waveform indicates proximal disease.

Peripheral Artery Duplex Scanning

Arterial duplex scanning provides detailed anatomic and hemodynamic information from the infrarenal aorta to the distal tibial vessels that cannot be determined by indirect testing. Arterial duplex scanning has been prospectively compared with angiography to establish standard criteria for normal and diseased arteries.[31] Sensitivity of duplex examination for detecting the presence of a hemodynamically important lesion (>50%) ranges from 89% at the iliac artery to 68% at the popliteal artery. Overall sensitivities for predicting interruption of patency are 90% for the anterior and posterior tibial arteries and 82% for the peroneal artery. The technique is versatile and does not appear to be significantly influenced by the presence of previous operations or multilevel disease (Fig. 85.12**A,B**).

Velocity Patterns and Classification of Percent Stenosis

In the absence of arterial stenosis or occlusion triphasic waveforms are maintained throughout the length of the lower extremity but PSV decreases from the iliac to the tibial vessels. There are no significant differences in velocity measurements among the three tibial arteries in normal subjects.

Important changes in the velocity waveforms that signify disease include the absence of an end-systolic reverse flow component and elevation of the PSV. A 50% reduction in arterial luminal diameter (equivalent to a cross-sectional surface area reduction of 75%) is associated with a pressure drop across the lesion. The University of Washington criteria for classification of peripheral arterial stenosis are shown in Table 85.4.[32]

A PSV ratio, comparing the velocity within the stenosis to the velocity just proximal to the stenosis, is also useful for grading degree of stenosis. PSV ratios are independent of changes in blood pressure, cardiac output, and vascular compliance. Grading stenosis using the PSV ratio has been found to be highly reproducible.[33,34] Fifty percent stenosis in lower extremity arteries correlates with a PSV ratio from 1.4 to 3.0.[31,35–38] A velocity ratio of 2.0 is a reasonable compromise and is used by many vascular laboratories as indicative of a 50% peripheral arterial stenosis.

Lower extremity duplex scanning can serve as an alternative to contrast arteriography in the preoperative assessment of candidates for arterial intervention. In selected centers, successful lower extremity

revascularization either by open arterial bypass grafting or with catheter-based techniques has been reported using only arterial duplex in a high percentage of cases.[39–41] The limiting factor with preoperative arterial duplex is the ability to accurately identify the best site for the distal anastomosis of a bypass graft, especially when the distal anastomotic site is below the knee.[42]

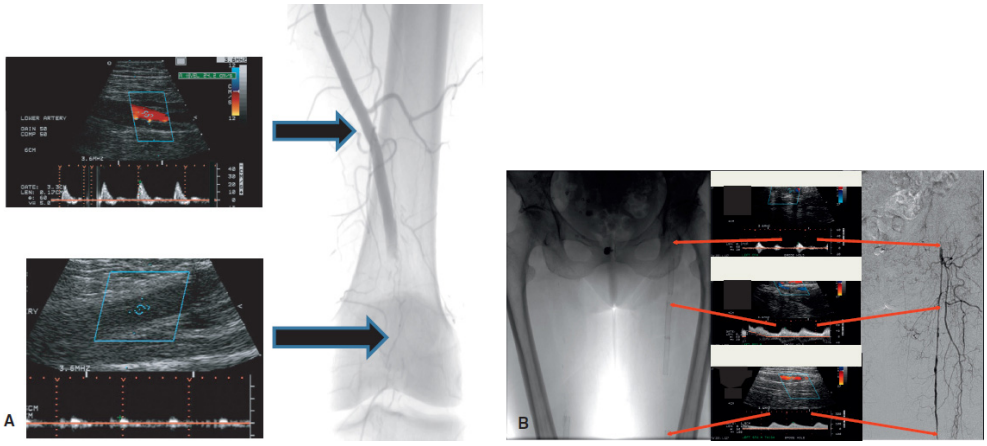

Figure 85.12 **A:** Duplex images/waveforms and corresponding angiogram of an abrupt popliteal artery occlusion. **B:** Duplex waveforms and angiographic images in a patient with severe in-stent stenosis of superficial femoral artery stents.

The role of duplex ultrasound scanning in the surveillance of lower extremity vein grafts has been well documented (Fig. 85.13**A,B**). Detection and repair of a graft-threatening stenosis detected by duplex scanning appears to improve secondary graft patency.[43–46] Twenty percent to 30% of vein grafts will develop a severe enough stenosis that revision is recommended.[47] Approximately 80% of these graft stenotic lesions develop in the first postoperative year. However, graft-threatening lesions can develop at any time. Surveillance is therefore generally recommended for the life of the graft. A widely utilized protocol for vein graft duplex surveillance is every 3 months for the first year and every 6 months to yearly thereafter. The examination involves point-to-point insonation of the proximal inflow artery, proximal anastomosis, midgraft, distal anastomosis, and the distal outflow artery. A PSV ratio of 4, or a PSV above 300 cm/s, indicates a critical graft stenosis, and repair of the lesion by open or catheter-based techniques should be considered.[48] If the PSV ratio is between 2 and 4, the patient should be evaluated again in 3 months with a duplex examination.

Table 85.4 University of Washington Duplex Criteria for Classification of Lower Extremity Arterial Stenosis

Disease Severity	Spectral Waveform Features
Normal	Triphasic waveform No spectral broadening
1–19% Diameter Reduction	Triphasic waveform with minimal spectral broadening PSVs increased <30% relative to the adjacent proximal segment Proximal and distal waveforms remain normal
20–49% Diameter Reduction	Triphasic waveform usually maintained (although reverse flow component may be diminished) Spectral broadening is prominent, with filling-in of the clear area under the systolic peak PSV is increased from 30% to 100% relative to the adjacent proximal segment Proximal and distal waveforms remain normal
50–99% Diameter Reduction	Monophasic waveform with loss of the reverse flow component and forward flow throughout the cardiac cycle Extensive spectral broadening PSV is increased >100% relative to the adjacent proximal segment Distal waveform is monophasic with reduced systolic velocity
Occlusion	No flow detected within the imaged arterial segment Preocclusive “thump” may be heard just proximal to the site of occlusion Distal (collateral) waveforms are monophasic with reduced systolic

velocities

Reprinted from Strandness DE Jr. *Duplex Scanning in Vascular Disorders*. 5th ed. New York: Raven Press; 1990:121–145.

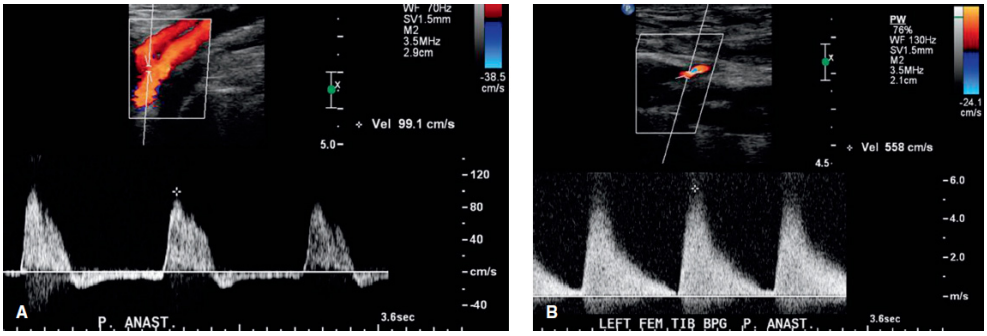

Figure 85.13 **A and B:** Duplex ultrasound images and velocity waveforms of normal **(A)** and stenotic **(B)** proximal anastomoses of femoral tibial bypass grafts. The abnormal study has a severe elevation in flow velocity of 558 cm/s indicating a high-grade stenosis.

Aneurysms and pseudoaneurysms of lower extremity arteries are also readily identified and characterized with duplex scanning with particular attention to the diameter of the aneurysm and the presence or absence of intraluminal thrombosis (Fig. 85.14**A,B**).

Upper Extremity Arterial Evaluation

Upper extremity arterial disease is a small but important component of vascular surgical practice. Both ultrasound and plethysmographic techniques are important in the evaluation of upper extremity arterial disease.

SEGMENTAL ARM PRESSURES

Upper extremity segmental pressures are obtained by measuring blood pressure with pneumatic cuffs above the elbow, below the elbow, and above the wrist while insonating the radial or ulnar artery at the wrist using a continuous wave Doppler. Doppler-derived or plethysmographic waveforms can also be recorded at the different levels. Abnormal waveforms or pressures will help diagnose arterial disease proximal to the wrist.

A 12-cm blood pressure cuff is usually sufficient for measuring the brachial artery pressure, whereas a 10-cm blood pressure cuff is used at the wrist to measure the systolic pressure from the radial and ulnar arteries. A systolic pressure measurement is taken from the upper arm (brachial artery) and at the wrist (radial and ulnar arteries). Normally, there is not a recordable gradient between any of these sites and a normal wrist/brachial blood pressure ratio is 1.0. If there is a blood pressure difference between the two arms of more than 15 mm Hg, it is likely that there is a stenosis or occlusion somewhere on the side of the lower pressure. Abnormal waveforms and decreased pressures at the above-elbow cuff site indicate axillary, subclavian, or brachiocephalic arterial occlusive disease. Similarly, abnormalities at the below-elbow and above-wrist sites indicate brachial and proximal ulnar/radial arterial occlusive disease, respectively. If there is a blood pressure difference between levels, or between the radial and ulnar arteries, of more than 15 mm Hg it is likely caused by a stenosis or occlusion (Fig. 85.15).

DIGITAL PRESSURES AND PLETHYSMOGRAPHY

Digital pressure measurements and digital plethysmography are extremely useful in the diagnosis of upper extremity arterial disease and can be as accurate as arteriography in assessing patients with hand ischemia.[49] Photo plethysmography (PPG) or strain-gauge plethysmography can be used to measure digital blood pressure and to obtain pulse waveforms. PPG is preferred because the equipment is easier to use and more durable. An additional advantage of PPG is that it is possible to record the volume pulses from the tips of the digits. This may also be useful in documenting obstruction within the digit arteries themselves.

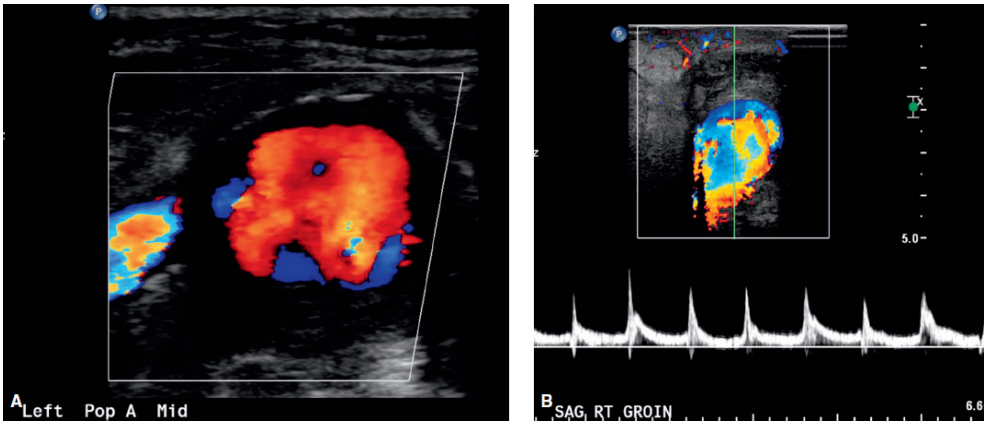

Figure 85.14 **A:** Native popliteal artery aneurysm with intraluminal thrombus. **B**: Large pseudoaneurysm of the right common femoral artery resulting from arterial infection from intra-arterial injection of street drugs.

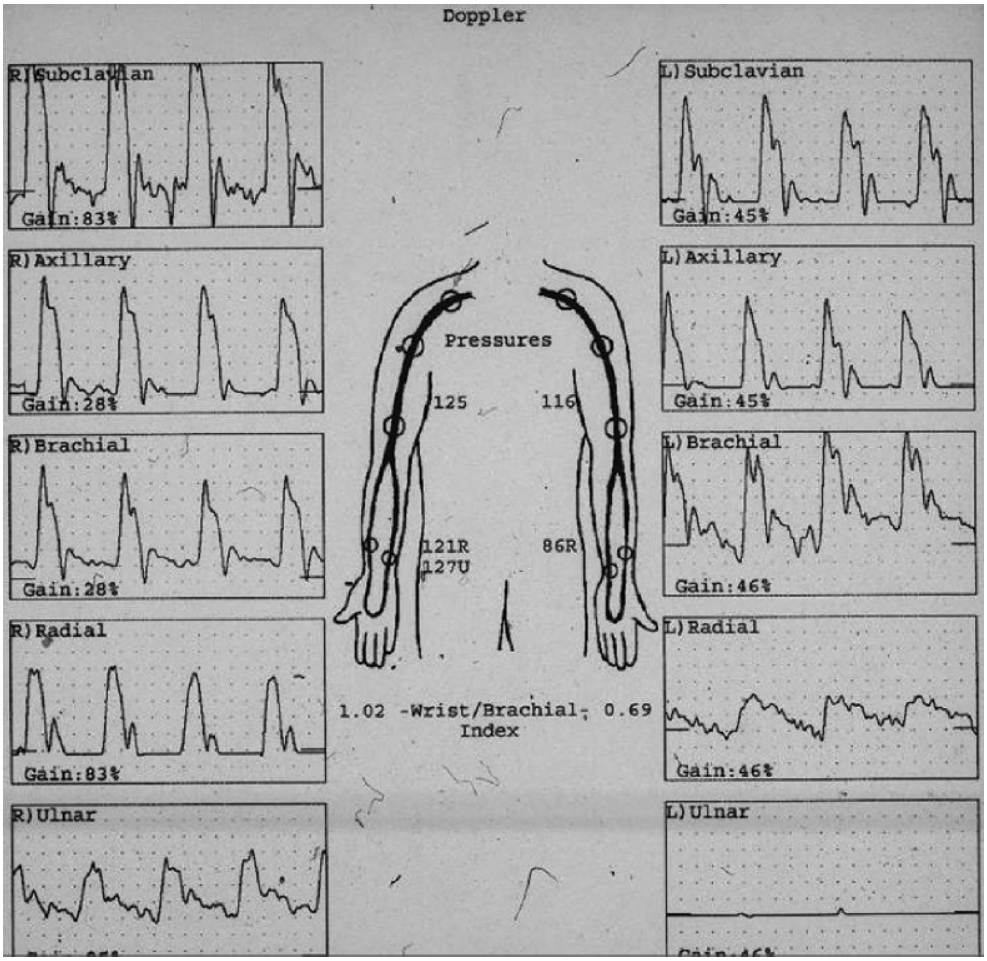

Figure 85.15 Upper-extremity segmental pressures and Doppler waveforms. The findings are normal on the **right** and suggest radial and ulnar artery or distal brachial artery occlusive disease on the **left**.

The photo cell is attached to the fingertip pulp with double-sided tape or small strain gauges are placed around the fingertip. One-inch (2.5 cm) blood pressure cuffs are placed around the proximal phalanx. Waveforms are recorded using pulse tracings obtained at high speed to evaluate the shape of the waveform. Waveforms are normal if the upstroke time is less than 0.2 seconds (Fig. 85.16**A**). They may or may not have a dichotic notch. An abnormal obstructive waveform will have a rounded peak, as opposed to the normal notched peak. Upstroke time is prolonged. The amplitude of the waveform is not important. Finger PPG waveforms are not quantitative. The amplitude of the waveform is primarily dependent on the gain setting, not blood flow.

Patients with vasospasm will often have an abnormally shaped waveform termed a "peaked pulse," which is thought to represent abnormal elasticity and rebound of the palmar and digital vessels (Fig. 85.16**B**).

Finger blood pressures are measured by inflating the cuffs placed at the base of the fingers. At reduced chart recorder speed the pulsations are recorded while the blood pressure cuffs are inflated. When digit pulsations are obliterated, the cuff is slowly deflated until the pulsation returns. The pressure reading at this point is recorded and represents the digital artery pressure.

It is extremely important to measure and record finger temperature before performing digital plethysmography and obtaining finger blood pressures. If the finger temperature is less than 28° to 30°C false-positive results may be obtained secondary to cold-induced vasospasm. It is recommend that hand and/or whole-body warming be performed in patients with low finger temperatures.

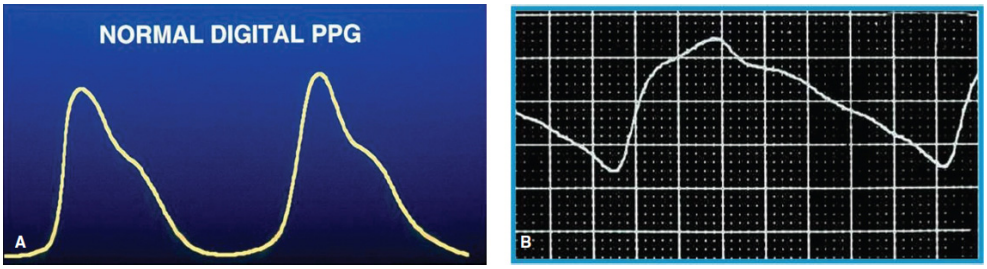

Figure 85.16 A and B: Normal **(A)** and "peaked pulse" **(B)** digital photoplethysmographic (PPG) waveforms. A normal waveform has a rapid upstroke and a sharp apex whereas an obstructive waveform would demonstrate a delayed upstroke and rounded apex. In a peaked pulse, waveform suggestive of vasospasm, the dichroitic notch slides to high on the systolic downslope of the waveform.

Digital blood pressure is normally within 20 to 30 mm Hg of brachial pressure. A ratio of finger systolic pressure to brachial systolic pressure of greater than 0.80 is normal but does not necessarily rule out digital artery occlusive disease. It is important to remember that there are occasional patients with very distal digital artery occlusive disease with normal finger pressures since the digital cuff is around the proximal phalanx. Also, occlusive disease in a single digital artery can be missed if the other digital artery in that finger is normally patent.

COLD CHALLENGE TESTING

The simplest cold intolerance test is to measure the digital temperature recovery time after immersion of the hand in ice water for a short time period. Preimmersion digital temperatures must be above 30°C. Hand and body warming may be required prior to immersion.

Using a thermistor probe to measure finger temperatures, the patient's hand is immersed in a container of ice water for 30 to 60 seconds. After the hand is dried, the fingertip pulp temperatures are measured every 5 minutes for 45 minutes, or until the temperature returns to preimmersion levels. Normal individuals will have a recovery time to preimmersion levels of less than 10 minutes. This test is very sensitive for detecting cold-induced vasospasm but is nonspecific, with approximately one-half of patients with a positive test having no clinical symptoms of cold sensitivity.[50] Cold immersion testing is

also uncomfortable and poorly tolerated by patients with significant Raynaud syndrome symptoms. Pressures often fall to unrecordable levels in such patients.

A better, but infrequently utilized, test for cold sensitivity is the digital hypothermic challenge test as described by Nielsen and Lassen (Fig. 85.17).[51] This test involves placing a finger cuff around the proximal phalanx on the test finger and perfusing the cuff with progressively cooler fluid. The pressure in the test finger is then compared with that in a reference finger that is not cooled. The Nielsen test is interpreted as positive for abnormal cold-induced vasospasm if the test finger pressure is reduced by more than 17% compared with the reference finger.

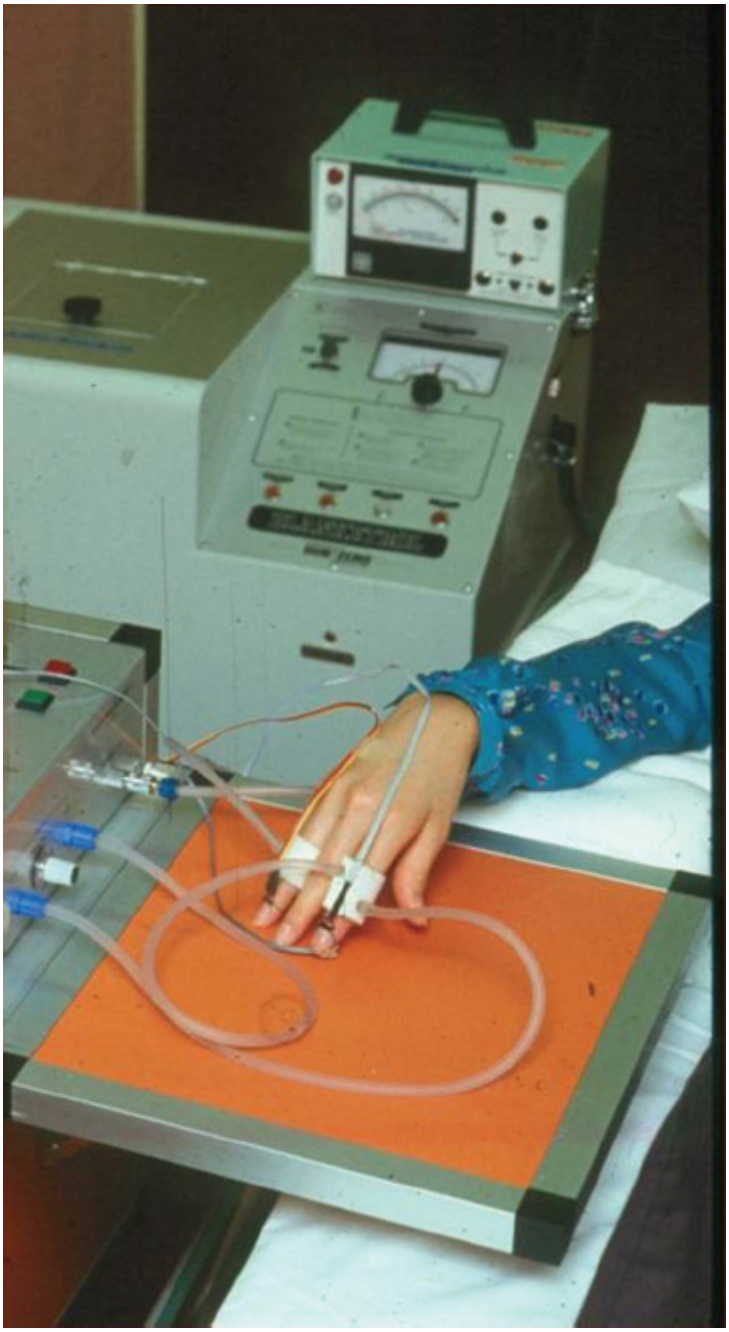

Figure 85.17 Device for performance of digital hypothermic challenge or Nielsen test. The cuff on the second finger is used to cool the test finger and measure digital pressure. This allows controlled application of cold to induce a vasospastic response. The fourth finger is the reference finger. Strain gauges on the finger tips are used to measure the digital pressures. See text.

Other tests for cold-induced vasospasm include thermal entrainment, digital laser Doppler response to cold, thermography, venous occlusion

plethysmography, and digital artery caliber measurement. None are widely accepted or employed.[52–54]

UPPER EXTREMITY DUPLEX SCANNING

Duplex scanning of the upper extremity is carried out in a manner similar to arterial examination elsewhere. The origins of the brachial cephalic vessels can be difficult to visualize with duplex scanning. For examination of the origin of the subclavian artery a 3- or 5-MHz transducer with a small footprint probe using the sternal notch as a window generally gives the best images. One study found 48 of 50 right subclavian artery origins (96%) and 25 (50%) of 50 left subclavian artery origins could be visualized by color duplex scanning.[55]

Criteria for stenosis at the origins of brachial cephalic arteries are slightly different than those used elsewhere. A PSV ratio of ≥2 indicates stenosis at the origin of a brachial cephalic artery. Stenosis can also be implied by monophasic flow without actual visualization of a high-velocity jet and by reverse flow in a vertebral artery. Such additional criteria are necessary to assess the origins of the brachiocephalic vessels. If only PSV ratios are utilized there would be higher numbers of both false-positive and false-negative results.[55]

More distally the upper extremity arteries are relatively superficial and fairly constant in location. They are best scanned with a higher-frequency probe such as a 7.5- or 10-MHz probe. Either a sector or linear scan head may be used, but in either case a standoff or mound of acoustical gel is helpful to visualize the vessel clearly and to assess the flow pattern within it. Color facilitates identification of the vessels, and tortuosity of the upper extremity arteries may be more easily seen with color flow imaging. Stenosis, occlusions, and aneurysms of upper extremity arteries are all readily identified with ultrasound (Fig. 85.18**A–C**).

The interpretation of duplex findings in the upper extremity beyond the origins of the vessels is similar to the interpretation of B-mode images and Doppler signals gathered in other arterial systems.[56] Normal waveforms in the upper extremity arteries are usually triphasic. As elsewhere in the arterial system, stenosis will produce high-velocity jets, poststenotic turbulence, and

dampened distal waveforms. There are, however, at present no specific frequency or velocity criteria with which to gauge the severity of stenosis in the upper extremity arteries. Some general guidelines are listed in Table 85.5. The diagnosis of arterial occlusion is made by imaging the artery and using the pulsed Doppler to show that there is no flow within the lumen.

For patients with unilateral symptoms who may have a surgically correctable lesion such as a subclavian artery aneurysm or stenosis, duplex scanning is quite useful.[57] The duplex evaluation of aneurysms is based upon the B-mode image appearance, with the most important feature being the size of the enlarged artery and the presence of intraluminal thrombus that may serve as a source of distal embolization. Presence or absence of flow within the aneurysm can be determined by the Doppler component.

Duplex scanning may be of use in patients with suspected embolization to identify proximal aneurysms, but the evaluation should also include echocardiography to look for mural thrombi and valvular lesions. While duplex scanning alone cannot be used to make the diagnosis of Takayasu arteritis, it can be a helpful adjunct in following the progression or regression of arterial involvement in response to treatment.[58]

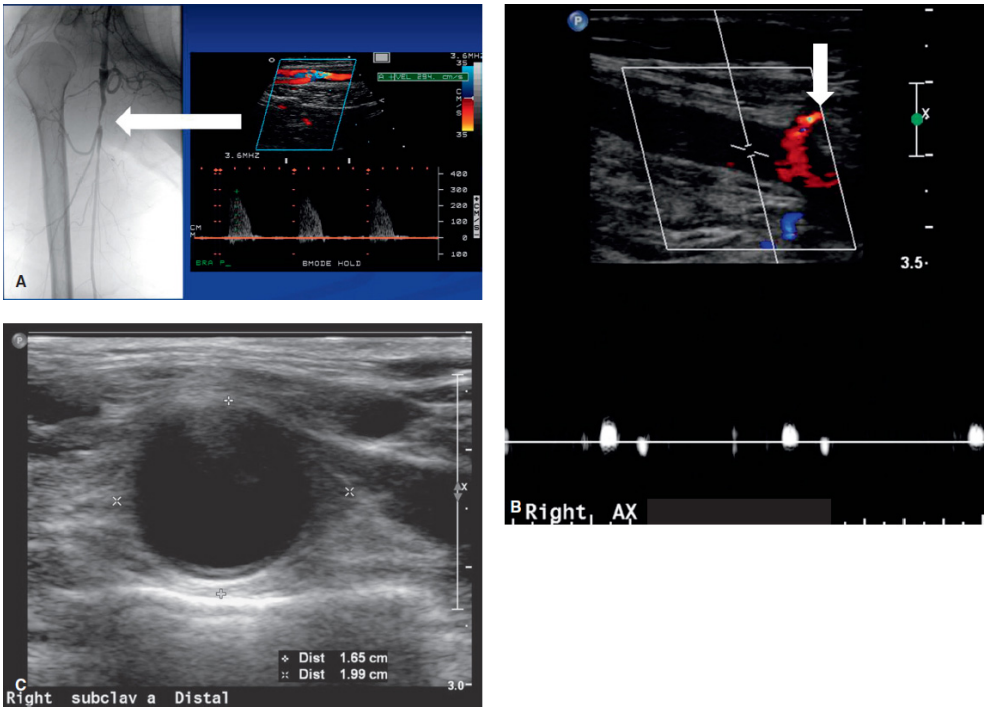

Figure 85.18 **A:** Duplex color flow image and velocity waveform with corresponding angiogram in a patient with brachial artery stenosis (*arrow*) and symptomatic arm ischemia secondary to a crutch injury. Note the loss of the end-systolic reverse flow component of the arterial waveform. **B:** Duplex image of a right axillary artery occlusion secondary to embolism. Note the occlusive waveform and reconstitution of the artery via a distal branch vessel (*arrow*). **C:** Grayscale image of a small subclavian artery aneurysm.

VISCERAL ARTERIES

Mesenteric Arteries

Duplex ultrasonography can serve as a valuable noninvasive screening test for splanchnic artery stenosis in patients with possible chronic mesenteric ischemia and for follow-up of mesenteric artery reconstructions. Aneurysms and dissections of the visceral arteries can also be identified (Fig. 85.19). Despite the accuracy of duplex detection of mesenteric artery stenosis, angiographic confirmation of high-grade stenosis or occlusion of the splanchnic vessels, and appropriate history and physical examination are still required for the diagnosis of chronic mesenteric ischemia. The examination is technically difficult and is best performed by vascular

technologists with extensive experience in intra-abdominal ultrasound techniques.

Table 85.5 Duplex Ultrasound Criteria for Evaluation of Upper Extremity Arterial Stenosis

Condition	Characteristics
Normal	Uniform waveforms; biphasic or triphasic waveforms; clear window beneath systolic peak
<50% diameter reduction	Focal velocity increase; spectral broadening; possibly triphasic or biphasic flow
>50% diameter reduction	Focal velocity increase; loss of triphasic or biphasic velocity waveform; poststenotic flow (color bruit)
Occlusion	No flow detected

Interpretation of Mesenteric Duplex Ultrasound Studies

In healthy individuals, fasting arterial waveforms differ in the SMA versus the CA. The arterial waveforms reflect end-organ vascular resistance. The liver and spleen have relatively high constant metabolic requirements and are therefore low-resistance organs. As a result, CA waveforms are generally biphasic, with a peak systolic component, no reversal of end-systolic flow, and a relatively high EDV. The normal fasting SMA velocity waveform is triphasic, reflecting the high vascular resistance of the intestinal tract at rest. There is a peak systolic component, often an end-systolic reverse flow component, and a minimal diastolic flow component (Fig. 85.20**A**).[59]

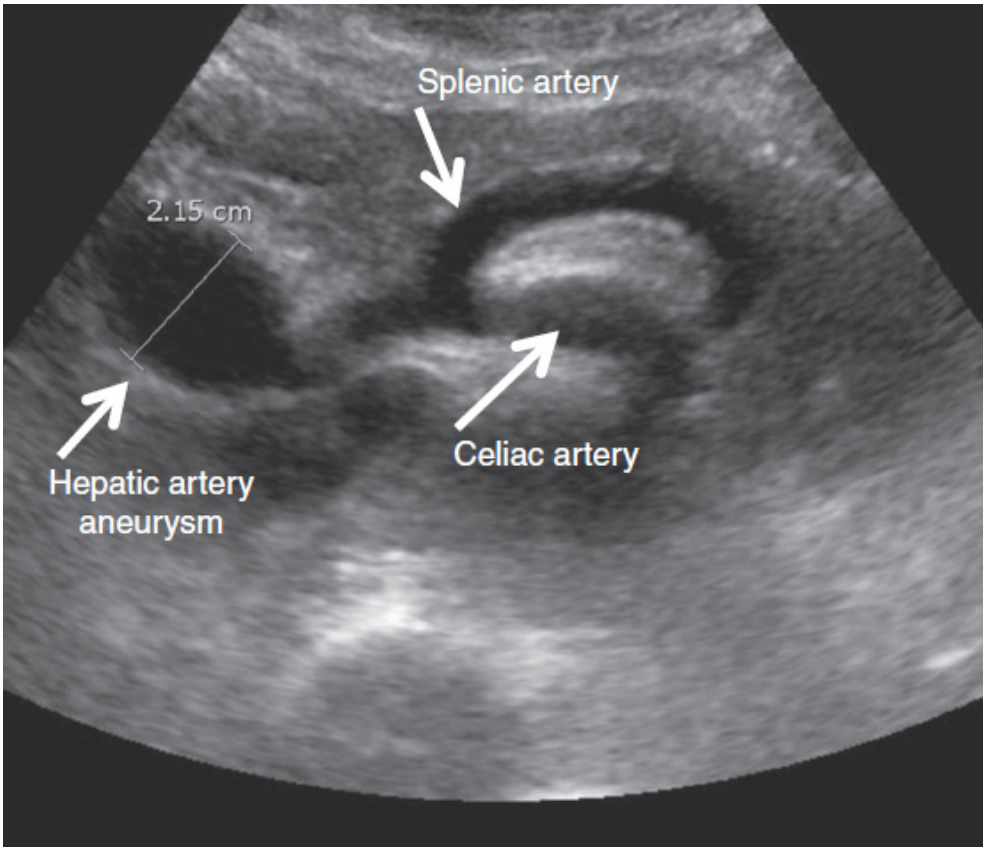

Figure 85.19 Grayscale image of a 2.15-cm hepatic artery aneurysm.

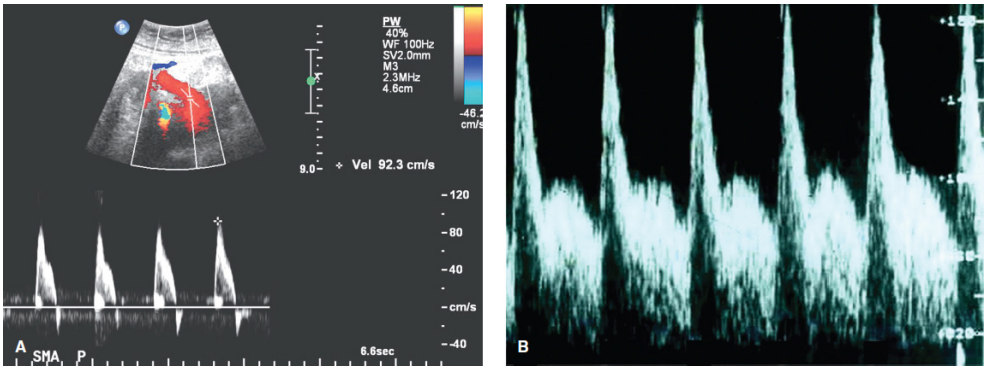

Figure 85.20 **A:** A normal fasting superior mesenteric artery (SMA) waveform may exhibit reverse flow at the end of systole and relatively low end-diastolic velocity reflecting relatively high resistance of the intestinal circulation in the fasting state. **B:** Postprandial SMA waveform. There has been, in comparison to **A,** loss of end-systolic reverse flow and an increase in end-diastolic flow as resistance in the intestinal arterial circulation falls following feeding.

Changes in Doppler-derived arterial waveforms in response to feeding are also different in the CA and SMA. Because the liver and spleen have

basically fixed metabolic demands, there is no significant change in CA velocity waveform after eating. Blood flow in the SMA, however, increases markedly after a meal, reflecting a marked decrease in intestinal arterial resistance. The postprandial waveform changes in the SMA include a near doubling of systolic velocity, tripling of the EDV, and loss of end-systolic reversal of blood flow (**Fig. 85.20B**).[60]

Postprandial changes are maximal at 45 minutes after ingestion of a test meal and depend on the composition of the meal ingested. Mixed nutrient composition meals produce the greatest flow increase in the SMA when compared with equal caloric meals composed solely of fat, glucose, or protein.[61]

Detection of Mesenteric Arterial Stenosis

8 Duplex ultrasound can detect hemodynamically significant stenosis in splanchnic vessels. In a blinded prospective study of 100 patients who underwent mesenteric artery duplex scanning and lateral aortography, a PSV in the SMA of 275 cm/s or more indicated a ≥70% SMA stenosis with a sensitivity of 92%, a specificity of 96%, a positive predictive value of 80%, a negative predictive value of 99%, and an accuracy of 96% (Fig. 85.21). In the same study, a PSV of ≥200 cm/s identified a ≥70% angiographic celiac artery stenosis with a sensitivity of 87%, a specificity of 80%, a positive predictive value of 63%, a negative predictive value of 94%, and an accuracy of 82%.[62]

Other duplex criteria for mesenteric artery stenosis are also in use. An SMA EDV greater than 45 cm/s correlates with a ≥50% SMA stenosis with a specificity of 92% and a sensitivity of 100%, whereas a CA EDV of 55 cm/s or greater predicts a ≥50% CA stenosis with a sensitivity of 93%, specificity of 100%, and accuracy of 95%.[63]

Surgical revascularization of the mesenteric arteries is a standard treatment for chronic mesenteric ischemia. Most often bypass grafts are constructed to the superior mesenteric and/or celiac arteries. Mesenteric artery bypass grafts can be followed postoperatively with mesenteric artery duplex scanning. Flow velocities within mesenteric artery bypass grafts vary little with the origin of the graft (supraceliac or infrarenal aorta or a common iliac artery) and remain stable over time. Serially increasing velocities over

time in a mesenteric bypass likely suggest the development of a graft or anastomotic stenosis.[64]

Placement of an intraluminal stent is a viable alternative in many cases to surgical bypass, for the treatment of mesenteric artery stenosis. Similar to the carotid artery, there is reason to suspect duplex criteria developed for stenosis in native mesenteric arteries may not be applicable without modification to stented superior mesenteric arteries. Mesenteric duplex scans pre- and postplacement of a superior mesenteric artery (SMA) stent have been compared and correlated with pressure gradients measured at the time of angiography. The data indicate that SMA stenting provides good anatomic results and significantly reduces angiographically measured pressure gradients. Duplex measured SMA PSVs are reduced post stent placement but, despite good angiographic results, remain in most cases above criteria predicting high-grade native artery SMA stenosis.[65]

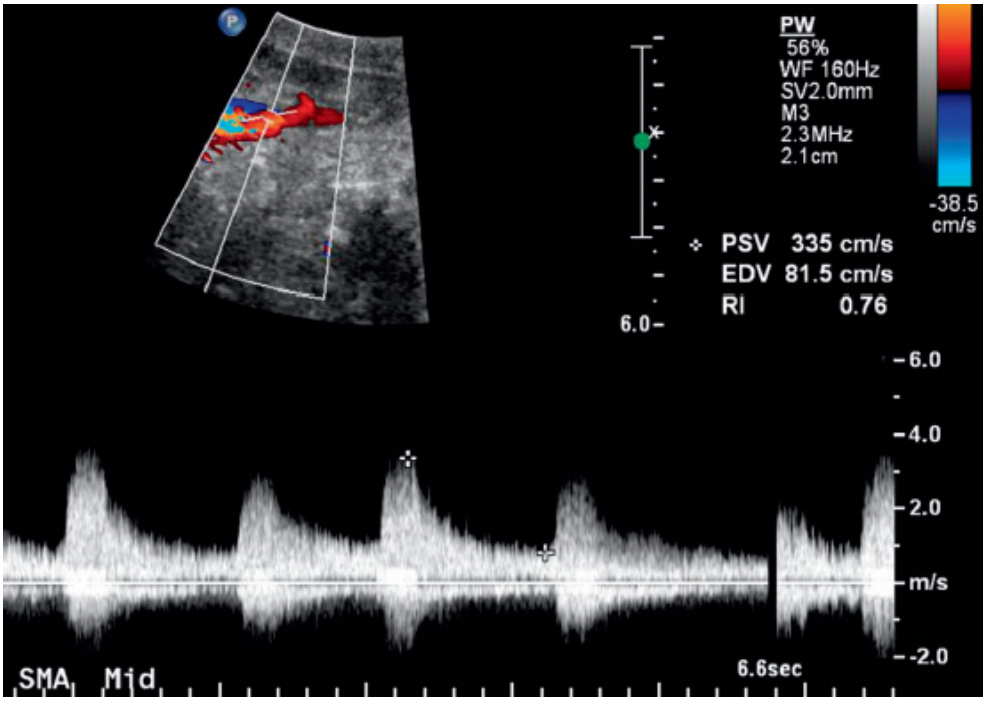

Figure 85.21 Color flow image and duplex-derived SMA waveform in a patient with possible chronic mesenteric ischemia. A peak systolic velocity of >330 cm/s indicates a high-grade SMA stenosis and is compatible with a clinical picture of chronic mesenteric ischemia.

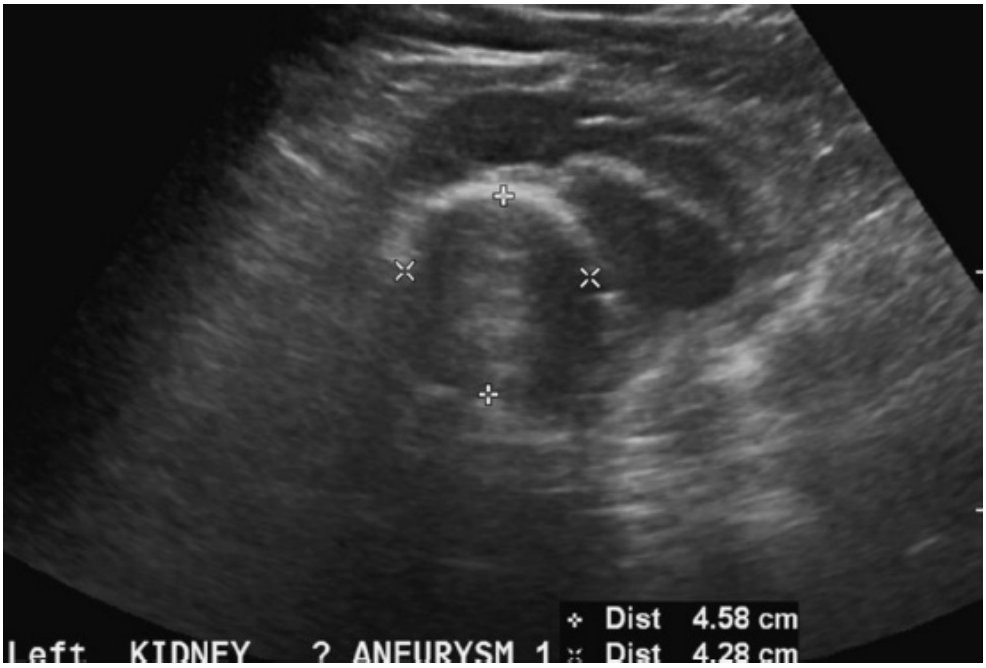

Figure 85.22 Grayscale image of a large renal artery aneurysm in the hilum of the kidney.

RENAL ARTERIES

Duplex scanning of the renal arteries is useful in evaluating for renal artery stenosis in patients with possible renal vascular hypertension and can also be used to detect renal artery aneurysms (Fig. 85.22), as well as provide a measure of the health of the renal parenchyma.

Indirect Assessment of Renal Artery Stenosis

Indirect methods to assess renal artery stenosis evaluate interlobar arteries. Decreased acceleration times and/or presence of tardus/parvus waveforms (waveforms with delayed or slowed upstrokes) may suggest the presence of a main renal artery stenosis. These techniques are quicker and easier to perform than direct examination of the main renal artery but have been not widely validated. Improved visualization of main renal arteries with modern duplex scanners has made indirect methods of assessing the main renal artery essentially obsolete. These techniques are even less accurate in patients with

bilateral stenosis and are not applicable in patients with a single patent renal artery.

Direct Assessment of Renal Artery Stenosis

Normal renal arteries have a PSV less than 180 cm/s and low-resistance waveforms reflecting the high metabolic demands of the kidney. A ratio of the PSV in the renal artery to that in the aorta (renal–aortic ratio, RAR) of ≥3.5 indicates a ≥60% diameter-reducing renal artery stenosis (84% to 88% sensitivity, 97% to 99% specificity, 94% to 98% positive predictive value) (Fig. 85.23).[66] A PSV of ≥200 cm/s has also been suggested to indicate a ≥60% renal artery stenosis whereas a velocity in the renal artery of >185 cm/s has been suggested to indicate a less than 60% renal artery stenosis. Therefore a renal artery can be considered normal when PSV is <180 cm/s and the RAR is <3.5. With a PSV >180 cm/s and a RAR <3.5, the renal artery can be considered to have a <60% stenosis. RARs of >3.5 indicate >60% renal artery stenosis regardless if the renal artery PSV is less than or more than 180 cm/s.[67] When the EDV exceeds 150 cm/s, data suggest a >80% renal artery stenosis.[68] The same criteria have been used to evaluate the patency of renal arterial reconstructions, but similar to stented carotid and mesenteric arteries may need modification for stented renal arteries.[69]

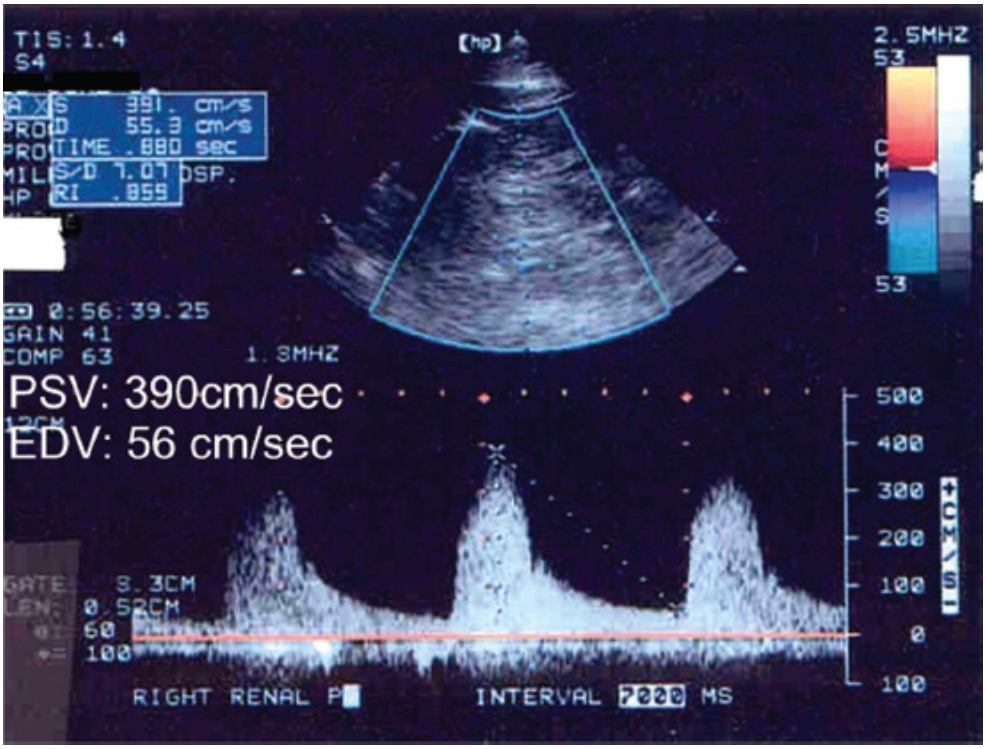

Figure 85.23 Renal artery waveform in a patient with severe hypertension. The high peak systolic velocity is compatible with a high-grade renal artery stenosis.

Predicting Success of Renal Artery Interventions

EDVs tend to be lower in patients with renal insufficiency, indicating decreased diastolic flow and suggesting increased parenchymal resistance to blood flow. Decreased parenchymal diastolic velocities may therefore suggest renal parenchymal disease (Fig. 85.24). Many patients, 20% to 40%, treated with renal artery angioplasty and stenting or open surgical reconstructions do not have postprocedure blood pressure or renal function improvement. An estimate of resistance to flow within the renal parenchyma can be made by comparisons of EDV and PSVs of renal artery waveforms obtained from renal parenchymal arteries. The so-called resistive index (RI) is calculated as follows:

$$RI = [1 - (EDV/PSV)] \times 100 \qquad (85.3)$$

In effect a high RI, >0.7 is bad, suggesting renal parenchymal disease whereas a low RI is good, indicating healthy renal parenchymal tissues.

Evaluation of parenchymal resistance has been suggested as a possible preprocedure predictor of clinical success of renal artery interventions.[70] Abnormal parenchymal resistance may also be a marker of renal allograft dysfunction or rejection (Fig. 85.25).

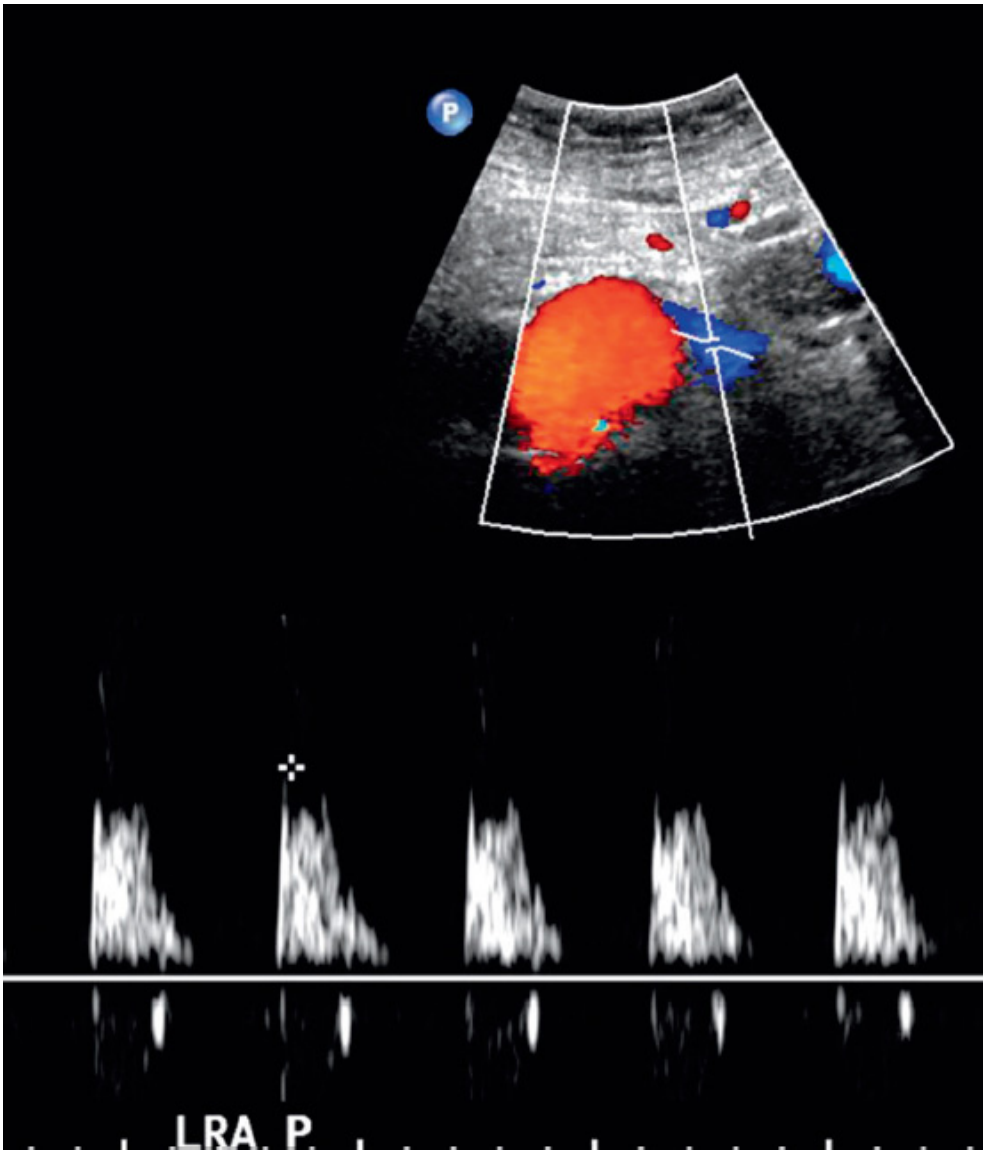

Figure 85.24 The absence of end-diastolic flow in the left renal artery indicates severe parenchymal disease of the left kidney.

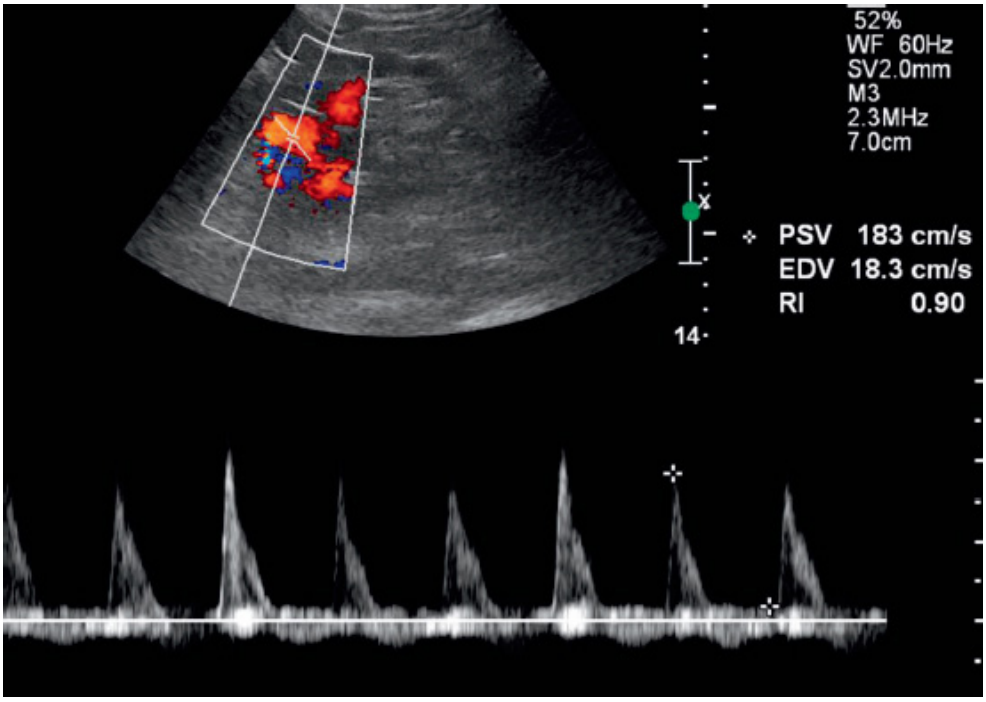

Figure 85.25 There is very little diastolic flow in the renal artery of the transplanted kidney consistent with rejection or primary allograft dysfunction.

VENOUS DISEASE

Acute Deep Venous Thrombosis

Physical examination is not sensitive or specific for the detection of acute deep venous thrombosis (DVT).[71] Prior to the acceptance and widespread use of venous duplex scanning, impedance plethysmography (IPG) was employed as the initial noninvasive test for patients with suspected acute lower extremity DVT. IPG is a reasonably sensitive (87%) and specific (up to 100%) test for proximal (above-knee) lower extremity DVT in symptomatic patients.[72–74] However, lower sensitivities for proximal DVT (65%) have been reported in studies that exclude clinical outcomes and only report in comparison to venography. IPG may not detect nonocclusive proximal DVT, occlusive proximal DVT present in parallel venous systems, such as duplicated femoral or popliteal veins, and cannot detect DVT isolated to the calf veins.[75,76] While IPG is still sometimes used for clinical situations felt to require serial evaluations of the proximal veins, the limitations noted above make it a substandard examination for routine

clinical assessment of lower extremity DVT.[77] Currently, color flow duplex scanning performed by skilled operators provides the most practical and cost-effective method for assessment of DVT of the lower and upper extremity veins as well as for detection of thrombosis in superficial veins.

At a minimum, vascular laboratory duplex ultrasound evaluation for lower extremity DVT should include examination of the common femoral, profunda femoris, femoral, and popliteal veins. Venous waveforms from the right and left common femoral veins should always be compared. A normal lower extremity examination will show patency of the veins on color flow imaging, collapsing of the veins with application of pressure by the ultrasound probe, and venous flow patterns in the common femoral and femoral veins that decrease with inspiration and increase with expiration. Flow within a patent vein should also increase with application of compression distal to the site of examination (Fig. 85.26).

9 The primary ultrasound diagnostic criteria for diagnosis of venous thrombosis is failure of the vein to collapse with application of pressure with the ultrasound probe (Fig. 85.27**A,B**). A continuous flow pattern in one common femoral vein and not the other suggests ipsilateral iliac vein thrombosis or external compression of the ipsilateral iliac vein. Bilateral pulsatile common femoral waveforms suggest volume overload, tricuspid regurgitation, or heart failure.

Not all venous ultrasound examinations for DVT are the same. Some vascular laboratories do not include evaluation of the calf veins as part of their routine evaluation for lower extremity DVT, even in symptomatic patients. This results from outdated perceptions of inaccuracy of calf vein ultrasound evaluation for DVT. Failure to perform a complete initial examination necessitates serial ultrasound examinations or alternative strategies to detect possible extension of venous thrombi initially isolated to the calf veins. Such strategies are inefficient, ineffective for noncompliant patients, and not cost-effective compared to a single stand-alone color flow duplex study of the proximal and calf veins in patients with suspected lower extremity DVT.

Limited ultrasound studies for acute DVT may include compression ultrasound (B-mode imaging only), duplex ultrasound (B-mode imaging and Doppler waveform analysis), and color Doppler alone. The sensitivities and specificities for detecting acute DVT differ among the examinations, and

different examinations are appropriate for different veins. Compression ultrasound is typically performed for evaluation of proximal deep veins, specifically the common femoral, femoral, and popliteal veins. A combination of duplex ultrasound and color Doppler is more often used for calf and iliac veins. Color flow alone may be used to assess patency of the calf veins as they are difficult to reliably compress in subjects with larger legs.

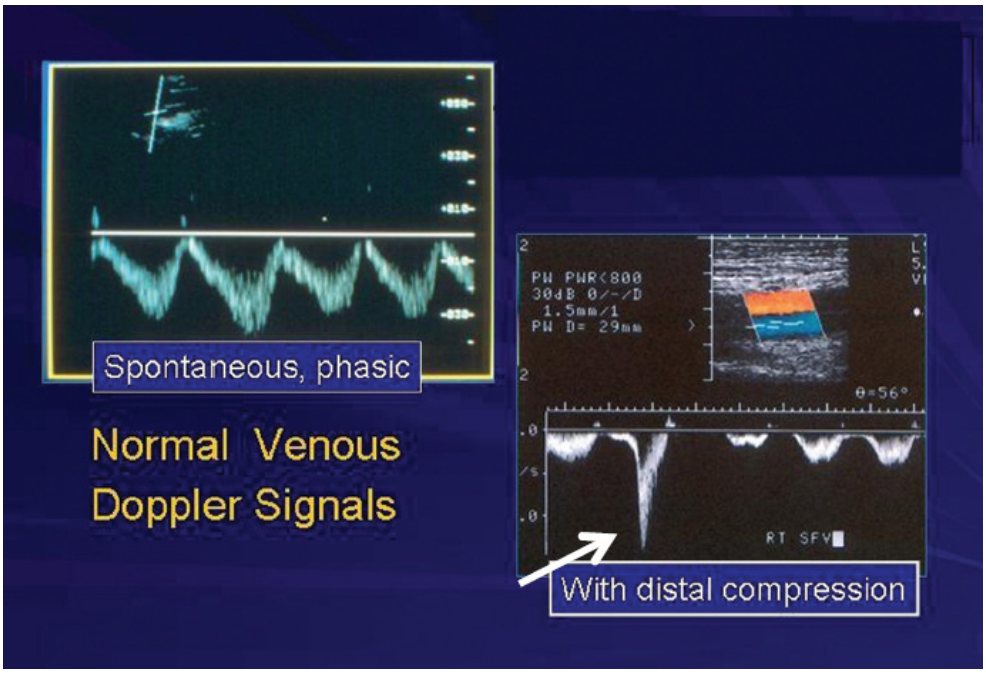

Figure 85.26 Venous flow is typically depicted below the baseline. Venous flow in the proximal lower-extremity veins should be spontaneous, vary with respiration, and augment with distal compression.

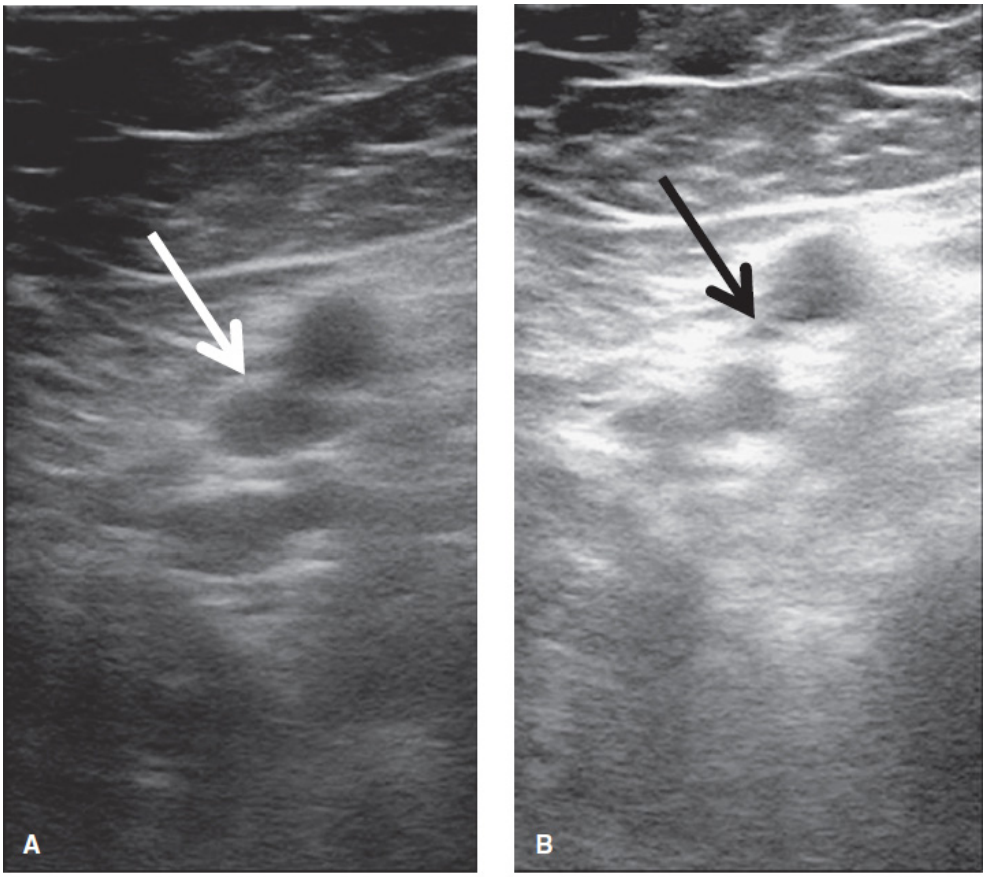

Figure 85.27 **A:** Without compression with the ultrasound probe the femoral vein is easily visible (*white arrow*). **B:** With compression the vein collapses and is no longer visible (*black arrow*). Failure of the vein to collapse with probe pressure would indicate the presence of thrombus within the vein.

Many factors will influence which venous segments can be evaluated in an individual examination. These include the presence of morbid obesity, lower extremity edema or tenderness, or the presence of immobilization devices and bandages. Overall, a complete color and Doppler examination has become the standard of care for assessment of lower extremity DVT. It is recommended that whenever possible, a venous duplex examination to exclude the presence of DVT consist of an evaluation of both the proximal and calf veins.

A well-trained technologist can interrogate calf veins in 80% to 98% of cases using a combination of B-mode, Doppler waveform analysis, and color Doppler.[78,79] Overall accuracy of venous ultrasonography in comparison to venography has been well established. The weighted mean sensitivity and

specificity of venous ultrasonography (including all types) for the diagnosis of symptomatic proximal DVT are 97% and 94%, respectively.[77] As suggested above, in technically adequate studies, the sensitivity and specificity of color Doppler to identify isolated calf vein thrombosis exceeds 90%.[79] The high specificity of venous ultrasonography allows treatment for DVT to be initiated without further confirmatory tests, and the high sensitivity in diagnosing proximal DVT makes it possible to withhold treatment if the examination is negative.

Some ultrasound examinations are limited by practical constraints. Inability of the patient to fully cooperate with regard to positioning for the examination and/or intolerance of the pressure of the ultrasound scan head on the skin, or inability of the examiner to obtain a complete examination secondary to bandages, casts, or extremity wounds, may lead to a requirement for serial examinations. An alternative diagnostic procedure, such as catheter-based contrast, MR, or CT venography may be indicated when a complete ultrasound examination is not possible or if the patient cannot or is unlikely to return for a follow-up examination. Currently, repeat or serial venous ultrasound examinations are advisable in follow-up for a limited negative examination in symptomatic patients highly suspicious for DVT in whom an alternative form of imaging is unavailable or contraindicated.

The diagnosis of pulmonary embolism (PE), like that for DVT, also cannot be established without objective testing. Several studies have evaluated lower extremity venous ultrasound examinations in patients suspected of PE. These studies, often employing ultrasound of only the proximal veins and nuclear medicine-based ventilation perfusion (V/Q) scanning, unfortunately have little relevance to modern practice where complete proximal and distal vein ultrasound examinations are usually routine, and where CT pulmonary angiography (CTPA) or MR pulmonary angiography (MRPA) have largely supplanted V/Q scanning.

The rationale for venous ultrasonography in patients who present with symptoms of PE is that a diagnosis of DVT may indirectly suggest a diagnosis of PE, making additional investigation to exclude PE unnecessary in some clinical settings. However, ultrasound cannot make a definitive diagnosis of PE. Patients can have DVT and pulmonary symptoms or hemodynamic instability from causes other than PE.

Normal bilateral proximal venous ultrasound scans do not rule out PE. When PE is definitively present, DVT of the proximal lower extremity veins is detectable by compression ultrasound in only 50% of patients.[80] When a PE is objectively diagnosed with no evidence of lower extremity DVT, the PE may have originated from pelvic veins, arm veins, or possibly embolized completely from a lower extremity vein. An objective diagnostic test for PE is therefore indicated in most cases. Currently, in most centers this would be a CT pulmonary angiogram.

Chronic Venous Insufficiency

The presence of venous insufficiency can also be evaluated with either air or PPG and with duplex scanning.[81] In theory, APG can provide an analysis of overall venous hemodynamics including evaluation of the individual components of venous function; reflux and the efficacy of the calf muscle pump. A flexible chamber is placed on the calf and volume changes then induced by a series of positional and exercise maneuvers. Measurements derived from these maneuvers are then used to calculate measures of venous reflux (venous filling index [VFI]), calf muscle pump function (ejection fraction [EF]) as well as a measure of overall venous function termed the residual volume fraction. Of these values VFI has the potential for being the most important. A VFI of >2 mL/s indicates abnormal reflux with values >10 mL/s indicating increased risk of cutaneous changes associated with chronic venous insufficiency (CVI). APG, however, while theoretically interesting, is used only infrequently in clinical practice.

Figure 85.28 Placement of PPG probes for assessment of venous reflux.

PPG is a variant of plethysmography techniques to assess venous reflux. It detects changes in the blood content of the skin that theoretically reflect venous volume. It consists of a light emitting diode and a photo sensor. The diode transmits light into subcutaneous tissues. Blood attenuates light in proportion to its content in tissue. The PPG machine amplifies the difference between the transmitted and reflected signal and converts it into a waveform. To assess for venous reflux the sensor is typically applied to the medial ankle area (Fig. 85.28). The patient performs a series of plantar and dorsal flexion maneuvers of the foot decreasing the venous volume of the extremity. The time for the waveform to return to baseline is termed the venous recovery time (VRT). A normal PPG VRT is 20 seconds or greater. Shorter

times indicate the presence of venous reflux. If the VRT returns to normal with the application of a superficial venous tourniquet then the reflux is confined to the superficial venous system (Fig. 85.29). If the VRT does not correct with a superficial venous tourniquet deep venous reflux is present. Neither, APG or PPG can provide information about the specific venous segments that are abnormal. That information can be provided by duplex ultrasound.

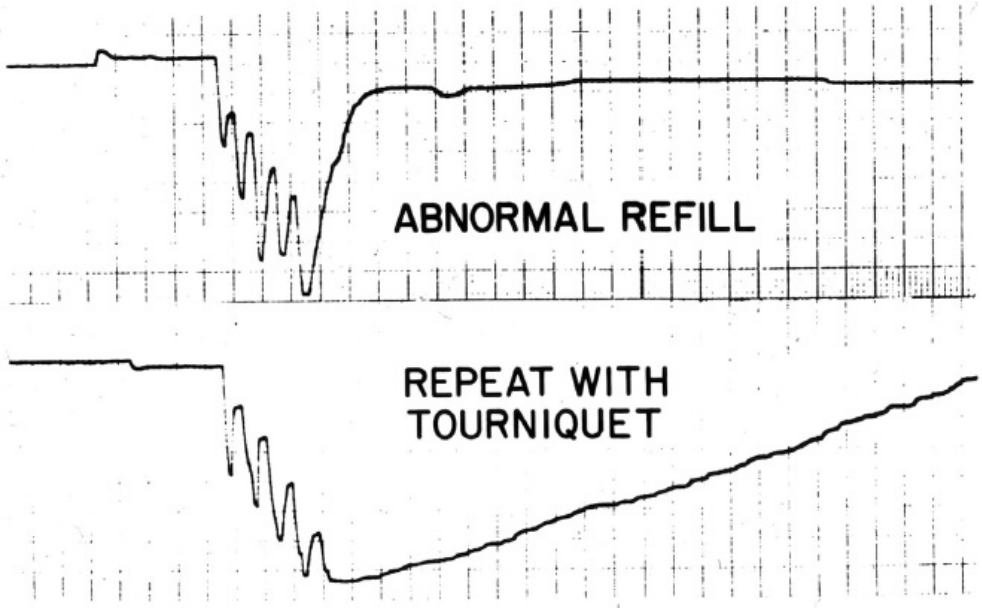

Figure 85.29 Venous PPG waveforms in a patient with superficial venous reflux. The patient is asked to perform 10 dorsal and plantar flexions of the ankle resulting in emptying the leg of venous blood. In the **top panel** the veins refill very rapidly indicating the presence of venous reflux. Refill slows with application of a tourniquet to occlude the superficial veins indicating this patient likely has only reflux in the superficial venous system and no deep venous reflux.

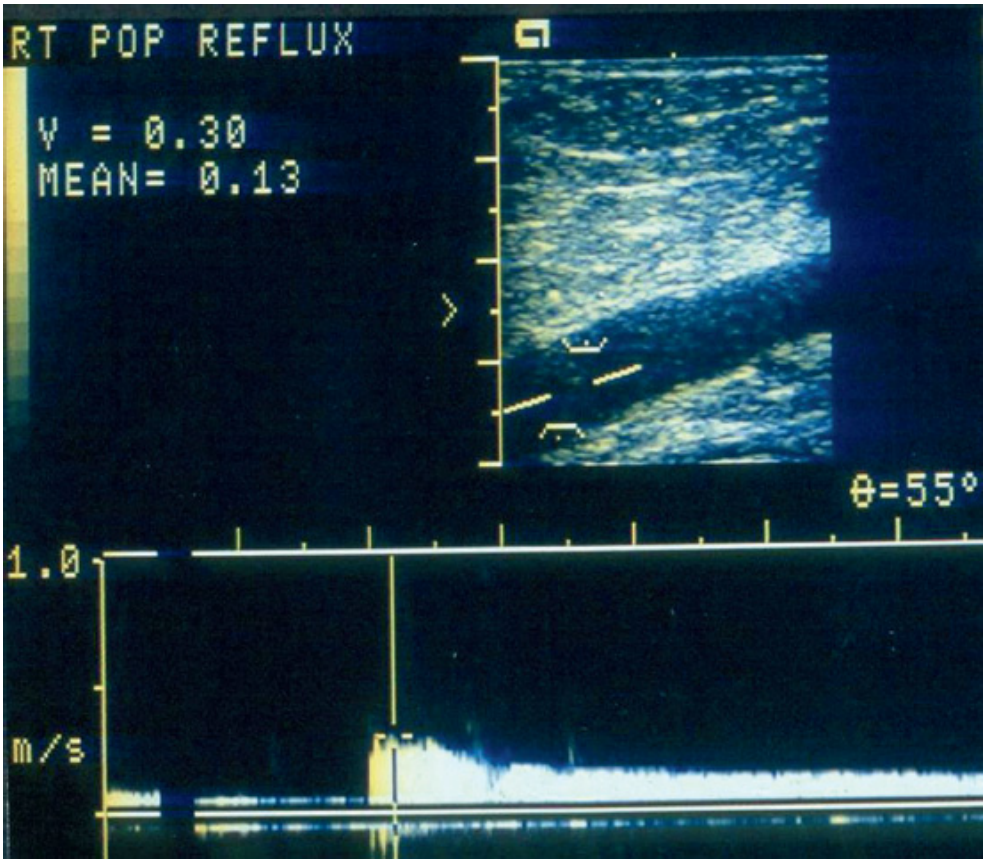

Figure 85.30 Popliteal venous waveform with cuff deflation for duplex assessment and localization of venous reflux. Reflux lasting >0.5 to 1 second is abnormal.

Duplex ultrasound can provide important physiologic and anatomic information in patients with possible CVI. Both sites of reflux and of venous obstruction can be determined in deep, superficial, and perforating veins. In patients with valve incompetence, reflux can be stimulated and then detected with duplex using a Valsalva maneuver, manual compression proximal to the transducer, or release of compression distal to the transducer. The examination has been standardized with the patient upright and using deflation of a series of pneumatic cuffs at specific sites on the leg with the leg under examination 10 not bearing weight. In the upright position, reflux stimulated by cuff deflation that lasts more than 0.5 second is indicative of pathologic reflux.[82] The technique allows localization of reflux to specific venous segments and can serve as a valuable preoperative planning tool to target specific venous segments for removal or reconstruction (Fig. 85.30). It has a sensitivity of 82% and specificity of 100% for the identification of

competent and incompetent perforating veins. Duplex determination of reflux sites and sites of venous occlusion as a means of assessing overall venous hemodynamics is not established. Currently duplex assessment of venous reflux provides the basis of planning for the large majority of venous procedures designed to treat the manifestations of superficial venous reflux.

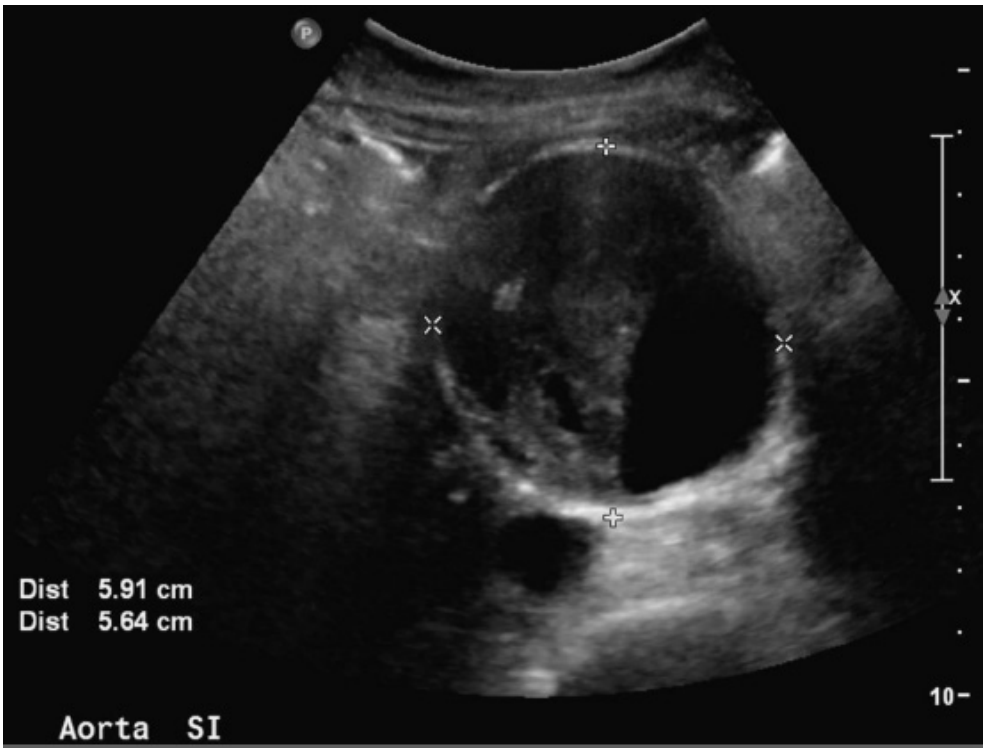

Figure 85.31 Ultrasound image of a 5.9-cm infrarenal abdominal aortic aneurysm with acentric intraluminal thrombus.

SELECTED MISCELLANEOUS EXAMINATIONS

Evaluation for Abdominal Aortic Aneurysm

Vascular laboratory ultrasound screening for abdominal aortic aneurysm (AAA) in males >65 years with a history of cigarette smoking has been shown to be effective in preventing aneurysm-related deaths in this cohort.[83] Ultrasound is highly accurate and reproducible in measuring the diameter of infrarenal AAAs (Fig. 85.31). Typically patients with AAA diameters below

accepted threshold levels for repair are followed with serial ultrasound examinations to monitor for enlargement of the aneurysm to a diameter where repair is indicated.

Evaluation of Aortic Endografts

Placement of endoluminal stent grafts is now standard therapy for most patients with AAA. With stent grafting of an AAA the aneurysm is left in situ and blood flow diverted through the stent graft. Some stent grafts eventually leak at proximal or distal attachment sites. AAAs with these so-called type I endoleaks are at increased risk of rupture. In addition, AAAs treated with stent grafts may also occasionally enlarge because of back pressure in the aneurysm sac from patent lumbar vessels; type II endoleak. Patients whose AAAs enlarge in association with type II endoleaks after endografting are also considered at risk for aneurysm rupture.

Standard monitoring of endoluminal stent grafts is with serial CT scans to detect endoleak and changing aneurysm sac diameter. However, there are increasing concerns about repeated doses of contrast and radiation exposure associated with serial CT scans. It now appears many stent grafts can be followed with serial duplex ultrasound examinations. Duplex ultrasound is capable of measuring sac diameter (Fig. 85.32) and detecting both type I and II endoleaks. Even if an endoleak cannot be detected by ultrasound an increase in sac diameter following stent grafting should prompt further investigation. In some centers duplex ultrasound has replaced CT scanning as the preferred method of follow-up of AAA stent grafts.[84,85]

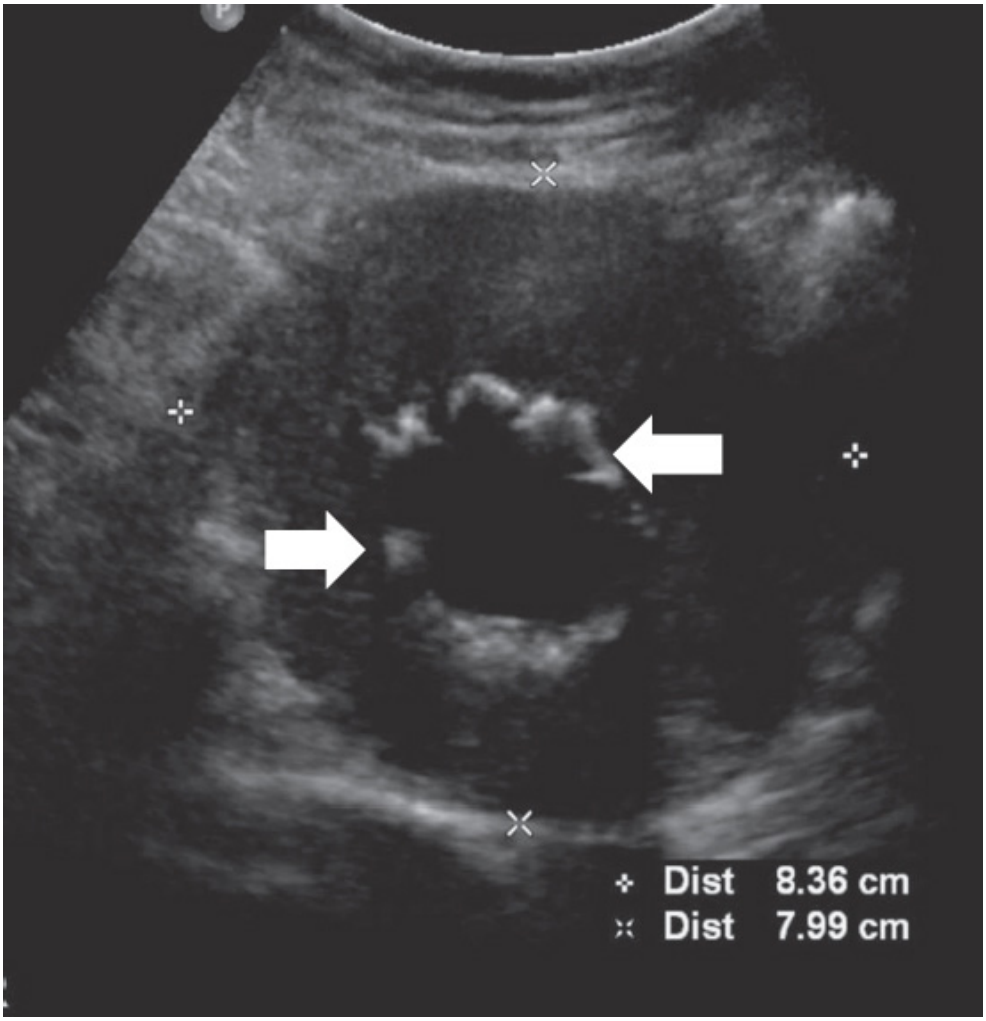

Figure 85.32 Ultrasound examination of an aortic stent graft. The aortic stent graft (*arrows*) is visible within the lumen of the residual aneurysm sac measuring 8.36 cm × 7.99 cm.

Evaluation and Treatment of Groin Pseudoaneurysms

Pseudoaneurysms can occur as a complication of an arterial puncture in the groin performed for diagnostic or therapeutic angiography. Groin pseudoaneurysms are readily detected with duplex ultrasound (Fig. 85.33). Color flow demonstrates a typical collection of flowing blood usually anterior to the artery from which the psuedoaneurysm originates. The native artery and the pseudoaneurysm are connected by a so-called "neck." To-and-

fro flow within the neck of the pseudoaneurysm is characteristic and pathognomonic of a pseudoaneurysm arising from an arterial puncture.

Treatment of pseudoaneurysms may be with direct surgical repair or, utilizing the vascular laboratory, direct compression of the pseudoaneurysm until it clots using the ultrasound scan head to both locate the pseudoaneurysm and apply pressure. Alternatively, the pseudoaneurysm is visualized with the ultrasound scan head and a needle introduced into the body of the pseudoaneurysm for injection of small amounts of thrombin to induce thrombosis of the pseudoaneurysm.[86] All techniques are effective but currently direct thrombin injection is favored in most cases as it is relatively noninvasive and less painful and more effective than prolonged compression alone.[87,88]

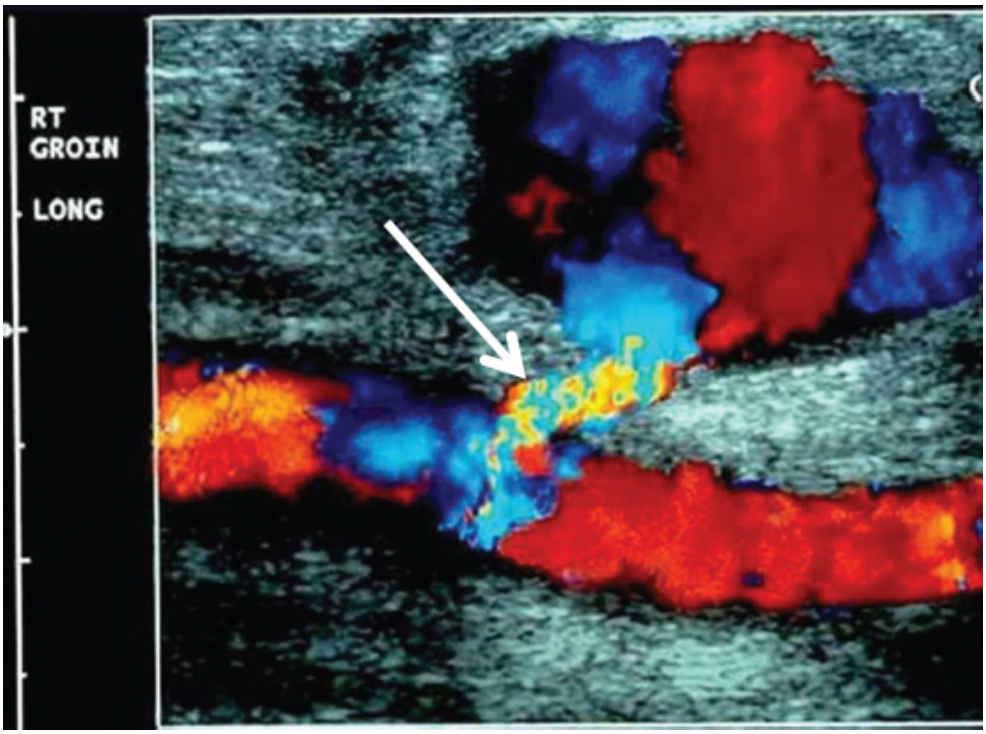

Figure 85.33 A pseudoaneurysm of the superficial femoral artery following arterial cannulation. The so-called neck of the aneurysm (*arrow*) is readily visible.

Figure 85.34 A transcutaneous oxygen probe. $TCpO_2$ measurements can serve as an aid in determining healing potential of pedal wounds or ulcers.

Transcutaneous Oxygen Measurements

Measurements of transcutaneous oxygen ($TCpO_2$) can be performed as an aid in predicting healing of pedal lesions or healing of an amputation at the site where the measurement is taken (Fig. 85.34). In general, a $TCpO_2$ >30 mm Hg indicates healing is likely, measurements between 20 and 30 mm Hg are equivocal for healing and measurements below 20 mm Hg indicate healing is unlikely.[89] Measurements are not influenced by the presence of diabetes but it has been suggested the level for predicting healing be increased to 40 mm Hg in patients with diabetes. The test is less accurate in the presence of edema, cellulitis, hyperkeratosis, and in older patients.

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86

Vascular Infection

Courtney E. Morgan and John E. Rectenwald

Key Points

1 The pathogenesis of infected aneurysms involves seeding of a pre-existing aneurysm by bacteremia.

2 The pathogenesis of microbial arteritis involves hematogenous seeding of an atherosclerotic plaque.

3 The pathogenesis of infected aortitis involves direct spread of infection to the aorta by contiguous septic structures, such as vertebral osteomyelitis.

4 The pathogenesis of arterial graft infections involves seeding of the graft from intraoperative contamination, erosion of adjacent structures, or hematogenous seeding from a distant source.

5 Characteristics of a prosthetic graft that predispose to graft infection include surface irregularity that permits bacterial attachment, abrogation of local defense against infection, creation of the bacterial biofilm that protects microbes from host defenses and antibiotics, all of which lowers the bacterial bioburden required to cause a graft infection.

6 The most common organisms causing arterial graft infections are skin flora, especially *Staphylococcus aureus* and *Staphylococcus epidermidis*.

7 Diagnosis of vascular infections requires a high index of suspicion as patients often present with nonspecific symptoms. This requires a thorough query of recent sources or risk factors for infection, evaluation of culture data and inflammatory markers, and understanding the pros and cons of various imaging techniques in detecting vascular infections.

8 Surgical treatment of arterial infections requires appropriate resuscitation, preoperative planning, resection of all infected material and tissue, and revascularization. No single approach is suitable for all patients, but understanding the algorithm and tailoring this to local surgical expertise is critical in caring for these patients.

9 Antibiotic therapy is imperative in treatment of arterial infections. Initial treatment involves broad-spectrum antibiotics followed by culture-driven therapy when possible, although up to 40% of patients are culture negative. While there are no guidelines directing the type, dose, duration, or route of therapy, most patients are treated with an initial

multiweek course of antibiotics with consideration for long-term suppression if not all graft material is excised.

10 Each method of aortic reconstruction after aortic graft excision has varied outcomes. Extraanatomic bypass with aortic ligation risks aortic stump blowout and poor graft patency. Reconstruction with in situ cryopreserved allograft has high cost, varied availability, and can demonstrate pseudoaneurysm degeneration. In situ reconstruction with rifampin-soaked Dacron has excellent patency, but has higher reinfection rates. In situ autogenous vein reconstruction is time consuming, but is resistant to infection and has excellent patency.

INTRODUCTION

Vascular infections are among the most daunting conditions that a surgeon may encounter in clinical practice. Vascular infections may afflict native arteries and veins or vascular prostheses. Primary arterial infections of native arteries are rare, but highly lethal conditions.[1] Secondary infections of prosthetic vascular grafts, albeit rare, are seen more frequently and are often more challenging because of the adhesions, scarring, and inflammation in the redo operative field.[2] These infections commonly occur in a compromised patient population with significant chronic medical conditions and relative immune deficiency. The clinical presentations for vascular infections range from indolent infections detected incidentally to overt sepsis or hemorrhage.[1] The management of vascular infections is individualized, based on the clinical presentation, anatomic location of the vascular infection, and the medical condition of the patient. In recent years, newer therapeutic adjuncts, such as covered stents and improved cryopreserved grafts offer additional options to surgeons managing and treating arterial graft infections. However, the basic tenets of timely diagnosis, antibiotic administration, resuscitation, operative planning, surgical resection, and revascularization remain the mainstays of therapy in most cases.

DEFINITIONS AND PATHOGENESIS

Pathogenesis of Primary Arterial Infections

1 Arterial infections commonly result in aneurysms, or more correctly pseudoaneurysms since there is disruption of the arterial wall in many infected aneurysms. Aneurysms or pseudoaneurysms related to infection are often loosely termed "mycotic aneurysms." However, the term mycotic aneurysm was initially coined to describe an arterial aneurysm or pseudoaneurysm caused by a septic embolus from the heart that lodges in a distal artery to create a septic focus that injures the adjacent artery.[3] "Mycotic aneurysm" is a misnomer as the vast majority of these are of bacterial origin, not fungal. Pre-existing aneurysms that are subsequently seeded by bacteremia 2 are "infected aneurysms." Arteries in which an atherosclerotic plaque becomes seeded develop "microbial arteritis." "Traumatic 3 infected aneurysms" describe those infected aneurysms or pseudoaneurysms that develop secondary to complications of iatrogenic or other trauma. "Infected aortitis" occurs when the aorta becomes infected by contiguous septic structures, such as vertebral osteomyelitis.[3] For simplicity, we will utilize the term "primary arterial infection" to refer to all infected arterial infections that occur in the absence of prosthetic graft or stent material.

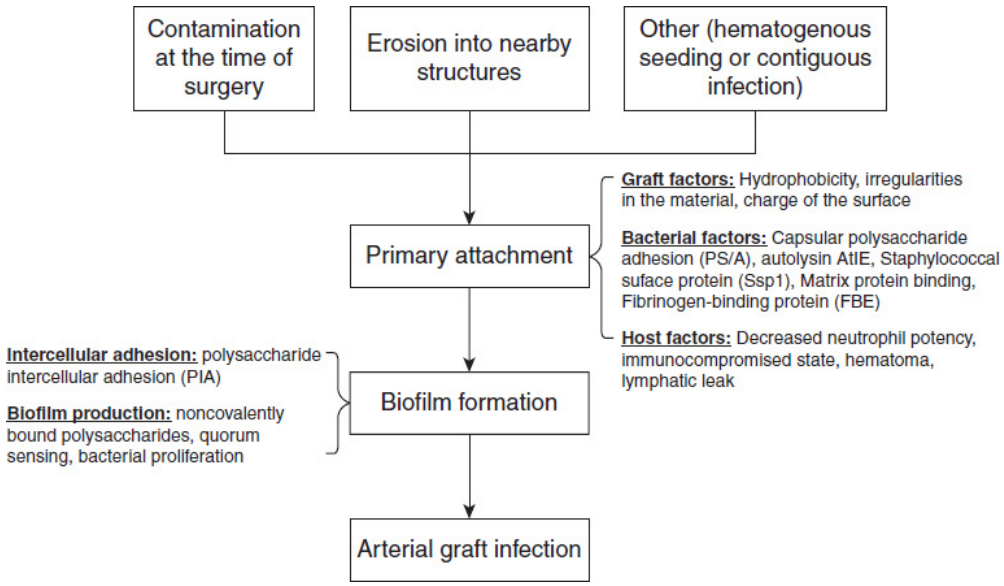

Figure 86.1 Proposed mechanism of *Staphylococcus epidermidis*–mediated graft infection.

Infective endocarditis is no longer the major source of primary arterial infections. Arterial trauma, due to iatrogenic trauma, or intravenous drug use, appears to be the most prevalent cause.[1,4] Risk factors for primary arterial infections include trauma to the arterial wall, atherosclerosis, and pre-existing aneurysmal degeneration. In an autopsy study, Miller reaffirmed that many of

infected aneurysms arise after pre-existing atherosclerotic lesions are seeded due to an episode of bacteremia, since 75% of the infected arteries had evidence of atherosclerosis in the resected specimen.[5] In Miller's study, 42% of arterial infections were located in the infrarenal aorta; the descending thoracic aorta was the next most common site of infection.[5] Immune compromise by systemic conditions or medications, such as chronic steroid use, malignancy, human immunodeficiency virus syndrome, chronic hepatitis, or malnutrition, is a common theme among patients with primary arterial infections. Predisposing conditions have been identified in nearly 70% of patients with mycotic aneurysms.[5–8]

Pathogenesis of Arterial Graft Infections

4 Prosthetic grafts are foreign bodies that are either seeded at the time of the operation, or become infected secondarily due to hematogenous seeding or contiguous infection. The incidence of aortic graft infection is about 1% with one study suggesting similar numbers for open prosthetic graft repair (1.4%) versus endograft (0.9%). This did not differ between thoracic and abdominal aortic aneurysms.[9] No particular endograft design or fabric appears to alter the risk of graft infection, but presences of infection at the time of the initial hospitalization occurs in 34% of patients.[10]

Lower extremity prosthetic grafts are at the highest risk of infection, which probably relates to the abundance of skin flora in the groin and the proximity of the graft to the incision. Infections of grafts originating from or terminating at the femoral artery complicate 4% to 6% of cases.[11,12] By comparison, carotid patches rarely become infected, with Mann reporting a single-center incidence of 0.8% over 20 years.[13] Polytetrafluoroethylene (PTFE) may be somewhat more resistant to infection than Dacron, as it has less porosity to sequester microbes.[14] Peripheral bare metal stents appear to be highly resistant to infection, with a presumed incidence of less than 0.1% based on isolated case reports.[15]

5 Prosthetic material is at risk for becoming infected for several reasons. First, a 10,000-fold lower bacterial bioburden is required to cause a graft infection, relative to healthy tissue.[16] Irregularly surfaced materials are also more likely to harbor microbes, as these surfaces create small pockets where shear stress is decreased to allow bacterial attachment.[14,17] Also, the local inflammatory response to implants abrogates the local defense against infection. Instead of being inert, the prosthetic material acts as a potent activator of host

defenses, which subsequently renders them less capable of defending the graft from infection. Multiple studies have shown contact with implants causes neutrophils to lose their ability to produce superoxide and reactive oxygen species, which are critical to their bactericidal activity.[18,19] Finally, communities of bacteria form slime to create biofilms, protecting microbes from host defenses and antibiotics.[14,17,20] Quorum-sensing is prevalent in biofilms, which decreases the virulence of microorganisms and makes them more difficult to eradicate by host defenses as the bacteria proliferate.[21] This is a critical step in the pathogenesis of prosthetic graft infections caused by *Staphylococcus epidermidis* (Fig. 86.1).[14,16,21]

MICROBIOLOGY

Primary Arterial Infections

For infected aortic aneurysms, blood cultures are negative in approximately one-fourth of subjects.[5] Intraoperative cultures are more reliable, although intraoperative cultures may be negative in many cases due to improper culture techniques or preoperative antibiotic administration that precludes isolation of 6 organisms.[5–8] In other series, up to 40% of infected aneurysms had negative blood and/or tissue culture.[6,10] The most frequent causative organisms vary by country. Hsu et al. found that 76% of primary aortic infections in Taiwan were due to *Salmonella* strains.[8] Reports from the United States show that *Staphylococcal* species (*S. aureus* or *S. epidermidis*) are most prevalent, followed by *Escherichia coli, Streptococcal* species, and *Salmonella.* Anaerobic, mycobacterial, and fungal infections represent rare causes of arterial infections.[5,7] European series are similar to the American experience, as Muller reported that 30% of infections in his series were related to *S. aureus* and *S. epidermidis*.[6] In Muller's series, *Salmonella* was the next most frequent isolate, followed by *Aspergillus, Enterococcus, Streptococcus,* and *E. coli*.[6] The causative organisms also appear to vary based on the artery involved. Infected femoral artery aneurysms are rarely true aneurysms, but are infected pseudoaneurysms related to prior catheterizations or intravenous drug use. Skin flora, such as *S. aureus* or *Streptococcal* species, are the predominant organisms isolated from infected femoral artery pseudoaneurysms.[22,23]

Arterial Graft Infections

The most common causal organisms for prosthetic grafts are *Staphylococcus* and *Streptococcus* except in the case of aortoenteric fistula (AEF) where *E. coli* is the most common organism. Up to 30% are polymicrobial, an equal number have negative intraoperative cultures.[10,24]

Prosthetic grafts infections involving the femoral artery are most often related to *Staphylococcal* species, which comprised 68% of the infections in one series.[11,12] *Enterococcal* and polymicrobial infections were less frequent among femoral artery grafts.[11,12] Endograft infections are predominantly caused by *Staphylococcal* species and other minor skin flora, such as *Propionibacterium*.[25] Similarly, *Staphylococcal* species predominate in peripheral arterial stent infections, with over 85% of the case reports attributed to *Staphylococcal* species.[15] In a report on carotid artery prosthetic patch infections, Mann found that 58% were related to *Staphylococcal* infection, one-third had an unidentified source due to negative cultures, and the remainder had gram-negative infections, with one beta-hemolytic *Streptococcal* infection.[13]

CLASSIFICATION OF ARTERIAL GRAFT INFECTIONS

Early graft infections are defined as those occurring less than 4 months after graft implantation. The Szilagyi classification system classified early surgical site infections[26] which was modified by Samson to further distinguish between different types of vascular infections.[27] Bundt's classification, developed in 1983, describes prosthetic graft infections according to the anatomic segment of the graft that is involved,[28] while the Management of Aortic Graft Collaboration was developed in 2016 in collaboration with vascular surgeons, infectious disease specialists, and radiologists to better define precise criteria for defining aortic graft infection.[29] These criteria are summarized in Table 86.1. Clinical management often varies significantly based on the extent of infection, according to these classification systems.

DIAGNOSIS

The diagnosis of primary arterial infection or prosthetic graft infection may be difficult due to the significant overlap of symptoms with other pathologies. While a thorough history and physical examination are essential, a high index of suspicion is critical to the diagnosis. Delays in diagnosis may have devastating consequences for the patient. Understanding some of the more common presentations of arterial infections can facilitate a timely diagnosis.

Common Clinical Presentations

7 Patients with vascular infections often present with nonspecific symptoms of malaise, fever, and pain in the region of the infected artery or graft, which may be accompanied by elevations in erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).[7,10] These symptoms are most commonly associated with arterial infections caused by more virulent organisms, such as *S. aureus, Pseudomonas aeruginosa, E. coli,* or polymicrobial infections. Arterial infections caused by lower virulence organisms, such as *S. epidermidis* or *Enterococcus,* are often even more indolent and may not be associated with local or systemic signs and symptoms.[12] Peripheral arterial infections (primary or graft infections) may exhibit local symptoms, such as erythema, swelling, tenderness, or a sinus tract with purulent drainage.[12] In contrast, local signs and symptoms are unlikely with infections of cavitary arteries or grafts.

Table 86.1 Classification of Arterial Graft Infections

Szylagi Classification[26]	Grade I: Cellulitis involving wound Grade II: Infection involving subcutaneous tissue Grade III: Infection involving native arteries or vascular graft		
Samson Classification[27]	Group 1: Infection does not extend beyond dermis Group 2: Infection involves subcutaneous tissue but does not contact graft Group 3: Infection involves body of graft, but not anastomosis Group 4: Infection involves the anastomosis, without anastomotic bleeding or bacteremia Group 5: Infection involves a graft to artery anastomosis and associated with septicemia bleeding at the time of presentation		
Bundt Classification[28]	P0: Infection of a cavitary graft P1: Infection of a graft whose entire anatomical course is noncavitary P2: Infection of the extracavitary portion of a graft whose origin is cavitary Graft-enteric erosion Graft-enteric fistula Aortic stump sepsis after excision of an infected graft		
MAGIC Criteria[29]	**Clinical/Surgical**	**Radiology**	**Laboratory**
Major	Pus around graft or in aneurysm sac Open wound with exposed graft or communicating sinus Fistula development (aortoenteric	Perigraft fluid on CT scan >3 mo after insertion Perigraft gas on CT >7 weeks after insertion Increase in perigraft gas volume demonstrated on serial imaging	Organisms recovered from implanted graft Organisms recovered from operative specimen organisms

	or aortobronchial) Graft insertion in an infected site		recovered percutaneous, radiologic aspirate of perigraft fluid
Minor	Localized clinical features of graft infection Fever >38°C as most likely cause	Other (e.g.) suspicious perigraft gas/fluid, soft issue inflammation, aneurysm expansion, pseudoaneurysm formation, focal bowel wall thickening, osteomyelitis, suspicious metabolic activity on FDG-PET/CT, radiolabeled leukocyte uptake	Blood cultures positive without apparent source except graft abnormally elevated inflammatory markers with graft infection as likely cause

If a primary arterial infection is suspected, the patient should be queried for potential sources of infection. Many patients with arterial or graft infections have a history of an antecedent infection, such as pneumonia or a urinary tract infection.[7] A recent gastrointestinal illness may be a source of exposure to *Salmonella*.[8] Other potential clues include a history or clinical stigmata of intravenous drug use or a recent invasive procedure, which could provide a mechanism for seeding of a native artery or graft.

Associated medical conditions may be cofactors in the pathogenesis of vascular infections. Any condition that produces relative immune compromise may predispose to primary arterial or graft infection. Examples include

malignancy, human immunodeficiency virus syndrome, chronic hepatitis, malnutrition, and conditions that require immunosuppressive medications. Predisposing conditions have been identified in up to 70% of patients with mycotic aneurysms.[5–8] Malignancy is especially relevant due to the association between *Clostridium septicum* arterial infections and malignancy.[30] Symptomatic atherosclerosis is important to note since atherosclerotic plaques may become seeded by episodic bacteremia to create a primary arterial infection.

For patients with a history of a prior bypass involving the femoral artery, occult infections frequently present with an anastomotic pseudoaneurysm in the groin. Over 60% of femoral pseudoaneurysms are ultimately found to harbor an occult infection.[31] Mertens found that 74% of patients with infected infrainguinal bypass grafts presented with a draining wound or sinus.[32] Infections with low virulence organisms, such as *S. epidermidis,* are less likely to be present with a draining sinus because the virulence of the organisms is insufficient to incite a vigorous inflammatory response to produce the sinus tract.[12]

Graft thrombosis is another underappreciated clinical presentation for an occult graft infection. Graft thrombosis is believed to predispose to subsequent graft infection.[33] The coagulated blood within a thrombosed prosthetic graft provides a rich media for the microorganisms to proliferate.[33] In addition, prosthetic materials are fomites that may harbor microorganisms. Some authors advocate removing occluded grafts when performing subsequent revascularization operations or amputations to prevent contiguous spread from the prior occluded grafts.[34]

AEF with gastrointestinal hemorrhage is a rare, but life-threatening presentation for graft infection that must be diagnosed expeditiously. Any patient presenting with gastrointestinal hemorrhage that has a history of prior aortic surgery, especially those with vascular prostheses, must have a rapid evaluation for an AEF. AEFs often present initially with a “herald bleed,” or a relatively small amount of gastrointestinal bleeding that temporarily abates prior to a full on fatal exsanguination several hours or days later.[35–39] The mortality rate for AEFs is 30% to 77%. Delay in diagnosis is frequently a contributing factor among patients who die from this condition. Approximately 75% of AEFs result from a communication between the aorta and the third or fourth portion of the duodenum.[35] The vast majority of AEFs occur in the setting of prior surgical or endovascular aortic reconstruction. Rarely AEFs occur as a complication of a primary aortic infection.[38] If a portion of the graft erodes through the adjacent

bowel without suture line involvement, gastrointestinal bleeding results from intestinal mucosal irritation. This phenomenon is termed "graft-enteric erosion."[39] Graft-enteric erosions are often discovered incidentally during surgery to excise an infected aortic graft.

Ureteral obstruction can occur due to a mechanical complication during the tunneling of an aortofemoral limb or as a consequence of the inflammatory reaction associated with an infected aortofemoral limb. Ureterohydronephrosis is strongly associated with aortic graft infections. Wright et al. found that the presence of a urologic complication after aortoiliac arterial reconstructions was associated with a fourfold increase in the risk of graft complications, including pseudoaneurysms, limb thrombosis, AEFs, and overt graft infections.[40] Ureteral complications are typically asymptomatic, so ureterohydronephrosis is often discovered incidentally during imaging studies for other indications and should alert the physician to the possibility of a graft infection.

Imaging for Vascular Infection

The history, physical examination, and laboratory findings for primary arterial infection or graft infections are often nonspecific, so imaging plays a pivotal role in establishing a diagnosis. Although advances in imaging techniques have improved the sensitivity and specificity significantly, no single modality is perfect. Confirming a physician's suspicion of occult infection with a low-virulence organism remains a challenge in many cases. Understanding the advantages and disadvantages of each imaging modality will allow the surgeon to choose the most appropriate examination, or combination of imaging studies, to optimize the diagnostic yield.

Computed Tomography (CT) and Computed Tomographic Angiography (CTA)

CT and CTA are the preferred imaging modalities for suspected aortic graft infections in most centers. CT is readily available in most hospitals, and standard protocols enable most centers to duplicate the diagnostic sensitivity achieved at centers of expertise. Contrast allergy, contrast-induced nephropathy, metal artifact, and radiation exposure are shortcomings of CT, but the benefit outweighs the risk in most cases. The addition of oral contrast agents can help to define the association with enteric structures if an AEF is suspected. Findings suggestive of graft infection on CT or CTA include inflammatory changes in the

soft tissues surrounding the graft (**Fig. 86.2**), thickening of the bowel adjacent to vascular structures, loss of tissue planes around the artery or graft, perigraft or periarterial air or fluid, or erosion into surrounding structures (**Figs. 86.3** and **86.4**).[41,42] The sensitivity and specificity of CT for the diagnosis of aortic graft infections may be as high as 95% and 88%, respectively,[42] although the diagnostic accuracy varies depending upon the organism and severity of the infection. The sensitivity and specificity for low-grade, indolent infections may be as low as 55% and 100%, respectively.[43,44] The presence of either fluid or air significantly enhances both the sensitivity and specificity of CT scans for detecting late graft infections (>4 months postimplantation).[41,42] Early graft infections (<4 months postimplantation) present a particular challenge for diagnosis. Perigraft air is a normal finding in the periaortic tissues for 2 months after open aortic reconstruction and should not be considered indicative of an aortic graft infection.[45] Similarly, a small amount of perigraft fluid is normal for 3 months after arterial reconstruction.[41] After endovascular aortic aneurysm repair, Sawhney found that air was visualized in the aneurysm sac, surrounding the endograft, in 58% of patients on early postoperative CTA.[46] The air is introduced during endograft deployment and dissipates over a period of weeks after surgery.

Figure 86.2 CT scan demonstrating thickened inflammatory wall around the aorta.

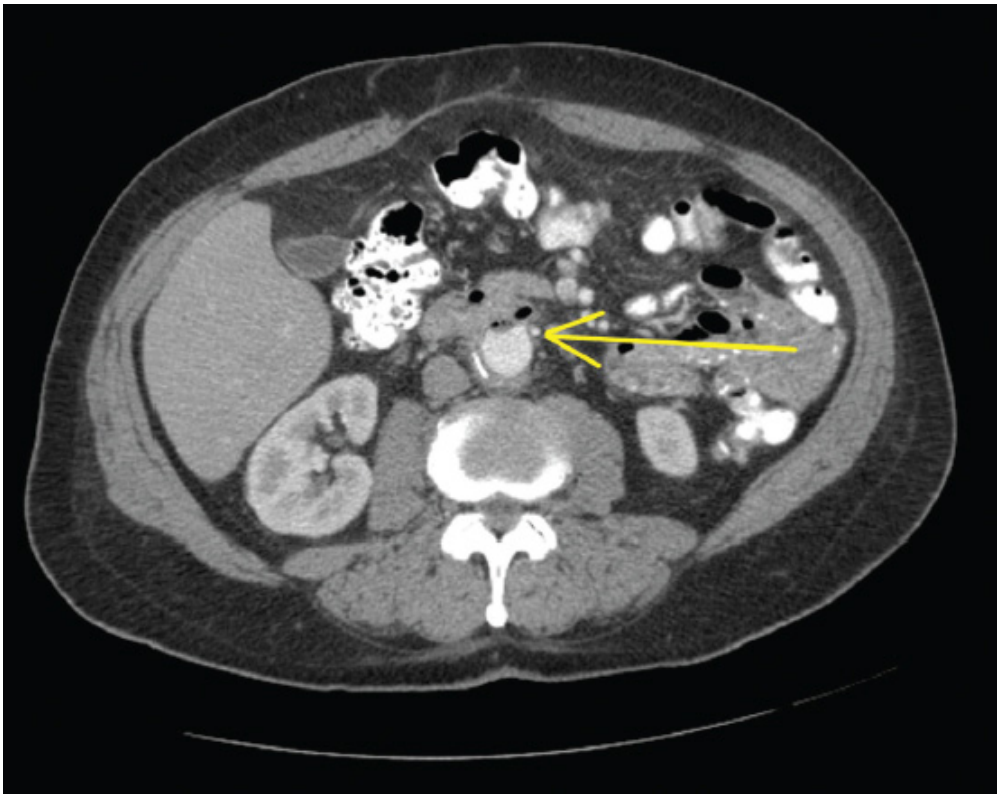

Figure 86.3 CT scan demonstrating loss of tissue planes around the aorta with foci of air as a sign of infection.

Duplex Ultrasonography

Duplex ultrasound offers a relatively safe and inexpensive tool for evaluating native arteries and bypass grafts for signs of infection. Ultrasound circumvents the risks of contrast allergy, contrast-induced nephropathy, and radiation associated with CT. The main limitations of ultrasound are the lack of availability in some centers of skilled ultrasound technicians capable of arterial imaging. Overlying structures, particularly bowel gas and the lungs, and body habitus can also obscure visualization and limit the efficacy of ultrasound evaluations within the chest or abdomen.[41] Findings on duplex ultrasound that are suggestive of infection include the presence of a pseudoaneurysm, hematoma, soft tissue masses, and perigraft gas and fluid collections. A "halo sign" surrounding an infected aortofemoral limb is a hypoacoustic shadow surrounding the graft that is indicative of perigraft fluid consistent with graft infection.[41]

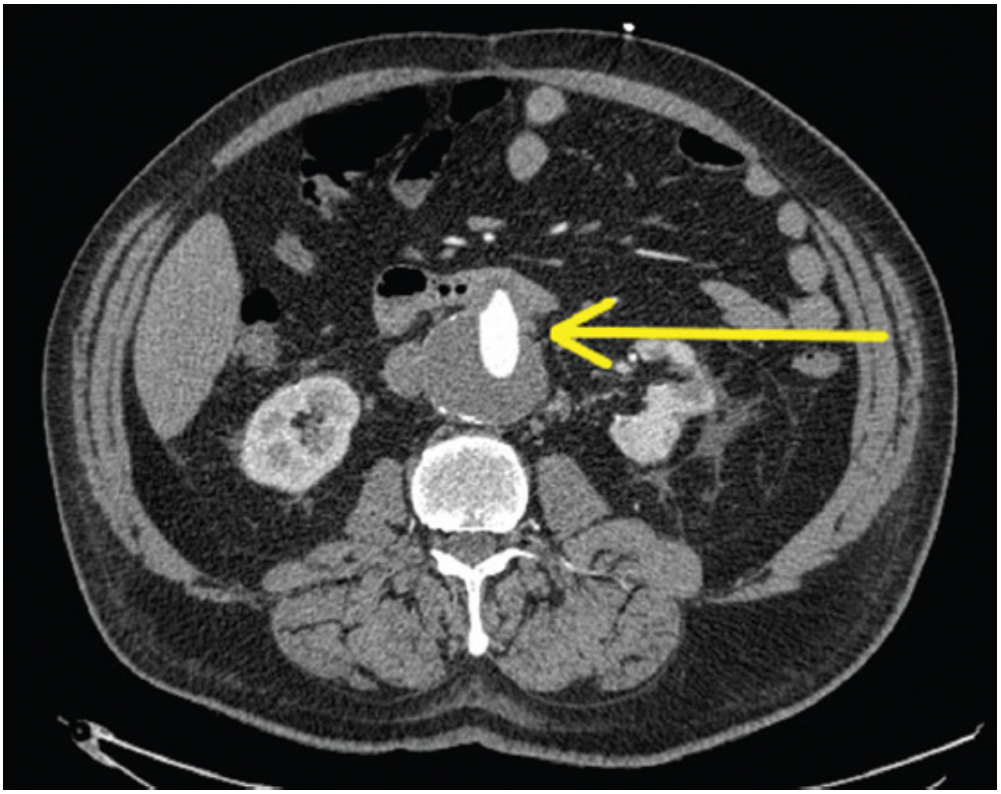

Figure 86.4 CT scan demonstrating erosion from the aorta into the overlying bowel consistent with an aortoenteric fistula.

Magnetic Resonance Imaging (MRI)

MRI offers some theoretical advantages over CTA for the diagnosis of vascular infections, including the avoidance of radiation and contrast-induced nephropathy. There are also clear disadvantages to MRI that have limited its utility in diagnosing graft infections. MRI studies for graft infection are time consuming, and MRI is contraindicated for patients with certain metal implants.[45] The sensitivity and specificity for graft infection is highly variable between institutions. MRI may be as useful as CT scan in the diagnosis of arterial infections at centers with expertise with MRI for arterial infections. In a study of 40 patients with suspected arterial graft infections, Shahidi found that the sensitivity, specificity, positive predictive value, and negative predictive value of MRI were 68%, 97%, 95%, and 80%, respectively.[47] MRI may detect small collections of biofilms, the hallmark of *S. epidermidis* infections, which are notoriously difficult to diagnose.[45] MRI creates a low-intensity "halo" around infected grafts on T_1 imaging, while also creating a hyperintense signal on T_2-weighted images.[45,48] Since gadolinium is not required, MRI may be useful in patients with chronic renal insufficiency. MRI is plagued by some of the same

limitations as CT in detecting early graft infections since air and fluid are normal findings on MRI for 2 to 3 months after graft implantation.[49]

Leukocyte Scintigraphy

Leukocyte scintigraphy may be performed using either ^{111}Indium- or ^{99m}Technetium-labeled leukocytes to localize infection within the arterial wall or graft. A theoretical advantage of leukocyte scintigraphy is the diagnosis of indolent infections with low-virulence organisms for which the symptoms are most ambiguous. Unfortunately there are numerous pitfalls to this modality. Leukocyte scintigraphy is time-consuming, labor-intensive, and prone to false-positive results due to undesired cross-labeling of platelets that may bind to grafts.[50,51] Uptake of the radionuclide-labeled white blood cells requires intact chemotaxis and a minimum total white blood cell count of 2,000/μL.[50] The net effect of these issues is that the sensitivity and specificity for tagged white blood cell scanning is highly variable between institutions, with sensitivity and specificity both ranging between 50% and 100%,[47,50] but notable false negatives have also been demonstrated.[51]

Single-Photon Emission Tomography (SPECT) Scanning

SPECT scanning, when combined with CT scanning, may enhance the specificity of leukocyte scintigraphy in the detection of vascular infections.[52] While there are limited data available at this time, the early results appear promising. In one study of SPECT–CT in 55 subjects with suspected vascular graft infections, SPECT–CT reduced the number of false positives by 37%, compared to CT alone. The sensitivity and specificity of SPECT–CT was 100%, which was superior to SPECT or CT alone.[52]

Fluorodeoxyglucose Positron-Emitting Tomography (FDG-PET)

FDG-PET utilizes glucose labeled with ^{18}fluoride, which is utilized by cells proportional to their metabolic activity. Initially, this technique was utilized to detect occult metastases in oncology patients. The protocols have been adapted for the detection of occult arterial infections.[53,54] FDG-PET can be advantageous in diagnosing endograft or peripheral stent infections since the images are less prone to metal artifact. Compared with leukocyte scintigraphy, FDG-PET offers the advantages of shorter examination times, less radiation exposure, higher

resolution, and improved interobserver agreement.[55] Unfortunately there is a high false-positive rate for diagnosing arterial graft infections because of the inflammatory response associated with prosthetic grafts, which is most prominent in the first 4 weeks postoperatively.[55] Poor uptake of the FDG-glucose can also yield nonspecific results, which is a limitation of using this test in diagnosing low-virulence infections, or after the administration of antibiotics. In addition, there is variability in both quantitative and qualitative parameters used among studies. In a meta-analysis by Rojoa, SUV_{max} and focal uptake had the best sensitivity and specificity (0.98 and 0.8 for SUV_{max} and 0.93 and 0.78 for focal uptake).[55] While the sensitivity and specificity of FDG-PET alone are inferior to CT scan alone, combining FDG-PET with CT scanning markedly improves the localization of infection and the sensitivity and specificity of the examination. Drawbacks of the fusion technology include longer study times and increased radiation exposure. Furthermore, expertise with FDG-PET-CT techniques and interpretation remains variable. Despite these limitations, the combined modality timed appropriately before antibiotic administration is a promising diagnostic option.[55]

Adjunctive Diagnostic Modalities

Arteriography, endoscopy, and image-guided biopsy should be viewed as adjunctive diagnostic modalities that have a limited role in diagnosing graft infections. Arteriography may be useful in planning reconstruction. Rarely, an occult AEF can be discovered with angiography by filling of the enteric structure. Esophagogastroduodenoscopy (EGD) is typically performed to exclude other sources of upper gastrointestinal hemorrhage in a patient with a suspected AEF. EGD was successful in diagnosing AEF in approximately 25% cases in one small series of primary AEFs (Fig. 86.5).[37] In spite of the low diagnostic yield, the authors recommended endoscopy in hemodynamically stable patients with a suspected AEF because of the devastating consequences of a missed diagnosis. Image-guided biopsy of the fluid or rind surrounding the affected vascular structure has been described when the diagnosis of graft infection is equivocal.[56] This approach could potentially distinguish between patients with benign early postoperative perigraft gas versus an early graft infection, however, sufficient sampling is difficult to achieve in all cases, as the tissue is often fibrotic and in close proximity to other major vascular structures and bowel.[56] Further study is needed to clarify if this modality has a role in the evaluation of arterial infections.

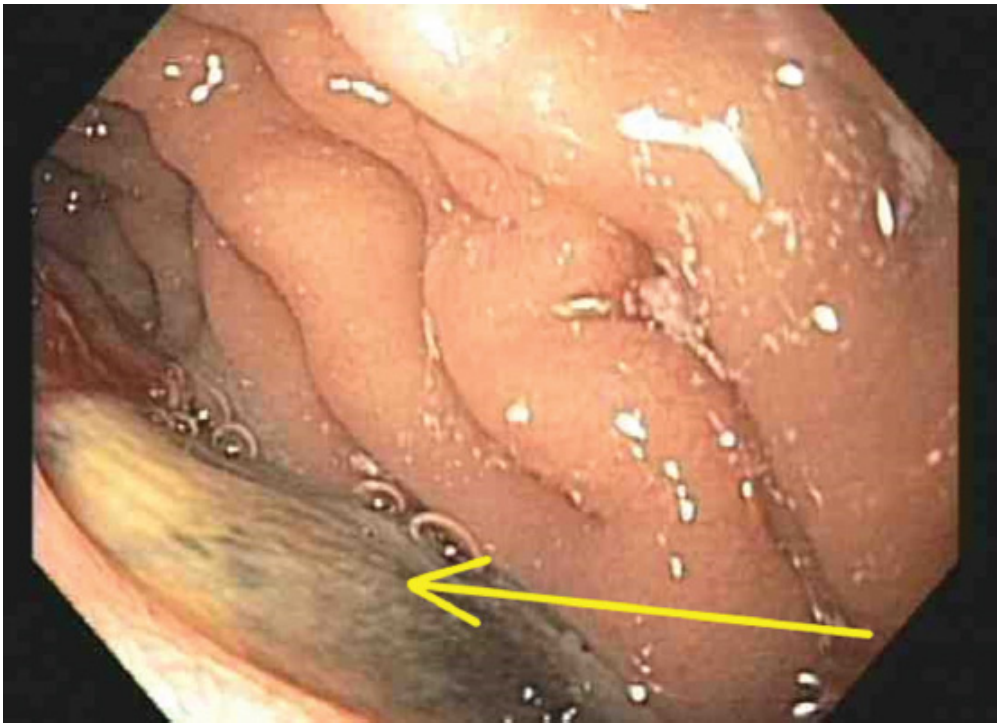

Figure 86.5 EGD demonstrating graft material visible in the bowel lumen consistent with graft-enteric fistula.

CONSERVATIVE MANAGEMENT

Primary Arterial Infections

Hsu et al. provided insight on the outcome of conservative management of subjects with primary aortic infections.[57] Hsu examined 22 subjects with infected aortic aneurysms with perceived contraindications to surgery. The predominant organism in the cohort was *Salmonella,* with two-thirds of subjects having infections of the abdominal aorta. All subjects received culture-specific intravenous antibiotics for at least 6 to 8 weeks, or until normalization of white blood cell count, daily temperatures, and CRP levels. After the acute phase treatment, oral antibiotics were continued indefinitely. In Hsu's series, the in-hospital mortality was 50% due to rupture or sepsis. The 1-year survival rate was 32%. Patients with *Salmonella* infections had a lower aneurysm-related mortality rate than patients with non-*Salmonella* infections.

Arterial Graft Infections

Calligaro advocated for complete or partial prosthetic bypass preservation in subjects with severe comorbidities precluding surgical repair.[58] Over a 20-year period, 51 extracavitary grafts (aortofemoral limbs or lower extremity bypasses) were treated with graft preservation and aggressive wound management without surgical graft resection. When wounds were present, aggressive debridement of all necrotic tissue and exudate surrounding the artery was performed. Nine cases utilized adjunctive muscle flaps to aid healing. Povidone–iodine 1% or antibiotic-soaked dressing changes were performed three times a day. With this regimen, 2 of 51 patients (4%) experienced major hemorrhage from the infected graft at 3 and 12 months after presentation. Eleven of the patients (22%) failed the treatment regimen, with nonhealing wounds or recurrent infections requiring total graft excision. Thirty-two subjects (63%) were ultimately treated successfully. Calligaro concluded that conservative management of extracavitary grafts is an acceptable option in the absence of sepsis or hemorrhage, especially when graft excision and revascularization is not feasible due to patient comorbidities. *Pseudomonas* infections, however, were particularly prone to failure with this regimen.

Building on the early reports of graft preservation therapy, subsequent reports have emerged utilizing vacuum-assisted negative pressure therapy with antibiotics and wound debridement to preserve extracavitary grafts with Szilagyi III wounds.[59,60] Wound healing with these regimens have ranged between 82% and 91% with excellent graft preservation rates.[59,60] Episodes of hemorrhage remain an issue with this approach,[59] and the failures have been associated with *Pseudomonas*.[59,60] Based on these reports, it appears that carefully selected patients with early infections involving extracavitary grafts may be treated without surgical graft excision with acceptable results.

Calligaro et al. used a nonoperative approach in six patients with intracavitary graft infections with a hostile abdomen or severe medical comorbidities.[61] All subjects underwent either open or percutaneous placement of drains along the graft with instillation of 10 mL of 1% povidone–iodine in 100 mL of normal saline or antibiotics (neomycin or a cephalosporin) three times a day. All subjects were treated concurrently with culture-directed intravenous antibiotic therapy for 6 weeks, followed by 6 months of oral antibiotic therapy. Of these six subjects, only one died due to sepsis. One patient ultimately required total graft excision and survived. The remaining patients (66%) were alive at last follow-up. These authors showed that in highly selected patients, conservative management can have reasonable outcomes. Stone et al. described the use of

antibioitic-loaded polymethylmethacrylate beads in treatment of prosthetic graft infection in 32 patients. This resulted in 87% wound sterilization, 50% rate of graft preservation, and reinfection rates of 12%.[62]

SURGICAL MANAGEMENT OF AORTIC ARTERIAL AND GRAFT INFECTIONS

Surgical treatment is based upon the central tenets of appropriate resuscitation, preoperative planning, resection of all infected material and tissue, and arterial revascularization. The optimal method of arterial reconstruction remains unresolved, as few direct comparisons between approaches have been published. Based on our extensive institutional experience with a variety of techniques, we have concluded that no single approach is suitable for all patients. We advocate tailoring the treatment algorithm based on each patient's clinical presentation and the local surgical expertise.

Aortic Infections Presenting with Hemorrhage or Sepsis

A minority of patients present with septic or hemorrhagic shock. For these patients, rapid intravenous access and resuscitation are essential prior to emergent surgery. In the authors' experience, the complexity of the operations required to manage these patients mandates a rapid CTA to obtain essential anatomic information. It is recognized that some of these patients will have either acute kidney injury or chronic kidney disease, but managing the life-threatening complications of the aortic graft infection outweighs the risk of contrast-induced nephropathy. Ideally, blood and wound cultures are obtained prior to the administration of broad-spectrum gram-positive and gram-negative antibiotic therapy. The surgical approach to managing patients presenting with hemorrhage or sepsis should be individualized based on the patient's anatomy and the expertise of the surgeons.

Endografting as Bridge Therapy

Endografts are being used with increasing frequency as a method to temporize hemorrhage in patients with aortoenteric or aortobronchial fistulas.[36,37,63–65] When the anatomy permits, endografting may temporarily prevent exsanguination

and allow time for resuscitation, medical stabilization, and further investigations to plan definitive surgery.[63] While earlier studies suggest that endografting should not be viewed as definitive therapy since recurrent hemorrhage occurs in majority of cases without further surgical treatment, often within 2 weeks,[36,64] additional studies suggest that in association with long-term antibiotics, this can be a definitive therapy in patients with short life expectancy (<6 months), while further surgical intervention should be planned for patients with longer life expectancy.[65] Some studies suggest endograft as definitive therapy. Sorelius et al. described 132 patients with mycotic abdominal aortic aneurysms, 77 of which were treated with endografts. They demonstrated improved short-term survival and 1-year survival for EVAR compared to open repair (96% vs. 74% and 84% vs. 73%). There were similar rates of infectious-related complications (24% vs. 18%) and reoperation (24% vs. 21%).[66] Patel et al. described TEVAR in conjunction with long-term antibiotics for infected thoracic aortic pathology in 27 high-risk patients. The short-term mortality was 11.5%, and 3-year survival was 57%.[67] These options expand our treatment options for aortic infection, especially in patients with high operative risk.

Definitive Surgery for AEF

Definitive surgery for an AEF involves resection of the infected graft, repair of the enteric defect, and revascularization of the lower extremities. The most appropriate surgical approach to achieve these goals has been the focus of considerable debate. For decades, the most common approach to AEFs was total graft excision with "triple" ligation of the infrarenal aortic stump and extraanatomic bypass.[68–69] In recent years, a variety of groups have touted the merits of in situ reconstruction of the aorta after graft excision, using a variety of conduits. The advantages, disadvantages, and technical details of these approaches are discussed later in the chapter (see "Aortic Infections in the Stable Patient").

Aortic Ligation and Extraanatomic Bypass for AEFs

In stable patients with a small herald bleed caused by an AEF, Reilly et al. at the University of California-San Francisco advocated staging of the two component operations at an interval of several days to minimize the physiologic impact on the patient.[69] The first stage of this approach consists of performing an axillobifemoral bypass or bilateral axillary–popliteal bypasses (depending on the configuration of the infected graft), followed several days later by resection

of the infected graft with aortic stump closure. In the patient with ongoing bleeding or hemodynamic instability, a staged approach is not feasible. Reilly reported a 26% mortality rate with the staged approach, compared to 43% for the traditional, nonstaged.[69] A subsequent study by Seeger reported a 19% treatment-related mortality rate.[70] In addition to a high mortality rate, this approach is plagued by a significant risk of aortic stump blowout (9%), reinfection of the extraanatomic bypass graft (16%), and major amputation (16%).[69]

In Situ Aortic Reconstruction for AEFs

In response to the sobering results associated with the traditional approach, in situ aortic reconstruction has been touted as a relatively simple and effective alternative.[71–75] Oderich et al. from the Mayo Clinic reported their results using in situ rifampin-soaked grafts with spiraled omental graft coverage in 54 patients with aortic graft-enteric erosions or fistulae.[71] In their series, operative mortality was 9%, and graft reinfection occurred in 4%. A subsequent multicenter study of 37 patients with AEFs treated with either in situ prosthetic grafts (n = 9), extraanatomic bypass (n = 25), or endografting (n = 3), reported a 30-day mortality rate of 43% for in situ reconstructions.[73] In that series, 3 of 11 (27%) long-term survivors with in situ grafts developed reinfection of the in situ graft, which was universally fatal.

Alternative conduits for in situ reconstruction for AEFs include cryopreserved aortoiliac allograft and creation of a neoaortoiliac system (NAIS) with femoral vein. Harlander-Locke et al. published a multicenter experience with 220 patients with aortic graft infections treated with in situ cryopreserved aortoiliac allograft, which included 33 patients with AEFs.[74] The reinfection rate in patients presenting with AEFs was 12%. In situ repair with autogenous femoral vein is not appropriate in the unstable patient due to the time required for femoral vein harvest, but may be reasonable in the stable patient with a herald bleed due to an AEF. Valentine reported a 42% mortality rate in 24 patients treated with in situ femoral vein for AEFs and graft-enteric erosions, so femoral vein may not offer any advantage over the alternative conduits for AEFs.[75]

Aortic Infection with Sepsis

Sepsis caused by an aortic infection poses a challenge because temporizing with an endograft is not an option since the septic focus is not eliminated. In unstable patients, CT-guided percutaneous drainage may be a reasonable option for

source control if there is a large perigraft fluid collection. In a series of 23 patients with graft infections, Belair et al. found that percutaneous drainage was associated with improved perioperative mortality, compared to surgery alone.[76] In the absence of a large perigraft fluid collection for percutaneous drainage, graft excision with extraanatomic bypass is the most reasonable approach.

Aortic Infections in the Stable Patient

Preoperative Evaluation

The incidence of coronary artery disease is high in surgical series of arterial infections, especially in subjects with infected endografts.[2,6] Thus, a thorough cardiovascular history, physical examination, 12-lead electrocardiogram, and echocardiogram should be obtained to evaluate for heart failure, valvular dysfunction, and pulmonary hypertension. These investigations may reveal a history of active cardiac conditions that may modify the type of operation selected or preclude surgery. Only rarely is stress testing or coronary arteriography indicated since coronary revascularization is usually contraindicated in the context of an active infection. However, this information may alter the surgical plan, provide valuable information for the anesthesiologists, and guide discussions with the patient or family regarding the expected outcomes. Pulmonary evaluations are rarely undertaken, as this information seldom alters the management of the patient. Only those patients with the most severe pulmonary insufficiency may benefit from formal testing to guide perioperative management.[77]

8 Operative planning is greatly facilitated by a preoperative CTA to define the arterial anatomy. Angiography of the lower extremities is reserved for cases when a concurrent infrainguinal bypass is considered likely. Noninvasive measurements of distal perfusion and lower extremity vein mapping should be performed. Ankle–brachial indices (ABIs) may forewarn the surgeon of the potential for infrainguinal revascularization after graft excision and aortoiliac reconstruction. Mapping of the bilateral greater saphenous veins and femoral–popliteal veins is essential if an autogenous conduit is contemplated. Femoral–popliteal veins with a diameter of less than 6 mm or evidence of vein wall sclerosis are inadequate for aortoiliac reconstruction.[2]

Anesthetic Considerations

Operations to excise infected aortic grafts are technically challenging, lengthy, and prone to a large volume of blood loss. The importance of a quality anesthesia team in managing these challenges cannot be overstated. Hypothermia, hypovolemia, and intraoperative anemia must be assiduously avoided with the use of warming blankets, warmed resuscitative fluids, warm ambient operating room temperature, and a low threshold for blood and crystalloid replacement. The blood bank should be prepared to provide fresh-frozen plasma, cryoprecipitate, or platelets on short notice if coagulopathy develops. Culture data are often not available at the time of operation, so broad-spectrum antibiotic coverage for gram-positive, gram-negative, and anaerobic organisms should be redosed throughout the operation.

Aortic Ligation and Extraanatomic Bypass versus In Situ Reconstruction

A major advantage of graft excision with extraanatomic bypass is the removal of all prosthetic graft material from the infected operative field. This approach also obviates the need to procure an aortoiliac allograft. Finally, use of an extraanatomic bypass circumvents any reticence a surgeon may have with harvesting femoral veins since some surgeons are not familiar with the technique. The obvious pitfalls of this approach are the risk of aortic stump blowout, reinfection of the extraanatomic bypass graft, and poor long-term patency of the extraanatomic reconstruction. In situ reconstruction is appealing because it avoids the risk of aortic stump blowout and the poor long-term patency of extraanatomic bypasses. For patients with insufficient infrarenal aorta for a secure three-layer closure, in situ may be the only reasonable option. Reinfection of new graft is the obvious risk of this approach. In the following sections, we will offer technical suggestions for performing these complex operations and summarize the published results for each approach.

Aortic Graft Excision

Common to each of the described surgical approaches to aortic graft infection is the need for complete graft excision. This is summarized in Table 86.2. For graft excision, aortic exposure can be performed via a transperitoneal or retroperitoneal approach. Proximal control of the infrarenal aorta can be challenging in a redo operative field, so the surgeon should be prepared to obtain proximal control of the aorta at the suprarenal or supraceliac level, or consider balloon occlusion as an adjunct. When treating an AEF, proximal control should

be obtained prior to mobilizing the duodenum since there may be uncontrolled hemorrhage in the absence of proximal aortic control. The left renal vein may be densely adherent to the graft or the native aorta, which may necessitate its division to gain access to the aorta near the renal arteries. Once proximal control is obtained, distal control of the bilateral common iliac arteries should ensue, unless these arteries are occluded. When excising an aortofemoral graft, the femoral limbs should be controlled in the abdomen to facilitate their removal. Removal of aortofemoral grafts requires considerable dissection in the groins for control of the prosthetic graft limbs and native common femoral, superficial femoral, and profunda femoris arteries. Femoral exposure may be performed through an incision directly over the femoral limb or incisions lateral to the sartorius muscle. The lateral incision avoids some of the prior scarring and may preserve soft tissue for arterial coverage. Systemic heparin is administered prior to cross-clamping, and the graft is removed in its entirety. Any arterial tissue that appears to be abnormally friable is probably infected and should be debrided. Remnants of graft and arterial tissue should be sent for Gram stain, culture, and sensitivity testing. A critical adjunct is wide debridement of the retroperitoneum, which is believed to decrease the residual bacterial bioburden that will predispose to recurrent infection. After completing graft excision and debridement, closure of the aortic stump or in situ aortoiliac reconstruction may ensue. The primary options for reconstruction include extraanatomic bypass or in situ repair using a variety of conduits including cryopreserved allograft artery, rifampin-soaked or silver-impregnated Dacron, or autogenous femoral vein. The results of these techniques are compared in Table 86.3.

Table 86.2 Excision of Aortic Graft Operative Steps

Step
Transperitoneal or retroperitoneal incision
Exposure for proximal control ▪ May require division of left renal vein ▪ Consider balloon control as adjunct
Distal exposure ▪ Control aortofemoral bypass limbs in the abdomen ▪ Consider lateral approach to femoral artery to avoid scarred field
Heparinize and cross clamp
Remove graft in entirety ▪ Send graft for culture
Wide debridement of the retroperitoneum ▪ Send tissue for culture
Aortic stump closure or in situ reconstruction ▪ Double layer running nonabsorbable polypropylene suture horizontal mattress followed by baseball stitch ▪ Omental wrap secured with sutures

Extraanatomic Bypass

For stable patients, staging of the extraanatomic bypass and graft excision should be considered, as proposed by Reilly.[69] The first stage of this approach consists of performing an axillobifemoral bypass or bilateral axillary–popliteal bypasses, meticulously avoiding any infected or contaminated planes when tunneling the new grafts. The second stage consists of aortic graft excision, retroperitoneal debridement, and aortic stump closure. Aortic stump closure requires a meticulous three-layer closure or "triple ligation" of the aorta. The first two layers consist of nonabsorbable polypropylene suture; a vertical mattress suture, followed by running "baseball" suture. The final layer is an omental wrap secured with sutures.[69] When staging the extraanatomic bypass and graft excision, the optimal time interval between the two operations has not been defined. It has been our experience, however, that the presence of both an

aortobifemoral bypass and an extraanatomic bypass creates competitive flow between the grafts that often results in thrombosis of the extraanatomic bypass graft. To minimize the risk of interval graft thrombosis, patients are anticoagulated with intravenous unfractionated heparin between operations, and a short (1 to 3 days) time interval (usually 1 to 2 days) between the two operations is planned. If the two operations are performed at the same operative setting, the clean portion of the procedure (the extraanatomic bypass) is performed prior to the infected portion of the case (graft excision) whenever feasible to minimize the risk of bacterial inoculation of the new graft.

Table 86.3 Complications Associated with Different Methods of Aortic Reconstruction after Aortic Graft Excision, Based on Selected Publications

Method of Aortic Reconstruction	Mortality	Graft Occlusion	Amputation	Reinfection (Stump Blowout)	Pros (+)/Cons (–)
Extraanatomic bypass with aortic ligation[72,73,78,79]	Early 11–45% Late 40%	27–34%	0–27%	3–27% (9–27%)	(+) reduced morbidity with staging (–) decreased patency, stump blowout, amputation rate, and reinfection
In situ autogenous vein[25,80]	Early 9% Late 40–55%	3%	6–7%	0–4%	(+) resistant to infection, excellent long term durability and limb salvage (–) time consuming, fasciotomy in up to 25%
In Situ Allograft[24,74]	Early 2.8–9% Late 3–48%	4–7%	1–2%	3–4%	(+) resistant to reinfection, excellent long-term durability and limb salvage (–) rupture and pseudoaneurymsal degeneration, cost, persistent infection
Rifampin soaked[68,73,78]	Early 8–31% Late 16–40%	0–9%	0%	0–12%	(+) excellent patency, convenience (–) higher reinfection rates
In situ silver-impregnated graft[81,82]	Early 16–18% Late 16–27%	0–8%	0–4%	9–13%	(+) excellent patency, convenience (–) highest reinfection rates

In Situ Reconstruction with Cryopreserved Arterial Allografts

Experience with allograft replacement of primary or secondary arterial infections began with Alexis Carrel more than a century ago.[83] Difficulties with procurement and preservation resulted in poor-quality control. Allografts were largely abandoned until their resurrection for the treatment of infectious pathologies of the ascending aorta in the 1980s.[84] Initial positive experience resulted in more widespread use, including the treatment of infected infrarenal aortic graft infections.[85] Initially, local tissue banks were responsible for procuring, preserving, and allocating allografts for clinical use. This resulted in

considerable variability in the processes of preparing and storing the product, which may have impacted the quality of the product. Currently, these processes have been centralized in both North America and Europe with primary suppliers of the cryopreserved allografts.

The primary advantage of cryopreserved allografts is its resistance to infection, while major disadvantages include cost (approximately $18,000 per aortoiliac segment), and that the grafts are not readily available at most centers or immediate use in urgent circumstances.

In Situ Reconstruction with Rifampin-Soaked and Silver-Impregnated Grafts

Rifampin shows unique activity against *S. epidermidis* biofilms, making it an excellent choice for prosthetic graft infections. Rifampin-soaked Dacron grafts (600-mg rifampin in 250 mL of normal saline, soaked for 30 minutes) with omental wrapping has been shown to have variable resistance to recurrent infection, ranging between 4% and 11.5%.[71,72] Recurrent infections have been fewer when treating AEFs, compared to prosthetic graft infections. Primary patency and limb salvage are also excellent. Circumferential omental wrapping of the grafts is a critical technical adjunct to decrease the risk of reinfection.[71]

Silver-impregnation relies upon the ability of silver to adsorb gram-positive and gram-negative bacterial membranes, resulting in disruption of the membrane and cell lysis. There has been no reported bacterial resistance to silver.[86] It is theorized that silver-impregnated grafts would have activity against *E. coli* and methicillin-resistant *S. aureus,* which would be an improvement over rifampin-soaked grafts, however limited clinical data suggest that silver-impregnated grafts are not equivalent to rifampin-soaked grafts based on higher reinfection rates.[81,87]

In Situ Reconstruction with Autogenous Femoral Vein

Autogenous femoral vein was proposed as an alternative conduit for in situ reconstruction for infected aortic grafts in the early 1990s.[88] Clagett described creating a “neoaortoiliac system” or NAIS using femoral veins harvested from both legs. The proposed advantages of femoral vein include an innate resistance to infection and excellent long-term patency. The major pitfall of using femoral vein for in situ reconstruction is the time required to harvest the veins. Although many surgeons have not had formal training in the technique for harvesting femoral veins, it is well within the capability of any vascular surgeon. The

technique is described in detail elsewhere, and summarized in Table 86.4.[89] Among clinicians who are not familiar with using femoral vein for aortoiliac reconstruction, there appears to be reluctance based on concerns with any venous morbidity associated with harvesting the femoral vein. Modrall et al. described their intial experience as requiring up fasciotomy of up to 17% of patients.[90] However, the need for fasciotomy in recent data is rare due to an increased tolerance leg swelling by the surgeons before performing fasciotomy.[91] Two preoperative predictors of a higher probability of fasciotomy were identified: concurrent harvesting of the greater saphenous vein in the same limb and a low ABI (<0.55) in the harvested limb. Prior harvest of the ipsilateral greater saphenous vein was not a risk factor for requiring a fasciotomy. Venous collaterals develop over time to normalize venous physiology in most patients, so long-term venous morbidity is minimal. One-third of patients experience mild chronic leg swelling, and the remainder are asymptomatic.[91] To our knowledge, no limbs have developed venous ulceration as a consequence of femoral vein harvest.

Table 86.4 Operative Steps for Femoral Vein Harvest

Step
Incision is extended along the lateral edge of the sartorius from the anterior superior iliac spine to the medial femoral condyle
Sartorius is reflected medially to preserve blood supply
Avoid saphenous nerve
Double ligate side branches >3 mm over suture ligation to avoid tearing vein wall
Expose entire length from the confluence with the profunda vein to the knee joint
Divide the vein flush with the profunda vein to prevent blind stump thrombus
Evert the intima for valve excision
Distend under pressure and repair defects with 6-0 or 7-0 polypropylene
Use in nonreversed orientation to improve mismatch

NONAORTIC ARTERIAL AND GRAFT INFECTIONS

Lower Extremity Arterial Infections

Lower Extremity Graft Infections

The nonoperative management of Szilagyi III wounds was described previously. Older studies show that lower extremity bypass graft infections carry a postoperative major amputation and mortality rate of nearly 50% due to the underlying atherosclerotic disease burden.[92] These patients often do not have other conduit suitable for bypass, which is a major impetus for graft preservation strategies for infected extremity bypass grafts. The use of local debridement with adjunctive vacuum-assisted closure and muscle flaps has yielded promising results. Siracuse cited an estimated 1-year limb salvage rate of 71%, which was attributed to the graft preservation techniques described above.[12]

Cryopreserved human allograft veins have been touted as an alternative if a prosthetic bypass graft must be removed for infection. Unfortunately, human allograft veins have yielded relatively poor results. In a series of bypasses for critical limb ischemia using cryopreserved greater saphenous vein, primary patency at 1 and 3 years was 27% and 17%, respectively.[93] Amputation-free survival at 1 and 3 years was 43% and 23%, respectively. Better results have been reported using cryopreserved human allograft arteries, especially when covered with muscle flaps. One series reported good long-term results with only 15% late conduit-related graft complications.[94] Cadaveric grafts are expensive, on the order of $5000–$10,000. In view of the outcomes and cost, the use of cryopreserved conduit must be weighed against the outcomes of graft preservation techniques on a case-by-case basis.

Extraanatomic bypass is an alternative to avoid inguinal infections. Obturator bypass yields reasonable results with 60% to 83% survival with healed wounds beyond 3 years, and 70% to 80% 3-year patency.[95,96] Lateral femoral bypass also yielded good results with 95% survival and wound healing, 83% 2-year patency, and 93% limb salvage.[97]

Infected Common Femoral Artery Pseudoaneurysms

The management of infected common femoral artery pseudoaneurysms diverges from the management of infected pseudoaneurysms in other anatomic locations.

The most frequent clinical scenarios involve infection after a history of recent arterial catheterization or intravenous drug abuse. The incidence of infection after cardiac catheterization is less than 1%, although the use of arterial closure device increases the risk due to the presence of a foreign body. Aggressive debridement, removal of the closure device, and revascularization remains the mainstays of therapy. In situ repair with autogenous greater saphenous or femoral vein is preferred if arterial replacement is necessary.[23] A rotational muscle flap may be necessary for graft coverage in some cases. Occasionally, in situ repair may not be advisable due to the quality of the arteries or the surrounding tissue. Ligation of the native arteries in the groin and an extraanatomic bypass, such as an obturator bypass or lateral tunneling may be preferable.[96,97] Ligation of the common femoral artery without reconstruction is utilized as a last resort and is less likely to threaten the limb if the femoral bifurcation remains intact.[23]

Conversely, infected common femoral artery pseudoaneurysms secondary to intravenous drug abuse should be preferentially managed with aggressive arterial and soft tissue debridement and ligation of all of the involved arteries. Immune suppression due to malnutrition and human immune deficiency virus infections, delayed presentation, and patient recidivism make arterial reconstruction hazardous in this setting. Reddy showed that ligation of the common, superficial, and profunda femoral arteries is associated with a 33% major amputation rate.[98] Rates of major amputation are very low in other series, with some authors reporting 0% to 1% amputation rates in their series.[23,99,100] Claudication is common, however one group reported only 11% early claudication all of which resolved over time.[23]

Arterial Infections in Other Sites

Carotid patch infection is a rare, but dreaded occurrence. Management entails removal of the patch, wide debridement, and primary closure of the artery versus vein patch closure. Interposition grafting with autogenous vein is often necessary after the artery is debrided adequately. Occasionally ligation of a bleeding, infected artery is necessary as a life-saving intervention.[13] In a series of carotid patch infections, the stroke rate after debridement and reconstruction was 8.1% and increased to 14% when carotid ligation was necessary.[13] Endografting is an acceptable option to control hemorrhage and permit stabilization and evaluation for definitive surgery.[101]

Case reports and small case series of infected pseudoaneurysms of the superior mesenteric, celiac, and splenic arteries have been reported.[102–104] Treatment is individualized by the patient's comorbidities and anatomy. Infected visceral artery aneurysms are prone to rapid growth and rupture.[102–104] The most common pathogens are streptococcus followed by staphylococcus.[101–104] Arteriography is often helpful to delineate the anatomic relationship of the aneurysms to nearby branch vessels and to define the quality of the collateral circulation. Excision, debridement, and arterial reconstruction with autogenous conduit remain the gold standard for infected pseudoaneurysms of main arterial trunks. Cryopreserved artery has also been described in the absence of autogenous conduit.[94] Resection and arterial ligation may be an option in some cases, depending on the anatomic location due the abundant collateral circulation between the mesenteric arteries and branches.[104] Coil embolization and long-term antibiotic therapy should be reserved for surgically inaccessible aneurysms, such as intrahepatic mycotic pseudoaneurysms, since coils may become infected.[105]

ANTIBIOTIC THERAPY

9 Unfortunately, there are no guidelines directing the type, dose, duration, or route of administration of antibiotics in treating arterial infections. This reflects the wide spectrum of causal organisms that are found in arterial graft infections, with approximately one-third of subjects having polymicrobial infections. Moreover, physician preference and patient tolerance of antibiotic regimens vary considerably. In addition, culture-directed therapy is not always possible since nearly 40% of patients have negative cultures, presumably due to preoperative broad-spectrum antibiotic therapy.[5] Finally, the consequences of a reinfection are dire, so there is a tendency among physicians to overprescribe antibiotics.

Initial broad-spectrum antibiotics should include agents with activity against gram-positive bacilli, gram-negative rods, and anaerobes, as these are the most prevalent organisms in graft infections. Currently our preferred combination therapy is vancomycin, piperacillin/tazobactam, and metronidazole. Blood cultures and graft and tissue cultures should be obtained to direct therapy. Recommendations for the duration of antibiotics vary widely, ranging from 2 weeks to 6 months after graft excision. If a graft or stent is not fully excised, indefinite antibiotic therapy should be considered. Fungal infections are

particularly difficult to eradicate and may require the use of micafungin (FK463) due to the increasing incidence of resistance to fluconazole and its related molecules.[106]

PREVENTION OF SECONDARY ARTERIAL INFECTIONS

Meticulous surgical technique is critical to minimizing arterial graft infections. Judging from the microbial flora associated with graft infections, intraoperative contamination and surgical site infections are the most likely sources of contaminations that result in arterial graft infections. Adherence to all perioperative guidelines for reducing surgical site infections is important, but the use of prophylactic systemic antibiotics appears to be critically important. A recent meta-analysis and systematic review performed by Stewart concluded that prophylactic systemic antibiotics decreased the risk of wound and early graft infection for peripheral arterial reconstruction.[107] No benefit was seen in continuing antibiotics for greater than 24 hours, prophylactic rifampin bonding to the grafts, suction groin wound drainage, or preoperative bathing with or without antiseptic agents. Using guidelines for prosthetic heart valves, some authors suggest similar antibiotic prophylaxis in patients with aortic graft undergoing dental procedures.[108]

CONCLUSIONS

10 Primary and secondary arterial infections constitute a myriad of some of the most technically, intellectually, and emotionally challenging cases that vascular surgeons may encounter in clinical practice. For aortic arterial infections, there is no consensus regarding the optimal method of in situ reconstruction. Autogenous vein reconstruction may be the most resistant to recurrent infection and most cost effective, but requires an additional, lengthy procedure for vein harvest. Reconstruction with either antibiotic- or silver-impregnated grafts may also be a reasonable alternative, but appears to have a higher rate of reinfection compared to the alternatives. Cryopreserved allografts have improved since their initial development, but are still hampered by a minority of hemorrhagic complications and pseudoaneurysmal degeneration. Moreover, cryopreserved

allografts are considerably more expensive than the other alternatives. Extraanatomic bypass remains a viable alternative for patients unable to undergo a more extensive operation. Endovascular stent grafts are excellent tools to stabilize patients with hemorrhagic complications of arterial infections prior to definitive surgery. Arterial infections in other locations utilize the same principles of wide excision and debridement, arterial reconstruction, and appropriate antibiotic coverage whenever technically feasible.

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Cerebrovascular Disease

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Key Points

1. Stroke is the fifth leading cause of death in the United States, worldwide stroke continues to be one of the most common causes of death and disability.
2. Stroke remains the leading cause of disability in the United States and costs an estimated $34 billion each year.
3. Duplex ultrasonography remains an invaluable tool in the diagnosis of significant carotid artery atherosclerotic disease.
4. The preferred management of symptomatic and severe asymptomatic carotid artery disease is surgical intervention over medical therapy alone.
5. Aggressive risk factor modification is imperative in all patients with atherosclerotic cerebrovascular disease.
6. Transcarotid artery revascularization (TCAR), with its CEA-like protective qualities, should be preferred over transfemoral carotid artery stenting in select patients not candidates for CEA.
7. Endovascular management of proximal vertebral artery atherosclerotic lesions has been shown to be safe and effective in small nonrandomized trials, but further studies are needed to sufficiently assess its efficacy.
8. Open surgical correction of brachiocephalic occlusive atherosclerotic disease should be preferred over endovascular management.

INTRODUCTION

Stroke continues to be a common cause of disability and death, accounting for the fifth leading cause of death in the United States.[1] Stroke disability can be debilitating, even more so than that of a myocardial infarction (MI). Quality-of-life sub-analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)[2] among 1-year survivors indicates that stroke

has greater adverse effect on a broad range of health-status domains than did an MI. Permanent disability from a stroke can lead to blindness, weakness, paralysis, or aphasia. Transient ischemic attacks (TIAs) have symptoms last <24 hours and manifest similarly, albeit without long-term sequelae. These sequelae have long-lasting social and financial burdens not only on patients and families, but on the healthcare system as well.

There are a multitude of etiologies leading to stroke with many modifiable risk factors. Some of the most common risk factors include hypertension, diabetes, hypercholesterolemia, obesity, genetics, and smoking. Eighty-five percent of all strokes are thought to be ischemic, whereas only 15% are embolic. Atherosclerotic plaque is the most common and important underlying pathology leading to ischemic strokes.[3] Since the first successful carotid endarterectomy (CEA) in 1953 by Michael DeBakey, carotid revascularization has been shown in multiple randomized clinical trials to decrease the risk of ipsilateral ischemic strokes. Minimally invasive endovascular techniques such as transfemoral carotid artery stenting (TFCAS) and transcarotid artery revascularization (TCAR) have been introduced as alternative options in patients who are high risk for CEA. However, CEA remains the gold standard option for symptomatic carotid artery stenosis. Ongoing randomized trials comparing surgical, endovascular and medical management of asymptomatic carotid artery occlusive disease are highly anticipated.

Vertebrobasilar insufficiency (VBI) can be a much more difficult diagnosis to obtain as compared to atherosclerotic carotid artery disease. Symptoms are often vague and are easily confused with other diagnoses. These symptoms are more likely posterior circulation symptoms that include diplopia, vertigo, drop attacks, and headaches. Traditional treatment for true VBI was open surgical treatment of the ostial vertebral artery atherosclerotic occlusive disease. Endovascular repair with balloon angioplasty and/or stenting is an attractive option, however, outcomes have not been extensively evaluated.

Atherosclerotic brachiocephalic occlusive disease typically involves the origins of the great vessels. Symptoms may be similar to atherosclerotic carotid stenosis including amaurosis, TIA, and stroke, but also can include arm fatigue and weakness. Again, traditional treatment has been open surgical repair with transthoracic repair versus extra-anatomic bypass.

Endovascular management with angioplasty and stenting has also been advocated for this disease entity, but experience is limited.

This chapter provides a comprehensive review of the epidemiology, pathophysiology, diagnosis, treatment, and controversies in management of atherosclerotic and nonatherosclerotic carotid artery disease, as well as VBI and brachiocephalic occlusive disease.

ATHEROSCLEROTIC CAROTID ARTERY DISEASE

Epidemiology

1 Worldwide, stroke continues to be one of the most common cause of mortality and disability. One in six people worldwide will have a stroke in their lifetime. Fifteen million people worldwide suffer a stroke each year and 5.8 million people die from it.[4] Despite the decreasing incidence in the United States, annual incidence of new or recurrent stroke is 795,000, of which 610,000 are first or new strokes.[5] Stroke prevalence is linked to patients' age, as older Americans over the age of 65 have a much higher prevalence as compared to Americans aged 18 to 44 years (8.4% vs. 0.7%).[6] Race also seems to play a role in stroke, as whites have a lower incidence of stroke when compared to blacks and Hispanics.[7] Stroke rates also vary by region in the United States, with the southeastern United States with higher incidence of stroke hospitalization rates as compared to the western United States. Stroke deaths, however, have been on the decline in the United States over the past few decades. Stroke is now the fifth leading causing of death, killing about 140,000 Americans each year.[8] This decrease in stroke mortality can be attributed to improvement in acute stroke care with the advent of intra-arterial thrombolysis and endovascular mechanical thrombectomy.[9] Improved recognition of the importance of medical management with statin and antiplatelet agents certainly has played a role as well. Despite the decreasing mortality and the earlier recognition of acute stroke symptoms and the timely use of acute stroke therapies, stroke remains the leading cause 2 of disability in the United States and costs an estimated

$34 billion each year. Care for stroke survivors cost an estimated $18.8 billion during 2008 and lost productivity and premature mortality cost an additional $15.5 billion.[10] The risk factors for stroke include age over 55, male sex, hypertension, family history, atrial fibrillation, hypercholesterolemia, renal insufficiency, obesity, diet, diabetes, smoking, and alcohol use. Of those, the five most significant factors that lead to stroke are: hypertension, smoking, obesity, diet, and physical inactivity.[11]

Pathogenesis of Stroke

Cerebrovascular accidents (CVAs) in the United States are overwhelmingly related to ischemia (87%), whereas intracerebral and subarachnoid hemorrhage account for 10% and 3%, respectively.[12] Carotid atherosclerotic disease may cause a stroke in a variety of ways. Most commonly, unstable plaque embolization to the middle or anterior cerebral artery will cause TIA or stroke. Rarely, reduced flow through a highly stenotic extracranial carotid artery may cause cerebral hypoperfusion in patients with poor cerebral collaterals, resulting in stroke. Additionally, acute thrombosis causing in situ obstruction from atherosclerosis, dissection, or fibromuscular dysplasia (FMD) is also a possible etiology for CVA.

Patients at highest risk for TIA or stroke are those with greater than 80% carotid artery stenosis secondary to soft, echolucent plaque or those whose plaque progresses from less than 80% to greater than 80% during a follow-up period.[13] These fibrous plaques will continue to have infiltration of lipids into the arterial wall leading to inflammation and infiltration of macrophages, which leads to lysis of proteolytic enzymes resulting in necrotic debris.[14] This can result in an unstable plaque that leads to intraplaque hemorrhage and rupture of the fibrous cap causing immediate embolization (**Fig. 87.1**). Once this embolization event occurs, the resulting ulcer will act as a nidus for the accumulation of platelet aggregates and other thrombotic debris, thereby putting the patient at risk for further embolization. This can be best illustrated by viewing photomicrographic images of an ulcerated plaque containing loosely adherent thrombotic debris prone to embolization (**Fig. 87.2**). Stroke from carotid vessel etiology has the highest recurrence rate at 30 days if not surgically treated.[15]

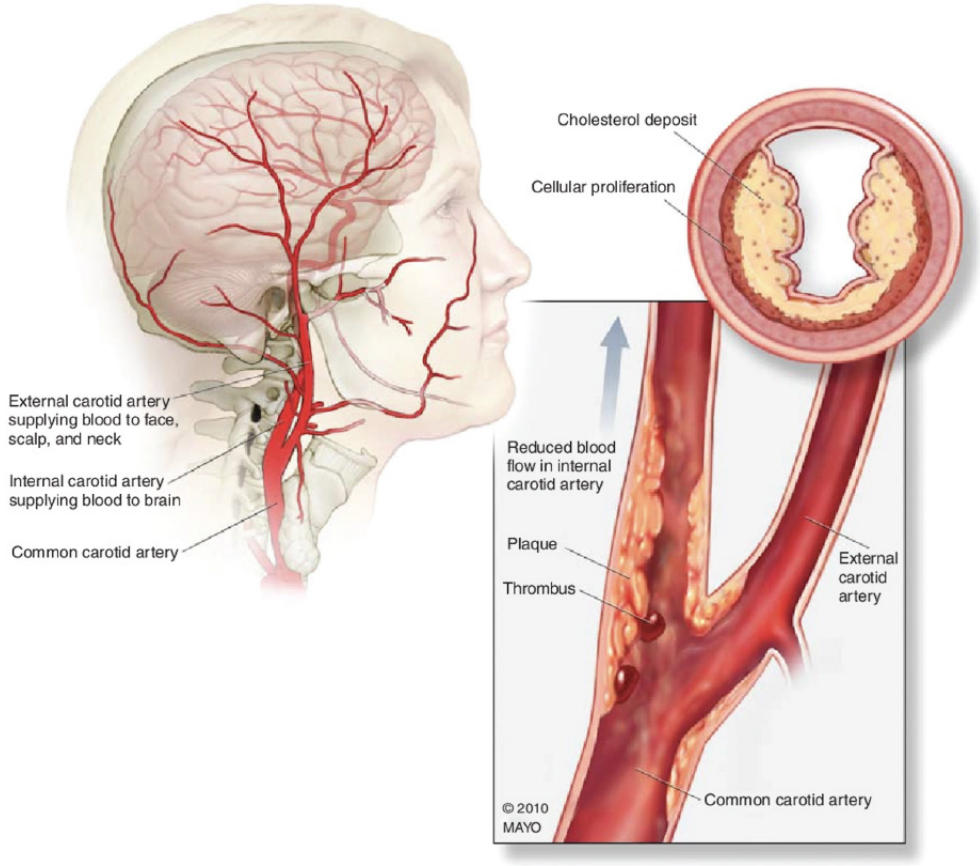

Figure 87.1 Stroke caused by carotid atherosclerotic disease is usually caused by atheroemboli from the internal carotid artery. As shown the majority of the anterior cerebral circulation comes from the internal carotid artery. As increasing carotid stenosis occurs, flow becomes more turbulent and carotid plaque can become more unstable, increasing the risk of atheroembolization.

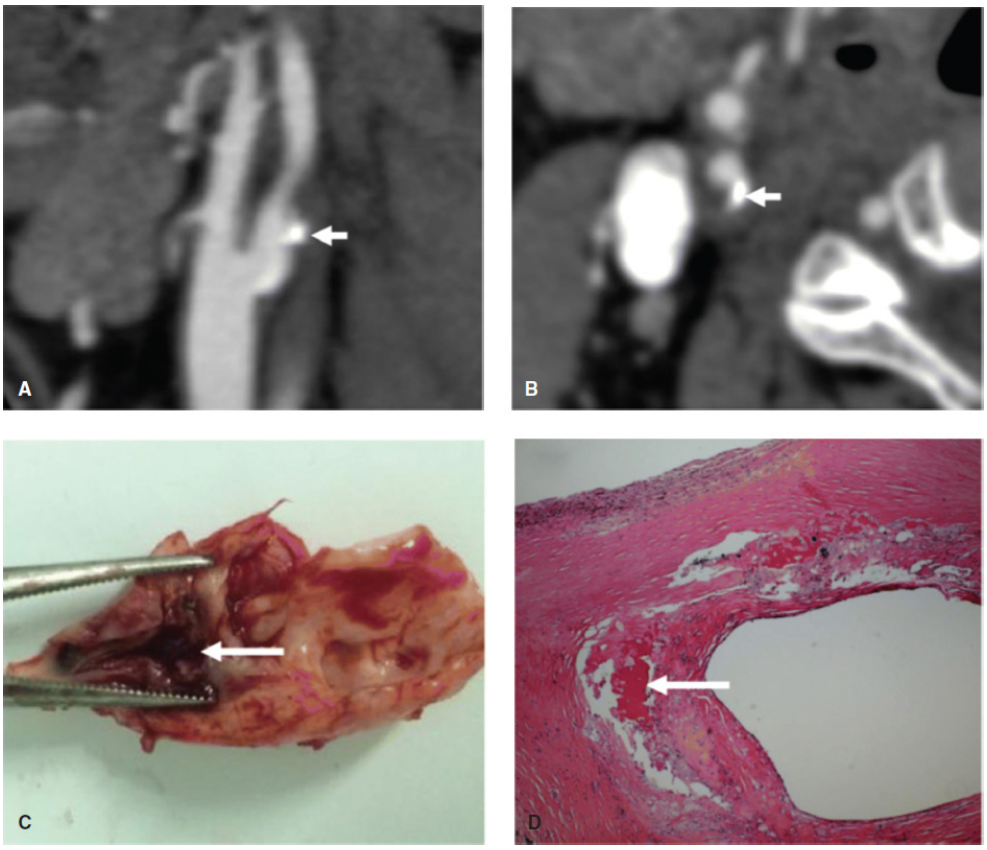

Figure 87.2 Panel showing unstable atherosclerotic plaque from CTA in figure **A** and **B** to endarterectomy specimen in **C**. **D:** (arrows) Photomicrograph of this ulcerated plaque demonstrates thrombus loosely adherent to the wall of the plaque, showing why embolization is very much a certainty in these cases.

The carotid bifurcation is especially susceptible to atherosclerotic plaque formation. The separation of flow between the high-resistance external carotid artery (ECA) and the low-resistance internal carotid artery (ICA), creates a low-flow and shear stress area, where turbulent flow is a set up for plaque formation on the walls opposite from the flow divider (**Fig. 87.3**). Constant nonlaminar flow at the carotid bifurcation with an inciting event, such as intimal injury, is the perfect storm that leads to platelet deposition, smooth muscle proliferation, macrophage infiltration and loss of luminal diameter. Reduced luminal size will thus lead to increasing velocities and more turbulent flow leading to increased risk of atheroemboli. As stated above, atheroemboli are more common when a thin fibrous cap ruptures as opposed to a thicker fibrous cap, which may be more stable (**Fig. 87.4**).

Clinical Syndromes

The clinical manifestations of symptomatic carotid atherosclerotic disease include TIA, stroke, and amaurosis fugax. TIAs are defined as neurologic events that are sudden in onset without a preceding aura and last less than 24 hours in duration. Patients return to their baseline neurologic function, which usually occurs within minutes of the inciting event. These are considered a precursor to a more serious neurologic event with a large number that will progress to stroke. Stroke symptoms can be broken down into motor and sensory changes. These include dysarthria, dysphasia, aphasia, monoparesis, hemiparesis, hemiplegia, monocular blindness, numbness, or paresthesias. When related to carotid stenosis, these symptoms occur on the contralateral side of the lesion due to ipsilateral cerebral embolization. Amaurosis fugax is temporary monocular blindness from cholesterol embolization to the retinal artery via the ophthalmic artery. An important, but often less recognized association with critical ipsilateral carotid stenosis is a severe chronic monocular visual deterioration known as chronic ocular ischemic syndrome.[16] Patients with chronic ocular ischemic syndrome may suffer from transient visual loss, gradual loss of visual acuity, and eye pain. Equally important is to recognize what symptoms are not likely related to carotid atherosclerotic disease. Dizziness, syncope, vertigo, seizures, migraines, bowl or bladder incontinence, and scintillating scotomas are not related to carotid atherosclerotic occlusive disease and other causes should be sought out. Once the symptoms progress pass 24 hours, the TIA has become a full stroke. It often will take weeks for the full severity of the stroke to manifest as the ischemic penumbra will either recover or it won't. The severity of stroke is graded by using a variety of severity scales. The most commonly used scale is that formulated by the National Institute of Neurologic Disease and Stroke (NINDS) of the National Institutes of Health (NIH). The NIH stroke scale yields a numeric score of 0 to 42 and can be used at the initial neurologic event and then throughout the evolution of the stroke to help map out the patient's clinical course (**Fig. 87.5**). A score of 5 or lower is considered a mild stroke; a score of 6 to 20, moderate stroke; and a score higher than 20 represents a severe stroke.

Initial Diagnostic Evaluation

Carotid atherosclerotic disease may be a difficult clinical diagnosis to obtain prior to the onset of neurologic symptoms. Physical examination in asymptomatic carotid atherosclerotic disease is limited to auscultation of a carotid bruit. Auscultation of a carotid bruit was once considered a part of the standard cardiovascular examination. Even though the auscultation may be an effective method for selecting further diagnostic tests, studies have shown that the sensitivity and positive predictive value are low for a carotid bruit detecting severe carotid stenosis.[17] The primary diagnostic tool for detection of hemodynamically significant carotid stenosis is duplex 3 ultrasonography (DUS). The benefits of DUS include excellent sensitivity and specificity (especially for high-grade carotid stenosis),[18] low cost, rapid availability, and ease of evaluation and avoidance of radiation. Decisions on carotid intervention are often solely based on information provided by the DUS. The severity of carotid stenosis is determined by measuring the peak systolic velocity (PSV), end-diastolic velocity (EDV), and the ratio of the PSV of the ICA to common carotid artery (ICA/CCA) (**Fig. 87.6**). There are two major DUS criteria for determination of carotid stenosis, modified University of Washington (UW) criteria (**Table 87.1**) and the Carotid Consensus Panel duplex Criteria (CCPC) (**Table 87.2**). Recent studies have shown that the CCPC criteria demonstrate a higher corroboration rate with measurements taken from computed tomography angiography (CTA), and may be more sensitive in classifying clinically significant stenosis and preventing unnecessary extra surveillance.[19] DUS can also give information regarding plaque morphology and aid surgeons in deciding which carotid atherosclerotic plaques may be at higher risk for embolization and thus benefit from carotid intervention. Despite the many benefits for initial use of DUS, there are few limitations related to operator experience, inability to visualize high carotid bifurcations, dampened waveforms due to proximal CCA lesions, excessive calcification causing acoustic shadowing, and inability to accurately measuring velocities.

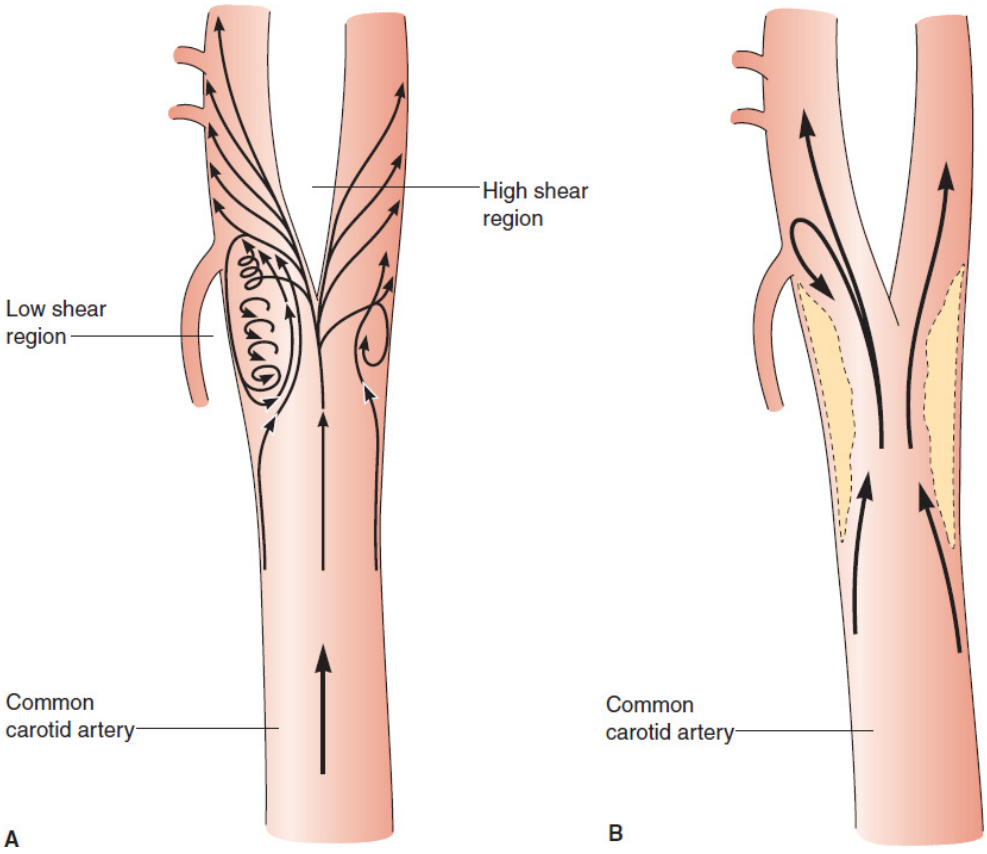

Figure 87.3 **A:** Carotid bifurcation represents an area of low-flow velocity and shear stress. As blood circulates this is a separation of flow between the low-resistance internal carotid artery and the high-resistance external carotid artery. **B:** Atherosclerotic plaque typically forms in the outer wall opposite the flow divider due in part to the low shear stress.

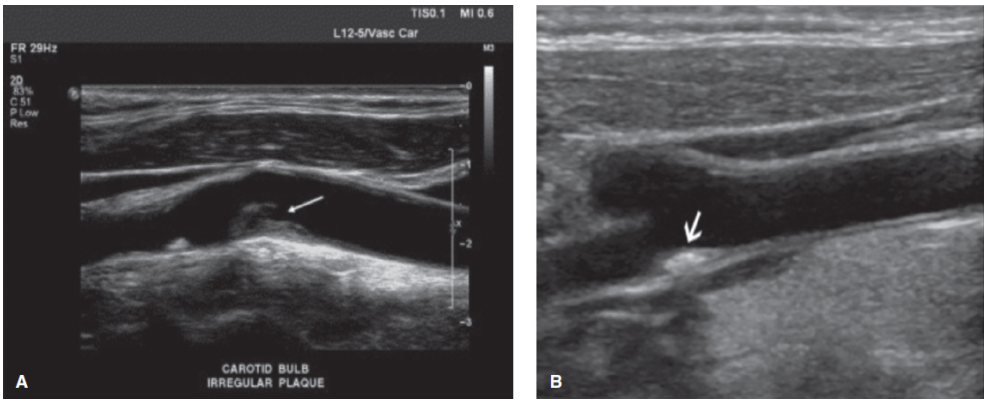

Figure 87.4 **A:** Duplex ultrasound showing unstable, hypoechoic plaque that is at high-risk for embolization. **B:** Duplex ultrasound showing stable plaque with thickened cap less likely to cause atheroemboli.

National Institutes of Health Stroke Scale score	
1a. Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b. Level of consciousness questions: What is the month? What is your age?	0 = Answers two questions correctly 1 = Answers one question correctly 2 = Answers neither questions correctly
1c. Level of consciousness commands: Open and close your eyes. Grip and release your hand.	0 = Performs both tasks correctly 1 = Performs one tasks correctly 2 = Performs one tasks correctly
2. Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3. Visual	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4. Ficial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of one or both sides
5. Motor arm 5a. Left arm 5b. Right arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity; limb falls 4 = No movement
6. Motor leg 6a. Left leg 6b. Right leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7. Limb ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs
8. Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe to total sensory loss
9. Best language	0 = No aphasia; normal 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia
10. Dysarthria	0 = Normal 1 = Mild to moderate dysarthria 2 = Severe dysarthria
11. Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Total score = 0–42.	

Figure 87.5 NIH stroke scale scoring from zero (no deficit) to 42 (most severe deficits in all areas).

The need for corroborative imaging is sometimes necessary for initial diagnosis and to help plan possible operative intervention. Improvements in

technology and acquisition times have made magnetic resonance angiography (MRA) and CTA attractive options for diagnosis of carotid atherosclerotic disease. These modalities can give information regarding the aortic arch, tortuosity, any anomalous anatomy, presence of brachiocephalic disease or proximal CCA disease, location of carotid bifurcation, and information regarding intracerebral collateral circulation (**Fig. 87.7**). The gold standard remains carotid angiography for definitive diagnosis in carotid atherosclerotic disease (**Fig. 87.8**). Major stroke has been reported in 1% of carotid angiography cases, with majority of these due to aggressive injection of contrast and introduction of air. Similar to transfemoral carotid stenting, microemboli do occur during carotid angiography. These microemboli can be seen postprocedure on diffusion-weighted MRI and may contribute to possible stroke or further neurologic derangements. With that being said, these microemboli also may be clinically silent and have not led to new changes on follow-up cerebral MRI.[20] Transcranial Doppler (TCD) is less used for initial diagnostic evaluation for atherosclerotic carotid disease, but TCD can give useful information regarding the significance of a carotid stenosis and how it alters intracerebral hemodynamics. TCD can be helpful identifying high-risk asymptomatic carotid lesions if silent emboli are detected during the study.

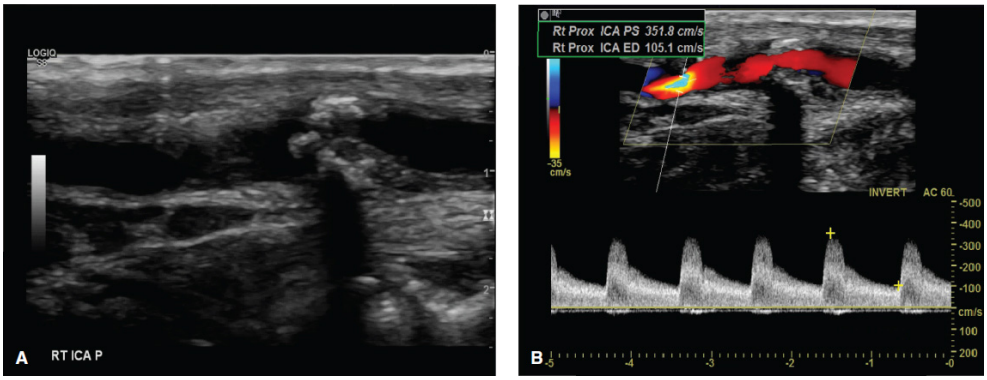

Figure 87.6 **A:** B-mode DUS showing severe calcified plaque and narrowing at proximal right ICA. **B:** Color flow Doppler showing PSV of 351 and EDV of 105 correlating to a >70% stenosis.

Treatment of Atherosclerotic Carotid Artery Disease

Atherosclerotic carotid artery disease can be broken down into asymptomatic and symptomatic carotid stenosis. A recent (<6 months) TIA, stroke, and amaurosis fugax are considered to be symptoms of atherosclerotic carotid occlusive disease. The benefit of carotid intervention in patients with recent ipsilateral carotid territory symptoms and moderate to severe carotid stenosis is much greater than the benefit of carotid intervention in asymptomatic patients. In patients with TIA, up to 15% will go on to CVA, 10% occur within 90 days.[10] Several landmark studies have examined the risk reduction of stroke with medical versus surgical management.

Symptomatic

Patients with symptomatic carotid lesions are at the highest risk of ipsilateral stroke. The degree of stenosis also corresponds with increased risk of ipsilateral stroke if not treated. Multiple landmark trials have validated the benefit of carotid intervention, namely CEA, over medical therapy for symptomatic carotid stenosis. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) study and The European Carotid Surgery Trial (ECST) both showed that degree of stenosis does correlate to risk of ipsilateral stroke. In patients with >50% ipsilateral carotid stenosis, those treated with medical therapy alone were more likely to progress to ipsilateral stroke when compared to those treated with surgical intervention. Benefit was highest among patients with the highest degree of carotid stenosis (70% to 99%). In the NASCET study, symptomatic patients were randomized to medical therapy (which at the time primarily consistent of aspirin therapy) or CEA for those found to have >50% ipsilateral carotid stenosis. After 2 years, in patients with severe >70% symptomatic carotid stenosis, CEA conferred a 6.7% absolute risk reduction for death or major disabling stroke over medical therapy. NASCET 4 also found benefit of CEA over medical therapy in patients with “mild to moderate,” 50% to 69% carotid artery stenosis, with a 5-year absolute risk reduction of 4.7%.[21] The ECST corroborated NASCET findings with regard to severe >70% carotid stenosis, however, no benefit was found for surgery over medical therapy in mild to moderate 50% to 69% carotid stenosis.[22] There have been significant advances in medical therapy for the treatment of carotid atherosclerotic

disease. HMG-CoA reductase inhibitors have significantly improved the ability to medically treat carotid atherosclerotic disease. Statin therapy has been shown to help stabilize atherosclerotic plaque and reduce stroke by some 30% in patients with atherosclerotic carotid disease.[23] Statins have also been shown 5 to independently reduce the risk of all-cause mortality and recurrent stroke in younger patients who have suffered an ischemic stroke.[24]

Table 87.1 Modified UW (Strandness) Criteria for Carotid Stenosis

Stenosis Severity (%)	ICA PSV (cm/s)	ICA EDV (cm/s)	Spectral Broadening
1–14	<125	N/A	None
15–49	<125	N/A	Present and minimal
50–79	>125	<140	Present
80–99	>125	>140	Diffuse and marked
Occluded	0	0	N/A

ICA, internal carotid artery; PSV, peak systolic velocity; EDV, end-diastolic velocity.

Table 87.2 Carotid Consensus Panel Duplex Criteria (CCPC) Duplex Ultrasound Criteria for Carotid Artery Stenosis

Degree of Stenosis (%)	ICA PSV (cm/s)	ICA EDV (cm/s)	ICA/CCA Ratio	Carotid Plaque (%)
Normal	<125	<40	<2.0	None
<50	<125	<40	<2.0	<50
50–69	125–230	40–100	2.0–4.0	>50
70–99	>230	>100	>4.0	>70

ICA, internal carotid artery; PSV, peak systolic velocity; EDV, end-diastolic velocity; CCA, common carotid artery.

Figure 87.7 CTA with 3D reconstruction showing intracerebral collateral flow and intact circle of Willis.

Figure 87.8 Diagnostic carotid angiography showing severe mid ICA stenosis at the level of C2.

Clearly, carotid intervention has been shown to be beneficial over medical therapy for patients with symptomatic carotid stenosis. What is less clear is the timing of intervention. Traditionally, surgeons have waited >6 weeks prior to intervention to allow of any ischemic penumbra to resolve. However, 30-day recurrent ipsilateral stroke rates have been well established in recent studies in patients with symptomatic >50% carotid stenosis.[25] Early (<48 hours), aggressive intervention was suggested as the

most optimal time to intervene, given the aforementioned risk of recurrent stroke. However, performing carotid intervention, namely CEA, <48 hours after onset of symptoms has been shown to increase the risk of postoperative stroke, death, and other complications.[26] In patients with mild to moderate TIA/stroke that have returned to baseline from their symptoms, current practice is to perform carotid intervention in the delayed phase (i.e., between 2 and 14 days). Urgent revascularization is still warranted in patients with crescendo TIA and evolving stroke in order to prevent a larger stroke, despite the known increase risk of perioperative complications.[27]

Asymptomatic

There is a clear body of evidence supporting carotid intervention for symptomatic carotid artery stenosis. What is less evident is the ideal treatment for asymptomatic carotid artery stenosis. One of the first and most important trials that has driven how the management of asymptomatic carotid stenosis is in the United States over the past 30 years is the Asymptomatic Carotid Atherosclerosis Study (ACAS) trial.[28] In ACAS, asymptomatic patients with >60% stenosis were randomly assigned to either medical management or CEA. At 5 years, best medical therapy (BMT) was found to be inferior to surgery in regard to ipsilateral CVA (11% for BMT vs. 5.1% for CEA). These findings were also corroborated in the European Asymptomatic Carotid Surgery Trial (ACST), with a benefit in patients undergoing surgery over BMT with >60% carotid stenosis.[29] Both trials showed a significant relative risk reduction of stroke when undergoing CEA (ACAS 53% and ACST 46%). The findings of these trials in the mid-90s led to an explosion in the number of CEA being performed for carotid artery atherosclerotic disease and have guided management of severe >80% carotid artery stenosis in the asymptomatic patient. BMT during these trials primarily comprised of aspirin therapy. Medical therapy has evolved since the initiation of these trials, with the use of statin therapy as well dual antiplatelet therapy (DAPT) for atherosclerotic carotid disease. This is coupled with significant improvement in glycemic control and smoking cessation leading to dramatic decrease in annual rates of ipsilateral or any territory stroke since the early 1980s. These rates have been purported to be at or below those seen in stroke prevention with carotid intervention.[30] The

upcoming CREST-2 randomized trial between current best BMT and carotid interventions (CEA or CAS) will hopefully shed more light on the most optimal management of asymptomatic, severe >80% carotid artery stenosis.

CAROTID ENDARTERECTOMY

Technique

The first carotid surgery is credited to be performed by Eastcott, Pickering, and Rob in 1954 in a woman with recurrent TIAs.[31] The carotid surgery involved the excision of the carotid bifurcation, ligation of the ECA, and reconstruction with direct anastomosis of the CCA to the ICA. The first CEA was actually performed the year prior by Dr. Debakey, but he did not publish his findings until 1959. Since the advent of the CEA in the 1950s, it has become one of the most common surgery performed by vascular surgeons in the United States. Numerous trials, previously mentioned in this chapter, have validated the safety and efficacy of CEA especially in patients with symptomatic carotid artery disease. A fundamental consideration prior to performing a CEA is deciding the type of anesthetic method. CEA may be performed under general anesthesia (GA), regional anesthesia (RA) with a deep or superficial cervical block and under local anesthesia (LA). Several studies have shown the benefit of RA with reduction in the risk of postoperative complications such as MI.[32] Second fundamental choice regarding CEA is choice of intraoperative cerebral monitoring. Choice of monitoring is dependent on the choice of anesthesia. Patients who undergo GA, typically have a multitude of cerebral monitoring devices that include: electroencephalogram (EEG) with somatosensory-evoked potentials (SSEPs), TCD, stump pressure measurement, and cerebral pulse oximetry (near infrared spectroscopy). If the patient has the surgery under LA/RA, their ability to respond to commands and monitor neurologic status dictates the adequacy of collateral flow. Cerebral monitoring devices aid the surgeon in deciding if a shunt is necessary for those patients deemed to have poor collateral flow. EEG is the most widely used cerebral monitoring tool and measures brain activity with 10 to 16 leads. A significant finding is a drop of

fast background activity of 50% indicating possible cerebral ischemia. TCD evaluates the middle cerebral artery (MCA) for changes in flow with clamping. Stump pressure requires clamping the CCA and ECA while maintaining the ICA open and using a transducer to measure the back pressure. A mean pressure less than 40 mm Hg has been adopted as the standard threshold to indicate intolerability of clamping. All these measures are used to guide the surgeon to place an intraoperative shunt to decrease the time of cerebral ischemia. Shunting continues to be a controversial topic with some studies showing decreased stroke risk, while others showing no benefit in shunting.[33] Routine shunting allows for a consistent endarterectomy technique with less anxiety as the shunt completely relieves intracerebral ischemia if done correctly. Routine shunters maintain excellent results with low perioperative stroke risk.[34] In a recent study, we have shown an interaction between anesthesia types and shunting (with LA/RA) putting patients at increased risk of postoperative stroke and death when intraoperative shunting is performed.[35]

Careful patient positioning is paramount to performing a successful CEA, especially for high lesions at or above the level of C2. The patient is placed supine on the operating room table with a roll placed behind the scapulae to allow for hyperextension of the neck. The neck is turned away from the operative side and the patient is usually placed in a “beach chair” position, this allows for optimal exposure to the neck and the slight reverse Trendelenburg with decreased jugular venous pressure. A longitudinal skin incision is made along the anterior border of the sternocleidomastoid (SCM) (**Fig. 87.9**). Smaller skin incisions (~4 cm) can be made with adequate exposure. To facilitate this, use of ultrasound intraoperatively will help locate the carotid bifurcation, allowing the surgeon to center a smaller incision over the carotid bifurcation. The incision is deepened through the platysma layer and the SCM is identified and its medial border is retracted laterally exposing the internal jugular vein. The facial vein is an important landmark and usually signifies the location of the carotid bifurcation. This is carefully double ligated and divided. The dissection can be carried inferiorly to the superior belly of the omohyoid muscle. The CCA is located inferior and medial to the internal jugular in the carotid sheath. Care must be taken when dissecting the CCA in the carotid sheath in order to avoid injury to the vagus nerve. Circumferential control of the CCA is then performed in the

base of the neck incision, ensuring adequate CCA exposure if carotid shunting is to occur. Next, the ECA and the superior thyroid artery are identified and controlled. Dissection at the carotid bifurcation may result in bradycardia due to stimulation of the carotid body. This can be alleviated by administration of less than 0.5 cc of 1% lidocaine into the adventia and directly into the carotid body. Great care must be taken when dissecting out the proximal ICA to avoid excessive manipulation to avoid distal embolization of the underlying lesion. Moving more superiorly and identifying the hypoglossal nerve is of the utmost importance and can allow for dissection of the mid portion of the ICA in an area above the carotid atherosclerotic lesion. If there is a high carotid lesion above the level of C2, several maneuvers can assist in exposing the distal ICA which include: division of the posterior belly of the digastric (care must be taken to not injure the underlying glossopharyngeal nerve), subluxation of the mandible, removal of the styloid process, and finally nasotracheal intubation.

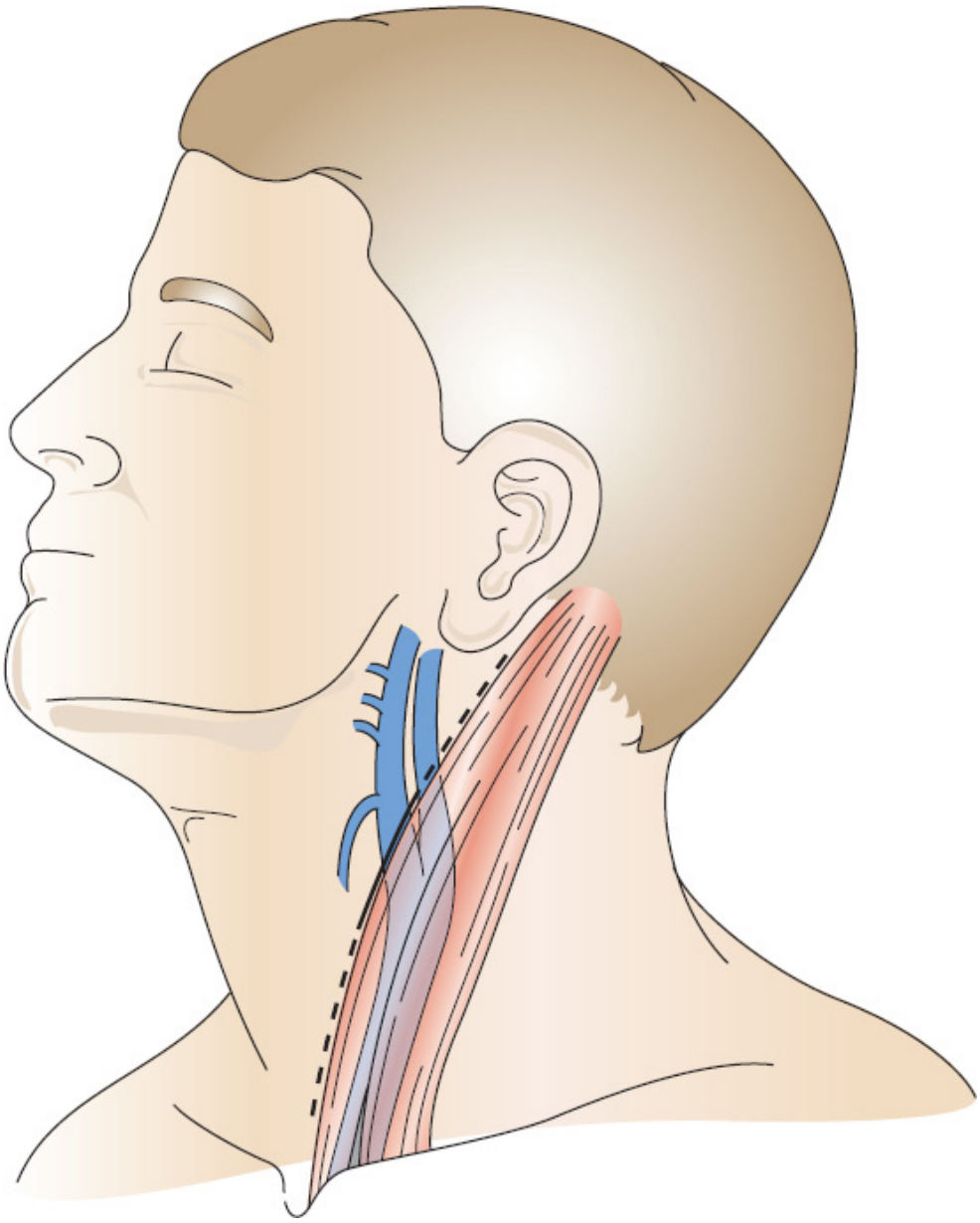

Figure 87.9 The patient's neck is slightly hyperextended and turned away from the ipsilateral side. An incision is made at the anterior border of the sternocleidomastoid muscle overlying the carotid bifurcation.

After complete vascular control of the CCA, ECA, and ICA, intravenous heparin (80 units/kg) is allowed to circulate for 3 to 5 minutes prior to clamping (**Fig. 87.10**). The ICA is clamped first in a safe area distal to the carotid plaque, in order to prevent embolization to the cerebral circulation. Next, the ECA and CCA are clamped. As discussed earlier, cerebral monitoring and use of carotid shunting is up to the discretion of the surgeon.

Endarterectomies of the carotid artery can be performed with a standard endarterectomy or an eversion endarterectomy. The standard endarterectomy consists of a longitudinal arteriotomy that is created on the distal CCA and extended onto the ICA. The arteriotomy should be extended just beyond the area of plaque in an area of normal ICA. At this point, if shunt is used it should be placed from the CCA into the ICA to maintain antegrade ipsilateral cerebral flow (**Fig. 87.11**). Endarterectomy is accomplished by teasing off the atherosclerotic plaque from the intimal layer. This can be done with a blunt elevator or sharply with a beaver blade (**Fig. 87.12**). In order to adequately endarterectomize the carotid artery, the plaque extending into the ECA is removed using an eversion technique (Fig. 87.13). Great care must be taken to ensure a nice stable feathered out endpoint of the endarterectomy plane on the ICA. The endarterectomized plane is then evaluated and any small flaps or debris are removed. Not uncommonly, the area of the distal endpoint on the ICA has soft intimal flap that should be tacked down with a 7-0 Prolene to avoid flaps being raised, causing dissection when antegrade flow is resumed. If not done appropriately, patients are at risk for acute carotid occlusion following CEA, which may have devastating consequences.

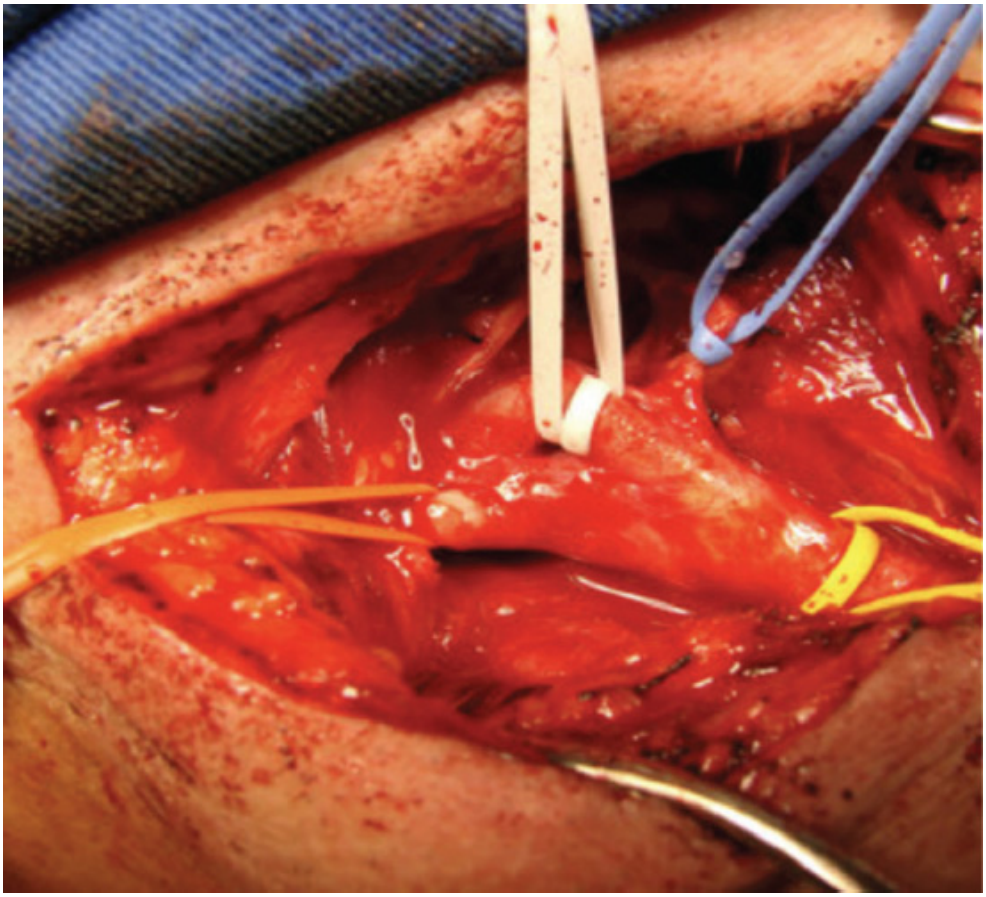

Figure 87.10 Circumferential vascular control surrounding CCA (*yellow loop*), ICA (*orange loop*), ECA (*white loop*), and superior thyroid artery (*blue loop*).

Repair of the arteriotomy should be accomplished with use of a patch angioplasty. Multiple studies[36–38] have shown the benefit of closing the arteriotomy with a patch versus primary closure to prevent late ipsilateral stroke and recurrent stenosis. Different patch materials include: Dacron, bovine pericardium, or autogenous materials. No difference has been shown to what type of patch material used and decision is up to surgeon preference. If shunt is used, patch should be almost completely closed prior to removal of shunt and resumption of clamping (Fig. 87.14). Prior to complete patch closure, it is necessary to appropriately back bleed and flush out any debris that may have accumulated within the endarterectomy site. Once patch is completed, allow reperfusion to the ECA first while keeping the ICA clamped to ensure any remaining debris of thrombus does not proceed into the anterior cerebral circulation. Meticulous hemostasis is obtained in the surgical bed and if needed heparin can be reversed with protamine. The

SCM is then reapproximated in the field and a surgical drain may be placed at the discretion of the surgeon in the subplatysmal layer. The platysma layer is then closed with absorbable suture followed by the skin. A full neurologic examination should be performed prior to extubation or while still in the operating room to ensure no neurologic deficits.

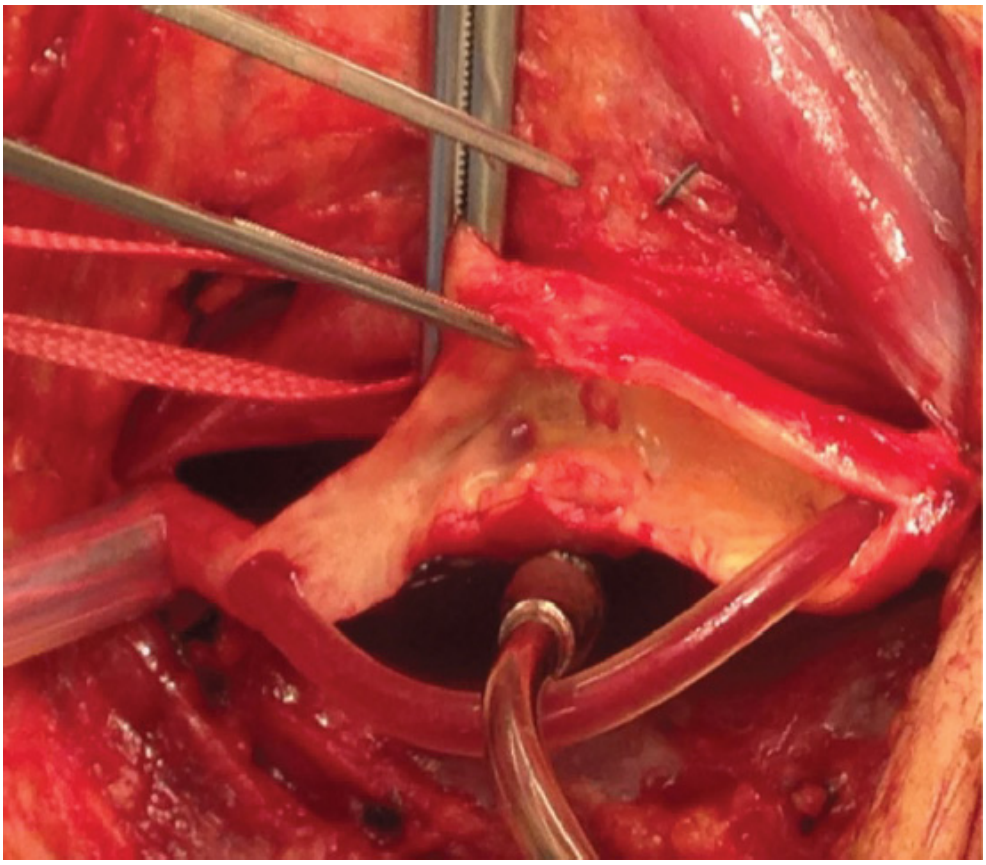

Figure 87.11 Intraluminal shunt placement from CCA to ICA.

Eversion endarterectomy (Fig. 87.15) is another CEA technique that has been employed and has the benefit of not requiring any prosthetic material for arteriotomy closure. Approach for eversion CEA is similar to standard CEA; similar incision is made and exposure of the carotid bifurcation occurs using similar standard techniques. The ICA is then transected obliquely at the carotid bulb including a small portion of the CCA. The edges of the ICA are the everted and peeled back performing an endarterectomy cleaving in between the intimal and medial layers. The atherosclerotic plaque plane is then removed as it proceeds distally until a clean portion is encountered. Several downsides to this technique are the difficulty of placing an

intraluminal shunt, if it is needed, and inability to easily use distal tacking sutures. Closure is accomplished primarily by anastomosing the ICA onto the CCA without compromising the lumen of the ICA. Eversion CEA has been shown to be safe, effective, and durable in long-term follow-up with similar results as seen with standard CEA.[39] In a recent study of over 95,000 CEA performed in the United States, we have shown no difference in outcomes between eversion CEA and CEA with patch angioplasty, however, eversion CEA was superior to CEA with primary closure with 30% reduction in the risk of stroke and death at 30 days.[40]

The avoidance of perioperative stroke during and immediately after CEA is of the utmost importance, especially when performing CEA for high-grade asymptomatic carotid stenosis. To minimize this risk, several intraoperative completion studies are available to aid the surgeon in ensuring a technically sound repair. These include use of intraoperative continuous-wave form Doppler, intraoperative duplex, and intraoperative angiogram. Continuous-wave Doppler is an inexpensive and readily available tool that is available in almost every operating room. It can confirm patency of the carotid vessels and indicate if there are potential issues based on the resistance heard or a high-pitch Doppler sound indicating a possible stenosis. An experienced operator can detect these subtle sounds; however, continuous-wave Doppler is insensitive at detecting small intimal flaps or more subtle stenoses. Duplex ultrasound, on the other hand, is a much more sensitive tool and can give detailed anatomic imaging regarding the existence of a possible intimal flap or high-grade stenosis. Like any duplex ultrasound, quality can be variable and is operator dependent. The "gold standard" continues to be intraoperative completion angiogram with injection of contrast directly into the common carotid. Completion studies are not uniform practice and have mixed results in the identification of clinically relevant defects. Furthermore, small questionable defects that are revised may do little to improve outcomes and may be predictive of possible perioperative stroke.[41]

Figure 87.12 **A:** Elevator with blunt edges. **B:** Half moon shaped sharp blade.

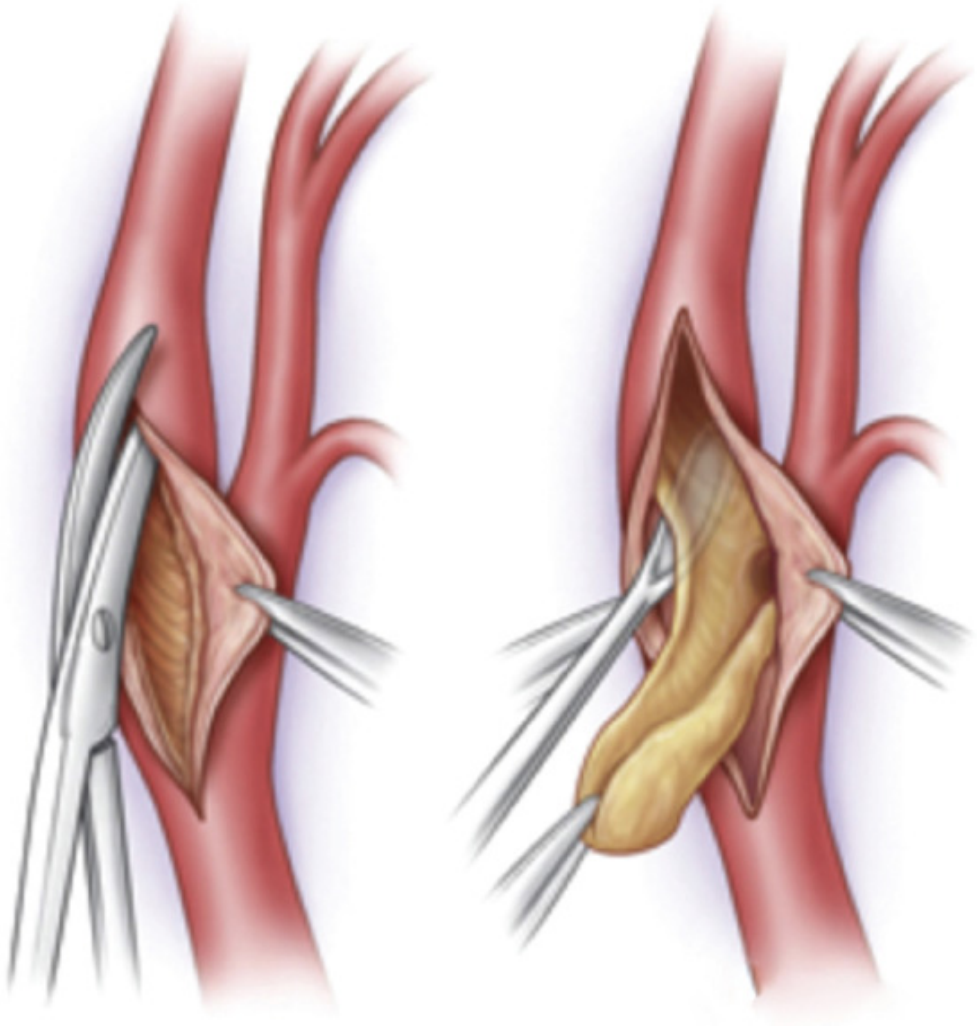

Figure 87.13 Conventional endarterectomy by removing plaque with blunt dissection and everting atherosclerotic plaque from ECA.

Complications

CEA can be safely done in the vast majority of cases and is well tolerated with most patients being discharged after 24 hours. However, a wide array of complications exists, from mild wound issue to life-threatening issues. The single biggest contributor to perioperative death continues to be MI. MI is responsible for 25% to 50% of all perioperative deaths after CEA and more late deaths are seen from MI than from stroke or other causes.[42] Significant advances have been made in the past two decades that have led to a significantly low rate of cardiac events during and immediately after CEA. One of the most feared complications, especially in treating asymptomatic

patients, is perioperative ipsilateral stroke. There are multiple etiologies for immediate postoperative stroke including embolization, hyperperfusion, and rarely acute occlusion. Embolization can occur from shunt placement, from the clamp site, thrombus forming during CEA, or inadequate flushing prior to arteriotomy closure. With manipulation of the carotid sinus, hypertension and hyperperfusion may ensue postoperatively and can lead to ipsilateral ischemic stroke if hypertension not controlled. This phenomenon usually occurs 24 to 72 hours after CEA and adequate postoperative blood pressure control is mandated prior to discharge home. Acute patch occlusion is rare but may be related to an intimal flap, platelet adhesion from the patch, dissection, or anastomotic stricture. This is why it is of the utmost importance to document a normal neurologic examination prior to extubation or prior to leaving the operating room. Intraoperative imaging is another important method to ensure normal flow prior to closing the wound. During CEA, cerebral ischemia can occur due to hypoperfusion of watershed cerebral area. This is related to inadequate collateral flow through the contralateral carotid artery and posterior circulation, which relies on a patent circle of Willis. Ipsilateral perioperative stroke rates continue to decline. Thirty-day stroke and death rate after CEA in CREST was 3.2% in symptomatic patients and 1.2% in asymptomatic patients. Additionally, for symptomatic patients, 30-day risk of MI was 2.2% and death rates were 1.1%; for asymptomatic patients, 30-day risk of MI was 2% and death rates were 1.1%. Overall, with CEA CREST showed a periprocedural risk of death at 0.3%, CVA of 2.3%, and MI of 2.3%.[2] Cranial nerve injury (**Table 87.3**) is the most common neurologic complication following CEA and one of the most problematic for patients. Incidence of postoperative cranial nerve injury ranges from 5% to 20% with the vast majority of these resolving at 6 months.[43]

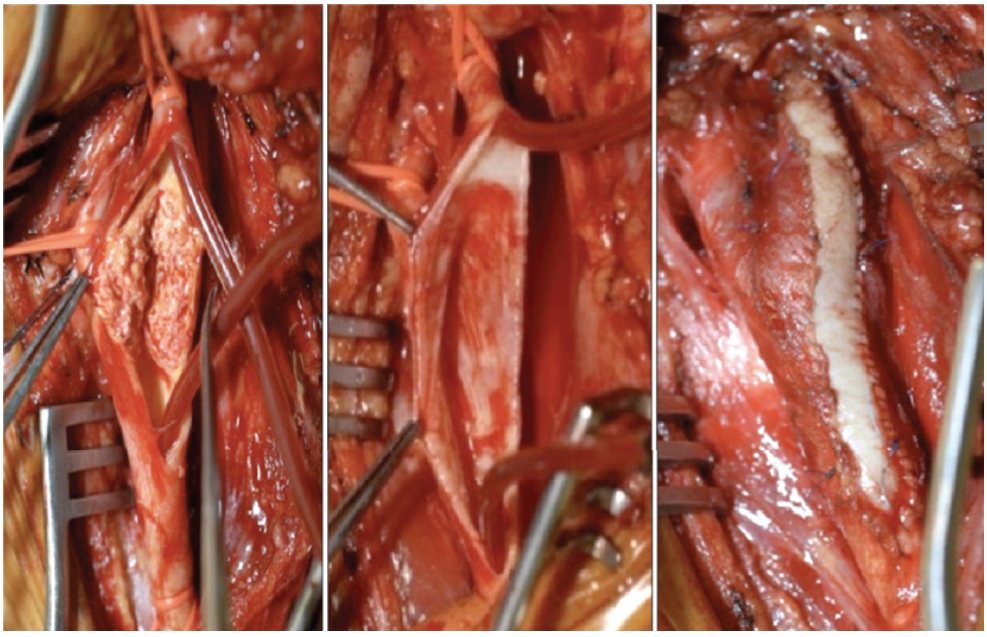

Figure 87.14 Carotid endarterectomy showing complete removal of atherosclerotic plaque with shunt placement and patch angioplasty closure.

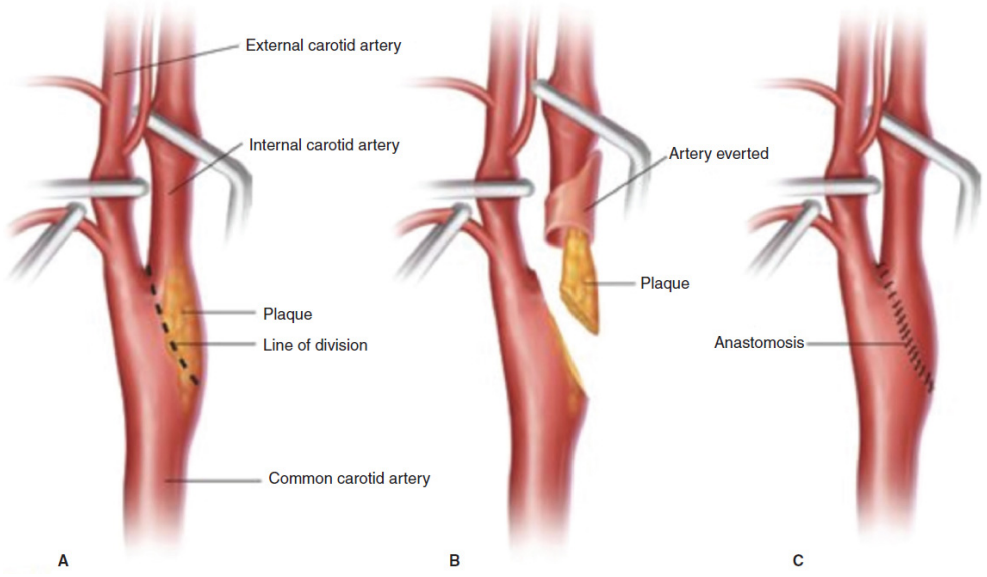

Figure 87.15 **A:** The ICA is divided from the CCA in an oblique plane. **B:** The divided ICA is everted and endarterectomy occurs until plaque endpoint, and is removed from the ICA. **C:** The ICA is then reattached to the CCA primarily.

Transfemoral Carotid Artery stenting

Technique

TFCAS with distal embolic protection device (EPD) has gained popularity since its advent in the early 90s. Since the Food and Drug Administration (FDA) approved TFCAS in 2004, there has been a proliferation of technology and expansion of its use for symptomatic and asymptomatic carotid artery stenoses. Similar to indications for CEA, TFCAS should be considered a viable carotid revascularization option in patients with symptomatic >50% stenosis and asymptomatic >80% stenosis. Most vascular surgeons believe CAS should be reserved for patients who are deemed high risk (surgical or medical) for CEA (**Table 87.4**). Currently, the Center for Medicare and Medicaid Services (CMS) will only reimburse for high-risk patients with symptomatic >70% carotid artery stenosis, limiting the use of TFCAS to these patients.

In order to obtain procedural success with low periprocedural complication rate, identification and examination of preoperative imaging is a must. Prior to planned TFCAS, axial imaging should be carefully reviewed. Typically, MRA or CTA with thin-cuts are performed with imaging including the aortic arch and the circle of Willis. Careful preoperative imaging examination will identify diseased arch and difficult tortuous anatomy for tracking wires and catheters into the carotid artery. Possible stroke can occur with excessive manipulation of the aortic arch and inability to recognize ostial disease. Arch types based on tortuosity are recognized on preoperative imaging (Fig. 87.16). In general, type III arches are now considered contraindication for TFCAS with mounting evidence of increased intraprocedure embolization. Preoperative imaging also can identify other high-risk lesion and anatomic criteria for TFCAS and potential contraindications for CAS (**Table 87.5**). Prior to TFCAS procedure, all patients should be on DAPT with 7 days of aspirin (typically 325 mg) therapy and 5 days of clopidogrel therapy (receiving a total of 450 mg of clopidogrel). Patients should also receive statin therapy prior to procedure, as we have shown a significant reduction in the risk of death following operative stroke or MI in patients on statin prior to TFCAS.[44] The procedure should be done in an angiographic suite or in a hybrid operating room with appropriate imaging quality. Preoperative arterial line placement is preferred for close blood pressure and HR monitoring. Alternatively, an arterial line can be hooked up to the arterial access sheath, however, during stent placement, the arterial line will be lost. TFCAS procedures should be done

under local only in order to adequately and frequently assess neurologic function. Performing this procedure under GA also increase the risk of cardiac complications including MI and arrhythmias.[45] The patient is placed in a supine position with bilateral groins prepped. Standard retrograde femoral access with US-guided micropuncture technique is obtained. The patient is systemically heparinized in order to maintain activated clotting time (ACT) between 250 and 300 seconds. If careful preoperative imaging evaluation was performed, then rarely should an arch aortogram be performed. Selective catheterization of the carotid artery is then obtained and catheter is placed just proximal to the carotid bifurcation. Multiple catheter types (**Fig. 87.17**) are available for use (e.g., H1, JB1, JB2, Vert, VTK, SIM, etc.). Angiogram is now performed to confirm carotid artery stenosis location and severity, assess ECA patency and evaluate distal carotid artery flow, and evaluate ipsilateral intracerebral circulation.

Table 87.3 Cranial Nerve Dysfunction and Incidence Following CEA

Cranial Nerve Injury	Clinical Sequelae	Incidence (%)
Vagus nerve (recurrent laryngeal nerve)	Unilateral—Hoarseness (rarely seen) Bilateral—Vocal cord paralysis	1.5–15
Superior laryngeal nerve	Fatigability of voice, difficulty with voice modulation	1.8–4.5
Hypoglossal nerve	Unilateral—Ipsilateral tongue deviation Bilateral—Difficult swallowing and articulation	4.4–17.5
Glossopharyngeal nerve	Aspiration, dysphagia	0.2–1.5
Marginal mandibular nerve	Drooping ipsilateral lip	1.1–3.1
Spinal accessory nerve	Shoulder droop, scapular winging	<1.0

Incidence data from Forssell C, Takolander R, Bergqvist D, et al. Cranial nerve injuries associated with carotid endarterectomy. A prospective study. *Acta Chir Scand* 1985;151:595–598

Table 87.4 High-Risk Medical and Surgical Patients for CEA

Clinical Criteria	Anatomic Criteria
Unstable angina	High lesion above C2
NYHA class III or IV CHF	CEA restenosis
LVEF <35%	Prior neck irradiation
MI <6 wk	Cervical immobility
Severe pulmonary disease	Tracheostomy
Contralateral recurrent laryngeal nerve injury	Previous neck surgery

NYHA, New York Heart Association; CHF, congestive heart failure; LVEF, left ventricular ejection fraction.

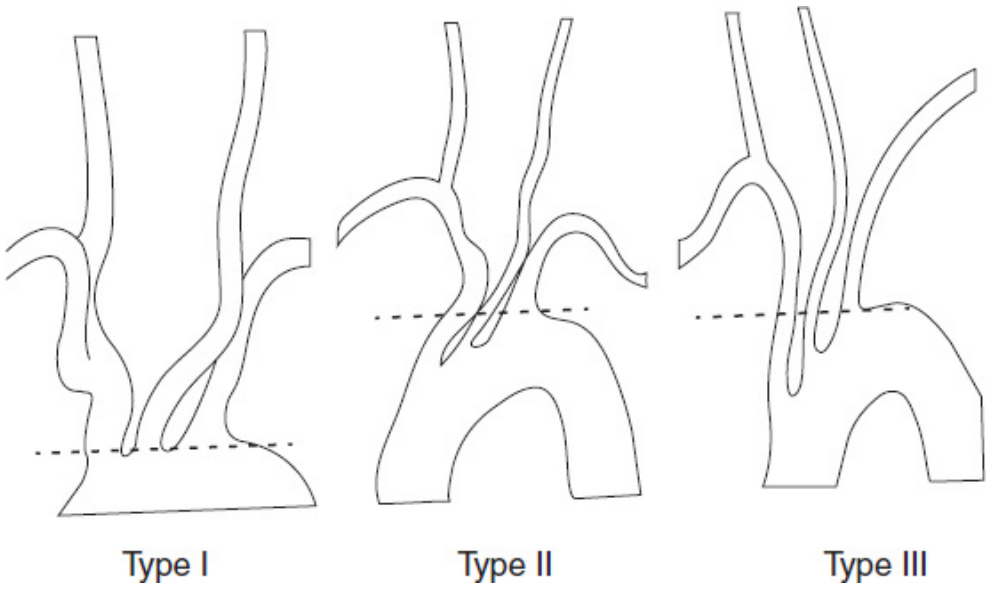

Figure 87.16 Arch types based on tortuosity.

Table 87.5 Contraindications and High-Risk Features for Carotid Artery Stenting

Carotid Artery Stenting Contraindications
Severe ICA kinking
Unstable plaque
Fresh thrombus
Brachiocephalic vessel tortuosity
Brachiocephalic vessel severe stenosis or occlusion
Acute aortic arch angle or anomalous aortic arch (type III arch)
Significant aortic arch plaque or thrombus
Circumferential calcification
Poor arterial access

Appropriate sheath (6-Fr shuttle select) is telescoped over the catheter and wire into the mid CCA, once decision is made to proceed with carotid artery stenting. Great care must be taken to avoid inadvertently manipulating the lesion and risk embolizing distally into the ICA. Alternatively, in difficult access anatomy, the ECA can be cannulated and stiff wire placed with advancement of the sheath into the CCA in a nontelescoped manner. Angiogram through the sheath is then performed to map out ICA anatomy to aid in cannulating the ICA for placement of EPD (Fig. 87.18). It is ideal to open and flush the appropriate size predilation balloon, carotid stent, and EPD so that minimal time is taken from predilation to completion stenting. Next, EPD is placed into the distal ICA in a straight area of the artery in order to minimize distal embolization and CVA during balloon angioplasty and stent placement. Depending on the type of carotid stent used, different EPDs are available for placement (Fig. 87.19). Filter placement requires wire manipulation and crossing of the lesion to access the distal ICA. Some filters are attached to the wire, while others can be advanced over the 0.014 wire into the distal ICA and deployed. The remainder of the stenting

procedure is performed over the EPD wire via a rapid exchange platform. Gentle predilation of the lesion is typically accomplished with an undersized 3- to 4-mm balloon at low atmospheric pressure. Bradycardia and hypotension can occur even with gentle ballooning of the carotid lesion, thus it's advisable to prophylactically administer or be ready to administer glycopyrrolate to minimize the risk or treat bradycardia and hypotension. Additionally, having available dopamine or phenylephrine infusions is wise in order to quickly treat prolonged or severe hypotension. Next, the predetermined stent size and length are advanced and carefully deployed encompassing the entire carotid lesion into the proximal portion of carotid stent into the CCA in order to stabilize carotid plaque. Stent size typically depends on the size of the ICA and CCA and comes in straight and tapered configurations. Type of carotid stent use is up to the discretion of the interventionalist. The stents are self-expanding and have either an open- or closed-cell stent design (Fig. 87.20). Flexibility of the stent depends on the number of connections between the cells of the stent. The less the amount of connections (open-cell design), the more flexible the stent will be and may be better used in tortuous ICA lesions. The more connections, the stiffer the stent will be (closed-cell design). Closed-cell stents may be better used in symptomatic patients to lessen embolization or extrusion of carotid plaque through the stent. However, the evidence is conflicting on the benefit of closed- versus open-cell design.[46] Postdilation of the stent should be carefully considered as studies suggest worse outcomes with higher stroke and death rates and more hemodynamic depression,[47,48] when routine postdilation is undertaken. Significant vasospasm in the distal ICA may occur with placement and removal of filter. Once EPD is removed, completion angiogram is performed (**Fig. 87.21**). Femoral access sheath is removed with closure device. Similar to CEA patients, close neurologic and hemodynamic assessments are made throughout the postprocedure period. Most patients are discharged home 24 hours after TFCAS and continue 1 month of clopidogrel and lifelong aspirin.

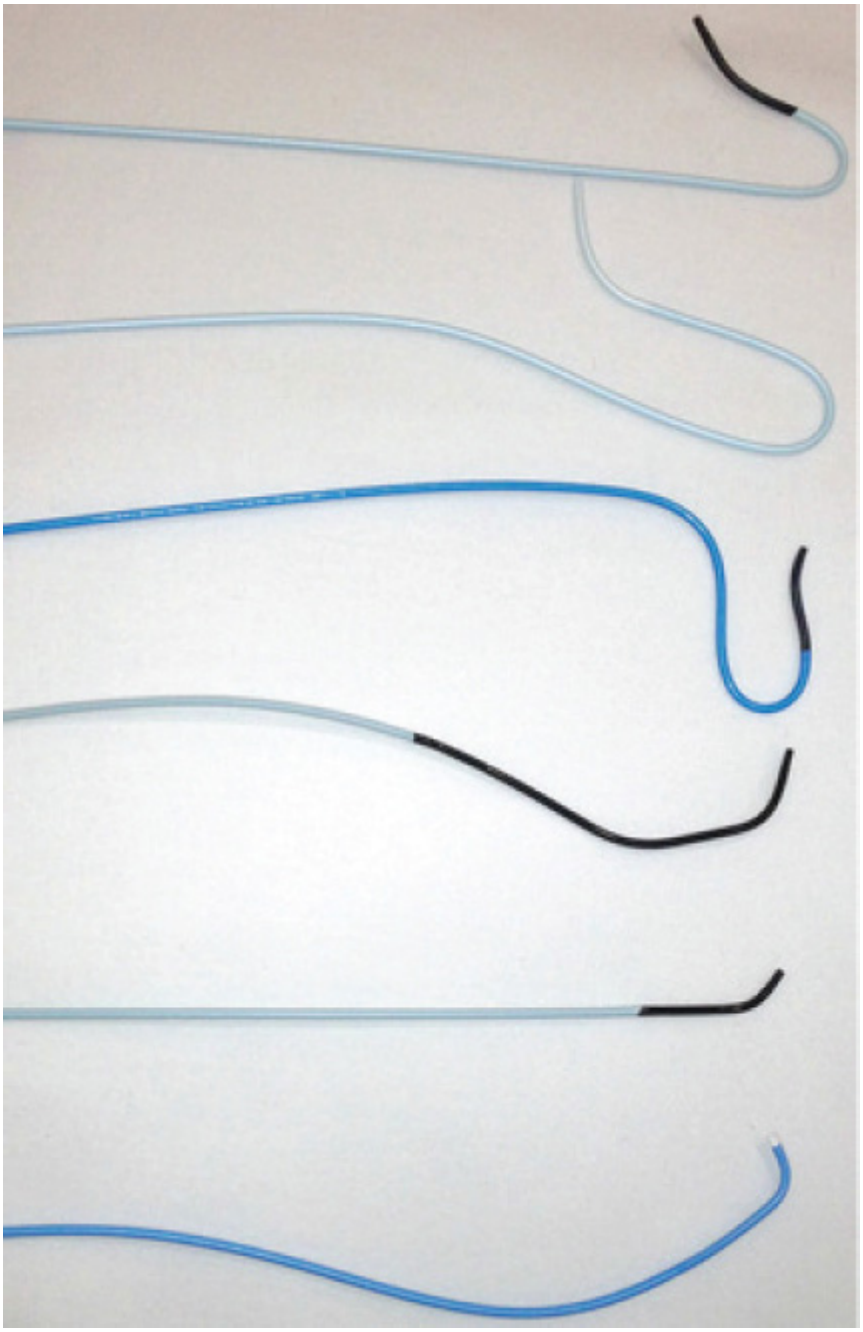

Figure 87.17 Catheters available for selective carotid cannulation during carotid angiogram and stenting.

Figure 87.18 Carotid angiogram shows high-grade stenosis with high lesion at level of C2 and poor anterior cerebral artery flow.

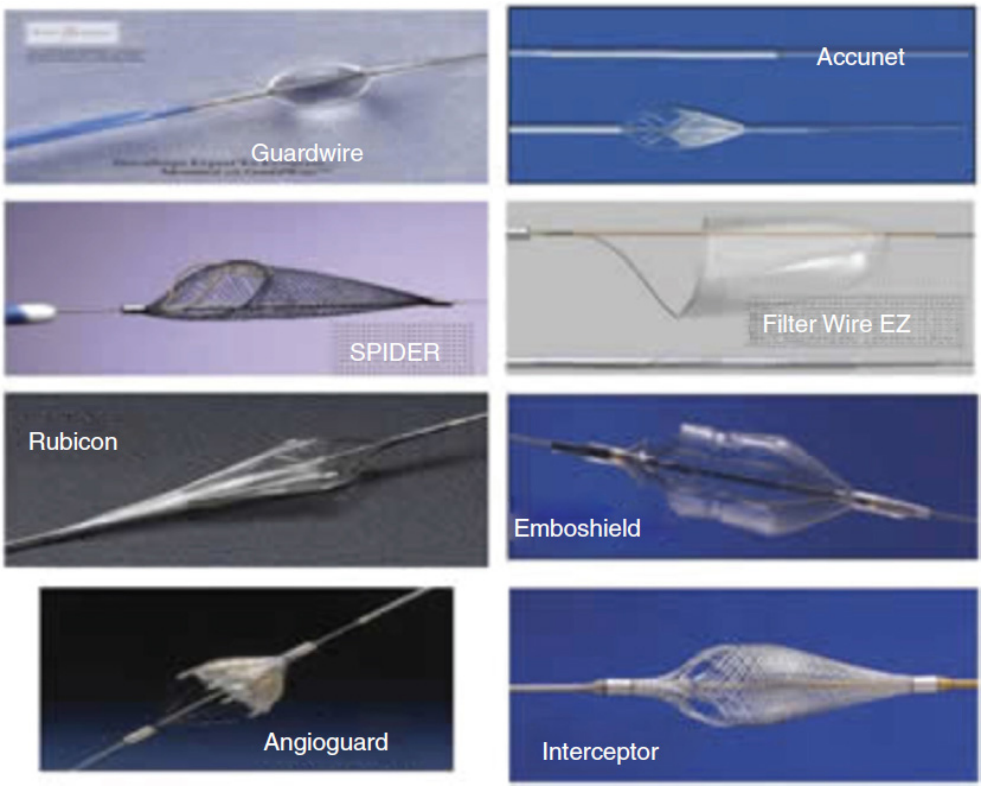

Figure 87.19 Types of embolic protection devices available for use.

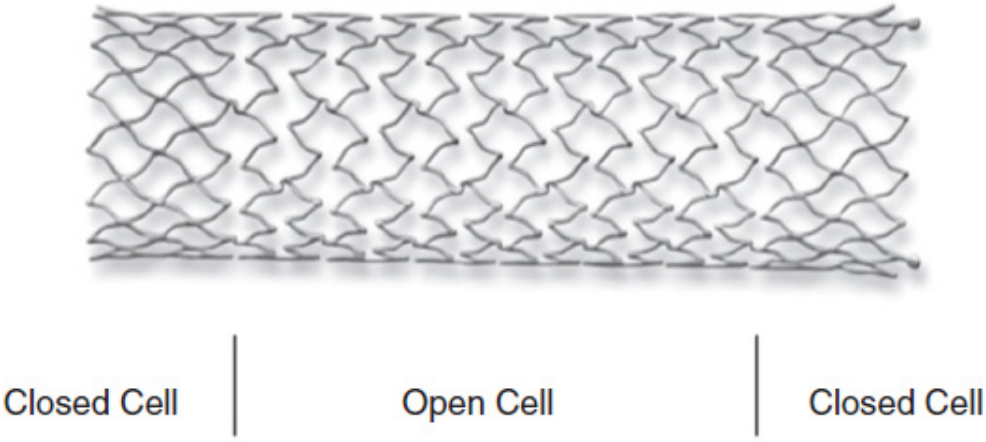

Figure 87.20 Self-expanding carotid artery stents with open- and closed-cell stent design.

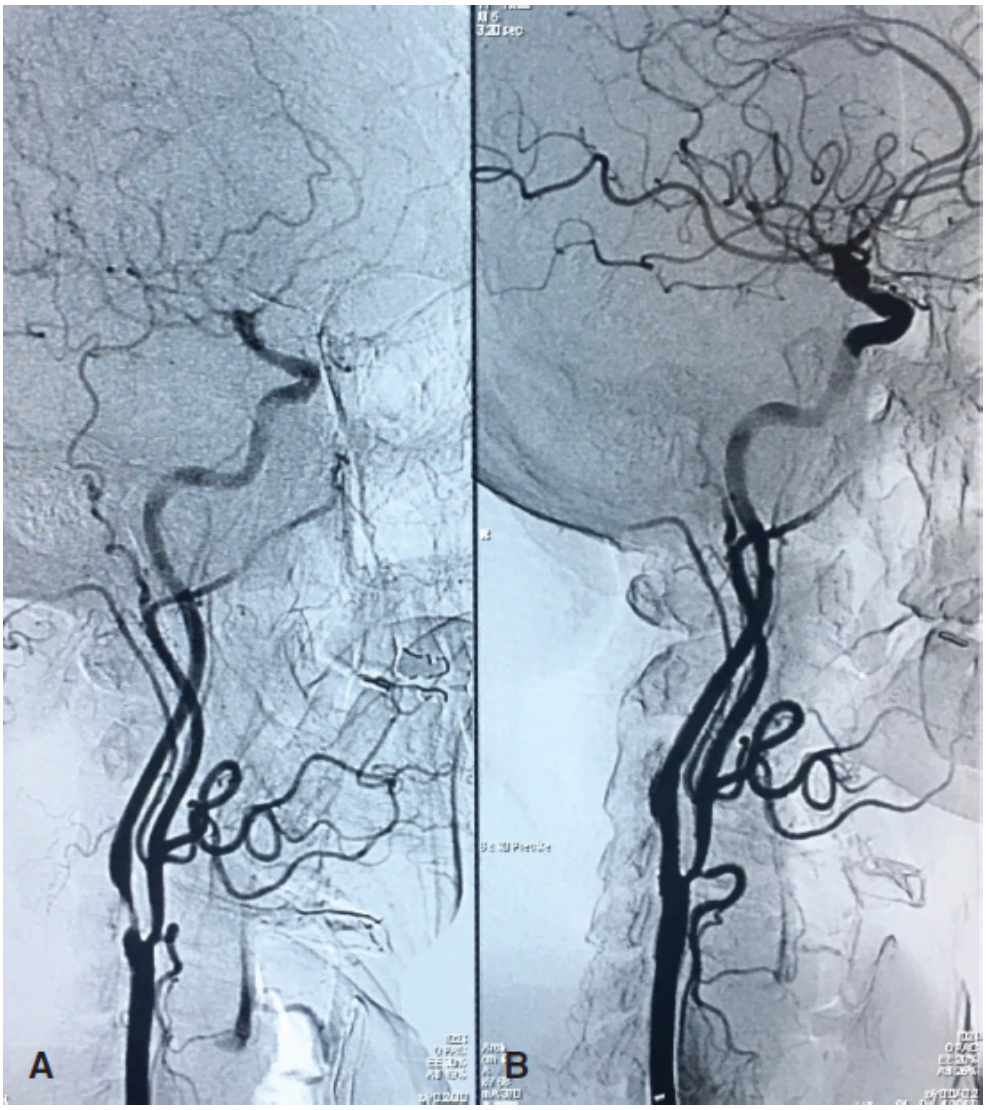

Figure 87.21 **A:** Prestent carotid angiogram showing severe ICA stenosis with poor distal flow. **B:** Poststent carotid angiogram showing resolution of stenosis and improved distal flow.

Complications

The most serious and important complication following TFCAS is periprocedural stroke. While cardiac events are less frequently seen, CREST found periprocedural MI rates to be lower in TFCAS patients versus CEA (1.1% vs. 2.3%, $p = 0.03$). Neurologic events following TFCAS can have devastating consequences and prompt recognition and treatment is needed. Potential causes of periprocedural stroke include: distal embolization from manipulation of the lesion, thrombosed EPD, acute stent thrombosis, kinking

after carotid stenting, carotid artery dissection, and hyperperfusion. Acute stent thrombosis may be related to failure of adequate expansion of carotid stent in densely calcified atherosclerotic plaque. This typically requires immediate stent explantation and conversion to CEA. Carotid dissection may require additional stenting versus antiplatelet therapy. Despite the necessity of using filter protection during transfemoral CAS, EPD can cause issues with placement. Distal filters may dissect or become full of thrombus/plaque causing thrombosis of the filter. Additionally, filter placement may cause severe vasospasm in the distal ICA that potentially could cause thrombosis of the vessel. Immediate EPD retrieval is performed when these complications occur. Distal embolization may require neurorescue techniques, such as: aspiration thrombectomy, catheter-directed thrombolysis, or stent retrieval. Access site complications can occur with or without use of a closure device. Such complications include hematoma, pseudoaneurysm formation, AV fistula, thrombosis, and possible infection.

Results

In its early phase, TFCAS was reserved for only high-risk, elderly patients who were deemed to be too high risk for CEA. Multiple randomized controlled trials (RCTs) have shown early efficacy in treatment of high-risk patients with TFCAS. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial examined TFCAS versus CEA for high-risk patients (medical comorbidities and anatomical features). The trial was designed to show noninferiority of TFCAS compared to CEA in patients with >50% symptomatic stenosis and/or >80% asymptomatic stenosis. There was no significant difference in 30-day major adverse events (stroke, death, and MI) between the two procedures, while TFCAS was associated with a lower risk of major events at 1 year, with a greater advantage in asymptomatic patients.[49] The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial randomized patients with >70% symptomatic stenosis to TFCAS versus CEA. This study failed to prove noninferiority of TFCAS.[50] The endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) was a European randomized trial in symptomatic patients with >60% carotid stenosis. This trial was

stopped prematurely due to a 2.5-fold higher risk for 30-day stroke and death in the TFCAS group.[51] Routine use of EPD was not required, which was a major drawback in the TFCAS group. Most recently, the CREST compared TFCAS to CEA in standard-risk symptomatic and asymptomatic patients. Long-term follow-up out to 10 years did not show a difference between CAS and CEA with regard to stroke and death.[52] With that being said, 30-day outcomes did show a significantly higher risk of stroke for TFCAS versus CEA (4.1% vs. 2.3%, $p = 0.01$).

TRANSCAROTID ARTERY REVASCULARIZATION

Technique

TCAR is an innovative hybrid procedure that combines CEA like neuroprotective effects by clamping of the carotid artery with a minimally invasive approach to treat carotid stenosis by direct placement of carotid artery stent avoiding the arch. The procedure is done under novel flow reversal in the carotid and ipsilateral cerebrum. Like with any carotid revascularization procedure, careful patient selection is paramount to have success with TCAR. Currently, TCAR is approved for high-risk patients with >50% symptomatic carotid stenosis or >80% asymptomatic stenosis. Participating hospitals must be involved in the Vascular Quality Initiative (VQI) Carotid Artery Stent Registry for the Society for Vascular Surgery (SVS). As compared to previous high-risk criteria used for standard TFCAS, TCAR has a wider high-risk inclusion criteria (**Table 87.6**). TCAR approach and set up is similar to that for CEA. Patients prior to TCAR procedure need to be on 5 days of DAPT and statins. Successful TCAR procedure relies on certain anatomic criteria which include: ≥6-mm diameter CCA, CCA puncture site at base of neck free of calcified plaque, ≥5 cm clavicle to carotid bifurcation distance, and ICA diameter of 4 to 9 mm. The patient is brought in to the operating room or a hybrid operating suite. Choice of anesthesia is up to the discretion of the surgeon with similar options to CEA: GA, RA, or LA. It is recommended that the first few TCARs performed be

under GA until the surgeon is comfortable with the procedure. A radial arterial line is placed for continuous blood pressure monitoring. Patients are positioned similar to CEA, supine on the operating room table with a shoulder roll and the neck turned to the contralateral side. Duplex ultrasound should routinely be performed to confirm adequate clavicle to carotid bifurcation distance and the CCA is free of significant atherosclerotic disease as well confirm patency of the ICA. A small incision is made at the base of the neck (either transverse or longitudinal) in order to isolate the CCA in between the two heads of the SCM muscle (Fig. 87.22). A 3- to 4-cm segment of CCA is circumferentially controlled and an umbilical tape with a Rummel tourniquet is placed as proximally as possible under direct vision. A purse string 5-0 Prolene suture is placed on the anterior advential surface the CCA to facilitate arterial closure at completion of TCAR. Attention is then paid to obtaining femoral venous access in order to perform flow reversal. Standard femoral venous access is obtained (typically in the contralateral side from the TCAR site) under ultrasound guidance and an 8-Fr sheath is inserted.[53]

Table 87.6 High-Risk Medical and Anatomic Inclusion Criteria for TCAR

Clinical Criteria	Anatomic Criteria
Patient >75 yrs of age	Contralateral carotid artery occlusion
Patient with >2-vessel CAD and history of angina	Tandem stenosis >70%
History of unstable angina	High cervical carotid artery stenosis
NYHA functional class III or IV	Restenosis after CEA
LVEF <30%	Bilateral carotid artery stenosis
MI >72 hrs and <6 wk prior to procedure	Hostile neck but amenable to transcarotid access
Severe COPD w/ FEV1 <50% predicted	
Permanent contralateral cranial nerve injury	
Chronic renal insufficiency (>2.5 mg/dL)	

NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

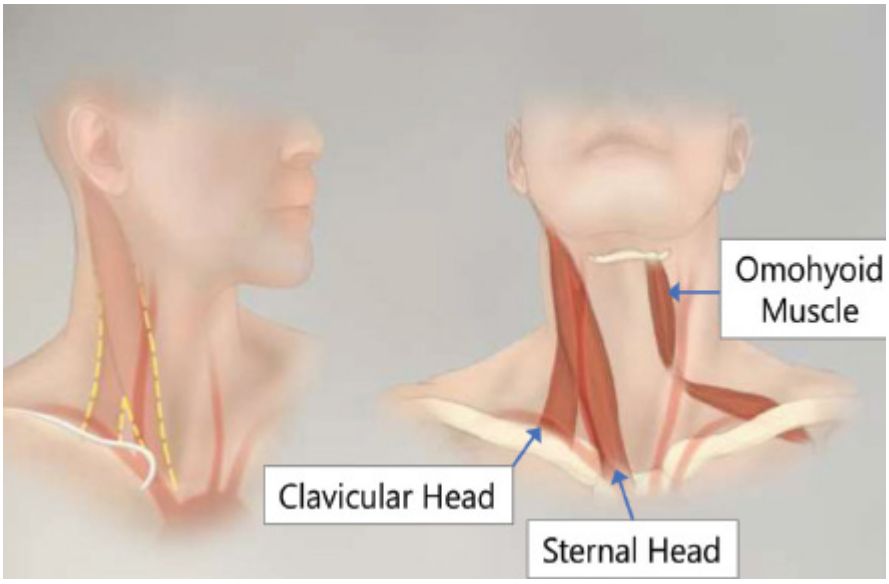

Figure 87.22 Illustration showing ideal location to isolate CCA in between the sternal and clavicular heads of the sternocleidomastoid muscle.

Figure 87.23 Silk Road ENROUTE sheath with angled tip.

The patient is then systemically heparinized, similarly to a CEA, with 80 units/kg of heparin with goal ACT >250 seconds. Access is then obtained in the CCA with micro needle, wire and sheath is advanced to just proximal to the carotid bifurcation. Angiogram is then performed to map out the carotid bifurcation. It is preferable to engage the ECA when patent with the microwire and sheath. A stiff wire is then placed into the ECA and the ENROUTE 8-Fr sheath (Silk Road Medical, Sunnyvale, CA) is advanced into the CCA and sutured in place (Fig. 87.23). Passive flow reversal is then activated by connecting the arterial to the venous sheath via the dynamic flow controller and integrated 200 μ filter (Silk Road Medical, Sunnyvale, CA) (Fig. 87.24). TCAR time out is then performed ensuring adequate anticoagulation with ACT, prophylactic administration of glycopyrrolate,

adequate mean arterial pressure (to allow for the significant delta between the arterial and venous pressure for flow reversal), and finally ensuring that the wire, balloon, and stent are open and flushed ready for use. Active flow reversal is initiated by clamping the CCA. Debris that may accumulate during carotid intervention is then reversed out of the carotid into the circuit and caught in the filter, while the blood returns to the venous system. The ICA lesion is then crossed with a 0.014-in wire. Standard predilation of the carotid lesion with a 3- or 4-mm by 20-mm balloon is then performed. Some have suggested more aggressive balloon dilation of the carotid lesion with a 5- or 6-mm diameter balloon, as the flow reversal is more protective for atheroembolic lesions occurring during prestent dilation. Next, the selected sized ENROUTE stent is then delivered and deployed using standard technique. Completion angiogram is then performed to confirm adequate treatment of the carotid lesion (Fig. 87.24). Poststent balloon dilation is reserved for severe residual stenosis, as the trend has been to move away from routine poststent balloon dilation due to severe hemodynamic issues with persistent poststent hypotension. Next, the flow reversal is left on for 1 or 2 minutes after stenting to ensure no further debris accumulates. The CCA is unclamped and the flow reversal is then stopped and the carotid sheath is removed while the purse string is sutured down. The venous sheath is then removed. The filter chamber can then be checked to evaluate for debris accumulation (Fig. 87.25). Meticulous hemostasis is obtained in the wound base and if need be a drain is left behind (Fig. 87.26). The layers are then closed in the standard fashion and like CEA, it is crucial to ensure no new neurologic symptoms prior to leaving the operating room. Patients are monitored closely for hemodynamic or neurologic issues post-TCAR procedure. Patients are usually discharged home 24 hours after procedure with 1 month of clopidogrel and lifelong aspirin therapy.

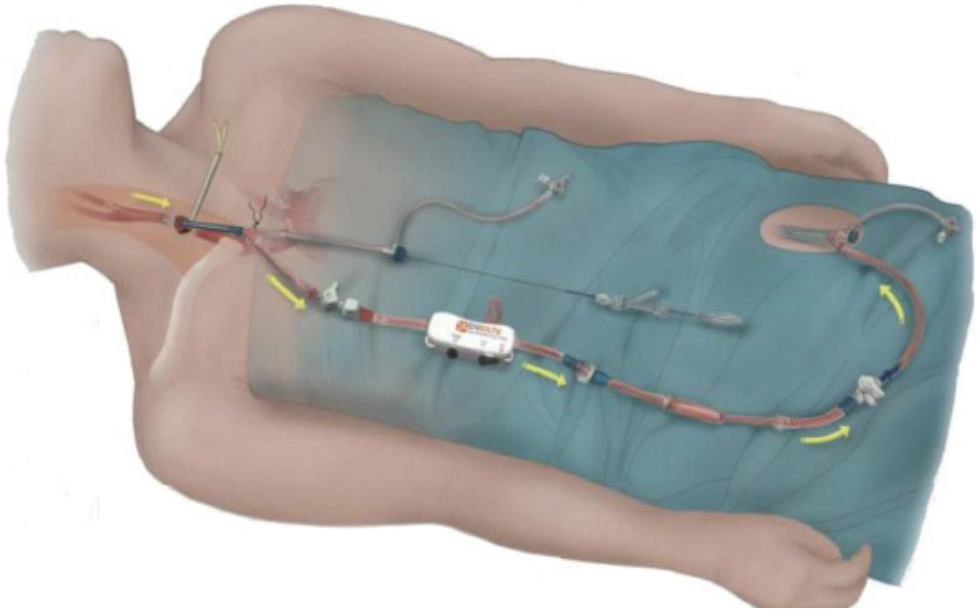

Figure 87.24 TCAR procedure utilizing the ENROUTE Transcarotid Neuroprotection and Stent System from Silk Road Medical with direct carotid access and percutaneous femoral vein access.

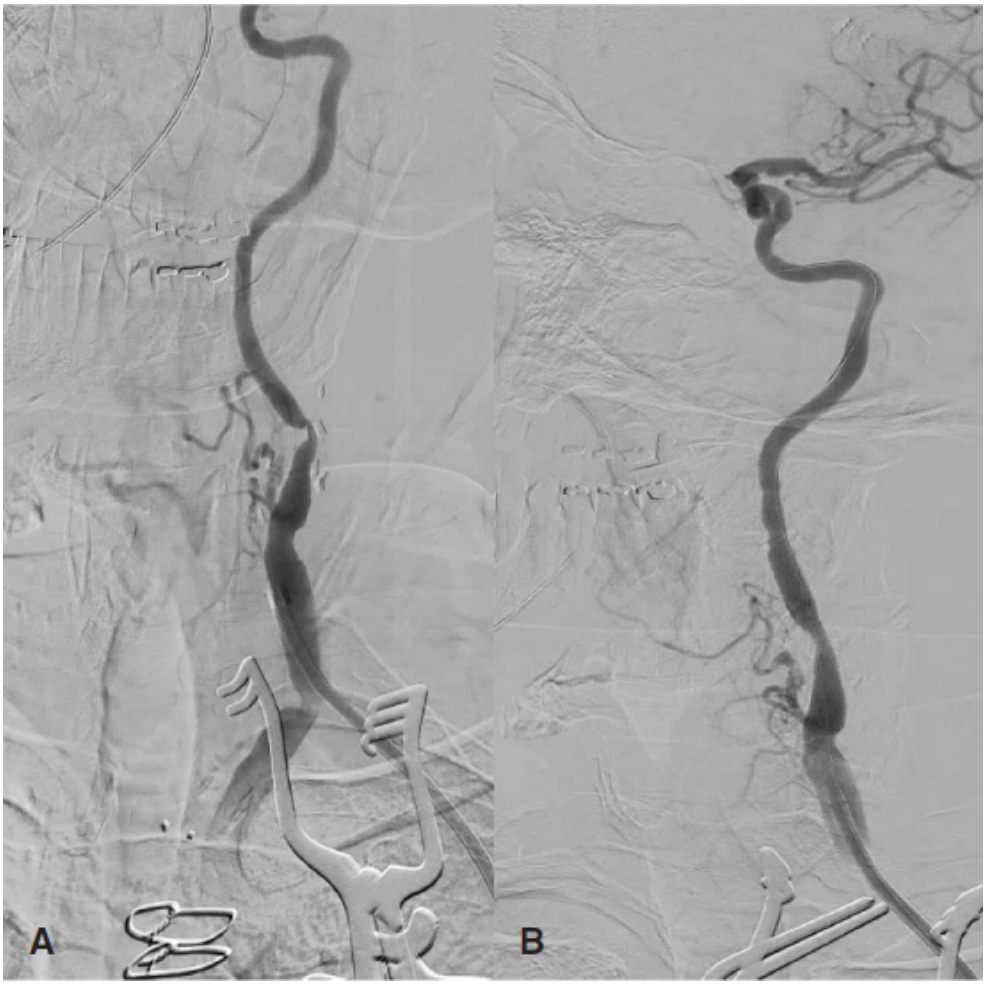

Figure 87.25 **A:** Prestent carotid angiogram showing severe ICA stenosis and clamp on CCA after carotid cut down. **B:** Poststent angiogram after TCAR stent deployment showing no significant residual stenosis and robust flow into the ICA.

Complications

Early results from the pivotal TCAR trial showed similar perioperative stroke rates as compared to CEA in what is deemed "high-risk" patients. At 30 days, in the pivotal TCAR group, all-stroke rate was 1.4% (2 of 141) and stroke and death rate was 2.8% (4 of 141).[54] MI rates in patients undergoing TCAR have been shown to be similar or slightly lower than those seen with traditional CEA. Postoperative cranial nerve injury is also much lower than in patients undergoing CEA. This is presumably due to the limited dissection of the carotid artery in the base of the neck, away from the cranial nerves. Initial ROADSTER results showed a 0.7% cranial nerve injury rate, with

that being one patient suffering from hoarseness from a potential cranial nerve X injury. This completely resolved at the 6-month postoperative visit. Other associated complications include wound complications and postoperative hematoma.

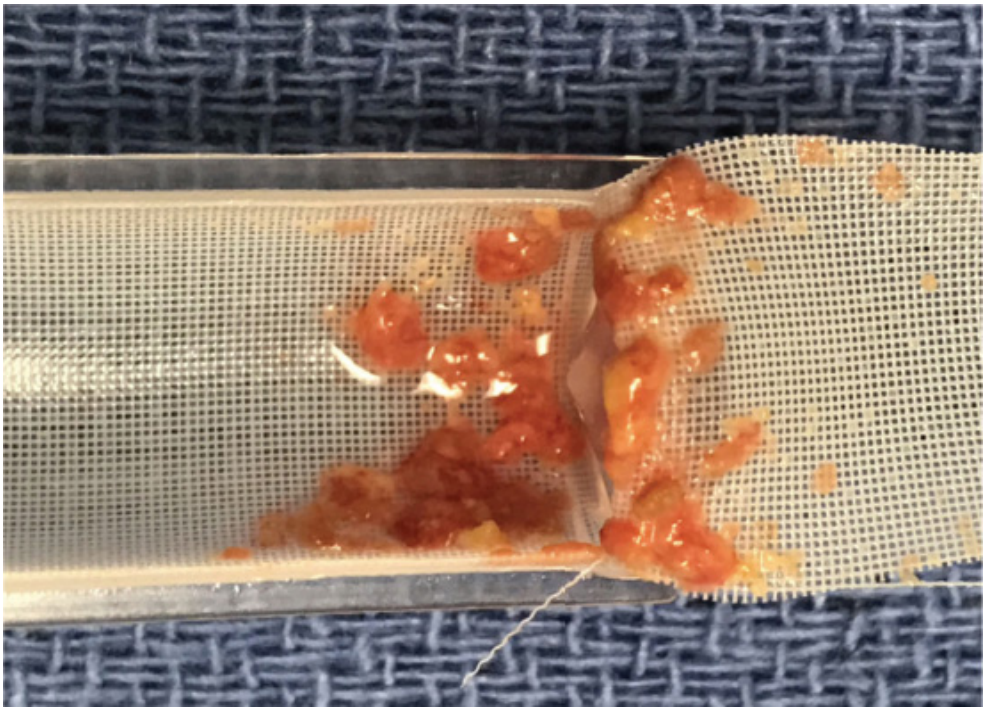

Figure 87.26 Post-TCAR stenting with flow reversal filtering system showing significant debris accumulated during procedure.

Results

TCAR provides an alternative to TFCAS in patients with carotid artery disease that are considered to be high risk for CEA, either anatomic or medical. The initial pivotal TCAR trial showed that at 30 days, TCAR was safe and effective. A further analysis was performed that included the initial ROADSTER patient and extended to analyze 1-year outcomes in terms of durability of TCAR with dynamic flow reversal. A total of 165 patients were examined, with majority of patients being male and asymptomatic. One-year ipsilateral stroke occurred in one patient (0.6%) from the pivotal cohort. One-year mortality rate was 4.2% following TCAR (no deaths were deemed neurologic in origin).[55] 30-day combined stroke, death, and MI rates were previously shown to be acceptably low (3.7% in ROADSTER 1) and with

further analysis of the effectiveness of TCAR, in the post approval study ROADSTER 2 showed a 1.7% combined stroke, death, and MI rate. Furthermore, ROADSTER 2 continued to show acceptable 30-day outcomes in terms of stroke/death rate (0.8% in ROADSTER 2 compared to 1.4% in pivotal ROADSTER 1).[56]

CAROTID ENDARTERECTOMY VERSUS TRANSFEMORAL CAROTID STENTING VERSUS TRANSCAROTID REVASCULARIZATION

Carotid interventions for patients with symptomatic (>50%) and asymptomatic (>80%) carotid artery stenosis is widely accepted. The choice of treatment modality is the next decision and is debatable and most certainly patient specific. CEA continues to remain the gold standard for treatment of atherosclerotic carotid artery disease. Higher-risk patients are now afforded multiple treatment types that are minimally invasive. Multiple previous clinical trials have examined the use of TFCAS versus CEA in high-risk patients. In every RCT, TFCAS failed to show similar outcomes to CEA as far as stroke and death.[49–51] Despite these results, TFCAS continues to have a role in treating patients with carotid artery disease who are not candidates for CEA.

With the recent advent of TCAR, multiple studies have compared treatment of carotid artery disease now with three treatment modalities: TFCAS, TCAR, and CEA. A multi-institutional analysis of TCAR compared to CEA showed similar 30-day and 1-year stroke rates (1.0% vs. 1.1%; 2.8% vs. 3.05%, respectively). These results were in spite of TCAR patients having higher rates of diabetes, hyperlipidemia, CAD, and renal insufficiency. TCAR was associated with a decreased rate of cranial nerve injury (0.3% vs. 3.8%; $p = 0.01$).[57] It has been previously shown that increasing age correlates with a higher embolic risk and thus higher ipsilateral stroke when performing TFCAS in elderly patients. However, at older ages, risk for stroke after CEA remains relatively constant across the age spectrum.[58,59] A comparative analysis was performed to evaluate the association between age

and outcomes after TCAR, TFCAS, and CEA. Rates of in-hospital stroke/death after TCAR were 1.4% in patients 70 years or younger, 1.9% in those 71 to 79 years, and 1.5% in those 80 years and older ($p = 0.55$). A comparison of TCAR with CEA across different age groups showed no significant differences in outcomes. When compared to 6 TFCAS, no differences were noted between TCAR and TFCAS in patients less than 80 years of age. However, in patients 80 years and older, TCAR was associated with a 72% risk reduction in stroke risk (4.7% vs. 1.0%; OR, 0.28; 95% CI, 0.12–0.065; $p < 0.01$), a 65% reduction in risk of stroke/death (4.6% vs. 1.5%; OR, 0.35; 95% CI, 0.20–0.62; $p < 0.001$), and 76% reduction in the risk of stroke/death/MI (5.3% vs. 2.5%; OR, 0.24; 95% CI, 0.12–0.47; $p < 0.001$) compared with TFCAS.[60] Finally, when comparing TCAR versus TFCAS, recently TCAR was shown to have lower rates of in-hospital stroke and death (1.6% vs. 3.1%) with no statistically significant differences in rates of perioperative MI (0.2% vs. 0.3%). At 1 year, TCAR was associated with lower rate of stroke or death as compared to TFCAS (5.1% vs. 9.6%). TCAR was associated with higher rates of access site complications resulting in interventional treatment (1.3% vs. 0.8%).[61,62]

NONATHEROSCLEROTIC CAROTID ARTERY DISEASE

Carotid Artery Dissection

Carotid artery dissection can either occur spontaneously or secondary to precipitating mechanical event (traumatic or iatrogenic). As in any arterial dissection, carotid dissection involves disruption or cleaving of the intima, which allows blood to extravasate in between layers of the vessel wall. The resulting hematoma usually extends distally and can lead to a high-degree distal ICA stenosis or occlusion (Fig. 87.27). Spontaneous dissections are more common in the carotid and vertebral arteries due to their mobility and proximity to bony structures. Even though carotid artery dissections account for a small number of overall strokes, up to 20% of stroke occurring in young patients are due to carotid artery dissection.[63] The classic triad of clinical

symptoms include ipsilateral headache or neck pain, ipsilateral Horner syndrome, and cerebral ischemia. It is quite rare to have all three clinical syndromes occur simultaneously. Headache appears to be the most common symptom and occurs in ipsilateral frontotemporal location. Even though largely asymptomatic, patient can also develop TIA, CVA, amaurosis fugax, cranial nerve palsies, and nausea. Similar to atherosclerotic carotid artery disease, multiple imaging modalities exist including: CTA, MRA, DUS; but the gold standard still remains angiography.

Figure 87.27 Digital subtraction carotid angiogram showing dissection starting in the proximal right ICA with classic appearing "flame" shape (*arrow*) resulting in distal occlusion.

Treatment options for asymptomatic carotid artery dissection begin with anticoagulation versus antiplatelet therapy. No studies have shown a difference with regard to mortality or stroke rate at 3 or 6 months when patients are treated with anticoagulation versus antiplatelet.[64] The only RCT, the Cervical Artery Dissection in Stroke Study (CADISS) trial, did have one major intracranial hemorrhage in the anticoagulation group versus none in the

antiplatelet group. These findings are similar to other nonrandomized studies.[65] Most common treatment continues to be IV heparin followed by anticoagulation for 3 months. Indication for acute surgical intervention include: inability to anticoagulate, worsening symptoms, symptoms refractory to anticoagulation, aneurysm formation, or severe neurologic symptoms with severe flow limitation. Options for open surgical repair include surgical bypass, patch angioplasty, or carotid ligation. Endovascular stenting for carotid dissection has had promising early results.[66]

Carotid Artery Fibromuscular Dysplasia

FMD involving medium-sized arteries is a rare clinical entity affecting up to 7% of the population.[67] This noninflammatory, nonatherosclerotic arteriopathy is most commonly seen in women, constituting 60% to 90% of patients with FMD.[68] The incidence of carotid FMD is even more rare, with an incidence of only 0.42% in 3,600 patients undergoing cerebral angiographic examination.[69] The exact etiology of FMD is unknown. Four subtypes of FMD exist, with the most common being the medial fibroplasia type, followed by perimedial fibroplasia, intimal fibroplasia, and medial hyperplasia. This type gives off the classic appearance of a "string of beads" (**Fig. 87.28**). This angiographic appearance is caused by segmental encroachment of the arterial lumen and poststenotic dilatation and can be a nidus for hypoperfusion and embolization. As seen in the previous figure, FMD typically occurs in the mid to distal ICA and avoids the carotid bifurcation. Duplex ultrasound imaging can be used to identify carotid FMD lesions, however, elevated velocities and the classic FMD appearance may not be well appreciated. CTA and MRA have largely replaced the need for angiography and are able to clearly show the "string of beads" appearance associated with classic FMD. With that being said, gold standard still remains carotid angiogram. The advantage of CTA or MRA is the ability to identify intracerebral aneurysms; which can occur in up to 50% of carotid FMD patients.[70]

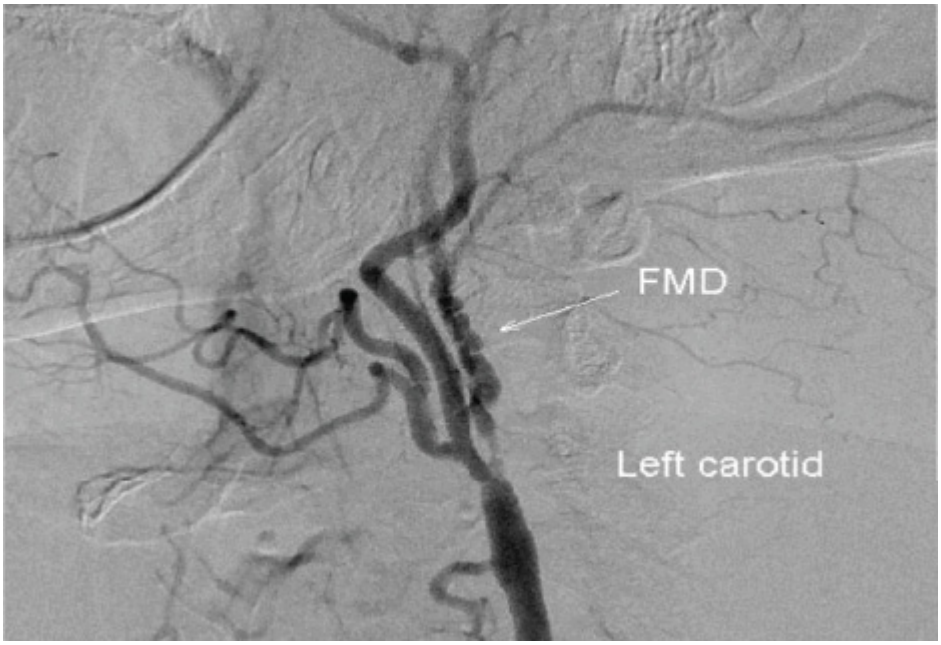

Figure 87.28 Carotid angiogram showing concomitant atherosclerotic carotid bifurcation disease and classic appearing mid ICA FMD.

The natural history of FMD is not well established, with few lesions progressing to the point of narrowing of the arterial lumen causing reduced perfusion, formation of thrombus leading to distal embolization, and dissection or rupture. However, the majority of lesions remain clinically silent for years and only require antiplatelet therapy.[71] Symptomatic patients should undergo repair, focusing on breaking the webs associated with FMD. This can be done with either open or endovascular means. In an open repair, serial rigid dilation occurs via a common carotid arteriotomy. This technique allows for back bleeding and removing of debris, however, stroke may occur from debris not washed out after breaking of the webs. Transfemoral angioplasty has been used as an alternative minimally invasive option. Stenting usually is not required. The anatomy of FMD prevents the use of EPD due to the increased risk of embolization. An attractive alternative is the use of TCAR and its novel flow reversal for angioplasty of FMD lesions.

Carotid Artery Aneurysms

Extracranial carotid artery aneurysms are rare and can occur as a result of atherosclerotic degeneration, traumatic injury, dissection or local infection,

or as a complication after CEA. True degenerative carotid artery aneurysms are quite rare, with an occurrence of 1% (Fig. 87.29). Pulsatile mass is the most common presenting symptom. A high index of suspicion is needed with bruit or pulsatile mass after traumatic head and neck injury. Other presenting symptoms may include cranial nerve dysfunction, Horner syndrome, neurologic complication, such as TIA or stroke. Rarely, carotid artery aneurysms become so large that they can cause dysphagia or present with hemorrhage or rupture. The natural history of carotid artery aneurysms is not well established, due to its rare incidence. Thus, almost all carotid artery aneurysms are referred for surgical repair. Open surgical repair may include ligation, interposition bypass with vein conduit, or primary end-to-end repair. Endovascular options include exclusion with covered stent graft placement. TCAR might be a reasonable option providing neuroprotection with flow reversal while placing the covered stent. This might be crucial in symptomatic distal carotid aneurysms with unstable thrombus where placement of EPD is difficult as with traditional TFCAS.[72]

Figure 87.29 3D reconstruction CTA showing degenerative extracranial carotid aneurysm emanating off of the ICA.

Carotid Body Tumors

Tumors arising from the carotid body are neural crest tumors and include paragangliomas, glomus tumors, or chemodectomas. The carotid body includes chemoreceptors located at the bifurcation of the CCA in the posterior and medial adventitia. Carotid body tumors (CBTs) are quite rare without a true known incidence. Risk factors for the development of CBT include hypoxemia, which can be the result of chronic obstructive pulmonary disease or living at high altitudes. These chronic hypoxic states can result in hyperplasia and/or neoplasia of the carotid body, leading to CBT.[73] The vast majority of these tumors are benign and malignant transformation can occur

in only about 5% of cases. A familial pattern has been recognized in about 20% of cases.[74] Since these masses arise at the carotid bifurcation, they can envelope the internal and external carotid arteries and the surrounding cranial nerves. CBTs are slow-growing tumors that typically present as asymptomatic lateral neck masses that may be associated with a thrill or bruit. Because these tumors are fixed to the carotid bifurcation, they are horizontally mobile but not vertically (Fontaine sign). With increasing size, associated symptoms such as neck pain, dysphonia, hoarseness, stridor, dysphagia, jaw stiffness, or sore throat may be present. DUS is a useful initial imaging modality to confirm the presence of CBT. A characteristic splaying of the internal and external carotid arteries is usually seen. Needle biopsy is not recommended due to the hypervascular nature of CBT. Confirmatory CTA of the neck will help delineate the extent of CBT invasion. Shamblin classification has been used to help with the extent of involvement and the degree of difficulty of possible resection. Three types have been described: type I are localized and easily resected; type II are adherent to or partially surrounding vessels; type III are intimately surrounded or encases in the vessels or nerves (**Fig. 87.30**). Treatment involves resection, with larger masses (i.e., >4 cm) may benefit from preoperative embolization.[75] Exposure for surgical resection involves a similar exposure to a CEA with careful dissection of the tumor off of the underlying arteries and nerves. Occasionally, in Shamblin type III cases, excision of the underlying artery is necessary and requires a bypass. Unlike CEA, there is a high incidence of cranial nerve injury at approximately 10%.[76]

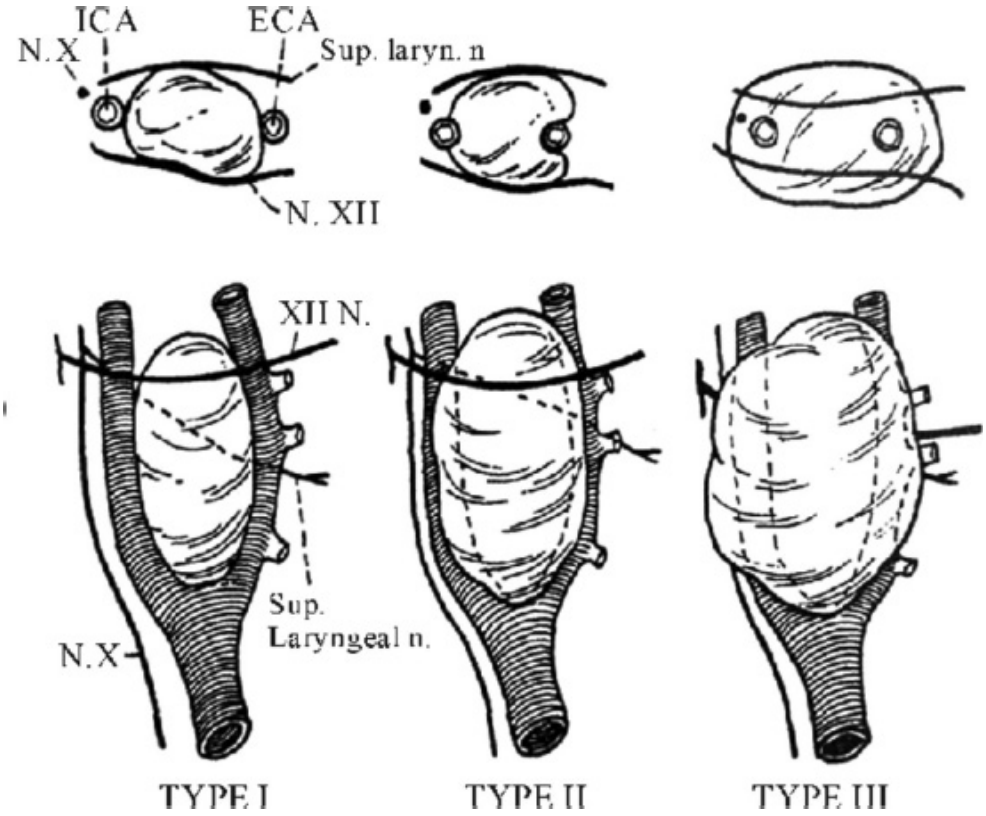

Figure 87.30 Shamblin classification for extent of carotid body tumors.

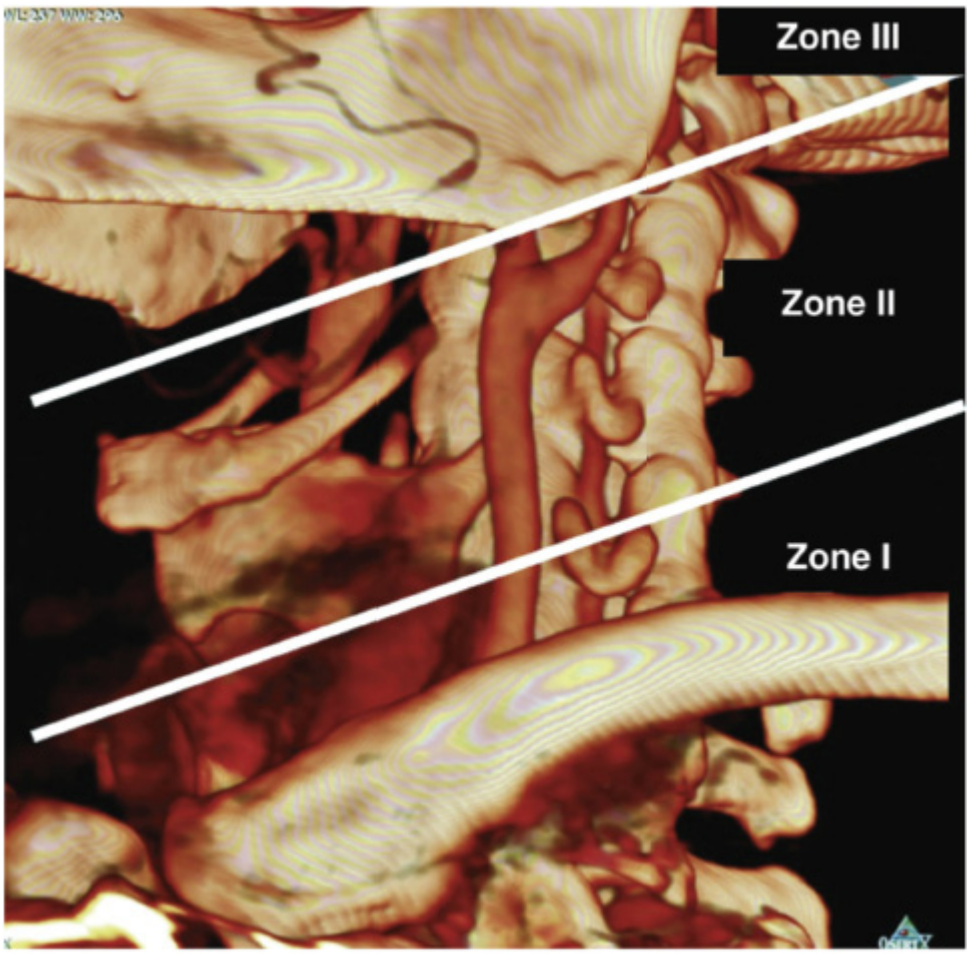

Figure 87.31 Anatomic zones of the neck for penetrating cervical injuries.

Carotid Trauma

Blunt or penetrating cervical trauma can involve the extracranial carotid artery, resulting in intimal disruption, dissection, thrombosis, pseudoaneurysm formation, or transection. Penetrating cervical trauma with injury to the carotid artery can account for a 7% to 27% stroke rate and a 7% to 50% mortality rate.[77] Penetrating cervical trauma with concern for major arterial injury should undergo evaluation and treatment based on location. The neck has classically been divided into three zones: zone I, below the cricoid cartilage; zone II, between the cricoid cartilage and the angle of the mandible; zone III, above the angle of the mandible (Fig. 87.31). Carotid artery injuries are most common in zone II (47%), followed by zone III (19%) and zone I (18%).[78] Injury to zones I and III require diagnostic work

up to determine if any vascular injury has occurred. Zone I injuries will require a median sternotomy for control, whereas zone III will require maneuvers similar to high exposure for an endarterectomy or the use of endovascular coil embolization or exclusion with covered stent graft placement. Traditionally, all zone II injuries should undergo immediate surgical exploration and repair if carotid artery injury is identified. This can include primary repair, bypass, or ligation. The diagnostic modality of choice is CTA for identification of carotid injury. CT scans can be rapidly obtained in the trauma bay or ED and leads to expeditious identification of possible carotid artery injuries that may require surgical intervention. Medical management can be undertaken in certain cases of asymptomatic carotid dissection with either anticoagulation or antiplatelet therapy. Close observation in asymptomatic traumatic carotid dissections are required to ensure that these injuries don't blossom into pseudoaneurysm formation or carotid thrombosis, necessitating either open or endovascular stent placement. Any patient with evidence of cerebral ischemia should undergo prompt carotid revascularization.

VERTEBROBASILAR INSUFFICIENCY

Introduction

Ischemic strokes in the vertebrobasilar territory can account for 25% of all ischemic strokes. The posterior cerebral circulation (i.e., vertebrobasilar system) supplies blood to the brainstem, cerebellum, and occipital lobes via paired vertebral arteries arising from the subclavian arteries. Anatomic variants can occur, the most common being a direct origin of the left vertebral artery arising from the aortic arch. The vertebral artery is composed of four segments: V1 is the origin of the vessel up to the level of C6, V2 is the segment that runs within the vertebral foramina to the level of C2, V3 is the next segment above C2 before it enters the base of the skull, and V4 is the intracranial portion of the artery before it joins with the contralateral side forming the basilar artery. VBI is less common than carotid artery ischemia, but it requires prompt diagnostic evaluation for possible

surgically correctable atherosclerotic lesions. Mortality associated with a posterior circulation stroke is 20% to 30%, significantly higher than those seen in anterior circulation strokes.[79]

Clinical Findings

VBI is a commonly misdiagnosed clinical syndrome, mostly due to the more subtle and broad symptoms associated with this entity in comparison to the anterior circulation. Unlike the anterior circulation, many times severe ipsilateral atherosclerotic vertebral artery stenosis may go unnoticed due to significant collateral filling due to sufficient collateral flow through a patent circle of Willis. Associated VBI symptoms are largely bilateral and include diplopia, headache, vertigo, drop attacks, ataxia, disequilibrium, and paresthesias.

Pathogenesis

The pathogenesis of vertebrobasilar disease can be broken down into ischemic low-flow mechanism versus embolic. The predominate cause of symptomatic VBI are due to low flow. Embolic issues are difficult to recognize and are most commonly originating from the heart, aorta, or brachiocephalic vessels. As previously mentioned, posterior circulation events are more likely to lead to irreversible ischemia and infarction, and thus far more debilitating. These infarctions are most likely the result of embolic events. Up to a third of vertebrobasilar ischemic episodes are cause by distal embolization from plaque or mural lesions of the subclavian, vertebral, or basilar arteries.[80]

Initial Diagnostic Evaluation

The diagnosis of true VBI can sometimes be difficult, given the vagueness of symptoms. Its subtle symptomatology can lend to a variety of other organ systems that can mimic these symptoms. Oftentimes, syncope or presyncope can be confused for vertebrobasilar symptoms. This can be due to a multitude of causes such as vasovagal, cardiac arrhythmias, neurologic, psychiatric, or idiopathic. Moreover, even though the vast majority of VBI is due to

atherosclerosis, other etiologies include dissection, trauma, FMD, aneurysms, and Takayasu disease. Patients with visual changes (i.e., diplopia) can be mistaken for myopia or presbyopia, cataracts, floaters, and amaurosis fugax. Vertigo type symptoms can be caused by many etiologies and can be confused for postural instability, hearing loss or nystagmus.

DUS can be a very useful initial study to help identify proximal vertebral artery atherosclerotic disease. With that being said, it is a more difficult examination than extracranial carotid arteries, and sometimes severe vertebral artery stenosis may be missed. Duplex can identify reversal of flow in the vertebral artery, which may indicate more proximal disease in the subclavian or innominate arteries. Evaluation of the vertebral artery between C2 and C6 is difficult with DUS. CTA and MRA allow for a complete and careful examination of the entire vertebral artery, this allows for identification of disease and illuminate collateral circulation. Additionally, MRI can help identify if embolic lesions and posterior cerebral infarctions have occurred. The "gold standard" remains angiography. Selective vertebral angiography will allow for a complete interrogation of the vertebral artery to identify proximal or distal stenosis. Collateral circulation can also be shown via contralateral and anterior circulation.

Treatment

Treatment of symptomatic VBI is based on the location of the offending vertebral lesion. The majority of lesions involve the proximal V1 segment of the vertebral artery. The prevalence of such lesions is approximately 20% to 40% in patients with cerebrovascular disease.[80] The most common pathology of the V2 segment is extrinsic compression of the vertebral artery by osteophytes. V3 segment lesions are mostly related to trauma and arterial dissection. The V4 segment is largely unaffected by atherosclerotic disease and given its intracranial location, it is more susceptible to direct trauma and stretch injuries as well as formation of AV fistulas or pseudoaneurysms. Proximal (i.e., ostial) V1 atherosclerotic lesions are the most common open operation for VBI. Vertebral artery transposition of the proximal vertebral artery on the adjacent carotid artery is the most common reconstruction. Less likely to be performed, bypass from the common carotid or subclavian artery (SCA) to the vertebral artery distal to the disease with a vein graft is a

viable option. The most common reason for open surgical repair of V2 lesions is hemorrhage and this typically requires proximal and distal ligation. Options for the V3 segment include bypass with greater saphenous or lesser saphenous vein, usually to the C1–2 segment. Other reported open surgical revascularizations for the V3 segment include use of ECA or radial artery. For more distal reconstructions (into the V4 segment) suboccipital exposure of the vertebral artery usually requires resection of the C1 transverse process. Vertebral artery transposition or other V1 segment operations are the most studied surgical operations for VBI. Stroke and death rates for these operations have been reported to be <1%.[81] Other complication includes nerve injury (vagus, recurrent, laryngeal), Horner syndrome and lymphatic leak. Vertebral artery transpositions experience excellent 5- and 10-year patency rates at 95% and 91%, respectively. More than 80% of patients will have relief of their symptoms after proximal surgical reconstruction.[82]

Endovascular 7 management of proximal vertebral artery atherosclerotic lesions has been shown to be safe and effective in a small amount of nonrandomized studies.[83,84] The relative ease in which angioplasty and stenting of a proximal vertebral lesion as compared to the open operation, has driven this increase in endovascular management (**Fig. 87.32**). As with carotid artery stenting, risk of embolization, stroke, thrombosis, dissection, or restenosis can occur. Use of EPD can reduce the risk of distal embolization and should be recommended when treating atherosclerotic proximal vertebral artery lesions. Stent placement has not been widely shown to be effective for the treatment of V2 or V3 traumatic dissections, given the location in the vertebral foramina. Similar to open ligation, endovascular management of vertebral artery transection or hemorrhage involves embolization to control bleeding.

ATHEROSCLEROTIC BRACHIOCEPHALIC DISEASE

Introduction

The great vessels arise from the aortic arch to give off (from proximal to distal) the innominate artery, the left CCA, and the left SCA. These arteries supply the upper extremities and brain and thus are commonly referred to as the brachiocephalic vessels. Anatomic variants do exist with regard to the origins of these vessels. Most commonly, the innominate and left CCA come of the arch in one common ostia, referred to as a "bovine arch" (**Fig. 87.33**). This variant is found in 8% to 25% of Americans, with higher incidence seen in African American patients.[85] Another common variant is the presence of the left vertebral artery directly emanating from the aorta between the left CCA and SCA. This occurs in about 6% of the patient population. Additionally, an aberrant right SCA can be seen with its origin coming the aorta distal to the left SCA and coursing posteriorly behind the arch. This variant is the rarest, occurring in 0.5% to 1% of the time.[86] The most common etiology of brachiocephalic disease continues to be atherosclerotic disease. Commonly, multivessel atherosclerotic disease can be present and is more often accompanied by symptoms of VBI from generalized low-flow. However, embolic phenomenon can be seen as well-exhibiting single-vessel symptoms, when multivessel disease is present. Other diseases affecting the brachiocephalic arteries include aneurysmal degeneration, dissection, vasculitis (e.g., Takayasu disease and giant cell arteritis), infection, and radiation arteritis.

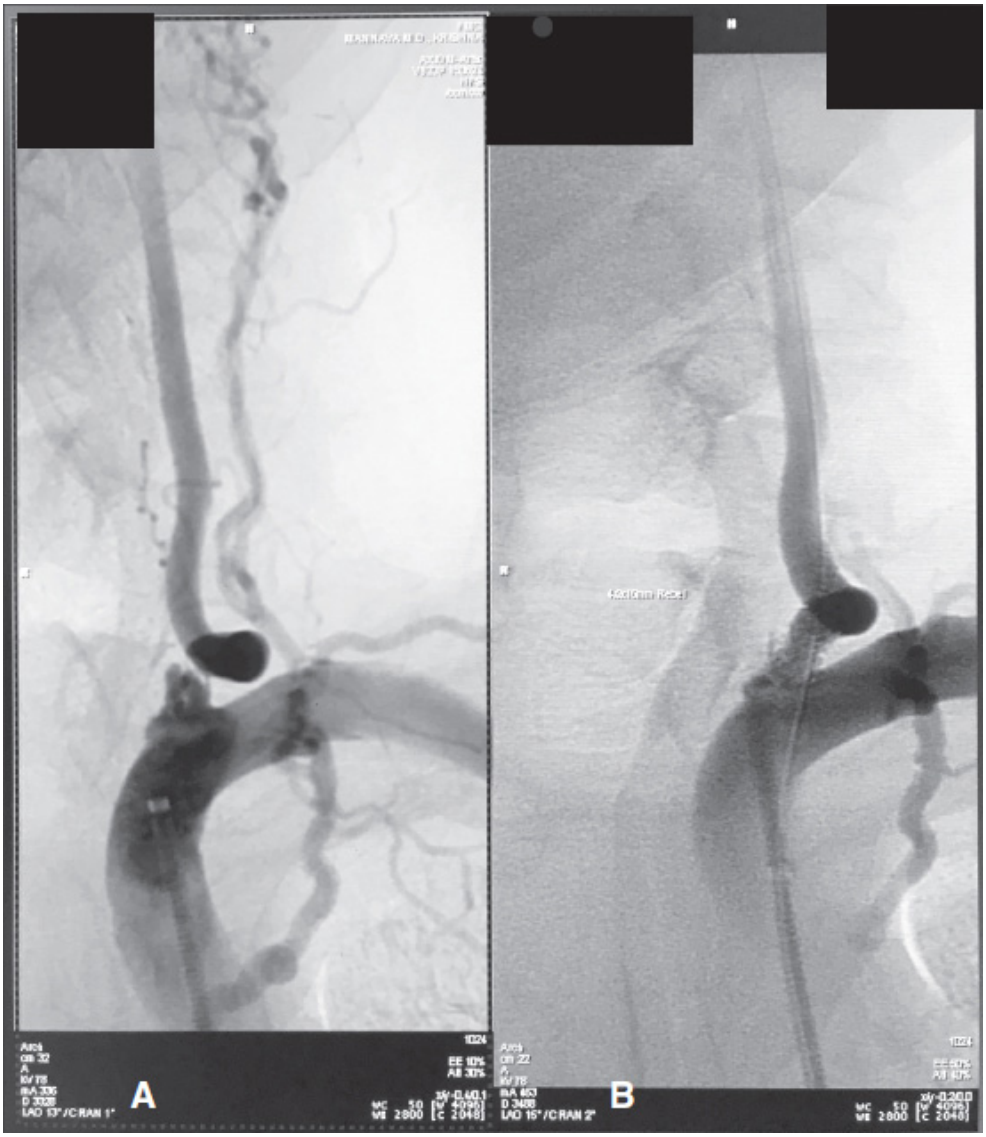

Figure 87.32 **A:** Angiogram showing severe proximal V1 vertebral artery stenosis in a patient with a posterior circulation stroke. **B:** Completion angiogram after successful balloon angioplasty and stenting.

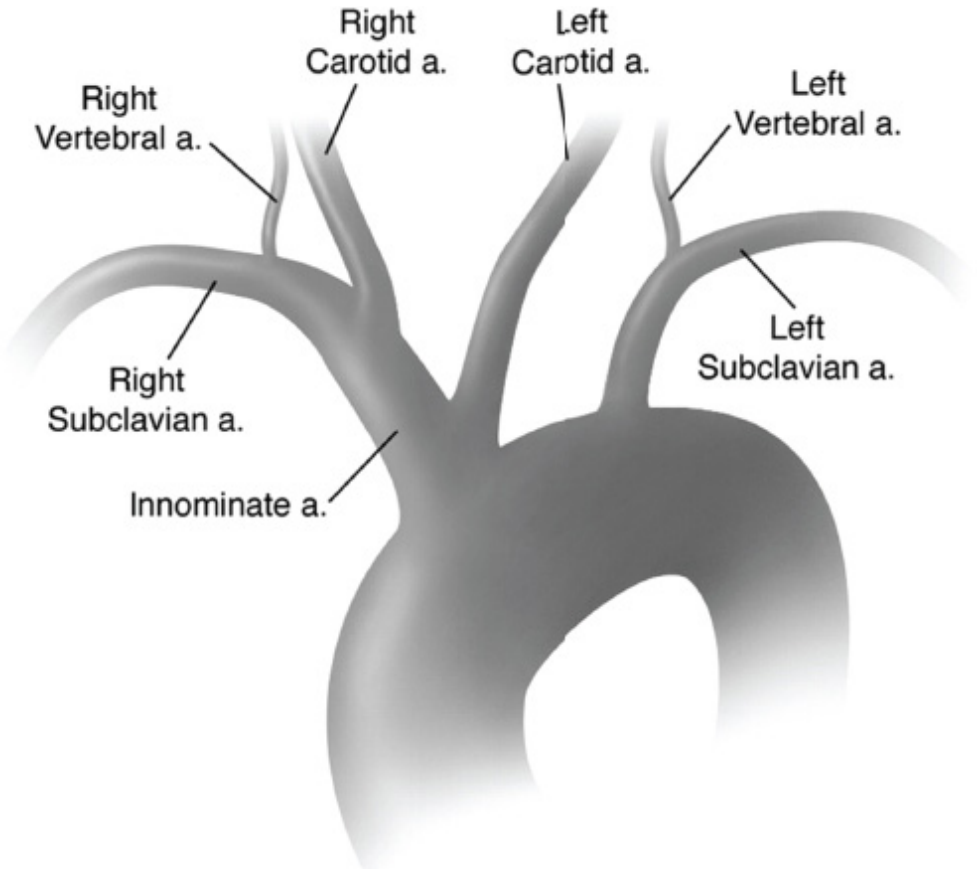

Figure 87.33 Most common aortic arch branch variants in humans with a common trunk for the innominate and left common carotid artery. (From Layton KF, Kallmes DF, Cloft HJ, et al. Bovine aortic arch variant in humans: Clarification of a common misnomer. *Am J Neuroradiol*. 2006;27(7):1541–1542; used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.)

Clinical Findings

As mentioned above, atherosclerosis is the most common disease that affects the brachiocephalic vessels. Clinical findings are dependent on location of the disease and how many vessels are involved. Up to 40% of the time, multivessel disease is encountered.[87] Single-vessel atherosclerotic occlusive disease typically causes symptoms as a result of hemispheric or upper extremity emboli, but low-flow states are also seen. When the innominate artery is involved, patient may suffer from stroke (anterior or posterior circulation), TIA, or upper extremity ischemia. Isolated CCA disease is typically manifested as stroke or TIA. Single-vessel proximal SCA occlusive disease can cause arm ischemia, as evidenced by limiting arm claudication,

with very rare instance of digital ischemia and gangrene. Subclavian steal syndrome can be seen in single-vessel occlusive disease, which can manifest as VBI or subclavian-coronary steal. When patient has a functioning LIMA coronary bypass, recurrent episodes of angina can be seen in instances when severe proximal SCA stenosis is present.

Diagnostic Evaluation

The mainstay for screening for brachiocephalic arterial disease continues to be a prudent physical examination. Careful assessment of the upper extremity pulses, individual upper extremity blood pressure measurements, and auscultation of carotid and SCA bruits are effective tools that allow the practitioner to suspect significant pathology. Blood pressure measurements in individual arms in patients with brachiocephalic disease can show a 20 mm Hg or greater difference between sides. Typically, the initial diagnostic study that is performed is a DUS. There are limitations in using DUS for evaluation of brachiocephalic atherosclerotic disease. Overlying bony structures make identification of aortic arch and proximal great vessels difficult. DUS can be useful in identifying reversal of flow in the vertebral artery, indicating a significant proximal stenosis, as well as rule out significant disease in the extracranial carotid arteries. A decrease in the waveform amplitude and slope (tardus–parvus waveform) can signify significant proximal CCA disease.

CTA and MRA provide excellent imaging of the aorta and brachiocephalic branches. The use of 3D reconstruction, can help facilitate planning of surgical interventions without the need of performing a diagnostic angiogram. Gated CT in coordination with electrocardiogram allows for more careful identification of the mobile ascending aorta and arch, and decreases the amount of motion artifact. Furthermore, CTA and MRA (Fig. 87.34) allow for a complete evaluation of arterial flow from the arch to the brain, as well as evaluation of collateral circulation, which is necessary for surgical planning. Angiography remains the “gold standard,” but does have associated risk of stroke, embolization (albeit very low), and arterial injury. Also, with advanced CTA and MRA techniques, this is quickly surpassing routine diagnostic angiography for routine identification of brachiocephalic disease.

Finally, transesophageal echo (TEE) can be used to evaluate for ascending and descending aortic pathology.

Indications for Repair

Any symptomatic brachiocephalic stenosis should be treated with either open or endovascular techniques. Asymptomatic disease can safely be monitored for progression of disease, as well as medically managing risk factors. Stroke and TIA should be promptly evaluated and underlying lesion should be repaired, due to the fear of ongoing embolization or continued symptoms from a low-flow state. Severe upper extremity ischemia, as evident by severe claudication, rest pain or tissue loss should undergo prompt repair. Also, a low threshold for repair should be given to those with a patent LIMA coronary bypass and proximal subclavian disease. Patients with a functional hemodialysis access and evidence of SCA disease, should also be considered for repair if ongoing low-flow issues are occurring within the dialysis access or signs of steal are apparent.

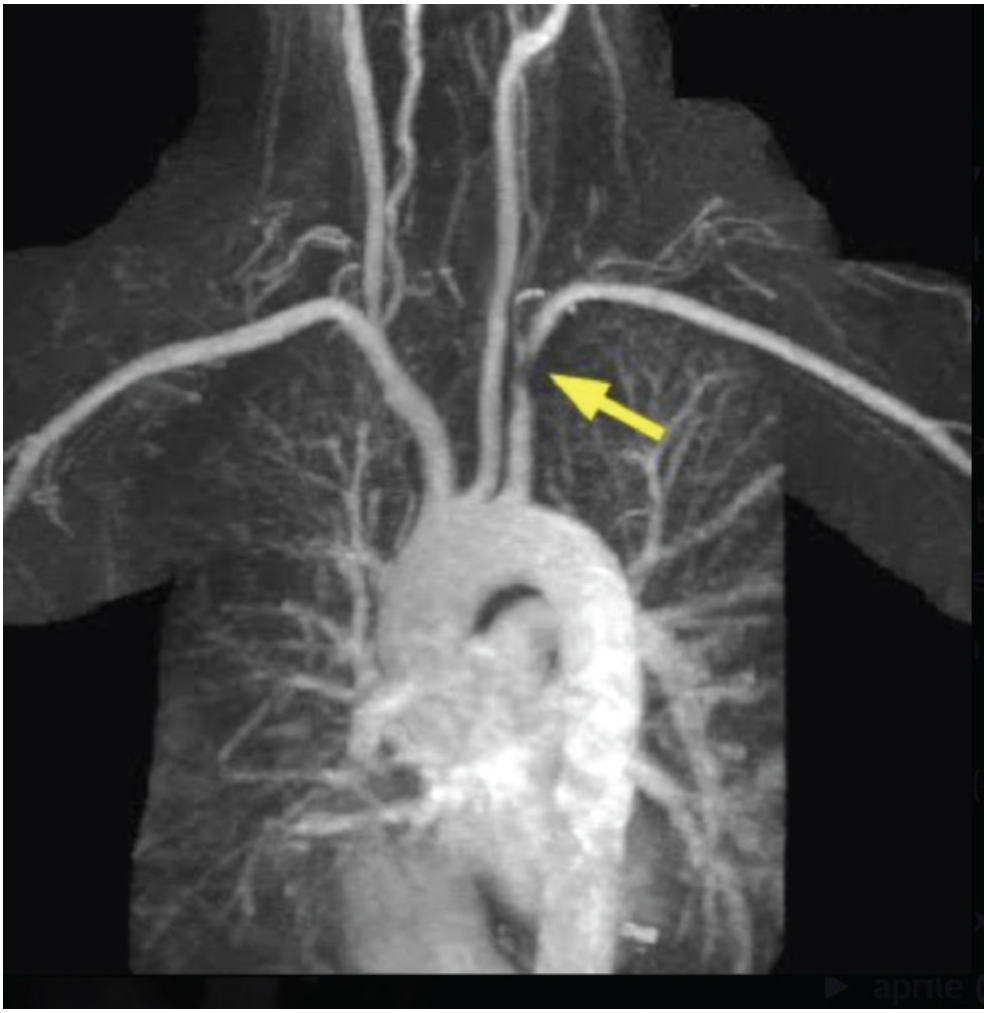

Figure 87.34 3D MIP reconstruction of a contrast-enhanced MRA demonstrating a focal left subclavian artery stenosis.

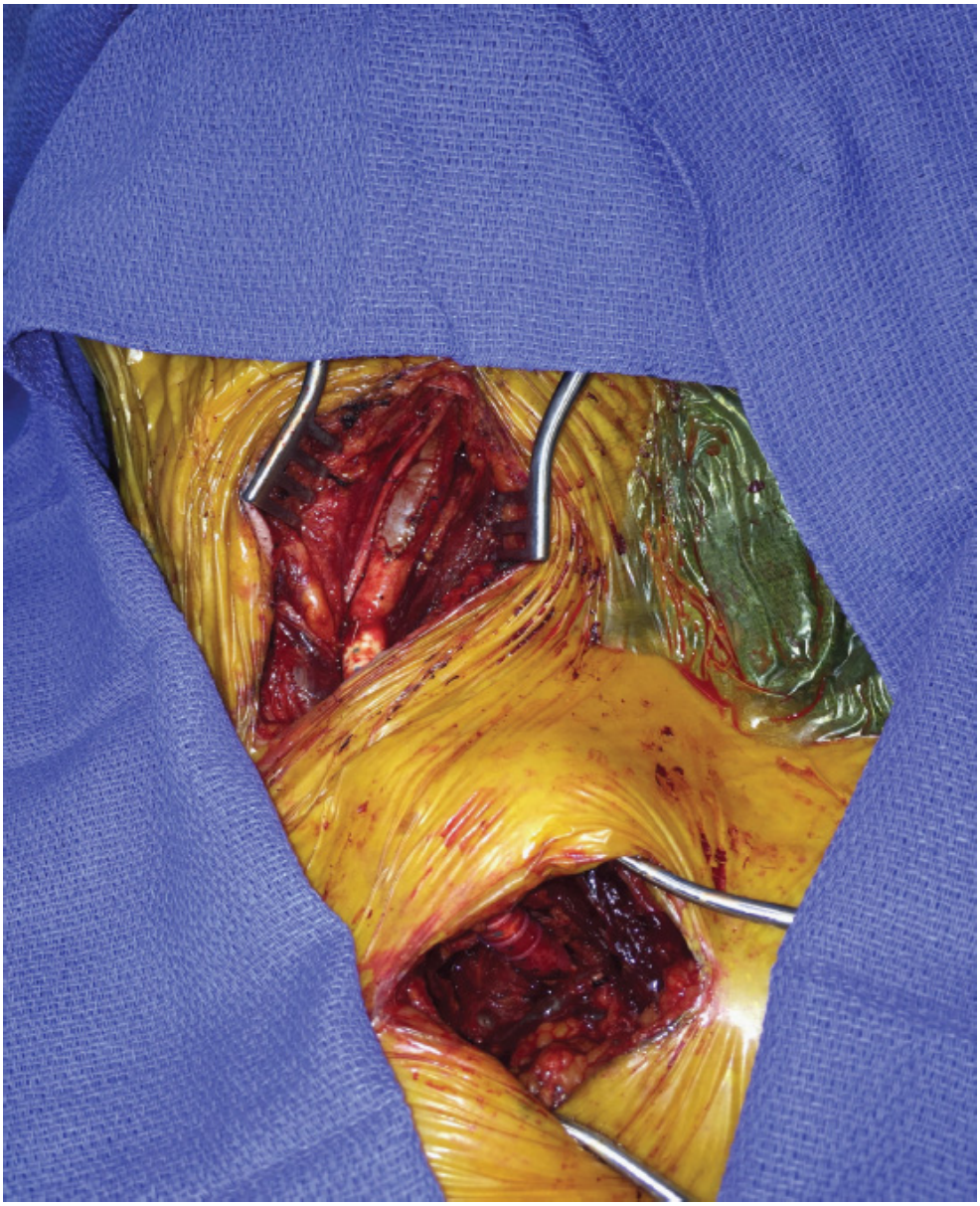

Figure 87.35 Patient with concomitant severe left ICA stenosis and symptomatic proximal and mid left SCA stenosis who underwent a left CEA with a left carotid-axillary artery bypass.

Surgical Treatment

Two main approaches are taken for the open surgical treatment of brachiocephalic disease: transthoracic and extra-anatomic revascularization. Transthoracic repair requires a median sternotomy and revascularization, with either direct arterial reconstruction or bypass from the ascending aorta to the involved brachiocephalic arteries. This approach is ideal for low-risk

patients and those with multivessel disease. When treating patients with multivessel disease, such as Takayasu arteritis, transthoracic repair with debranching off the ascending aorta to healthy vessels avoids diseased arterial segments and is the ideal repair. In appropriately selected patients, this approach can have excellent results with acceptable morbidity. Complications include mortality and stroke rates of 3% to 8% and MI rates of 1.5% to 3%. Excellent 10-year patency of approximately 90% can be achieved with direct transthoracic reconstruction.[88,89]

For single-vessel brachiocephalic disease and for higher-risk patients, extra-anatomic revascularization may be more suitable. This technique can also be used in hybrid approaches when treating patients with open surgical and endovascular techniques. Options for repair include a carotid–carotid bypass, axilloaxillary bypass, carotid–subclavian bypass, or carotid–subclavian transposition. The vast majority of extra-anatomic bypasses are done for single-vessel severe SCA stenosis. Transposition is technically more difficult than a carotid–subclavian bypass, but has the advantage of avoiding prosthetic material. Mortality and stroke rates are far less than those that undergo transthoracic repair.[90] Results are also excellent for carotid–subclavian bypass or subclavian transposition, with 5-year patency of 95% and 100%, respectively. Carotid–subclavian bypasses are one of the few bypasses that favor the use of prosthetic graft over autogenous vein graft, 5-year patency of 94% versus 58.3% ($p < 0.01$).[91] When considering carotid–subclavian bypass, if patients have concomitant, severe carotid stenosis, it is feasible to perform a CEA, followed by a carotid–subclavian bypass in order to prevent a low-flow state to the ipsilateral anterior circulation (Fig. 87.35).

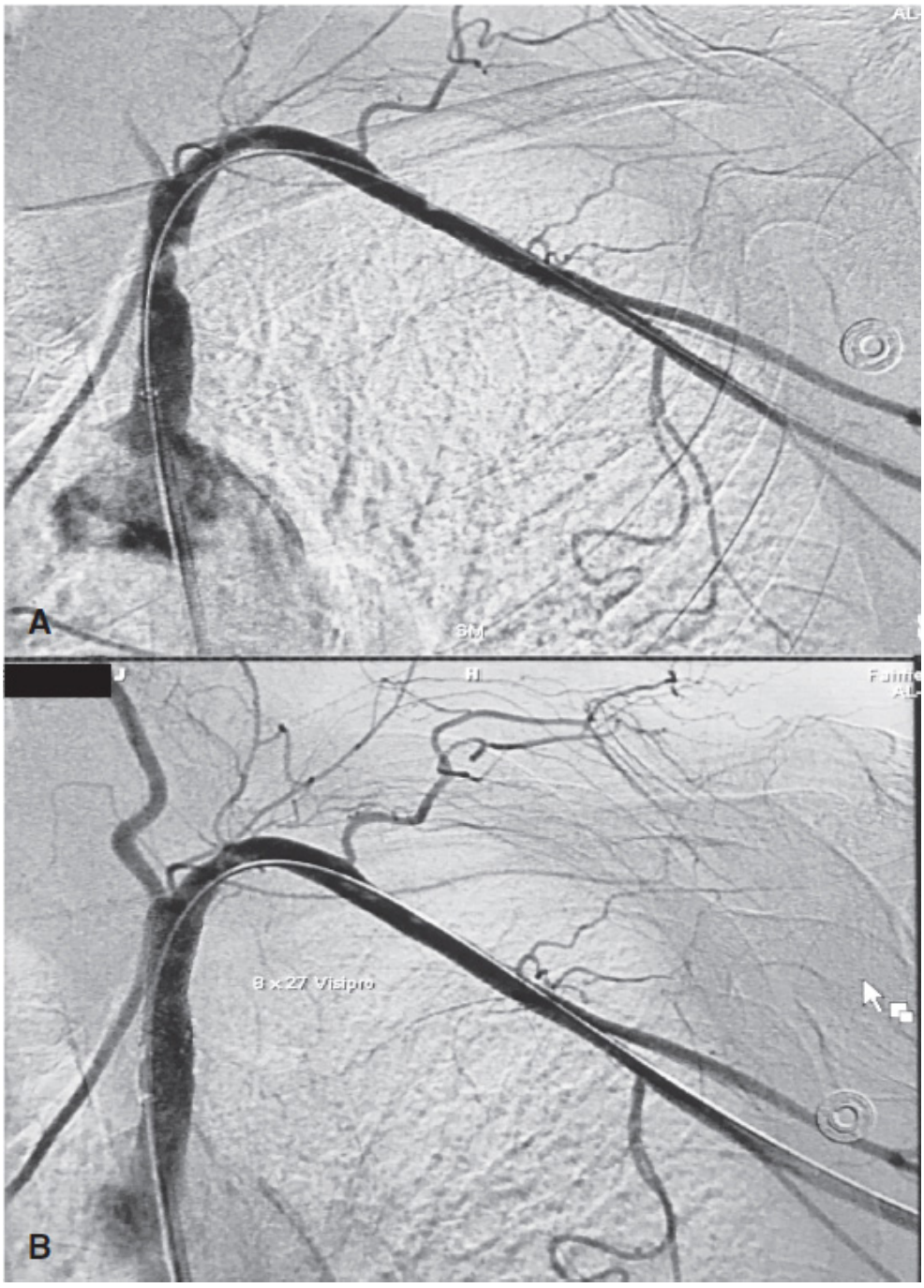

Figure 87.36 **A:** Prestent angiogram revealing high-grade left subclavian artery stenosis with ulcerated plaque. **B:** Poststent angiogram with stenting showing excellent flow throughout the subclavian artery with increased filling of the left vertebral artery.

Endovascular management of brachiocephalic lesions has gained wide popularity over the past 20 years. Single-vessel brachiocephalic stenosis is better suited for endovascular management, however, in a certain subset of

patients that are too ill to undergo an open repair, aggressive endovascular treatment in multivessel brachiocephalic stenosis can also be performed. As with carotid stenting, endovascular treatment of brachiocephalic lesions depends on aortic anatomy, anatomical variants, baseline renal function, arch type, lesion characteristics, and proximity to branch vessels. Endovascular management consists of angioplasty and stenting (Fig. 87.36). Similar to cervical carotid artery stenting, use of intraprocedural heparin and dual antiplatelet therapy afterward is a must. EPD can be used to minimize the risk of embolization when treating innominate or proximal 8 CCA stenosis. Endovascular results do not appear to compare favorably with open repair. One-year patency appears to be close to 90%, however, at 5-year patency drops to 77% to 89%.[92] Alternatively, retrograde approach through a cut down on the CCA allows for better protection with clamping. However, the risk of stroke is higher when concomitant CEA is performed.[93] When intervening on proximal SCA stenosis, great care must be used to avoid encroachment on or embolization to the vertebral artery. Similarly, great attention must be paid to avoiding embolization to the cervical ICA when treating innominate or proximal thoracic CCA stenoses. Sometime, alternate access (brachial) is needed to help facilitate protection of the vertebral or carotid artery during stenting of proximal brachiocephalic lesions.

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88

Upper Extremity Arterial Disease

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Key Points

1. Presentation includes arm claudication, distal embolism, finger necrosis, and vasomotor changes described as Raynaud phenomenon.
2. Given the multiple potential etiologies of upper extremity ischemia, a thorough occupational and social history is necessary.
3. Unilateral hand ischemia points toward an isolated anatomic lesion whereas bilateral hand ischemia is more often related to systemic diseases.
4. A variety of noninvasive tests are available for the initial investigation of arm ischemia while detailed, bilateral arterial imaging is mandatory for treatment planning.
5. Although endovascular revascularization is an excellent option for many causes of upper extremity ischemia, open surgical revascularization is required for some of the diseases causing arm ischemia (i.e., thoracic outlet syndrome [TOS], hypothenar hammer syndrome, etc.)

INTRODUCTION

1 Compared to arterial occlusive lesions in the lower extremity, occlusive disease of the arteries of the upper extremity is often better tolerated and less frequently presents with severe ischemic symptoms. This not only can be attributed to the presence of an extensive collateral network, but also to the very different physiologic requirements of the upper extremities when compared to the legs. Another major difference between arterial disease in the arms compared to that of the legs is their etiologies. Whereas in the lower extremities, atherosclerosis is responsible for the overwhelming majority of cases of critical limb ischemia, in addition to atherosclerosis, numerous anatomic, occupational, and iatrogenic etiologies are responsible for occlusive disease in the arms.

PRESENTATION

Patients suffering from upper extremity arterial insufficiency can present with a variety of symptoms. Arm claudication (pain during exercise) is rare and often points to a proximal lesion (innominate, subclavian, or axillary arteries). More commonly, patients present with skin changes affecting the hands or fingers. Splinter hemorrhages of the bed of the nail, livedo reticularis, cyanosis of segments of the fingers, and gangrene are signs of embolism or ischemia affecting the arteries of the hand (Fig. 88.1).[1] Raynaud phenomenon indicates an episodic series of skin changes affecting the fingers or the hands triggered by changes in temperature or emotional stress. The classic presentation is a sequential appearance of first pallor, then cyanosis, and finally erythema. These correspond to (in order) vasospasm (pallor), desaturation of hemoglobin (cyanosis), and finally compensatory vasodilation, also known as reactive hyperemia (erythema).

Raynaud phenomenon (also called secondary Raynaud syndrome) can be the manifestation of occlusive disease or, more commonly, is associated with autoimmune conditions (scleroderma, Sjögren syndrome, rheumatoid arthritis, lupus).[1] In contrast, the term *Raynaud disease* (or primary Raynaud syndrome) is used to describe a condition of unknown etiology that occurs in patients without occlusive lesions or autoimmune disease. These patients can

experience vasomotor symptoms in both arms, and sometimes even the legs.[1,2]

ETIOLOGY

2 A myriad of conditions can cause upper extremity occlusive disease (Table 88.1). Atherosclerosis typically affects the origins of the supra-aortic trunks with ostial lesions at the origin of the subclavian artery being most common. The innominate artery and distal arteries can also be affected. Involvement of multiple segments of the upper extremity circulation is possible and is often asymptomatic even in the presence of total occlusion. Patients with renal failure typically have normal proximal vessels with severe disease in the blood vessels of the forearm and hand (Fig. 88.2). In this patient population, hand ischemia tends to occur at a younger age and is frequently associated with calciphylaxis.[3]

Inflammatory conditions like Takayasu arteritis or giant cell arteritis (GCA) can also affect the great vessels.[4] Takayasu arteritis is a rare, inflammatory vasculitis that affects the aorta and its major branches. Sometimes called "pulseless disease" from difficulty in obtaining peripheral pulses, this disease typically occurs in women in the second or third decades of life. An initial acute inflammatory phase of causes vessel thickening and is followed by a late chronic phase where long segments of stenosis occur in the vessels (Fig. 88.3). These lesions have low embolic potential generally present with end-organ ischemic symptoms secondary to high-grade stenosis (Table 88.2).[5] In chronic cases, revascularization of affected organs is attempted by either endovascular or surgical treatment. GCA, in contrast, is another more common inflammatory vascular disease. GCA typically affects older patients (more than 50 years old) and involves medium to large blood vessels. The typical pattern of disease is that of areas of normal luminal diameter alternated with dilated or stenotic lesions. The most common symptoms are headaches and visual changes related to involvement of the extracranial carotid arteries. Lastly, Buerger disease is an obliterative vasculitis that typically affects medium and small caliber arteries. It affects the lower extremities more commonly than the upper limbs and occurs more frequently in males than females.

Figure 88.1 Manifestations of upper extremity ischemia. Splinter hemorrhages in the nails arising from a proximal embolic source (**A**). Gangrene affecting the tip of the third finger (**B**). Advanced, severe gangrene in the radial artery distribution secondary to complications related to an arterial line (**C**).

Table 88.1 Conditions and Risks for Upper Extremity Ischemia

- Occupational injury
  - Vibration syndrome
    - Pneumatic tools
    - Chainsaws
    - Grinders
  - Electrical burns
  - Hypothenar hammer syndrome
    - Mechanical work or auto repair
    - Lathe operation
    - Carpentry
    - Electrical work
  - Occupational acroosteolysis–polyvinylchloride exposure
- Athletic activities
  - Thoracic outlet compression
    - Baseball pitching
    - Kayaking
    - Weight lifting
    - Rowing
    - Butterfly swimming
    - Golfing
  - Hand ischemia
    - Baseball catching
    - Frisbee
    - Karate
    - Handball
  - Pharmacologic history
  - Ergot poisoning
  - Beta blockers
  - Drug abuse, cocaine use
  - Cytotoxic drugs
  - Dopamine overdose
- Medical conditions
  - Atherosclerosis
  - Arteritis

- Collagen disease
  - Scleroderma
  - Rheumatic arteritis
  - Systemic lupus erythematosus
  - Dermatomyositis
- Allergic necrotizing arteritis
  - Takayasu disease
  - Giant cell arteritis

Blood dyscrasias
- Cold agglutinins
- Cryoglobulins
- Polycythemia vera

Behçet syndrome

Antiphospholipid syndrome

Thoracic outlet syndrome

Congenital arterial wall defects
- Pseudoxanthoma elasticum
- Ehlers–Danlos syndrome

Fibromuscular dysplasia

Iatrogenic injury
- Arterial blood gas and pressure monitoring
- Cardiac catheterization
- Arteriography

Frostbite

Renal transplantation and related problems
- Azotemic arteriopathy
- Hemodialysis shunts

Radiation
- Breast carcinoma
- Hodgkin disease

Aneurysms of the upper extremity

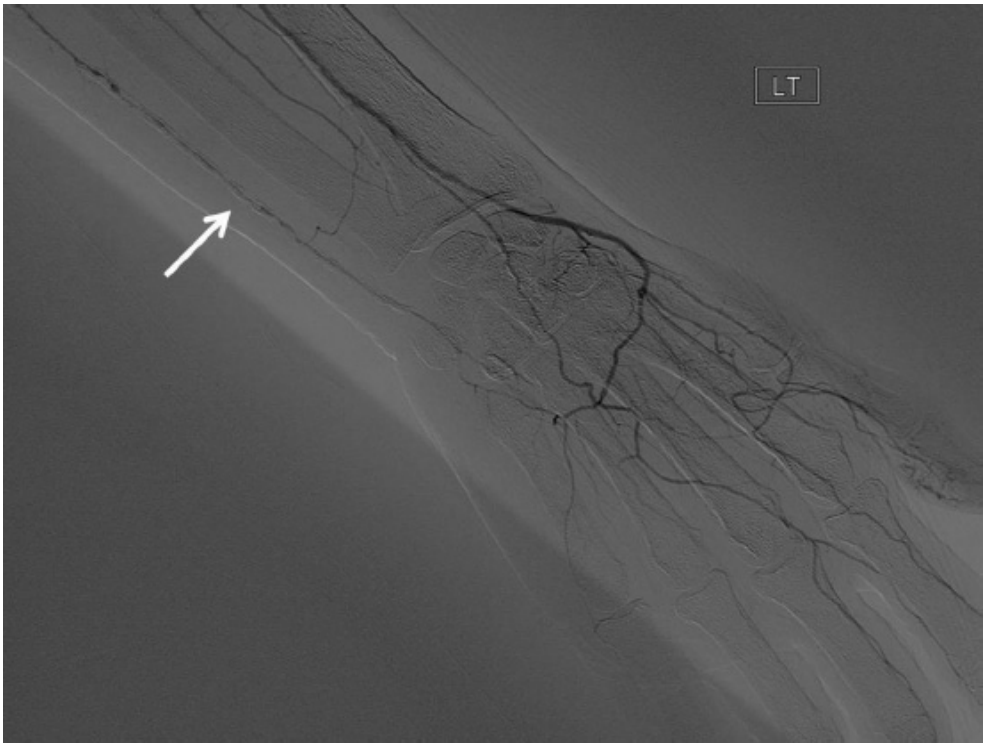

Figure 88.2 Selective left-hand angiogram in a patient with chronic renal insufficiency. There is severe, diffuse disease affecting a heavily calcified ulnar artery (*arrow*). In addition, there is lack of contrast opacification in several of the digital arteries.

Ergotamine is a substance that narrows vasculature. Ergot-induced vasospasm can create ischemia of the hands and the feet. Historically, epidemics occurred in Europe during the Middle Ages caused by the ingestion of rye contaminated by alkaloid-producing fungi. Today, most cases of ergotism are due to antimigraine drugs or recreational substance abuse.[6]

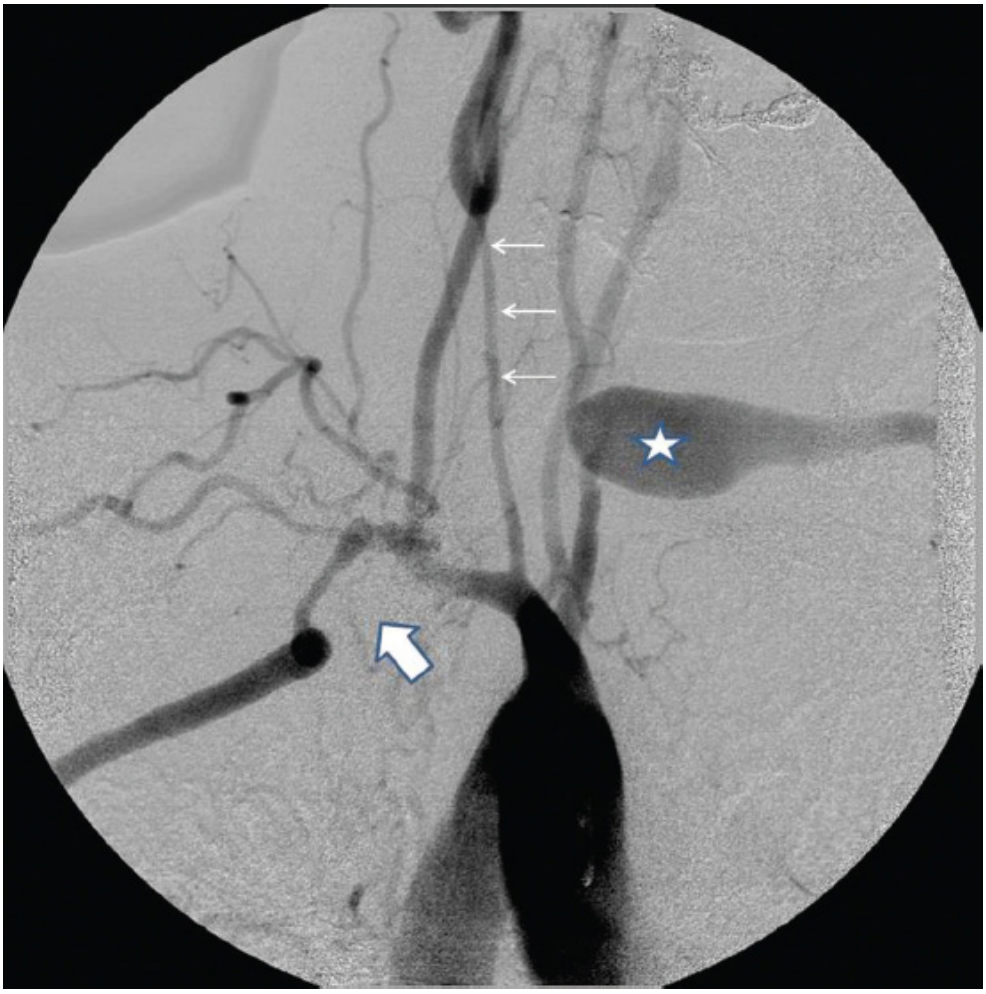

Figure 88.3 Aortogram in the right oblique projection of a patient with Takayasu arteritis. Long-segment right common carotid stenosis (*small arrows*) leading into a normal-appearing carotid bifurcation. Segmental occlusion of the right subclavian artery (*block arrow*) just distal to the origin of the right vertebral. There is distal reconstitution via a large collateral. There is also an aneurysm (*star*) of a previous bypass in the left subclavian artery.

Table 88.2 Takayasu Arteritis
Headache, often related to high blood pressure and kidney failure
Exertional chest pain
Fatigue and shortness of breath
Transient ischemic attacks, dizziness, vision changes, or fainting
Nausea, vomiting, and abdominal pain, generally from poor mesenteric blood flow
Exertional muscle pain in arms or legs

Connective tissue disorders are a common cause of upper extremity ischemia. Lesions typically affect the distal vasculature and are more common in scleroderma, rheumatoid arthritis, CREST syndrome, mixed connective tissue disorders, and lupus. Raynaud phenomenon is often the manifestation in early stages whereas digital gangrene occurs in late stages of the disease.

Thoracic outlet syndrome (TOS) is a term encompassing a group of signs and symptoms related to compression of the brachial plexus, subclavian vessels as they pass from the thorax into the axilla. There are three types: neurogenic, arterial, and venous. Only 1% of all TOS cases are arterial in etiology.[7] Although TOS is often asymptomatic, patients may present with a range of signs and symptoms, from fatigue or pain in the affected arm upon exertion and Raynaud phenomenon to critical ischemia of the upper extremity due to emboli. These emboli arise from a chronically injured artery or from a mural thrombus in a poststenotic aneurysm sac and can result in irreversible digital or hand ischemia.[8] Aneurysms can also form because of repetitive trauma in branches of the subclavian artery. The artery is compressed as it passes through the thoracic outlet into the axilla. This is a narrow outlet formed by the clavicle superiorly, the first rib inferiorly and the subclavius muscle anteriorly and superiorly, as well as the scalene muscles posteriorly (Fig. 88.4). Bony anomalies, such as a cervical rib or an abnormal first thoracic rib, are often structural contributors to arterial TOS. Pectoralis minor syndrome is a similar condition that causes compression of the

subclavian artery but this time by the pectoralis minor as it inserts on the coracoid process (Fig. 88.4).

Ischemia caused by flow disruption in the axillary, brachial, radial, and ulnar arteries is often the result of iatrogenesis. One of the most common causes of ischemia seen in our practice is due to hemodialysis access. Hand ischemia due to steal phenomenon is common and ischemia from intra-arterial catheters also occurs frequently.

Examples of occupational injuries to the hand arteries of the hand are thenar or hypothenar hammer syndromes. The ulnar artery is vulnerable to injury at the hypothenar eminence, just distal to the wrist where the ulnar artery passes through Guyon canal bound by the pisiform and hamate bones. Here, the ulnar artery is cushioned only by skin, subcutaneous tissue, and the thin palmaris brevis muscle. Repetitive use of the palm of the hand as a "hammer" compresses the unprotected ulnar artery against the nearby hook of the hamate bone. Both aneurysm formation and occlusive disease can result (Fig. 88.5).[9]

HISTORY AND PHYSICAL EXAMINATION

3 Given the frequent association of upper extremity ischemia with systemic and occupational disorders, a thorough medical and social history is mandatory. Interrogation should include history of tobacco and/or drug use. Antimigraine medications, HIV antivirals, and most commonly recreational drugs, like cocaine and other alkaloids, can cause ergotism. Occupational history is of particular importance when evaluating upper extremity vascular issues. TOS occurs in athletes who perform repetitive overhead shoulder motion (swimmers, baseball pitchers, weight lifters, etc.). Repetitive trauma to the palmar eminences (thenar and hypothenar) is typically observed in manual laborers (machinists, carpenters, and construction workers) but has also been described in athletes, musicians, and even computer workers who may have repetitive palmar injury due to the nature of their work.

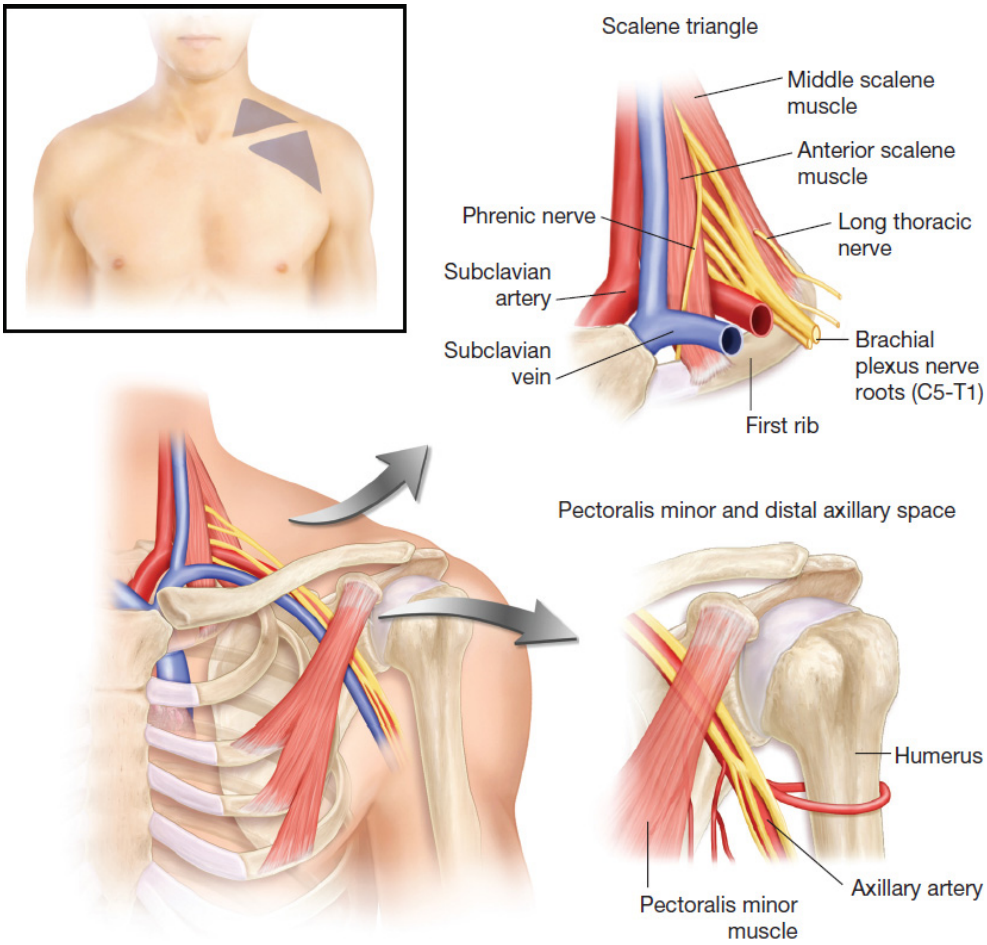

Figure 88.4 Compressive zones of the thoracic outlet. The subclavian structures can be compressed at the costoclavicular space, the scalene triangle, or distally at the border of the pectoralis minor muscle.

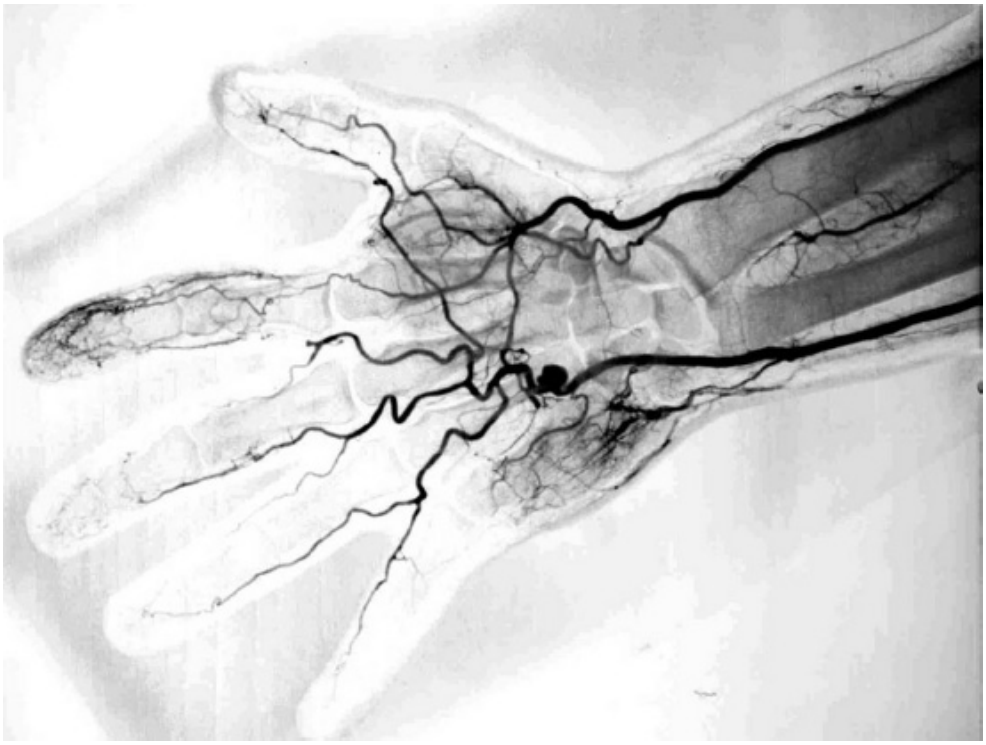

Figure 88.5 Ulnar artery aneurysm resulting from repetitive trauma in a construction worker.

The presence of atherosclerotic disease in the heart or other vascular beds should also be investigated given the potential for involvement of the origins of the great vessels. History of connective tissue disorders or their symptoms (dysphagia, arthritis, telangiectasia, and other skin abnormalities) cannot be obviated during the evaluation of upper extremity ischemia. Changes in the appearance of the skin of the hands suggestive of Raynaud's should be explicitly investigated.

It is necessary to obtain clear documentation of any prior intervention in the arm such as hemodialysis access, biopsies, and brachial or axillary access for cardiac catheterizations. Additionally any prior trauma (clavicular or rib fractures, humeral, shoulder, or elbow injuries) (Fig. 88.6) should be reviewed and documented.

A complete physical examination needs to include a systemic evaluation looking for signs of atherosclerotic, inflammatory, or autoimmune disease. Meticulous inspection, auscultation and palpation of both sides of the neck, periclavicular areas, shoulders, arms and hands should be done in the resting, neutral position, and also while abducting the arm. A bruit or a thrill

in the periclavicular area would suggest the presence of stenosis or poststenotic dilation arising from TOS and a prominent pulse should point to an aneurysm in the subclavian artery. Comparison between the two upper extremities is of crucial importance as bilaterality can point to a systemic disorder. A careful hand examination includes inspecting for splinter hemorrhages under the beds of the nails, skin evidence of embolism or gangrene, or skin color changes related to vasospasm and signs of trauma in the hand. Careful palpation of the radial, ulnar, snuffbox, and even digital pulses should be done. An Allen test should also be performed. In this test, digital pressure is applied to the ulnar and radial arteries in the wrist. After the patient opens and closes his or her hand, pressure is removed from one of the wrist arteries and inspection of the color of the hand and palpation of the distal pulses is repeated. The test is normal if the entire hand recovers its color and capillary refill. If a portion of the hand fails to normalize, then it is likely that the palmar vascular collateral circulation (palmar arch) is incomplete. Lastly to complete the physical examination, bilateral blood pressure measurements should be obtained and compared (brachiobrachial index).

Figure 88.6 Old clavicular fracture treated with a metallic prosthesis. Notice the luminal abnormality in the subclavian artery as it crosses the clavicle. This lesion was caused by periosteal scarring and caused distal embolism in the hand.

LABORATORY AND NONINVASIVE TESTING

4 A series of serologic tests is typically obtained if autoimmune disease is suspected (Table 88.3). A variety of tests are available from the blood flow laboratory to aid in the management of upper extremity occlusive disease.[10] All patients should be subjected to segmental arterial pressure measurement and waveform analysis, at the minimum. In the upper extremities, this test usually includes photoplethysmography (PPG) of the digital vessels. The absence of triphasic flow and the presence of "blunted" PPG tracing in the affected arteries and digits, respectively, help to localize obstructive lesions. If intermittent occlusion is suspected due to TOS, noninvasive testing can be performed along with the use of provocative maneuvers (Fig. 88.7). Historically, the cold challenge test has been used to assess patients with symptoms suggestive of vasomotor disorders (cold intolerance, skin color changes, etc.). In this test, the hands are immersed in iced water and digital temperatures are measured every 5 minutes. For a normal response, temperatures should normalize within 1°C of pre-immersion measurements. Cold intolerance is confirmed with failure to restore digital temperature in 20 minutes. Several variations of this test exist.[11]

Table 88.3 Lab Tests for Systemic Causes for Hand Ischemia
Erythrocyte sedimentation rate
Rheumatoid factor
Antinuclear antibody
Immunoglobulin electrophoresis
Cryoglobulins
Cold agglutinins
VDRL (Venereal Disease Research Laboratory) test
Complement (C3, C4)
Anticardiolipin antibody
Blood cell counts

A more sophisticated version of the Adson test can also be obtained in most blood flow facilities by adding the analysis of waveforms obtained before and after ulnar and/or radial artery occlusion at the wrist. Duplex ultrasound is useful when an obstructive lesion is localized by physical examination, waveform analysis, or segmental pressure recordings. B-mode imaging and color Doppler can further define the characteristics of the lesion and its hemodynamic severity. Finally, measurement of digital PPG tracings can be obtained with and without manual pressure causing temporary occlusion of hemodialysis grafts and fistulae when evaluating arterial steal in patients with renal failure.

ANGIOGRAPHY

Accurate imaging of the arterial anatomy of both arms, from the aortic arch to the digital arteries is mandatory when obstructive lesions are suspected on clinical evaluation or noninvasive testing. Although conventional angiography remains the gold standard, modern computed tomography angiography (CTA) and magnetic resonance angiography (MRA) have

essentially replaced this modality (Fig. 88.8). For comparison, both upper extremities should be imaged. If TOS is suspected, provocative maneuvers should be done while obtaining arterial images (Fig. 88.9). Of particular importance is obtaining clear images of the hand circulation to assess collateral circulatory pathways. Typically, the deep palmar arch arises from the terminal part of the radial artery and the superficial arch by the ulnar artery. Nevertheless, several variations exist (Fig. 88.10).

MANAGEMENT

5 The specific mode for revascularization used to treat upper extremity ischemia depends on the location of the lesion, its etiology, and the available local resources and expertise. Atherosclerotic lesions affecting the origin of the subclavian or innominate arteries are most frequently treated with percutaneous transluminal angioplasty and stenting. This is usually achieved via a femoral approach but can also be performed using a retrograde radial, brachial or even a carotid approach. A percutaneous approach is popular due to being minimally invasive, well tolerated by patients, and widely available to multiple disciplines. Immediate angiographic results that are usually excellent as well, however, several disadvantages should be considered when choosing this form of therapy. Deployment of intravascular devices across the origin of a vertebral artery, an internal mammary previously used as a coronary bypass, or under the clavicle should be avoided due to the obvious possibility of catastrophic results. Second, the long-term durability of intravascular stents in the ostia of the aortic arch is not clearly established. And finally, we have seen an elevated rate of stent fractures in this position.[12] This is likely due to the extreme motion of the aortic arch and the supra-aortic trunks around the cardiac cycle. Alternatively, open surgical bypasses and transpositions can be performed via small incisions in the neck with excellent long-term results. For example, the subclavian artery can be transposed to the common carotid artery using a small transverse neck incision. This procedure allows for preservation of the vertebral artery and its long-term patency rate is nearly 100%.[13] A short carotid to subclavian bypass using prosthetic material can also be used with excellent long-term results (Fig. 88.11). Finally, in some patients the best option resides in single

or multiple-branched bypasses arising from the aortic arch. A ministernotomy is used to expose the ascending arch and the bypass can be anastomosed to the aorta using a side-biting clamp thus obviating the need for cardiopulmonary bypass (Fig. 88.12).

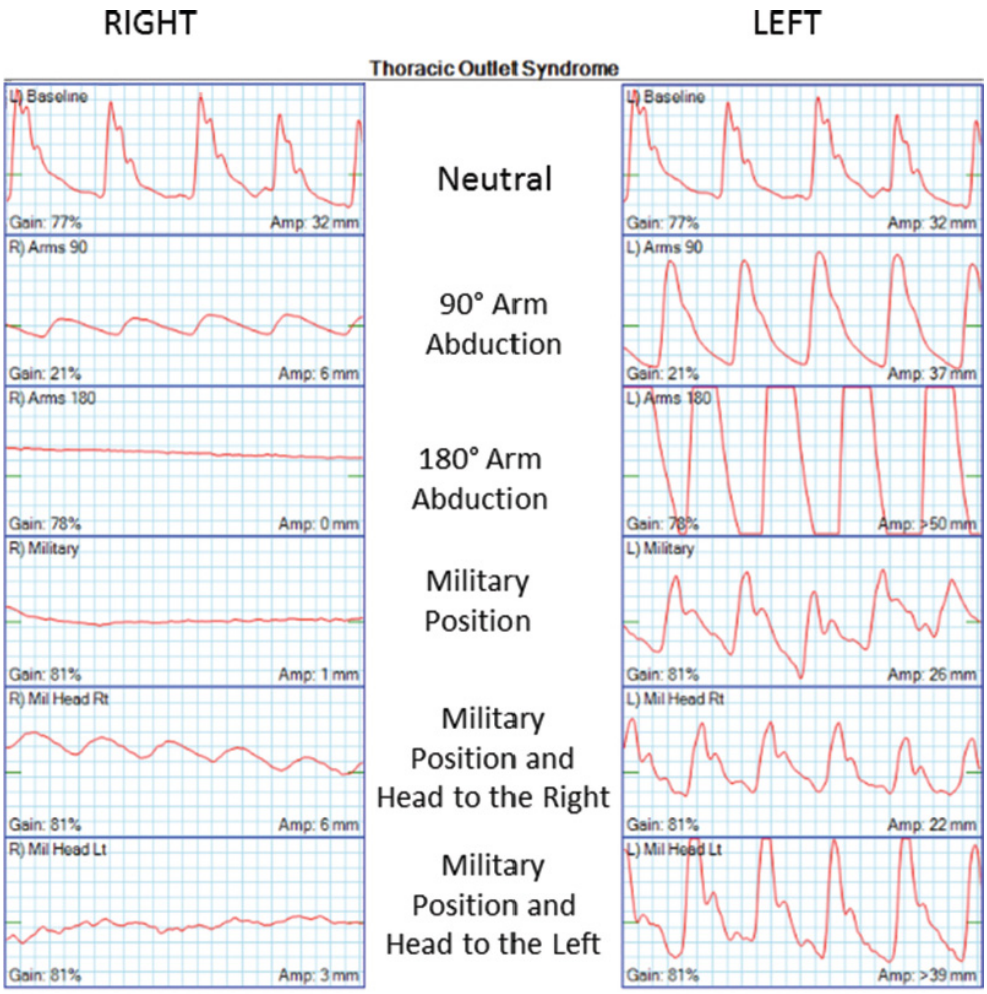

Figure 88.7 Noninvasive blood flow study in a major league baseball pitcher showing loss of normal signals during proactive maneuvers.

Intervention during the acute inflammatory phase of Takayasu arteritis should be avoided. The mainstay of treatment during the active phase is with corticosteroids. Patients with more severe disease may require additional immunosuppressant drugs (e.g., methotrexate or azathioprine). Any intervention should be delayed until the acute, active phase of the disease undergoes remission.[14] This is often indicated by normalization of serologic inflammatory markers, most commonly erythrocyte sedimentation rate (ESR)

and C-reactive protein (CRP). Antiplatelet therapies may lower the frequency of ischemic events. During the chronic phase, reconstruction is carried out using similar techniques as those used for the management of atherosclerotic occlusion (Fig. 88.13).

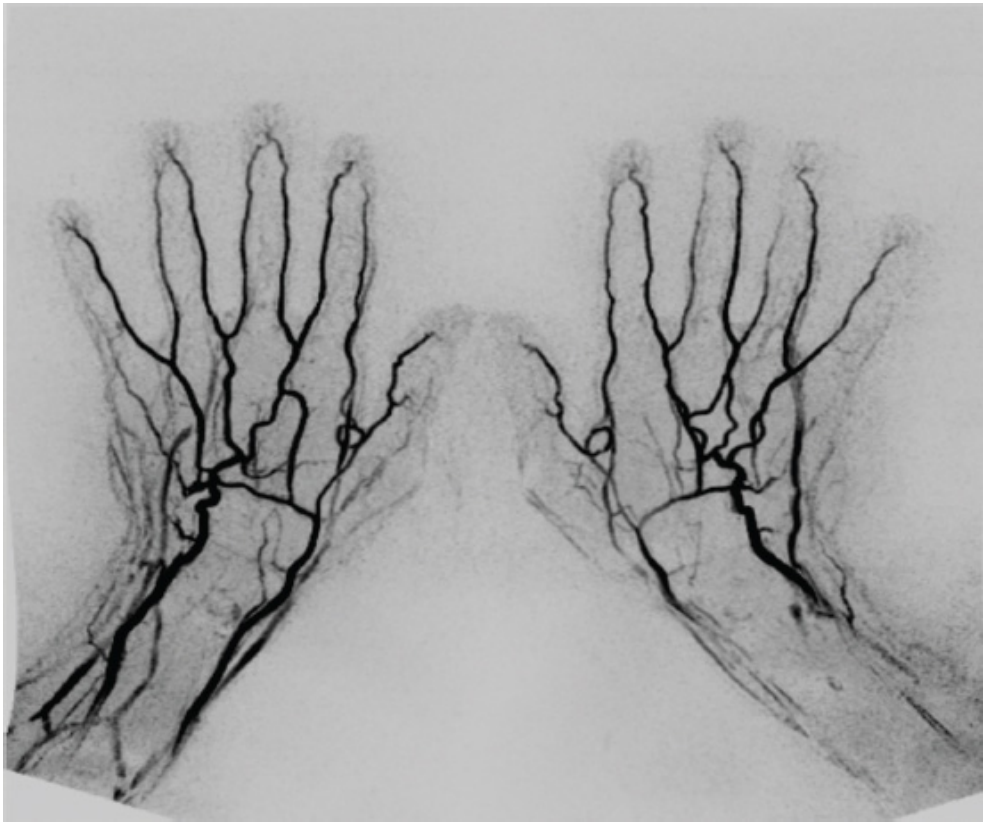

Figure 88.8 Focused magnetic resonance angiogram of the hands.

There is little controversy about the management of patients with arterial TOS. Untreated arterial injury due to repetitive torsion and compression leads to stenosis, poststenotic aneurysmal dilation, and distal embolism. In the majority of cases, evidence of distal embolism with compromise of the arteries of the hand is already present by the time of presentation. Thus, thoracic outlet decompression often with arterial reconstruction is mandatory. The subclavian artery can be compressed at any point from the root of the neck to the pectoralis minor tendon, therefore the decompressive approach depends on the specific anatomy of the patient. The surgical plan depends on the details obtained by imaging studies and the experience of the surgeon. In the absence of anatomic anomalies and with compression

demonstrated only during arm abduction and elevation, first rib resection via the supraclavicular approach appears to be the best choice. If chronic compression has caused arterial damage, arterial reconstruction is necessary. Interposition grafts from the ipsilateral common carotid to the axillary artery are commonly used. This can best be achieved by a combination of supra- and infraclavicular exposure. Eight-millimeter prosthetic grafts tunneled underneath the clavicle or subcutaneously have excellent patency rates. If present, cervical ribs are resected whereas full thoracic outlet decompression with scalenectomy is only necessary if concomitant neurogenic TOS exists.[15]

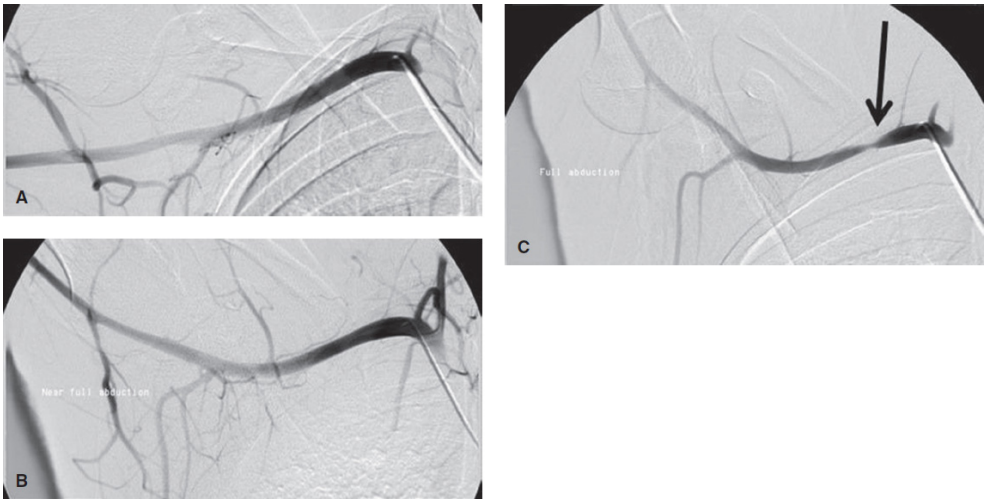

Figure 88.9 Selective digital subtraction angiography of the right arm in a patient with suspected arterial thoracic outlet syndrome. Subclavian artery stenosis is not seen when injecting contrast with the arm in neutral (**A**) and moderate abduction (**B**), but is evident when the arm is hyperabducted (*arrow*) (**C**).

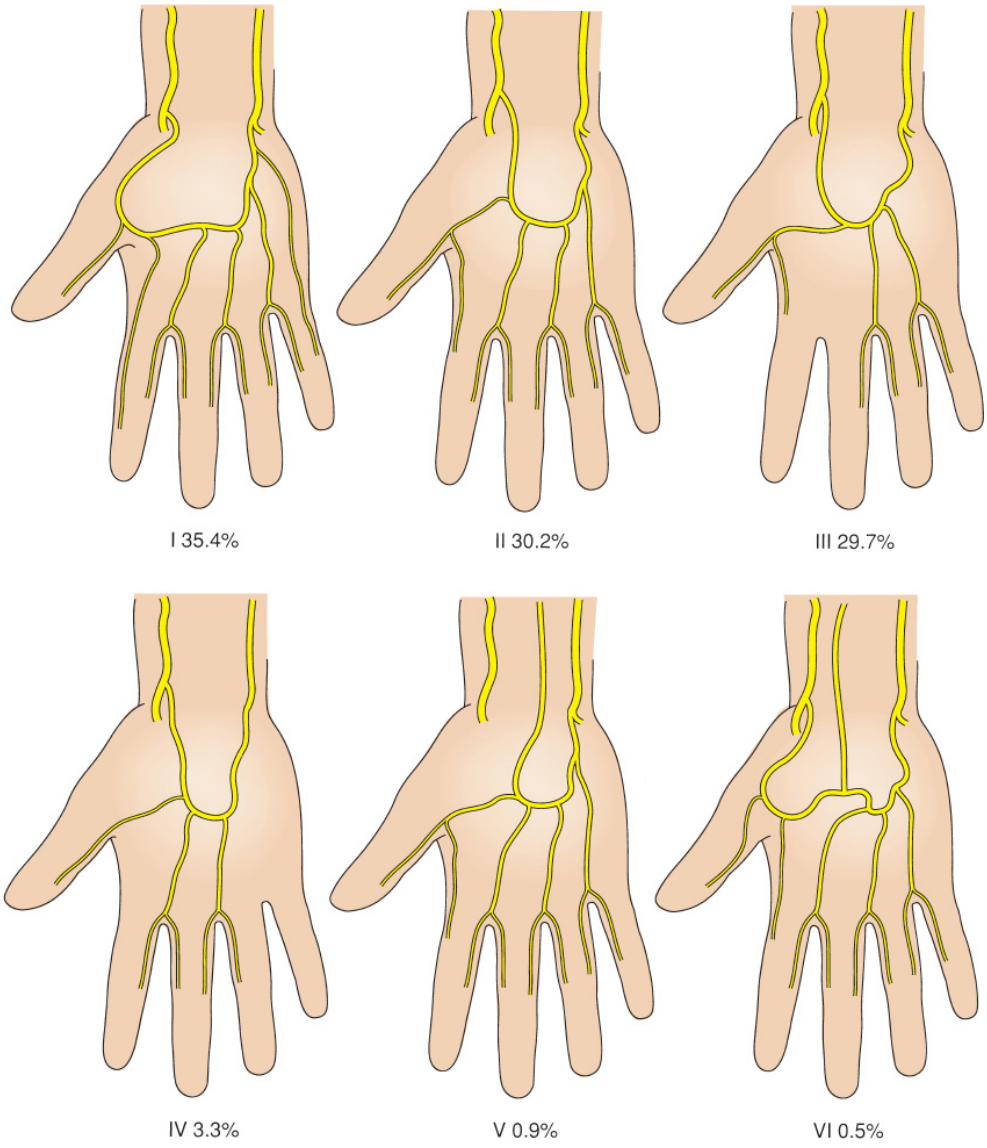

Figure 88.10 Different types of complex superficial palmar arch found on 500 hand arteriograms.

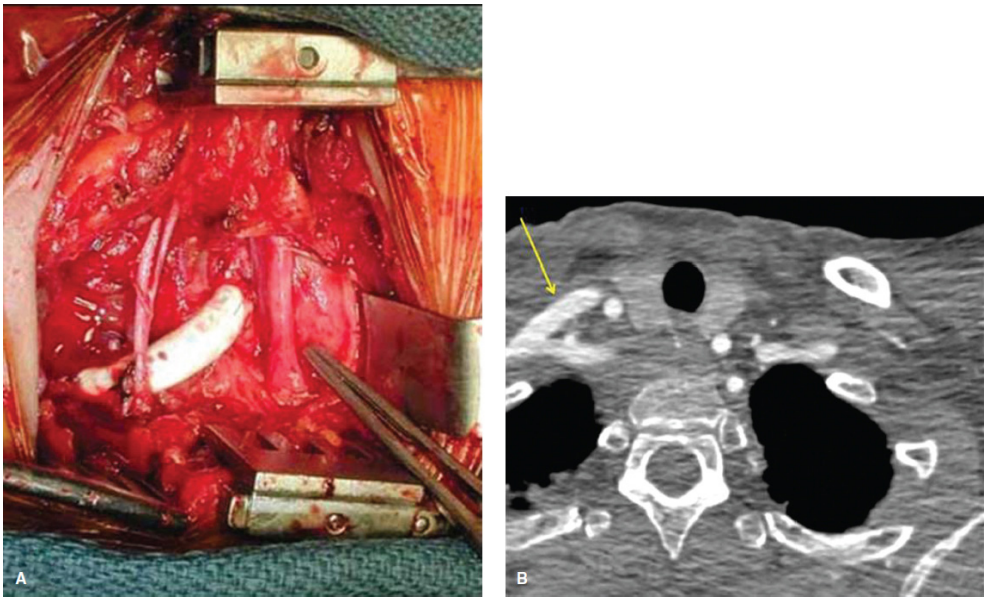

Figure 88.11 **A:** Right carotid to subclavian bypass performed via a supraclavicular incision using a prosthetic 10-mm conduit. **B:** CT scan showing patency of the bypass (*arrow*).

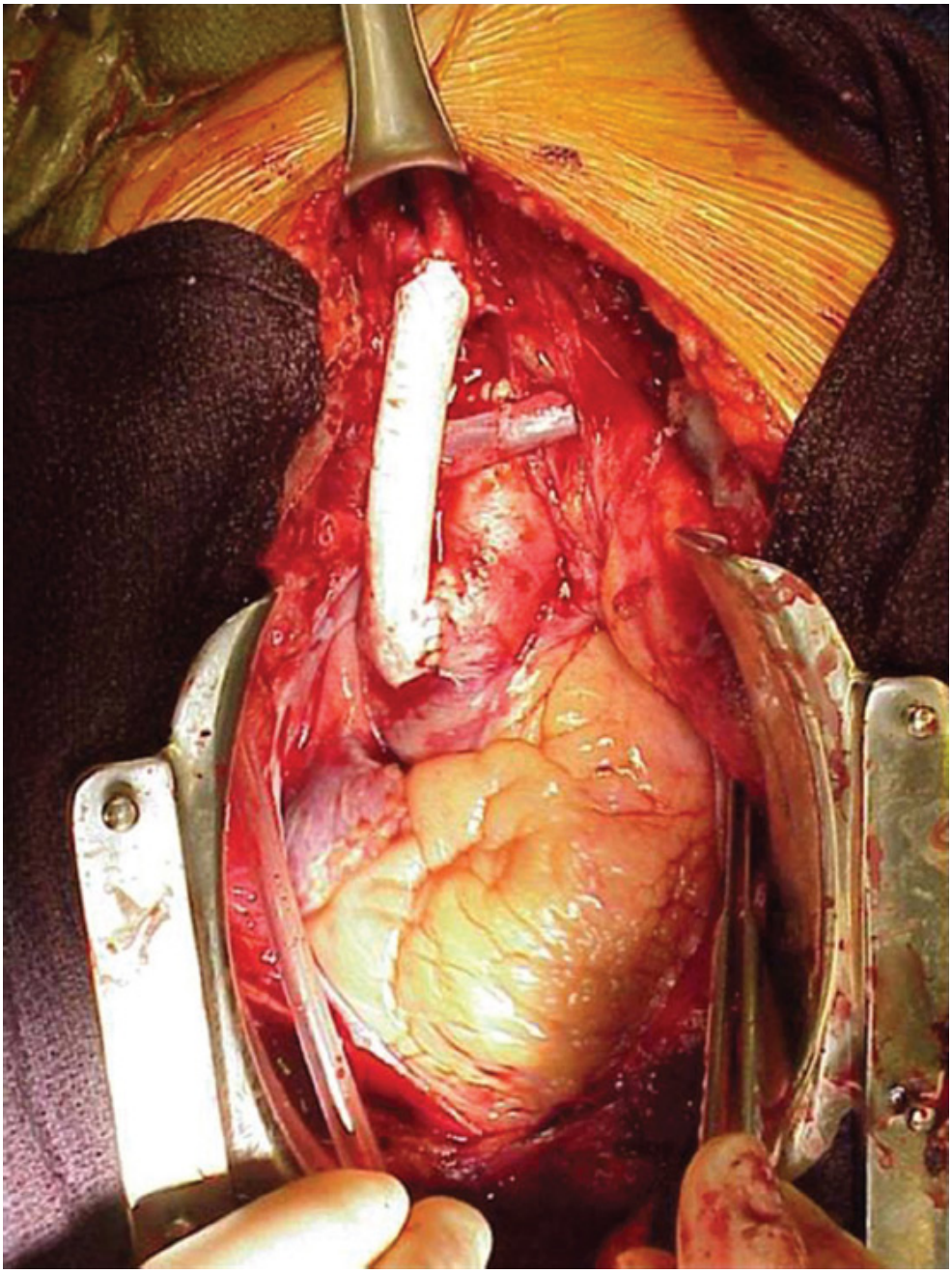

Figure 88.12 Aorto to inominate bypass. A ministernotomy is done and a side-biting clamp is used for creation of the proximal anastomosis in the ascending aorta. The distal anastomosis is created at the bifurcation of the innominate artery.

Other occlusive lesions of the subclavian, axillary, and brachial arteries are best treated with surgical revascularization. Due to potential compression at the costoclavicular space, the high mobility of the shoulder joint, and the caliber of the brachial artery, endovascular approaches are rarely indicated in this segment of the circulation. Many different bypass

configurations are available. The supraclavicular subclavian artery can be exposed by an incision at the base of the neck and used as inflow for bypasses tunneled subcutaneously over the clavicle and into the brachial artery. Alternatively, an excellent source of inflow is the common carotid artery. The outflow anastomosis can be created in the distal brachial artery, the radial or ulnar arteries in the proximal forearm (Fig. 88.14), or at the wrist and even in the arteries of the hand (Fig. 88.15).

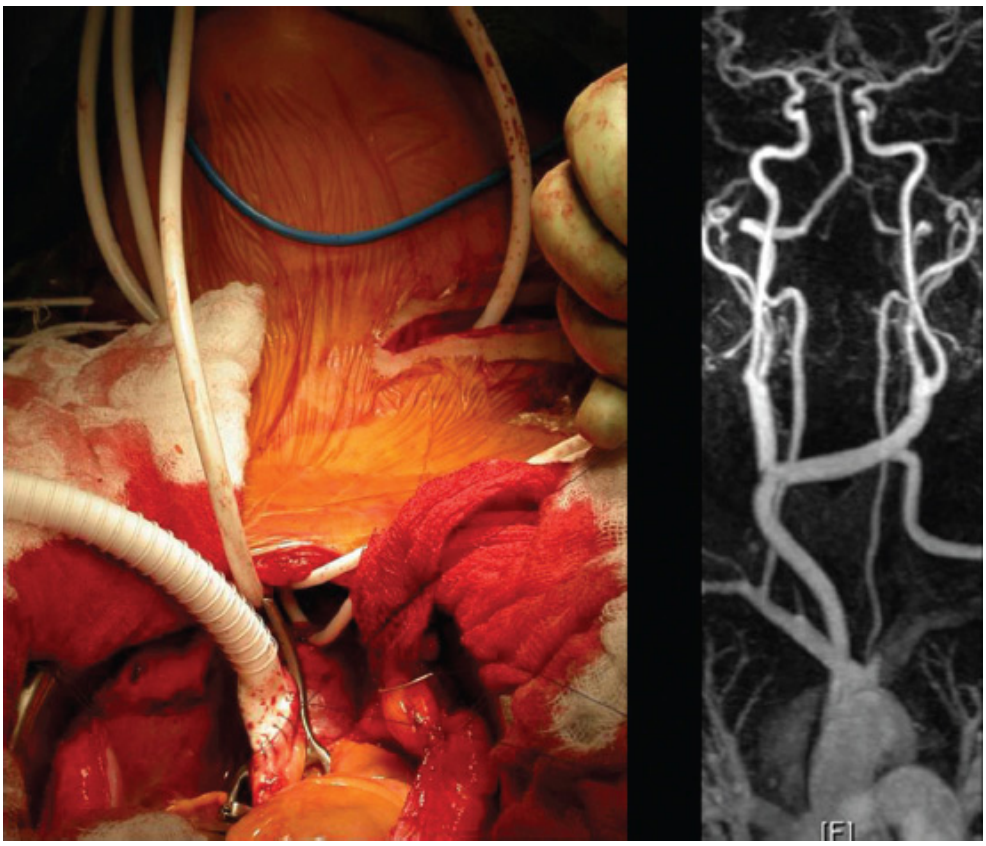

Figure 88.13 Arterial reconstruction on the patient with Takayasu arteritis shown in Figure 88.3. A median sternotomy with bilateral neck incisions was used. The proximal anastomosis was done in the ascending aorta. One branch was anastomosed in an end-to-end fashion to the right subclavian. A second branch was anastomosed to the right carotid (side-to-end) and then tunneled via the prevertebral space and anastomosed end-to-end to the left carotid bifurcation. Finally, a side arm was used to revascularize the left subclavian artery.

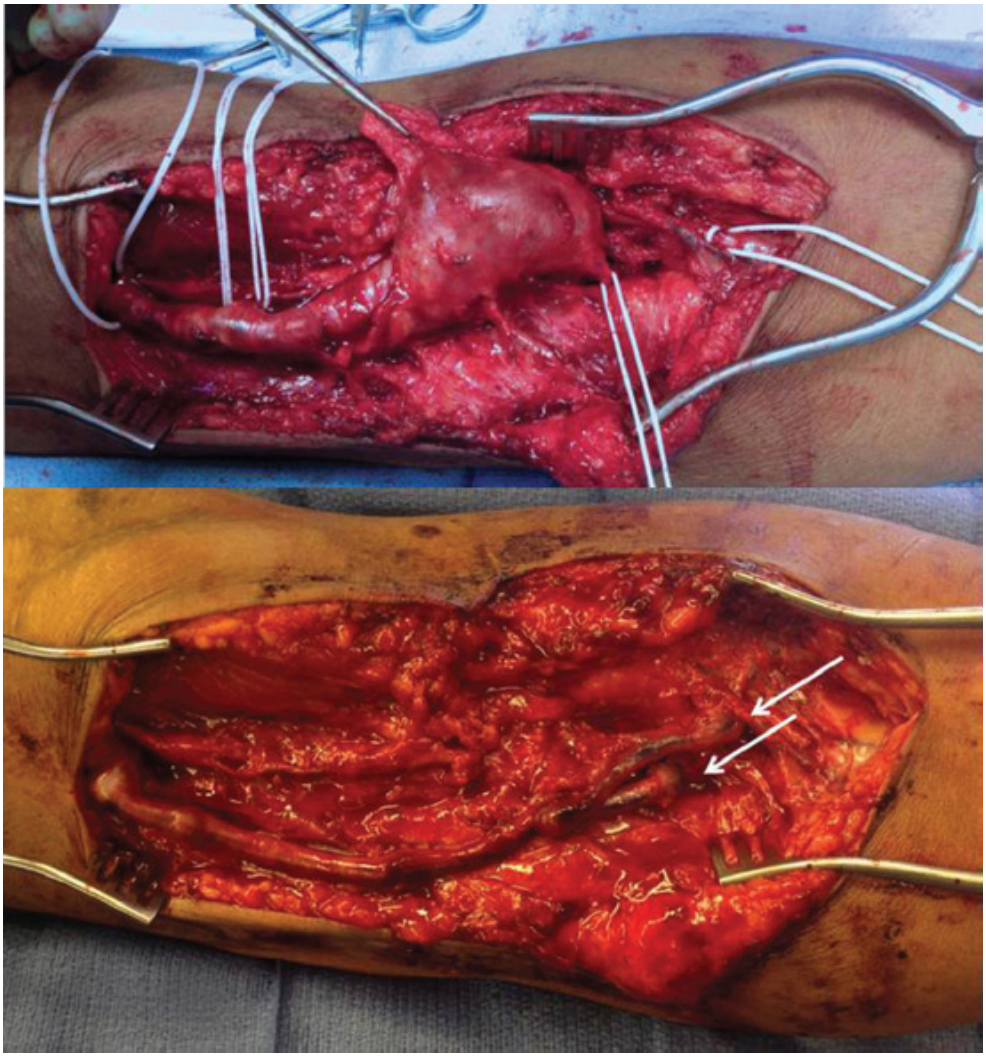

Figure 88.14 Large aneurysm of the distal brachial artery treated with a bifurcated bypass created with great saphenous vein. The distal anastomosis (*arrows*) were created into the radial and ulnar arteries just distal to the elbow.

Patients suffering from hypothenar hammer syndrome with mild symptoms and no aneurysm can be treated nonoperatively. Padded hand protection, avoidance of further repetitive trauma, tobacco cessation (if applicable), and the use of calcium channel blockers, antiplatelet agents, and/or anticoagulation all have been tried with some degree of success. Surgical intervention can include simple ligation of the aneurysm if there is adequate collateral circulation; typically resection of the affected segment with reconstruction is required (Fig. 88.16).

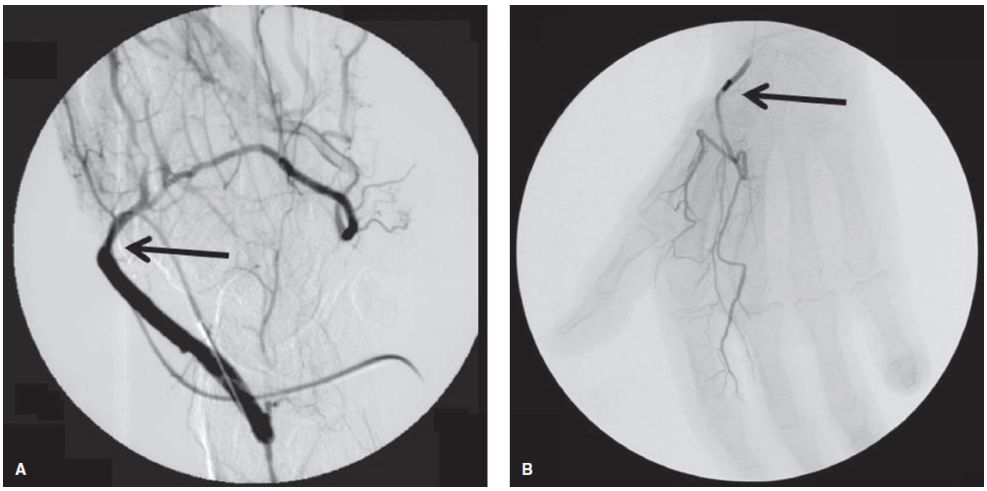

Figure 88.15 Completion angiograms of two different saphenous vein bypasses with distal anastomosis (*arrows*) to the palmar arch (**A**) and radial artery at the snuffbox segment (**B**).

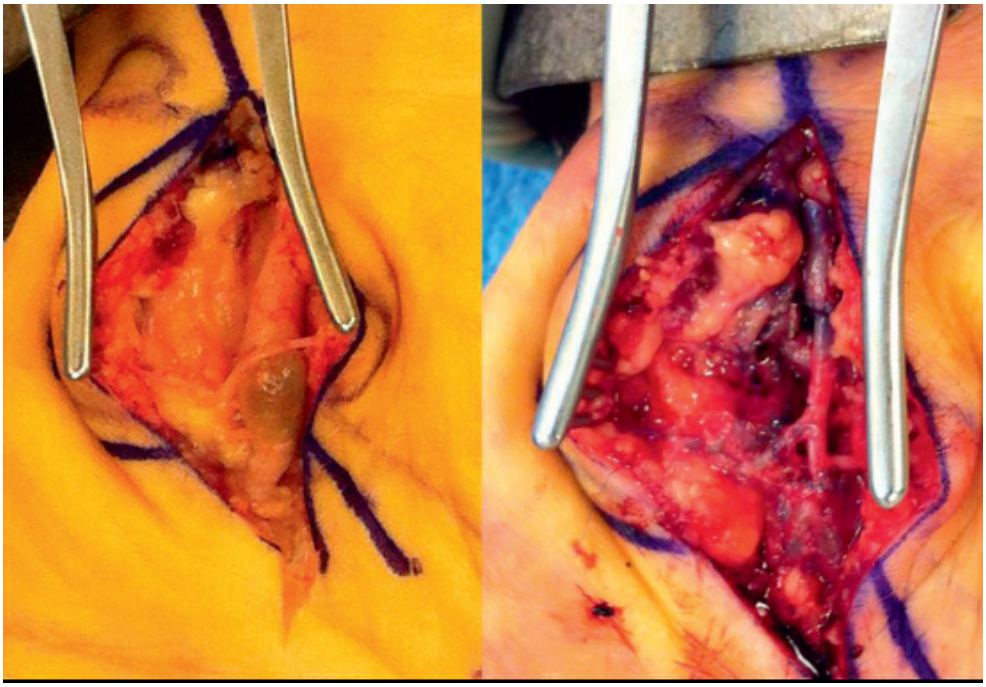

Figure 88.16 Ulnar artery aneurysm treated with arterial conduit (profunda femoris branch harvested from the thigh) in a patient with hypothenar hammer syndrome.

The management of Raynaud syndrome consists of the use of calcium channel blockers and vasodilators.[15]

CONCLUSIONS

Although atherosclerosis is still the most common cause of upper extremity arterial disease, a myriad of conditions associated with occupational, autoimmune, and social risk factors are often the cause of arm and hand ischemia. A complete history and physical examination often discloses a potential etiology and usually points to the anatomic location of the culprit lesion. Bilateral hand ischemia is often associated with systemic conditions, whereas unilaterality more commonly occurs with obstructive lesions. Accurate delineation of the anatomy by the use of imaging modalities is necessary in order to plan revascularization. Multiple endovascular and open surgical options are available for the management of upper extremity arterial disorders.

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89

Renal and Splanchnic Vascular Disease

Dawn M. Coleman, John E. Rectenwald, and Gilbert R. Upchurch Jr

Key Points

1 Splanchnic vascular disease is uncommon across the spectrum of vascular surgery practice, but remains central to the specialty.

2 Intestinal ischemia may result from pre-splanchnic conditions that decrease total mesenteric blood flow (i.e., heart failure and hypovolemia), splanchnic conditions that decrease regional blood flow through the mesenteric circulation (i.e., thromboembolism) or post-splanchnic venous congestion (i.e., mesenteric vein thrombosis and cirrhosis).

3 The most common causes of acute mesenteric ischemia (AMI) include: embolization (40% to 50%), arterial thrombosis (25% to 30%), nonocclusive mesenteric ischemia (15% to 20%), and mesenteric venous thrombosis (5% to 15%).

4 Patients with AMI warrant immediate medical management that includes the establishment of adequate intravenous access and hemodynamic monitoring, systemic anticoagulation with heparin, fluid resuscitation, correction of electrolyte abnormalities, and administration of broad-spectrum antibiotics.

5 The progression from minor symptoms to AMI and intestinal infarction is unpredictable; almost half of patients presenting with AMI describe previous symptoms of chronic mesenteric ischemia (CMI).

6 Distribution of splanchnic artery aneurysms is as follows: Splenic artery (60%) > hepatic arteries (20%) > superior mesenteric artery (5.5%) > celiac artery (4%) and gastric and gastroepiploic arteries (4%) > ileocolic arteries (3%) > pancreaticoduodenal arteries (2%) > gastroduodenal artery (1.5%) > inferior mesenteric artery (<1%).

7 Renal artery occlusive disease is the most common cause of correctable hypertension (HTN) in adults and the third most common cause of HTN in children and should be considered in the clinical context of: (1) childhood HTN, (2) severe HTN in women <45 years of age, (3) acute and rapid escalation of mild HTN in older patients (>50 years), (4) initial diastolic BP >115 mm Hg, and (5) rapid deterioration in renal function following the administration of antihypertensive therapy (especially with ACE inhibition).

8 Medical therapy remains the mainstay of treatment for renovascular hypertension (RVH) with comprehensive goals of care that should encompass glycemic control, cholesterol reduction, smoking cessation, blood pressure reduction, and antiplatelet therapy with aspirin for primary prevention. ACC/AHA guidelines support the use of Angiotensin converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARBs), calcium channel blockers, and beta blockers with a class I indication.

9 Several recent clinical trials comparing renal artery stenting to best medical management for renal artery stenosis have failed to demonstrate a conclusive clinical benefit to the endovascular treatment of renal artery stenosis.

SPLANCHNIC VASCULAR OCCLUSIVE AND ANEURYSMAL DISEASE

Introduction

1 Spl anchnic vascular disease is uncommon across the spectrum of vascular surgery practice, but remains central to the specialty. Patients often seek medical attention from alternative specialists, emphasizing the

importance of cross-disciplinary awareness. Acute mesenteric ischemia (AMI) remains associated with delayed diagnosis and dismal mortality despite notable progress in the diagnosis and treatment of patients with vascular disease. This section elaborates on the current treatment standards for both splanchnic vascular occlusive disease and aneurysms.

Anatomy and Physiology

Three branches of the abdominal aorta perfuse the gastrointestinal tract. The celiac artery originates at the level of T12 and branches into the left gastric, common hepatic and splenic arteries in a classic pattern in 65% to 75% of cases.[1] Variations are noted in Table 89.1 and may include a true trifurcation of these vessels (25% of the population), replaced and accessory hepatic vasculature, a common celiacomesenteric trunk (<1% of the population), and a persistent ventral anastomosis between the proper hepatic, and a replaced right hepatic artery (off the SMA) denoted as an "arch of Buhler" (<4% of the population). Additionally, the splenic artery can be found to originate directly off the aorta, SMA, left gastric or hepatic arteries. The celiac axis supplies primarily the stomach, duodenum, spleen, liver, and pancreas. The SMA originates approximately 1 to 2 cm caudad to the celiac artery and branches into the inferior pancreaticoduodenal artery, 4 to 6 jejunal and 9 to 13 ileal branches, the middle colic artery, the right colic artery, and terminates as the iliocolic artery. The SMA supplies primarily the lower portion of the pancreas gland, jejunum, ileum, ascending colon, and the proximal half of the transverse colon. The inferior mesenteric artery (IMA) originates off the terminal aorta at the level of L3 and divides into the left colic artery, sigmoid branches and continues as the superior hemorrhoidal artery.[1] This small and most distal mesenteric branch artery supplies primarily the large bowel from the level of the mid-transverse colon to the rectum.

Table 89.1 Normal and Variant Mesenteric Arterial Anatomy

Vessel	Incidence (%)
Celiac	
▪ Classic (3 branches)	65–75
▪ Four branches (including dorsal pancreatic artery)	5–10
▪ Celiacomesenteric trunk	<1
Hepatic	
▪ CHA from celiac artery	75
▪ CHA from SMA	2.5
▪ Replaced RHA	15–18
▪ From left gastric	11–12
▪ From SMA	2.5
▪ Accessory RHA	7–8
▪ Accessory LHA	2.5
Gastric	
▪ Left gastric artery	
▪ From celiac artery	90
▪ From aorta	3
▪ Accessory branches from or to left hepatic artery	23
▪ Right gastric artery	
▪ From proper hepatic artery	40
▪ From left or middle hepatic artery	40
▪ From RHA	10
▪ From GDA	8

CHA, common hepatic artery; SMA, superior mesenteric artery; RHA, right hepatic artery; LHA, left hepatic artery; GDA, gastroduodenal artery.
Adapted from Rosenblum JD, Boyle CM, Schwartz LB. The mesenteric circulation: anatomy and physiology. *Surg Clin North Am* 1997;77:289–306.

Collateralization is a crucial concept when considering the mesenteric circulation. On the grounds of redundancy, given multiple potential sources of collateral flow, at least two of the three major branch vessels must be occluded or have a critical stenosis for mesenteric ischemia to manifest. While arterial collaterals may be small in the physiologic circulation, they have the potential to hypertrophy dramatically when increased flow is required. Figure 89.1 demonstrates several important collateral pathways. The gastroduodenal artery (GDA) and pancreaticoduodenal arcade make up the primary potential pathway for collateral flow between the celiac axis and the SMA. In addition to the aforementioned arc of Buhler, the

arc of Barkow consists of arteries in the omentum (SMA branches) that connects to the right and left gastroepiploic arteries (celiac branches). The marginal artery of Drummond is the major collateral route between the SMA and IMA; it lies within the colon mesentery giving rise to the vasa recta. The arc of Riolan lies within a more central portion of the mesentery connecting the middle and left colic arteries. Finally, the IMA may also receive collateral flow from lumbar branches of the aorta, hemorrhoidal branches of the internal iliac artery, and the middle sacral artery.

Splanchnic venous anatomy parallels the arterial system to drain into the portal venous system. The splenic and superior mesenteric veins join to form the portal vein. Hepatic venous blood is drained by the right, middle, and left hepatic veins. Portal–systemic connections are multiple and important when considering portal hypertension.

Physiologic intestinal function relies on adequate perfusion and oxygenation of the microvascular splanchnic circulation. Splanchnic blood flow is estimated as 300 to 1,200 mL/min, or about 10% to 35% of the cardiac output, with approximately 70% of this blood flow supplying the mucosa and submucosa.[1,2] Various intrinsic and extrinsic autoregulatory mechanisms including tissue metabolites, myogenic mechanisms, and the autonomic nervous system ensure adequate gut circulation through both vasoconstriction and relaxation of arterial smooth muscle. The degree of visceral artery dilation and constriction determines the relatively large fluctuations in splanchnic blood flow during fasting and postprandial states.

Duplex ultrasound demonstrates moderate to high arterial resistance in the SMA, with low diastolic flow and slight flow reversal during fasting states. Figure 89.2 demonstrates duplex ultrasonography of normal aorta and SMA. Vessel diameter, flow velocity, calculated volumetric blood flow, spectral analysis, and response to physiologic stimuli allow for precise assessment of the visceral circulation. In the postprandial period (30 to 90 minutes), low-resistance signals are noted throughout systole and diastole, indicative of dilated splanchnic arteriolar beds. Flow reversal does not occur. In contrast, low arterial resistance signals are noted in the celiac artery circulation regardless of feeding, likely due to the influence of the low-resistance hepatic vascular bed.

2 Intestinal ischemia may result from presplanchnic conditions that decrease total mesenteric blood flow (i.e., heart failure and hypovolemia), splanchnic conditions that decrease regional blood flow through the mesenteric circulation (i.e., thromboembolism) or postsplanchnic venous congestion (i.e., mesenteric vein thrombosis [MVT] and cirrhosis). Regardless of the mechanism, impaired perfusion of the intestine results in hypoxia-associated sequelae that include cytokine release, free radial production, microcirculatory damage, and bacterial translocation. Mucosal barrier function is compromised secondary to physical disruption of the mucosa, a change in normal intestinal microflora resulting from treatment with broad-spectrum antibiotics, and impairment of host immune defenses.[3] Intestinal ischemia may rapidly progress to tissue necrosis causing severe metabolic derangements and ultimately multiple organ dysfunction and death. In addition to ischemia-related bowel injury, splanchnic reperfusion exaggerates injury patterns. Reperfusion injury is associated with increased microvascular permeability, increased epithelial permeability with leaking of fluid and molecules into the bowel lumen, and decreased intestinal blood flow.

Acute Mesenteric Ischemia

> *"Occlusion of the mesenteric vessels is apt to be regarded as one of those conditions of which . . . the diagnosis is impossible, the prognosis hopeless and the treatment almost useless."*[4]

AMI remains an uncommon event but carries catastrophic potential as illustrated by AJ Cokkinis' statement above from 1926. Klass is credited with the first successful restoration of arterial blood supply in an attempt to salvage AMI in 1951 by SMA embolectomy.[5,6] While clear medical and technologic progress has been made in the interim, delayed diagnosis and treatment continues to impede improvements in contemporary patient morbidity and mortality rates that approach 80%.[6,7]

AMI accounts for <1 in every 1,000 hospital admissions, presents most commonly during the seventh and eighth decades of life, and epidemiologic study suggests that women are affected with three times the frequency of males, at least in part attributed to relative female longevity.[6] A Swedish epidemiologic study cites an AMI incidence of 12.9/100,000 people years (as diagnosed by autopsy or operation).[8]

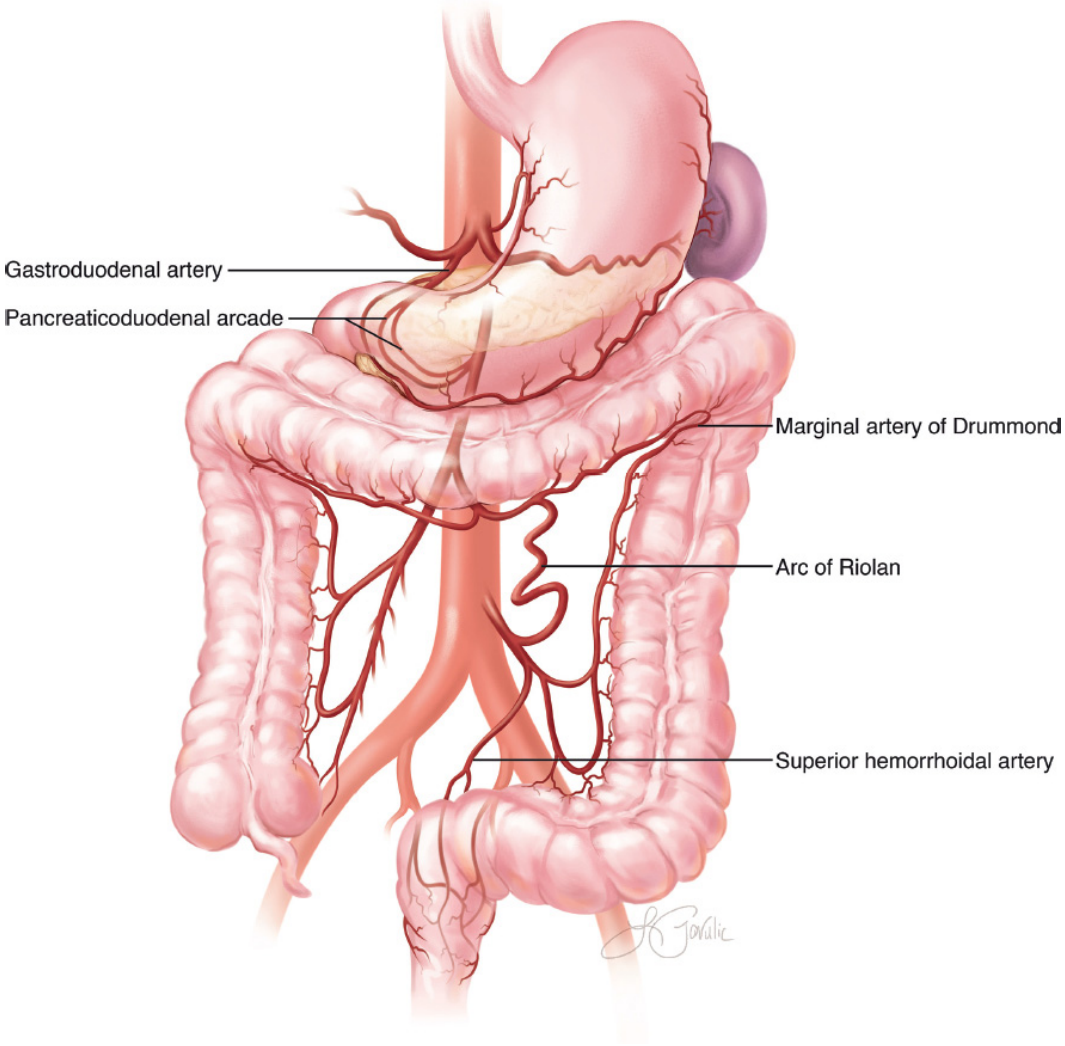

Figure 89.1 Mesenteric collateral circulation.

3 The most common causes of AMI are referenced above and include: embolization (40% to 50%), arterial thrombosis (25% to 30%), nonocclusive mesenteric ischemia (NOMI) (15% to 20%), and mesenteric venous thrombosis (5% to 15%).[6,8] Additional causes may include visceral malperfusion associated with aortic dissection, mesenteric arterial dissection, and trauma. Historic mortality rates for AMI are as high as 93%, although more contemporary series suggest in-hospital mortality rates of 17% to 62% and a systematic review of 45 observational studies cites a mean mortality rate of 71.6% for 3,692 patients with AMI.[8–13] While there is no validated prediction model for mortality in this clinical setting, authors have shown with logistic regression models that age, duration of symptoms, age-adjusted comorbidity, specific EKG markers, and shock index may be associated with higher mortality.[12,14,15]

Patients with AMI complain predominantly of abdominal pain followed by nausea, vomiting, and diarrhea. Pain is often described as "out of proportion" to the clinical examination as tenderness to palpation may be minimal until transmural necrosis of the intestine develops. Patients can be tachycardic

and demonstrate melena or heme-positive stools. Fever, guarding, and rebound are typically late findings associated with bowel infarction.

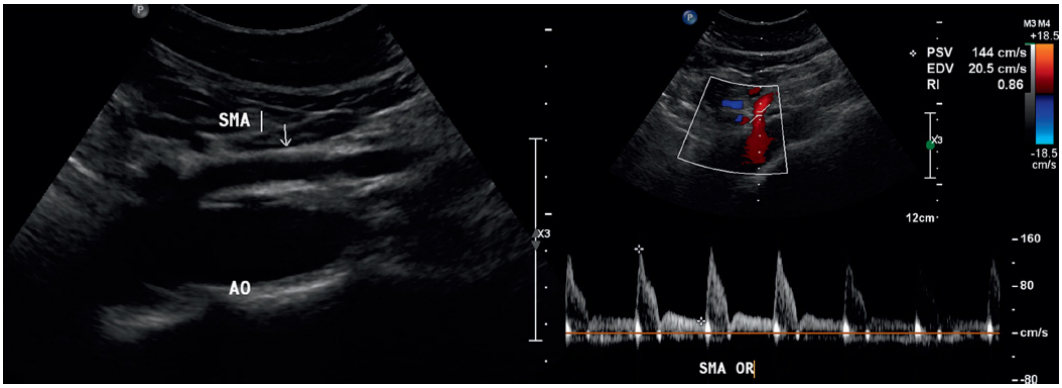

Figure 89.2 Mesenteric duplex ultrasound of a normal aorta and SMA that demonstrates moderate to high arterial resistance in the SMA, with low diastolic flow and slight flow reversal during fasting states. AO, aorta; SMA, superior mesenteric artery; PSV, peak systolic velocity; EDV, end-diastolic velocity; RI, resistive index; OR, origin.

Laboratory abnormalities may include hemoconcentration, leukocytosis, lactic acidosis, and elevated anion gap, amylase, aspartate aminotransferase, and lactate dehydrogenase. While a reliable biomarker for AMI remains elusive, D-dimer offers 96% to 100% sensitivity as an exclusionary test for early AMI with low specificity.[16,17] Intestinal fatty acid binding globulin (I-FABP), α-glutathione S-transferase, and D-lactate are currently promising plasma markers.[16,18] I-FABP and α-glutathione S-transferase are located in the small bowel mucosa while D-lactate originates from bacteria in the intestinal lumen as a normal product of bacterial fermentation. These markers leak into the blood stream during early ischemia from damaged enterocytes and may offer increased specificity for small bowel ischemia.

Diagnostic work-up often starts with a plain abdominal radiograph which may reveal ileus and vascular calcifications; bowel wall edema (i.e., thumbprinting), pneumatosis (Fig. 89.3), pneumobilia, and pneumoperitoneum may become evident with advanced ischemia and infarction, respectively. High-quality computed tomography angiography (CTA) has become the gold standard for imaging AMI given near-universal availability and its ability to assess for bowel perfusion while excluding alternate sources of abdominal pain. Additionally, "biphasic" CT offers arterial and delayed phase imaging that permits visualization of the portal venous system in addition to arterial stenosis, occlusions, and bowel wall features that support the diagnosis of AMI with a negative and positive predictive value reported up to 96% and 100%, respectively.[19,20] Duplex ultrasonography, magnetic resonance angiography (MRA), and diagnostic laparoscopy may serve as adjuncts for diagnosis but secondary to intrinsic limitations should not be considered first line. Finally, the role for arteriography remains important and will be described further as it allows for simultaneous therapeutic measures.

Mesenteric emboli most commonly affect the SMA given its oblique orientation off the aorta. Most emboli are cardiac in origin; less common embolic sources may include proximal aortic aneurysm, atrial myxoma, and paradoxical embolus secondary to venous thromboembolism with cardiac shunting. Patient history will likely reveal atrial fibrillation, myocardial infarction, congestive heart failure or cardiomyopathy, rheumatic heart disease or ventricular aneurysm. Most emboli will spare the SMA origin and lodge distal to the middle colic artery and early jejunal branches. This pattern of ischemia, in the absence of well-formed collaterals, results in a classic pattern of ischemia that compromises the bulk of small bowel and ascending colon while sparing the proximal jejunum and distal transverse colon (Fig. 89.4).

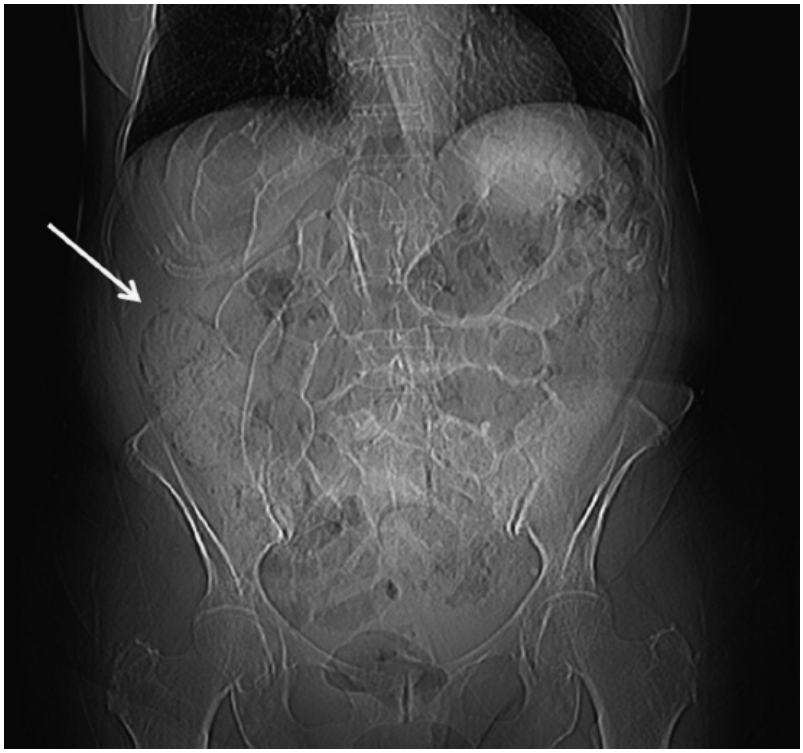

Figure 89.3 Abdominal radiograph demonstrating diffuse ileus and intestinal pneumatosis (*arrow*) in a patient with acute mesenteric ischemia.

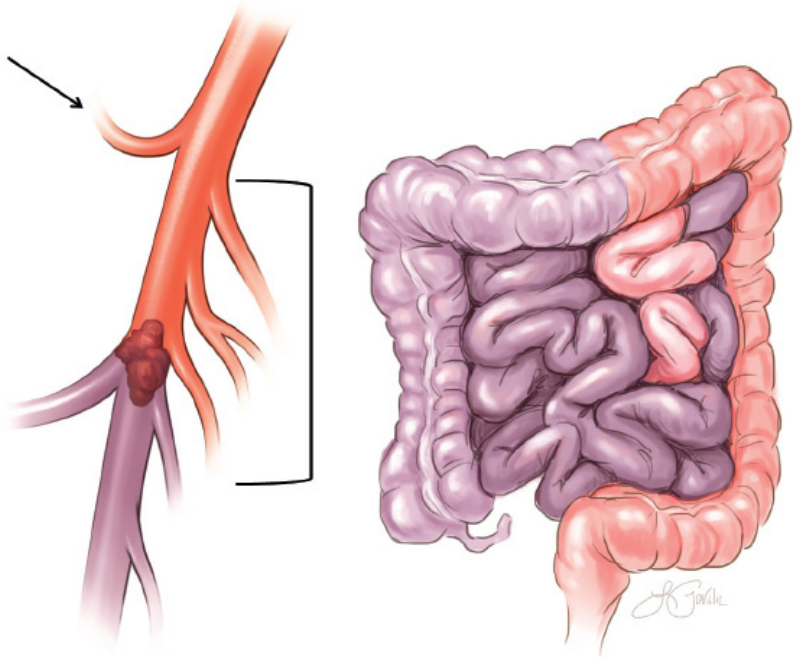

Figure 89.4 Pattern of embolic mesenteric ischemia—SMA emboli typically spare the middle colic artery (*arrow*) and proximal jejunal branches (*bracket*) resulting in an ischemic pattern that spares the jejunum and distal transverse colon.

Acute in situ arterial thrombosis typically coincides with pre-existing atherosclerotic disease. Up to 20% to 50% of patients will describe antecedent postprandial abdominal pain and weight loss consistent with CMI.[2,6,9] Clinical presentation may be more subacute given the presence of preformed collaterals that are

typically absent in cases of embolic AMI. Patient history will likely reveal common cardiovascular risk factors. Figure 89.5 demonstrates the highly calcified aorta of a patient presenting with AMI and chronic celiac artery occlusion, SMA thrombosis (encircled), and IMA occlusion.

Management of AMI

4 Patients with AMI warrant immediate medical management that includes the establishment of adequate intravenous (IV) access and hemodynamic monitoring, systemic anticoagulation with heparin, fluid resuscitation, correction of electrolyte abnormalities, and administration of broad-spectrum IV antibiotics. Further vasoconstrictive insult with vasopressors should be avoided if possible. Patients with AMI and evidence of threatened bowel viability warrant immediate surgical exploration. Frankly necrotic or perforated bowel should be resected and left in discontinuity to limit contamination while definitive intestinal management should never delay revascularization.

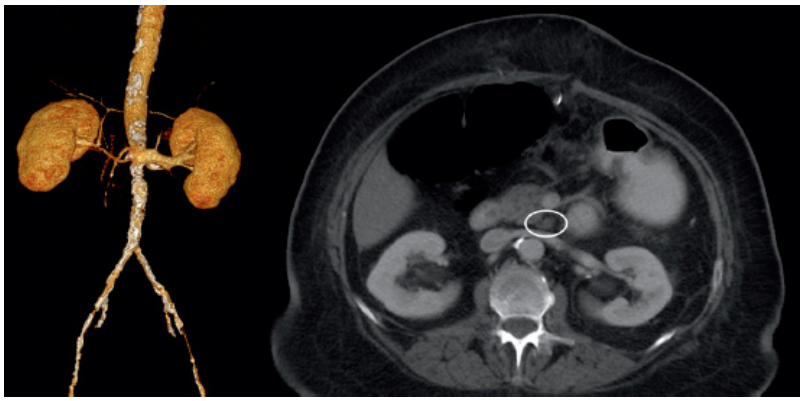

Figure 89.5 CT imaging demonstrating in situ SMA thrombosis in the setting of highly calcified aortoiliac occlusive disease and chronic celiac and IMA occlusions presenting as acute mesenteric ischemia.

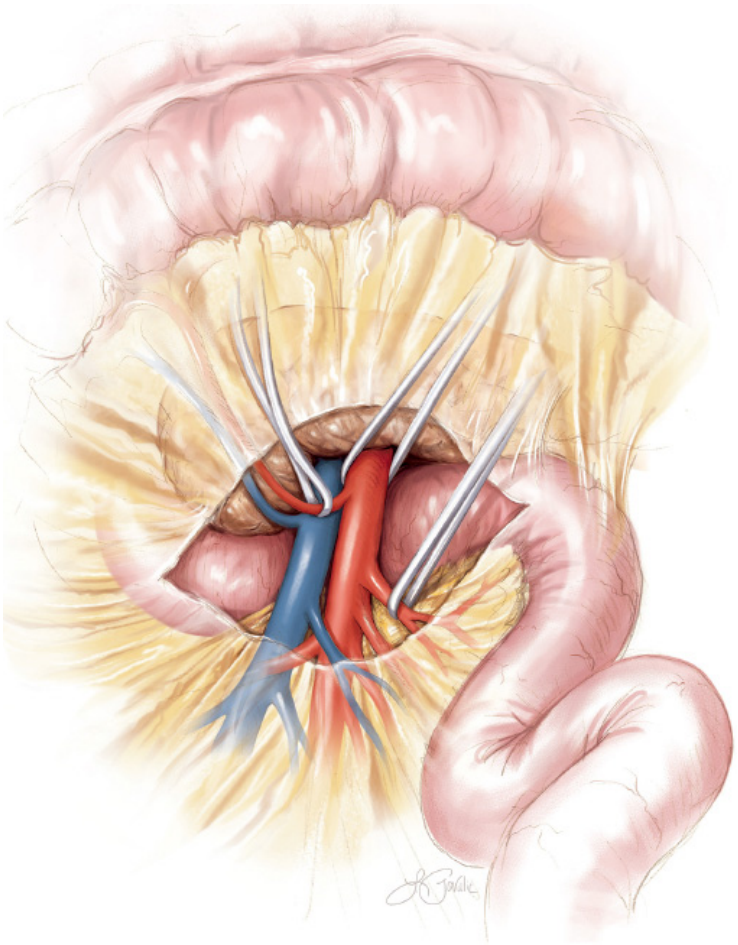

Figure 89.6 SMA exposure at the base of the colonic mesentery (*SMA encircled proximal to the middle colic artery*).

SMA thromboembolectomy is the standard technique for embolic disease. Figure 89.6 illustrates anterior exposure of the SMA at the base of the colonic mesentery. Typically, venous tributaries, small lymphatics, and autonomic nerve fibers require ligation to facilitate arterial exposure. The inferior pancreatic border may require mobilization for more proximal SMA exposure. The SMA is exposed and controlled proximal to the middle colic artery; the middle colic artery and jejunal branches are similarly controlled. After a therapeutic level of systemic anticoagulation is confirmed a transverse arteriotomy is created sharply (Fig. 89.7). The proximal SMA is vented; in the absence of robust and pulsatile antegrade flow a balloon thromboembolectomy should be performed with a 3-Fr or 4-Fr catheter. Distal vasculature is fragile and thromboembolectomy is best accomplished with a smaller catheter (i.e., 2 Fr or 3 Fr). During balloon thromboembolectomy the balloon should be inflated with heparinized saline (not air) as the catheter is withdrawn. The same person should control the balloon inflation that is controlling catheter removal. Finally, consider flushing regional heparin or thrombolytic agent directly into the distal SMA and branches. Balloon thromboembolectomy should be repeated until the balloon is withdrawn free of thrombus burden. Following the successful clearance of all macroscopic thrombus the arteriotomy can be repaired primarily with simple sutures of 5-0 or 6-0 monofilament suture placed in an interrupted fashion. Vein patch angioplasty should be considered over primary repair for diminutive vessels.

In cases of SMA occlusive disease with in situ thrombosis, bypass is typically required for successful revascularization. In cases of such acuity, typically single-vessel reconstruction (SMA) is all that is required. While there are multiple options for graft orientation and conduit, a retrograde bypass off the right common iliac artery oriented in a “lazy-C” configuration is most often favored (Fig. 89.8). The lateral

portion of SMA is exposed cephalad to the fourth portion of the duodenum. This exposure requires opening of the peritoneum adjacent to the duodenum with full exposure of the terminal aorta and iliac arteries. Synthetic graft (i.e., 6- or 8-mm externally supported polytetrafluoroethylene) is typically favored over autogenous conduit given its favorable size match, ready availability, and resistance to kinking. Saphenous vein graft may be considered for cases of gross enteric contamination. The terminal aorta or left common iliac artery may also be used for inflow. Antegrade bypass off the supraceliac aorta may be considered in cases of prohibitive anatomy. While this exposure adds additional technical complexity and operative time combined with the physiologic stress of aortic cross-clamping, contemporary data supports a lower risk of reintervention with an antegrade configuration.[21]

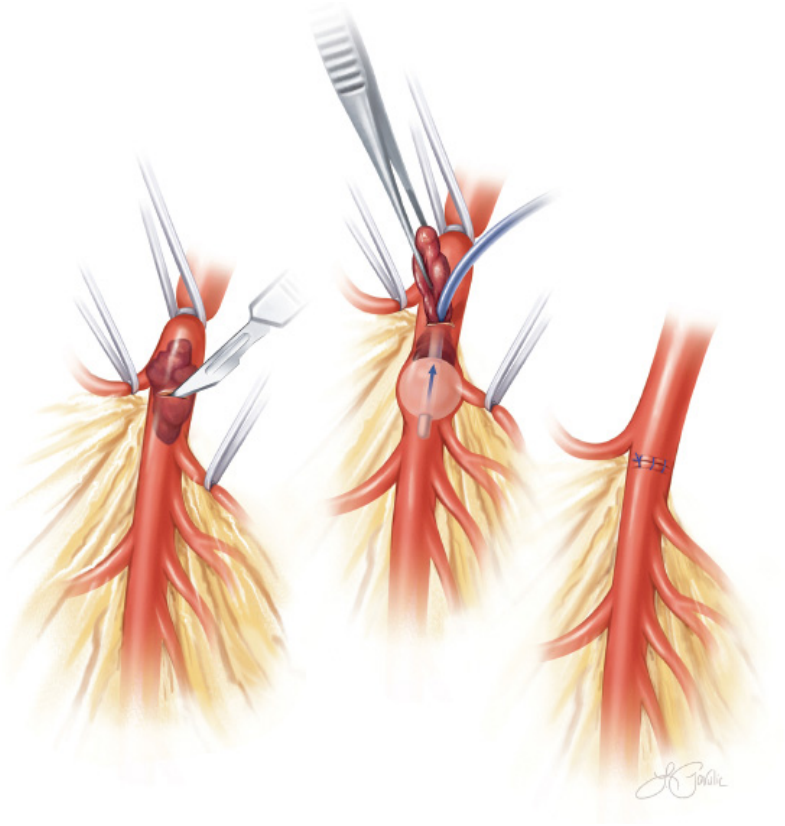

Figure 89.7 Illustration of balloon SMA thromboembolectomy through a transverse arteriotomy.

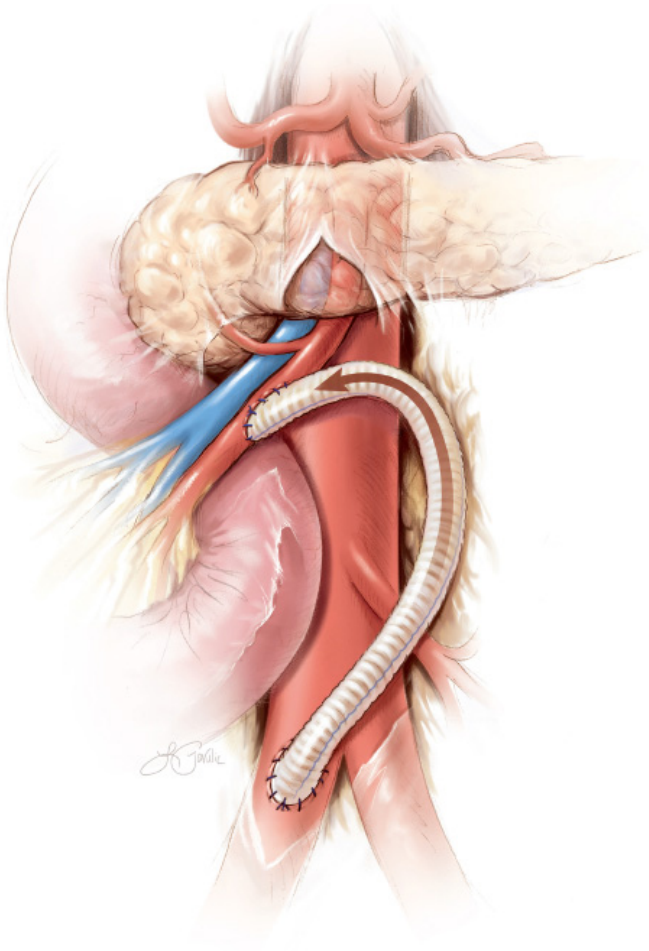

Figure 89.8 Retrograde bypass off the right common iliac artery oriented in a "lazy-C" configuration.

While surgery has remained the standard of care for AMI over previous decades, a hybrid procedure for SMA thrombosis has become widely embraced for its efficiency and decreased invasiveness for mesenteric revascularization. This approach negates the need for aortic cross-clamping, prosthetic conduit, and difficulty with arterial quality. Retrograde open mesenteric stenting (ROMS) was first described by Milner et al. in 2006 and further popularized by Wyers et al. in a 2007 case series.[22,23] The infracolic SMA is exposed at the base of the transverse colonic mesentery as previously described for retrograde cannulation following local patch angioplasty with vein or bovine pericardium. This hybrid approach allows for simultaneous assessment and treatment of nonviable intestine with mesenteric revascularization by way of SMA stenting. Contemporary series on ROMS report technical success rates of 93% and primary-assisted patency rates of 91% at 12 months with similar complication and reintervention rates when compared to mesenteric bypass with significantly reduced operative times.[24,25]

Regardless of the approach to successful revascularization, intestinal viability must be assessed; this decision is typically deferred for 20 to 30 minutes following reperfusion and aided by Doppler interrogation of the mesenteric arcade, observation of serosal color, and the presence of peristalsis. Adjuncts also include the use of fluorescein with a modified Wood's lamp or perfusion fluorometer.[6] Nonviable bowel is resected and in cases of unclear viability the intestine may be left in discontinuity, the abdomen left open, and plans for a second-look laparotomy at 24 to 48 hours secured for definitive intestinal management. Postoperative complications and mortality rates are high following open revascularization for AMI. Thirty-day mortality rates approximate 30%, with morbidity rates as high as 70%.[26,27]

Exclusive endovascular treatments for AMI are increasingly reported despite historic concerns that this approach increases time to revascularization, prohibits assessment of bowel viability, and that endovascular failure might delay traditional revascularization thereby worsening patient outcomes. Successful cases of percutaneous mechanical thrombectomy, aspiration thrombectomy, and intra-arterial thrombolysis, with or without adjuvant angioplasty and stenting, have been reported in patients without evidence of advanced bowel ischemia.[28–33] The largest single center experience with endovascular therapy for AMI reported a success rate of 87%, with failures most often requiring surgical embolectomy.[34] These authors compared outcomes following open and endovascular therapies for AMI and identified a reduction in need for laparotomy, length of bowel resected, and morbidity including acute renal failure and pulmonary failure in the endovascular group. Additionally, successful endovascular therapy was associated with improved mortality (36% vs. 50%) and those endovascular failures succumbed to similar mortality rates as the open surgical group. Most recently a National Inpatient Sample (NIS) review identified a significant increase in the utilization of endovascular therapy for AMI and reported that mortality, hospital length of stay, need for bowel resection, and need for postoperative parenteral nutrition were reduced in those patients receiving endovascular therapy in comparison to traditional open surgical revascularization.[35]

Nonatherosclerotic Mesenteric Arterial Occlusive Disease

Intestinal ischemia may result from iatrogenic injury (i.e., arterial dissection or thromboembolism during endovascular techniques), aortic dissection resulting in visceral malperfusion, trauma, inflammatory arteritides, and fibromuscular dysplasia (FMD). Indeed, these patients warrant an individualized approach to treatment. In cases of aortic dissection branch revascularization or aortic fenestration is essential. Traumatic injuries often require urgent surgical repair or revascularization. Inflammatory arteritides are typically managed medically (i.e., immunosuppression) with surgical bowel resection reserved for nonviability.

Mesenteric Vein Thrombosis

Splanchnic vein thrombosis is defined by thrombosis of the portal venous system which includes the superior mesenteric, inferior mesenteric, splenic, and portal veins. The sequelae of such may include bowel or splenic infarction and chronic portal hypertension. MVT is a less common form of intestinal ischemia that may present in a more subacute fashion. While AMI symptoms are similar to those aforementioned, patients with MVT may also complain of days to weeks of a prodrome that includes crampy abdominal pain, distension, nausea, and malaise. Whether thrombosis originates in the small or large splanchnic veins, intestinal infarction requires the involvement of venous arcades and vasa recta resulting in occlusion of venous return, venous engorgement of the bowel wall, cyanosis, and mucosal ischemia that can progress to transmural infarction.[36] Idiopathic MVT represents a minority of cases as more than 50% of patients have at least one predisposing risk factor. Risk factors for MVT include heritable and acquired thrombophilia, hypercoagulable states resulting from systemic disorders (including malignancy and heparin-induced thrombocytopenia), and local intra-abdominal processes (i.e., pancreatitis or trauma). A high index of suspicion is necessary for diagnosis given the nonspecific nature of presenting symptoms, signs, and laboratory studies.[36] CT imaging with portal phase venous contrast (CT venogram) is the imaging modality of choice. Findings suggestive of MVT include a sharply defined, enhancing venous wall with central low attenuation.[36,37] MRA, angiography, and laparoscopy are useful adjuncts. Emergent laparotomy should be considered for signs of advanced intestinal ischemia; intraoperatively blood-tinged ascites is likely to be encountered and the bowel will appear dusky, thick, and rubbery. Systemic anticoagulation is the mainstay of treatment as it reduces mortality, decreases recurrent thrombosis rates from approximately 30% to <5%, and decreases mortality associated with recurrent thrombosis.[36,38–41] Additionally, with anticoagulation most patients will demonstrate partial or complete venous recanalization with time. In the absence of a defined risk factor, patients with MVT should undergo a work-up for thrombophilia. A finite duration of anticoagulation is recommended for those with a reversible provoking risk factor with cessation of anticoagulation encouraged after 3 months; remaining cases of idiopathic MVT or persistent risk warrant indefinite anticoagulation.[42] Historically open venous thrombectomy was employed for advanced cases of

MVT at the time of laparotomy. More recently various systemic and percutaneous thrombolytic techniques have been applied to cases of large vessel disease; however, no large or well-controlled trials exist to guide recommendations for such over anticoagulation alone.[36,43–46]

Nonocclusive Mesenteric Ischemia

NOMI results from diffuse mesenteric vasospasm. This rare form of intestinal ischemia most often affects critically ill patients with hemodynamic instability. Risk factors include decreased cardiac output (i.e., heart failure or arrhythmia), hemodialysis, shock, vasoactive medications (i.e., vasopressors or digitalis), and drug abuse (i.e., cocaine). Angiography is required for diagnosis and will demonstrate diffuse vasoconstriction and nonopacification of branch vessels (Fig. 89.9). Treatment centers on improving mesenteric perfusion by optimizing volume status, limiting vasoactive medications and correcting contributing comorbidities. Intra-arterial infusion of vasodilators (i.e., papaverine or nitroglycerin) or IV infusion of glucagon or prostaglandin E2, which selectively increases splanchnic blood flow, have been advocated in treating this form of intestinal ischemia without robust, large, or well-controlled trials to support treatment guidelines.[47–49]

Figure 89.9 Nonocclusive mesenteric ischemia—mesenteric arteriogram revealing diffuse vasoconstriction and nonopacification of SMA branch vessels.

Chronic Mesenteric Ischemia

Symptoms of CMI are often referred to as "intestinal angina." Ostial stenosis secondary to arteriosclerosis is the most common etiology and patients typically share risk factors of overt atherosclerosis and long-standing tobacco abuse. Additional causes of CMI may include arterial FMD, vasculitis, aortic coarctation, and connective tissue disorders. In light of aforementioned mesenteric collaterals, the responsible anatomic lesions of CMI typically affect at least two of three splanchnic arteries, although isolated lesions of the SMA distal to the middle colic branch may yield intestinal angina by excluding collateralization.[2] Patients classically present with postprandial abdominal pain that occurs within 30 minutes of eating and may last up to 4 hours postprandial. Consistent postprandial symptoms typically result in the modification of eating habits that may range from the consumption of smaller meals to "food phobia" that subsequently results in weight loss and malnutrition. There is an increasing incidence of overweight patients presenting with CMI. These patients have been reported to undergo significantly more diagnostic testing to confirm the diagnosis of CMI, possibly delaying diagnosis.[50] Additionally, BMI ≥25 has been associated with poorer long-term survival following mesenteric revascularization for CMI in comparison to nonobese patients.[51]

5 The progression from minor symptoms to AMI and intestinal infarction is unpredictable; almost half of patients presenting with AMI describe previous symptoms of CMI.[52] The incidence of CMI also remains unclear. Population studies suggest that up to 18% of individuals over 65 years of age have asymptomatic radiographic mesenteric stenosis.[53] Duplex ultrasonography should be considered the first-line diagnostic modality for CMI. Specifically, high-grade stenosis of the SMA and celiac artery in a fasting state are suggested by a peak systolic velocity of >275 cm/s and 200 cm/s, respectively.[54] CTA and MRA support the diagnosis of CMI while offering additional vascular anatomic evaluation such as the presence of aneurysm, calcific burden, dissection, wall features suggesting vasculitis and venous anomalies that may impact open reconstruction. An additional advantage of MRI is the opportunity to perform blood flow measurements (i.e., measurements of flow profiles, stroke volumes, peak velocities).[55] Importantly, mesenteric blood flow will increase after a meal in healthy controls, while significantly less increase in postprandial blood flow of the SMV in patients with CMI can be shown with MR flow technique.[56] Aortography with anteroposterior and lateral views has been commonly cited as the gold standard for diagnosis and allows for simultaneous mesenteric arteriography, manometry, provocative measures (i.e., vasodilator infusion), and intervention (i.e., angioplasty and stenting) as appropriate. This modality is often favored over cross-sectional imaging when an endovascular approach for treatment is being considered over open revascularization. Growing data suggest there may be a role for additional work-up, especially in those patients with single-vessel mesenteric stenosis, to guide the decision to perform revascularization. Pressure measurements may help define a clinically relevant CA or SMA stenosis, with a pressure distal [Pd]/pressure aorta [Pa] ratio of 0.8 following vasodilator administration supporting clinically significant mesenteric stenosis.[57] Functional work-up to assess gastrointestinal mucosal perfusion may include PCO_2 tonometry and visual light spectroscopy. Often patients will present having undergone extensive gastrointestinal work-up (i.e., contrast motility studies, endoscopy) before the diagnosis of CMI is considered.

Management of CMI

Treatment goals in the management of CMI include symptomatic relief, restoration of normal weight, and the prevention of bowel infarction. Mesenteric revascularization provides immediate symptom relief in most patients. Classically, open surgical revascularization options consider patient cardiopulmonary reserve to tolerate aortic cross-clamping and aortic and arterial calcific burden to dictate vascular sites for clamping and sewing. Elective revascularization in the lower-risk patient favors two-vessel (i.e., celiac and SMA) antegrade reconstruction when anatomically feasible. Contingent on vessel calcification, the supraceliac aorta through a transperitoneal approach serves as a preferential target for inflow. After entering the lesser sac, division of the left triangular ligament allows for retraction of the left hepatic lobe. With the esophagus retracted toward the patient's left (confirmed by palpation of the existing nasogastric tube), transection of

the diaphragmatic crura exposes the supraceliac aorta. The celiac trunk, common hepatic artery, and splenic artery are exposed at this time. Subsequently with retraction of the transverse mesocolon cephalad, the SMA is exposed as described above at the root of the mesentery. A retropancreatic tunnel is created that courses anterior to the renal vein. The patient is systemically anticoagulated with heparin and the proximal anastomosis can be constructed with partial aortic occlusion. Most often a knitted polyester synthetic graft is utilized for conduit. There are multiple acceptable variations that include the use of two separate aortomesenteric bypass grafts (**Fig. 89.10**) or the use of a bifurcated graft. It is conventional to utilize a prefabricated bifurcated graft (e.g., 14 × 7 mm) for reconstruction. In this case a short main body is beveled to create the proximal end-to-side aortic anastomosis; the left limb is tunneled through the retropancreatic tunnel and an end-to-side distal anastomosis created next to the SMA; the right limb is subsequently cut to size and beveled to create an end-to-end anastomosis to the celiac artery directly or an end-to-side anastomosis with the common hepatic artery. These authors favor the approach presented in Figure 89.11. A limb of a bifurcated knitted polyester graft is transected off the main body in such a way that there is a phalange created. This limb is specifically utilized for creation of the aorto-SMA bypass, with the phalange incorporated into the proximal aortic anastomosis as shown. The remaining limb is cut to size and beveled accordingly; the proximal anastomosis is constructed end-to-side off the aorto-SMA bypass graft and the distal anastomosis constructed end-to-side to the common hepatic artery. This facilitates a very short celiac limb with a natural lie that may reduce the risk of limb kinking or torsion. Finally, the descending thoracic aorta may serve as an alternative source for inflow when supraceliac aortic anatomy is prohibitive or has previously been utilized for revascularization (Fig. 89.12). For those patients with comorbidity or anatomy (i.e., calcification) that precludes aortic clamping, a retrograde ilio-SMA bypass is favored as described above (Fig. 89.9).

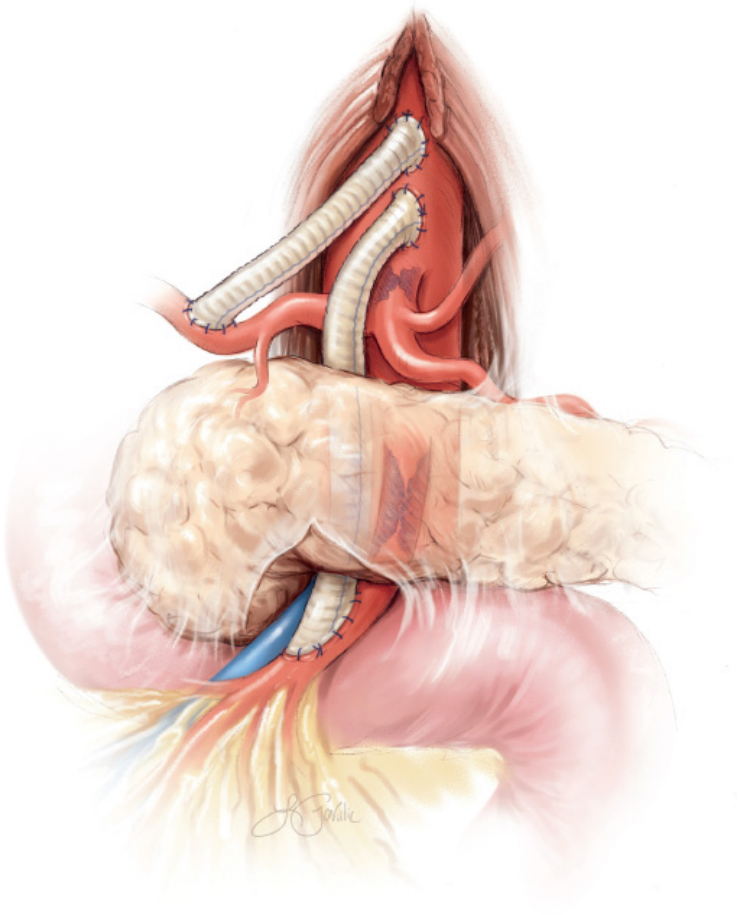

Figure 89.10 Two-vessel antegrade aortomesenteric bypass.

Transaortic endarterectomy is less often utilized in contemporary practice, but may be applicable for those patients with bowel perforation or contamination, hostile abdominal conditions (extensive adhesive disease or abdominal wall hernia), and bulky coral reef aortomesenteric plaque with lower-extremity ischemia. A retroperitoneal approach to the perivisceral aorta through a thoracoabdominal incision permits a longitudinal or trapdoor aortotomy, endarterectomy and repair with primary closure or patch aortoplasty as illustrated in Figure 89.13.

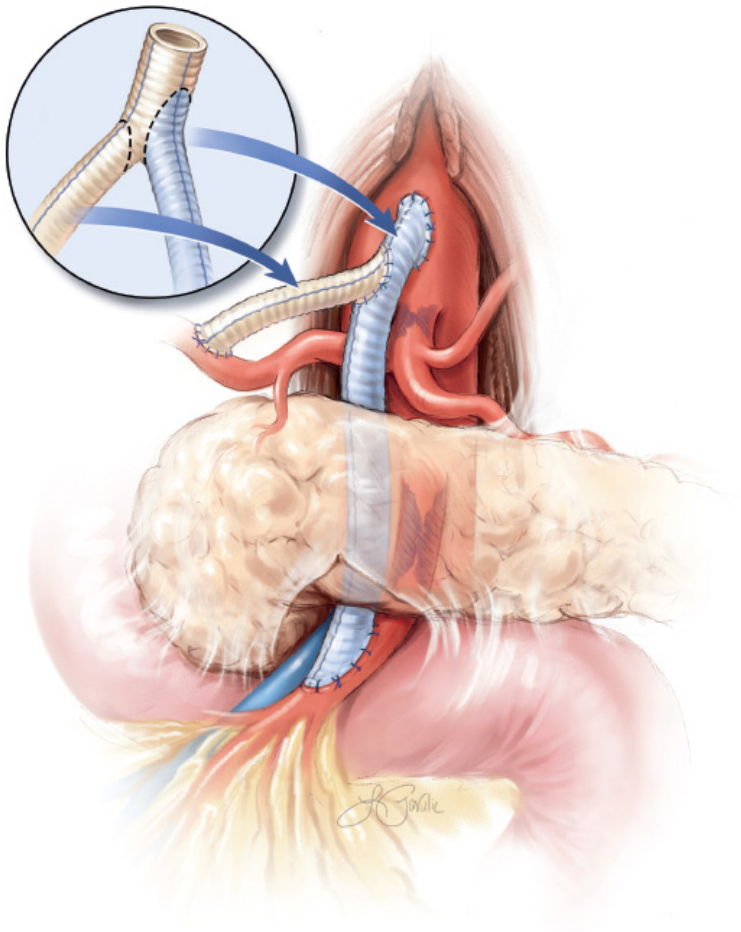

Figure 89.11 Two-vessel antegrade aortomesenteric bypass based off the supraceliac aorta using a presewn bifurcated graft.

While historically criticized for high mortality rates (up to 15%), contemporary outcomes following open mesenteric bypass at high-volume centers support mortality rates <4%, likely secondary to technical refinements, improved patient selection and advances in medical, anesthetic, and critical care management.[58–65] Open mesenteric revascularization boasts excellent symptom improvement (77% to 100%) with low recurrence rates at 3 to 5 years (0% to 32%) and perioperative morbidity rates approximating 35% to 40%.[65,66]

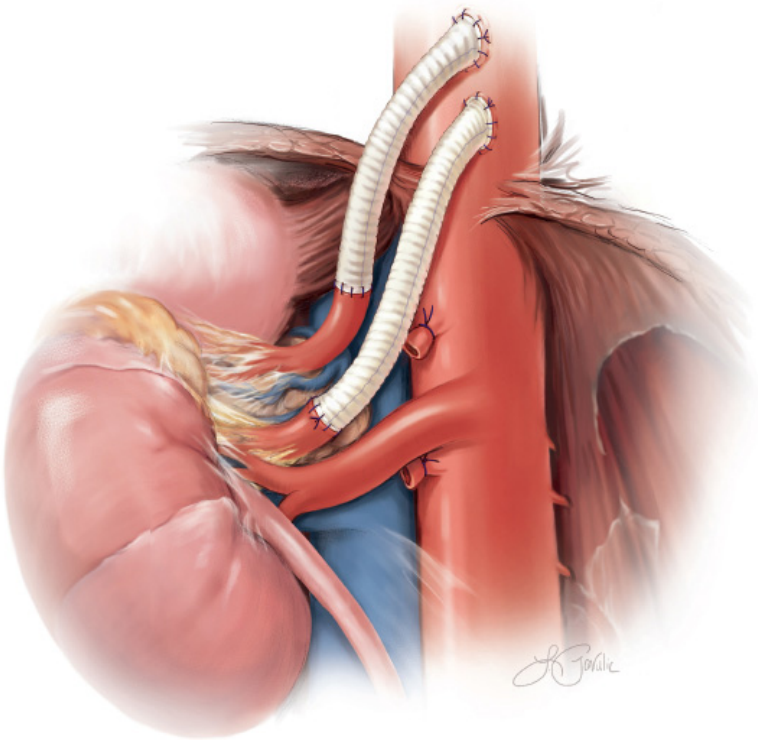

Figure 89.12 Two-vessel antegrade aortomesenteric bypass based off the supraceliac aorta using two separate grafts.

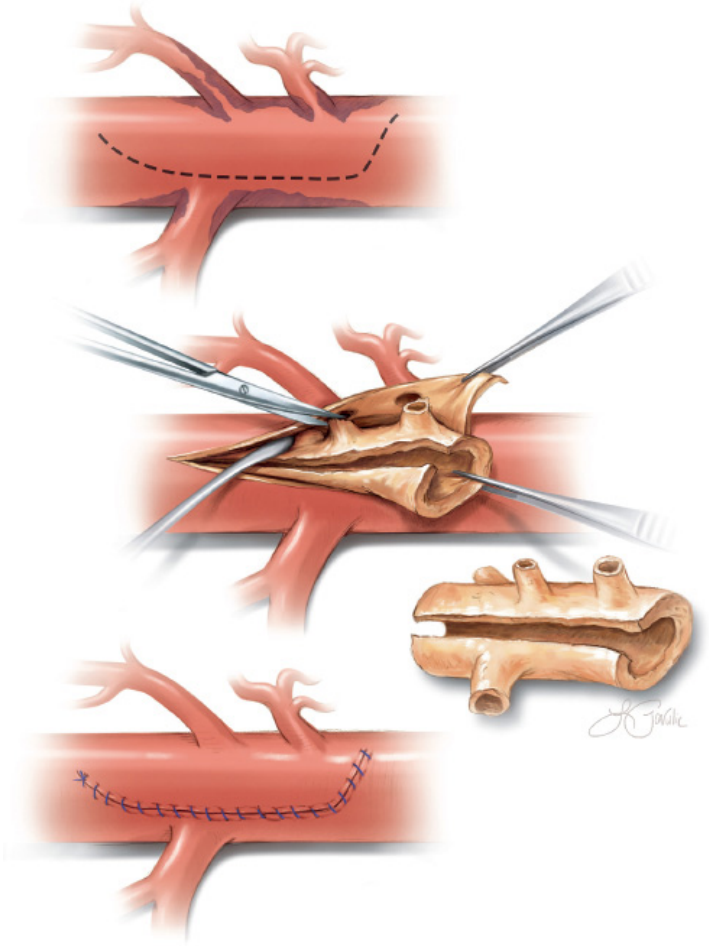

Figure 89.13 Endarterectomy of the aorta, celiac and superior mesenteric arteries through a longitudinal trapdoor aortotomy with primary closure.

Endovascular mesenteric revascularization has increasingly become utilized for chronic mesenteric ischemia. Stenting of the mesenteric vessels is recommended over angioplasty alone for favorable anatomy that excludes long-segment occlusion (i.e., >2 cm), small-diameter vessels, heavily calcified stenosis/occlusion and extrinsic compression (i.e., arcuate ligament compression of the celiac artery).[67–70] Endovascular revascularization offers success rates approaching 100% with immediate symptom relief. While perioperative morbidity is notably lower in comparison to open surgical revascularization, endovascular interventions are more likely to result in restenosis, recurrent symptoms (within 3 years), and require reintervention.[62,71–74] Primary and secondary patency rates approximate 40% and 88%, respectively at 5 years (in comparison to 88% and 97% following open revascularization) emphasizing the importance of patient counseling preoperatively and close surveillance postprocedure.[65] There is no significant difference in 3-year survival between open surgical and endovascular revascularization.[74] Two-vessel (celiac and SMA) stenting does not appear to reduce the risk of recurrent symptoms or reintervention when compared to single-vessel (SMA) stenting and moreover, isolated celiac artery stenting carries a higher risk of recurrence.[75] Covered stents may be associated with less restenosis, recurrence, and reintervention in comparison to bare metal stents.[76,77] Complications (average rates) may include symptomatic embolization (2.5%), thrombotic mesenteric arterial occlusion (1%), iatrogenic dissection (2%), stent dislodgement (2%) and access site–related complication (9%).[69]

A large review of mesenteric revascularization from the Nationwide Inpatient Sample between 1988 and 2006 demonstrated increased overall revascularization procedures for CMI.[78] Additionally, these authors

noted that mesenteric angioplasty and stenting not only surpassed open revascularization procedures for CMI in 2002, endovascular interventions more than doubled open procedures by 2005. An updated sampling of the same database between 2007 and 2014 supported decreased mortality, shorter hospital length of stay, reduced costs and decreased perioperative morbidity when compared to surgery.[79] These data are clouded by both the expansion of treatment indications and the fact that a greater risk of restenosis and recurrent symptoms may increase overall interventions. Moreover, these reinterventions for recurrence likely carry a variable risk for in-hospital morbidity and mortality. Regardless, mesenteric stenting has become the first-line therapy for most patients with atherosclerotic CMI and maintains an important role as a temporizing measure to facilitate weight gain in the high-risk malnourished patients (as a bridge to open revascularization) and for those patients with medical comorbidities that would further complicate or prohibit open surgical revascularization. Open mesenteric bypass surgery is recommended for low-risk patients with unfavorable mesenteric occlusive disease anatomy, failed prior endovascular revascularization, or multiple recurrences of in-stent stenosis/occlusion.

Median Arcuate Ligament Syndrome

Median arcuate ligament syndrome (MALS) remains a controversial diagnosis, first described in the 1960s.[80] Chronic abdominal pain is associated with radiographic evidence of celiac artery compression by the overlying fibrous arch of the median arcuate ligament (MAL) and adjacent celiac ganglion. The pathophysiology remains poorly understood and evidence suggests both ischemic and neurogenic etiologies for pain.[81] Gastric tonometry has documented evidence of mucosal ischemia in patients prior to treatment.[82] The 7% to 21% incidence of celiac artery compression in asymptomatic patients combined with the typical robust mesenteric collaterals and widely patent superior and inferior mesenteric arteries present in these younger individuals favor a neurogenic etiology.[83,84] Specifically, compression of the celiac plexus somatic nerves by the MAL may produce abdominal pain that is improved with a celiac ganglionectomy that accompanies ligament release or percutaneous celiac plexus block.

Patients with MALS are typically females in their third decade of life. Symptoms most commonly include postprandial pain, weight loss, and less commonly nausea and diarrhea. Diagnosis is supported by duplex ultrasonography that demonstrates elevated peak systolic velocities through the celiac artery on expiration that normalize or improve with inspiration and reverse flow through the hepatic artery.[85] Cross-sectional imaging like CTA and MRA can support the diagnosis as well, and may reveal poststenotic dilation of the celiac artery. Angiography demonstrating dynamic compression or occlusion during peak expiration remains the gold standard for the diagnosis of MALS (Fig. 89.14). Additionally, as MALS remains a diagnosis of exclusion, some authors favor gastric exercise tonometry test and celiac ganglion block to support patient selection.[86]

Release of the MAL should include complete dissection and skeletonization of both the MAL and surrounding nerve ganglion. This can be accomplished through an open approach whereby the aortic hiatus and celiac artery are exposed through the lesser sac. Additionally, laparoscopic and more recently robotic techniques have been described. The most contemporary literature review and large series suggest immediate postoperative symptoms relief in approximately 80% to 90% of patients.[81,82,87–92] Adjunctive procedures for celiac artery revascularization are utilized in a minority of cases and may include celiac angioplasty, celiac artery patch angioplasty, and celiac artery bypass (i.e., aortoceliac bypass). Late symptom recurrence approximates 6% and only Reilly and colleagues have demonstrated a reduction in recurrence following MAL release with celiac artery revascularization in comparison to MAL release alone (24% vs. 44%).[81,93] Multiple authors have highlighted the importance of patient selection for treatment suggesting that specific patient criteria may correlate with successful outcomes including: consistent postprandial abdominal pain, young age, female gender, weight loss >20 lb and anatomic features of poststenotic dilation or increased collateral flow.[93–95] Psychiatric diagnoses are common in adults with MALS, and may predict worse patient-reported quality of life outcomes following surgery.[96] A reasonable approach may reserve adjunctive revascularization for those patients with objective angiographic pressure

or ultrasound velocity gradients following open surgical MAL decompression or those with persistent symptoms following laparoscopic or robotic release.

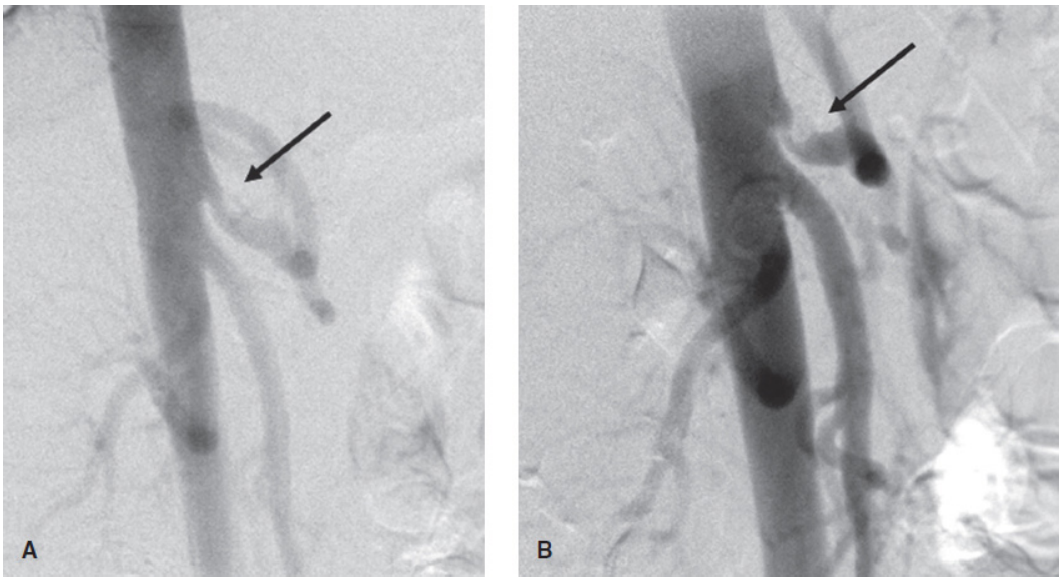

Figure 89.14 Lateral aortography demonstrating (**A**) external compression (*arrow*) of the celiac artery on peak inspiration that (**B**) worsens dynamically (*arrow*) during peak expiration.

Laparoscopic release of the MAL is increasingly employed for MALS.[81,87,91,92] While no procedure-related mortality has been reported for open or laparoscopic ligament release, there is a 9.1% incidence across series of open conversion for hemorrhage that follows laparoscopic release, which heightens morbidity and mortality risk.[81] Certainly independent operator learning curve, institutional technical enhancements, and patient selection may strongly affect this result. More recently, safe and effective robotic-assisted MAL release has been reported to offer benefits over laparoscopic release in light of improved visualization, extra degree of motion provided by robotic arms with "wrist movement" and scaled operator movements (including tremor elimination).[97] A contemporary study recently proposed a predictive model for MALS patients that uses preoperative data (age, baseline celiac artery expiratory velocity) to predict symptom improvement following release.[98] These same authors were the first to show a significant improvement in all eight AF-36 categories, and particularly bodily pain. While surgical intervention may treat this controversial but debilitating condition, long-term (>5 year) follow-up data remain lacking, as is a consensus as to the optimal surgical approach.[99]

Splanchnic Artery Aneurysms

Splanchnic artery aneurysms are historically cited as rare and mainly asymptomatic. In the past, most were syphilitic or mycotic, while contemporary visceral aneurysms are largely true aneurysms caused by atherosclerosis or medial degeneration.[100] True aneurysms are defined by the involvement of all three arterial wall layers (intima, media, and adventitia) while false aneurysms, or pseudoaneurysms, represent a collection of extravasating blood outside of the artery that remains confined next to the vessel by surrounding tissue. The incidence of splanchnic artery aneurysms is estimated at 0.1% to 2% and autopsy series suggest a prevalence that may approach 10%.[101,102] A minority of aneurysms present with life-threatening rupture and while historic-associated mortality rates approached 25% to 70%; more contemporary series suggest mortality rates of 15%, possibly reflecting improvements in perioperative management and the increasing use of endovascular techniques.[103] Most splanchnic aneurysms are asymptomatic however, and diagnosed as incidental findings by cross-sectional imaging.[104] False

aneurysms may carry a higher rate of rupture in comparison to true aneurysms (76% vs. 3% in once series).[105]

The natural history of these aneurysms remains elusive in light of their rarity and anecdotal, mainly institutional and retrospective, evidence to date. Indications for intervention remain conservative, especially as no significant difference has been identified between the diameters of ruptured and nonruptured aneurysms.[105] Additionally, aneurysm calcification and intraluminal thrombus are not associated with rupture risk. Historically, treatment had been recommended for symptoms and size >2 cm or aneurysm diameter three times greater than the respective normal artery, although contemporary guidelines support evidence-based guidelines for size threshold for repair by phenotype.[106] Patients with splanchnic aneurysms generally have 10-year survival rates >80% and open surgical treatment provides excellent, durable long-term results with low perioperative mortality and morbidity following elective surgery.[103,107,108] While surgical repair has remained the mainstay of treatment, minimally invasive endovascular techniques continue to evolve and are increasingly applied for both elective treatment and that of rupture. Endovascular intervention with local anesthesia offers excellent technical success, negligible morbidity and mortality in elective cases, and brief hospital stays.[103,105,108–112] Transcatheter embolization of visceral artery aneurysms offers additional advantages that include precise aneurysm localization, assessment of collateral flow, and negate the need for certain (i.e., intrahepatic) difficult arterial exposures.[100] Notably, embolization has become the standard of care for splanchnic artery pseudoaneurysm.[110,113] Additionally, endovascular therapy may offer decreased postoperative morbidity and mortality rates in cases of rupture when compared to open surgery (2.7% to 7% vs. 24% to 29%, respectively).[103,109]

6 Distribution of splanchnic artery aneurysms is as follows: Splenic artery (60%) > hepatic arteries (20%) > superior mesenteric artery (SMA) (5.5%) > celiac artery (4%) and gastric and gastroepiploic arteries (4%) > ileocolic arteries (3%) > pancreaticoduodenal arteries (2%) > GDA (1.5%) > IMA (<1%).[101,104] Most patients present in the sixth decade of life.[104,105] Symptomatic patients will present with abdominal pain and frank hemorrhagic shock with rupture. Rupture may be intra-abdominal, although erosion into a gastrointestinal lumen may result in sporadic gastrointestinal bleeding (i.e., herald bleed) and erosion into adjacent mesenteric veins results in arteriovenous fistulae. The asymptomatic patient inconsistently reveals a bruit on auscultation and rarely a palpable mass on examination. Each splanchnic aneurysm warrants individual consideration.

Splenic Artery Aneurysm

Splenic artery aneurysms account for 60% of all splanchnic artery aneurysms and are the third most common intra-abdominal arterial aneurysm. Their prevalence in the general population is very low approximating 0.16% to 0.8%.[114] These aneurysms occur two to four times more frequently in women than men and are associated with multiparity.[100,104,108,114,115] Hormonal and local hemodynamic events likely contribute to the evolution of splenic aneurysms. An etiologic classification system has previously been proposed by *Stanley and Fry* that implicates arterial dysplasia, portal hypertension, local inflammation, and hormonal and hemodynamic events in the pathogenesis of these aneurysms.[114] Hypertension is a common comorbidity affecting 50% to 60% of patients with splenic aneurysm, and up to 20% of patients will demonstrate concurrent aneurysms affecting alternate arterial beds.[112,113,116] Additional etiologic risk factors for true aneurysms may include dissection, septic emboli, polyarteritis nodosa, systemic lupus erythematosus, and connective tissue disorders like Ehlers–Danlos syndrome, while splenic pseudoaneurysms are typically attributed to chronic pancreatitis and trauma.[104] Splenic aneurysms most often arise at branch points off the mid- and distal main splenic artery. Tortuosity of the main splenic artery is common (Fig. 89.15). The majority (80%) of splenic aneurysms are solitary and saccular, although 90% of patients with portal hypertension will demonstrate multiple splenic aneurysms. Those aneurysms measuring >5 cm are often described as “giant lesions” and appear to be more common in older males.[117]

Splenic aneurysms typically rupture into the lesser sac with limited self-containment. Later hemorrhage into the peritoneal cavity results in cardiovascular collapse and the so-called “double rupture.” The

incidence of splenic aneurysm rupture approximates 2% to 5% and is not associated with calcification, blood pressure, or age.[101,104,113,114] Increased levels of aneurysmal peripheral calcification are associated with smaller aneurysm size at the time of diagnosis, but appear to have no impact on aneurysm growth.[113] Growth rates among surveyed aneurysms (out to 3.1 years) have been calculated as 0.2 mm/yr.[113] Rupture-associated mortality is dramatically increased in the peripartum patient (68% to 75% vs. 25%), and associated fetal mortality approaches 100%.[114,116,118] Rupture in this setting occurs most commonly during the last trimester.[100] While historically a strong association between pregnancy and splenic aneurysm rupture was reported, a contemporary series reporting on >67,000 consecutive live births over 5 years identified no cases of splenic artery aneurysm rupture.[116] There is no apparent role for routine screening for splenic aneurysm in the pregnant patient.[119] Rupture risk is increased twofold by liver transplantation, the mortality following which is 50%.[120,121]

Contemporary data have supported an indolent natural history of surveyed splenic aneurysms, of null to slow growth (0.02 to 0.06 cm/yr) without rupture or aneurysm-related complications.[113,122] As such, accepted indications for treatment include rupture, symptoms, asymptomatic aneurysms measuring 3.0 cm, and any size asymptomatic aneurysm at the time of liver transplantation or in women of childbearing age.[104,106,113,123,124] Historically, the open surgical treatment of splenic artery aneurysms included aneurysm resection or splenectomy. Recognizing the immunologic benefits of splenic preservation, arterial ligation, and aneurysm excision is preferred when possible; however, those patients with multiple and perihilar aneurysms may still require splenectomy. Laparoscopic and robotic techniques at ligation, aneurysm resection and splenectomy have become common-place offering negligible risk of open conversion, need for reoperation and mortality.[125–127] Splenic vaccinations and education regarding the need for booster vaccinations at regular 5-year intervals should be provided. Perioperative morbidity and mortality are estimated as 9% to 25% and 1% to 5%, respectively, across series.[113,114,128–130]

Endovascular therapy has been utilized with increasing frequency for both elective and ruptured cases boasting decreased early morbidity, mortality, and hospital length of stay. While only 2% of all splenic aneurysms were managed with endovascular therapies in 1999, this proportion increased to 70% between the years 2010 and 2013.[130] Embolization with coils, gelfoam, glue, thrombin, and vascular plugs has been advocated for saccular aneurysms with narrow necks (Fig. 89.16). Larger vessels with complex wide-neck aneurysms may be better approached with covered stents or stent-assisted coil embolization.[131] Technical success for endovascular treatment is 93% to 98%, limited primarily by vessel tortuosity that may be overcome with newer, steerable catheters.[113,130,132,133] Conversion to open surgery is rarely necessary (<2%) to accomplish successful aneurysm exclusion.[130] Postembolization syndrome (PES) complicates 10% to 30% of cases across series and may include left upper quadrant pain, fever, ileus, platelet dysfunction, leukocytosis, and pancreatitis following embolization with and without radiographic evidence of splenic infarction.[113,130,133,134] Up to 21% of patients will demonstrate major splenic infarct and may require reintervention for splenic abscess by way of percutaneous drainage or splenectomy.[113,132] Portal hypertension appears to increase dramatically the risk of major splenic infarction.[132] With late follow-up, endovascular repair is associated with an average regression in aneurysm size of 1.5 mm/yr.[113] Late complications may arise at an average rate of 3.7% per year, and there is a 3.2% rate of reintervention per year following endovascular repair.[130]

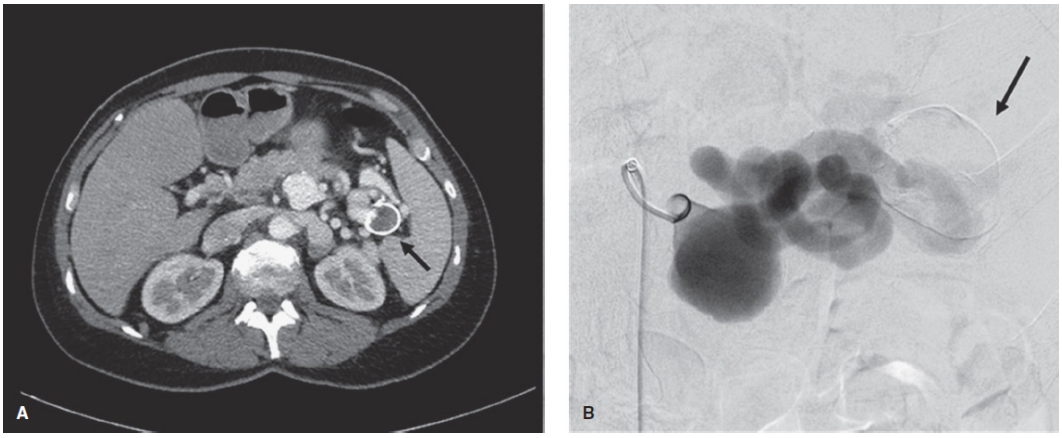

Figure 89.15 (**A**) CT angiogram and (**B**) splenic arteriogram revealing a tortuous splenic artery with two large aneurysms affecting the main splenic artery; the distal aneurysm (*arrow*) has extensive calcification and mural thrombus.

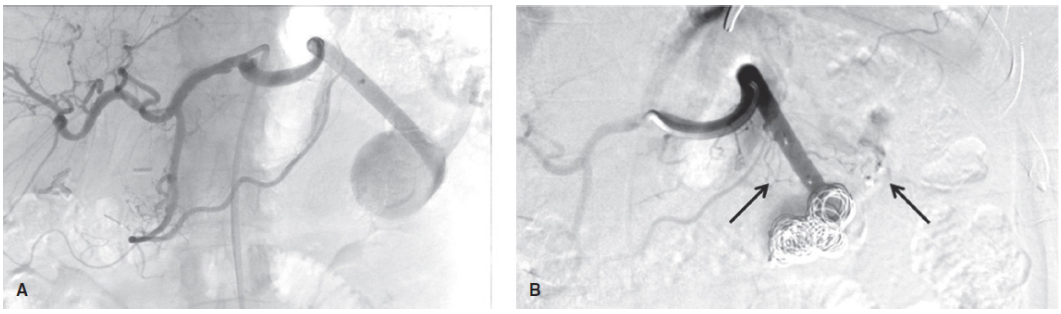

Figure 89.16 (**A**) Celiac arteriogram of a 78-year-old woman with a 4-cm splenic artery aneurysm; (**B**) Splenic arteriogram demonstrating a catheter in the proximal splenic artery. Vascular occlusion devices (*arrows*) have been positioned in the main splenic artery outflow (distal to the aneurysm) and inflow (proximal to the aneurysm) with multiple vascular coils embedded within the aneurysm sac.

Patients with splenic aneurysms have long-term survival rates that approach 90% at 10 years following aneurysm-directed treatments; cause of death is typically unrelated to aneurysm.[113] The most recent meta-analysis of splenic aneurysm therapies identifies significantly greater technical success balanced with greater 30-day mortality following open repair in comparison to significantly higher rates of acute minor complications, late complications, and reinterventions following endovascular repair.[130] Moreover, a recent decision analysis investigating the cost-effectiveness of open repair, conservative management, and endovascular repair for splenic aneurysm identified endovascular therapy as the most cost-effective treatment independent of gender and risk profile of the patient.[135]

Hepatic Artery Aneurysm

Hepatic artery aneurysms (Fig. 89.17) account for 20% of all splanchnic artery aneurysms, affecting men twice as often as women.[100,101,136] These aneurysms are mainly solitary and while small hepatic artery aneurysms (<2 cm) are typically fusiform, larger aneurysms will more often appear saccular.[136] The vast majority of these aneurysms are extrahepatic with the common hepatic artery and right hepatic artery most often affected; 20% to 30% of hepatic aneurysms however, are intrahepatic.[101,115,136] Hepatic artery pseudoaneurysms are increasingly frequent and account for approximately 50% of hepatic artery aneurysms.[104,115] Pseudoaneurysms may result from diagnostic and therapeutic interventions that require liver penetration (e.g., biliary stents), liver transplantation, and trauma; their incidence appears to be increasing secondary to the more frequent and regular use of CT imaging following blunt liver trauma and hepatobiliary intervention.[105,115] True aneurysms present most often during the sixth decade of life and proposed etiologic mechanisms include mainly atherosclerosis and acquired medial degeneration.

Polyarteritis nodosa, cystic medial necrosis, portal hypertension, infection, arterial fibrodysplasia, neurofibromatosis, and other arteriopathies are less commonly implicated.[104,136]

As with most splanchnic artery aneurysms, hepatic artery aneurysms rarely cause symptoms. Symptomatic patients will most commonly describe right upper quadrant or epigastric abdominal pain that may radiate to the back, while those patients with rapidly expanding aneurysms may describe abdominal complaints that mimic pancreatitis. Large aneurysms may erode into the stomach or duodenum resulting in gastrointestinal hemorrhage or they may obstruct the biliary tract resulting in biliary colic, hemobilia, and obstructive jaundice.[104] Additional physical examination findings like a palpable pulsatile mass and bruit are uncommon. Diagnosis is often made incidentally by cross-sectional CT/MRI, ultrasound or arteriography performed for a nonvascular indication.

Rupture appears to complicate a minority of hepatic artery aneurysms (20% to 30%) and results in an equal distribution of hemorrhage into the peritoneum and the biliary tract.[101,104] Rupture into the biliary tract results in hematobilia, hematemesis, and cholangitis; rarely is there melena and chronic anemia. Rupture-related mortality approximates 35% to 40%.[136] The relationship of rupture risk to aneurysm size remains unclear and a small series of 22 patients with a mean hepatic artery diameter of 2.3 cm (range 1.5 to 5 cm) were followed for a mean of 68.4 months without complication.[104,136] The presence of multiple aneurysms and nonatherosclerotic etiology are proposed risk factors for rupture.[136] While historically treatment was recommended for all asymptomatic aneurysms >2 cm in size, some authors have proposed elective intervention for all and any-size nonatherosclerotic aneurysms and for those patients with multiple hepatic artery aneurysms while reserving a more conservative approach for those atherosclerotic hepatic artery aneurysms measuring 2 to 5 cm in size.[136] Contemporary guidelines support elective repair in asymptomatic at a size threshold of >2 cm in patients without significant comorbidity at a size >2 cm (Grade 1A), or if the aneurysm enlarges >0.5 cm/yr (Grade 1C), at a size threshold of >5 cm in patients with significant comorbidity (Grade 1B), and at any size in those patient with vasculopathy or vasculitis (Grade 1C).[106]

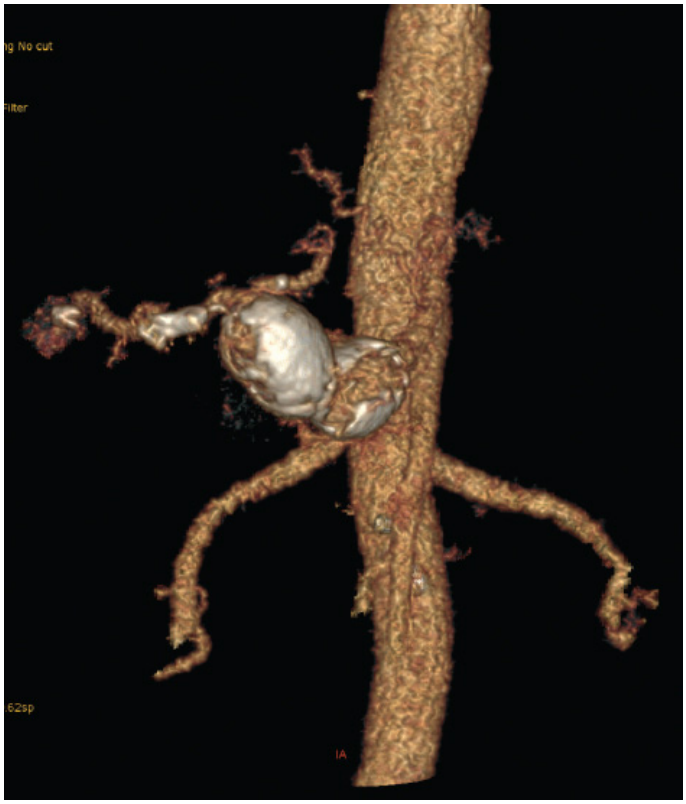

Figure 89.17 Reformatted CT angiogram demonstrating a bilobed and calcified hepatic artery aneurysm.

Open reconstruction has been favored for aneurysms of the extrahepatic artery by way of aneurysmectomy or exclusion, although current guidelines support an endovascular-first approach to all hepatic artery aneurysms (Grade 1A).[106] Often revascularization is not required in light of extensive foregut collaterals from the GDA and right gastric artery that preserve hepatic perfusion. When necessary, options for reconstruction may include primary or patch angioplastic closure of the common hepatic artery, aortorenal bypass, and splenohepatic bypass. Proper hepatic artery aneurysms may be treated by aneurysmectomy requiring reconstruction using a saphenous vein interposition graft or simple aneurysmorrhaphy. Distal or intraparenchymal lesions may require resection of the involved liver parenchyma, and lobectomy is advised for patients with large intrahepatic aneurysms to avoid significant liver necrosis.[106,107] Elective open surgical repair is associated with approximately 30% morbidity and negligible mortality.[108,110,136] Additional options include transcatheter embolization, which may be an especially useful adjunct for intrahepatic arterial aneurysms obviating the need for hepatic lobectomy, and stent graft exclusion for high-risk patients.[100,104,108,110,112,137] Technical and clinical success rates with transcatheter embolization approach 100% and 79%, respectively and offers efficient control of hemorrhage, shorter hospital length of stay and lower transfusion requirements in cases of rupture specifically.[138] Transient success and recanalization is well described however, mandating thoughtful postembolization surveillance.

Superior Mesenteric Artery Aneurysm

Superior artery aneurysms account for up to 7% to 14% of all splanchnic aneurysms, depending on the series.[101,103,105,108,109] These aneurysms affect men more frequently than women in their sixth decade of life and are mainly solitary.[101,139,140] SMA aneurysms may result from infection (i.e., nonhemolytic streptococci in bacterial endocarditis), dissection (Fig. 89.18), medial degeneration, atherosclerosis, FMD, vasculitis, connective tissue disorder, and trauma.[101,105] Additionally, false aneurysms may occur in the setting of pancreatitis and complicated peptic ulcer disease.[139] Concomitant hypertension is common, affecting >20% of patients with SMA aneurysm, as are associated aortic and peripheral/splanchnic aneurysms.[108,112,140,141]

In contrast to other splanchnic aneurysms up to 70% to 90% of SMA aneurysms may present with symptoms at diagnosis. While most patients with SMA aneurysm are asymptomatic, abdominal pain is the most common symptom followed by nausea, emesis, GI bleeding, and fever in cases of mycotic aneurysm.[139–141] Clinical examination may reveal a pulsatile mass in up to one-third of patients. Diagnosis is most commonly established by CT imaging, although these aneurysms can be appreciated by ultrasound, MRI, and angiography. Complications may include AMI resulting from thromboembolism and rupture. The natural history of SMA aneurysms appears to be that of expansion and rupture with 38% to 50% presenting with rupture.[105,139] Rupture risk has historically been considered rare and while rupture-associated mortality has historically approached 50%, more contemporary series cite 30-day mortality rates as low as 12.5% to 38%.[101,109,140] No comorbidities or aneurysm characteristics have been found to predict rupture risk.[140] Contemporary guidelines support repair of all SMA aneurysms at diagnosis, regardless of size (Grade 1A).[106]

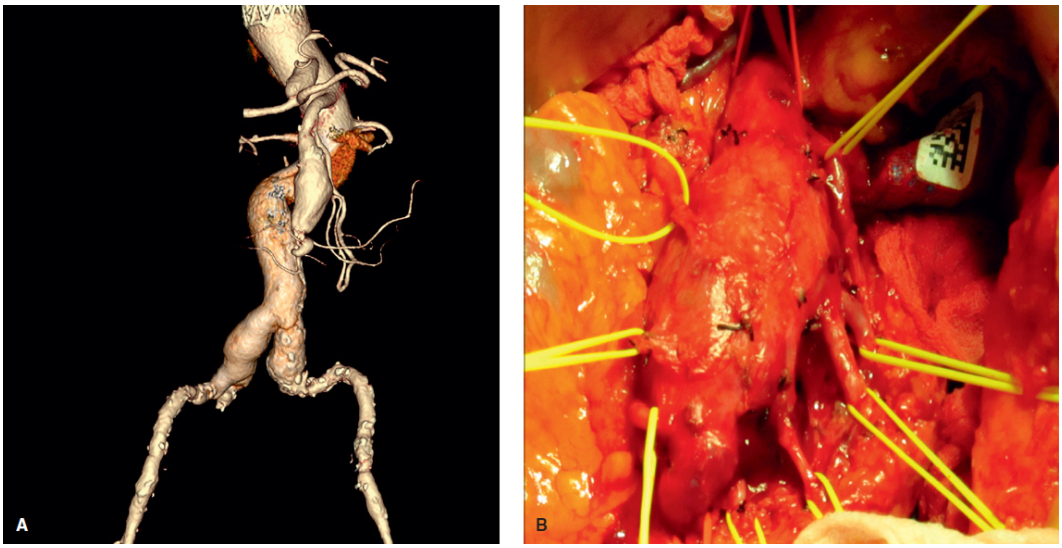

Figure 89.18 (**A**) CT angiogram and (**B**) intraoperative photo of a large 3.6-cm asymptomatic SMA aneurysm associated with extensive thoracoabdominal aortic and SMA dissection. The aneurysm was repaired by way of an SMA interposition bypass graft using nonreversed great saphenous vein; additionally the proximal SMA dissection flap was sharply fenestrated.

Surgical management of SMA aneurysm most often requires aneurysm excision (or exclusion) with revascularization, most often by way of aortomesenteric bypass.[108] Both autologous and prosthetic conduits have been described. Autologous conduit is favored in cases of mycotic aneurysm and frank contamination complicating intestinal ischemia while reinforced prosthetic conduit resists compression/kinking and future dilation.[112] Aneurysmorrhaphy and simple ligation of inflow and outflow vessels (in those patients with appropriate collateralization) have also been described with success.[101,112,139] Contemporary elective surgical results boast negligible morbidity and mortality.[112] Endovascular SMA aneurysm exclusion with a stent graft and embolization have been described and increasingly employed for patients with severe cardiopulmonary disease; these therapies remain limited by thromboembolic risks to the collateral circulation, endoleak, and limited long-term follow-up.[108,140–144] Aneurysms with a small neck distal to the SMA origin may be conducive to transcatheter embolization provided angiographic determination of collateral flow is determined as adequate.[140]

Celiac Artery Aneurysm

Celiac artery aneurysms account for approximately 4% of all splanchnic aneurysms affecting men more frequently than women in their sixth decade of life.[145,146] The incidence in the general population is unknown. Historically celiac artery aneurysms were primarily associated with infection like syphilis or tuberculosis and primarily diagnosed postmortem.[145] Contemporary etiologic risk factors include primarily atherosclerosis, developmental risk factors such as common celiacomesenteric trunk, arterial dysplasia with medial degeneration, collagen vascular disorder, trauma, and dissection.[145,146] Concomitant hypertension (20%), aortic aneurysm (18% to 40%), and alternate splanchnic aneurysms (38%) are common in patients with celiac artery aneurysm.[145,146]

As with most splanchnic artery aneurysms, celiac artery aneurysms rarely cause symptoms.[146] Symptoms may include abdominal pain, primarily epigastric in location with radiation to the back.[145] Less common associated symptoms may include nausea, emesis, dysphagia, anorexia, weight loss, and GI bleeding. Abdominal mass and bruit may be appreciated on physical examination. Diagnosis is most commonly established by CT imaging, although these aneurysms can be appreciated by ultrasound, MRI, and angiography.[146] Historically, rupture complicated approximately 70% of celiac artery aneurysms, resulting in near-certain mortality.[145] More contemporary estimates suggest rupture rates of 13% with associated 50% mortality.[145] Hypertension, aneurysm calcification, presence of thrombus, gender, and aneurysm

etiology do not appear to influence risk of rupture, which has been described in aneurysms ranging in size from 2 to 6 cm.[145,146]

Treatment should be individualized for cases of rupture and elective cases for patient symptoms and aneurysm size >2 cm. Aneurysm ligation and resection, without reconstruction, has previously been endorsed for those patients with adequate foregut collateral circulation. Simple ligation and transcatheter embolization may be considered as lifesaving in cases of rupture, but both offer substantial risk of perioperative hepatic and intestinal ischemia, necrosis, and patient mortality.[145–147] Aneurysmectomy with arterial reconstruction remains the preferred treatment of celiac artery aneurysms. Surgical revascularization may be accomplished by primary arterial–arterial anastomosis following aneurysm resection, direct aortic reimplantation of the celiac artery or its branches, or aortoceliac bypass. Prosthetic conduit may offer superior patency rates in comparison to autogenous reversed saphenous vein, which tends to kink.[146] Elective surgical repair offers patients symptomatic relief with a 0% to 5% risk of perioperative mortality.[146,147] Endovascular options for aneurysm treatment are increasingly described including celiac artery stent grafting.[148]

Gastric and Gastroepiploic Artery Aneurysm

Gastric and gastroepiploic artery aneurysms account for approximately 4% to 5% of all splanchnic aneurysms affecting men three times more frequently than women (Fig. 89.19).[101] Etiologic risk factors include primarily arterial dysplasia with segmental arterial mediolysis and periarterial inflammation like pancreatitis and vasculitis; atherosclerosis when present is felt to be a secondary process.[100,101,149] Gastric artery aneurysms are 10 times more common than gastroepiploic artery aneurysms. While patients may present with abdominal pain, up to 90% of patients have historically presented acutely ruptured with evidence of GI bleeding more common than intraperitoneal rupture.[100,101]

Treatment is recommended for all gastric and gastroepiploic arterial aneurysms, regardless the size. Arteriogram is invaluable for aneurysm identification preoperatively and operative planning. Surgical management has historically relied on simple arterial ligation or excision without reconstruction while intramural aneurysms required a wedge excision of involved gastric wall.[101,107] Contemporary literature would suggest that catheter-based embolization of these arteries is the new standard for care with multiple case reports and small series documenting successful aneurysm occlusion with coils and thrombin injection.[103,150,151]

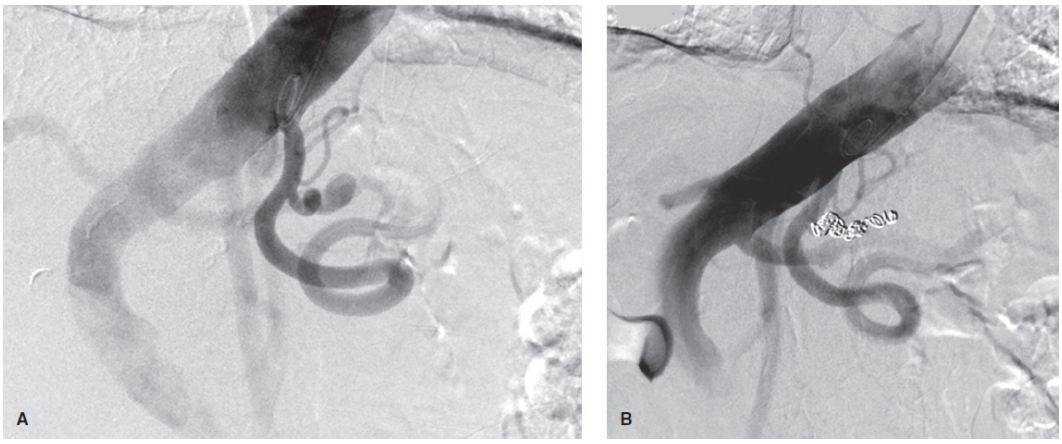

Figure 89.19 **A:** Diagnostic aortogram of an 82-year-old woman with a highly tortuous abdominal aorta, aberrant hepatic arterial anatomy, and two sequential gastric artery aneurysms measuring 10 mm in maximum diameter. **B:** Completion arteriogram following endovascular embolization.

Jejunal, Ileal, and Colic Artery Aneurysm

Aneurysms of the jejunal, ileal, and colic arteries account for <3% of all splanchnic aneurysms, affecting men and women equally beyond the sixth decade of life.[101] These aneurysms are associated with medial

degeneration, infection, connective tissue disorder, and polyarteritis nodosa with multiple aneurysms identified in approximately 10% of cases.[101,149,152] Atherosclerosis, when present, is felt to be a secondary process. While patients may present with abdominal pain, most have no symptoms. Rupture may complicate up to 30% of cases resulting in gastrointestinal bleeding and mortality rates that approach 20%.

Treatment is recommended for all mesenteric branch aneurysms, regardless of the size. Arteriogram is invaluable for aneurysm identification preoperatively and operative planning. Surgical management has historically relied on simple arterial ligation or excision without reconstruction.[101] Intramural aneurysms and those associated with bowel necrosis required resection of the involved intestine at the time of aneurysm exclusion. Transcatheter embolization has been increasingly utilized, and supported by contemporary guidelines, especially for cases of acute rupture and GI bleeding with intestinal necrosis, perforation, and late stricture potential complications.[153–155] Medical management is recommended for nonruptured asymptomatic ileal, jejunal and colic artery aneurysms associated with polyarteritis nodosa.[106]

Gastroduodenal and Pancreaticoduodenal Artery Aneurysm

Gastroduodenal and pancreaticoduodenal artery aneurysms account for <2% of all splanchnic aneurysm.[101] Men are affected four times more often than women during the sixth decade of life.[101] Periarterial inflammation resulting from pancreatitis with vascular necrosis or vessel erosion by pseudocyst reflects the most common etiology, while additional causes include arteriosclerosis, congenital medial degeneration, and trauma.[101] Concomitant celiac artery stenosis and occlusion are common in noninflammatory aneurysms and GDA and pancreaticoduodenal aneurysms are suggested to represent the effect of inordinately high-volume blood flow on branchings of the collateral circulation (Fig. 89.20).[156–158] Symptoms of abdominal pain are common; additional symptoms may include gastric outlet obstruction and compressive symptoms like nausea and emesis.[139,159] Rupture is also common, complicating up to 75% of inflammatory and 50% of noninflammatory aneurysms resulting most often in gastrointestinal bleeding and less commonly bleeding into the biliary or pancreatic ductal systems, peritoneum or retroperitoneum.[158] Rupture-associated mortality approximates 20% to 50%.[158,160] While it remains unclear if aneurysm size is a risk factor for rupture, rupture has been described at a small median size of 12 mm.[109,157,161]

Open surgical repair remains appropriate for most patients. These aneurysms are most often amenable to simple ligation, aneurysm resection, or aneurysmorrhaphy without revascularization.[103,108,112,139,158,162,163] Celiac artery revascularization should be considered in select noninflammatory cases. Pancreatitis-associated inflammatory aneurysms may require arterial branch ligation from within the aneurysm sac or pancreatic resection in severe cases. Transcatheter embolization with coils, glue, thrombin, and electrocoagulation has been successfully reported, especially for high-risk patients and those presenting with rupture.[108,137,158,160,164,165]

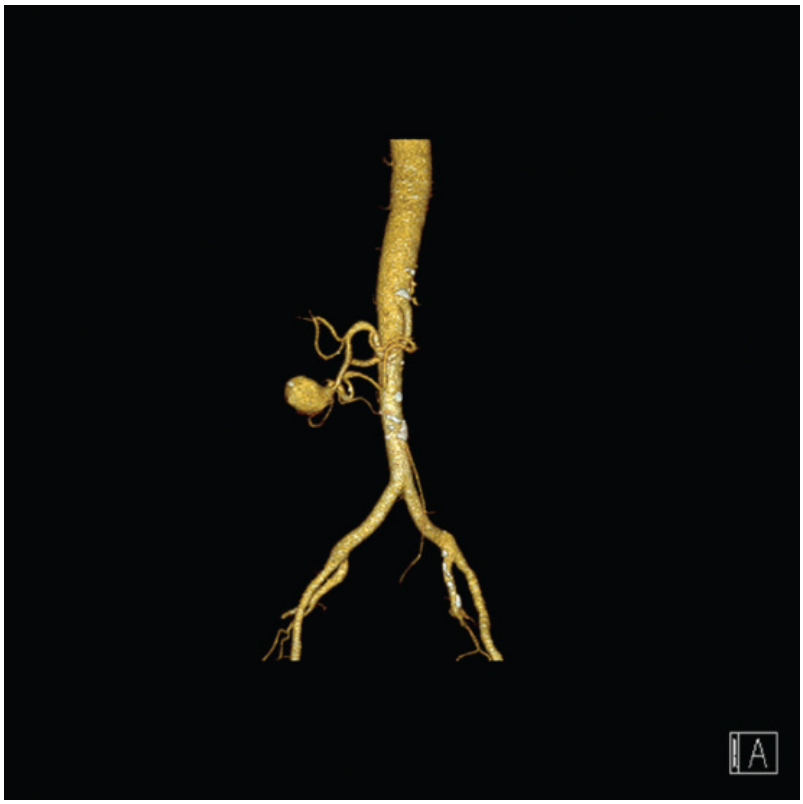

Figure 89.20 CT angiogram of an 87-year-old woman with a large 3.4-cm gastroduodenal artery aneurysm associated with celiac artery occlusion.

Inferior Mesenteric Artery Aneurysm

IMA aneurysms account for <1% of all splanchnic aneurysms. Our understanding of these aneurysms is limited to case reports. Men appear to be most commonly affected.[139] Atherosclerosis is the most common etiologic factor with additional risk factors including infection, polyarteritis nodosa, inflammatory arteritides, segmental arterial mediolysis, Behçet disease, and neurofibromatosis.[166] Concomitant celiac and SMA occlusion is common; it has been hypothesized that turbulent blood flow through tortuous marginal arteries originating from the IMA results in a high-flow state, or "jet disorder phenomenon," and subsequent dilation of the IMA and small collaterals which can lead to weakness of the arterial wall and aneurysmal disease.[166–169] Patients rarely have symptoms. Incidence of rupture approximates 20% with rupture-related mortality approaching 40%.[166]

Surgical management in cases of chronic celiac and SMA occlusion requires revascularization of at least one vessel (most commonly the SMA) to minimize intestinal ischemia during IMA aneurysm exclusion and theoretically decrease the risk of recurrent IMA aneurysm postoperatively. IMA aneurysm ligation and/or excision may be sufficient for treatment in certain cases of robust collateral intestinal circulation; in contrast certain cases will dictate IMA revascularization.[169] The role for endovascular therapy remains poorly defined.

RENAL ARTERY OCCLUSIVE AND ANEURYSMAL DISEASE

Introduction

Renovascular hypertension (RVH) is a well-defined form of secondary hypertension (HTN) that results from renal arterial insufficiency at some level. The pathophysiology of such ischemia is broad, and with both an increasing prevalence of atherosclerotic renal artery occlusive disease and ongoing clinical trials, treatment standards remain in flux.

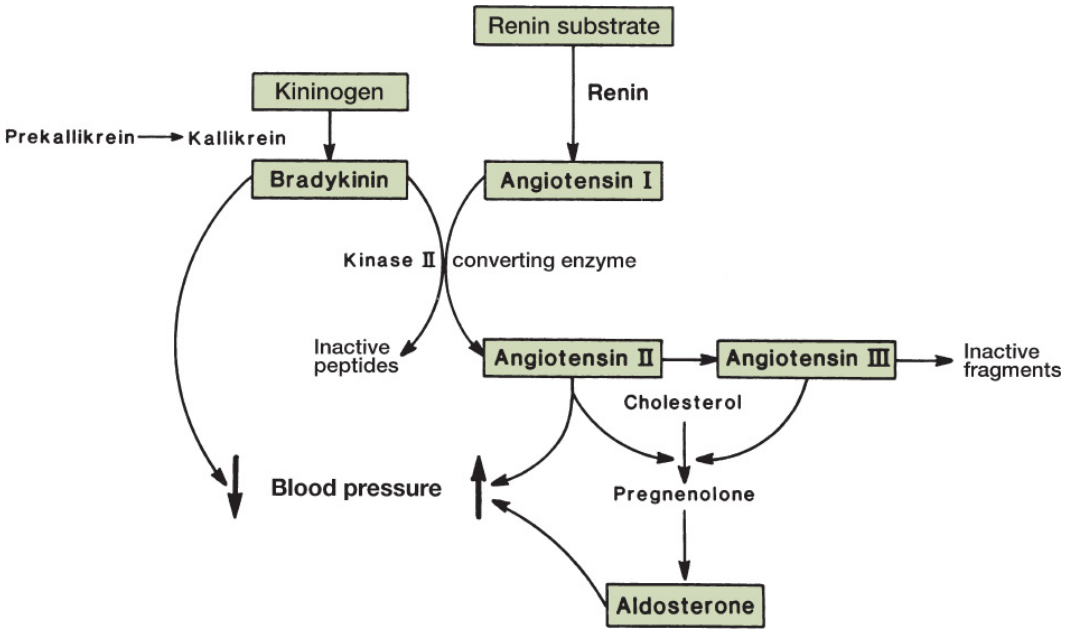

Figure 89.21 Renin–angiotensin system interrelation with aldosterone and bradykinin in blood pressure regulation. (Adapted from Stanley JC, Graham LM, Whitehouse WM Jr. Renovascular hypertension. In: Miller TA, Rowland BJ, eds. *Physiologic Basis of Modern Surgical Care*. St. Louis, MO: CV Mosby; 1988:734.)

Pathophysiology of Renovascular Hypertension

Renal artery stenosis resulting in a decrease in mean renal artery perfusion pressure by 10% to 15% stimulates renin release from the kidney. Renin is a proteolytic enzyme produced by the juxtaglomerular apparatus of the kidney that cleaves angiotensinogen to form angiotensin I. Angiotensin I is further processed to angiotensin II by angiotensin-converting enzyme (ACE), which is produced in the lung endothelium and vasculature (Fig. 89.21). Angiotensin II stimulates hepatic production of renin, while providing a continuous negative feedback on the renal release of renin.[170] Angiotensin II is a potent vasopressor that increases arterial blood pressure by a variety of mechanisms (Fig. 89.22). Glomerular filtration rate (GFR) is increased via vasoconstriction of the efferent arteriole. Additionally, antidiuretic hormone (ADH) is released from the posterior pituitary gland, causing water conservation. Release of aldosterone from the adrenal glands enhances exchange of sodium in the nephron-promoting volume retention. Finally, angiotensin increases sympathetic tone. All of these mechanisms coalesce to increase arterial pressure by way of arteriolar constriction, enhanced cardiac output, and the retention of sodium and water. Renin has a half-life of 20 to 30 minutes and is primarily cleared by the liver.[171] Normal physiology and sodium balance support a “steady state” of renin activity that is approximately 50% greater in the bilateral renal veins than that in the infrarenal inferior vena cava or peripheral circulation. In cases of unilateral renal artery stenosis, HTN is characterized by renin hypersecretion from the affected kidney and suppression of renin production in the contralateral kidney.[172,173] Additionally, angiotensin-mediated vasoconstriction causes pressure diuresis of the unaffected kidney. In cases of chronic bilateral or unilateral RVH in those patients with solitary kidney, sodium retention accounts for late reductions in renin secretion.

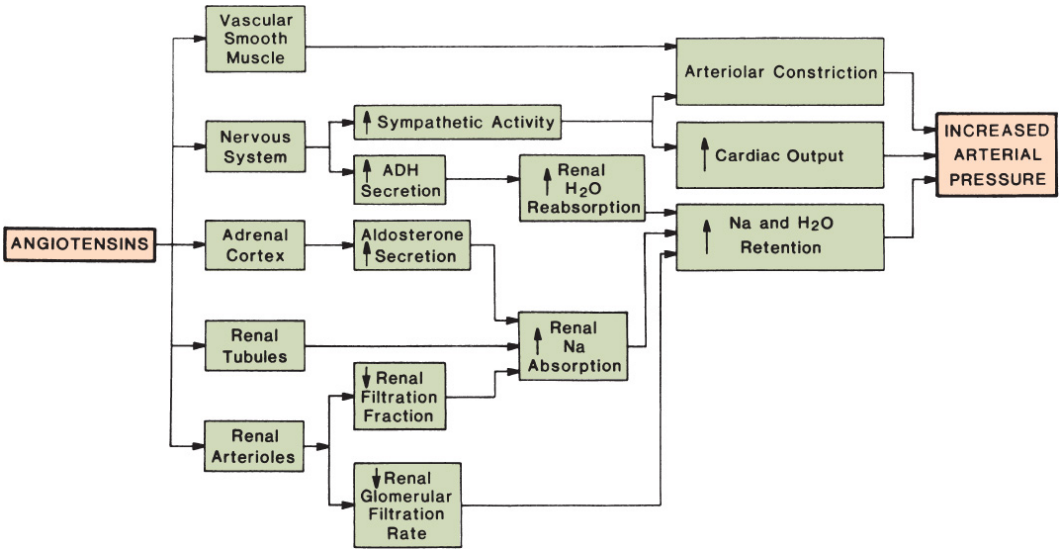

Figure 89.22 Effects of angiotensins contributing to increased arterial pressure. (Adapted from Stanley JC, Graham LM. Renovascular hypertension. In: Miller TA, ed. *Physiologic Basis of Modern Surgical Care*. 2nd ed. St. Louis, MO: Quality Medical Publishing; 1998:918.)

Renal Artery Occlusive Disease

7 Renal artery occlusive disease is the most common cause of correctable HTN in adults and the third most common cause of HTN in children and should be considered in the clinical context of: (1) childhood HTN, (2) severe HTN in women <45 years of age, (3) acute and rapid escalation of mild HTN in older patients (>50 years), (4) initial diastolic BP >115 mm Hg, and (5) rapid deterioration in renal function following the administration of antihypertensive therapy (especially with ACE inhibition). Renovascular HTN can be notoriously resistant to traditional medical management. Clinical examination may reveal an upper abdominal bruit during systole and diastole.

Diagnostic work-up should begin with serologies to assess renal function (BUN, creatinine) and electrolyte levels. Additional blood hormone levels may help differentiate the diagnosis as high plasma renin activity supports RVH while altered aldosterone, thyroid, and catecholamine levels may indicate endocrine dysfunction. Urinalysis may reveal hematuria or azotemia concerning for intrinsic renal disease. Ultrasonography is the first-line imaging modality for screening patients with RVH. While a high-quality duplex ultrasound examination in an experienced center is extremely accurate for the diagnosis of main renal artery and ostial stenosis or occlusion, sensitivity is compromised when surveying branch or parenchymal renal arteries and technically challenging in obese patients or in the presence of abdominal gas.[174] An elevated peak systolic velocity (>180 or >200 cm/s) or elevated renal aortic ratio >3.5 (calculated by dividing the peak systolic velocity of the renal artery by the peak systolic velocity of the adjacent aorta) detects renal artery stenosis with sensitivity and specificity of 84% and 97%, respectively.[175] Ultrasonography additionally facilitates a determination of renal length and symmetry, the presence of main renal artery aneurysm (RAA), visualization of adjacent structures (i.e., obstruction, masses, aortic aneurysm), and the assessment of intrinsic vessel renovascular disease by way of the resistive index.

Axial imaging with CTA and MRA are both useful adjunctive imaging modalities that better evaluate stenosis, aneurysms, renal infarcts, dissections, and adjacent structures. These imaging modalities have collectively received a class I indication (level B evidence) as screening tests to establish the diagnosis of renal artery stenosis from the American College of Cardiology (ACC) and American Heart Association (AHA).[176] CTA offers excellent spatial resolution and generated three-dimensional multiplanar images which can be very helpful in treatment planning. CTA, however, is limited by the risk of contrast-induced

nephropathy and in detecting subtle FMD lesions and branch vessel involvement. Multidetector CTA offers sensitivity and specificity ranging from 86% to 93% and 90% to 100%, respectively.[177] MRA is often favored in younger patients as it offers diagnostic sensitivity and specificity of 97% and 93% without the associated risks of irradiation.[178] Gadolinium is less nephrotoxic than iodinated contrast and while it may be advantageous for those patients with mild renal insufficiency, the risk of nephrogenic systemic fibrosis prohibits the use of gadolinium contrast in those patients with a GFR ≤30 mL/min/1.73 m^2. MRA offers the additional benefit of estimating renal perfusion and GFR via calculations of gadolinium clearance.

Catheter-based arteriography remains the gold standard imaging modality for the diagnosis of renal artery stenosis given its unmatched spatial resolution and capacity to detect reliably branch vessel and parenchymal involvement. Additionally, pressure gradients can be measured across a stenosis (a systolic pressure gradient <10 mm Hg is considered normal); intravascular ultrasound may be used to further characterize the renal artery; and any clinically indicated therapeutic interventions can be performed in the same clinical setting.

In cases of complex and equivocal disease, renal vein renin assessments may be used to calculate the renal vein ratio. This ratio reflects a renin comparison between peripheral and renal venous blood. With unilateral renal artery stenosis, the renal vein renin ratio (RVRR) is calculated by dividing the renin activity in venous blood from the affected kidney by that from the (normal) contralateral kidney. A ratio >1.48 supports a functionally relevant renal artery stenosis.[172,173] In patients with bilateral renal artery stenosis, a renal:systemic renin index (RSRI) is calculated by subtracting systemic renin activity from individual renal vein renin activity and dividing the remainder by systemic renin activity; this index reflects individual kidney renin release.[172] As aforementioned, there is a steady state of normal renal renin release; normal renal vein renin activity from each kidney is approximately 24% higher than systemic activity (with the total of both kidneys being then 48% higher than systemic activity). Documentation of renin hypersecretion (RSRI >0.48) associated with contralateral kidney renin suppression (RSRI 0 to 0.24) provides a method to differentiate those patients that will be cured or improved of RVH following renal revascularization or nephrectomy.[172,179]

Captopril scintigraphy (also known as isotopic or captopril renography) and hypertensive urography have fallen out of favor and are no longer recommended as diagnostic studies for the diagnosis of renal artery stenosis.

Arteriosclerosis

Arteriosclerosis is the most frequent cause of RVH affecting men twice as often as women, most commonly in the sixth decade of life.[180] Ostial stenosis is most common representing “spillover” of diffuse aortic atherosclerosis, which is present in approximately 80% of patients. Arteriosclerotic renal artery stenosis affects primarily the proximal third of the vessel, with more severe distal extrarenal disease limited mainly to black patients.[181] A contemporary prospective, multicenter, population-based study of cardiovascular health has estimated the incidence of renovascular disease in men and women aged >65 years as 6% to 7%.[180,182] Although early angiographic- and image-based studies in selected patients with arteriosclerotic RVH have suggested radiographic progression in approximately a third of renal artery lesions with 10% progressing to occlusion, this longitudinal cohort study reported anatomic progression to hemodynamically significant disease in only 4% of participants with an annualized progression rate of 0.5% per year and no disease progression to arterial occlusion. Importantly, renovascular disease has consistently been associated with cardiovascular disease across coronary, cerebrovascular, mesenteric, and peripheral vascular beds with a significant and independent relationship noted with prevalent coronary manifestations.[183–187]

Fibromuscular Dysplasia

FMD is thought to account for approximately 5% to 10% of RVH.[188,189] FMD is a nonatherosclerotic, noninflammatory vascular disease that may result in arterial stenosis, occlusion, aneurysm or dissection that affects primarily younger women.[190] The prevalence of FMD in the general population is unknown, although renal involvement is the most common phenotype comprising 58% to 75% of all FMD cases.[191,192] FMD

until recently has been described by histopathologic classification.[193,194] By this classification *medial fibroplasia* is the most common variant accounting for 60% to 90% of FMD cases. Deposition in the media of loose collagen in zones of degenerating elastic fibrils results in the generation of fibromuscular ridges with resultant arterial stenoses alternating with areas of smooth muscle loss with consequent arterial dilation producing a classic "string of beads" appearance angiographically (Fig. 89.23).[191] The distal two-thirds of the main renal artery and its branches are most commonly affected and bilateral disease is common. *Intimal fibroplasia* accounts for approximately 2% to 5% of all dysplastic renal artery stenoses and presents as a smooth, focal stenosis of the distal main renal artery. This histologic variant is notable for the accumulation of fibrous tissue within the intima with a moderately cellular component with mainly intact or partially fragmented elastic lamina (Fig. 89.24). *Perimedial fibroplasia* and *medial hyperplasia* are uncommon variants.

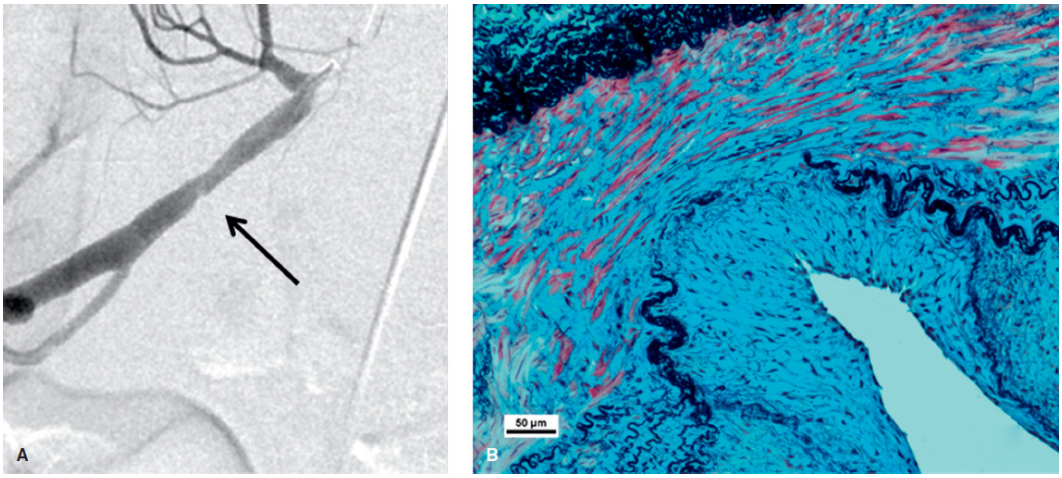

Figure 89.23 **A:** Right renal arteriogram demonstrating a radiographically subtle focal midartery stenosis (*arrow*); manometry across this lesion revealed a significant pressure gradient. **B:** Intimal fibroplasia as represented by pronounced intimal proliferation and partial fragmentation of the elastic lamina (*Movat stain, 20×*).

Medical Management of Renovascular Hypertension

8 Medical therapy remains the mainstay of treatment for RVH with comprehensive goals of care that should encompass glycemic control, cholesterol reduction, smoking cessation, blood pressure reduction, and antiplatelet therapy with aspirin for primary prevention. ACC/AHA guidelines support the use of ACE inhibitors (ACE-I), angiotensin receptor blockers (ARBs), calcium channel blockers, and beta blockers with a class I indication.[176] While beta blockers are often utilized first line, ACE-Is and ARBs are a mainstay of treatment for most antihypertensive regimens offering 86% to 92% efficacy.[189] Renal function monitoring is essential with the initiation of these agents as the resulting modulation of the renin–angiotensin system with renal artery stenosis affecting a solitary functioning kidney, severe bilateral RAS or advanced chronic kidney disease may result in acute renal failure.

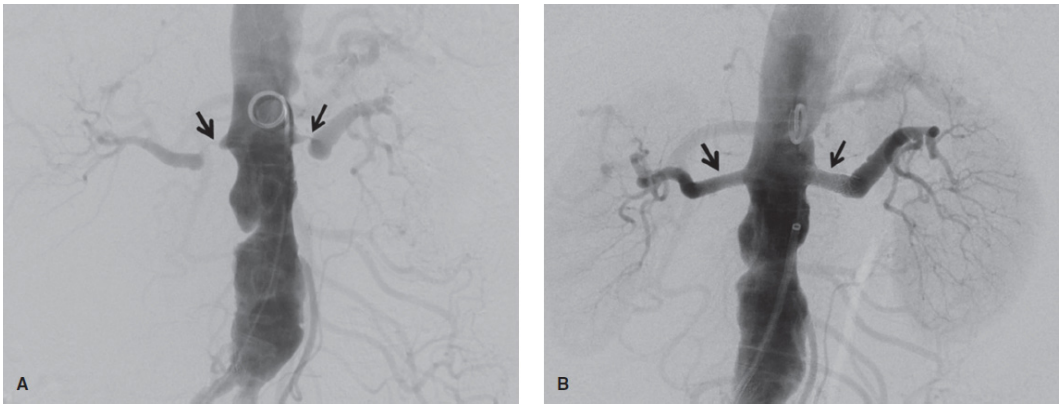

Figure 89.24 Aortogram demonstrating a highly irregular perirenal aorta with (**A**) high-grade bilateral renal artery stenosis (*arrows*) successfully treated with (**B**) bilateral renal artery stents (*arrows*). The stents are positioned with appropriate overlap into the aorta and are ballooned proximally such that they "flower" into the aorta.

Surgical and Endovascular Management of Renal Artery Occlusive Disease

As RAS may progress with concomitant renal atrophy, renal revascularization should be considered in select cases. Current ACC/AHA guidelines support renal revascularization for hemodynamically significant RAS in several clinical scenarios (Table 89.2).

Arterial Reconstructive Surgery for Renal Artery Occlusive Disease

Historically open revascularization procedures represented the standard of care in the treatment of RVH. The most common option for open renal revascularization remains aortorenal bypass with either autogenous reversed saphenous vein or prosthetic conduit. Alternatives may include (1) nonanatomic renal bypass based off the hepatic, splenic, or iliac arteries, (2) ex vivo renal artery reconstruction, and (3) aortorenal endarterectomy. Nonanatomic (or extra-anatomic) renal artery bypass may benefit those patients with medical comorbidities or aortic anatomy that prohibit aortic cross-clamping and aortorenal bypass.[196–200] The hepatic artery is used for a right-sided renal reconstruction, the splenic artery for a left-sided reconstruction. Ex vivo renal artery reconstruction may be considered selectively for those patients with complex, distal segmental arterial occlusive disease when balanced with the risk of prolonged operative time, disruption of pre-existing collaterals, and the need for renal cooling.[201,202] Transaortic and direct renal artery endarterectomy is particularly useful for those patients with bilateral disease, or when arteriosclerotic renal artery occlusive disease affects multiple (i.e., accessory) renal arteries.[203–205]

Open surgical revascularization offers significant blood pressure and renal function improvement in 85% and 50% of patients, respectively across high-volume centers with mortality rates of 2% to 5%.[188,206–209] While to date there has been no definitive trial comparing open surgical revascularization directly to endovascular therapy, angioplasty, and stenting appears to offer similar effectiveness with lower morbidity and mortality. As such, endovascular measures have replaced surgery as first-line therapy for RVH.[209,210] Contemporary open surgical renal reconstructions most commonly accompany hybrid endovascular interventions for aortic aneurysmal disease and may be considered for failed endovascular renal revascularization.

Endovascular Renal Revascularization

Since its introduction in 1978, percutaneous renal artery angioplasty (PTA), with or without stent placement, has virtually replaced open surgical reconstruction of arteriosclerotic renal artery stenosis. This technique has exploded in use and for over a decade has been utilized at times perhaps inappropriately as "prophylactic" therapy to treat clinically irrelevant renal artery stenoses.[211,212] Renal artery angioplasty alone risks arterial dissection from lesion/vessel recoil and early restenosis. Technical success rates of PTA may be as low as 30% to 50% in patients with significant aortic "spill over" lesions. PTA with

stenting offers improved success and very reasonable long-term patency with 5-year secondary patency rates >90%.[213,214]

9 Several recent clinical trials comparing renal artery stenting (RAS) to best medical management for renal artery stenosis have failed to demonstrate a conclusive clinical benefit to the endovascular treatment of renal artery stenosis (Table 89.3).[215–219] Moreover, RAS is associated with a 1.5% to 8% risk of major morbidity that can include infected hematoma, atheroemboli, renal failure requiring dialysis, and lower-extremity limb loss. Significant limitations apply to all of these studies, including design flaws and selection bias.

The appropriate patient for revascularization remains elusive, resulting from significant design flaws in existing trials. Most would suggest that those patients with refractory hypertension despite an appropriate medical regimen that includes a combination of ACE inhibition or angiotensin receptor blockade + diuretic + amlodipine with both a hemodynamically significant stenosis by manometric pressure gradient and overall preserved renal mass should still be considered for therapy.[220] Notably, evolving data have identified several promising predictors for clinical improvement following renal revascularization including bilateral RAS, mean arterial pressure >110 mm Hg, elevated baseline brain natriuretic peptide, elevated pulse pressure, and renal perfusion as measured by "renal frame count" during angiography (defined as the number of frames required for dye to pass through the renal parenchyma).[220–224] A contemporary study recently validated three preoperative markers of blood response to RAS from a single institution series with data from the CORAL trial.[225,226] These data supported (1) the requirement for ≥4 medications, (2) preoperative diastolic blood pressure >90 mm Hg, and (3) preoperative Clonidine use as predictors of hypertension improvement. Ongoing study remains necessary to identify consistent indications for RAS and reliable clinical predictors of successful outcomes following renal revascularization.

Table 89.2 Indications for Renal Revascularization for Hemodynamically Significant Renal Artery Stenosis[a]

Indication	Class Recommendation	Level of Evidence
Resistant HTN[b] and bilateral or or solitary severe RAS	2A	B
Accelerated HTN, resistant HTN, malignant HTN, HTN with unexplained unilateral small kidney, and HTN with intolerance to medication	2A	B
Stage IV chronic kidney disease with bilateral RAS (kidney size >7 cm pole-to-pole length)	2A	B
Stage IV chronic kidney disease and global renal ischemia (unilateral severe RAS with a solitary kidney or bilateral severe RAS) without another explanation	2B	B
Cardiac disturbance syndrome (i.e., Recurrent unexplained congestive heart failure, flash pulmonary edema, unstable angina)	1	B
Recurrent congestive heart failure with hemodynamically significant RAS		

[a]Hemodynamically significant renal artery stenosis defined as a resting translesional mean gradient of ≥10 mm Hg.

[b]Resistant hypertension defined as uncontrolled hypertension having failed maximally tolerated doses of at least three antihypertensive agents, one of which is a diuretic agent.

HTN, hypertension; RAS, renal artery stenosis.

Adapted from the 2005 Practice Guidelines for the management of patients with peripheral arterial disease and 2019 Prince et al. State of the Art Review.[176,195]

Table 89.3 Contemporary Clinical Trials Comparing the Effectiveness of Endovascular Renal Artery Revascularization to Medical Therapy

Trial	Number of Patients	Degree Stenosis	Indications for Renal Artery Revascularization	F/U (yrs)	BP Response	Renal Function Improvement or Stabilization
DRASTIC Trial[216] (PTA)	106	≥50%	Resistant HTN	1	No difference	N/A
STAR Trial[215] (RAS)	140	>50%	Renal impairment (GFR <80 mL/min)	2	No difference	No difference
ASTRAL[217] (RAS)	806	Variable	Refractory HTN or unexplained renal dysfunction with RAS suggested by imaging	5	No difference (systolic)[a]	Decreased progression of renal impairment and lower mean Cr level following revascularization
CORAL[218] (RAS)	931	≥60% + 20 mm Hg systolic pressure gradient -or- ≥80%	Systolic HTN ≥155 mm Hg despite at least two antihypertensives	43 mo	2.3 mm Hg reduction following RAS (vs. medical therapy) ($p = 0.03$)	No difference[b]

[a]The decrease in diastolic BP was smaller in the revascularization group.

[b]Composite end point included death from cardiovascular or renal causes, myocardial infarction, stroke, hospitalization for congestive heart failure, progressive renal insufficiency, or the need for renal-replacement therapy.

HTN, hypertension; PTA, angioplasty alone; RAS, renal artery stent; BP, blood pressure; Cr, creatinine.

Although randomized, controlled trials assessing renal revascularization for renal artery FMD are lacking, current guidelines support the following indications for renal revascularization in this patient cohort: (1) resistant HTN despite an appropriate three-drug regimen, (2) HTN of short duration with the goal being a cure of hypertension, (3) renal artery dissection, (4) RAA, and (5) preservation of renal function in patients with severe stenosis.[191,227] PTA of the renal artery is the procedure of choice for patients with renal artery stenosis secondary to FMD offering cure rates that approach 50%, with up to 86% of patients improved following PTA, a 20% risk of reintervention, and low risk of minor complications.[191] Hemodynamic significance must be documented by manometry prior to any intervention in these patients and success should be defined by resolution of this gradient postangioplasty. Stenting should be utilized selectively.

Developmental Dysplasia

Renovascular HTN secondary to renal artery stenosis and abdominal aortic coarctation remain an important cause of pediatric HTN, the natural history of which risks failure to thrive, heart failure, hypertensive encephalopathy, impaired mental development, hemorrhagic stroke, and early mortality.[228] It is estimated that 5% to 10% of pediatric HTN may be explained by renovascular disease, following thoracic aortic coarctation and parenchymal renal disease in incidence.[228,229] The pathophysiology of pediatric

renovascular disease remains ill defined, as are the mechanisms by which pediatric renovascular disease occur. FMD and neurofibromatosis type 1 (NF1) are reported as the most common causes of pediatric renal artery stenosis in the western world.[230] While the intimal FMD variant described above is uncommon in adults, it is the most common form identified in children with renal artery stenosis. Furthermore, histopathologic review of operative renal artery samples excised from patient with developmental arterial stenosis reveal mainly consistent findings of intimal hyperplasia, medial thinning, and disruption of the elastic lamina (Fig. 89.21).

Open surgical revascularization of renal artery stenosis remains the gold standard for children with developmental lesions.[228] Aortorenal reimplantation with spatulation of the renal artery and interrupted suture lines is favored. Alternatively, aortorenal bypass using hypogastric artery as conduit is favored over autogenous venous conduit, which can dilate over time to become aneurysmal. Approximately one-third of children will demonstrate associated aortic coarctation and require concomitant patch aortoplasty or aortoaortic bypass. The University of Michigan experience recently reported the largest single-center experience with surgical revascularization of 169 children with RVH supporting a sustainable hypertension benefit in 90% of children, including those with abdominal aortic coarctation, with no mortality or renal insufficiency requiring dialysis.[231] The authors noted that interventions in the very young and in those with concurrent abdominal aortic coarctation significantly increased the likelihood of reoperation, and those children undergoing remedial surgery after prior revascularization failures were less likely to be cured of HTN.

There may be a role for angioplasty for selected cases of pediatric renal artery stenosis. Certainly this procedure has gained substantial momentum in the past decade. The most robust U.S. experience includes the treatment of 19 hypertensive children aged 2 to 18 years that underwent PTA for renal artery stenosis, of which 7 patients carried the diagnosis of NF.[232] While immediate technical success was reported as 91%, only 39% of patients achieved a cure in HTN and an additional 17% of children demonstrated improvement. In total there was a 44% rate of clinical failure and these authors conclude that despite a high rate of technical success, PTA provides a clinical benefit in a smaller majority of children. This is consistent with improvement or cure rates that mainly average 50% to 60% across larger series of pediatric renal artery stenosis treated with PTA.[233–235] Notably, renal PTA for the treatment of pediatric RVH due to ostial disease may be complicated by failures requiring remedial operations that are made more complicated by such or nephrectomy.[236] Moreover, HTN cure is less likely following remedial operation (24% in comparison to 70% as referenced above).

Renal Artery Aneurysm

RAAs are rare with an incidence of 0.1% in the general population.[237–240] The natural history of RAAs appears to be that of slow to null growth with contemporary series estimating a median annualized growth rate of 0.06 to 0.6 mm.[241–243] Aneurysm growth rate does not seem to be affected by aneurysm morphology or calcification.[242] While historic series describe rupture rates as high as 14% to 30% with associated mortality of 80%, contemporary rupture rates are estimated at 3% to 5% with nongestational mortality <10%.[237,240,244–247] Most ruptures are diagnosed at the time of presentation and several authors have supported no rupture during the surveillance of nonoperative RAAs.[248]

Similar to other splanchnic artery aneurysms, RAAs typically present in the sixth decade with women more commonly affected than men.[237,244] Most patients will describe no symptoms, although flank pain and hematuria are most common when symptoms do arise. Clinical examination may reveal HTN, renal bruit or a palpable abdominal mass. Aneurysms are typically solitary, saccular, located at arterial bifurcations, and affect the right renal artery more often than the left.[248] Almost 70% of RAA may be associated with FMD and up to 30% of patients will have an alternate arterial aneurysm.[237,248,249] These aneurysms are commonly identified as an incidental finding by axial imaging; CT is the most common contemporary diagnostic modality, followed by magnetic resonance imaging, ultrasonography, and catheter-based arteriography.[242]

Conventional preoperative arteriography is warranted given the frequency of multiple aneurysms and arterial dysplasia affecting distal branches that may be missed on conventional cross-sectional imaging.

Historically accepted indications for RAA intervention included size >2 cm, female gender within childbearing age, symptoms like pain and hematuria, medically refractory HTN including that associated with functionally important renal artery stenosis, thromboembolism, dissection and rupture. Given the low risk of rupture, slow to null rate of growth, and improved survival following rupture some authors have suggested that a size threshold alone of 2 cm may be antiquated and too aggressive for surgical indication.[241,242] In fact, recently published contemporary guidelines support elective repair in patients with noncomplicated RAA of acceptable operative risk at a size >3 cm (Grade 2C), and at any size in those patient of childbearing potential (2B) or medically refractory HTN and functionally important RAS (2C).[106] The potential for gestational rupture remains a valid indication for repair in women of childbearing age as rupture during pregnancy has been described in aneurysms as small as 1 cm and historic reports suggest maternal and fetal mortality rates that approach 92% and 100%, respectively.[250,251] Pregnancy has previously been associated with a higher rate of RAA rupture, thought to result from increased vascular flow and hormonal changes resulting in weakening of the vessel wall elastic tissue, no large scale studies report the true incidence.[238,248] Gestational RAA ruptures occur mainly in the third trimester with only a few case reports of rupture postdelivery.[252] Notably, contemporary outcomes for both mother and fetus may be improving, as there are recent case reports of gestational rupture resulting in both maternal and fetal survival.

Approximately 70% of patients with RAA have HTN, with up to 100% affected in some series.[237,241,243,247,249,251] Hypotheses for the mechanism of HTN include (1) coexistent renal artery occlusive disease, (2) distal parenchymal embolization, (3) compression or kinking of associated renal artery branches, and (4) hemodynamic changes from turbulent blood flow within the aneurysm results in decreased distal renal artery perfusion.[237,247] Most series suggest improvement or cure in the majority of hypertensive patients undergoing RAA reconstruction, with postoperative improvement more likely when RVH or renal artery stenosis is identified preoperatively.[244,248,251]

Open surgical repair remains the gold standard for RAA management as these procedures performed in the elective setting offer low morbidity, negligible mortality, and durable patency.[241,242,244–247,249,253,254] Options for conventional in situ reconstruction may include aneurysm resection with (1) primary angioplastic closure with or without branch reimplantation, (2) patch angioplasty, (3) primary reanastomosis, (4) interposition bypass, (5) aortorenal bypass, (6) splanchnorenal bypass, and (7) plication of small aneurysms. While complex distal branch lesions were historically treated with nephrectomy, they may rather best be approached with ex vivo repair and autotransplantation which offers excellent technical success without major morbidity or mortality.[202,255] Most recently, robotic techniques have been introduced that may become more prevalent in future practices.[256,257] Most authors advocate completion imaging before hospital discharge and long-term follow-up with surveillance imaging.

While traditional endovascular therapies for RAA have utilized coil embolization for distal and parenchymal aneurysms and stent graft exclusion for main renal artery lesions, the indications for endovascular repair have broadened with the introduction of three-dimensional detachable coils, nonadhesive liquid embolic agents (i.e., Onyx), remodeling techniques (which include balloon- and stent-assisted coiling), and flow diverter stents (i.e., the Cardiatis multilayer stent).[248,258–260] Technical success is suggested as 73% to 100% across series with highly variable rates of morbidity (13% to 60%) that include primarily radiographic evidence of end-organ malperfusion from thromboembolism and subsequent postembolization syndrome, negligible evidence of arterial dissections or renal compromise, and low rates of recanalization requiring reintervention (4% to 13%).[254,261–263] Although prospective data are lacking, limited comparisons of open surgical and endovascular procedures have reported no significant difference in mortality, perioperative morbidity, freedom from reintervention, decline in renal function, or length of stay.[242,254,264]

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90

Aortoiliac Occlusive Disease

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Key Points

1. Aortoiliac occlusive disease is mainly the result of atherosclerosis.
2. Claudication is the most common presenting symptom of patients with significant isolated aortoiliac occlusive disease. Some patients may complain of erectile dysfunction.
3. Physical examination typically reveals diminished or absent femoral pulses.
4. Medical treatment of atherosclerotic aortoiliac occlusive disease is key to long-term success. This includes risk factor modification (smoking cessation, control of hypertension, lipid abnormalities, and diabetes mellitus), supervised walking programs and pharmacotherapy.
5. Smoking is the most important reversible risk factor for the development of lower extremity atherosclerotic occlusive disease.
6. Endovascular approaches are favored for most candidates with aortoiliac disease requiring intervention.

INTRODUCTION

1 Peripheral a rterial disease (PAD) is usually a manifestation of systemic atherosclerosis. It affects 3% of the general population older than 40 years and 15% of those older than 70 years, with approximately 50% of patients with PAD being asymptomatic.[1,2] Atherosclerotic occlusive disease of the aorta and iliac arteries alone, or in combination with femoropopliteal or tibial occlusive disease, is the most frequent cause of chronic lower extremity arterial insufficiency.

The wide availability of computed tomographic angiography (CTA) and magnetic resonance angiography (MRA) has facilitated diagnosis, anatomic definition, and subsequent intervention for aortoiliac occlusive disease (AIOD). Selection of a patient-specific treatment from an increasing array of treatment alternatives, although challenging, will usually alleviate symptoms and reduce the risk of disease progression. Endovascular and open reconstructive procedures for AIOD have become routine, with low perioperative morbidity and mortality and excellent early and long-term outcomes.

ETIOLOGY

Atherosclerosis is a systemic disease. The earliest lesions tend to occur at arterial bifurcations and in areas of relative fixation, where disruption of normal laminar flow is greatest, and where eddy currents result in areas of low arterial wall shear stress. Arteriopathies other than atherosclerosis, such as Takayasu disease and radiation arteritis, can also involve the aortoiliac system. Smoking is the most important reversible risk factor for the development of lower extremity atherosclerotic occlusive disease. Other risk factors include hypertension, lipid abnormalities, diabetes mellitus, male sex, older age, and genetic predisposition.

Anatomy and Pathophysiology

The arteries supplying blood to the lower extremities are frequently divided into abdominal, or “inflow,” arteries (the aorta and iliac arteries) and

infrainguinal, or "outflow," arteries (the femoropopliteal and tibial arteries).

In slowly developing aortoiliac occlusive lesions, hemodynamic alterations lead to the enlargement of a network of collateral channels around the involved segments; this collateral network is usually sufficient to provide enough blood flow to meet the resting metabolic needs of the lower extremities (**Figs. 90.1** and **90.2**). These channels, however, do not have the capacity to increase blood flow to the level necessary to meet exercise demands of the lower extremity musculature.

PRESENTATION

Patients with symptoms of AIOD usually present in their 50s and 60s, whereas patients with infrainguinal disease or multilevel disease (AIOD plus infrainguinal) generally present in their 70s.[3]

- 2 Claudication (Latin *claudicare* = "to limp") is the term used to denote the characteristic exercise-induced, cramping pain in the muscles of the lower extremity that results from demand ischemia.[4] Claudication is the most common presenting symptom of patients with significant aortoiliac disease. Induced by ambulation and quickly relieved by rest, claudication is usually described as a cramping pain or easy fatigability of the involved muscle groups. Although patients with aortoiliac disease classically present with claudication of the thighs, hips, and buttocks, a significant number complain of calf claudication or have significant overlap. Erectile dysfunction in men secondary to reduced hypogastric perfusion is another common complaint and may be reported in as many as 30% to 50% of men with AIOD. 3 The combination of bilateral lower extremity claudication, atrophy of the lower extremity musculature, impotence, and diminished or absent femoral pulses is known as Leriche syndrome, after the French physician René Leriche who first described this constellation of findings in 1940.[5]
- Chronic limb-threatening ischemia (CLTI)[6] symptoms manifest in the lower leg or foot as ischemic rest pain, nonhealing wounds, or gangrene. Such symptoms may be a manifestation of AIOD alone but almost always occur in combination with more distal femoropopliteal/tibial disease which is known as multilevel arterial occlusive disease. In the absence of

infrainguinal disease, aortoiliac collaterals are usually capable of maintaining adequate resting distal tissue perfusion.

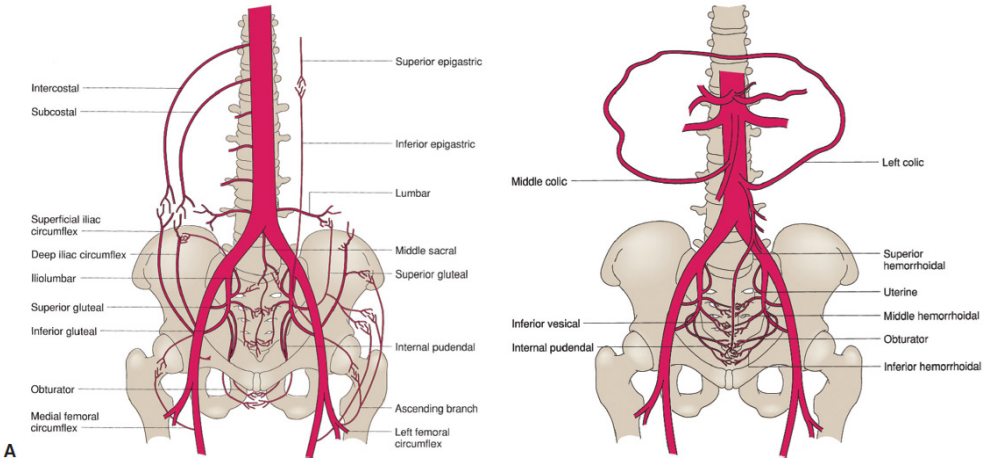


Figure 90.1 **A, B:** Major visceral and parietal collateral networks that may become prominent with aortoiliac occlusive disease.

- Acute arterial occlusions from emboli lodging at the aortic, iliac, or femoral bifurcations do not allow time for collateral pathways to mature and compensate for the sudden loss of blood supply. This situation leads to the acute onset of symptoms, with the resulting five “Ps” of acute ischemia: pain, pallor, pulselessness, paresthesia, and paresis/paralysis.

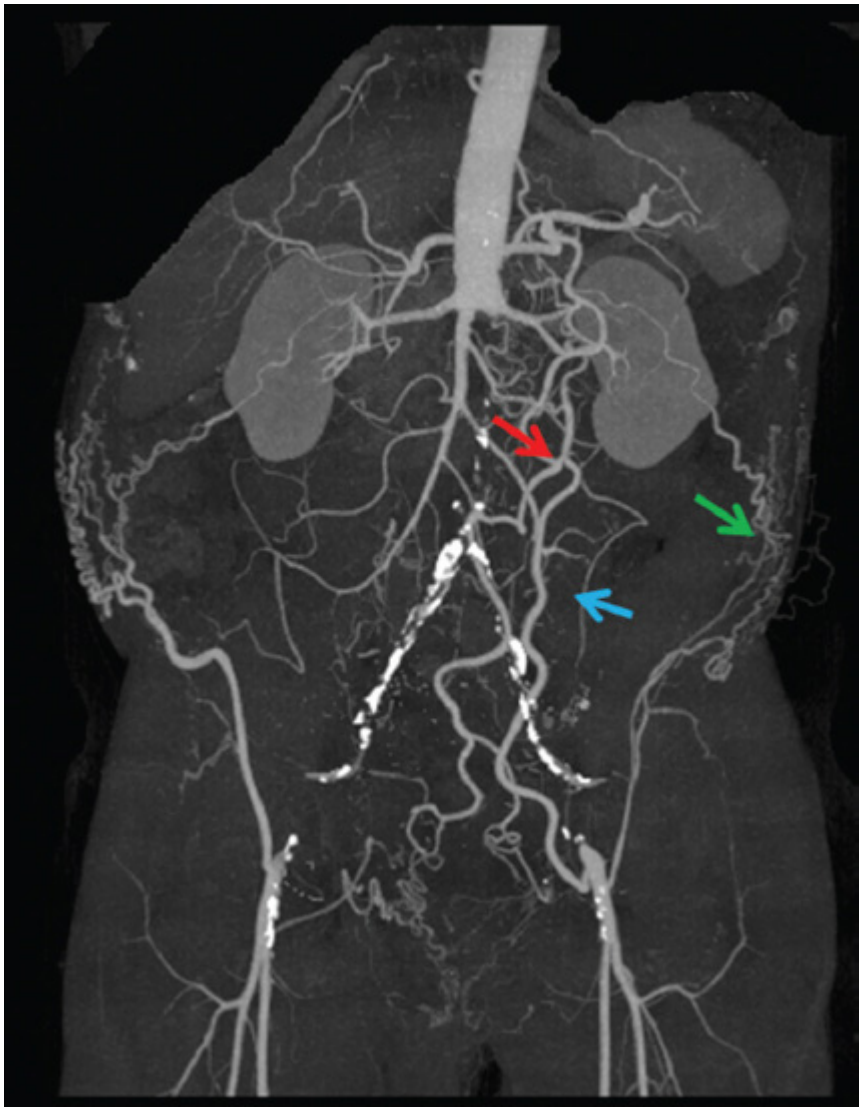


Figure 90.2 CTA with 3D reconstruction demonstrating severe aortoiliac occlusive disease with juxtarenal aortic occlusion. Note the extensive collateral networks reconstituting the inferior mesenteric artery (*red arrow:* marginal artery) and femoral arterial segments (*blue arrow:* inferior epigastric artery) (*green arrow:* subcostal arteries and superficial iliac circumflex artery collaterals).

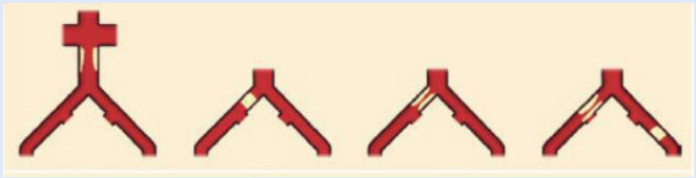
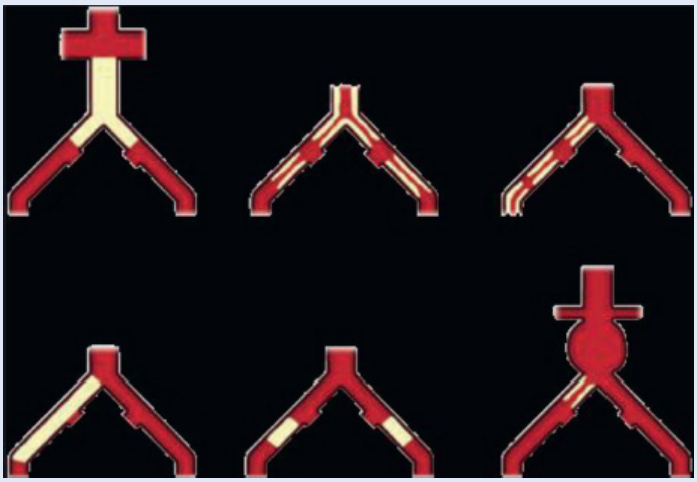
Downstream embolism of debris from proximal atherosclerotic disease into the microcirculation of the lower extremities ("trash foot") can produce dermal discoloration in a characteristic reticular pattern (livedo reticularis), digital ischemia, or even gangrene (**Fig. 90.3**). Such patients may have palpable pedal pulses. Embolic events can occur spontaneously or can be induced by interventions, such as guidewire manipulation (e.g., during

angiographic procedures or placement of an intra-aortic balloon pump) or clamping an artery with unstable plaque during open vascular surgery.

Physical examination typically reveals diminished or absent femoral pulses. A bruit auscultated over the groins or lower abdomen is not specific for critical stenosis. Severely diseased, calcified femoral arteries may be palpable as firm, tubular structures in the groins. Normal femoral and distal pulses may be palpable, even in the presence of hemodynamically significant aortoiliac stenosis. These pulses, however, rapidly disappear following ambulation, as the increased flow demands of the exercising leg muscles lead to lowered peripheral vascular resistance and reduced distal arterial pressure. Patients with longstanding aortoiliac atherosclerosis may have disuse atrophy of the lower extremity musculature. Other common signs of lower extremity arterial occlusive disease include trophic changes, such as hair loss on the legs or toes, and thin, shiny skin on the feet; patients with severe reductions in pedal blood flow may display pedal rubor with limb dependency, coupled with pallor on elevation.

Figure 90.3 Digital atheroembolization progressed to gangrene.

Table 90.1 TASC II Classification

Type A: Limited stenoses (<3 cm) of the common or external iliac arteries	
Type B: Short stenoses of the infrarenal aorta and short stenoses or occlusion of the iliac arteries	
Type C: Longer stenoses and/or occlusions of the iliac arteries, especially when calcified	
Type D: Infrarenal aortic occlusion sometimes with multiple iliac occlusions and stenoses or associated aneurysm disease	

Clinical Pathologic Types of Aortoiliac Disease

The Trans-Atlantic Inter-Society Consensus for the Management of PAD (TASC II) has classified AIOD into four types, A through D (**Table 90.1**).[7] Patients with focal disease (TASC II types A, B) requiring intervention can usually be treated with endovascular means, while those with more advanced

disease (TASC II C, D) are more challenging and may require more complex endovascular, hybrid surgical, or open surgical approaches.

Aortoiliac hypoplasia also known as *small aortic syndrome* or *hypoplastic aortic syndrome* is encountered in young to middle-aged women who smoke cigarettes. The infrarenal aorta and iliac arteries are unusually small in caliber and hence prone to significant narrowing, even with modest disease. Operative treatment of such patients can be particularly challenging.[8]

DIAGNOSIS

In most cases, diagnosing significant AIOD and its severity can be made on the basis of history and physical examination alone. A clinical diagnosis, however, should always be supplemented by noninvasive vascular testing. Such tests provide valuable information by confirming the presence of disease, assessing the degree of ischemia, objectively documenting the arterial segment(s) involved, and establishing a baseline from which the patient can be followed and appropriate interventions planned. Treatment results can be assessed by repeated testing. Formal imaging studies (CTA, MRA, and arteriography) are usually reserved for those patients considered for intervention.

Noninvasive Vascular Testing

Segmental Doppler-derived pressure measurements or pulse volume recordings are useful for demonstrating the physiologic significance of disease and can help localize hemodynamically significant lesions. Measurement of systolic arterial pressures at different levels of the lower extremity with a continuous wave Doppler flow probe is the simplest and most useful noninvasive method to assess arterial occlusive disease. The ratio of the ankle systolic pressure (measured at either the dorsalis pedis or the posterior tibial artery) to the brachial systolic pressure (using the higher of the two brachial pressures) is the ankle-brachial index (ABI), or pressure ratio, and is a good measure of the degree of ischemia present.[9] Normal ABIs are generally equal to or slightly greater than 1.0 (**Fig. 90.4**). PAD is

designated when the ABI is ≤0.90. Patients with claudication usually have ABIs ranging from 0.50 to 0.90, whereas patients with rest pain, tissue loss, or gangrene usually have ABIs of <0.50 (**Table 90.2**).[9]

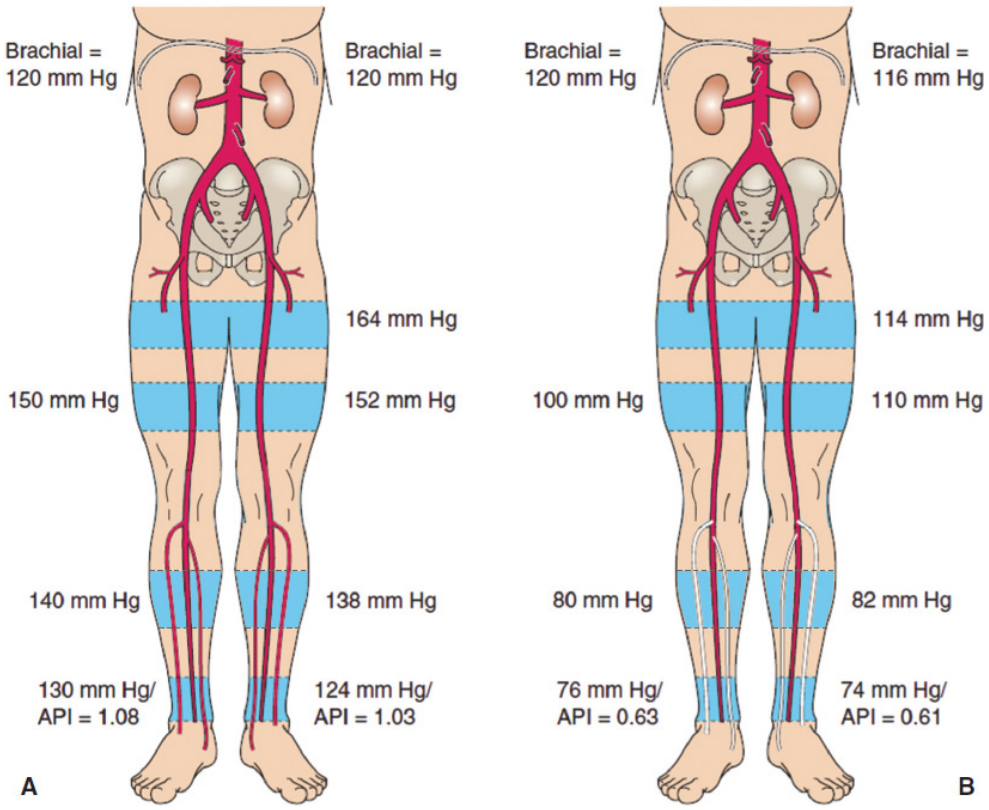


Figure 90.4 Segmental pressure measurements typical of normal results (**A**) and aortoiliac occlusive disease (**B**).

Determination of limb systolic pressures at different locations (with the "four-cuff" technique, where pressures are measured at the upper thigh, lower thigh, calf, and ankle) provides information concerning which arterial segments are involved with occlusive disease (**Fig. 90.4**) and helps define the presence of inflow artery disease, outflow (runoff artery) disease, or a combination of the two.[10] A pressure drop of more than 20 mm Hg between adjacent levels indicates significant disease within the intervening arterial segment. A reduced upper thigh pressure signifies occlusive disease in the aortoiliac or common femoral segments.

In patients with extensive calcification in the walls of the tibial arteries (as is frequently seen in diabetes mellitus or end-stage renal disease), may have incompressible arteries and have falsely elevated ABIs. In this

situation, the pressure in the digital arteries of the great toe can be measured, since small vessels are generally spared calcification. A toe pressure of less than 30 mm Hg indicates severe ischemia. Inspection of the Doppler-derived arterial waveforms can provide additional information.

Patients with claudication occasionally have normal or nearly normal ABIs. In such cases the arterial stenosis is not severe enough to cause a pressure drop in the limb at rest but does produce a significant hemodynamic change under conditions of higher flow rates when the distal vasculature dilates, as occurs with exercise. When the distal pressure drops because of vascular dilation, the stenosis prevents increased blood flow into the extremity so that a significant distal pressure drop results. The classic treadmill test involves walking on a treadmill at 1.5 miles per hour at a 14% incline for as long as the patient can go, up to 5 minutes. ABIs are measured before and after the treadmill exercise; a drop of 15% or more in the ABIs following exercise is indicative of a hemodynamically significant stenosis.[9]

Duplex scanning of the aorta and iliac arteries has been advocated by some as a noninvasive diagnostic tool. Accurate imaging of the abdominal arteries, however, can be difficult because of their deep retroperitoneal and pelvic locations, which can be further degraded by body habitus and overlying bowel gas. These drawbacks have limited the widespread use of this modality.[11] Arteriography, CTA, and MRA may be used for diagnosis, but are usually performed when interventional therapy is contemplated, and are, therefore, discussed later.

Table 90.2 Ankle-Brachial Indices

Ankle Brachial Indices (ABI) and Toe Brachial Indices (TBI)			
ABI Value	**TBI Value**	**Doppler Waveform**	**Disease**
> 1.2			Heavily calcified (incompressible) vessels
0.95–1.2	>0.63	Biphasic or triphasic	Normal
0.8–0.95	0.4–0.62	Biphasic or monophasic	Mild
0.5–0.8	0.2–0.39	Biphasic or monophasic	Moderate
<0.5	<0.2	Monophasic	Severe

Table 90.3 Differential Diagnosis of Claudication

The Differential Diagnosis for Intermittent Claudication (IC)

Condition	Location	Prevalence	Characteristic	Effect of Exercise	Effect of Rest	Effect of Position	Other Characteristics
Calf IC	Calf muscles	Common	Cramping, aching, discomfort	Reproducible onset	Quickly relieved	None	
Thigh and buttock IC	Buttocks, hip, thigh	Rare	Cramping, aching discomfort	Reproducible onset	Quickly relieved	None	Impotence. May have normal pedal pulses with isolated iliac artery disease
Venous claudication	Entire leg, worse in calf	Rare	Tight, bursting pain	After walking	Subsides slowly	Relief faster with elevation	History of deep vein thrombosis
Nerve root compression	Radiates down leg	Common	Sharp lancinating pain	Induced by sitting, standing, or walking	Often present at rest	Improved by change in position	History of back problems. Present with sitting, standing, or walking
Spinal stenosis	Often bilateral buttocks, posterior leg	Common	Pain and weakness	Induced by standing, or walking	Variable relief but can take a long time to recover	Relief by lumbar spine flexion	Worse with standing and extending spine
Symptomatic Baker cyst	Behind knee, down calf	Common	Swelling, tenderness	With exercise	Present at rest	None	
Hip arthritis	Lateral hip, thigh	Common	Aching discomfort	After variable degree of exercise	Not quickly relieved	Improved when not weight bearing	History of degenerative arthritis
Chronic compartment syndrome	Calf muscles	Rare	Tight, bursting pain	After much exercise (jogging)	Subsides very slowly	Relief with elevation	Usually athletes

Differential Diagnosis

The diagnosis of AIOD is usually straightforward, but occasional diagnostic difficulty may arise when other causes of lower extremity pain are present (**Table 90.3**). Irritation of lumbosacral nerve roots by spinal stenosis or intervertebral disc herniation may cause buttock and leg pain that is associated with activity. Such symptoms (neurogenic claudication), however, usually cannot be reproduced at the same level of activity, frequently occur when the patient is standing, and are relieved only by sitting or lying down. In addition, the pain is usually in a classic sciatic distribution.

Degenerative arthritis of the hip joints may produce similar buttock, hip, and referred thigh pain. There is usually a history of morning stiffness that progressively improves over the course of the day. Physical examination typically reveals tenderness directly over the hip joint that is exacerbated by moving the joint.

Peripheral neuropathy, particularly that associated with diabetes mellitus, may masquerade as ischemic rest pain.

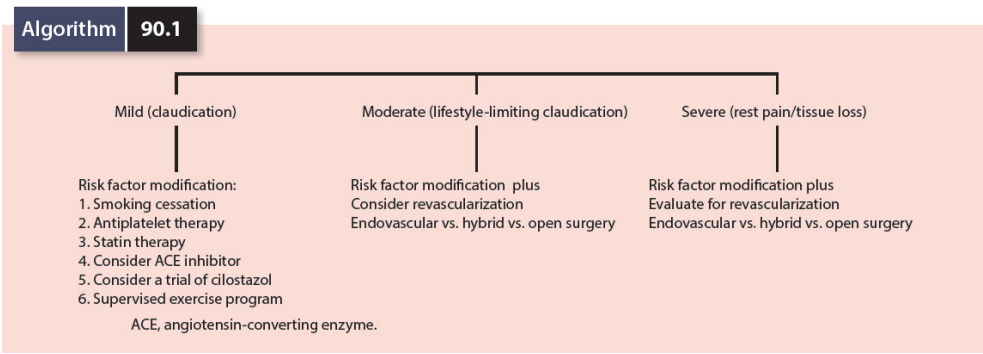
In all these situations, segmental limb pressure measurements, with or without stress testing, can be helpful in determining the contribution of arterial occlusive disease to the patient's symptoms.

TREATMENT

The aims of therapy in AIOD are to relieve symptoms and, in cases of CLTI, to prevent limb loss (**Algorithm 90.1**). Medical therapy should be instituted in all patients with atherosclerotic disease but is insufficient as sole therapy in patients with limb-threatening ischemia.

4 Medical Therapy (Table 90.4)[12]

Atherosclerosis is a systemic disease. Medical therapy is, therefore, key to reducing the risk associated with cardiovascular morbidity and death in these patients. Risk factor modification, including management of diabetes mellitus, control of hypertension, treatment of hyperlipidemia, and finally modification of lifestyle including smoking cessation, appropriate diet, and exercise, are perhaps the most important components of the care of patients with atherosclerotic disease.[12,13] Although risk factor control will not reverse the atherosclerotic process, it can limit disease progression; furthermore, some data indicate that smoking cessation lessens the severity of symptoms in many patients.[14]



Algorithm 90.1 Patient with symptomatic aortoiliac occlusive disease.

5 Smoking Cessation

Smoking is associated with a subclinical inflammatory reaction. The degree of damage caused by smoking is directly related to the amount of tobacco consumed.[15] All patients who are smokers or former smokers should be asked about the status of tobacco use at every visit. All patients should be strongly advised to stop smoking by their physicians. All patients should be offered pharmacotherapy, behavior modification, referral to a smoking cessation program, and counseling.[16] Smoking cessation alters the progression of the atherosclerotic process and may even reduce the severity of claudication.[17] Furthermore, it is an important step to reducing postprocedure complications in patients undergoing intervention.[18]

Exercise

Supervised exercise programs have been consistently demonstrated to improve walking time and walking distance, and in some studies supervised exercise has been as effective as revascularization.[18,19] Home- and community-based therapy are effective for improving walking tolerance but are less effective than formal supervised exercise programs and are associated with a high dropout rate, underscoring the need for ongoing psychological support.[20] Outcomes of supervised exercise programs have been shown to be similar and longer lasting than those of endovascular interventions for mild claudication. Patients are usually advised to walk until the onset of pain, rest until the pain subsides, and repeat the cycle, for a total of 30 minutes a day, three to five times per week. A 3- to 6-month trial of

exercise should be initiated before revascularization is considered in patients with intermittent claudication.

Table 90.4 AHA Guidelines for Medical Therapy of Patients with PAD

	Recommendations
Smoking cessation	Quit smoking
Weight reduction	Counseling to reduce weight if BMI >25
Hyperlipidemia	LDL <100 mg/dL for all patients or <70 mg/dL if diabetes or other vascular disease
Hypertension	BP <140/90 or <130/80 in patients with diabetes or renal failure
Diabetes	Hemoglobin A1c goal <7.0% or as close to 6% as possible
Antiplatelet therapy	ASA for all patients with symptomatic PAD. Clopidogrel may be an effective alternative to ASA

Diet

A well-balanced diet with low salt, low fat, and moderate amounts of added sugar intake, as per the American Heart Association Guidelines, reduces the risk of chronic diseases in general, and cardiovascular disease in particular, and should be followed.[13]

Glycemic Control

American Heart Association Guidelines recommend aggressive blood glucose control, with a target A1C goal of <7.0%, and as close to 6.0% as possible.[13]

Antiplatelet Therapy

Some form of platelet inhibition should be considered for all atherosclerotic patients in order to reduce the risk of myocardial infarction, stroke, and death.[13] Aspirin is the agent of choice, but clopidogrel may be used if aspirin is not tolerated. The effectiveness of antiplatelet therapy in reducing symptoms of claudication is not established; however, the risk of PAD progression requiring revascularization is significantly reduced by antiplatelet therapy, compared with placebo. Adding aspirin to clopidogrel does not reduce major vascular events, but does increase the risk of major life-threatening bleeding.[21]

Low-Dose Anticoagulation

The combination of a vitamin K antagonist (warfarin) and aspirin in patients with PAD resulted in a higher rate of bleeding without reducing the rate of cardiovascular events. There is some evidence that low-dose Rivaroxaban may decrease the incidence of cardiovascular death, stroke, and/or myocardial infarction in PAD patients but further study is needed.[22]

Antihypertensive Therapy

Antihypertensive therapy reduces mortality from atherosclerotic cardiovascular disease, with a goal blood pressure of less than 130/80 mm Hg. Antihypertensive therapy is, therefore, recommended despite the lack of data substantiating that it alters the progression of PAD.[7]

Lipid-Lowering Therapy

Lipid-lowering therapy with at least a moderate dose of a statin medication is recommended for all patients with atherosclerotic cardiovascular disease, irrespective of the baseline low-density lipoprotein cholesterol. Lipid-lowering therapy reduces disease progression (as measured by arteriography), helps alleviate symptoms, and improves total walking times, pain-free walking distance, and amputations.[23,24]

Other Pharmacologic Therapy

Cilostazol and naftidrofuryl can be valuable adjuncts in selected patients with severe lifestyle-limiting claudication.[25] A therapeutic trial (3 to 6 months) may be tried. Although the mechanisms of action of these agents are

unclear, a modest but significant reduction in claudication symptoms has been shown in controlled trials. Benefit has not been firmly established for other agents.

Indications for Revascularization

Revascularization is clearly indicated in patients with CLTI; without intervention, these patients can progress to limb loss in a fairly short period of time. At 1 year following onset of CLTI symptoms, it is estimated that 25% of patients will lose their limb, 25% will suffer a cardiovascular death. One to 2% of patients with claudication will progress to CLTI per year.[26]

Patients with significant or repetitive atheroembolism from an aortoiliac source represent a group that clearly benefits from early operative intervention. Removal or bypass of the culprit lesion(s) eliminates the risk for further macro- and microembolism.

The treatment of patients with claudication secondary to AIOD remains controversial and must be individualized. Patients with mild to moderate symptoms can usually be treated medically with satisfactory results, while patients with severe, disabling, and lifestyle-limiting symptoms of claudication can benefit from revascularization therapy.

Preintervention Imaging Studies

Once a decision has been made to proceed with revascularization, imaging studies are paramount for developing a treatment strategy.

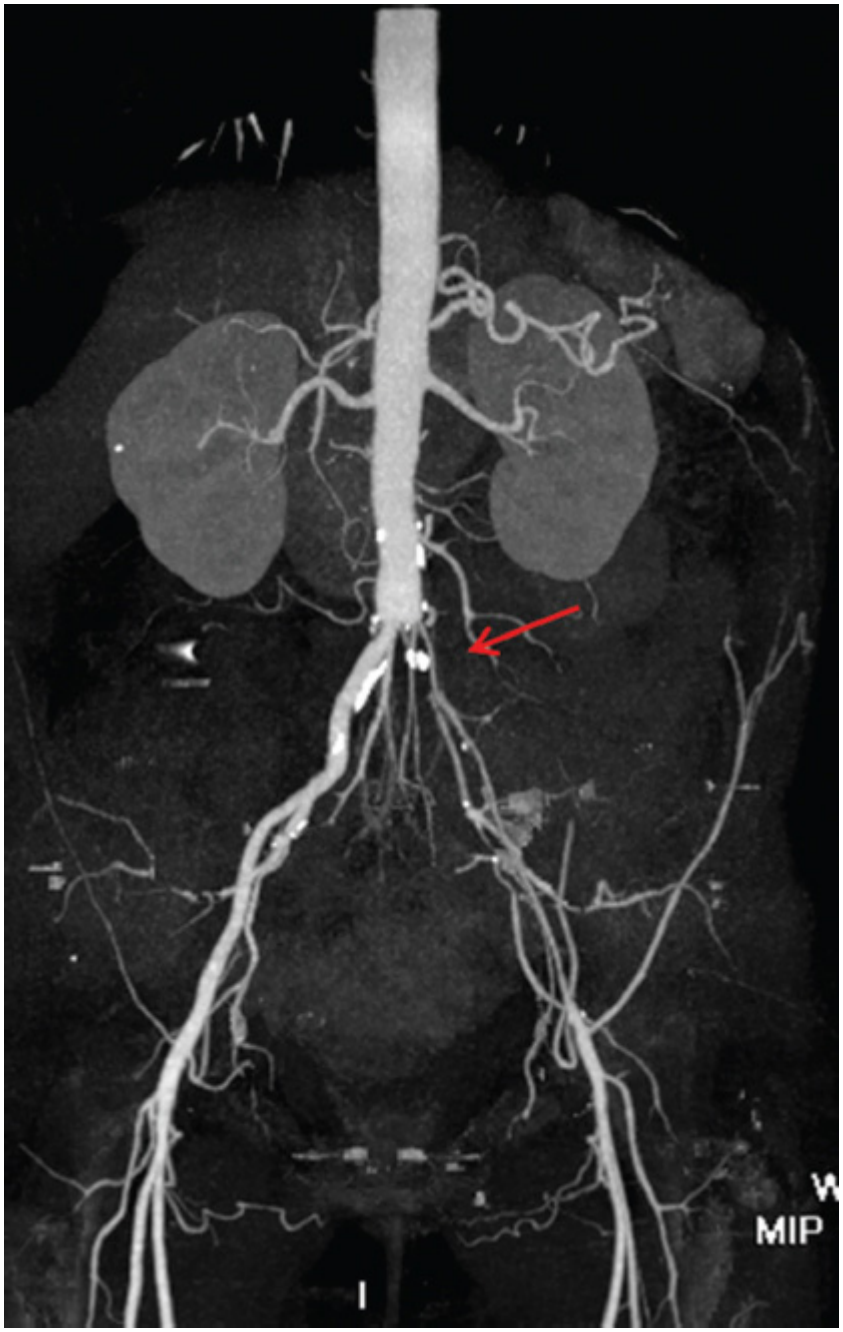


Figure 90.5 CTA 3D reconstruction showing left iliac artery chronic total occlusion (*red arrow*).

Computed Tomographic Angiography

CTA with reformatting requires the intravenous administration of iodinated contrast material, followed by a timed CT scan of the pertinent anatomy. The images are then processed into axial, coronal, and sagittal imaging planes and three-dimensional images (**Figs. 90.2**, **90.5** to **90.7**). For most patients,

120 mL of iodinated contrast is used (300 to 370 mg of iodine per liter of contrast). Sensitivity and specificity are greater than 92% and 93%, respectively, for detecting >50% stenosis. The main drawbacks of CTA are the ionizing radiation and the use of iodinated contrast, which can cause allergic reactions in addition to contrast-induced nephropathy.[27]

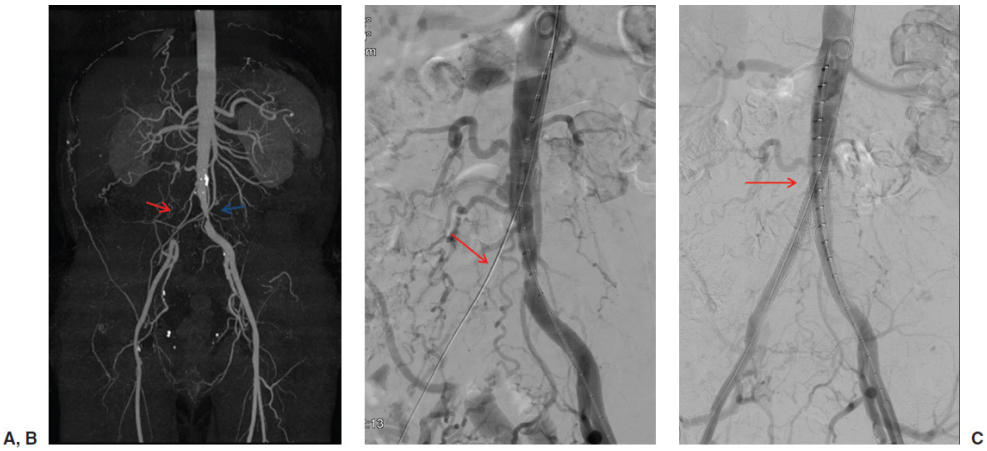


Figure 90.6 **A:** CTA 3D reconstruction demonstrating right common iliac artery chronic total occlusion (*red arrow*) and severe left common iliac artery stenosis (*blue arrow*). **B:** Abdominal aortogram redemonstrating right common iliac artery chronic total occlusion and left common iliac artery stenosis. Note successful wire traversal of the right common iliac artery occlusion (*red arrow*). **C:** Abdominal aortogram demonstrating successful endoluminal bilateral common iliac artery revascularization following percutaneous balloon angioplasty and stent placement. Note the "kissing" stents in the distal aorta (*red arrow*).

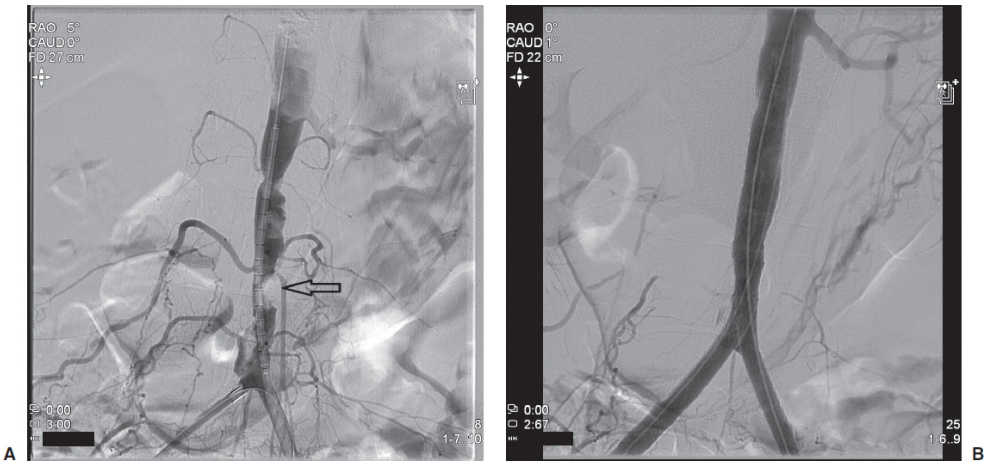


Figure 90.7 CERAB (covered endovascular reconstruction of aortic bifurcation). **A:** Infrarenal aortic stenosis (*arrow*). **B:** Post deployment of bifurcated stent graft.

Magnetic Resonance Angiography

Contrast-enhanced MRA uses intravenous administration of paramagnetic gadolinium-based agents. With good technique, contrast-enhanced MRA has a sensitivity of 80% to 97%, and a specificity of 73% to 96% (**Fig. 90.8**).[28] The disadvantage of MRA is that it cannot be used in patients with metallic implants such as pacemakers and patients with claustrophobia. Furthermore, in patients with moderately severe renal dysfunction (glomerular filtration rate of <60 mL/min/1.72 m^2), concerns for nephrogenic systemic fibrosis secondary to gadolinium limit the use of this technology.[29]

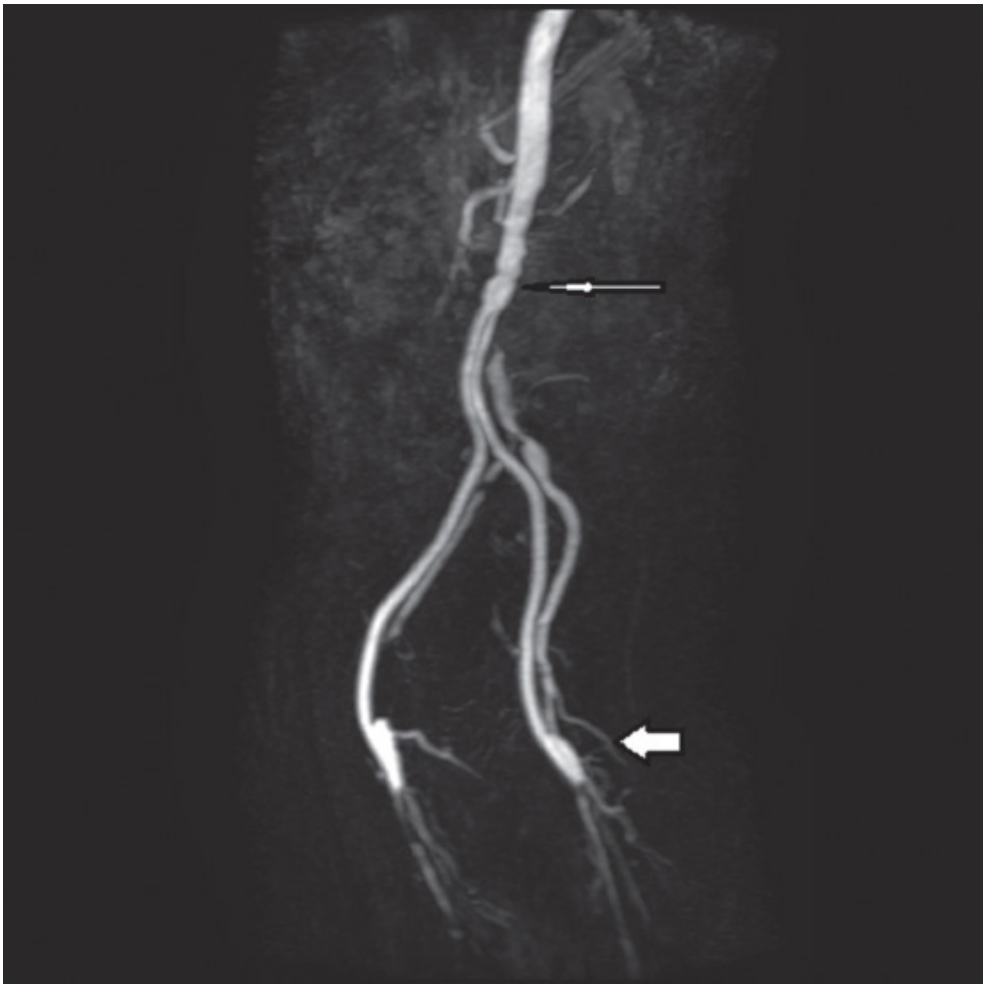


Figure 90.8 MRA of a patient who had an aortobifemoral bypass. Note the proximal anastomosis (*thin arrow*) and the distal anastomosis (*thick arrows*). Also note the retrograde flow into the iliac arteries.

Digital Subtraction Arteriography

Abdominal aortography, with or without demonstration of the arterial tree below the inguinal ligament ("runoff"), is performed after a full workup is completed and may be coupled with a therapeutic intervention. This procedure is most commonly performed via the femoral artery with the better pulse by means of a retrograde Seldinger technique. When neither femoral artery is suitable for puncture, an upper extremity approach may provide the necessary access. Hemorrhage, local hematoma, pseudoaneurysm, arterial thrombosis, or distal embolism of thrombus or atheromatous debris can occur in up to 0.2% of diagnostic procedures and in up to 3% of therapeutic procedures.[30] Anteroposterior views of the aortoiliofemoral segments demonstrate the extent of the occlusive process and the pattern of collateral formation. Oblique views of the iliac and femoral arteries are necessary to document posterior wall plaques and stenoses at the origins of the hypogastric and deep femoral arteries. Views of the "runoff" arteries to at least the midcalf level are required to assess the degree of associated infrainguinal occlusive disease. In cases of CLTI, visualization of the pedal circulation is also necessary. In patients with borderline kidney function, carbon dioxide may be utilized as a contrast agent.

Occasionally, the hemodynamic effect of a stenosis or series of stenoses along an iliac arterial segment may be difficult to determine, even with oblique views. When the significance of a stenosis remains in question, pressures proximal and distal to the lesion(s) can be measured. A systolic pressure gradient of more than 10 mm Hg (or a 5 mm Hg mean gradient) across the stenosis is indicative of a hemodynamically significant lesion.[31] For borderline cases, distal pressure measurements can be obtained before and after interarterial injection of a vasodilator (e.g., 100- to 200-µg nitroglycerin or 25-mg papaverine) to simulate the hyperemic hemodynamics of exercise. A pressure drop of more than 15% systolic pressure (or around 20 mm Hg) during hyperdynamic flow simulation is considered indicative of a hemodynamically significant stenosis.

The information supplied by CTA, MRA, or arteriography is crucial to the success of a revascularization procedure. In addition to providing a detailed "road map" of the exact arterial segments involved, such imaging identifies associated anatomic variations (e.g., accessory renal arteries) and aortic wall characteristics (e.g., extensive calcification and ulcerated plaque), which may alter the operative approach and the conduct of the procedure.

During an open revascularization procedure, a surgeon who knows that the aortic wall just below the renal arteries is heavily diseased with ulcerated plaque may, for example, opt to control the aorta at a more proximal level rather than risk dislodging atheromatous debris with standard infrarenal aortic clamping. Similarly, documented occlusive lesions in the visceral or renal arteries (e.g., a patent inferior mesenteric artery with a large "meandering mesenteric artery") may best be addressed at the time of aortic reconstruction, or require particular attention to avoid complications.

Preoperative Evaluation

Evaluation of patients for whom aortoiliac revascularization is being considered should include a careful assessment of overall operative risk. Age per se is not a contraindication to an open aortic reconstruction, if it is required. A less invasive procedure of more limited durability, however, may provide a similarly excellent outcome in a patient with reduced life expectancy. Patients with significant AIOD may have atherosclerotic occlusive disease in other vascular territories (e.g., coronary and cerebral) that can increase their operative risk. The detection and treatment of significant coronary artery disease is particularly important, because myocardial infarction is the leading cause of both perioperative and late mortality. In patients with significant aortoiliac disease, more than 50% have clinical or electrocardiographic evidence of coronary disease.[32] In the Coronary Artery Revascularization Prophylaxis (CARP) trial, patients undergoing elective, open, abdominal aortic surgery for aortoiliac occlusive or aneurysmal disease at Veterans Administration hospitals were assessed for cardiac risk.[33] With optimal medical management, there was no difference in outcome between those who underwent coronary revascularization prior to aortic surgery and those who did not. Only selected patients, therefore, require cardiac catheterization and occasional coronary angioplasty or bypass grafting before undergoing open aortic reconstruction, and these patients need to be stratified according to risk guidelines.[34]

Respiratory complications occur in 10% to 15% of patients after open aortoiliac repair, and pulmonary function should be assessed preoperatively only if clinical evaluation cannot determine that the patient is at his/her best

achievable baseline pulmonary function and that airway obstruction has not been optimally treated. There is otherwise no indication for routine preoperative pulmonary function testing, as the American College of Physicians Guidelines state that routine preoperative spirometry is not useful for predicting the risk of postoperative pulmonary complications.[35] Smokers who quit more than 4 weeks before surgery have a significantly lower risk of respiratory complications and improved wound healing.

Choice of Revascularization Technique

A variety of surgical procedures, both endovascular and open, are available for revascularization in the patient with AIOD. Selection depends on a number of factors, including the pattern of the occlusive process, patient risk, surgeon experience, and patient preference.

Commonly used techniques include (a) catheter-based balloon dilation (angioplasty) with or without luminal stenting, (b) arterial reconstruction with an anatomically placed bypass prosthesis (aortofemoral or iliofemoral bypass), (c) arterial reconstruction with a remote (or extra-anatomically placed) bypass prosthesis (axillofemoral or bifemoral, femorofemoral, thoracofemoral bypass), (d) aortoiliac endarterectomy, and (e) a hybrid approach encompassing a combination of endovascular and open procedures.

Catheter-based techniques are best suited for localized lesions of the common iliac arteries. However, this approach is currently being used as the main therapeutic modality for the majority of patients; it has essentially replaced endarterectomy procedures in patients with focal AIOD, and even more complex lesions. Prosthetic aortofemoral bypass is the procedure of choice for most patients with advanced, extensive aortoiliac atherosclerosis. Femorofemoral bypass can be chosen in poor-risk patients with diffuse unilateral iliac disease. Axillofemoral or axillobifemoral bypass is reserved for the subset of patients in whom standard aortic reconstruction is considered too risky, either for medical reasons (usually severe pulmonary or cardiac disease) or for technical reasons (e.g., aortic reoperations, multiple prior abdominal procedures with dense adhesions, prior abdominal irradiation, and prosthetic graft infection).

Percutaneous transluminal angioplasty (PTA) with or without stenting has become the most commonly performed and, in many cases, the preferred therapy for iliac artery occlusive disease. Like open operative reconstruction, PTA, when properly selected, has a high rate of success owing to the large caliber and high rates of flow in the aortoiliac segment. The pattern of the occlusive process and patient comorbidities are primary considerations in selecting PTA as the mode of therapy. The best results are obtained with short, focal, stenotic lesions in the common iliac arteries. Patients with severe atherosclerotic lesions, complicated stenoses, and occlusions may also benefit from complex endovascular approaches, with many series documenting excellent short and intermediate-term success. Atheromatous embolism (blue toe syndrome) from an ulcerative plaque may be treated with placement of a stent to trap the debris, relieve the stenosis, and prevent recurrent embolism.

Description of Technique

Preprocedure planning sets the stage for a successful endovascular intervention. Although not absolutely necessary, CTA or MRA can delineate the location, extent, and degree of stenosis and associated calcification (**Fig. 90.6A**). Other considerations include the possible need for a concomitant femoral endarterectomy. When there is significant common femoral artery disease (>50% stenosis) along with iliac occlusive disease, a femoral endarterectomy with patch angioplasty is performed. The endarterectomy should extend as high as possible under the inguinal ligament into the external iliac artery to facilitate stent deployment into the proximal endarterectomized segment but avoid its placement into the common femoral artery itself. A hydrophilic wire with an angled tip, and a straight or angled catheter for support are utilized to cross the stenosis or occlusion. Common iliac artery disease is treated through an ipsilateral retrograde approach if the external iliac is open. If the common iliac artery is occluded, bilateral punctures of the femoral arteries will be necessary to perform aortography to delineate the extent of obstruction (**Fig. 90.6B**). In the absence of significant ipsilateral common femoral artery disease, external iliac disease is usually approached antegrade through a contralateral femoral puncture and “up and over” the aortic bifurcation. Crossing total occlusions may be challenging, and reentry into the true lumen from the subintimal space can be difficult. If

crossing an occlusion cannot be achieved from the chosen point of vascular access (e.g., the ipsilateral common femoral), an attempt should be made from a new access site (e.g., contralateral common femoral or brachial). For more challenging cases, reentry devices such as the OUTBACK (Cordis Corp., Bridgewater, NJ) or Pioneer (Medtronic, Fridley, MN) catheters may be used. Once the lesion is successfully crossed with a wire, the mode of intervention should then be considered. The typical balloon size used for common iliac arteries is 8 to 10 mm in diameter, and for external iliac arteries 7 to 8 mm in diameter. The principal cause of balloon angioplasty failure is recoil of the atherosclerotic artery or a flow-limiting dissection. Stents serve as support to oppose the elastic recoil of the media and adventitia of the artery after angioplasty. They are also highly effective in sealing dissection planes within the atherosclerotic plaque resulting from the angioplasty procedure. Stents are also indicated for residual postballoon stenosis (>30%), persistent gradients (>10 mm Hg), ulcerative plaques that have a high risk of showering debris, and after recanalization of an occluded artery. Most vascular interventionalist stent iliac lesions primarily, rather than ballooning first to see if there is an issue requiring stenting (e.g., a residual dissection). Primary stenting for complex aortoiliac disease is thought to decrease complications and reduce overall long-term failure.[36,37]

Self-expanding stents come precovered with a sheath and can be introduced into the lesion directly. Pulling back the sheath allows the compressed stent to assume its expanded form. Self-expanding stents may be more flexible and less likely to get crushed in the event they are deployed close to or past the inguinal ligament into the common femoral artery and are, therefore, used more frequently in the external iliac artery. With self-expanding stents, postdeployment balloon angioplasty is usually needed to achieve full expansion. These stents are usually chosen 10% to 15% larger than the intended lumen diameter; undersizing must be avoided as self-expanding stents cannot be dilated past their nominal diameter.

Balloon expandable stents are sometimes preferred to self-expanding stents in the common iliac artery, owing to their ease and precision of deployment, their better visibility under fluoroscopy, and the increased radial force of their design. These stents are usually introduced through a long sheath passed through the lesion to prevent dislodgment of the stent as it traverses the lesion. The sheath is pulled back once the stent is in satisfactory

position, and the stent is deployed under fluoroscopic guidance. Balloon expandable stents are usually sized to the diameter of the normal adjacent artery. Slight undersizing of the stent can be easily managed by further dilating the stent, using a larger balloon. Covered balloon-expandable and self-expanding stents have been introduced and are purported to offer a longer patency rate by controlling neointimal hyperplasia that may grow through the interstices of a noncovered stent.[38] Covered stents may also be useful for ulcerated plaques, because they reduce the chance of distal atheromatous embolism and for heavily calcified or tortuous iliac arteries that are more prone to rupture with balloon inflation.

Lesions just above the aortic bifurcation are usually complex, exophytic, and calcific, and commonly involve both common iliac arteries. Safe and effective intervention in this situation typically requires the use of two stents, one in each iliac artery, that partially project into the aorta so that they "kiss" in the distal aorta (**Fig. 90.6C**). Theoretically, treating only one common iliac artery orifice can result in plaque shifting during the angioplasty, causing a new obstruction of the contralateral lumen. Treating both sides simultaneously ("kissing stents") avoids this complication. Endovascular stent grafts, similar to those used in the treatment of abdominal aortic aneurysms, have been evaluated for the treatment of AIOD; this is known as covered endovascular reconstruction of the aortic bifurcation (CERAB) (**Fig. 90.7**). Flow dynamics seem better with CERAB[39] and covered stents are associated with the purported advantages outlined previously. In one CERAB series, the 3-year primary and secondary patency rates were 82% and 97%, respectively.[40] Although these rates are inferior to conventional open reconstruction, they suggest that endovascular reconstruction affords a reasonable alternative when open procedures are high risk or contraindicated.

Table 90.5 Complications of Endovascular Therapy

Complication	
Access site hematoma	5%
Pseudoaneurysm	1.60%
Distal embolization	1.10%
Rupture	0.50%
Thrombosis	0.60%

Complications of Endovascular Interventions

The overall procedure-related complication rate has decreased over the years. It is cited to be around 10% of cases, while the rate of major complications is 5% with access site complications being the most common (**Table 90.5**).[41,42] The incidence of contrast-induced nephropathy is low but is troubling in patients with pre-existing renal insufficiency. Depending on the risk factors and amount of contrast used, the risk of any renal dysfunction ranges from 5% in low-risk patients to >50% in the high-risk groups.[43] Low-osmolality or iso-osmolality agents should be used in patients with moderate renal insufficiency. Volume expansion should be considered in the periprocedural period. The most serious intraoperative complication is arterial rupture during angioplasty (0.5% to 3%). This is seen as active extravasation on the postintervention angiogram and can be heralded by abdominal pain and hypotension. Treatment is quick passage and reinflation of the balloon to occlude the rupture site to maintain hemodynamic control and then either deployment of a covered stent across the rupture site or open repair in the operating room.

Outcome of Endovascular Interventions (*Table 90.6*)

Initial technical success is quite high (>90%).[41] The most common reasons for technical failure are inability to cross an occluded arterial segment, thrombosis after intervention, or arterial rupture. Surveillance with ABIs and possible duplex ultrasound play a major role in maintaining patency in these patients. The primary patency of iliac artery stenting is 60% to 80% at 5

years, but this can improve to >90% with close surveillance and reintervention as necessary.[41,42,44]

Table 90.6 Results of Endovascular Interventions for AIOD

Procedure	Technical Success	5-y Primary Patency	5-y Secondary Patency	Mortality
Iliac angioplasty and stenting	85–100% Technical success	60–80% 3-y primary patency	80–98% 3-y secondary patency	1–6%
CERAB[a]	97%	86%	97%	N/A

[a]CERAB, covered endovascular reconstruction of aortic bifurcation.

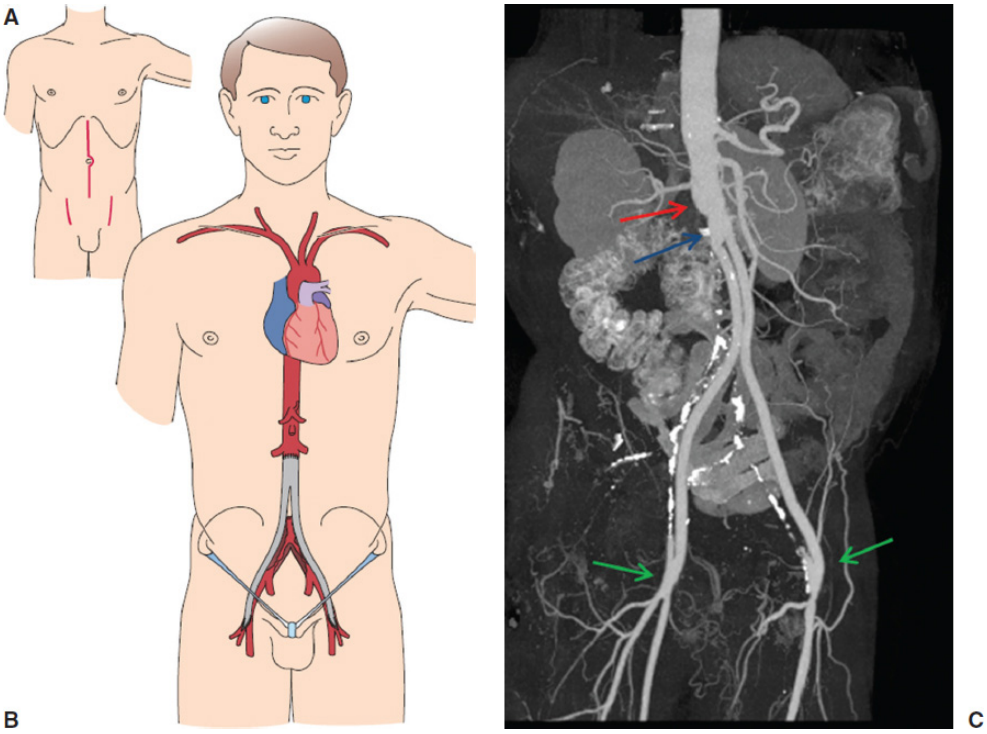


Figure 90.9 **A:** A midline abdominal incision and bilateral groin incisions overlying the common femoral arteries offer exposure for performance of aortobifemoral bypass. **B:** This image demonstrates an end-to-end proximal aortic to graft reconstruction with the respective graft limbs anastomosed end to side to the common femoral arteries. **C:** Computed tomographic angiographic postprocessed and reformatted image demonstrating open aortobifemoral arterial reconstruction of juxtarenal aortic occlusion (see **Fig. 90.2**, preoperative image) with prosthetic bifurcated graft. Note endarterectomy of aorta immediately distal to renal arteries (*red arrow*), followed by proximal end-to-end anastomosis between graft and aorta (*blue arrow*). Distal anastomosis to femoral arteries is performed in end-to-side fashion (*green arrows*).

Open Surgical Management

Aortobifemoral (AF2) bypass has been the gold standard open surgical procedure for treating AIOD for decades. Five-year patency rates are in excess of 95%, which is unmatched by any endovascular procedure.[45,46] However, direct revascularization of the aortoiliac segment is currently reserved for patients with advanced occlusive disease, for whom the risk of surgery is acceptable and a durable long-term result is required.

Description of Aortofemoral Bypass (Fig. 90.9)[46]

The operation begins with bilateral groin incisions to expose the common, superficial, and deep femoral arteries as needed. Starting the operation in the groins minimizes the duration of time the abdomen is open; this limits fluid loss and hypothermia, and decreases the risk of graft infection. If the femoral arteries are severely atherosclerotic, the external iliac just above the inguinal ligament is often a soft, disease-free segment that is amenable to safe clamping. The profunda femoris (deep femoral) artery is a critical collateral pathway for the entire lower extremity. If disease is present at its origin, exposure of the profunda femoris beyond its take off is required for a complete endarterectomy.

The abdominal aorta is usually exposed via a midline, transperitoneal, inframesocolic approach. The transverse colon is retracted cephalad, the ligament of Treitz taken down, and the duodenum (third and fourth portions) mobilized to the right. The left renal vein is identified in the retroperitoneum and serves as the most cephalad limit of exposure in most cases (0.5% to 3% of patients have a retroaortic left renal vein). The anterior surface of the aorta is then exposed from the lower border of the left renal vein to just below the inframesenteric artery (IMA). Numerous lymphatics are usually encountered in the para-aortic retroperitoneal space particularly at the level of the left renal vein. These should be ligated to decrease the chances of a chyle leak. The left renal vein is mobilized if more proximal aortic control is needed; this is performed by ligating and dividing its adrenal, gonadal, and lumbar branches. It is generally unnecessary to divide the renal vein. Distal control of the aorta is dictated by the extent of disease. When exposing sites for distal control, the location of the hypogastric plexus and the presacral nerves, which course anterior to the aorta and travel caudally over the aortic bifurcation and origin of the left common iliac artery, needs to be kept in mind. Injury to the sympathetic nerves can cause retrograde ejaculation in

males. Retroperitoneal tunnels are then developed between the exposed infrarenal aorta and the groins by means of blunt finger dissection. The tunnels are directed posterior to the ureters to avoid postoperative obstructive uropathy from entrapment of the ureter between the graft limb and the native iliac artery. A retroperitoneal approach to the aorta via a left flank incision is an accepted alternative, especially in those patients with "hostile" abdomen; however, it makes creation of the tunnel for the right limb of the bypass graft slightly more challenging.[47]

A bifurcated vascular prosthesis of appropriate size is selected, typically a presealed knitted Dacron or a polytetrafluoroethylene graft, and the patient is heparinized. With an occluding clamp below the renal arteries and another just above the IMA, the proximal anastomosis between the graft and the aorta is performed in either an end-to-end or end-to-side fashion. Though most vascular surgeons prefer an end-to-end anastomosis for technical simplicity, the end-to-side technique has been found to be just as good, depending on the pattern of occlusive lesions and need to maintain flow to patent hypogastric arteries.[48] The proximal anastomosis is placed as close to the renal arteries as practical to prevent future compromise of the bypass resulting from progression of atherosclerosis in the remaining infrarenal cuff. The limbs of the prosthesis are then delivered through the retroperitoneal tunnels into the groins. The distal anastomoses are performed to the common femoral arteries and should be carried onto the profunda femoral arteries if there is any disease at the femoral bifurcation (**Fig. 90.8**). Common femoral and profunda femoris origin endarterectomy may be needed and should be carried out prior to the anastomosis. Maintaining good outflow through the profunda femoris is very important as many of these patients have concomitant superficial femoral arterial disease, which may compromise long-term graft patency. In the rare patient with tissue loss secondary to multilevel disease (AIOD associated with an occluded superficial femoral artery and compromised deep femoral collaterals), a concomitant distal bypass (femoropopliteal–tibial) may also be required.

Endarterectomy

Endarterectomy was more commonly performed in the era before reliable vascular prosthetic conduits were available. The high success rates of

angioplasty and stenting for the more limited disease patterns amenable to endarterectomy have rendered aortoiliac endarterectomy essentially obsolete in most current practices.

Extra-Anatomic Bypass

Patients who are at high risk for open aortic surgery due to either physiologic or anatomic constraints and are not endovascular candidates may be better served with extra-anatomic reconstruction. Although these operations are less risky, they have a documented lower patency rate and are, therefore, reserved for patients with CLI and generally not performed for intermittent claudication.

Axillofemoral extra-anatomic reconstruction has been used for revascularization in poor-risk patients and in those with a "hostile" abdomen and has been reported to be an acceptable alternative to aortofemoral bypass (**Fig. 90.10**).[49] The axillary artery supplying the arm with the higher brachial blood pressure is chosen as the inflow vessel, usually the right side. The operative sequence starts with exposure of the first portion of the axillary artery through an infraclavicular, pectoralis major muscle-splitting incision. The common, superficial, and deep femoral arteries are then dissected through bilateral groin incisions. An externally supported polytetrafluoroethylene graft is then passed between the pectoralis major and minor muscles and through a subcutaneous tunnel in the anterior axillary line, connecting the axillary incision with the ipsilateral groin incision. Next, a cross-femoral limb of the graft is delivered through a subcutaneous suprapubic tunnel connecting the two groins. An anastomosis between the proximal axillary artery and the prosthesis is then constructed in an end-graft–to–side-of-artery fashion. The distal anastomoses are performed end to side to the common femoral arteries and may be carried over or onto the deep femoral arteries to ensure adequate graft outflow. Providing flow through both femoral arteries (axillobifemoral bypass) rather than one ipsilateral femoral artery (axillounifemoral) has been shown to increase flow velocities within the long main shaft of the graft and improve long-term patency of the bypass.[49] The lower patency of the axillofemoral bypass limits its application to patients with advanced aortoiliac disease who are poor surgical risks with a reduced life expectancy or those with a "hostile"

abdomen. For high-risk patients with diffuse advanced disease limited to one iliac artery, cross-femoral (or femoral artery–to–femoral artery) bypass or an iliofemoral bypass is an option.

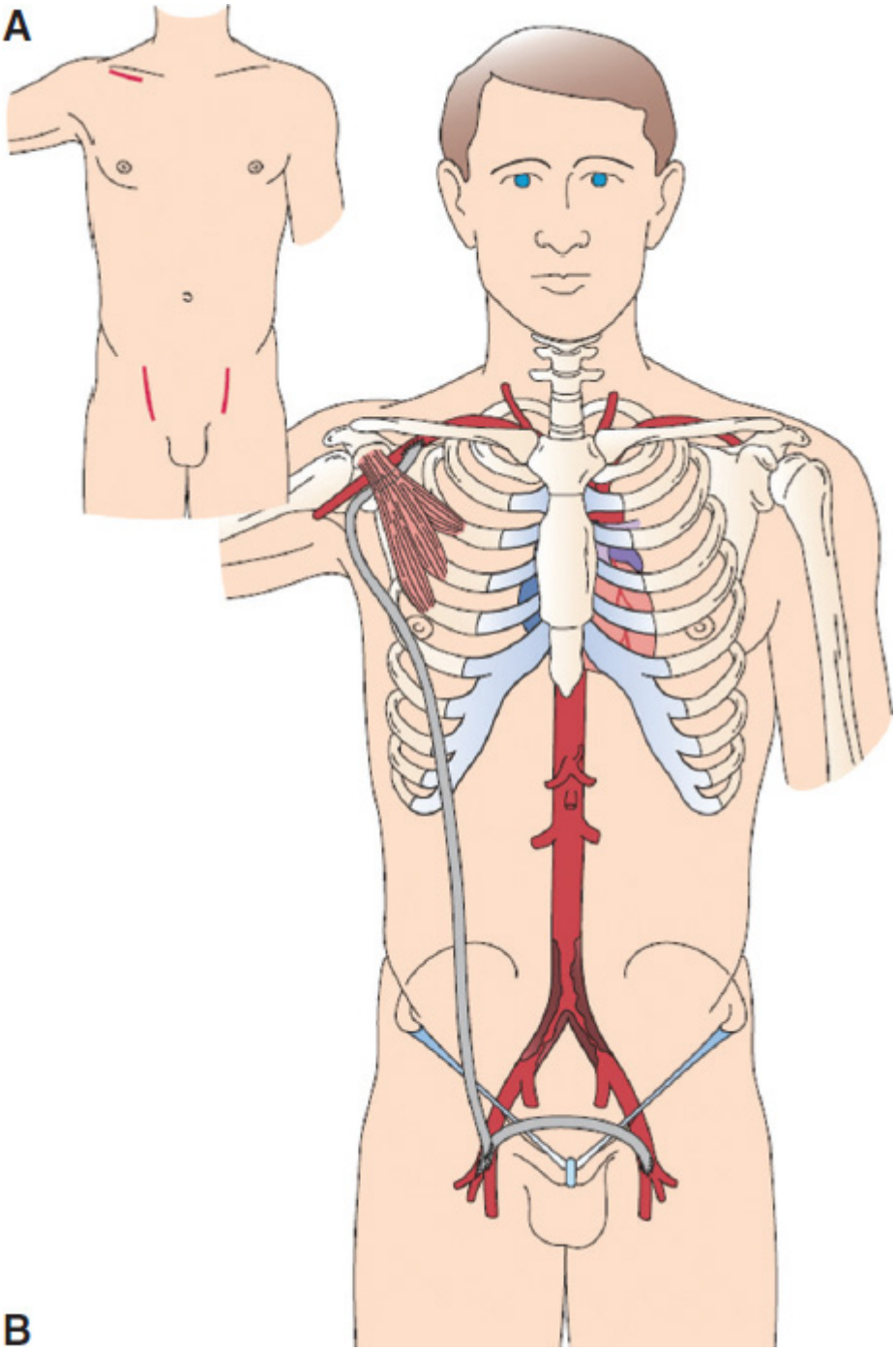


Figure 90.10 **A:** Ipsilateral infraclavicular incision and bilateral femoral incision locations for extra-anatomic axillary to bifemoral artery bypass. **B:** Image demonstrates unilateral axillary to ipsilateral femoral artery bypass graft with cross-femoral to femoral artery bypass graft.

Outcomes

The excellent durability of aortofemoral bypass is related to the large caliber and high flow rates of the vessels involved. Results of direct surgical revascularization are listed in **Table 90.7**. Aortofemoral bypass has excellent primary graft patency rates of approximately 85% to 95% at 5 years and 75% to 88% at 10 years. Factors associated with lower long-term patency of these reconstructions include female sex (in part due to smaller vessel size), multilevel arterial occlusive disease (poor run-off), and younger age (<50 years) where premature and aggressive atherosclerosis and/or hypercoaguability are usually present.[50,51] The most common cause of failure of surgical reconstructions is the progression of atherosclerosis proximal and/or distal to the graft or the development of anastomotic neointimal hyperplasia.[52]

Complications

Due to advances in anesthesia and surgical critical care, aortofemoral bypass can be performed with perioperative mortality and morbidity below 5%.[53] The perioperative morbidity and mortality for axillofemoral bypass is similar but is performed, in general, on a much higher-risk population of patients.

Early Complications

- Postoperative cardiac events have decreased to less than 5%. This is due to diligent preoperative screening and following the excellent perioperative guidelines promoted by numerous professional societies including the use of aspirin, statins, and perioperative beta blockers.

Table 90.7 Results of Direct Surgical Revascularization

Procedure	5-y Patency (%)	Operative Mortality (%)
Aortofemoral bypass	80–95	2–4
Femorofemoral bypass	50–60	1–3
Axillobifemoral bypass	30–50	1–4

- Pulmonary complications are not infrequent, occurring in up to 7% of patients. Adequate pain control with epidural anesthesia to facilitate pulmonary toilet and avoiding volume overload can help reduce these complications.
- Atheroemboli can occur during the procedure, manifesting as end-organ ischemia of the skin, pelvis, spinal cord, and bowel. Attention to detail during arterial clamping and flushing out the graft before unclamping can minimize this complication.
- Ischemic colitis and pelvic ischemia are rare and can be minimized by planning a procedure that maintains pelvic perfusion and blood flow to the IMA when collateral flow is insufficient to maintain left colon viability. Selective reimplantation of the IMA can be performed when poor IMA perfusion is anticipated or demonstrated. Ischemic colitis may require colectomy for treatment, but this is associated with a 50% mortality.
- Acute kidney injury can result from either atheroembolism from aortic clamping close to the renal arteries or from corticomedullary renal shunting induced by the acute increase in afterload with aortic clamping.
- Other possible complications include wound complications, particularly in the groin (lymphocele, lymphocutaneous fistula, wound infection), postoperative hemorrhage, erectile dysfunction in men, bowel injury, pancreatitis from retraction injury, and very rarely spinal cord ischemia. Groin wound complications can be particularly troublesome for axillofemoral and femorofemoral bypasses because of the subcutaneous location of these prosthetic grafts.

Late Complications

- Graft thrombosis is largely due to progression of native atherosclerotic disease either proximal or distal to the graft, or to anastomotic neointimal hyperplasia.
- Pseudoaneurysms from material fatigue, suture fracture, artery wall degeneration, or occult infection.
- Graft infection. A graft enteric fistula (most frequently to the third/fourth portions of the overlying duodenum) may present as a gastrointestinal bleed. Every gastrointestinal bleed in a patient with a history of aortofemoral bypass or other aortic reconstruction should be considered to be an aortoenteric fistula until proven otherwise.

QUIZ

1. A 60-year-old man with severe aortoiliac occlusive disease can walk half a block before he needs to stop due to severe lifestyle-limiting claudication. Before offering any interventional therapy, maximal medical therapy includes:
   - **a.** Aspirin and Plavix (dual antiplatelet therapy) is indicated in most patients with severe aortoiliac disease.
   - **b.** Statin therapy is not needed if the patient's LDL is <100 mg/dL.
   - **c.** Smoking cessation alters the progression of the atherosclerotic process and may even reduce the severity of claudication.
   - **d.** Cilostazol has shown modest but significant reduction in claudication symptoms in all patients.

Discussion: Medical therapy is key to treating any patient with aortoiliac occlusive disease. Risk factor modification includes management of diabetes mellitus, control of hypertension, treatment of hyperlipidemia (starting a statin regardless of LDL level because of its pleiotropic effects on the vascular wall), smoking cessation, appropriate diet, and exercise. Antiplatelet agents are beneficial in all patients with atherosclerotic disease but there is no benefit to dual antiplatelet therapy in the average patient. Cilostazol improves claudication symptoms in >50% of patients, but by no means all.

Correct answer—c.

2. The previous patient has attempted medical therapy for 6 months with no significant improvement. He has TASC D aortoiliac occlusive disease based on CTA with no aneurysm. He had a cardiac stress test 6 months ago that was negative. Which of the following is correct?
   - **a.** With appropriate medical therapy progression to critical limb ischemia is around 20% per year.

b. Endovascular repair may be a good treatment option with periprocedural mortality of 2% and a 5-year primary patency rate of 95%.
c. Open repair (with an aortobifemoral bypass) is the gold standard for operative revascularization with a periprocedural mortality of approximately 5% and a 5-year patency >90%.
d. There is no other revascularization option if he is not an operative candidate and has failed endovascular therapy.

Discussion: With medical therapy progression of disease is around 2% per year. Endovascular therapy has a low mortality (around 1% to 2%) but the need for further intervention is high. Open repair with an aortobifemoral bypass has the best long-term patency. Extra-anatomic bypasses are an option for sicker patients who cannot tolerate a standard aortobifemoral bypass.

Correct answer—c.

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Peripheral Arterial Disease

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Key Points

1. Chronic obliterative atherosclerosis of the infrainguinal vessels is the most prevalent manifestation of peripheral arterial disease (PAD) encountered by the vascular surgeon.
2. The major risk factors for the development of PAD include smoking, diabetes, advanced age, male gender, hypertension, dyslipidemia, and chronic kidney disease.
3. PAD is a powerful risk factor for cardiovascular morbidity and mortality.
4. The most common lesion seen below the inguinal ligament is that of a short-segment total occlusion of the superficial femoral artery.
5. The diagnosis of infrainguinal occlusive disease is generally made based on patient symptomatology, physical examination, and noninvasive tests, such as ankle–brachial index (ABI), segmental pressure measurements, and pulse volume recordings.
6. A novel Wound, Ischemia, and foot Infection (WIfI) classification system allows for staging of limb-threat severity and guides initial management as well as additional adjunctive operative procedures for salvage of the foot and limb.
7. Percutaneous endovascular therapy is often applied as first-line therapy, particularly in patients with more limited extent of anatomic disease and/or high operative risk.
8. Open surgical revascularization remains the gold standard for those patients with disabling claudication, ischemic rest pain, and ischemic ulceration or gangrene.
9. Infrainguinal arterial bypass surgery remains the signature operation distinguishing vascular surgeons from other specialists involved in the treatment of peripheral vascular disease.
10. Infrainguinal bypass surgery is best performed with autogenous vein conduit, preferably the ipsilateral greater saphenous vein if available.

INTRODUCTION AND EPIDEMIOLOGY

The term "Peripheral Arterial Disease (PAD)" broadly denotes stenotic, occlusive, and aneurysmal diseases of the aorta and its branch arteries, exclusive of the coronary arteries. In common clinical usage, PAD, which is defined as an ankle–brachial index (ABI) <0.9, denotes atherosclerotic stenosis or occlusion of the arteries supplying the lower extremities.[1] Atherosclerotic occlusive disease of the aorta and iliac arteries is covered in Chapter 108. This chapter will cover PAD located in the femoropopliteal and tibial (infrainguinal) arteries. PAD affects 12% of the U.S. adult population and almost 20% of U.S. adults older than age 70 years.[1–3] PAD involving the lower extremities is the third leading overall cause of atherosclerotic morbidity worldwide after coronary artery disease and stroke.[4] With the aging of the American population, the prevalence of lower extremity occlusive disease has steadily 1 increased in recent decades. Symptomatic PAD in the form of claudication affects more than 10 million Americans including 1% to 2% of those aged <50, 5% of those aged 50 to 70, and 10% of those aged >70. Of those aged >50 with PAD, 1% to 3% will have chronic limb-threatening ischemia (CLTI) in the form of rest pain or gangrene.[5,6] The incidence of CLTI ranges from 220 to 1,000 new cases per year in a European or American population of 1 million people.[7] Not surprisingly, therefore, the clinical manifestations and complications of atherosclerosis are the most common therapeutic challenges encountered and treated by vascular surgeons.

The tendency for atherosclerotic lesions to develop at specific anatomic sites and follow recognizable patterns of progression was first appreciated in the late 1700s by the British anatomist and surgeon John Hunter. Considered one of the forefathers of vascular surgery, his dissections of atherosclerotic aortic bifurcations are preserved at the Hunterian museum in London and presage the disease process that Leriche would give his name to 150 years later.[8] The modern era of surgical reconstruction for complex atherosclerotic occlusive disease began in earnest in 1947, when the Portuguese surgeon J. Cid dos Santos successfully endarterectomized a heavily diseased common femoral artery.[9] Four years later, building on the pioneering work of Alexis Carrel, Kunlin would report the first long-segment vein bypass in the lower extremity.[10,11] It would be another 10 years before

the initial efforts to extend vein grafting to the tibial level were described by McCaughan.[12] The last three decades have seen tremendous advances in both the understanding of atherosclerosis biology and refinement in the techniques of infrainguinal surgical revascularization that have greatly improved surgeons ability to preserve limbs and improve quality of life in patients with femoropopliteal and tibial occlusive disease. Moreover, in the last two decades, advances in percutaneous treatment have revolutionized the treatment of infrainguinal occlusive disease. The concept of intravascular intervention was pioneered in the late 1960s by the radiologist Charles Dotter, and advanced greatly with the advent of the angioplasty balloon by Gruntzig in the early 1970s.[13,14] Nevertheless, endovascular intervention for infrainguinal disease was not utilized significantly until the 1990s. The technology remains in rapid development and surrounded by ongoing controversy as to its proper role.

Although a diverse range of technical skill is required of the contemporary vascular and endovascular surgeon, it is worth noting that infrainguinal arterial bypass surgery remains the signature operation distinguishing vascular surgeons from other specialists involved in the treatment of PAD. This distinction stems primarily from the fact that the outcome of infrainguinal reconstruction is highly dependent on the judgment and technical skill of the surgeon, with the end result often being either successful limb salvage or major limb amputation. This chapter reviews the surgical and endovascular management of femoropopliteal and tibial arterial occlusive disease and details standard and advanced techniques underlying successful infrainguinal operative revascularization. Endovascular intervention is introduced, though a comprehensive review of endovascular techniques used to treat femoropopliteal and tibial occlusive disease is beyond the scope of this chapter.

INFRAINGUINAL ARTERIAL OCCLUSIVE DISEASE

Risk Factors

2 The risk factors for infrainguinal occlusive disease are the same as those for the development of atherosclerosis in general and include age, male gender, hypertension, diabetes mellitus (DM), smoking, dyslipidemia, family history, and homocysteinemia. Smoking and diabetes are the most powerful risk factors. Smokers are at four times the risk of symptomatic PAD than nonsmokers while diabetics are more than three times more likely to develop symptomatic PAD in comparison to nondiabetics.[7] The propensity for heavy smokers to develop superficial femoral artery disease and for diabetics to develop tibial disease should be noted. More recent evidence indicates that nonwhite ethnicity, inflammatory markers such as C-reactive protein, and perhaps chronic renal insufficiency (CRI) are also associated with an increased risk of PAD.[15–17]

Presentation and Natural History

Chronic obliterative atherosclerosis of the infrainguinal vessels is the most prevalent manifestation of PAD encountered by the vascular surgeon. Patients are classified into two broad categories depending upon their symptomatology: claudicants and those with CLTI. Claudication, the reproducible ischemic muscle pain resulting from inadequate oxygen delivery during exercise, is the cardinal presenting symptom. Natural history studies indicate patients with claudication have increased rates of cardiovascular mortality, but an overall low risk of limb loss.[18,19] Seventy percent to 80% of patients with claudication demonstrate a stable pattern of disease throughout their lifetime or have improvement in their symptoms as a result of risk factor modification, whereas 20% to 30% undergo operation within 5 years as a result of disease progression. Claudication will progress to CLTI in 3 only 5% to 10% of patients over their lifetime. However, PAD leading to claudication is a marker of severe systemic atherosclerotic burden and increased cardiovascular morbidity and mortality. Twenty percent of claudicants experience a nonfatal myocardial infarction or stroke and 10% to 15% died of cardiovascular-related mortality at 5 years.[6] The annual rates of mortality and limb loss in patients with claudication are approximately 2% to 5% and 1%, respectively.[6,20]

4 The most common atherosclerotic disease pattern encountered distal to the inguinal ligament is that of a short-segment total occlusion of the

superficial femoral artery. Isolated disease of this nature typically presents as calf muscle claudication. It is not uncommon, however, for patients with significant single-level lesions, even those with long-segment arterial occlusions, in the superficial femoral artery or more distal arterial beds to be only minimally symptomatic or even asymptomatic. While this can sometimes be the result of exercise limitations imposed by concomitant coronary arterial disease or other physiologic impairments such as lung disease or arthritis, it is more often a result of compensatory collateral flow. Collateral perfusion from the profunda femoral artery around a heavily diseased or occluded superficial femoral artery frequently reconstitutes the distal superficial femoral artery or popliteal artery with enough well-perfused arterial blood to ensure adequate resting tissue perfusion. Similarly, the rich network of geniculate collaterals can sometimes compensate for a diseased popliteal arterial segment to a sufficient degree to prevent rest pain or overt tissue loss but will usually prove insufficient to meet the increased metabolic demands of ambulation and forestall claudication.

CLTI, which must be differentiated from acute limb ischemia, is the most severe form of PAD and refers to the presence of either rest pain or tissue loss in the lower limb. Rest pain occurs when blood flow is inadequate to meet resting metabolic requirements. In the lower extremity, ischemic rest pain is localized to the foot, frequently in the metatarsals or the instep, and should be easily distinguishable from benign muscle cramps in the calf commonly seen in older patients. Patients with rest pain are often awakened by severe discomfort in the forefoot and hang the affected extremity over the edge of the bed for temporary symptomatic relief. Trophic changes, such as muscle wasting, thinning of skin, thickening of nails, and hair loss are frequently also seen in the distal affected limb. Rest pain is an ominous symptom and usually requires revascularization given the tendency for progression to tissue loss. Ischemic ulcerations usually begin as small, dry ulcers of the toes or heel area, and progress to frankly gangrenous changes of the forefoot or heel with greater degrees of arterial insufficiency (**Fig. 91.1**). Patients with diabetes or renal failure are more susceptible to the development of ischemic pedal ulcers. Disease progression can be very rapid, as up to 50% of patients with CLTI are asymptomatic 6 months before onset of pain or ulceration.[21] Such progressive disease, affecting multiple

levels of the peripheral vasculature tree, is more frequently encountered in the elderly.

The natural history of CLTI is dismal as these patients are generally of advanced age and possess significant comorbidities contributing to their advanced limb ischemia. Overall, approximately 25% of patients with CLTI will die at 1 year, 30% will undergo major amputation, and 45% will be alive with two limbs.[6,7] The rate of amputation is 10 times higher in diabetics than nondiabetics and 5- and 10-year mortality in patients with CLTI have been reported to be 60% and 85%, respectively.[21] CLTI mandates revascularization for limb salvage when feasible, as limb salvage with medical therapy and wound care is virtually futile; success rates for rest pain and tissue loss have been reported to be as low as 27% and 5%, respectively.[21]

Several identifiable patterns of infrainguinal PAD are well recognized. It is important to note that symptoms and signs of ischemia generally involve the limb one level distal to the level of hemodynamically significant disease. Patients with an extensive history of cigarette smoking typically have lesions limited to the superficial femoral artery and corresponding symptoms of calf claudication (**Fig. 91.2**). Patients with rest pain or ischemic tissue loss typically manifest more extensive involvement of the femoral, popliteal, or tibial arteries than patients with claudication. Those with tissue loss also more commonly have multilevel disease involving the femoropopliteal system in combination with occlusive disease of the aortoiliac vessels or the infrageniculate runoff.[22] Diabetes often targets the tibial vessels, and patients may present with frank tissue necrosis in the presence of a palpable popliteal pulse and no prior history of claudication.

Diagnosis

5 The diagnosis of infrainguinal occlusive disease is generally based on patient symptomatology, physical examination, and noninvasive tests, such as the ABI, segmental pressure measurements, and pulse volume recordings. Accurate history-taking and physical examination are crucial to clarifying the diagnosis and guiding management aimed at maximizing symptom relief and limb preservation. Intermittent claudication (IC) indicative of infrainguinal occlusive disease is typically a cramping, aching discomfort consistently

reproducible at a given distance and relieved soon after cessation of ambulation. This must be differentiated from lower extremity pain secondary to nerve root compression or spinal stenosis which, in contradistinction to vasculogenic pain, often develops when patients maintain a stationary standing posture. Vasculogenic claudication must also be distinguished from venous claudication, hip and ankle arthritis, symptomatic Baker cyst, and chronic compartment syndrome. IC patients with isolated infrainguinal disease will likely have palpable femoral pulses but diminished popliteal and/or pedal pulses.

Figure 91.1 **A–C:** Examples of digital ischemic ulcerations resulting from progressive arterial insufficiency.

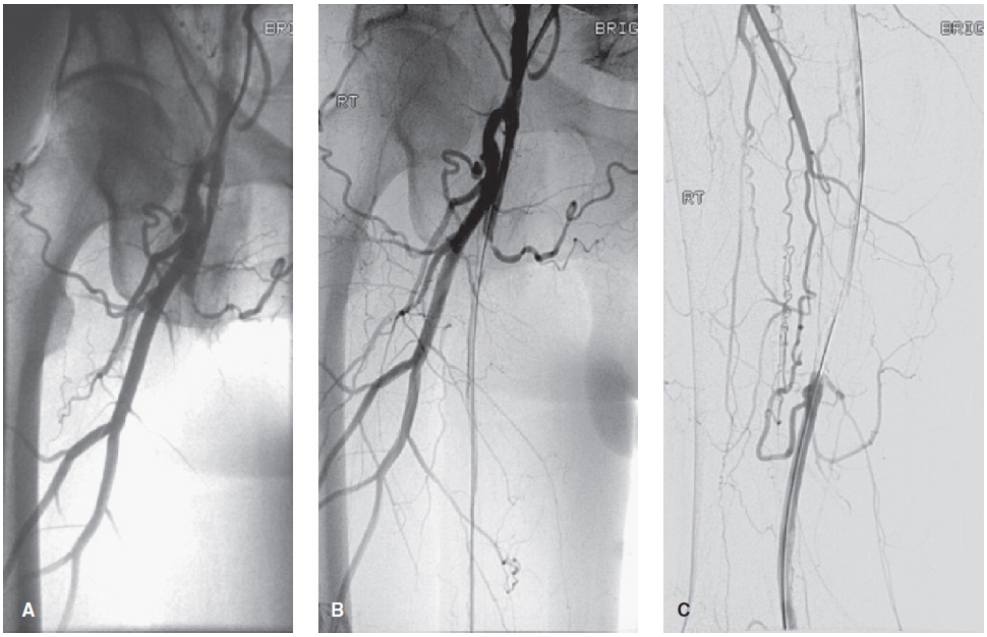

Figure 91.2 Long-segment total occlusion of superficial femoral artery (sfa) in a patient with a long history of cigarette smoking and severe claudication. Proximal sfa occlusion is demonstrated (**A**), followed by wire traversal of the occlusion (**B**), which will allow endovascular treatment of the occluded segment of the sfa proximal to reconstitution of the above-knee popliteal artery (**C**).

As is true with claudication, ischemic rest pain must be carefully distinguished from other sources of pain in the elderly population, most commonly arthralgia and neuropathy. Although tissue necrosis and gangrene are usually self-evident when caused by critical ischemia, similar lesions associated with venous stasis, severe anemia, decubitus ulcers, and diabetic neuropathy must be excluded.

Noninvasive physiologic arterial testing allows confirmation of infrainguinal occlusive disease when it is suspected based upon history and physical examination. Measurement of the ABI is the most useful diagnostic adjunct. A properly performed ABI in a claudicant without significant evidence for vascular calcification would be expected to be between 0.5 and 0.9. Ischemic rest pain generally occurs at ABI 0.4 to 0.5, whereas an ABI less than 0.4 is generally associated with tissue loss. Segmental pressure measurements at the level of the upper thigh, lower thigh, upper calf, ankle, and metatarsal level also aid in localizing the level of hemodynamically significant disease. A decrease in pressure greater than 20 mm Hg between levels indicates a hemodynamically significant stenosis in the intervening

arterial vasculature. In patients with DM or CRI leading to extensive vascular calcification, the ABI will often be erroneously elevated due to medial calcinosis and subsequent noncompressibility of the vessels. In such circumstances, pulse volume recordings, which ascertain the volume of blood flowing into segment of the limb, remain a reliable indicator of perfusion to the various levels of the lower extremity. Measurement of toe pressures also effectively quantitates distal perfusion as the digital arteries are generally spared of calcium which inhibits compressibility. A toe–brachial index less than 0.7 is considered abnormal. Absolute toe pressure less than 30 to 50 mm Hg generally indicates severe lower extremity occlusive disease with inadequate perfusion to heal tissue loss, particularly in diabetics.[7]

Further anatomic mapping is warranted only after the diagnosis of hemodynamically significant infrainguinal disease has been made based upon physical examination and noninvasive testing and the decision to pursue intervention has been made. The goal of anatomic imaging is to determine if adequate revascularization is anatomically feasible and to delineate the options for both endovascular therapy and open surgical revascularization. Duplex ultrasonography, magnetic resonance angiography (MRA), and computed tomographic angiography (CTA) are increasingly being utilized as first-line modalities in planning the optimal revascularization approach, and have supplanted contrast angiography as the initial imaging study of choice in many centers.[23] Nevertheless, due to inherent limitations with each of these techniques, digital subtraction angiography remains the gold-standard technique for imaging of the vascular tree prior to intervention.[24]

Although a growing literature supports the use of duplex scanning as a stand-alone preoperative mapping modality,[25] this use requires a highly dedicated vascular laboratory and to date has not gained wide acceptance. CTA is increasingly being utilized as a preoperative road-mapping technique in institutions able to provide high-quality three-dimensional reconstructions. MRA is also particularly useful as a noninvasive screening test to determine the suitability for percutaneous therapy, as advances have solved many of the technical limitations of earlier studies (**Fig. 91.3**). Should a lesion amenable to percutaneous therapy be identified, angiography is then pursued. Alternatively, in some instances of femoropopliteal reconstruction, operative planning may be based solely on MRA scanning if high-quality time of flight

and gadolinium-enhanced images are obtained.[26–28] In many cases, however, surgeons are reluctant to proceed to surgery without the confirmation of anatomy afforded by standard contrast angiography. This reluctance is particularly true if the distal target is at the tibial or pedal level, where anatomic detail provided by CTA and MRA remains more limited.[29]

When digital subtraction angiography is undertaken for preoperative planning, a retrograde femoral approach is typically utilized from the contralateral limb. In general, a catheter is placed in the infrarenal aorta to perform aortography and iliac angiography. If there is no aortoiliac disease which precludes catheter traversal, the wire and catheter are utilized to go "up and over" the aortic bifurcation to place the catheter in the common femoral artery of the affected limb. Lower extremity digital subtraction angiography is then carried out. Selective catheterization of the affected limb via "up and over" approach allows contrast volume to be minimized. It also allows the surgeon or interventionalist to proceed immediately with infrainguinal endovascular intervention through a single vascular access should endovascular therapy be the preferred treatment based on the patient's presentation and infrainguinal anatomy defined in the angiogram.[24] In patients in whom noninvasive imaging indicates a widely patent common femoral and proximal superficial femoral artery and body habitus is not prohibitive, an antegrade approach can serve as useful alternative. In ambiguous lesions or when iodinated contrast must be minimized, pull-back pressure measurements, both before and after the administration of a systemic vasodilator such as papaverine or nitroglycerine or the application of a tourniquet to induce reactive hyperemia, can be useful in documenting the hemodynamic significance of a particular stenotic zone.[30] The utilization of gadolinium or carbon dioxide as contrast agents in patients with compromised renal function, although perhaps less effective in the periphery than in the aortoiliac vasculature, can minimize or eliminate the nephrotoxic effects associated with standard iodinated contrast medium.[31,32]

Medical Treatment

Risk factor modification remains a cornerstone of the management of lower extremity occlusive disease. Smoking cessation has been shown to reduce the risk of disease progression, amputation, cardiovascular mortality, and may

lead to symptom relief in some patients. Smoking cessation has been best achieved with repeated physician assistance, group counseling, nicotine replacement or nicotinic receptor agonists, and antidepressant drug therapy in some patients. Weight and blood pressure reduction and aggressive efforts at lipid control should be addressed with every patient with atherosclerotic disease. Lipid-lowering therapy involves dietary modifications first and utilization of hydroxymethylglutaryl–coenzyme A–reductase inhibitors ("statins") to lower LDL cholesterol and fibrates or niacin to raise HDL cholesterol. Patients with lower extremity occlusive disease should have a goal LDL cholesterol of <70 mg/dL.[6] Statin therapy also has benefits in patients with PAD which are independent of their effect on lipid reduction. Stains stabilize atherosclerotic plaque and reduce vascular inflammation. Statin therapy has been shown to reduce cardiovascular events in patients with PAD.[33,34] In addition, statin therapy is associated with improved 1-year survival in patients undergoing lower extremity bypass for CLTI.[25] Patients with diabetes should have aggressive control of blood glucose toward a goal hemoglobin A1c of <7%. Antiplatelet therapy in the form of either aspirin or clopidogrel is a critically important element of the treatment of established occlusive disease, given its documented ability to prevent thrombosis and embolization and possibly even to arrest the progression of atherosclerosis.[35] Aspirin and clopidogrel have both been shown to reduce cardiovascular morbidity and mortality in patients with PAD.[36,37] A sub-analysis of patients with PAD from the COMPASS trial demonstrated a decreased incidence of major adverse limb events (MALE) and its complications in patients treated with combination therapy of daily aspirin and rivaroxaban 2.5 mg twice daily.[38] When evaluating this same treatment strategy in patients following lower extremity revascularization, the Voyager PAD investigators found significantly lower incidences of acute limb ischemia, major amputation, myocardial infarction, ischemic strokes, and death.[39]

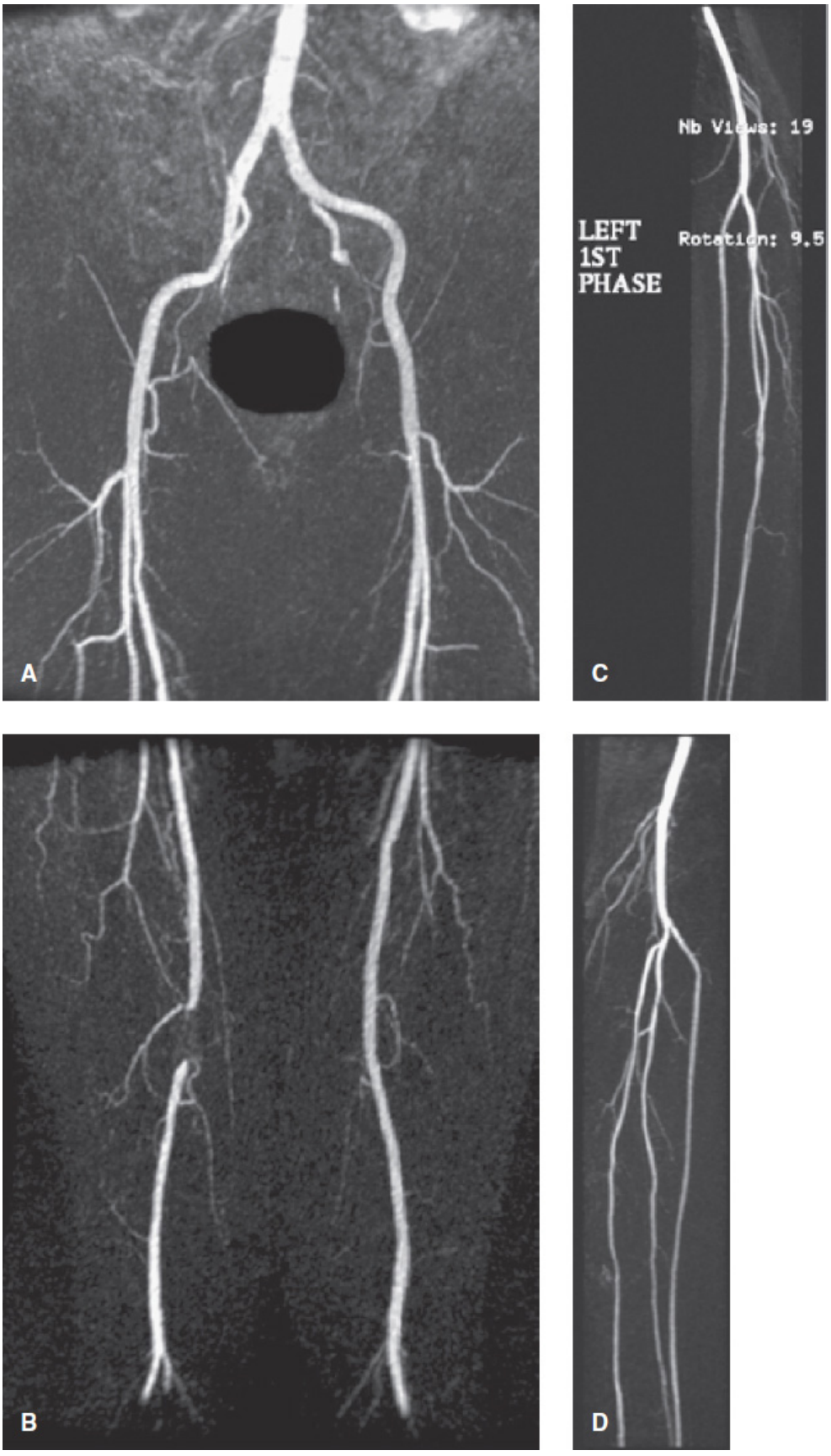
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Figure 91.3 Magnetic resonance angiogram identifying patent inflow vessels (**A**), short-segment occlusion of right superficial femoral artery (**B**), and patent popliteal and tibial vessels (**C and D**), a lesion amenable to attempt at percutaneous therapy.

Strong evidence exists supporting the benefit of a supervised, structured walking program in increasing the walking distance of patients with claudication.[40] The benefit of walking outside of a structured regimen with close follow-up is more debatable.[41] Nevertheless, patients should be encouraged to "walk through" the onset of lower extremity pain, resting intermittently as required. Overall, pharmacotherapy has not had a significant impact on relieving symptoms of infrainguinal occlusive disease. There is some evidence to suggest cilostazol, a phosphodiesterase inhibitor, improves walking distance and quality of life.[42,43] While early studies showed that pentoxifylline, a rheologic agent, had beneficial effects on walking distance, later studies have questioned its clinical benefit.[44,45] Similarly, although older studies suggested that prostanoids improved healing of ischemic ulcers, the current evidence does not support the utility of any systemic drug for the relief of ischemic rest pain or the treatment of ischemic ulcerations.[46–48]

Indications for Revascularization

The two major indications for the intervention of infrainguinal arterial occlusive disease are lifestyle-limiting claudication and CLTI. Although there are certainly cases in which primary amputation represents the safest and most advisable solution in the face of irreversible ischemia, particularly in nonambulatory patients or in cases in which extensive infection or tissue necrosis is present, an attempt at revascularization is generally indicated when a limb is threatened by severe ischemia. However, given the morbidity and mortality associated with CLTI, it is paramount to tailor therapy to an individual's overall medical condition and life expectancy as well as the patient's goals of therapy. In the often frail CLTI population, postoperative outcomes are most strongly impacted by patients' preoperative medical condition and functional status.[49] Nevertheless, improvements in endovascular technology and techniques as well as perioperative management and surgical technique have allowed progressively more distal revascularizations to be successfully completed in an older, sicker, and

challenging patient population. In general, high limb salvage (80% to 90%) rates may be anticipated for patients with critical ischemia at institutions devoted to peripheral bypass surgery.[50–52] In addition, occlusive disease of the tibial vessels is increasingly being treated percutaneously.[53] Though the long-term durability of various endovascular revascularization approaches is limited, similar rates of limb salvage from 1 to 3 years have been demonstrated.[53–55] 6 CLTI, and limb threat in particular, has been recognized as a more broad disease spectrum that incorporates limb perfusion, presence and extent of a wound, and the presence and severity of infection. The Society for Vascular Surgery sought to create a novel classification system that better reflects these important considerations impacting the threatened lower extremity. The Wound, Ischemia, and foot Infection (WIfI) classification system provides a grade for each component; and, based on the patient's overall score, their amputation risk and revascularization benefit can be stratified.[56] The WIfI classification system has been found to correlate with need for revascularization and patient-centered outcomes, including wound healing and risk for major amputation, while also reinforcing the necessity of treatment of additional components of limb threat beyond ischemia.[57–60] The importance of WIfI restaging following revascularization to assess risk of limb loss and adequacy of the revascularization has also been acknowledged.[61]

Claudication is a relative indication for intervention given the natural history of the disease, and it remains a subjective assessment on the part of both patient and surgeon as to the relative degree of disability a particular level of claudication pain represents. For example, two-block claudication in a younger patient whose livelihood depends on walking tolerance constitutes a more significant disability than the same degree of claudication in an older, retired individual able to attend to his or her daily affairs without significant consequence. Thus, proximal above-knee surgical reconstruction in a patient with disabling claudication and a patent popliteal artery with intact runoff may be justified in view of its minimal operative mortality, excellent long-term palliation, and absence of added risk of limb loss beyond that expected from the natural history of the disease process. Classically, it has been thought that the benign natural history of claudication does not warrant aggressive femorotibial reconstruction in patients with diffuse superficial femoropopliteal and tibioperoneal disease, though reconstruction will often

provide symptomatic benefit and can be considered in a good-risk patient.[62,63]

In recent years, the low morbidity of endovascular revascularization in combination with patient desire for intervention seems to have lowered the threshold for offering catheter-based revascularization for claudication. Patients once considered most appropriate for risk factor modification, exercise therapy, and medical treatment are now increasingly being offered percutaneous revascularization.[64,65] Nevertheless, endovascular revascularization is not without risk and is at present of limited durability. It is therefore prudent to follow the classical surgical axiom that because most patients with claudication remain stable for years, it is important to allow sufficient time for collaterals to develop and enlarge; some patients may improve to such an extent that intervention proves unnecessary.[19]

Approach to Revascularization

The last two decades have seen increasing utilization of endovascular revascularization of infrainguinal occlusive disease.[65] In this light, it cannot be overemphasized that symptom status and not anatomic findings should serve as the basis for revascularization. Once the decision to intervene has been made, a variety of factors should be considered in choosing whether to proceed with an endovascular, surgical, or combined (hybrid) approach. The goals and outcomes of revascularization should be considered in the context of the individual patient's comorbidities, operative risk and overall life expectancy, the extent of the occlusive disease present, and the expected durability of the procedure.

Anatomic variables appear to be the key determinant of the success and durability of endovascular therapy. With the promulgation of endovascular therapy has arisen, the need to classify the anatomic severity of disease in order to guide potential therapy and compare outcomes between various modes of revascularization. The Trans-Atlantic Intersociety Consensus Document on Management of Peripheral Arterial Disease (TASC) was published as the result of a multidisciplinary collaboration between key medical and surgical vascular societies in 2000 and an abbreviated update was published in 2007.[7,66] This document classified infrainguinal occlusive lesions into classes A, B, C, and D based upon the location of the lesion and

the number, length, and severity of the stenoses and/or occlusions present. Their recommendations, which reflect current practice to a variable extent, include initial endovascular treatment for TASC A lesions, primary surgical treatment for TASC D lesions, and individualized tailoring of treatment for TASC B and C lesions depending upon endovascular suitability and surgical risk. While a complete description of this classification schema is beyond the scope of this chapter, a few general principles are worth noting. The patency of endovascular revascularization decreases the more distal the disease and is less in patients with stenoses that are multiple, longer, and more severe.[7,53,67] On the other hand, the success of open bypass surgery is largely dependent on the quality conduit.[68,69] Sustained hemodynamic improvement in the affected limb is the measure of effective revascularization and the goal of therapy. Neither "endovascular first" nor "bypass first" approach can be applied to all patients and they are often complementary strategies.[70,71] A recognized limitation to the TASC document is its emphasis on anatomic lesions. A more recent collaboration, the Global Vascular Guidelines (GVG) on the Management of Chronic Limb-Threatening Ischemia, published in 2019 stress a "whole-limb" approach. The GVG endorse the utilization of the WIfI classification described above to stage the severity of limb threat. They also outline evidence-based revascularization strategies relying on patient risk, limb severity, and anatomic complexity. A proposed Global Anatomic Staging System (GLASS) focuses on defining a preferred target artery path to estimate limb-based patency. The GVG incorporate patient risk, anatomic data, severity of limb threat, and conduit availability to guide selection of optimal revascularization strategy.[72] The complexity of decision making emphasizes the importance not only of interventional expertise, but of thorough training in vascular disease and comprehensive experience in the care of vascular patients.[73]

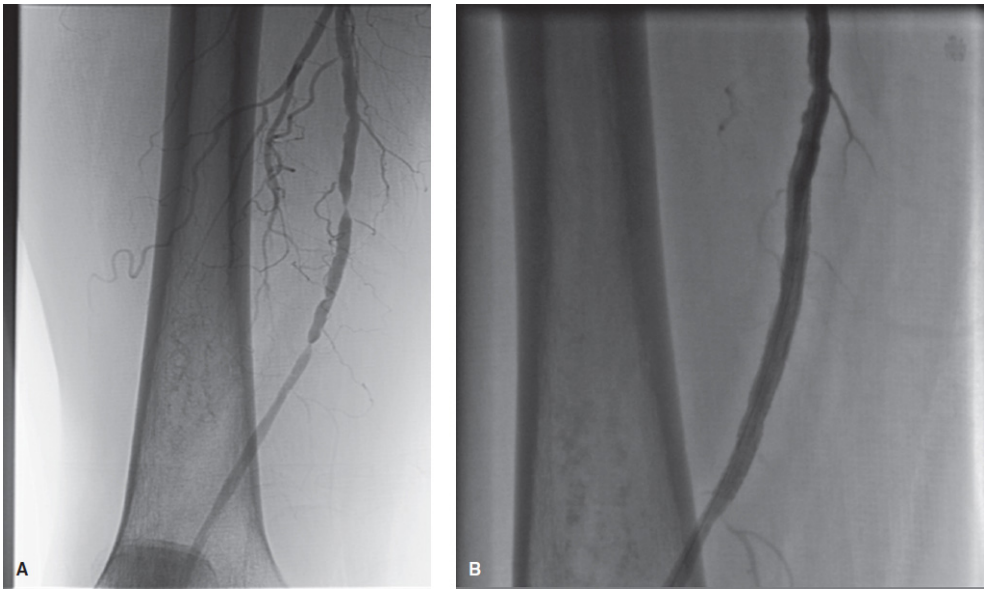

Figure 91.4 Angiogram of the right superficial femoral artery demonstrating short-segment occlusion and more diffuse stenosis in Hunter canal (**A**), which was treated with angioplasty and self-expanding bare metal stent placement (**B**).

Endovascular Therapy

A marked increase in the number and versatility of available balloons, stents, and other devices has helped to fuel the increasing application of percutaneous technology. While a complete description of endovascular treatment options and outcomes is beyond the scope of this chapter, a brief introduction is necessary. Percutaneous vascular intervention is generally performed under local anesthesia with minimal intravenous sedation as either a day surgical procedure or involving an overnight admission. Percutaneous vascular intervention first involves wires traversal of hemodynamically significant stenosis or occlusions in the arterial tree. Dilatation of the lesion with percutaneous transluminal angioplasty (PTA), with or without stenting, or obliteration of the lesion via atherectomy or other modalities is utilized to reestablish blood flow through the diseased segment (**Fig. 91.4**). For interventions on the femoropopliteal and tibial arteries, retrograde contralateral femoral access allows angiography of the affected limb and establishment of a stable treatment platform via an "up and over" approach across the aortic bifurcation. Ipsilateral antegrade femoral access can also be utilized. More recently, retrograde ipsilateral pedal and tibial access has

been described to allow wire traversal and endovascular treatment of disease not amenable to the standard antegrade approach.[74]

Periprocedural outcomes with endovascular therapy are excellent. Technical success, which is generally defined as the presence of antegrade flow through the tree to lesion with less than 30% residual stenosis at the conclusion of the procedure, is reported at 80% to 95% for both femoropopliteal and infrapopliteal procedures.[53,75,76] Associated overall morbidity in recent reports ranges between 8% and 17% while mortality is low at approximately 0.2%. Contrast-induced nephropathy remains a common complication. With the development of hypoosmolar and isoosmolar contrast agents; the overall incidence is approximately 8%, whereas the rate of acute renal failure requiring dialysis is less than 1%.[76–78] Higher rates are found in patients with pre-existing renal failure and diabetes.[79,80]

Substantial morbidity can result from access-site complications, predominantly pseudoaneurysms, groin hematomas, and arteriovenous fistulas (AVFs), which occur in 1% to 4% of patients.[76,81] Stable pseudoaneurysms in patients without coagulopathy can also be managed with ultrasound-guided compression therapy or ultrasound-guided thrombin injection into the pseudoaneurysm sac to induce thrombosis.[82] Maldeployment of these devices can lead to embolic or thrombotic sequelae causing compromise of distal flow.[83]

Reports indicate that endovascular therapy has good short-term efficacy for femoropopliteal disease (**Table 91.1**). In claudicants, PTA for femoropopliteal lesions has generally yielded 1-year patency of approximately 77% and 65% for stenoses and occlusions, respectively.[67,84] In patients with CLTI, PTA for femoropopliteal lesions has yielded 1-year primary patency of 60% and 40% for stenoses and occlusions, respectively.[84] Review of the literature does not provide compelling evidence that stent placement improves the results of all femoropopliteal PTA.[54] Many practitioners thus utilize stents selectively for failure of PTA (defined as greater than 30% residual stenosis or flow-limiting dissection) in femoropopliteal lesions. However, there is strong evidence, including two randomized trials, that primary self-expanding stent placement yields higher short-term patency than PTA and/or provisional stenting for more advanced femoropopliteal lesions.[84–86] Primary self-expanding stent placement is therefore preferred over angioplasty alone for femoropopliteal occlusions

and long-segment lesions by most surgeons and interventionalists. Infrapopliteal disease appears less amenable to endovascular therapy (**Fig. 91.5**). Primary patency is generally reported at 45% to 55% at 1 year.[53,87] Patency does not appear to be improved by stenting in the infrapopliteal segment.[88,89]

Table 91.1 Patency of Femoropopliteal Angioplasty and Stenting[a]

	1-Year % Patency (Range)	3-Year % Patency (Range)	5-Year % Patency (Range)
PTA: stenosis	77 (78–80)	61 (55–68)	55 (52–62)
PTA: occlusion	65 (55–71)	48 (40–55)	42 (33–51)
PTA+stent: stenosis	75 (73–79)	66 (64–70)	
PTA+stent: occlusion	73 (69–75)	64 (59–67)	

[a]Adapted from Norgren L, Hiatt WR, Dormandy JA, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). J Vasc Surg 2007;45(Suppl S):S5–S67.

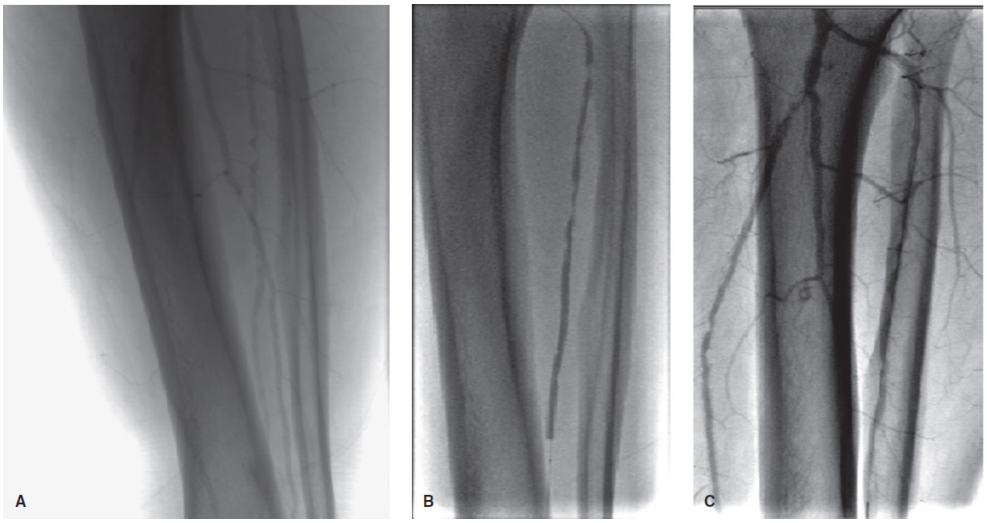

Figure 91.5 Angiogram of the tibial arteries showing diffuse anterior tibial artery high-grade stenosis (**A**) which was treated with long-segment balloon angioplasty, (**B**) completion angiogram showed patent anterior tibial artery with no significant residual stenosis (**C**).

Lack of durability has been the Achilles heel of infrainguinal endovascular intervention. Three-year patency after PTA has generally been reported to be 43% to 61% and 30% to 48% for femoropopliteal stenoses and occlusions, respectively.[84] Five-year patency data are seldom reported but have been generally reported to be between 26% and 45% after PTA for femoropopliteal lesions.[7]

There is a scarcity of high-level data comparing PTA and bypass surgery for infrainguinal occlusive disease. Heterogeneous study populations and the lack of standardized methodology and endpoints have limited the ability to compare the effectiveness of endovascular surgical therapy.[90] In addition, there have been only four randomized trials comparing angioplasty and lower extremity bypass surgery and these have included a heterogeneous group of patients, measured different outcomes, and generally included limited anatomic detail.[91–94] Pooled analysis of these trials demonstrates that surgical bypass generally had superior patency to PTA at 1 year, but there were no differences in progression to amputation. The BASIL (bypass vs. angioplasty in severe leg ischemia) trial which randomized 452 patients with "severe limb ischemia" to a "bypass first" or "balloon angioplasty" first strategy is the most widely cited trial. There was no difference in the primary endpoint of amputation-free survival at 6 months, although a "surgery-first"

strategy was associated with greater cost and morbidity.[91] It is necessary to note that the endovascular arm of this trial did not include adjunctive procedures such as stenting which are now frequently utilized in current day practice. Upon long-term follow-up of at least 3 years and more than 5 years in the majority of patients, bypass was associated with improved overall survival and a strong trend toward improved amputation-free survival in patients who survived at least 2 years. In addition, most balloon angioplasty patients ultimately required bypass surgery. Bypass after failed balloon angioplasty had significantly worse patency than that of primary bypass.[95] This finding corroborated other reports demonstrating that surgical bypass after failed endovascular treatment is inferior to primary bypass, indicating that a universal "endovascular first" approach may not be appropriate as failed endovascular intervention may "burn bridges" for surgical revascularization. Careful consideration must be given to the best initial therapy for infrainguinal occlusive disease.[96]

7 For patients with favorable anatomy and significant operative risk, and for the treatment of claudication in general, percutaneous therapy has assumed a primary initial role. When medical therapy or percutaneous treatment has proven 8 inadequate, open surgical revascularization remains the gold standard for those patients with disabling claudication. Furthermore, until the efficacy and durability of infrainguinal percutaneous intervention is better defined, surgical revascularization remains the gold standard for any patient with CLTI, especially those with extensive tissue loss. The relative roles of surgical and percutaneous intervention are actively being refined. It nevertheless appears that the rising popularity and success of femoral and tibial wire-based interventions may be reducing the volume, or ultimately just delaying the timing of, subsequent infrainguinal reconstructive surgery. Furthermore, many patients are best treated with a combination of percutaneous and open surgical therapy, often in a single procedure (hybrid procedure). In many instances, endovascular and open surgical revascularization are thus complementary modes of therapy.

Operative Management

9 Successful infrainguinal arterial bypass requires sound planning as well as technical expertise. As such, it remains the signature operation which

distinguishes vascular surgeons from other specialists involved in the treatment of PAD. Successful infrainguinal bypass grafting requires adequate arterial inflow. While aortobifemoral, femorofemoral, and axillofemoral bypass grafting remain routinely performed inflow procedures, aortoiliac angioplasty and stenting are increasingly becoming the preliminary procedures performed to attain sufficient inflow prior to construction of a more distal bypass graft. At times, the necessity of improving the inflow to support an infrainguinal graft is determined intraoperatively, either by direct visual assessment of the arterial flow at the desired donor site or by comparison of a transduced pressure tracing from the donor site with that of a systemic pressure tracing, typically obtained from a radial arterial line. Of equal importance to the outcome of any infrainguinal graft is target vessel selection. In general, the target vessel should be the least diseased artery that is the dominant supply to the foot. If tissue necrosis is present, restoration of pulsatile flow to the foot is often required to obtain full and sustained wound healing.

Infrainguinal surgical bypass can be performed under general anesthesia, or in the appropriate patient, under regional, spinal, or epidural anesthesia. In cases involving multiple sites of dissection, such as those necessitating more tedious arm vein or lesser saphenous vein harvesting, the procedures are particularly amenable to a two-team approach, with the time saved having direct benefit in minimizing the total anesthetic load and physiologic insult. For patients with superficial femoral artery disease, the initial dissection is most commonly at the level of the common femoral artery. This vessel is exposed through a longitudinal or oblique incision centered directly over the femoral pulse. Lymphatic tissue overlying the femoral vessels is best ligated and divided to prevent the postoperative development of lymph fistulas or lymphoceles. The severity of any concomitant common femoral and profunda femoral disease and the level of reconstruction planned dictate the extent of exposure of the femoral vessels. In most instances, the dissection extends from the inguinal ligament to the common femoral artery bifurcation, where the origins of the superficial and profunda femoral arteries are individually isolated.

If a profundaplasty is required, the dissection is extended distally along a sufficient length of the profunda femoral artery to attain an endpoint suitable for clamping and sewing (**Fig. 91.6**). Similarly, the inguinal ligament can be

partially divided to facilitate access to the distal external iliac artery in cases in which a more extensive proximal endarterectomy is necessary. In these circumstances, it is customary to close the endarterectomized bed with a vein, bovine pericardial or Dacron patch, onto which the proximal anastomosis can subsequently be attached.[97] In patients with a hostile groin crease from prior surgery or radiation therapy or in obese, diabetic patients with an intertriginous rash at the inguinal crease, meticulous skin preparation, close attention to draping, careful surgical technique, and judicious use of a short course of intravenous antibiotic therapy help minimize the chances of a postoperative wound or graft infection.

If all or part of the superficial femoral artery is spared of significant atherosclerotic involvement, the proximal anastomosis can be moved distally as dictated by the particular anatomic pattern of disease, and a so-called "distal origin graft" can be fashioned (**Fig. 91.7**).[98] This situation is particularly applicable to the diabetic population, in whom infrapopliteal disease is the rule and sparing of the superficial femoral and popliteal arteries is not uncommon. It is also utilized in situations in which conduit is sparse, and a moderately diseased proximal vessel is accepted as an inflow source for a more distal origin bypass graft in the interests of performing a fully autologous vein graft rather than utilizing prosthetic material. An increasingly popular approach when only limited conduit is available is to combine, either concurrently in the operating room or as a staged preoperative procedure, catheter-based treatment of the superficial femoral or popliteal artery inflow with more distal bypass.[99]

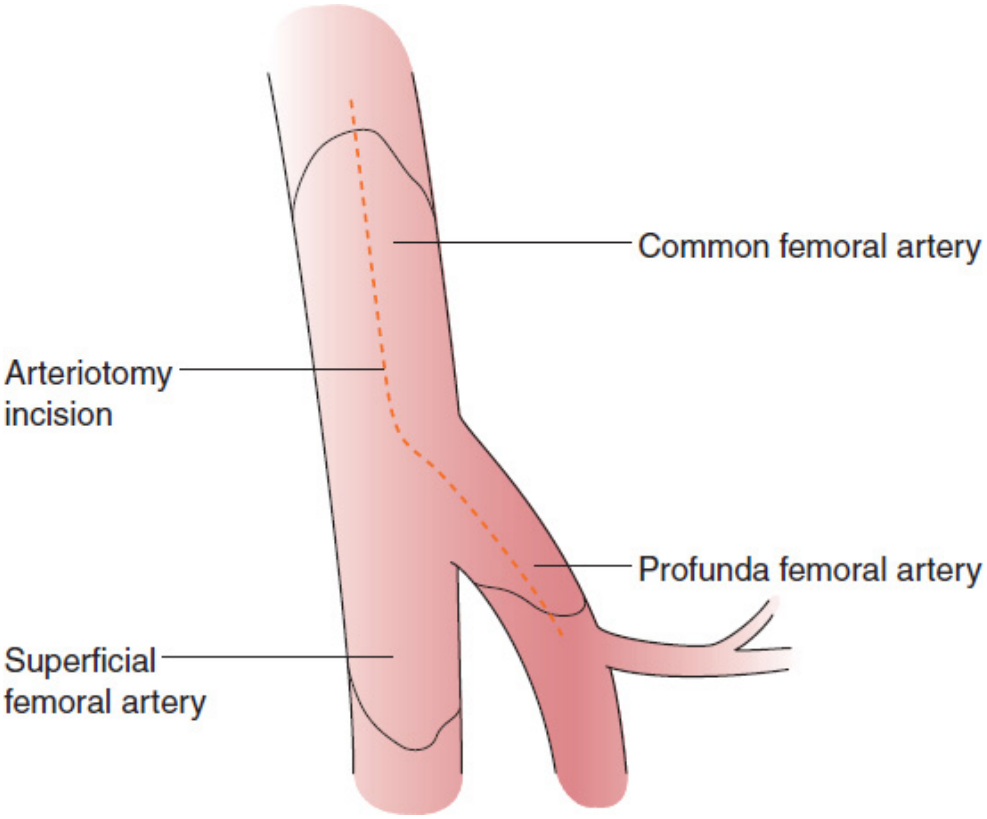

Figure 91.6 In the setting of orificial profunda femoral artery disease, extending the common femoral arteriotomy into the origin of the profunda and performing a profundaplasty will maximize profunda flow in the event of graft thrombosis.

The above-knee popliteal vessel is easily exposed through a medial thigh incision, with subsequent posterolateral retraction of the sartorius muscle. The popliteal artery with its accompanying vein and nerve is found just posterior to the femur. The vessel is palpated to determine the presence of atherosclerotic plaque, which will guide the extent of dissection and the optimal bypass target site. The below-knee popliteal artery is also exposed through a medial incision in the proximal calf (**Fig. 91.8**). If the saphenous vein is to be harvested, the incision is made directly over the vein to minimize the creation of devascularized skin flaps. With the exposed vein carefully protected, the incision is carried through the deep muscular fascia and the medial head of the gastrocnemius is reflected posterolaterally to expose the below-knee popliteal fossa. The distal popliteal artery is then dissected free from the adjacent tibial nerve posteriorly and popliteal vein medially. If the distal target is the tibioperoneal trunk, the dissection is

continued along the anteromedial surface of the distal popliteal artery after dividing the origin of the soleus muscle from the tibia (**Fig. 91.9**).

Although exposure of the proximal posterior tibial and peroneal vessels can be gained by extending the tibioperoneal trunk dissection distally, more distal exposure of these vessels is best gained through targeted medial incisions. The posterior tibial artery is found beneath the divided musculotendinous origin of the soleus muscle, and the peroneal artery is deeper and more lateral. The posterior tibial artery at the level of the ankle is a relatively easier target given the proximity of the vessel to the skin surface. The initial incision is made just posterior to the medial malleolus, and the artery exposed by division of the overlying retinaculum. Further distal dissection allows access to the bifurcation and medial and lateral plantar branches.[74] The more distal peroneal artery may be approached laterally via an incision placed over the distal fibula. Excision of a short segment of fibula will expose the underlying artery.

The anterior tibial artery is typically approached from the anterolateral aspect of the calf (**Fig. 91.9**) and is found deep within the anterior compartment with the adjacent deep peroneal nerve and anterior tibial veins. It is best identified by developing the intermuscular plane between the tibialis anterior muscle belly medially and the extensor digitorum longus laterally. The dorsalis pedis artery is easily exposed through an axial incision on the dorsum of the foot just lateral to the extensor hallucis longus tendon (**Fig. 91.9**). The artery lies just deep to the extensor retinaculum.

Figure 91.7 Arteriogram indicating preservation of the superficial femoral artery and popliteal arteries (**A–C**) with mid-calf occlusions of all three infrageniculate vessels (**D**), with reconstitution of the dorsalis pedis artery in the foot (**E**). This anatomic pattern of disease is amenable to "distal origin" vein grafting from the below-knee popliteal or proximal posterior tibial artery to the dorsalis pedis artery.

Autogenous Vein Bypass

10 Infrainguinal bypass surgery is best performed with autogenous vein conduit, preferably the ipsilateral greater saphenous vein if available.[100] This preference is particularly true for grafts extending below the knee, where prosthetic conduits of Dacron or polytetrafluoroethylene have significantly poorer patency rates. Given the orientation of the vein valves, the vein can be reversed such that the distal end of the vein is sewn to the proximal inflow artery and the larger proximal end of the vein is sewn to the distal outflow artery. However, it is our general practice to utilize the greater saphenous vein in the nonreversed orientation as will be discussed shortly. The vein is harvested through a long incision overlying the course of the vein or by more tedious but less invasive sequential skip incisions with intervening cutaneous skin bridges (**Fig. 91.7**). All side branches are ligated and after harvest, the vein is cannulated and gently dilated with a solution containing heparin and papaverine to assess its suitability. Veins with chronic fibrosis or that fail to dilate to a diameter of 3 mm or greater will likely have poor long-term function.

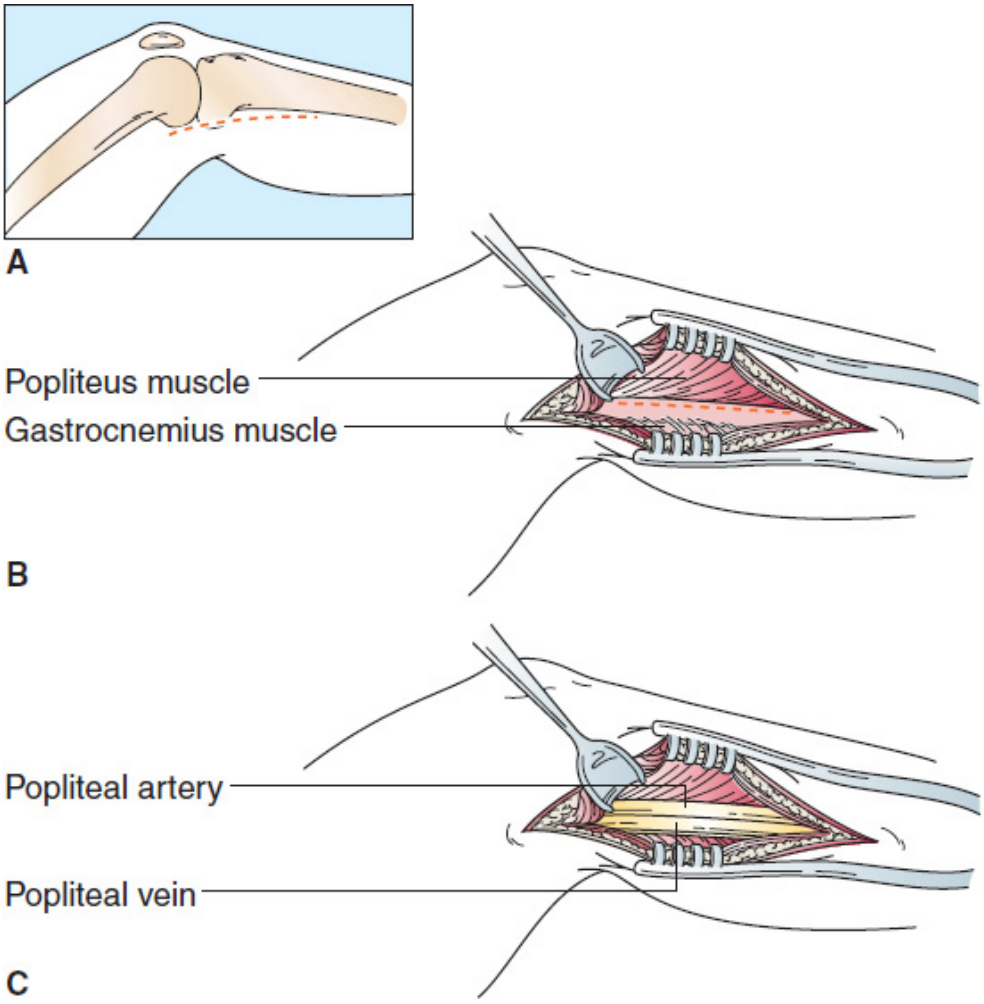

Figure 91.8 Exposure of the popliteal artery below the knee. The medial incision is made directly overlying the course of the greater saphenous vein (**A**), with posterior retraction of the gastrocnemius muscle (**B**), to reveal the popliteal vessels in the popliteal fossa (**C**).

An alternative and less invasive approach to saphenous vein harvest involves the use of endoscopic technology. In the case of harvesting of the greater saphenous vein, small skin incisions are made over the saphenofemoral junction and the distal vein, and guided by a videoscope inserted distally and advanced proximally, the side branches of the vein are serially identified and either cauterized or clip-ligated. Advocates of this method cite a significant reduction in wound complication rates and reduced rates of hospital stay, although patency rates may be compromised.[101,102]

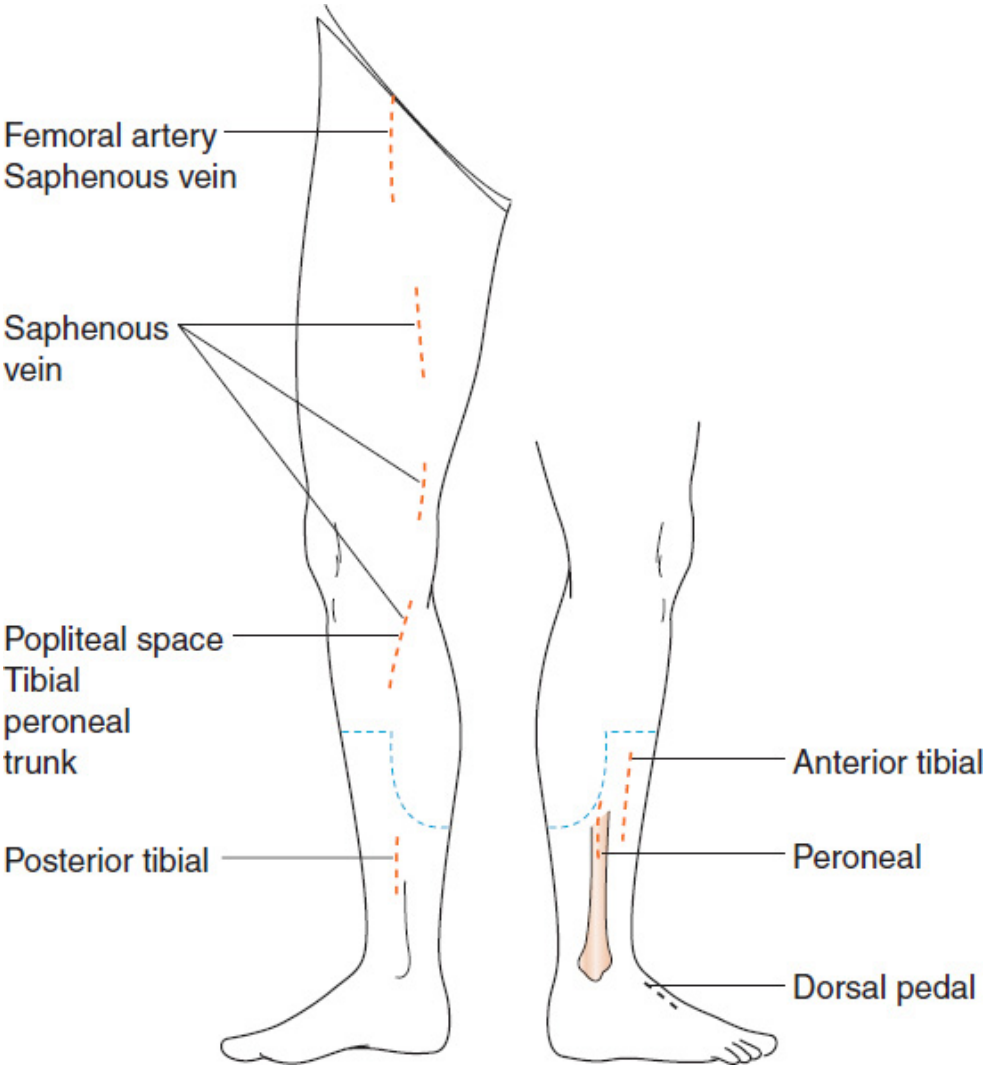

Figure 91.9 Placement of incisions for femoropopliteal and femorotibial bypass and for greater saphenous vein harvest. These should avoid the incision lines for a below-knee amputation.

For prosthetic grafts, a tunnel is usually fashioned through the subsartorial plane between the groin incision and the above-knee popliteal space in the interests of protecting the graft from subsequent infection. For vein conduits, it remains the surgeon's preference as to whether the graft is tunneled deeply or in a superficial location in the subcutaneous space. The more superficial configuration greatly facilitates ongoing clinical examination and ultrasonographic surveillance as well as later surgical revision, but carries a risk of graft exposure should there be wound-healing problems. Occlusion from trauma to grafts placed superficially has been of theoretical, but not a practical concern.

It is our practice to perform the proximal anastomosis prior to the distal anastomosis. First, this allows confirmation of adequate inflow before the bypass is performed. Second, performance of the proximal anastomosis first allows the graft to be tunneled and tailored to appropriate length under arterial pressure. This is of critical importance to prevent kinking along the length of the graft. An additional benefit of performing the proximal anastomosis first is that adequacy of flow through the graft can be assessed, both before and after tunneling, with brief release of the clamp.

Prior to occluding the inflow vessel, the patient is systemically anticoagulated with 5,000 to 10,000 units of heparin. Additional heparin is given throughout the procedure to maintain the activated clotting time near the target range of 250 to 300 seconds. After allowing sufficient time for the heparin to circulate, atraumatic vascular clamps are placed proximally and distally, and the artery is incised. The vein is then spatulated and a beveled anastomosis carried out. Typically a 5-0 monofilament suture of polypropylene is used for the femoral anastomosis, a 6-0 is used at the popliteal level, and a very fine 7-0 suture used at the tibial or pedal level. If the target tibial vessel is deep within the calf and visibility is challenging, a technique of "parachuting" the heel of the distal anastomosis is often employed. After completing the proximal anastomosis, the graft is carefully tunneled under arterial pressure. Occasionally, such extensive calcification of the target vessel is encountered that the risk of a significant injury from clamping, even with the minimally traumatic clamps in use today, is prohibitively high. In such cases, proximal inflow and distal artery back-bleeding can be controlled by occlusion balloons placed intraluminally. For distal anastomoses at the knee or more distal level, another alternative technique is the use of a proximally placed sterile pneumatic tourniquet. This technique is particularly advantageous when sewing to diminutive distal tibial or pedal targets, where the impact of a crush injury or plaque dislodgment on graft function could be considerable. Removing the need for clamps by using the tourniquet has two further advantages. First, it improves the operative visibility. Second, and more importantly, given that less longitudinal and circumferential dissection is needed, the degree of vessel spasm and venous bleeding that frequently accompanies vessel exposure at this level is kept to a minimum.

Flow through the graft and the outflow arteries are assessed following completion of the bypass with a continuous-wave Doppler. Ideally, a contrast angiogram is also performed after directly cannulating the proximal graft (**Fig. 91.10**); this allows for immediate repair of any technical defects that are identified, such as intraluminal thrombus, twisting or kinking of the graft, or retained valve cusps.[77] Intraoperative completion duplex ultrasonography is an additional sensitive screen for hemodynamically significant abnormalities within the graft, and its use further serves to prevent early graft loss caused by correctable technical problems.[103,104]

Current reports of the 5-year results of reversed saphenous vein graft using modern techniques have been excellent, with primary and secondary patency rates of up to 75% and 80%, respectively and limb salvage rates greater than 90% (**Table 91.2**).[73,105–107]

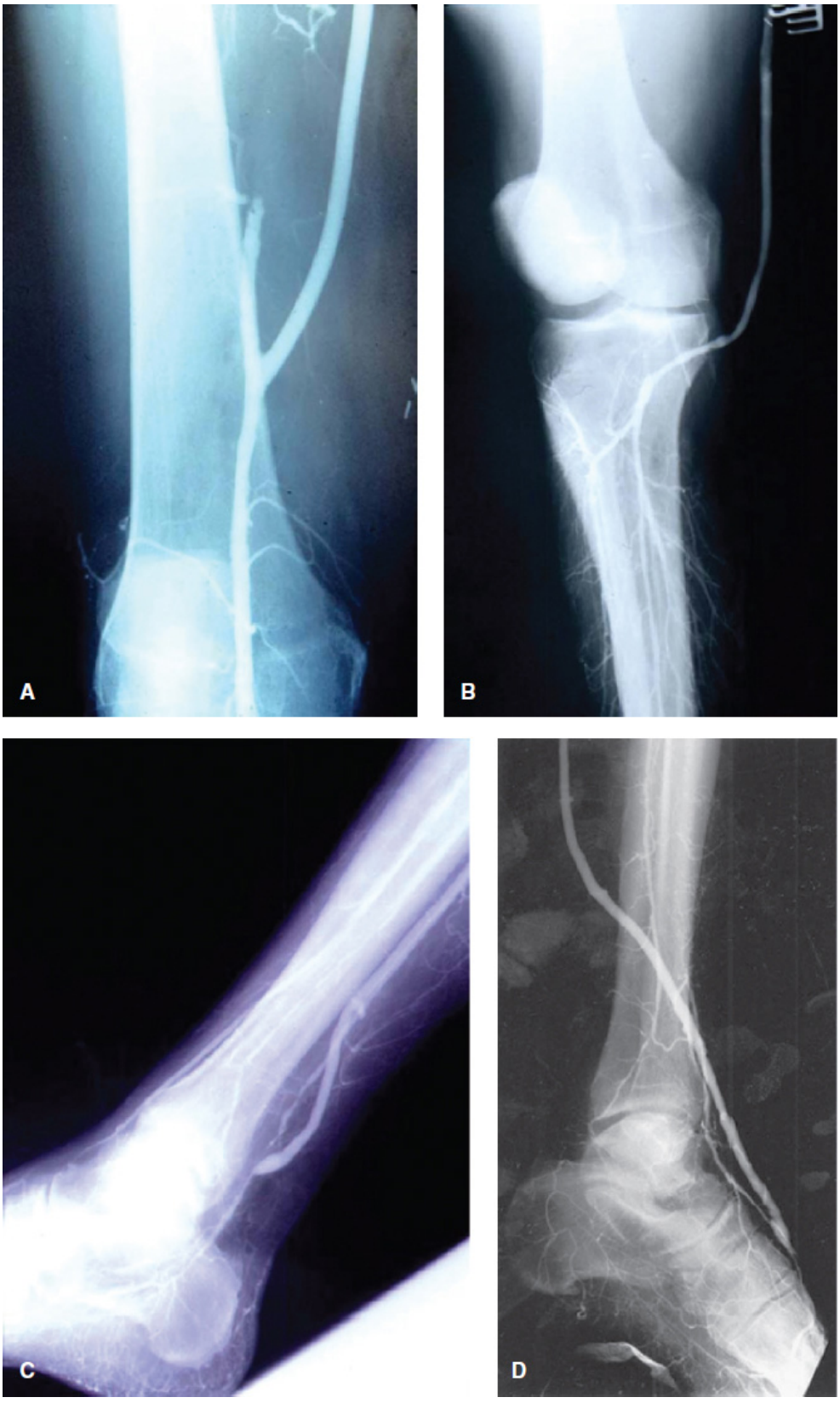

Figure 91.10 Intraoperative completion arteriograms of distal anastomoses to the above-knee popliteal (**A**), below-knee popliteal (**B**), distal posterior tibial (**C**), and

dorsalis pedis (**D**) arteries.

Table 91.2 Five-Year Patency and Limb Salvage Results of Infrainguinal Bypass Grafting

Study	Patients, *n*	Conduit	Primary Patency	Secondary Patency	Limb Salvage
Conte, 2001[52]	1,642	Autogenous vein	63	73	85
Belkin, 1996[56]	568	In situ vein	72	82	90
	189	Nonreversed vein	65	65	82
Shah, 1995[57]	2,058	In situ vein	72	81	95
Taylor, 1990[103]	564	Reversed vein	75	81	90
Veith, 1986[96]	338	PTFE to popliteal	38		70
	254	PTFE to tibial	12[a]		61[a]

[a]4-year data.
PTFE, polytetrafluoroethylene.

In Situ Grafting

There has been ongoing enthusiasm in some circles for in situ vein bypass grafting, whereby except for its proximal and distal extent, the greater saphenous vein is left undisturbed in its native bed. This technique was first described in 1962, but was later popularized by Leather and Karmody in the late 1970s.[108,109] Recent reports of in situ saphenous vein grafting have indicated 5-year graft patency rates of up to 80% and limb salvage rates of 84% to 95% (**Table 91.1**).[51,106,110–112]

The in situ approach minimizes trauma to the vein during excision and handling and in theory enhances preservation of the vasovasorum and endothelium. It further lowers the considerable risk of wound-healing complications seen with traditional vein harvesting, increases vein utilization, and facilitates the creation of more technically precise anastomoses because the proximal and distal vein diameters are more closely matched to those of the inflow and outflow target vessels (**Fig. 91.11**). The extent of the proximal vein mobilization is dictated by the location of the saphenofemoral junction relative to the proposed site of the proximal anastomosis. It may at times be necessary to perform an endarterectomy of the superficial femoral artery if the length of proximal vein is insufficient. Lysis of the valve cusps is obligatory given the nonreversed configuration, and is facilitated by newer, less traumatic valvulotomes that

function safely through the blinded segments of undissected graft. Critics of this technique argue that the advantages listed above have not translated into improved graft function or patency. They further argue that the time required and dissection involved in finding and ligating substantial side branches that can develop into physiologically important AVFs that “steal” distal flow obviates the stated benefits of this approach.

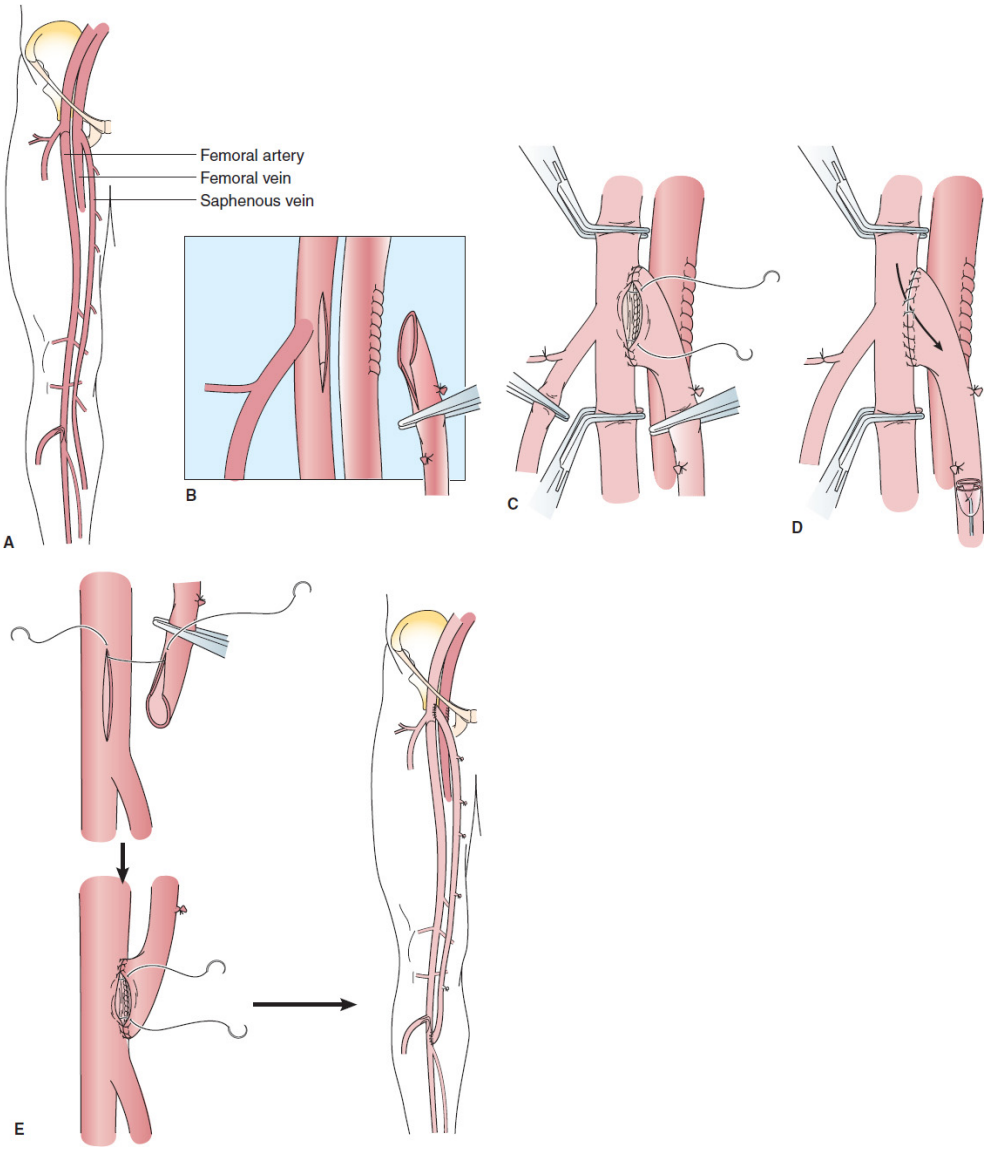

Figure 91.11 **A:** In the in situ method of infrainguinal reconstruction, the saphenous vein is left undisturbed in its native bed except for at the proximal and distal anastomotic sites, in this case, the common femoral artery and the tibioperoneal trunk, respectively. **B:** The saphenofemoral junction is transected in the groin, the venotomy in the femoral vein is oversewn and the proximal end of the saphenous vein spatulated is prepared for anastomosis. **C:** After the first venous valve is excised under direct vision, the graft is anastomosed end-to-side to the femoral artery. Flow is then restored through the vein graft and the valvulotome passed from the distal end to lyse the residual valves (**D**), before the distal anastomosis is performed (**E**).

Angioscopic-assisted valve lysis has been employed for over a decade, but has not gained widespread favor. Although there is a significant learning curve with this technology and operative times, at least initially, are

significantly prolonged, advocates cite fewer wound complications, shorter hospital stays, and decreased recuperative periods as potential benefits.

Nonreversed Saphenous Vein Grafts

Recognizing the many practical advantages inherent to the in situ technique, some surgeons have modified the approach to infrainguinal bypass grafting with venous conduit to incorporate several of the same principles.[50] In particular, if the harvested vein is tapered to any significant extent, it is used in a nonreversed fashion. By optimizing the size matching between the artery and vein at both the proximal and distal anastomosis sites as discussed previously, one can often accept for use, smaller veins than would be unsuitable for reversed vein grafting. The nonreversed configuration also allows preservation of the saphenous vein hood, which both extends the available conduit length and is especially beneficial when the femoral artery is thick walled and diseased.

The vein is harvested and dilated in a similar fashion to reversed vein grafts and the cusps of the proximal valve of the greater saphenous vein are excised under direct vision with fine Potts scissors. There are currently two main types of valvulotomes available. The modified Mills valvulotome is a short, metal, hockey stick-shaped cutter that can be introduced through the distal end of the vein or through the side branches. After the proximal anastomosis is performed, and with the perfused conduit on gentle stretch, the valves are carefully lysed in a sequential fashion by pulling the valvulotome inferiorly. An alternative, recently designed self-centering valvulotome allows lysis of all valves in a single pass and is thought by some to be less traumatic. Once acceptable pulsatile flow is ensured, the distal anastomosis is performed in the standard fashion.

It is important to note that similar patency rates have consistently been demonstrated regardless of which technique is applied, and so surgeon preference and comfort level is an acceptable reason for choosing one method over another.[111,112]

Prosthetic Bypass

It is recommended that infrainguinal bypass surgery be performed with saphenous vein or an autologous substitute whenever feasible given the clearly demonstrated enhanced patency rates.[45,113] Some institutions more frequently rely on prosthetic grafts. When the distal target is the above-knee popliteal artery and the tibial outflow is relatively well preserved, this is an acceptable approach, as patency rates in this situation approach those of vein grafts.[114] A variety of surgical adjunctive procedures, from patching the distal anastomotic target vessel to the creation of a distal AVF or various autogenous vein cuffs interposed between the distal prosthetic and the target artery, have all been attempted as a means of improving the patency rates of grafts extending below the knee.[115] Polyester (Dacron) and polytetrafluoroethylene (Teflon) grafts are the two main types of prosthetic available and, as in other anatomic positions, available data show generally equal results with either choice. The entire procedure is carried out through two small proximal and distal incisions between which the graft is tunneled anatomically. The selection of a 6-, 7-, or 8-mm graft is dictated by the size of the native vessels.

Reoperative Bypass Surgery

As the patient population treated by vascular surgeons has increased in age, and more and more challenging cases are accepted for primary treatment, there has been a corresponding increase in the incidence of reoperative bypass surgery performed for infrainguinal arterial occlusive disease. Such reoperative procedures are particularly challenging, both because of the scarring present at the inflow and outflow target sites and because there is typically a lack of ipsilateral greater saphenous vein. Whenever possible, the first problem is addressed by choosing anastomotic sites just above or below the previous touchdown points, thereby avoiding dissection through often densely scarred tissue planes. When ipsilateral greater saphenous vein is absent because of prior infrainguinal or coronary artery bypass surgery or prior saphenous vein stripping, there are a number of alternative conduit sites available. Investigators examining the consequence of using the contralateral greater saphenous vein in these situations found it to be the optimal conduit; despite the presumably high incidence of contralateral lower extremity as

well as coronary occlusive disease in this population, the short- and long-term impact was found to be minimal.[94]

In the absence of any greater saphenous vein, preoperative venous duplex ultrasonography is employed to evaluate the cephalic and basilic veins of the arms and the lesser saphenous veins of the legs in an effort to determine the best conduit available. Often the veins distal to the antecubital crease are scarred and of small caliber, but their more proximal counterparts are often of excellent size and quality. The use of arm veins in general can be technically challenging and for that reason has not been universally adopted. The dissection of the basilic vein can be particularly tedious as it has multiple side branches and lies adjacent to several important nerves. As arm veins are often relatively short, a venovenostomy is often required to create composite grafts long enough to complete the arterial reconstruction (**Fig. 91.12**). This is performed with generous spatulation of each vein hood to create a widely patent vein-to-vein anastomosis. Given their thin-walled nature, arm vein grafts are also quite prone to twisting and kinking, and special care must to taken during the tunneling process to avoid these problems. The more proximal arm veins can be relatively large, and it is often advantageous to use one or more of the segments in a nonreversed fashion to better match the graft to the inflow vessel size.

Not surprisingly, the results of reoperative infrainguinal bypass surgery do not match those of primary reconstruction. With autogenous vein, 5-year patency rates of 60% and limb salvage rates of 70% to 80% have been reported.[116] Anticoagulation is often used postoperatively in patients with compromised outflow or in whom the conduit was of marginal quality and has been associated with improved long-term patency.[117]

Postreconstruction Management

Unless otherwise contraindicated, all patients are maintained indefinitely on an antiplatelet regimen with either aspirin or clopidogrel following surgical bypass. As stated previously, in cases in which a graft is at increased risk of failure, such as in the setting of reoperation or in cases in which compromised outflow or a marginal conduit was accepted, the antiplatelet agent may be supplemented with heparin and then warfarin.[117] Patients with distal calf or pedal incisions should have consistent leg elevation in the early

postoperative period to minimize leg swelling and wound-healing complications. Thereafter, aggressive rehabilitation maximizes the chances of, and shortens the time to a return to full function after extensive reconstructive surgery.

Graft Failure and Surveillance

Postoperative graft failures are typically classified according to the time interval from surgery as early, intermediate, or late. Graft thrombosis occurring within 30 days, the so-called “early graft failures” are generally thought to be a result of technical or judgment errors by the surgeon. Included in this list would be such technical errors as twists, kinks, incompletely lysed valves, or anastomotic defects, as well as judgment errors in using a poor quality vein or targeting an outflow vessel with inadequate runoff to support the graft. Intermediate graft failures include those between 30 days and 2 years and are generally attributed to the proliferation of intimal hyperplasia at the anastomoses or prior valve sites within the graft (**Fig. 91.13**). Late graft failures occurring beyond 2 years are typically a result of the progression of atherosclerotic occlusive disease within the inflow or outflow arteries.

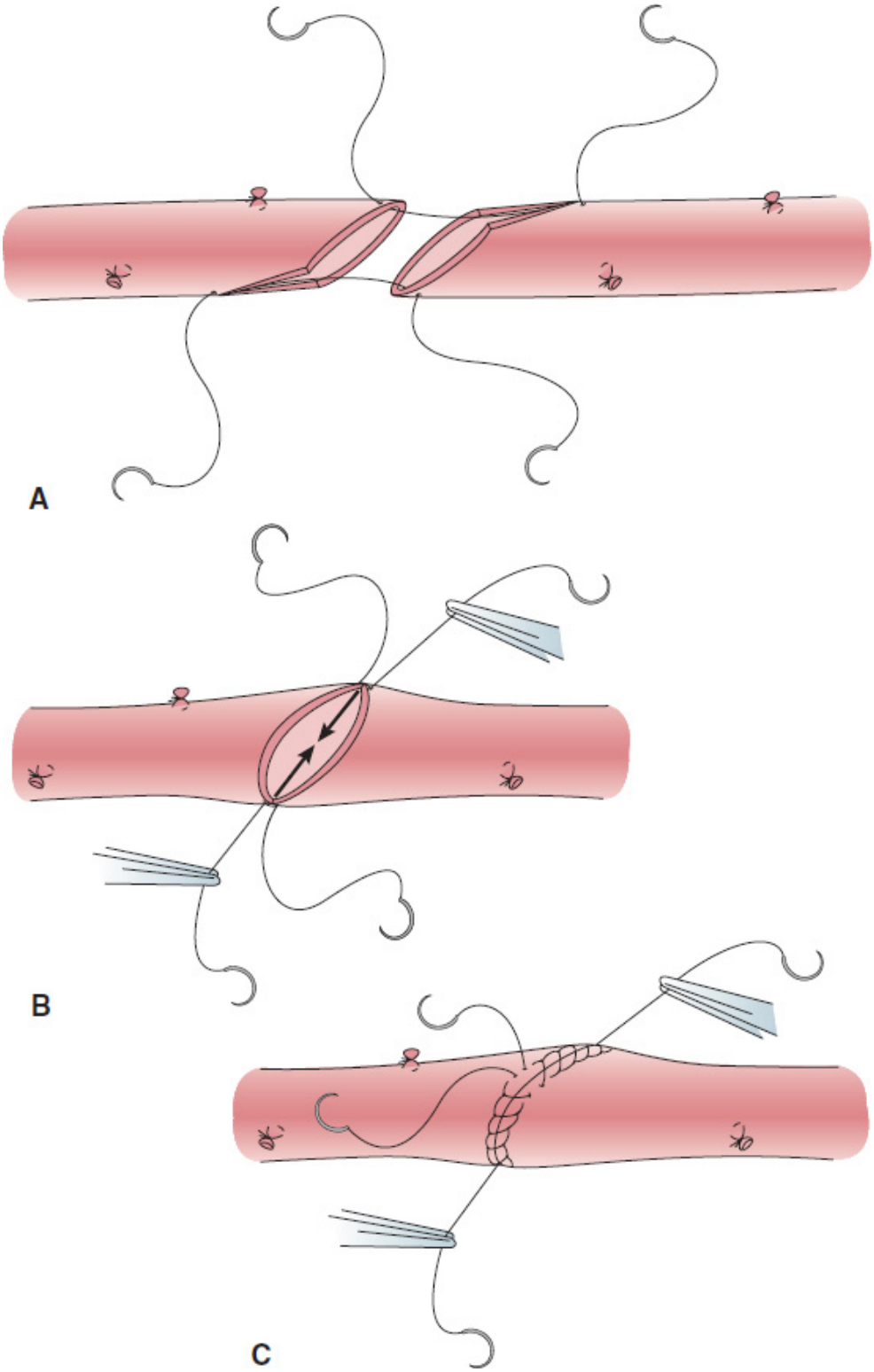

Figure 91.12 Creation of a composite graft from two or more segments of arm vein or lesser saphenous vein (**A**) is sometimes necessary to obtain the desired length of fully autogenous conduit for infrainguinal bypass. A widely spatulated venovenostomy (**B and C**) is optimal.

Given the known incidence of graft failure and the potentially dire consequence in terms of limb salvage or preservation of limb function in a patient with limited options for secondary or tertiary bypass, the ability to maintain graft patency through early identification and prompt correction of graft stenosis is of paramount importance.[118] Serial postoperative surveillance scanning with duplex ultrasound has proven an excellent means of accurately identifying hemodynamically significant stenosis within the vein graft that threaten the graft patency.[119] Velocity criteria have been developed for high-grade lesions that may warrant either more intensive surveillance or prophylactic intervention. Absolute velocities less than 40 cm/s or greater than 300 cm/s or a threefold increase in velocity in one segment compared with that of an adjacent segment are all indicative of impending graft failure. Confirmation by angiography and expeditious treatment by percutaneous cutting balloon angioplasty, surgical patch angioplasty, or interposition grafting of such significant lesions minimizes the risk of graft thrombosis and ensures optimal long-term graft patency.

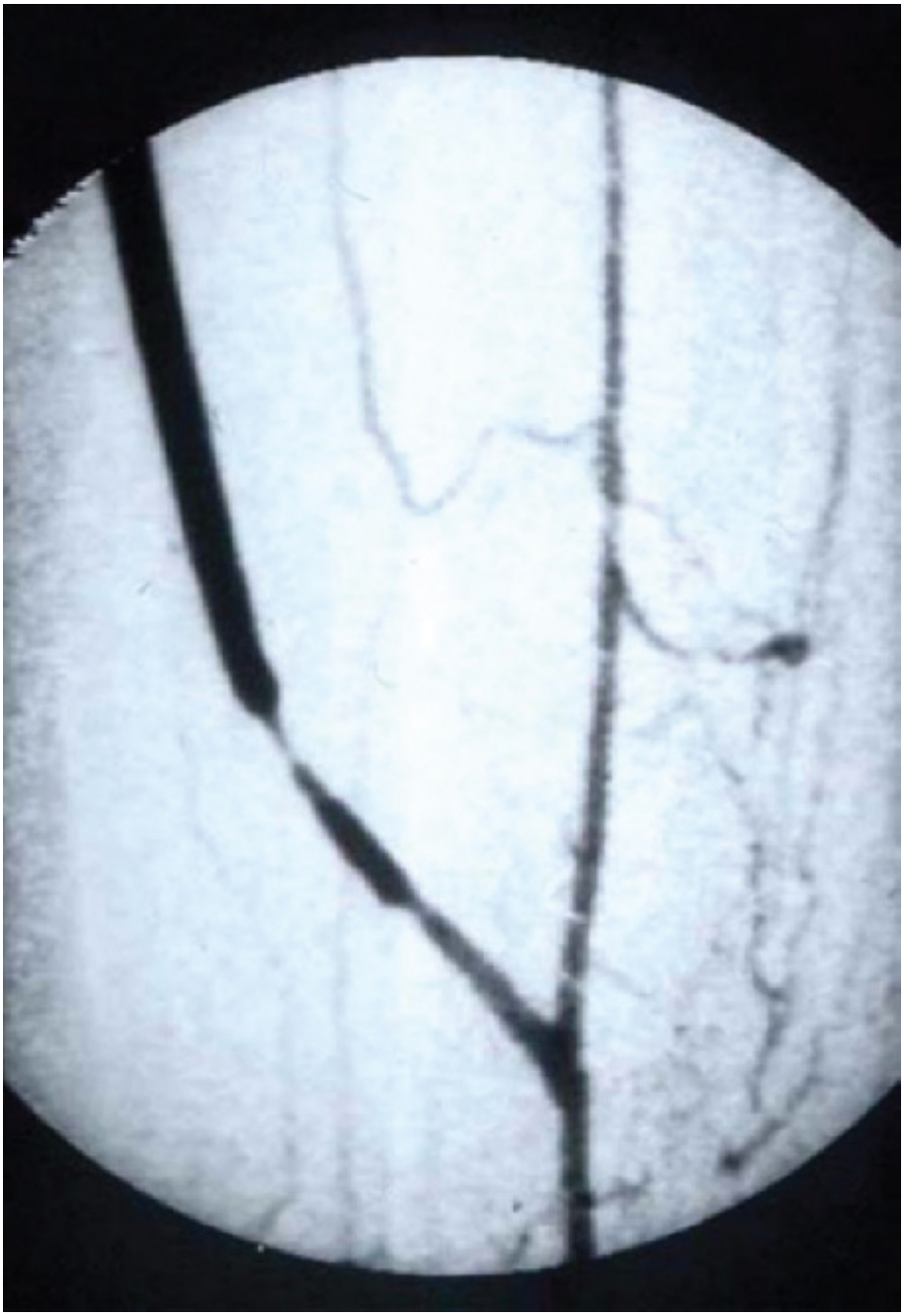

Figure 91.13 Arteriogram demonstrating severe stenosis of distal graft from intimal hyperplasia, likely at prior valve site.

Complications

The most commonly seen major complications of infrainguinal bypass surgery are cardiac in nature, and include myocardial infarction, congestive heart failure, and arrhythmias. In a recent review spanning 20 years and

involving more than 1,600 procedures, the perioperative myocardial infarction rate was 3%, and the rate of cerebrovascular accident was 1%.[105] Patients with diabetes mellitus or preoperative renal insufficiency are at particular risk for developing postoperative renal failure (defined as an elevation of serum creatinine >3 mg/dL, doubling of the serum creatinine or the need for hemodialysis), which is seen in up to 2% of patients overall. Patients undergoing lower extremity revascularization are also prone to wound complications, given the length of incisions and the prolonged operating times often required. Overall wound complications, including cellulitis and abscess formation, wound dehiscence, and skin flap necrosis, can occur in up to 40% of patients and can best be avoided by gentle handling of the tissue and the use of skin bridges and careful avoidance of skin flaps during vein harvesting.[120] Postoperative hematomas, usually caused by slow capillary or venous oozing, or seromas are seen in 5% of patients; and less commonly encountered hemorrhage, typically a result of either a slipped vein branch ligature or anastomotic disruption, is seen in less than 1% of cases.

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92

Lower Extremity Amputation

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Key Points

1. The annual incidence of major amputations has decreased over the past two decades.
2. The vast majority of lower extremity amputations are performed for complications of diabetes or arterial insufficiency.
3. Emergent amputation is indicated in the face of uncontrolled or ascending infection.
4. Primary amputation is occasionally indicated in cases of treatment for lower extremity trauma.
5. Revascularization is often performed in conjunction with a minor amputation, either simultaneously or as a staged procedure.
6. The choice of amputation level depends on the indication for the procedure, the condition of the patient, and the rehabilitation potential of the patient.
7. The energy required to ambulate following a lower extremity amputation increases with ascending level of amputation.

INTRODUCTION

1 Surgeons are often involved in treating patients requiring lower extremity amputation. Increasing incidence of diabetes, peripheral arterial disease, and the aging population has put more patients at risk for amputation. The explosion of endovascular interventions over the past decade has resulted in decreasing numbers of major amputations performed annually.[1] A review of the Nation Hospital Discharge Survey and Medicare claims data confirms this trend.[2] Clinical judgment is critical to a successful outcome. Factors to consider are primary amputation, revascularization, repeat revascularization, level of amputation, and timing of amputation. The surgeon must remember that the goal is to maintain maximal function of the patient not necessarily maximal length of the limb. Consequently, experience of the surgeon has been shown to be key to a successful outcome.[3]

INDICATIONS

2 Most lower extremity amputations are performed for complications of diabetes or arterial insufficiency (**Table 92.1**). Chronic infection and trauma account for less than 10% of the total number of amputations. Other indications include neuroma, frostbite, malignancy, chronic pain, arterial embolization, venous insufficiency, and cryoglobulinemia.[4]

Elective lower extremity amputation in diabetic and vascular patients is indicated for gangrene (dry gangrene), gangrene with infection (wet gangrene), unremitting and unreconstructable rest pain, and nonhealing ulcers. The goal of the operation is to remove all nonviable tissue, relieve ischemic rest pain, ensure primary wound healing, and facilitate rehabilitation. Elective amputation should only be performed following an evaluation for revascularization procedure by a surgeon capable of performing such procedures. Veith et al.[5] reported that 96% of patients who underwent lower extremity arteriography for limb-threatening infrainguinal arteriosclerosis were candidates for arterial reconstruction. Advances in percutaneous management have expanded treatment options to patients who were not otherwise operative candidates. Not all patients are candidates for arteriography, including those with chronic renal insufficiency, organic brain

syndrome, nonfunctional limbs, fixed joint contractures, insensate feet, and those with extensive gangrene.

Spinal cord stimulation (SCS) may offer a chance for limb salvage for patients with chronic ischemia in whom reconstruction is not an option. Based on Melzack and Wall theory for the treatment of chronic pain,[6] the mechanism of pain relief and increased blood flow in end-stage peripheral vascular disease is unclear. Despite this, there is peripheral vasodilatation on the microvascular level which leads to pain relief,[7] increased claudication distance,[8] ulcer healing,[9] and possible limb salvage.[7,10,11] The 1-year foot salvage rate is 60% to 70% on average, according to a review of the literature.[12] SCS is only appropriate when surgery for revascularization is no longer possible. Furthermore, SCS only dilates microvasculature and does nothing for the underlying, progressive peripheral vascular disease that is causing the ischemia. SCS, therefore, is only a temporizing measure, but can potentially give an extended functional period with a procedure that is well tolerated and relatively simple to perform.[12] Recently, Gersbach et al. have shown that the benefits of SCS persist longer than initially thought.[13]

Table 92.1 Indications for Lower Extremity Amputation

Indication	Percentage (%)
Complications of diabetes mellitus	60–80
Nondiabetic infection with ischemia	15–25
Ischemia without infection	5–10
Chronic osteomyelitis	3–5
Trauma	2–5
Miscellaneous (neuroma, frostbite, tumor, pain, and nonhealing wound)	5–10

From Malone JM. Lower extremity amputation. In: Moore WS, ed. *Vascular Surgery: A Comprehensive Review*. Philadelphia, PA: WB Saunders; 1993:810.

3 Emergent amputation is indicated in the face of uncontrolled or ascending infection. In the case of uncontrolled sepsis, it can even be a

lifesaving maneuver. A diabetic patient with a foot abscess is a surgical emergency. Frequently, incision and drainage with or without a toe or a combined toe and metatarsal resection is sufficient to control the acute problem. The wounds should be left open in the setting of acute infection. If the process extends beyond the foot, a staged amputation should be performed proximal enough to control the infection. This can include an ankle disarticulation, a guillotine below-knee amputation (BKA), a knee disarticulation, or a guillotine above-knee amputation (AKA). Disarticulations have the advantage of preserving limb length and avoiding an open bone in the incision. After the infection is controlled, the appropriate amputation can be completed. A one-stage primary AKA can be considered in patients who are nonambulatory, have infection involving the entire lower leg, have a fixed knee contracture, or those with a nonfunctional limb. Patients who are too unstable for surgery can be temporized with a cryoamputation.[14]

4 Primary amputation is occasionally indicated as treatment for severe lower extremity trauma. Both penetrating and blunt injuries of the lower extremities are frequently associated with vascular, nerve, bone, and extensive soft tissue injuries. Several treatment guidelines have been developed for lower extremity trauma. Lange[15] recommended primary amputation for open tibial fractures with associated vascular injuries if the posterior tibial nerve was disrupted in an adult or if the duration of warm ischemia was greater than 6 hours in a crush injury. In addition, he suggested that primary amputation was relatively indicated in patients with polytrauma, severe ipsilateral foot injuries, and in those with an expected protracted postoperative course. These suggestions are supported in work by Bosse et al.[16] demonstrating, in the case of high-energy lower extremity trauma, amputation and reconstruction have equal functional outcomes at 2 years. Additional guidelines have been provided by Johansen et al.[17] who devised a Mangled Extremity Severity Score to predict the need for amputation based on the extent of skeletal or soft tissue damage, limb ischemia, shock, and age. Unfortunately, none of these guidelines are predictive of functional recovery in patients who undergo limb salvage.[18] Therefore, treatment with primary amputation is an extremely difficult decision and requires extensive clinical judgment as well as multidisciplinary input. Contributing factors include the

severity of the injury, the overall clinical status, and the ultimate rehabilitation potential of the patient.

EVALUATION FOR REVASCULARIZATION

Modern vascular surgery techniques allow successful limb salvage in situations not previously possible. All patients who present for possible lower extremity amputation, including minor amputations, should have their peripheral vascular circulation evaluated preoperatively. Any patient with absent pedal pulses or abnormal ankle–brachial indices should be evaluated by a vascular surgeon skilled in both open and endovascular revascularization techniques. The evaluation may require only a thorough history and physical examination if there is an obvious contraindication to revascularization (e.g., nonfunctional limb, severe organic brain syndrome). Noninvasive vascular laboratory examinations are a mandatory minimum for patients with abnormal vascular examinations. Additional imaging with either computed tomographic angiography (CTA), magnetic resonance angiography (MRA), or contrast angiography can be done based upon the patient's initial evaluation and vascular lab results. The information obtained from these tests is heavily dependent on the quality of the machinery, the skill of the technologist, and the knowledge of the interpreting physician. All of these factors must be taken into account when deciding which test to order. Contrast angiography with selective lower extremity injections may be necessary to fully define the patient's anatomy and suitability for reconstruction; however, it is generally preferred to perform this invasive procedure for preoperative planning or for planned percutaneous intervention. Contrast arteriography should not be considered a *diagnostic* examination.

Exponential advances in endovascular techniques have occurred over the past two decades. These have found their way into the peripheral circulation and have applicability in limb salvage. Percutaneous techniques include balloon angioplasty (including conventional, cutting, and drug-coated balloons), stenting (including balloon expandable, self-expanding, drug eluting, and covered stents), intravascular lithotripsy, and percutaneous atherectomy (including laser, directional, orbital and rotational). The BASIL

trial showed no significant difference in amputation-free survival among patients with critical limb ischemia when randomized to open or percutaneous revascularization.[19]

In terms of surgical reconstruction, upper extremity[20] and cryopreserved cadaver vein[21] have increased the options for conduit in limb salvage situations. Prosthetic grafts with vein cuffs[22,23] provide other alternatives when appropriate autogenous conduit is not available. Heparin-bonded prosthetic grafts have been shown to be effective as well.[24–26] An operation for limb salvage should never be denied *only* for lack of conduit.

5 Revascularization is often performed in conjunction with a minor amputation, either simultaneously or as a staged procedure. This allows management of the acute problem of sepsis and the underlying chronic ischemia. Caution must be taken if there is active infection and the only available conduit is prosthetic for fear of infecting the graft. Amputation with control of infection followed by revascularization is the more prudent course. In extreme cases, a limited amputation can be combined with revascularization and a tissue transfer (free or rotational flap) to achieve limb salvage.[27,28]

CHOICE OF AMPUTATION LEVEL

General

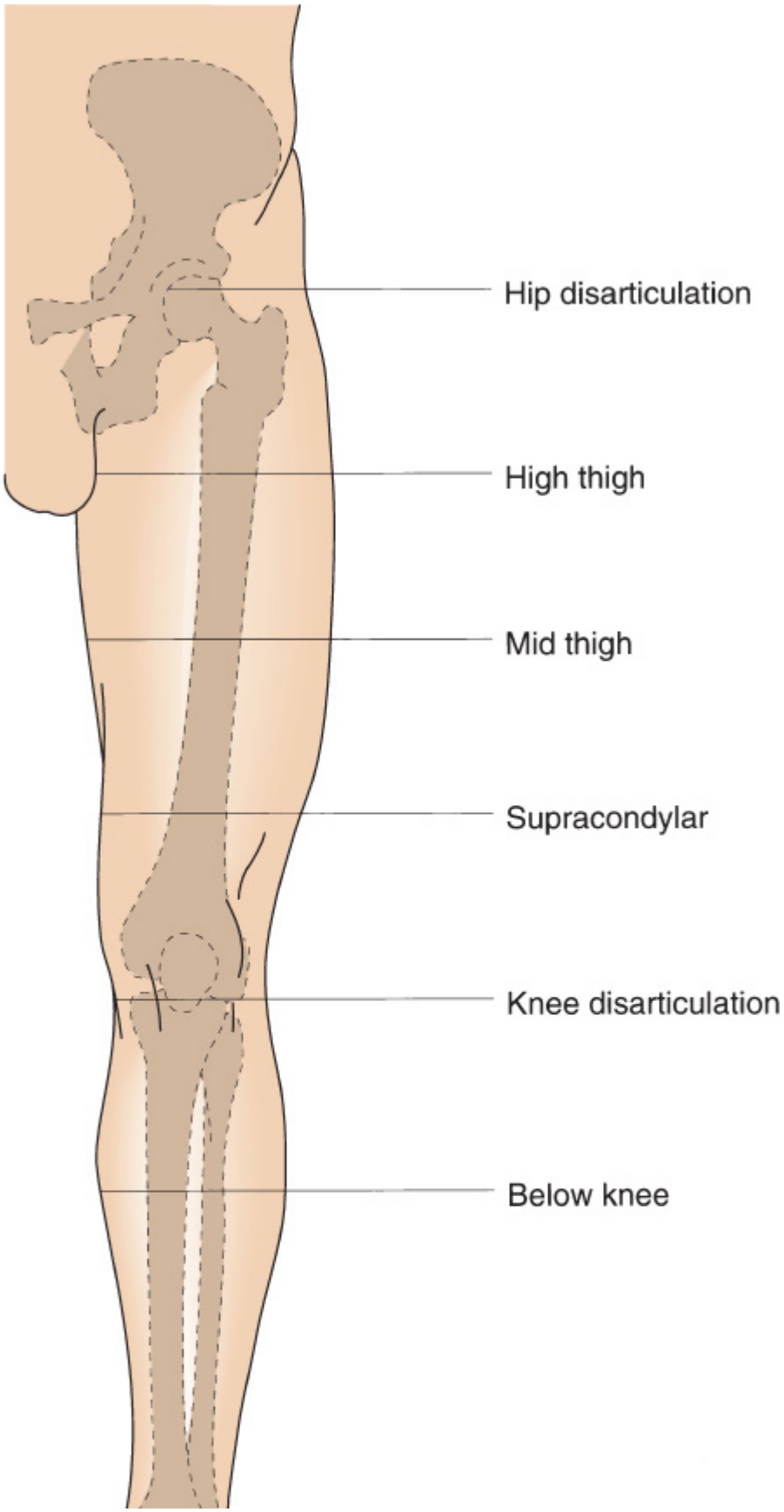
6 The choice of amputation level depends on the indication for the procedure, the condition of the patient, and the rehabilitation potential of the patient. The most common amputation levels are illustrated in **Figure 92.1**. Because most amputations are performed for complications of diabetes or arterial insufficiency, the selected level must remove all nonviable, painful tissue, allow primary healing, and maximize rehabilitation potential. Selection of the amputation level for malignant disease is dependent on the biologic characteristics of the neoplasm and will not be discussed further.

The general medical condition and the rehabilitation potential of the patient are important factors in deciding to proceed with amputation and in selecting the appropriate level. If a patient is ambulatory and independent preoperatively, the level with the greatest likelihood of maintaining function

should be selected. If the patient is not ambulatory or has significant comorbid conditions, the primary wound-healing rate should be the determining factor.

Specific Situations

Aggressive attempts to salvage a distal amputation level are not indicated for patients who are unlikely to ambulate with a prosthesis.[29] For example, patients with fixed joint contractures greater than 15 degrees at the knee or 10 degrees at the hip are unlikely to ambulate with a prosthesis. BKAs are relatively contraindicated in patients with paraplegia because flexion contractures at the knee can lead to stump ulceration.


Hip disarticulation
High thigh
Mid thigh
Supracondylar
Knee disarticulation
Below knee

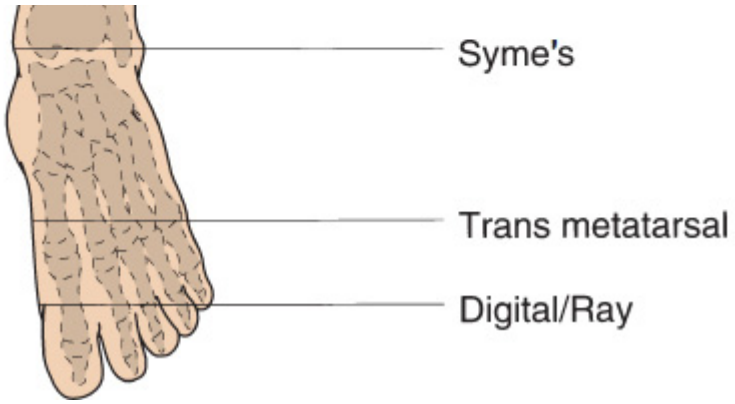


Figure 92.1 Common amputation levels for the lower extremity.

Energy Requirement

7 The energy required to ambulate following a lower extremity amputation increases with ascending level of amputation. The more proximal the amputation, the less likely a patient will be able to ambulate postoperatively. **Table 92.2** illustrates the increased energy cost of the common lower extremity amputations. In clinical practice, the most significant increase is between a BKA and an AKA. Ambulation on an above-knee prosthesis requires the use of muscle groups poorly suited for that purpose. These increased energy costs are minor issues for young trauma or cancer patients; however, they represent a considerable obstacle for the older diabetic or vascular patient.

Clinical Assessment

The primary preoperative consideration for wound healing is the status of the skin and muscle blood flow. Operative technique, the patient's nutritional status, and the presence of infection also affect wound healing. Clinical judgment by an experienced surgeon accurately predicts healing of a BKA in approximately 80% of cases.[30] A palpable pulse at the level immediately proximal to the proposed amputation essentially ensures healing[31]; however, the converse is not true. Noninvasive arterial testing is the most common adjunctive test used to predict healing of a specific amputation level. Its usefulness is limited when medial sclerosis prevents vessel compression, a condition common in diabetic patients. Because the digital vessels are often

spared from this process, digital pressure readings may be helpful in this setting. Transcutaneous oxygen measurement has been shown to predict primary healing although it is less able to predict failure to heal.[32,33] It has become more widely available and has supplanted previous less reliable tests that were more limited in availability. **Tables 92.3** to **92.6** summarize the results of various preoperative tests to predict wound healing for toe, foot and forefoot, below-knee, and above-knee amputations, respectively. The Society for Vascular Surgery WIfI (Wound, Ischemia, and foot Infection) classification system has more recently been shown to be very helpful in predicting the risk of amputation and benefit of/requirement for revascularization.[34–38]

Table 92.2 Rehabilitation Energy Cost of Amputation at Various Levels

Amputation Level	Energy Cost
Digital or ray	Minimal (except first ray)
Transmetatarsal	Minimal during normal walking
Below knee	30–60% increase in energy required for ambulation
Above knee	60–100% increase in energy required for ambulation
Hip disarticulation	100–110% increase in energy required for ambulation

Table 92.3 Preoperative Level Selection: Toe Amputation

Selection Criteria	Successful Healing, Primary and Secondary per Total
Empiric	86/115 (75%)
Presence of pedal pulses	357/365 (98%)
Doppler toe pressure >30 mm Hg	47/60 (78%)
Doppler ankle pressure >35 mm Hg	44/46 (96%)
Photoplethysmographic digit or TMA pressure >20 mm Hg	20/20 (100%)

TMA, transmetatarsal.

From Durham JR. Lower extremity amputation levels: indications, methods of determining appropriate level, technique, prognosis. In: Rutherford RB, ed. *Vascular Surgery*, 3rd ed. Philadelphia, PA: WB Saunders; 1989:1693.

Table 92.4 Preoperative Level Selection: Foot and Forefoot Amputation

Selection Criteria	Successful Healing, Primary and Secondary per Total
Empiric	11/24 (46%)
	36/50 (72%)
Doppler ankle systolic pressure	
<40 mm Hg	5/9 (56%)
>40 mm Hg	20/60 (33%)
40–60 mm Hg	4/5 (80%)
>50 mm Hg	14/21 (66%)
>60 mm Hg	68/91 (75%)
>70 mm Hg	70/93 (75%)
Doppler toe systolic pressure	
>30 mm Hg	4/5 (80%)
Doppler ankle–brachial pressure index	
>0.45 (nondiabetic)	
>0.50 (diabetic)	58/60 (97%)
Photoplethysmographic toe systolic pressure	
>55 mm Hg	14/14 (100%)
>45 and <55 mm Hg	2/8 (25%)
<45 mm Hg	0/8 (0%)
Transcutaneous Po_2	
>10 mm Hg (or a >10 mm Hg increase on Fio_2 = 1.0)	6/8 (75%)
>28 mm Hg	3/3 (100%)

Transcutaneous Pco_2	
<40 mm Hg	3/3 (100%)

From Durham JR. Lower extremity amputation levels: indications, methods of determining appropriate level, technique, prognosis. In: Rutherford RB, ed. *Vascular Surgery*, 3rd ed. Philadelphia, PA: WB Saunders; 1989:1695.

OPERATIVE TECHNIQUE

General Considerations

Diabetic patients who present septic require adequate fluid resuscitation, broad-spectrum antibiotics (including anaerobic coverage), and an emergent operation. Whereas maintenance of limb length and function is admirable, control of sepsis and wide debridement of all nonviable tissue are essential and potentially lifesaving. All patients require atraumatic tissue handling. Avoid forceps on the skin edge. Excessive skin flaps and dead space are also not desired. Amputations done in the face of active infection are kept open and treated with dressing changes. Consider delayed primary closure in cases where perfusion is intact.

Postoperatively, the limb is elevated to minimize tissue edema and promote healing. Weight bearing on the amputation is delayed until healing is assured. This patient population requires effective prophylaxis against deep venous thrombosis and venous thromboembolism.

Digital and Ray Amputations

Digital amputations are indicated for some severe and irreducible deformities as well as gangrene or osteomyelitis localized distal to the base of the proximal phalanx. A technique for partial digital amputation is illustrated in **Figure 92.2A**. The circumferential or racquet-shaped skin incision is made over the distal end of the proximal phalanx and carried down to bone. Nerves and tendons are transected under tension and allowed to retract. The proximal phalanx is divided with bone shears or power saw and the transected end smoothed with a rongeur. Soft tissue coverage can be performed with either medial/lateral flaps or dorsal/plantar flaps depending

on skin tension and viability. The wound is closed with simple interrupted skin sutures. Judicious use of subcutaneous sutures is advised due to danger of vascular compromise to the small remaining flaps. Non–weight-bearing restrictions or protected weight bearing on the heel only in a rigid soled postoperative shoe or walking boot until the wound heals is recommended.

Table 92.5 Preoperative Level Selection: Below-Knee Amputation

Selection Criteria	Successful Healing, Primary and Secondary per Total
Empiric	794/974 (82%)
Doppler ankle systolic pressure	
>30 mm Hg	66/70 (94%)
Doppler calf systolic pressure	
>50 mm Hg	36/36 (100%)
>68 mm Hg	96/97 (99%)
Doppler thigh systolic pressure	
>100 mm Hg	31/31 (100%)
>80 mm Hg	104/113 (92%)
Transcutaneous $Po_2 = 0$	0/3 (0%)
>10 mm Hg (or >10 mm Hg increase on $Fio_2 = 1.0$)	76/80 (95%)
>10 and <40 mm Hg	5/7 (71%)
>20 mm Hg	25/26 (96%)
>35 mm Hg	51/51 (100%)
Transcutaneous Po_2 index >0.59	17/17 (100%)
Transcutaneous Pco_2 <40 mm Hg	7/8 (88%)

From Durham JR. Lower extremity amputation levels: indications, methods of determining appropriate level, technique, prognosis. In: Rutherford RB, ed. *Vascular Surgery*, 3rd ed. Philadelphia, PA: WB Saunders; 1989:1700.

Table 92.6 Preoperative Level Selection: Above-Knee Amputation

Selection Criteria	Successful Healing, Primary and Secondary per Total
Empiric	390/430 (91%)
Transcutaneous Po_2	
>10 mm Hg (or 10 mm Hg increase on $Fio_2 = 1.0$)	15/23 (65%)
>20 mm Hg	12/12 (100%)
>23 mm Hg	2/2 (100%)
>35 mm Hg	21/24 (100%)
Transcutaneous Pco_2 <38 mm Hg	5/5 (100%)

From Durham JR. Lower extremity amputation levels: indications, methods of determining appropriate level, technique, prognosis. In: Rutherford RB, ed. *Vascular Surgery*, 3rd ed. Philadelphia, PA: WB Saunders; 1989:1707.

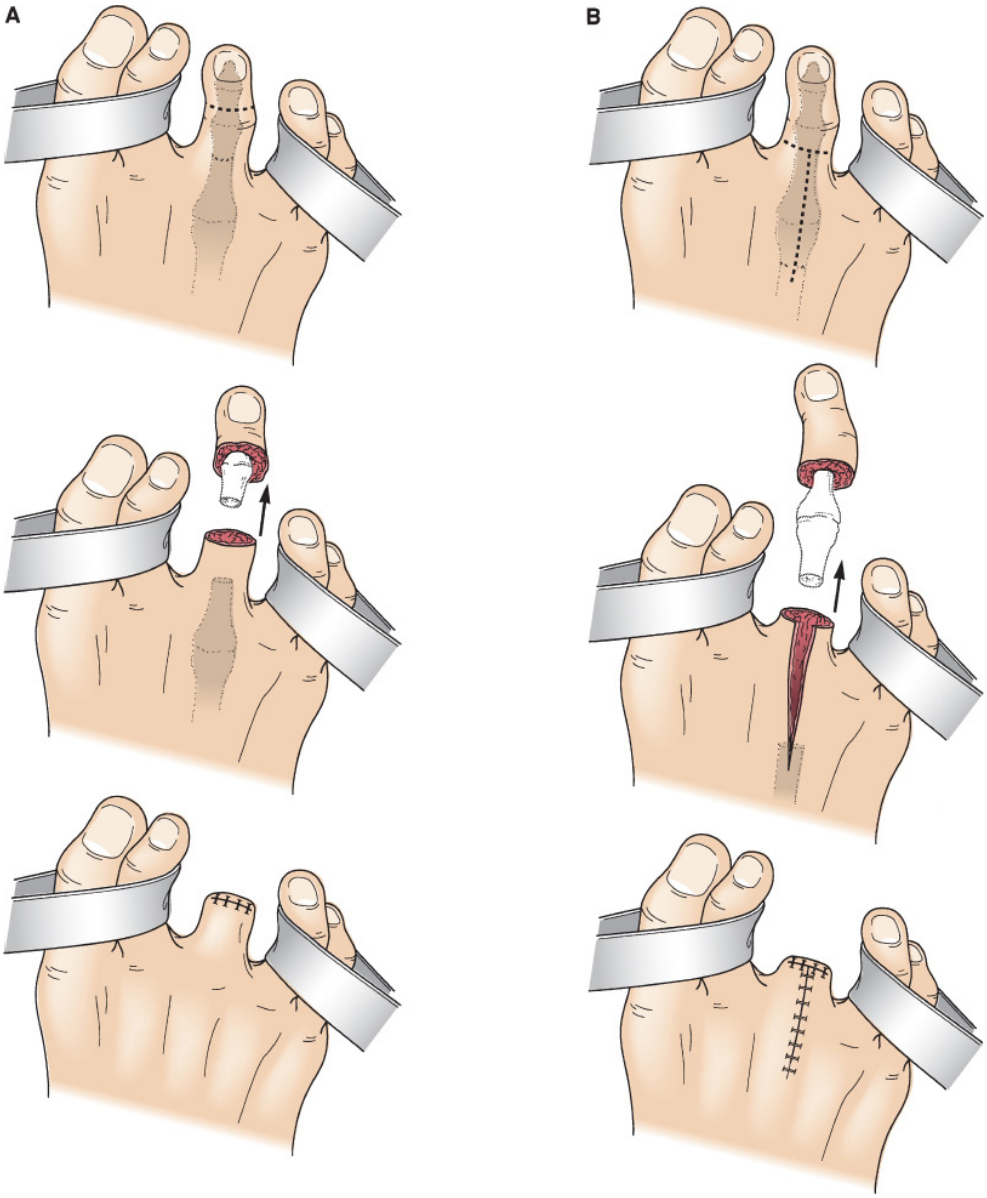


Figure 92.2 **A:** Digital amputation. A circumferential skin incision is made proximal to the gangrenous process. The proximal phalanx is transected and the soft tissue approximated. **B:** Metatarsal head resection (ray amputation). A racquet-shaped skin incision is made with the circular component extending circumferentially around the digit and the longitudinal component extending proximal to the metatarsal head. The metatarsal is transected proximal to the head and the soft tissue approximated.

A ray amputation is indicated when the disease process extends to the metatarsal phalangeal joint. The technique is similar to a digital amputation and is illustrated in **Figure 92.2B**. A circumferential incision is made at the base of the involved toe and extended proximally on the dorsum of the foot

over the metatarsal. The incision is extended to bone. The periosteum is cleared circumferentially and the bone is transected using a power saw at a level that will allow tension-free closure of the wound. In the case of the first or fifth toe, the incision is extended on the medial or lateral aspect of the foot, respectively. Care should be taken to bevel the distal metatarsal stump to minimize any prominence that may lead to skin breakdown with weight-bearing or shoe gear wear. Typically, the first metatarsal is beveled from proximal medial to distal lateral and proximal planter to distal dorsal. Metatarsals 2, 3, and 4 should be beveled from proximal plantar to distal dorsal. The 5th metatarsal is beveled from proximal lateral to distal medial and proximal plantar to distal dorsal.

In selected cases of neuropathic ulcers, the metatarsal head can be resected leaving the toe intact. A dorsal longitudinal incision is made over the metatarsal bone and the metatarsal head is resected with a power saw. Pulsed lavage and careful soft tissue inspection will help guide appropriate care for the plantar wound (i.e., packing, negative-pressure therapy, or ellipse of wound with closure). The dorsal wound is typically closed unless severe infection is encountered.

Transmetatarsal Amputation

Transmetatarsal amputation (TMA) is a useful procedure that maintains a patient's ability to ambulate without the aid of a prosthesis. It is indicated when the gangrenous or infectious process involves multiple digits or a portion of the forefoot. Care must be taken to plan for the appropriate soft tissue coverage if primary closure is desired. Maximizing the plantar flap is most common, but coverage can also be gained from medial or laterally based flaps and even filleted toe flaps. If adequate soft tissue coverage is not available and a more proximal foot amputation (i.e., Chopart joint amputation) is not desired then an open amputation through the metatarsal bones can be performed. The wound is allowed to close secondarily or covered with a skin graft. Skin grafts in this position, however, are susceptible to breakdown secondary to the pressure related to ambulation.

The technique is demonstrated in **Figure 92.3**. A skin incision is made on the dorsum of the foot immediately proximal to the metatarsal heads and extended medially and laterally to a point midway between the plantar and

dorsal surfaces. The plantar incision is made along the digital crease and extended diagonally medially and laterally to connect to the dorsal incision. The dorsal incision is deepened to the periosteum, which is cleared with a small periosteal elevator. The metatarsal bones are transected 0.5 to 1.0 cm proximal to the dorsal skin incision. The plantar flap is fashioned by continuing the dissection just superficial to the metatarsal heads. Care is taken to maintain plantar flap thickness. The nerves and tendons are transected sharply under tension and allowed to retract. The plantar flap is rotated anteriorly and assessed for length. Excess tissue is excised sharply and the deep tissue is approximated with absorbable suture. The skin is closed without tension using monofilament suture or skin staples.

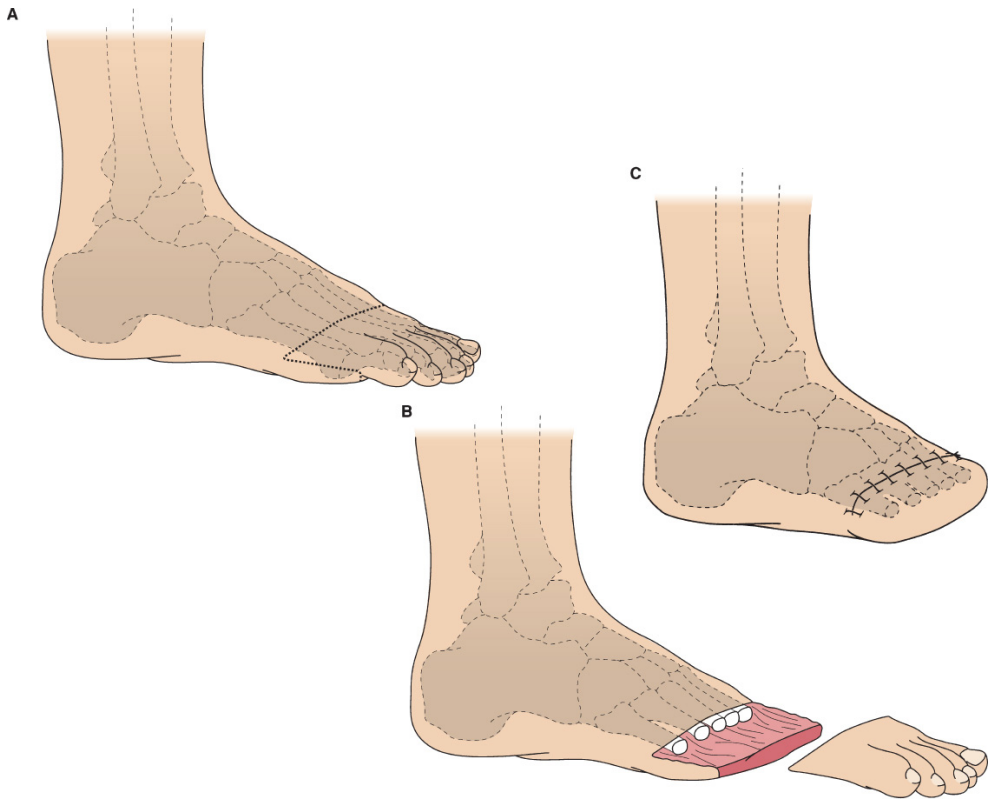


Figure 92.3 **A:** The skin incision for the transmetatarsal amputation is made on the dorsum of the foot immediately proximal to the metatarsal heads and on the plantar surface within the digital crease. **B:** The metatarsal heads are transected proximal to the skin incision and separated from the plantar soft tissue flap along a plane adjacent to the bone. **C:** The plantar soft tissue flap is rotated anteriorly and approximated.

Weight bearing is delayed for 1 month to allow adherence of the plantar flap. Either a soft dressing or a short leg cast can be used for a postoperative dressing.

Staging a tendo-Achilles lengthening (TAL) is important to consider following (or at the same time if no infection is present) a partial foot amputation. Ulcer formation at the TMA stump site is often related to equinus formation due to the ensuing flexion/extension imbalance that occurs after resection of the forefoot. A simple triple-hemisection percutaneous TAL can effectively lengthen the Achilles and reduce future pressures at the stump site.[39] Other tendon-balancing procedures may be needed to control varus and valgus contraction deformities that can develop.

Syme Amputation

The Syme amputation is a foot amputation that preserves limb length and the epiphyseal growth plates and allows occasional ambulation without a prosthesis. It is indicated in cases of extensive foot trauma or other nonviable tissue conditions distal to the hindfoot. The Syme amputation is contraindicated if a supple intact heel pad and a well-vascularized hindfoot tissue flap are not available.

The procedure can be performed in one or two stages, as illustrated in **Figure 92.4**. The initial steps for both procedures are identical, except that the skin incision for the two-stage procedure is located 1.5 cm more distally. The skin incision for the one-stage procedure extends from the medial to the lateral malleolus in the horizontal and vertical planes. The dorsal incision is extended to the bone, and the tendons are transected under tension. The anterior tibial artery is identified, divided, and suture ligated. The dissection is carried into the tibiotalar joint space as the foot is forcibly plantar flexed. The ligaments are transected and the talus is dislocated. The plantar aspect of the incision is deepened to the calcaneus, and the calcaneus is sharply dissected from the plantar fascia. The plantar fascia is densely adherent and care must be taken to prevent damage to the heel pad, especially at the level of the Achilles tendon. The posterior tibial artery must be preserved because it perfuses the heel pad. The foot is then removed. The two procedures differ from this point forward.

In the one-stage procedure, the medial and lateral malleoli are transected flush with the tibiotalar joint space, and the heel pad is rotated over the ends of the tibia and fibula. The deep fascial layers are approximated with absorbable suture and the skin is closed with monofilament suture or skin staples. Securing the distal end of the remaining plantar fascia to a small drill hole in the distal anterior tibia will help anchor the plantar flap and reduce posterior migration. In the two-stage procedure, the heel pad is similarly positioned and the wound is closed without further bone transection. In 6 weeks, elliptical incisions are made over the medial and lateral malleoli and the distal ends of the tibia and fibula are transected flush with the ankle joint. In addition, the distal flares of the tibia and fibula are transected, creating the rectangular stump of the two-stage procedure. The wound is closed in a similar fashion. For both procedures, weight bearing is delayed for at least 4 weeks to allow heel pad fixation. A soft dressing or a short leg cast can be used.

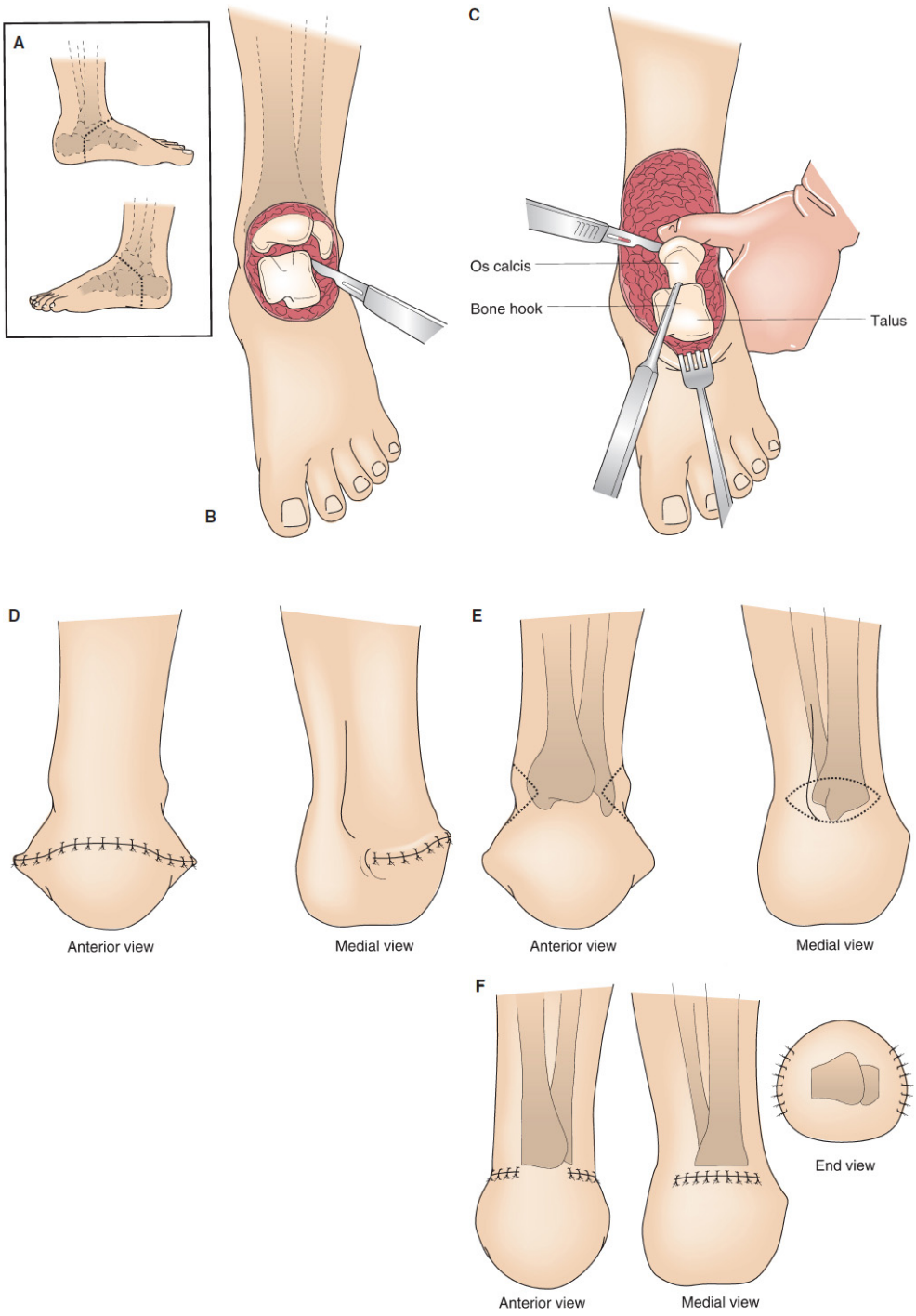


Figure 92.4 **A:** The skin incision for the one-stage Syme amputation connects the medial and lateral malleoli in both the horizontal and vertical planes. The skin incision for the two-stage procedure is located approximately 1.5 cm further distally. **B:** The incision is extended into the tibial—talar joint space, and the foot is placed in forced plantar flexion. **C:** The calcaneus is sharply dissected from the adherent plantar fascia along a plane adjacent to the bone. **D:** The heel pad is rotated anteriorly and approximated after the calcaneal dissection in the two-stage procedure and after the additional transection of the medial and lateral malleoli in

the one-stage procedure. **E:** Elliptic incisions are made over the medial and lateral malleoli during a second operation for the staged procedure. The medial and lateral malleoli are transected flush with the ankle joint, and the distal flares of the tibia and fibula are removed. **F:** The two-stage procedure results in a less bulbous, more cosmetically acceptable residual limb.

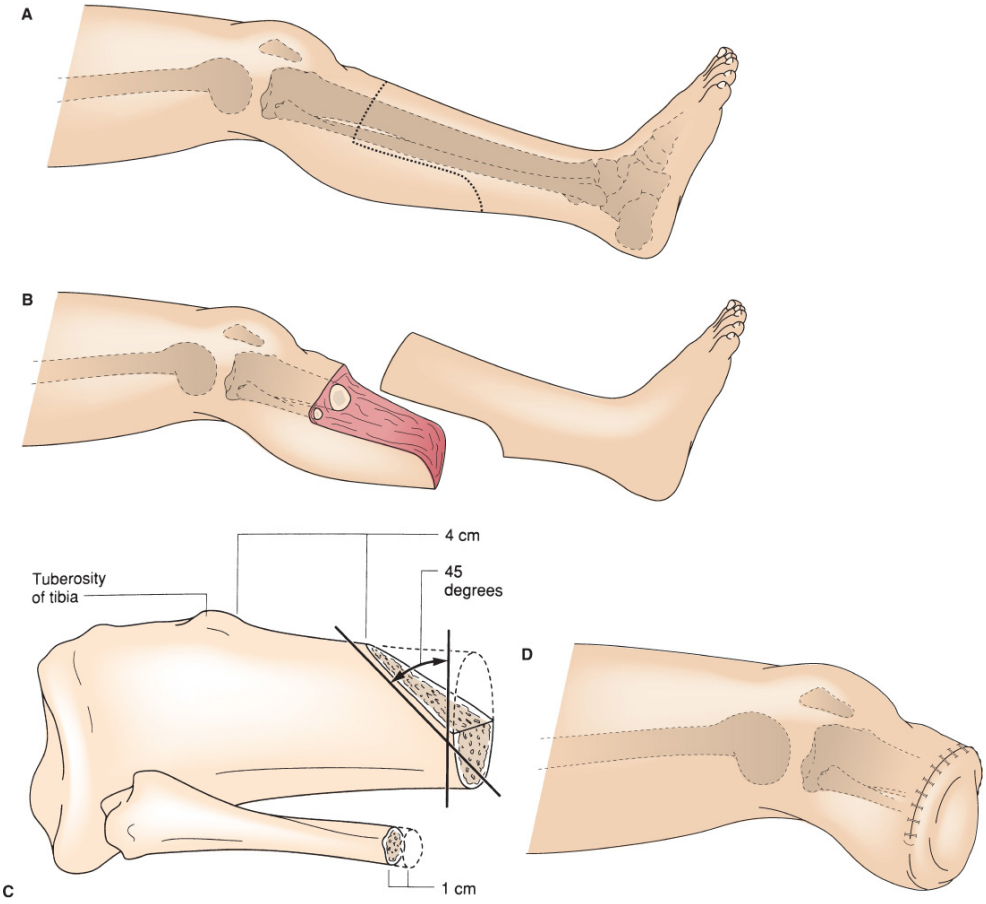


Figure 92.5 A: The skin incision for a below-knee amputation based on a posterior flap is made 11 cm distal to the tibial tuberosity and extended medially and laterally to the midpoint of the calf. The length of the posterior flap is about 2 cm longer than the diameter of the calf at the point of the proximal incision. **B:** The tibia is transected 1 cm proximal to the skin incision. The fibula is transected an additional 1 cm proximal to the level of the tibial transection, and the posterior calf muscles are incised along the plane of the skin incision. **C:** The anterior aspect of the tibia is beveled at an angle of about 45 degrees, and the bone edges are filed. **D:** The posterior flap is rotated anteriorly and approximated.

Below-Knee Amputation

The complications of diabetes and arterial insufficiency constitute most of the indications for BKAs. **Tables 92.5** and **92.6** outline the criteria used to

decide between a BKA and an AKA in this setting.

The most common technique, using a long posterior flap, is illustrated in **Figure 92.5**. When gangrene, wounds, or incisions preclude the use of a posterior flap, equal anteroposterior or sagittal flaps can be used; however, the posterior flap is associated with the highest incidence of primary healing and is thus preferred whenever possible. This higher rate of healing reflects the fact that the posteriorly located gastrocnemius and soleus muscles are supplied by the sural arteries that originate proximal to the knee.

The proposed skin incision is drawn on the leg with a marker. The tibia should be transected 10 cm distal to the tibial tuberosity and the anterior aspect of the skin incision should be 1 cm distal to the site selected for the tibial transection. The anterior incision is extended medially and laterally. The length of the anterior incision should equal two-thirds of the circumference of the leg at the proposed level of the tibial transection. The incision is then extended longitudinally along the medial and lateral aspects of the leg. The length of the longitudinal incisions should equal one-third of circumference of the leg at the level of the tibial transection. It is prudent to err on the side of making the posterior flap too long and trim excess length at the time of closure. The medial and lateral incisions are connected posteriorly. Curving the transitions of the incision prevents the accumulation of redundant tissue at the medial and lateral aspects of the completed amputation. The skin incisions should be down to the fascia to allow separation of the skin edges. This step decreases the chance of inadvertent injury to the posterior flap later in the procedure; however, the greater and lesser saphenous veins need to be ligated and transected.

The anterior aspect of the incision is deepened through the periosteum of the tibia. The muscles of the anterior compartment are divided at the level of the skin incision and the anterior tibial neurovascular bundle is identified and suture ligated. The proximal tibia is circumferentially cleared of periosteum and transected one fingerbreadth proximal to the skin incision. The anterior aspect of the tibia is cut on a 45-degree angle. The fibula is cleared and transected 2 cm proximal to the transected tibia. The bones are divided with either a power-driven reciprocating saw, or a manual saw. Regardless, care must be taken to avoid trauma to the anterior skin flap.

The posterior tibial and peroneal neurovascular bundles are identified and suture ligated. The tibia is retracted anteriorly and the posterior musculature

is divided along the plane of the longitudinal skin incisions using an amputation knife or Bovie electrocautery. Extreme caution must be taken to avoid injury to the skin edges of the posterior flap during this step. Often a scalpel is needed to complete the division of the gastrocnemius tendon distally. The specimen is removed and manual compression achieves temporary hemostasis while the remaining vascular structures are identified and ligated. The posterior tibial nerve is retracted distally, ligated, transected sharply, and allowed to retract. The posterior flap is rotated anteriorly to assess thickness and length. Frequently, the musculature needs to be debulked to allow a tension-free closure. Rough edges of the bones are filed smooth and the wound is irrigated. Bone wax is not used. A closed-system drain may be placed to prevent a hematoma. The end of the tibia is covered and stabilized with the deep posterior musculature using absorbable sutures. The gastrocnemius fascia is approximated to the anterior fascia using absorbable suture. The subcutaneous tissue is closed with absorbable suture to minimize tension on the skin edges and the skin is closed with monofilament suture or staples.

The length of the BKA may be shortened if required by the infectious or gangrenous process. Although not ideal, a short BKA is functionally superior to an AKA. In the extreme case, the tibia can be transected at the level of the tibial tuberosity and the stump can still be fit with a prosthesis. If a BKA is necessary at this level, the biceps tendon and collateral ligament should be sutured to the tibia, the common peroneal nerve should be transected above the knee, and the fibula should be removed.

A variation of the BKA is the osteomyoplastic transtibial amputation also known as the Ertl amputation. This technique has been well described[40] and involves creating a bone bridge between the tibia and the fibula using a piece of the amputated fibula. Proposed advantages of this technique include a more stable end bearing of the stump and prevention of fibular instability.

In the face of extensive foot infection, an open (guillotine) amputation should be performed as the first part of a staged procedure. A circumferential incision is made in the distal leg just proximal to the malleoli. The fascia is divided, and the tibia and fibula are dissected free. The bones are divided at the level of the skin incision. All major neurovascular bundles are suture ligated and the remaining soft tissue is divided to complete the amputation. Several sutures are placed through the skin and underlying fascia to prevent

retraction. The wound is left open and dressed. A negative-pressure dressing may be used and simplifies wound care. A definitive BKA is delayed until the infectious process has resolved which typically occurs within a week. Ankle disarticulation is an alternative to a guillotine BKA. An incision is made at the level of the ankle joint. Vascular structures are suture ligated. The tendons are divided sharply entering the ankle joint. The capsule is circumferentially incised removing the foot from the leg. The wound is packed open or with a negative-pressure dressing.

Above-Knee Amputation

An AKA is indicated for patients requiring an amputation with a fixed-knee contracture, a nonfunctional limb, or insufficient circulation to heal a BKA. Typically, a transverse fish-mouth incision is made in the lower thigh. The initial skin incision should be carried through the subcutaneous tissue to allow the edges to separate. This step will decrease the likelihood of inadvertent injury to the posterior skin flap during transection of the posterior muscle groups. The greater saphenous vein needs to be identified and ligated. The dissection is carried down to the femur that is cleared using a periosteal elevator to a level 2 to 3 cm proximal to the skin incision. The superficial femoral artery is dissected free and suture ligated. The bone is transected with a reciprocating or manual saw, and the posterior muscle flap is divided with an amputation knife or Bovie electrocautery. Manual compression with a laparotomy pad on the newly divided stump will easily control hemorrhage while vessels are identified and ligated or electrocoagulated. The sciatic nerve is identified and placed on gentle traction. It is then highly ligated, sharply divided, and allowed to retract into the wound. The flaps should be irrigated and hemostasis assured. The fascia is then closed with absorbable suture. The subcutaneous tissue is closed with absorbable suture to minimize tension on the skin edges and the skin is closed with monofilament suture or staples. Alternative incisions can be made to accommodate surgical wounds. Most AKA wounds will heal even when the femoral pulse is nonpalpable. More proximal thigh amputations are performed when arterial perfusion is in question.

Hip Disarticulation

Lower extremity amputation at the level of the hip is an uncommon operation. The indications include malignancy, trauma, infection, and, rarely arterial insufficiency. Hip disarticulation performed for an ischemic AKA is often associated with complications in the absence of revascularization.[41] This technique is well described.

Cryoamputation

Rarely, a patient may require an emergent amputation yet have overwhelming medical problems that preclude any operative intervention. In this situation, a temporizing cryoamputation (aka, medical or physiologic amputation) is indicated.[14] A tourniquet is placed proximal to the infectious or gangrenous process and the extremity is packed in dry ice. This prevents the systemic release of muscle degradation products and allows the required procedure to be delayed while the patient's condition can be stabilized. This technique can be performed at any level on the extremity. Consideration of the level of tourniquet application is extremely important to preserve as much viable tissue as possible and avoid higher levels of limb loss. The dry ice should be placed about 3 in below the tourniquet to reduce the chance of the "freeze line" extending proximal to the tourniquet. Adequate pain management should always be employed.

It should be noted that the use of cryoamputation constitutes a commitment to eventual surgical amputation (primary or staged). Once initiated, maintenance of the physiologic amputation is vital until definitive surgical removal is possible. As the frozen tissues thaw, a systemic inflammatory response syndrome (SIRS) or sepsis with hemodynamic instability may occur as inflammatory mediators are liberated back into the circulatory system. The ideal timing to proceed to the operating room would be as soon as reasonably possible. However, the literature describes the successful maintenance of this technique over many days if necessary.[14,42,43]

Other Lower Extremity Amputations

Three additional partial-foot amputations have been well described. A Lisfranc amputation is performed at the tarsometatarsal joint level and may be an option if there is inadequate soft tissue coverage for a TMA.[44] A Chopart amputation is performed at the level of the calcaneocuboid–talonavicular bones. Consideration of adding a percutaneous heel-cord lengthening with these amputations has been recommended.[45] A partial calcanectomy hindfoot amputation has shown good utility for chronic posterior heel wounds and calcaneal osteomyelitis.[46,47] This amputation involves removal of the posterior body of the calcaneus behind the posterior facet of the subtalar joint. Primary closure is typically possible, and patients can ambulate following this procedure using a custom orthotic with a heel filler.

Knee disarticulation is a useful amputation for patients with immature growth plates. It is superior to an AKA and allows end-weight bearing, improved proprioception, and improved prosthetic control. The required prosthesis is bulky and less cosmetically appealing than that used for a BKA. The technique is well described.[48] Rotationplasty is an uncommon procedure performed primarily for treatment of osteogenic sarcoma of the thigh.[49] It involves nerve-sparing resection of the femur and knee, 180-degree rotation of the leg, and reattachment of the leg. This results in a functional, sensate foot that can easily be fit with a prosthesis.

Wound Dressings

An important consideration after amputation is the type of wound dressings applied to the stump. Two important factors in the success of an amputation are time to rehabilitation and complete wound healing, both of which are influenced by postoperative wound care.[50] With transtibial amputations, there are a number of options, such as soft gauze dressings with elastic wrap, rigid plaster dressings without immediate prosthesis, rigid plaster with immediate postoperative prosthesis, and prefabricated pneumatic postoperative prosthesis. Several studies have compared two or more of these options. Endpoints are not standardized, however, and most studies are not randomized and prospective, making comparisons and meta-analysis difficult.[50]

Benefits and drawbacks are found for each postoperative option.[50] Gauze dressings with elastic wrap are simple and low cost and provide good accessibility to evaluate wound healing. On the other hand, they may lead to higher rates of joint contraction, increased time to ambulation, and risk pressure ischemia from poorly placed elastic wrap. Despite these drawbacks, no convincing data show that soft gauze dressings are inferior to other options.[50,51] A removable knee immobilizer may be used in conjunction with gauze dressings to minimize the risk of joint contracture.

Rigid plaster casts help with joint contracture and protect the wound from trauma. With addition of a temporary prosthesis, the rigid plaster also promotes early ambulation. The plaster, however, does not provide easy access to evaluate and care for the wound and if not fitted properly will result in sheer stress and thereby break down the wound. Consequently, a level of skill in plaster placement is required of the surgical team to make appropriate and often frequent plaster changes.[50]

Finally, a prefabricated pneumatic postoperative prosthesis allows early ambulation and weight bearing, easy wound access for examination, prevention of joint contracture, and wound protection. The prosthesis, however, is bulky and upfront is more expensive than the simple gauze. Prospective studies have demonstrated statistically fewer postoperative complications with the pneumatic prosthesis and statistically fewer limbs requiring higher revisions.[52]

Table 92.7 Amputation Mortality

Category	Percentage	Number
Below knee	2	25/1,200
Above knee	9	54/609
Diabetic vs. nondiabetic	No difference	
After amputation revision	5.5	12/218

From Frang RD, Taylor LM, Porter JM. Amputations. In: Porter JM, Taylor LM, eds. *Basic Data Underlying Clinical Decision Making in Vascular Surgery*. St. Louis, MO: Quality Medical; 1994:154.

Complications

Morbidity and Mortality

Operative mortality depends on the indication and the level. Mortality rates for major lower extremity amputations in vascular and diabetic patients have been reported to be between 0% and 35%.[53] Combined mortality rates from multiple series are shown in **Table 92.7**.[54] Cardiovascular causes account for two-thirds of these deaths, with myocardial infarction responsible for one-third.[54] These review data are further supported by recent studies by Sandnes et al.[55] and Aulivola et al.[56]

Long-term survival following major amputation in the vascular population is shown in **Table 92.8**. The 5-year survival rate is only 37% compared with 85% for age-matched controls.[57]

Deep Venous Thrombosis and Pulmonary Embolism

The incidence of deep venous thrombosis following lower extremity amputation ranges from 4% to 38%.[58–60] Prophylactic measures including subcutaneous heparin, low–molecular-weight heparins, early mobilization, and pneumatic compression devices should be used as indicated.

Stump Complications

Stump complications include nonhealing, infection, hematoma, contractures, ulceration, phantom pain, and trauma. Although most amputations heal primarily, a small percentage do not. Amputation at a more proximal level usually is successful. Postoperative infections complicate 12% to 28% of all amputations with the percentage higher in cases performed for infection.[61] Infected wounds should undergo incision and drainage with debridement of all nonviable tissue. The wound should then be treated with local wound care using gauze or negative-pressure dressings, depending on the appearance of the wound and surgeon preference. Broad-spectrum systemic antibiotics should be instituted and then tailored based on wound cultures. Wound hematomas are best treated with prevention. Meticulous hemostasis and avoidance of subcutaneous cavities decrease their incidence. Hematomas should be treated in the operating room with evacuation, irrigation, and closure of the wound.

Table 92.8 Survival after Amputation for Ischemia

Time (yrs)	Survival Rate (%)
1	75
2	60
3	50
4	45
5	37

From Frang RD, Taylor LM, Porter JM. Amputations. In: Porter JM, Taylor LM, eds. *Basic Data Underlying Clinical Decision Making in Vascular Surgery*. St. Louis, MO: Quality Medical; 1994:115, with permission.

Joint contractures complicate 1% to 3% of all amputations.[57,61] These contractures can occur rapidly postoperatively and are best treated by prevention. Rehabilitation specialists and physical therapists should evaluate patients preoperatively. Active and passive range of motion should be initiated immediately postoperatively. Adequate pain medication, ideally

with patient-controlled or epidural anesthesia,[62,63] is crucial. Pillows and bed positions that result in hip or knee flexion are to be strictly avoided.

Ulcers tend to develop over bony prominences. Poorly fitting prostheses or shoes are the most common causes. Diabetic patients with peripheral neuropathy are especially susceptible to the development of ulcers following toe and limited foot amputations. They can also form on the anterior aspect of AKAs secondary to the disproportional contraction of the hip flexors relative to the hip extensors. Local wound care and bedrest usually lead to healing if the ulcer is superficial. Deep skin ulcers with involvement of the soft tissue and the underlying bone are more complicated. They often suggest borderline perfusion of the stump and require formal revision to a higher level to treat definitively.

Another option in complicated wound closure is negative-pressure wound dressing, which has been used for a wide range of difficult-to-heal lesions. Studies indicate that this dressing technique decreases wound volume, whereas traditional moist gauze dressings do not.[64] The dressings result in granulation tissue and healing in otherwise difficult tissue beds, such as diabetic foot ulcers[65] and decubitus pressure ulcers.[66] In addition to helping contract the size of the wound, negative-pressure dressings also decrease the number and frequency of dressing changes drastically when compared with wet-to-dry dressings.

Neuromas are regenerative nerve tissues that form in response to transection. They can lead to pain if trapped in the fibrous scar or if irritated by a prosthesis. Proximal nerve division under tension during the original operation decreases the incidence of this complication. Symptomatic neuromas should be treated with proximal resection of the nerve because local excision of the neuroma is rarely adequate.

Some element of phantom extremity pain occurs in nearly all amputations,[67] although these complaints are not always directed to the treating surgeon. It is necessary to describe these common symptoms to the patient and specifically inquire about their presence. The pain is disabling in 5% to 30%[68] of patients surveyed. Currently, pain is felt to be a component of a central pain syndrome and unrelated to either a neuroma or the perception of an intact extremity. Although there is no universally effective treatment, Malone[53] has reported a low incidence with an aggressive rehabilitation program, including immediate prosthetic fitting.

Trauma to a limb following an amputation can convert a healed amputation to a nonhealing wound requiring a more proximal amputation. Perioperatively, patients with a BKA must be observed closely to prevent attempted ambulation. Diabetic patients with retinopathy should not walk barefoot following toe and foot amputations secondary to the risk that minor trauma may lead to a major wound healing problem.

Additional Amputation

The incidence of future amputation in vascular patients is not insignificant. Snyder et al. evaluated outcomes after forefoot amputations and found that 26% underwent a subsequent forefoot amputation and 37% had a more proximal amputation over 2 years.[69] Cruz et al. demonstrated 17% contralateral amputation in their series.[70] These dismal figures reflect the systemic nature of the underlying diseases and emphasize the importance of appropriate foot care, patient education, close follow-up, and early intervention.[71] A concerted multidisciplinary approach can dramatically decrease the incidence of initial and subsequent lower extremity amputation.[72]

Special Situations

In selected cases, hyperbaric oxygen (HBO) therapy can provide benefit in treating nonhealing amputation sites. Patients require thorough evaluation of their cardiopulmonary status before initiating such treatment. In addition, the treating vascular surgeon must determine that revascularization is completed or is not indicated. Patients may benefit from treatment if there is a substantial increase in transcutaneous oxygen pressure ($TcPO_2$) near the wound with administration of 100% oxygen. Daily treatments are typically continued for 30 days. Platelet-derived growth factor (becaplermin [Regranex]) is approved for use in the United States and has been effective in the management of diabetic foot ulcers and following open foot amputations or debridements. The wound must be clear of all necrotic tissue before initiating therapy.

REHABILITATION AND PROSTHETIC MANAGEMENT

General Considerations

Rehabilitation must be individualized. For some patients, successful rehabilitation means ambulation on a prosthesis and resumption of an independent lifestyle. For others, success may mean being able to pivot on the contralateral limb to be able to assist with transfer. Ambulating with a prosthesis depends on the physiologic status of the patient. **Table 92.2** illustrates the dramatic increase in energy requirement with increasing level of the amputation. As expected, the chance of ambulating on a prosthesis decreases with ascending amputation level. The percentages of diabetic and vascular patients who can ambulate with amputations at various levels are shown in **Table 92.9**. The likelihood of ambulating postoperatively is inversely related to the patient's age and the length of the rehabilitation process.[73] Consideration should be given to inpatient rehab immediately after the acute care of the amputation is complete. Not only does this allow strengthening of the upper extremities and improved transfers, but it has been shown to reduce 1-year mortality in amputees as well.[74]

Table 92.9 Ambulation after Lower Extremity Amputation for Diabetes or Occlusive Disease

Amputation Level	Postoperative Ambulation (%)
Digit or ray	100
Transmetatarsal	100
Syme amputation	90–100
Below knee	75
Above knee	39
Hip disarticulation	<100

From Frang RD, Taylor LM, Porter JM. Amputations. In: Porter JM, Taylor LM, eds. *Basic Data Underlying Clinical Decision Making in Vascular Surgery*. St. Louis, MO: Quality Medical; 1994:155, with permission.

Specific Considerations

Digital and Ray Amputations

All patients who were ambulatory preoperatively should be able to achieve their preoperative functional status following a digital or ray amputation. The first digit and metatarsal head are important for weight bearing and for power. A shoe orthosis should effectively compensate for these functions when the patient has some training.

The most important component of postoperative rehabilitation for patients following a digital or ray amputation is education. The rate of repeat amputation (other toe, more proximal level, and contralateral limb) is extremely high. Several studies have indicated that the rate of repeat amputation is diminished with a coordinated education program.[75,76]

Transmetatarsal Amputation

A TMA minimally increases the energy requirement of ambulation; therefore, postoperative ambulation is expected following successful healing. The absence of the toes and metatarsal heads results in the loss of some forward

thrust during the push-off phase of ambulation. This deficit can be overcome with either a steel-shank or a rigid, roller-soled shoe. The void in the distal shoe is filled with an insert.

Syme Amputation

The prognosis for return to bipedal ambulation following a Syme amputation is excellent. The required energy expenditure is only 10% more than baseline.[77] A significant advantage of this amputation is the ability to ambulate on the stump with only a cup slipper. Even though this activity is permitted on only a limited basis in the home, it is much more convenient for the patient, especially when arising at night. For routine activity, the patient uses a prosthesis composed of a nonmotion foot attached to a leg shaft. The shaft has a cutout on the medial aspect to allow passage of the flared distal end of the stump. The configuration of the distal end of the stump results in a bulbous ankle, which is less aesthetically pleasing than the typical below-knee prosthesis.

Below-Knee Amputation

The rehabilitation potential following a BKA is very good. Even when the indication for amputation is arterial insufficiency, approximately 75% of patients are able to ambulate with a prosthesis.[54] Multiple design options are available; however, the patellar tendon and the medial and lateral tibial flares are the weight-bearing surfaces for most prostheses. A variety of foot designs are possible to permit extension, flexion, rotation, and energy storage.

Above-Knee Amputation

Ambulation on an above-knee prosthesis is achieved by less than 40% of patients with arterial insufficiency.[54] In this patient population, the rate of ambulation on bilateral above-knee prostheses is less than 10%.[78] Most above-knee prostheses use the ischial tuberosity as the primary weight-bearing surface and are secured either by a belt or a suction socket. For younger patients, a suction socket works well. Patients with groin scars from previous revascularization attempts may benefit from a belt mechanism. The knee design depends on the patient's general condition and thigh strength. A

knee that engages during the stance phase of gait is more stable and is frequently used in older patients.

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93

Thoracic and Thoracoabdominal Aorta: Aneurysm and Dissection

George J. Arnaoutakis and Eric Y. Pruitt

Key Points

1. There have been vast improvements in surgical outcomes for the management thoracoabdominal aortic aneurysms.
2. Improved preoperative care, surgical technique, and implementation of surgical adjuncts such as distal aortic perfusion and cerebrospinal fluid drainage have played pivotal roles in this improvement.
3. Neurologic outcomes have seen the most improvement with neurologic deficit seen in less than 2% of patients.
4. Endovascular repair of these aneurysms is not without risk and continued research and device development is needed for this complex disease.

BACKGROUND

In 1955, Ethridge reported the first repair of a thoracoabdominal aortic aneurysm (TAAA) using a homograft with DeBakey performing the first

descending and infrarenal aortic replacement using a Dacron graft just 1 year later.[1,2] This was soon followed by the establishment of the "clamp-and-go" technique by Crawford; introducing the three main tenets of aortic surgery: the inclusion technique, the use of Dacron tube graft conduit, and reimplantation of the visceral and renal arteries.[3] During this time, few adjuncts were available and cross-clamp time was the single biggest predictor of adverse outcome. As adjuncts have emerged, organ protection and outcomes have improved. Regardless of the advancements, the morbidity and mortality associated with emergent operations for TAAA are quite high, but surgery remains the only chance to save patient lives. Moreover, elective repair remains the only way to prevent the risk of TAAA rupture (**Fig. 93.1**). In this chapter, we will discuss a comprehensive approach to the diagnosis and management of TAAA and recent surgical results and advances in organ protection.

EPIDEMIOLOGY

Aortic aneurysm disease remains a significant cause of death in developed countries and its prevalence appears to be increasing. While part of this increase may be due to improved imaging techniques, increasing mean population age and overall heightened awareness of this disease, there is no doubt that this disease continues to be a serious issue.[4] The estimated prevalence of abdominal aortic aneurysms ranges from 2.3% to 10.7%, while the prevalence of TAAA is estimated to be much lower at 10.4 cases per 100,000 person-years.[5] Of the 51,000 aneurysms repaired each year, only 1,000 are TAAAs. The disease predominately affects males at 2 to 4 males to 1 female with an average age of 59 to 69 years old.[6]

Rupture is the leading cause of death in this population with 60% of affected patients rupturing at 5 years.[3,6–8] Rupture rates rapidly increase when the aortic size rises above 6 cm and the rate of rupture increases rapidly as size increases beyond 7 cm.[7,9] The median size at which TAAAs rupture is 7 cm with an 80% risk of rupture within 1 year as aneurysms approach 8 cm.[7,10] The lifetime risk of rupture is 75% to 80%, but how long it takes to reach the point of rupture is not easily determined. The median growth rates for TAAAs tend to be somewhat lower (0.20 to 0.34 cm per

year) than those of abdominal aortic aneurysms, but TAAAs tend to present at a larger diameter.[11]

PATHOGENESIS

As the aorta dilates beyond 50% of its normal diameter it is considered aneurysmal regardless of whether the dilation is focal or diffuse. Aneurysms are the result of degenerative changes within the aortic wall in a process that is similar to that seen in abdominal aortic aneurysm development. Arteriosclerosis has long been noted to be associated with aneurysm development, but these two processes are histologically distinct. Arteriosclerosis is the result of intimal changes leading to occlusive disease. Aneurysm disease is the result of thinning of the media with destruction of smooth muscle cells and elastin, infiltration of inflammatory cells, neovascularization and compensatory collagen deposition.[12–15] Inflammatory cells are predominately macrophages which secrete proteases and elastase that cause degradation of the aortic wall. The degradation byproducts serve as chemokines that promote further inflammatory cell recruitment.[12] Matrix metalloproteinases (MMPs) are peptidases that are highly prevalent in aneurysm development, particularly MMP9, MMP2, and MMP12.[12,16–19]

There is clearly a genetic role in aneurysm development with 20% of patients with thoracic aneurysm disease having a first-degree relative with the disease as well and this is regardless of the presence of connective tissue disorders.[20,21] Marfan syndrome is a connective tissue disorder that is the most common cause of inherited aneurysm disease and is also associated with ocular, skeletal, and cardiovascular abnormalities. It affects males and females of all races equally and affects 1 in 5,000 to 10,000 individuals. The aortic dilation is due to a mutation in *FBN1* which codes for fibrillin 1. Additional associated connective tissue disorders are Elhers–Danlos, Loeys–Dietz syndrome, and Turner syndrome.[22–24] Previously, autosomal dominant polycystic kidney disease was associated with aortic aneurysm development, but this linkage has failed to be replicated aside from the isolated ascending aneurysm disease.[25] There are familial cases of TAAA with an autosomal dominant inheritance pattern. Patients in these families develop aneurysms earlier and have aneurysms that expand more rapidly, but

penetrance is variable.[26] As TAAA is a complex disease with both environmental and genetic factors at play, identifying a true genetic cause of the disease is challenging, but the most strongly associated mutation is in *ACTA2* which codes for α-actin in smooth muscle and is estimated to account for 15% of familial aneurysm cases. Other genes that have been replicated are *MYH11*, *TGFBR1*, *TGFRB2,* and *SMAD2*.[27–31]

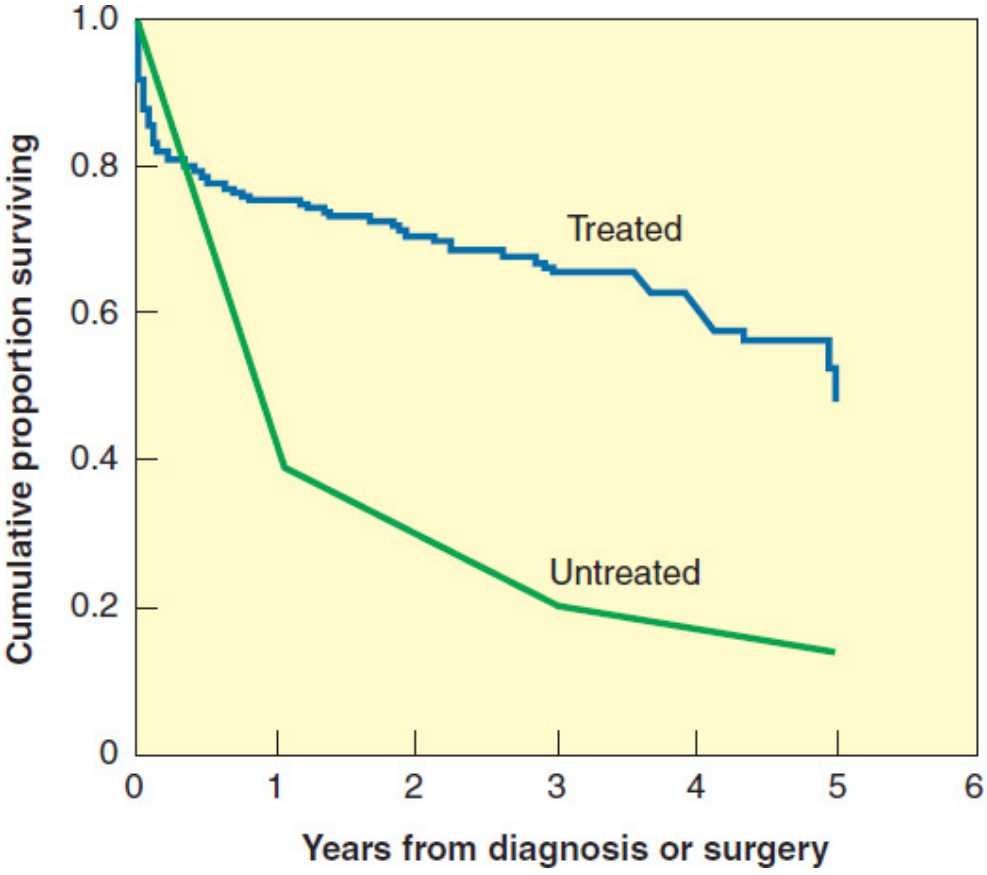

Figure 93.1 Thoracoabdominal aortic aneurysm: comparison of survival rates in untreated patients versus surgically treated patients.

Mycotic aneurysms are infectious in nature and are caused by bacterial or septic emboli seeding an atherosclerotic aorta or by spread from empyema or adjacent infected lymph node. These account for only 0.6% to 2% of aneurysms in developed countries. The most common organisms are *Salmonella* species, *Staphylococcal* species, *Streptococcus* species, or *Escherichia coli*.[32] Morphologically these aneurysms tend to be more saccular and are more prone to rupture. Trauma can also lead to a pseudoaneurysm of the aorta which can be unrecognized initially, but chronic

pseudoaneurysms are prone to rupture and should be repaired at the time of diagnosis.

An aortic dissection will often degenerate and form aneurysms with 40% of those who present with type B aortic dissections managed medically requiring surgical intervention for aneurysm degeneration.[33] There are several factors that appear to increase the risk of degeneration which include: entry tear size >10 mm, initial aortic diameter >40 mm, free-floating true lumen and false lumen patency.[33,34] Chronic dissection and patent false lumen are not linked to a higher risk of aortic rupture.[35]

It is common for an aneurysm to occur in more than one segment of the aorta which occurs in 20% of cases. In rare circumstances, the aneurysm can extend from the ascending aorta, through the arch and down through the abdominal aorta creating a "mega" aorta. This rare entity is frequently associated with Marfan syndrome and chronic aortic dissection.

CLINICAL MANIFESTATIONS

The symptoms of TAAA are frequently ill defined, but include back pain with flank, chest, and/or epigastric pain. A description of worsening pain is concerning as it can be a sign of pending rupture. Rarely, hoarseness can occur due to proximal descending thoracic aortic aneurysms causing compression of the left recurrent laryngeal nerve or vagus nerve. Shortness of breath can result from compression of the tracheobronchial tree. The aneurysm can also erode into the GI tract causing massive hematemesis or melena or can erode into the tracheobronchial tree causing massive hemoptysis. This bleeding can sometimes be intermittent and the diagnosis of aortoenteric or aortotracheal fistula should be considered even when patients describe episodic bleeding, but present without signs of overt bleeding. Compression of the intercostal arteries or spinal cord is rare, but can cause paraplegia. Paraplegia is more frequently a sign of malperfusion in acute aortic dissection. Embolization to the renal, mesenteric, or lower extremities from mural thrombus is very rare.

The initial presentation for many TAAA patients is rupture, which is seen in an estimated 10% to 20% of patients (**Fig. 93.2**). If a patient presents in shock with acute onset of chest, abdominal, or back pain, ruptured aneurysm

should be high on the differential. The thoracic cage frequently prevents the frequently described pulsatile mass on examination. Rupture is nearly universally fatal without operative intervention, but in rare instances the vessel wall may seal for several hours to days before there is free rupture. Most patients with free rupture are dead prior to arrival to the hospital.

DIAGNOSTIC IMAGING

The mainstay of imaging for TAAA diagnosis is computed tomography angiography (CTA) which is useful in defining extent of the TAAA as defined by the modified Crawford Classification (**Fig. 93.3**). It is also useful in identification of true and false lumens when dissection is also present and in allowing for measurement of the entire aorta as well as the presence of inflammation or thrombus. Fluid around the aneurysm can signal free or contained ruptures. CTA aids in surgical planning as patent intercostal or spinal arteries can be identified on high-resolution imaging. Coronal and sagittal views can also be useful in characterizing proximity to surrounding organs. In patients with renal insufficiency or contrast allergy, contrast can be omitted but this is less desirable.

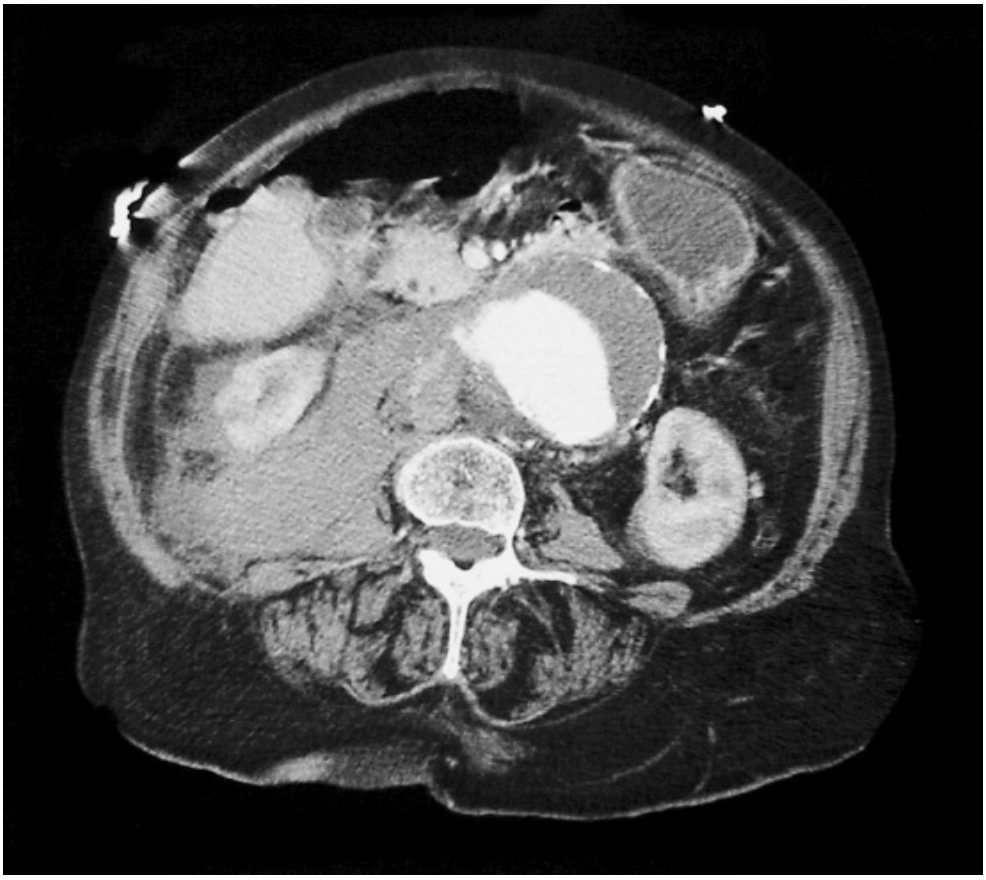

Figure 93.2 Computed tomography scan of a ruptured thoracoabdominal aortic aneurysm. Note stranding in the retroperitoneum denoting extravasation of blood.

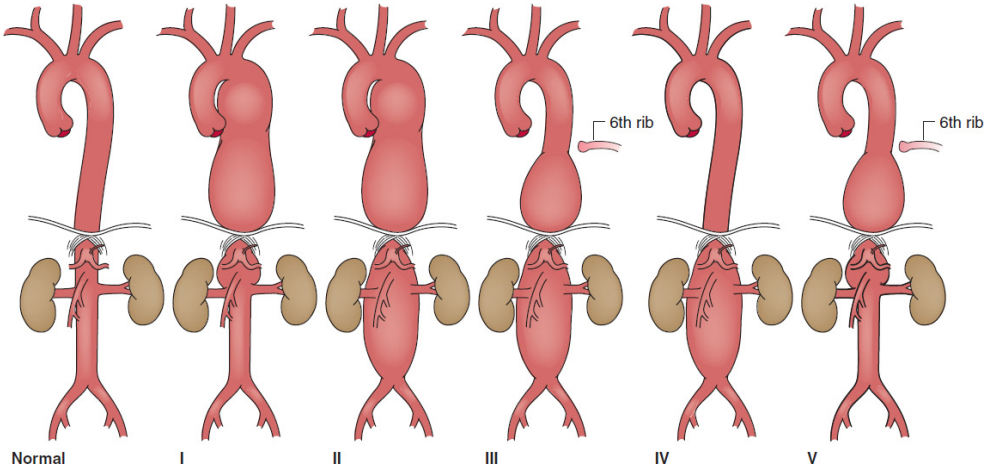

Figure 93.3 Thoracoabdominal aortic aneurysm classification. Extent I, distal to the left subclavian artery to above the renal arteries. Extent II, distal to the left subclavian artery to below the renal arteries. Extent III, from the sixth intercostal space to below the renal arteries. Extent IV, the 12th intercostal space to the iliac bifurcation (total abdominal aortic aneurysm). Extent V, below the sixth intercostal space to just above the renal arteries.

Magnetic resonance arteriography (MRA) has emerged as an alternative screening test for aortic disease and its branches. Advantages are the lack of contrast or radiation exposure in those undergoing surveillance, but it lacks the same degree of spatial resolution seen with CTA. Additionally, CTA is better at identifying intramural thrombus and calcifications. Other limitations are cost, duration, contraindication in patients with metallic implants, and claustrophobia.

Transesophageal echocardiography (TEE) provides excellent imaging of the ascending and descending thoracic aorta, provides real-time imaging and can be performed intraoperatively or at bedside. It is particularly useful when patients are too unstable to transport to the CT scanner. It can show aortic wall disease, differentiating plaque from intimal tear. It can also help identify optimal cross-clamping sites and to assess ventricular and valvular function. Imaging of the abdominal aorta is limited past the GE junction due to loss of contact with the aorta. TEE is invasive and should only be performed by those with experience due to risk of injuring the esophagus.

Intravascular ultrasound (IVUS) is also useful as it allows for characterization of intramural relationships which is particularly useful in aortic dissection. It requires access through a femoral sheath, but is very important in planning during endovascular repairs, particularly in dissection. Epiaortic ultrasound can also be used to allow better characterization of the thoracic aorta for cannulation and clamping.

PREOPERATIVE EVALUATION

As there are few signs or symptoms related to the aneurysm itself, a thorough history and physical examination are important to identify comorbidities. Aneurysm extent is determined via preoperative imaging. Risk stratification frequently must be determined via consultation with cardiologists, pulmonologists, and nephrologists. Pulmonary evaluation is frequently needed due to the need for single-lung ventilation and left lung surface trauma during open repair.

The risk-factor profile of those with TAAA overlaps with ischemic heart disease. As a result, these conditions frequently coexist. In patients with TAAA, ischemic heart disease is the most common cause of death. If

possible, coronary revascularization via coronary artery bypass grafting or via percutaneous coronary intervention (PCI) (stenting or balloon angioplasty) should be performed prior to TAAA repair to minimize risk of an ischemic event. However, the timing of repair should be balanced with the risk of rupture if TAAA repair is delayed. If bypass grafting is pursued before TAAA repair, the use of the left internal mammary artery is typically avoided in the event the aortic cross-clamp needs to be proximal to the left subclavian artery. Additionally, this vessel may provide collateral blood supply to the spinal cord and chest wall. Percutaneous coronary intervention is an option in many patients, but the use of bare metal stents is preferred as they do not require long-term antiplatelet therapy. It is very rare to require simultaneous coronary artery bypass grafting and TAAA repair in the same operation.

OPERATIVE TECHNIQUES

Prior to repair, a spinal drain is placed in the third or fourth lumbar space by the anesthesia team. The patient is brought to the operating room and placed in the supine position. Continuous arterial pressure monitoring is provided by cannulation of the right radial artery. For open repairs, a dual-lumen endotracheal tube is placed for single-lung ventilation after induction of general anesthesia. A bronchial blocker can alternatively be used. This maneuver avoids the need for tube exchange at the conclusion of the procedure, but requires careful positioning by the anesthesiologists and may not afford optional lung isolation. Continuous pulmonary artery pressure monitoring is provided by a balloon-tipped pulmonary artery catheter placed through central venous access via the internal jugular vein. Large-bore central and peripheral access is needed. Core body temperature is monitored via esophageal and Foley catheter temperature probes. If transesophageal echo (TEE) is to be used, it is inserted. A right femoral arterial catheter is useful for monitoring distal perfusion. The patient is then placed in the right lateral decubitus position and all pressure points are padded. If continuous electroencephalograph is used, monitors are placed on the scalp and along the spine for motor and somatosensory monitoring (MEP and SSEP). The spinal drain is then attached to the spinal cord pressure monitor and the drain

is set to maintain CSF pressure at 10 mm Hg or less. The field is then prepped and draped.

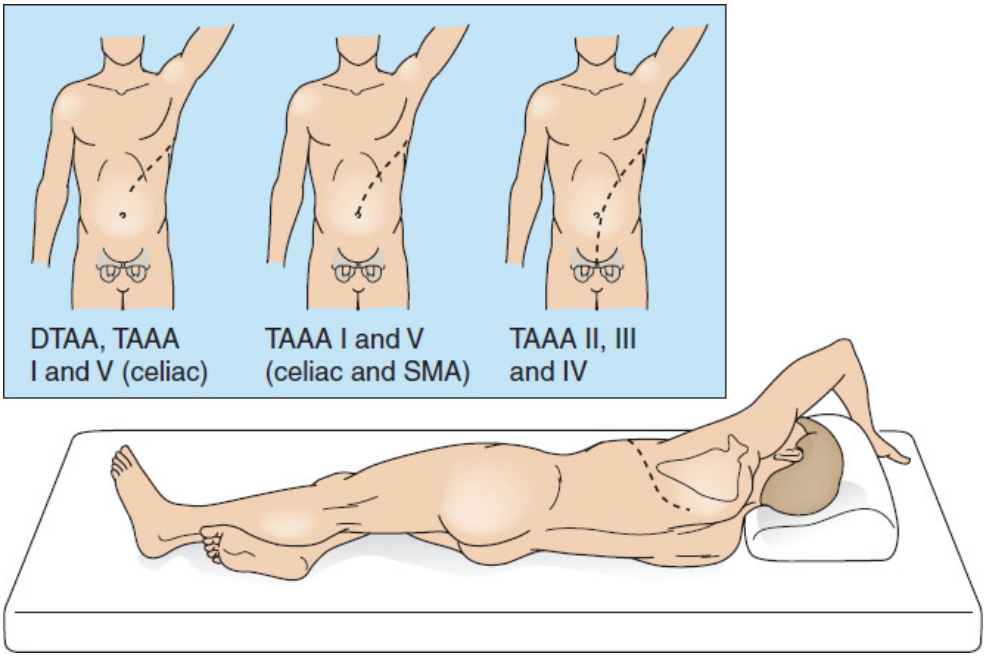

Figure 93.4 Tailoring of thoracoabdominal incisions for aneurysm extent. DTAA, descending thoracic aortic aneurysms; TAAA, thoracoabdominal aortic aneurysm; SMA, superior mesenteric artery.

An incision is made to fit the extent of the aneurysm (**Fig. 93.4**). A standard incision starts between the tip of the scapula and the spinous process. It curves along the sixth intercostal space to the costal cartilage and then obliquely to the umbilicus. The insertion of the serratus anterior muscle is mobilized after the latissimus dorsi is divided. The left chest is entered after the lung is deflated. For extent II, III, and IV TAAA, the full incision is typically needed. The incision can be shortened or lengthened as needed depending on the extent (**Fig. 93.4**). The use of a self-retaining retractor allows optimum visualization of the thoracic and abdominal aorta.

Dissection begins at the level of the hilum of the lung cephalad to the proximal thoracic descending aorta. Transection of the ligamentum arteriosum is performed with care to avoid the recurrent laryngeal nerve. The muscular portion of the diaphragm is incised with care taken to avoid the phrenic nerve (**Fig. 93.5**). Division of the diaphragm may be performed with electrocautery or with vascular stapler device and marking sutures placed along the diaphragm are often useful to aid with later reapproximation. A

retroperitoneal plane is established and a medial visceral rotation is performed, mobilizing the spleen, bowel, and left kidney to the right of the aorta. After dissection, mobilization and achieving hemostasis, 0.5 to 1 mg/kg of heparin is administered in preparation for distal aortic perfusion (**Fig. 93.6**). Different activated coagulation time (ACT) targets may be achieved based on institutional preference but we favor ACT >480 seconds. Posterior to the left phrenic nerve, the pericardium is opened to allow direct visualization of the pulmonary veins and left atrium. The left inferior pulmonary vein is cannulated. The arterial inflow is established through the left common femoral artery via a Dacron graft sutured to the artery in an end-to-side fashion. If the common femoral artery cannot be accessed, the descending thoracic aorta can be accessed. The circuit is run through a centrifugal cardiopulmonary pump with an inline heat exchanger. At this point, distal aortic perfusion is initiated. An alternative cannulation strategy is to cannulate both left common femoral artery and vein to establish full cardiopulmonary bypass. Constant communication between anesthesiologist and perfusionist is mandatory to achieve appropriate perfusion pressures.

A site is chosen just distal to the left subclavian and padded clamps are applied with additional clamps placed in the mid thoracic aorta. If the proximal extent of the aneurysm is too close to the left subclavian, a site is chosen between the left common carotid and the left subclavian arteries and the left subclavian artery is clamped separately. An alternative approach if no clamping site is available is to perform deep hypothermic circulatory arrest, with systemic cooling to 18°C. This approach is very effective for difficult proximal anatomy in the aortic arch; however, requires careful assessment of aortic valve competence and left ventricular venting as necessary to avoid ventricular distention during the period of myocardial fibrillation.

As there is risk for developing a graft–esophageal fistula, the inclusion technique is not used and instead the aorta is transected to separate it from the underlying esophagus (**Fig. 93.7A**). A woven Dacron graft is used for replacement. The graft is sutured to the descending thoracic aorta proximally in an end-to-end fashion with a running 2-0 or 3-0 monofilament polypropylene suture. Pledgeted polypropylene sutures are placed as needed for reinforcement at the anastomosis. After completing the proximal anastomosis, the midthoracic aortic clamp is moved distally onto the

abdominal aorta at the celiac axis in preparation for intercostal reattachment. Patent lower intercostal arteries from T8 to T12 are reimplanted whenever possible. Exceptions to reimplantation of the intercostals include occluded arteries, heavily calcified aorta, acute aortic dissection, or as guided by neuromonitoring (MEPs and SSEPs). If no change is noted in the MEP or SSEP signal without reattachment of the intercostals, they can be safely ligated with less concern for spinal cord ischemia. For patients with connective tissue disorders or who are over the age of 60 years old, a loop graft has replaced the island patch for reattachment of the intercostal arteries. If reattachment is performed, the proximal clamp is moved distal to the intercostal artery patch to restore pulsatile flow to the reattached intercostal arteries (**Fig. 93.7B**). At this point, the distal clamp is moved to the infrarenal aorta and the abdominal aorta is opened with the graft passed into the abdominal cavity. Celiac, superior mesenteric, and renal arteries are identified and can be perfused via 9- or 12-Fr balloon-tipped catheters based off the ostia (**Fig. 93.7C**). Cold perfusate (4°C) delivery to the viscera is dependent upon proximal aortic pressure (maintained between 300 and 600 mL/min). Reattachment of the visceral vessels is typically performed via an island patch. Typically, this island patch accommodates the reattachment of the visceral and renal arteries, but if the left or right renal artery is located too great a distance from the other arteries a separate interposition bypass graft may be necessary. Visceral patches are not recommended in patients with connective tissue disorders and in patients under the age of 60 years old due to the risk of recurrent patch aneurysm. In these scenarios, a commercially available Dacron graft with 10- and 12-mm side arms is used to provide separate attachments of the celiac, superior mesenteric, and renal arteries. A straight Dacron graft can be modified with openings made by the surgeon to sew on 10-mm limbs in a customized fashion. Regardless of the technique used, once the anastomosis is completed, the proximal clamp is moved distal to the renal arteries to restore pulsatile flow to the viscera and kidneys. The final anastomosis is then performed at the aortic bifurcation, or into the common iliac arteries if disease extends to the terminal aorta. A Wylie vascular clamp can be useful to obtain distal clamping of the right common iliac artery.

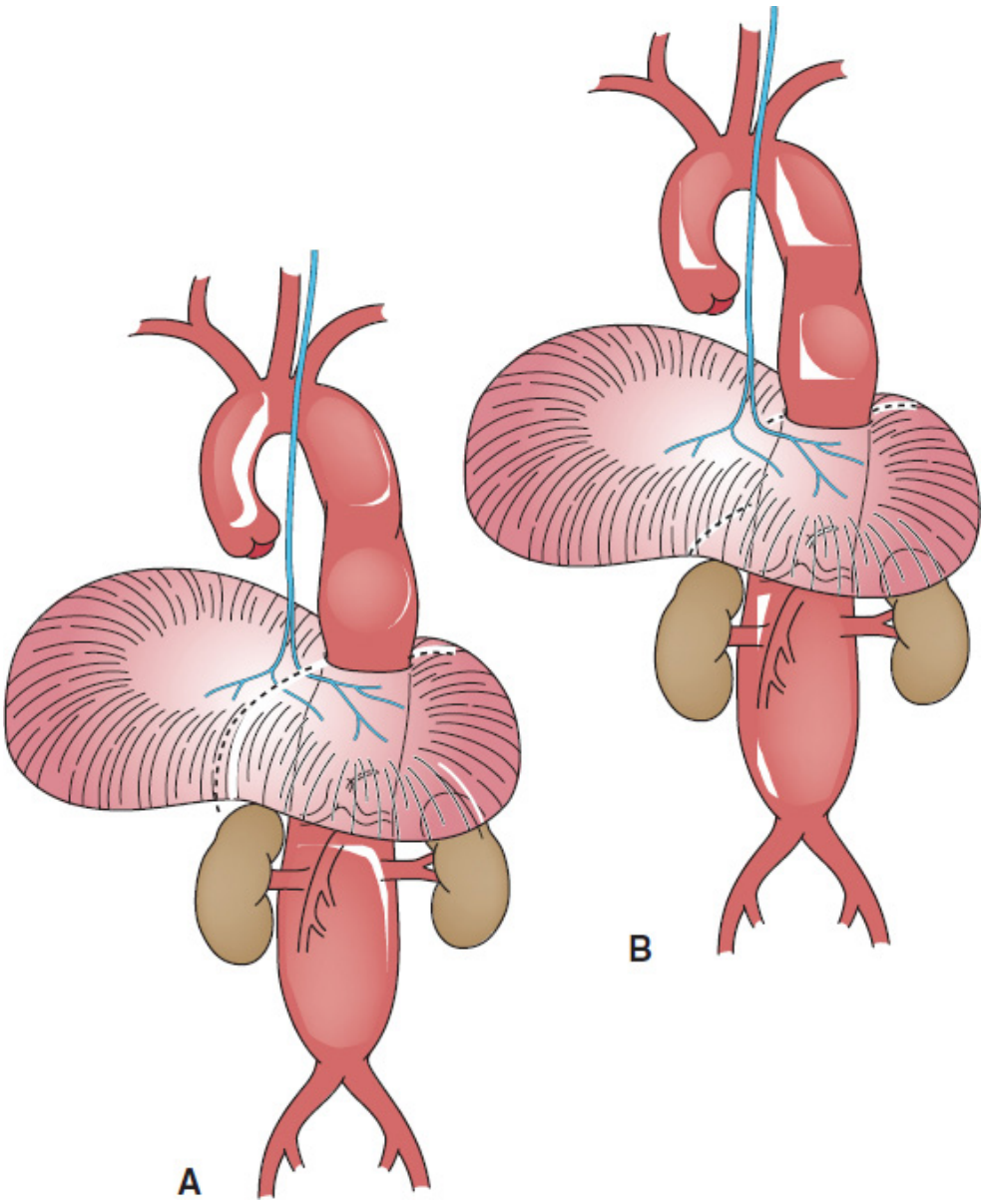

Figure 93.5 In previous surgical practice, the diaphragm was divided (**A**); currently, only the muscular portion of the diaphragm is cut (**B**).

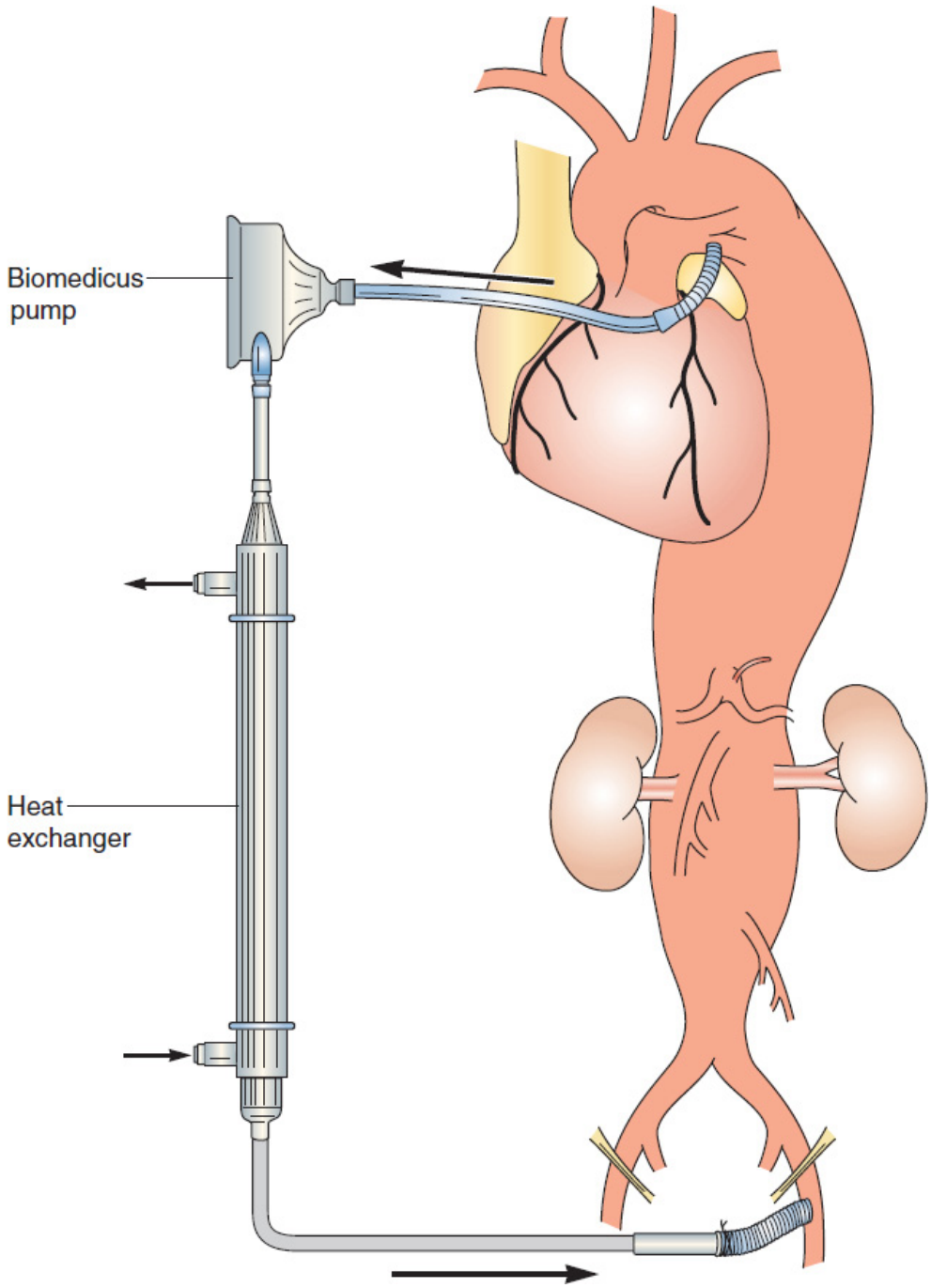

Figure 93.6 Distal aortic perfusion from the left inferior pulmonary vein to the left common femoral artery.

Once the core body or nasopharyngeal temperature returns to 36°C, the patient is weaned from bypass, protamine is administered (1 mg protamine per 10 IU of heparin) and the cannulas are removed. After hemostasis is achieved, two or three chest tubes are placed in the pleural space for

drainage. The diaphragm is reapproximated with running 1-0 polypropylene suture. The left lung is reinflated and the incision is closed in standard fashion. The patient is then returned to the supine position, the dual-lumen endotracheal tube is changed to a single-lumen tube and the patient is transported to the ICU.

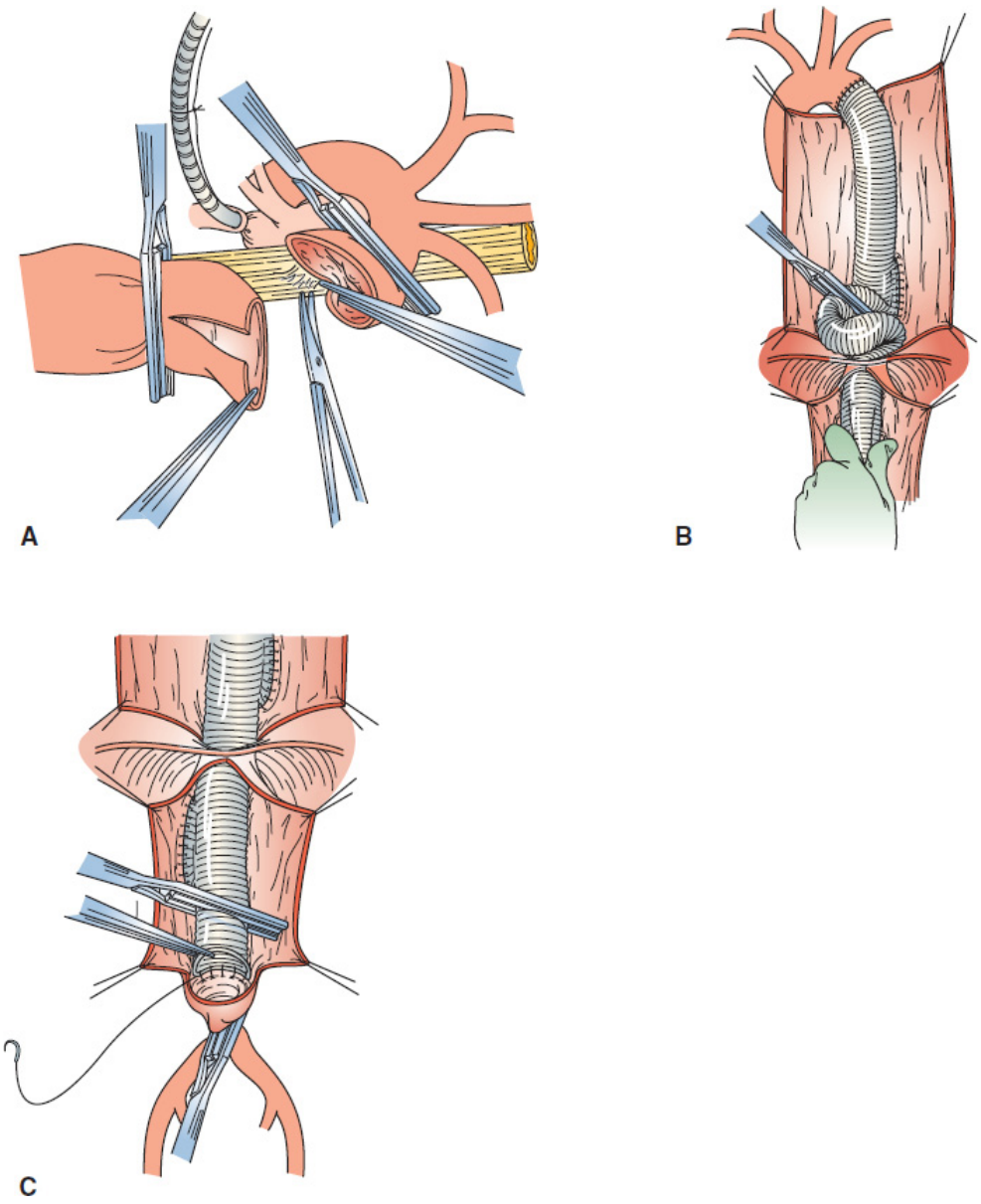

Figure 93.7 Sequential clamping and graft replacement. Padded clamps are placed on the proximal and mid-distal descending thoracic aorta. **A:** The proximal part of the aneurysm is opened. The aortic neck is completely transected and separated from the esophagus. The proximal anastomosis is fashioned. Subsequently, the patent lower intercostal arteries are reattached via an elliptical hole in the graft. **B:** The proximal clamp is then moved onto the graft to restore pulsatile flow to the intercostal arteries, and the graft is pulled through the hiatus into the abdomen. The distal clamp is reapplied onto the infrarenal aorta. The remainder of the aneurysm is opened. Balloon-tipped catheters are inserted into the celiac, superior mesenteric, and renal arteries to permit perfusion. **C:** An elliptical hole is made in the graft for reimplantation of the visceral and renal arteries.

Elephant Trunk Technique for Extensive Aortic Aneurysms

Extensive aneurysms involving the ascending, arch, and thoracoabdominal aorta can be repaired in a single stage, but not without significantly increased risk. Increased risk is secondary to prolonged operative times, multiple incisions, need for multiple surgical adjuncts, protracted clamp times and considerable blood loss. As such, staged repairs offer at least a partial solution to this elevated risk. The development of the elephant trunk technique by Borst in 1983 has greatly facilitated staged repair of extensive thoracic aortic aneurysms involving the entire thoracic and thoracoabdominal aorta.[36] Prior to this, staged repairs were plagued by complications, particularly bleeding from the pulmonary artery and thoracic aorta in the second stage repair of the thoracic or thoracoabdominal aorta. The elephant trunk technique avoids the issue of cross-clamping the native proximal descending aorta during the second stage and may simplify high dissection in the aortic arch via left thoracotomy.

The first stage of the operation is performed similarly to standard ascending and transverse arch surgery aside from the use of either an inverted distal graft or a commercially available collared graft inserted distally (**Fig. 93.8A**). An anastomosis is made between the folded edge or the collared portion of the elephant trunk and the aorta just distal to the left subclavian artery. Once this is performed, the inner portion of the graft is retrieved and the side limbs allow for reimplantation of the aortic arch vessels. The proximal anastomosis to the ascending aorta is then performed while the distal portion of the graft (the elephant trunk) is left floating in the proximal descending aorta. During this stage, cardiopulmonary bypass, profound hypothermia, circulatory arrest, and adjunctive antegrade cerebral perfusion protect the brain against hypoxia and stroke.

The second stage of the repair is performed in a similar fashion to the traditional TAAA repair using distal aortic perfusion and CSF drainage. After initiation of bypass, the distal clamp is applied to the mid descending thoracic aorta and the proximal descending aorta can be clamped between carotid and left subclavian or distal to the left subclavian artery. An alternative technique is to open the proximal aorta without a proximal clamp

being applied, but this risks significant bleeding unless performed under hypothermic circulatory arrest. The elephant trunk placed in stage 1 of the operation can be identified and clamped (**Fig. 93.8B** and **C**). The elephant trunk serves as the site for the proximal anastomosis for the remaining aneurysm to be replaced.

The frozen elephant trunk procedure is a newer strategy in patients with thoracic aortic aneurysm or dissection involving ascending, arch, and descending thoracoabdominal aorta. This concept combines endovascular technology with the advantages of conventional elephant trunk repair. Via median sternotomy for ascending or arch replacement, this technique involves antegrade deployment of an endograft device under direct vision into the descending aorta. The distal aortic suture line incorporates the endograft fabric material for added hemostasis. In staged fashion, at the time of thoracotomy for TAAA repair, the distal end of the endograft may be the site of the proximal anastomosis.

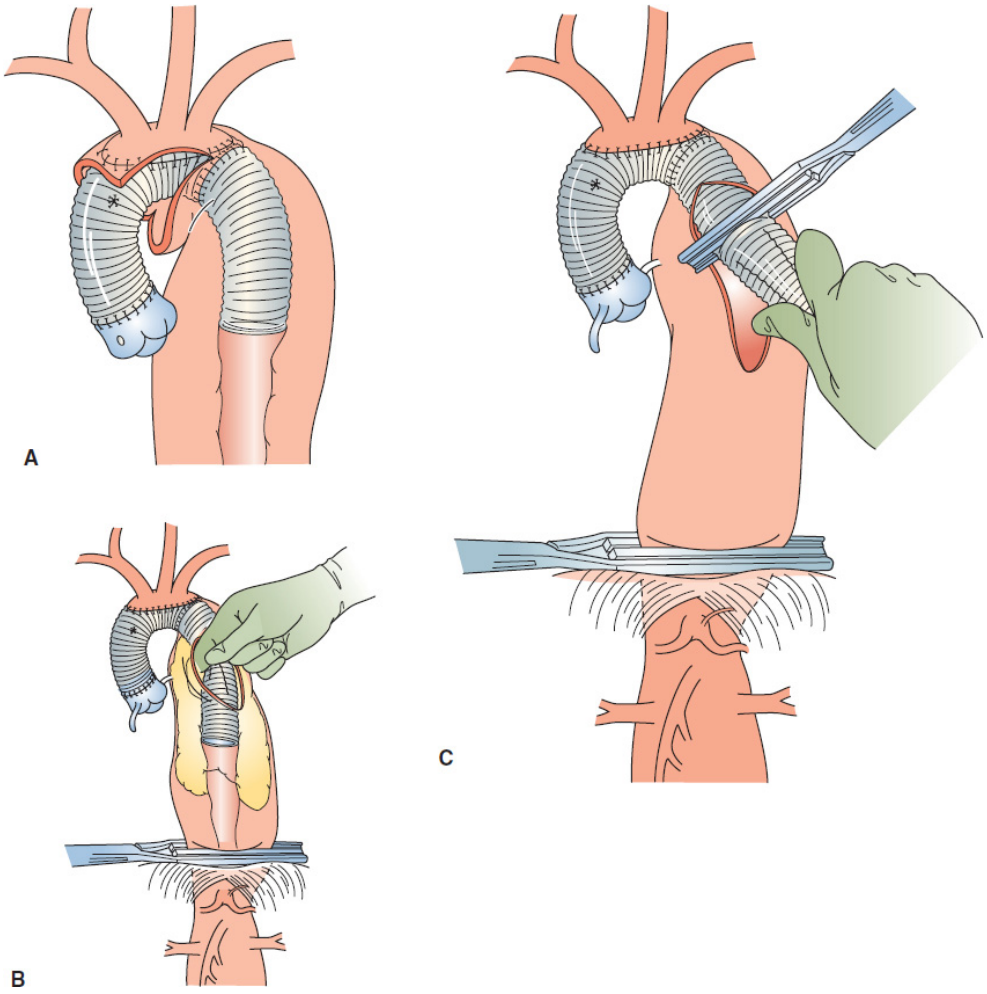

Figure 93.8 Elephant trunk technique. Illustration of completed stage 1 elephant trunk (**A**). In stage 2, the proximal aneurysm is opened and the existing graft is quickly grasped (**B**) and clamped (**C**). The remainder of the surgery follows the standard technique for thoracoabdominal aortic aneurysm.

POSTOPERATIVE MANAGEMENT

The patient is admitted to the ICU postoperatively for close hemodynamic monitoring and awakened as early as deemed safe in order to evaluate neurologic status, with particular emphasis on lower extremity motor function. Early extubation is appropriate when deemed hemodynamically stable. Mean arterial pressures (MAPs) are maintained between 80 and 90 mm Hg as hypotension (even brief) can be devastating for spinal cord perfusion and should be avoided. CSF pressures are continuously monitored and pressure is maintained at 10 mm Hg or less. Oral diet can be resumed

when the patient is extubated and can be advanced as tolerated. Ileus is not uncommon after surgery and diet should not be advanced until resolved.

Frequent neurologic checks after extubation should be performed in order to evaluate for delayed neurologic deficit (DND). While the strongest predictors of DND are low MAP and CSF drain complications, other risk factors for the development of DND are hypoxemia and low hemoglobin.[37] In the absence of DND, the CSF drain is generally removed POD 2 prior to transfer to the ward with telemetry. Typical ICU length of stay is 3 to 4 days depending on neurologic and pulmonary status.[38] Physical therapy should work with patients throughout their hospitalization.

Follow-up after repair consists of yearly CT scans or MRA if indicated to detect graft-related pseudoaneurysms or new aneurysms. The frequency of follow-up may change in circumstances such as Marfan syndrome, unoperated dissection, concurrent aneurysm, or family history of aneurysms.

SURGICAL OUTCOMES

Mortality rates for patients undergoing TAAA and descending thoracic aortic aneurysms repair range between 5% and 21% and vary with aneurysm extent.[39] Overall 70% of patients recover without significant postoperative complications.

Neurologic Outcomes

Neurologic deficit remains one of the most devastating complications following TAAA. This results from spinal cord ischemia from cross-clamping the descending thoracic aorta which also causes increased CSF pressure. Historically, under the "cross-clamp–and go" era, cross-clamp time was the single biggest predictor of neurologic deficit. With the current adjuncts of distal aortic perfusion and spinal drains for CSF pressure reduction, longer cross-clamp time appears to be tolerable. Keeping CSF pressure below 10 mm Hg has been shown to improve spinal cord perfusion in both animal and human studies.[40] Meta-analysis of CSF drainage in TAAA repairs has shown an absolute risk reduction of 10%.[40] The use of such adjuncts should be limited to centers with experience with TAAA. Distal

aortic perfusion and CSF drainage consistently show a significant decrease in risk of acute neurologic deficit.[41–43] Previously, cross-clamp time was a significant predictor of neurologic deficit, but with the use of adjuncts this appears to be less of a risk.[41] The highest incidence of neurologic deficits occurs in extensive (extent II) TAAA. Prior to the use of adjuncts, the rates of deficit were reported as high as 30% to 40%.[44] With the use of adjuncts, this has been reduced to a rate of 7.2% (**Fig. 93.9**).[43] In addition to extent, age, emergency presentation, renal dysfunction, active smoking and cerebrovascular disease have also been shown to be predictive of neurologic deficit.[41] The use of intraoperative distal aortic perfusion and perioperative CSF drainage should be considered in all elective cases as they prevent 1 neurologic deficit in 20 for all patients and 1 in 5 for extent II TAAA.[43]

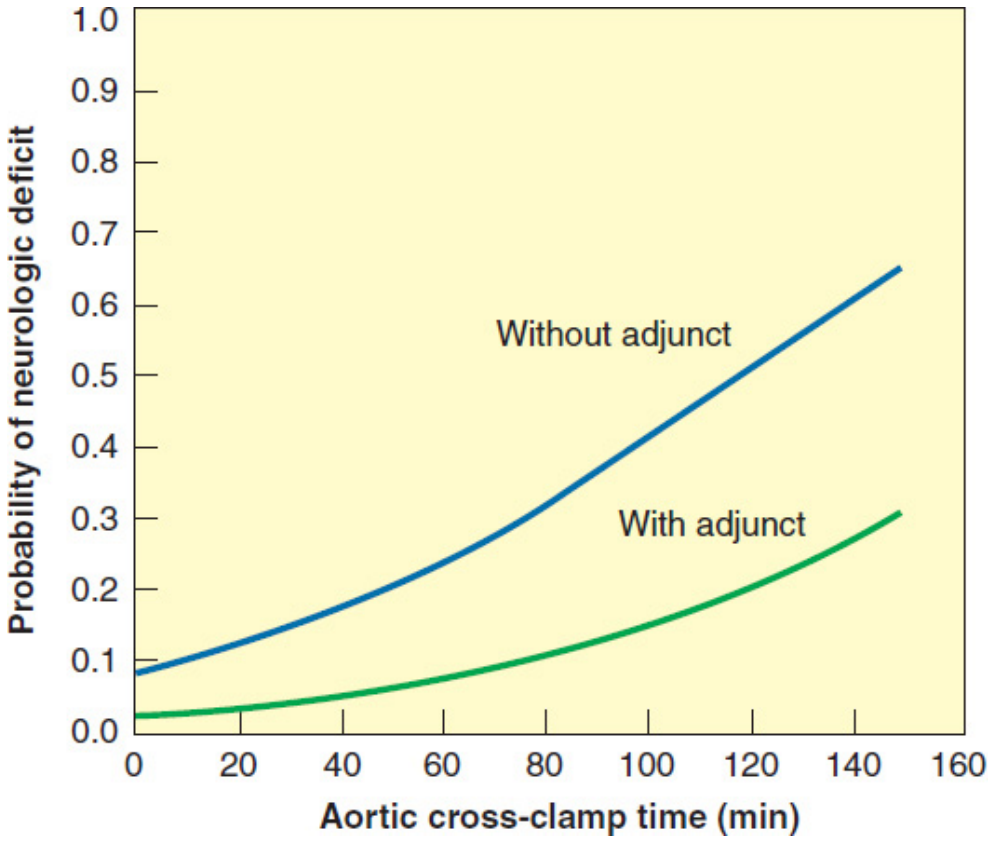

Figure 93.9 The probability of neurologic deficit increases with clamp time and is markedly higher in patients undergoing thoracoabdominal aortic aneurysm surgery without adjuncts.

In addition to CSF drainage and distal perfusion, reimplantation of the intercostal arteries has been shown to decrease risk of spinal cord ischemia.

The major blood supply to the anterior spinal artery of the spinal cord is thought to be the anterior radicular artery—*artery of Adamkiewicz* and while the origin is variable, it commonly branches from one of the lower intercostal arteries with or without additional collateral branches. It has been shown that ligation of intercostal arteries from T9 to T12 increases the risk of neurologic deficit and is believed to be due to decreased flow to the anterior radicular artery.[43] As such, these intercostals should be reimplanted when patent and feasible. This can be performed as one large patch to the graft, as separate buttons or with interposition grafts when the vessels are too far apart. If these lower arteries are occluded, it is important to reimplant the upper arteries as they likely assume a more important role in supplying the spinal cord.

Adequate spinal cord perfusion pressure should always be maintained with avoidance of hypotension during and after surgery as even brief episodes of hypotension can lead to neurologic deficit. Nitroprusside should not be used as an antihypertensive agent intraoperatively or postoperatively as it can potentially increase CSF pressures in addition to causing systemic hypotension.[45] Maintenance of adequate systemic arterial pressure cannot be overemphasized and should be achieved with judicious use of blood products as needed in addition to vasopressors.

Many institutions rely on intraoperative motor-evoked potentials (MEPs) and somatosensory-evoked potentials (SSEPs). For SSEP, monitoring is performed by placing probes on bilateral malleoli (stimulating posterior tibial nerve) and recordings are performed on the popliteal fossa, C5, and the vertex with positive finding defined as a drop in amplitude by 50% and/or a change in latency by 10%. For MEP, the precentral gyrus is stimulated and recording is measured at three sites: abductor digiti minimi, tibialis anterior, and abductor hallucis muscle (**Fig. 93.10**). Compound muscle action potential is monitored and results are binary with loss of potential being a positive finding. SSEP and MEP monitoring have been shown to be highly correlated with irreversible neurologic deficit, but have not been shown to correlate with reversible deficit. While MEP is more complex, the detection rate of irreversible injury is identical to SSEP. Both forms of monitoring have strong negative predictive value in that it is highly unlikely to have neurologic deficit immediately following surgery if there was no loss of signal intraoperatively.[46,47] If there are signal changes, rescue procedures

should be performed including increasing the MAP to >80 mm Hg, increasing distal aortic perfusion pressure to >60 mm Hg, lowering the CSF pressure, increasing the hemoglobin level, and attaching more intercostal arteries. Even with these adjuncts, the rate of deficit remains 3.1%.[46]

Delayed Neurologic Deficits

DND is normal defined as paraplegia or paraparesis after a period of observed neurologic function. When first described in 1988, this condition was irreversible.[48] CSF drainage has been shown to provide improvement in neurologic outcomes in select cases of DND.[49] DND can present nearly immediately after surgery or up to 2 weeks postoperatively (median 3 days) in 2.7% of patients.[50] There is no single predictor of delayed deficit, but rather a combination of risks leading to the development of DND. MAP less than 60 mm Hg and drain complications are the highest predictors of delayed deficit.[37]

The exact mechanism for the development of DND are not fully understood, but are hypothesized to be related to the "second hit" phenomenon in that adjuncts can clearly protect the spinal cord intraoperatively and reduce risk of neurologic deficit immediately postoperatively, but the spinal cord remains vulnerable postoperatively. During this time frame a "second hit" in the form of hypotension or drain malfunction can lead to DND. Any rise in CSF pressure during the early postoperative period can lead to increased compartment pressure and decreased perfusion, as such any sign of DND should be initially treated with free drainage of CSF to relieve the compartment pressure. Many institutions also routinely implement naloxone infusions and administration of steroids in the initial postoperative period as some studies have shown decreased incidence of DND with its use,[51–54] however strong evidence for its effect is lacking.

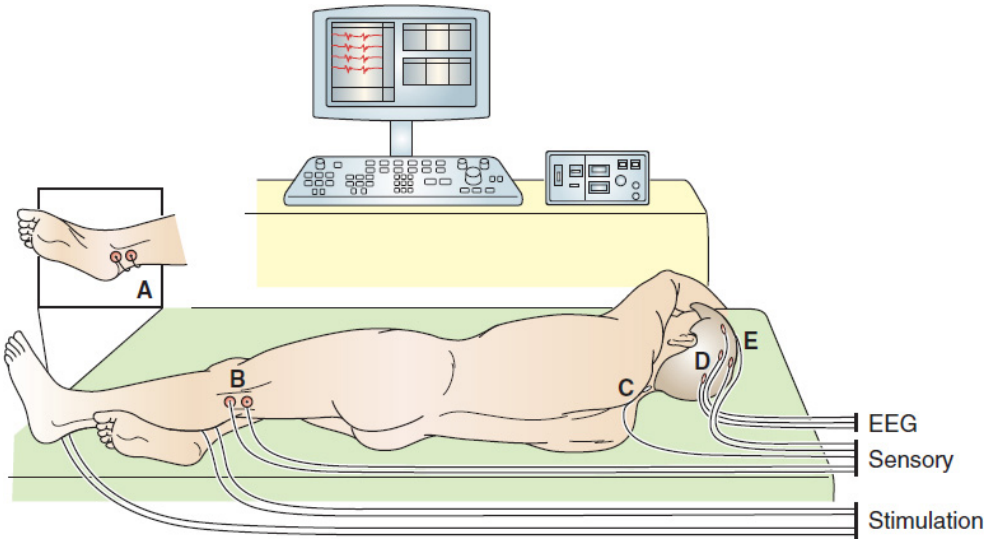

Figure 93.10 Somatosensory- and motor-evoked potentials are recorded at three sites: the popliteal fossa (**A**, **B**), C5 (**C**), and the vertex (**D**, **E**).

To optimize spinal cord perfusion in the early postoperative period the MAP is maintained between 90 and 100 mm Hg, hemoglobin greater than 10 mg/dL, and cardiac index greater than 2.0 L/min. Rescue protocols are initiated if any signs of DND emerge. These include laying the patient flat, checking the drain for malfunction, reinsertion of the drain if it was removed, free drainage of the CSF until the pressure is <10 mm Hg, increasing the MAP, liberalization of blood transfusion protocols, and increasing oxygen saturation. CSF drainage is continued for at least 72 hours after onset of DND. Using this multimodal approach, improvement in neurologic function has reportedly been improved in 57% of patients suffering from DND.[50]

Renal Failure

Acute postoperative kidney injury (AKI) is defined according to modern consensus Kidney Disease: Improving Global Outcomes (KDIGO) or Acute Kidney Injury Network (AKIN) criteria. These criteria define acute kidney injury as an increase in serum creatinine by ≥0.3 mg/dL (≥26.5 micromol/L) within 48 hours; increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or urine volume <0.5 mL/kg/hr for 6 hours. AKI is a known independent predictor of postoperative morbidity and mortality with associated mortality reported as high as 70%.[55,56] The reported rate of postoperative AKI falls within the

range of 5% to 40% with dialysis-dependent renal failure reported in 1.5% to 10.7% for elective repairs.[57] Additionally, these patients are more likely to experience nonrenal complications such as respiratory failure, central nervous system dysfunction, sepsis, and gastrointestinal hemorrhage. For those who develop AKI, continuous venovenous hemodialysis or daily intermittent hemodialysis is initiated. In a large series, patients requiring permanent hemodialysis were low at 7%.[58] Preoperative renal dysfunction and emergency surgery are known predictors of postoperative AKI, but age, previous aortic surgery, return to operating room, and surgical blood loss have also been shown to be predictors of AKI.[57]

Perioperative renal protection remains a concern and general management strategies include maintaining adequate renal oxygen delivery, reducing renal oxygen utilization, and direct renal tubular injury. The advantages of metabolic suppression via cold temperatures are well known and there is some evidence that local cooling of the kidneys may be protective. Cold renal perfusion with 4°C solution has shown promising outcomes for renal protection but needs further investigation.[57]

Renal insufficiency is a known predictor of 30-day postoperative mortality. Estimated glomerular filtration rate (eGFR) has been shown to be superior to serum creatinine in prediction of 30-day mortality following TAAA repair. In those with normal eGFR mortality has been reported at 5%, while mortality was reported as 10%, 18%, and 28% for mild, moderate, and severe renal insufficiency, respectively. Five-year survival was 77% in those with normal eGFR yet was less than 25% for the severe renal insufficiency patients (**Table 93.1**).[59]

Table 93.1 Complications of Open TAAA Repair

Complication	Results
Early mortality	4–21%
Immediate neurologic deficit	2–33%
Delayed neurologic deficit	2–10%
Acute renal failure–need for dialysis	2–13%
Acute renal insufficiency	6–40%
Bleeding–reoperation for bleeding	5–10%
Vocal cord paralysis/paresis and hoarseness	10%
Cardiac complication–MI, CHF	5–15%
Pulmonary insufficiency (prolonged ventilation >48 h)	10–41%
Stroke or transient ischemic attack (reversible)	2–6%
Gastrointestinal complications (pancreatitis, ischemic colitis, small bowel, cholecystitis, hepatic insufficiency)	7–10%
Chylothorax	<1%
Hospital length of stay	10–22 days
Survival	1 y = 60–80% 5 y = 65–80% 10 y = 40%

CHF, chronic heart failure; MI, myocardial infarction.

COMPLICATIONS

A summary of complications is shown in **Table 93.1**. These have been compiled from a series of sources.[60–70]

Elephant Trunk Technique

Two-staged elephant trunk technique for the repair of extensive aortic aneurysms involving the ascending, transverse arch and thoracoabdominal aorta has proven to be a durable, but challenging approach to a complex problem. Complication rates have improved as advancements in surgical adjuncts have been made. In a large series of 348 patients who underwent a two-stage TAAA repair using the elephant trunk technique, mortality rates after the first stage ranged from 5% to 10% after stage 1 and 5% to 15% after stage 2 depending on renal function. A 5% mortality was reported in both stages for patients with normal GFR. In the interim between the two stages, mortality ranged from 4% to 17% (mean of 6.5%) depending on why the second stage was not completed. In their series 32% of patients failed to follow up after 5 years due to death. Stroke rates for the first stage were low at 2% and no neurologic deficits were noted after the second stage. While timing of the second stage of the repair is challenging, it is recommended that the second stage be performed after 4 to 6 weeks due to the risk of rupture.[71]

IMPACT OF AORTIC DISSECTION

Historically, aortic dissection was reported as a risk for developing neurologic deficits, but these reports are from the "clamp-and-go" era. In a series of 729 patients no difference in neurologic outcome was reported between those with chronic dissection and those without. The rate of paraplegia was 3.6% for those with dissection and 4.7% for those without.[72,73] These improved outcomes are likely the result of the adjuncts (mainly distal aortic perfusion and CSF drainage) as described previously.

The same is not true for acute aortic dissections requiring graft replacement as these patients have a neurologic deficit rate of 32%.[74] These patients are undergoing surgery urgently and are typically critically ill and typically the methods for spinal cord protection are suboptimal. In particular, reimplantation of the intercostal arteries is ill advised due to the friable dissected tissue and the risk for hemorrhage. Additionally, the addition of distal aortic perfusion and CSF drainage may not be possible due to hemodynamic instability.

ENDOVASCULAR REPAIR

Since the first thoracic stent graft repair in 1994, there has been a rapid evolution in endovascular management of thoracic aortic disease with multiple new devices entering the market. Endovascular repair of TAAA was initially purported to have the benefit of improved morbidity and mortality however meta-analysis regarding this has mixed results, but may slightly favor endovascular repair.[75] Regardless, further outcomes research in this area is needed. These procedures were initially developed to accommodate those deemed poor open surgical candidates, but are now frequently preferentially used in select patients.[76] There are currently four different methods for endovascular repair of TAAA: hybrid repair, use of parallel "chimney" grafts and custom-made branched fenestrated devices, as well as investigational endograft used inside of clinical trials or investigator-initiated device trials.

Hybrid Repair

The hybrid approach requires open debranching of the aorta with subsequent endovascular coverage of the aneurysmal segment.[77] Debranching is achieved via a retroperitoneal or transperitoneal approach for extra-anatomical bypass of the visceral and renal arteries via either iliac artery. The patient is allowed to recover and then the aneurysmal segment is covered with a stent graft. Advantages of this approach are the avoidance of a thoracotomy, single-lung ventilation, or aortic cross-clamping. Despite these advantages, the morbidity and mortality using this approach is comparable to that of an open repair.[76,78,79] As such, this method is likely only suited for those who will not tolerate an open repair and are not candidates for other endovascular repair techniques.

Parallel Grafts

This technique involves the use of parallel grafts (chimneys, periscopes or snorkels, commonly referred to as CHIMPS) to preserve blood flow to branch vessels. This was initially described in 78 patients in Brazil (15 patients had TAAA).[80] At 17 months, the primary patency rate was 96.7%

and early mortality was 5.1% (later 1.3%). This technique is advantageous in that off-the-shelf, modular grafts can be tailor fit to any anatomy.[81] This is beneficial in patients with small and tortuous vessels, history of dissection or significant thrombus burden in the paravisceral aorta. Endoleaks from the "gutters" are the main disadvantage and endoleak rates have been reported as high as 18.5%.[82] Meta-analysis of this technique showed 98.9% early success rate and perioperative mortality of 4%.[82,83]

Total Endovascular Repair

This method is performed via custom-made branched and/or fenestrated devices. The largest experience reported is by Greenberg et al. using this method in 406 patients with perioperative mortality of 2.3% for extent IV, 5.2% for extent II and III, and 12.5% for extent I aneurysms.[84] Estimated 24-month survival was 82%, 74%, and 70%, respectively. A multicenter prospective study of 268 patients reported 30-day mortality of 6.7%, in-hospital mortality of 10.1%, and severe complications of 22%.[85] These high rates of mortality prompted the authors to encourage investigation of new strategies. Despite this high mortality, our institution found this method to have the lowest mortality (4%) in extent II and III TAAA and has adopted this as our first-line treatment in those with favorable anatomy.[76] Regardless of the progress that has been made, the field needs to continue to evolve to allow for safer procedures and provide off-the-shelf devices that can be tailored to a variety of circumstances.

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94

Abdominal Aortic Aneurysms

Dean J. Arnaoutakis, Gilbert R. Upchurch Jr, and Thomas S. Huber

Key Points

1. An aneurysm is defined as a permanent, focal dilation of an artery that exceeds 1.5 times the normal, expected diameter.
2. Risk factors for abdominal aortic aneurysm (AAA) include age, male gender, smoking, family history, hypertension, chronic obstructive pulmonary disease (COPD), and the presence of other aortoiliac or peripheral aneurysms.
3. The diameter of an aneurysm is the greatest predictor of rupture as estimated by the tangential stress of the vessel wall.
4. AAAs increase in size over time with a mean growth rate of 0.4 cm/yr.
5. Computed tomography (CT) arteriography is both the diagnostic study of choice and the sole imaging study required for operative planning.
6. The treatment of AAA represents a balance between the risk of rupture and the operative morbidity and mortality rate.
7. Infrarenal AAAs should be repaired in men when their diameter reaches 5.5 cm and in women when the diameter reaches 5 cm provided they are of reasonable operative risk.
8. Endovascular repair has supplanted open repair as the preferred choice by both patients and providers in the United States.
9. Endovascular aneurysm repair (EVAR) mandates long-term follow-up with serial imaging to confirm the integrity of the device and repair.

INTRODUCTION

Abdominal aortic aneurysms (AAAs) are a common problem in developed countries and represent a significant public health concern globally. Operative repair is the only means to reduce the risk of rupture and the associated mortality. The treatment algorithm represents a balance between

the risk of repair and the operative morbidity and mortality rate. Open surgical repair has been the traditional approach since its description by Dubost et al. in the early 1950s.[1] However, a catheter-based endovascular approach has emerged as the preferred treatment since its commercial release at the turn of the 21st century and has truly revolutionized the care of patients with AAAs.

DEFINITIONS AND CLASSIFICATIONS

1 An aneurysm is defined as a permanent, focal dilation of an artery that exceeds 1.5 times the normal, expected diameter.[2] The diameter of a normal abdominal aorta in an adult male is approximately 2 cm (range, 1.4 to 3 cm). The abdominal aorta is consistently larger in men than in women and increases slightly with age for both genders. AAAs should be differentiated from other conditions in which the size of the aorta is increased, including ectasia and arteriomegaly. In aortic *ectasia,* the diameter is increased by less than 1.5 times of the normal, expected diameter. *Arteriomegaly* refers to a diffuse (nonfocal) enlargement of several arterial segments with increases in diameter greater than 50% of the normal expected diameter. Arterial segments in patients with arteriomegaly may be considered aneurysmal if the diameter of a segment is increased by more than 50% of the diameter of an adjacent segment.

AAAs are classified primarily according to how far they extend cephalad (**Fig. 94.1**).[3] More than 85% of all AAAs are classified as infrarenal. These aneurysms are located sufficiently below the renal arteries such that there is adequate healthy aorta for an infrarenal cross-clamp position. Juxtarenal aneurysms refer to those that encroach upon the origin of the renal arteries such that a suprarenal cross-clamp position is necessary with a planned infrarenal proximal anastomosis. Suprarenal AAAs extend above the renal orifices to the level of the superior mesenteric artery (SMA) and typically require a supraceliac cross-clamp position. Aneurysms involving the thoracic and abdominal aorta are designated as thoracoabdominal aortic aneurysms and are classified according to how far they extend both cephalad and caudal (extent 1 through 5). Aneurysms that extend above the renal arteries complicate both endovascular and open repair and are associated

with greater morbidity. Newer techniques and endograft design have expanded the indications for endovascular repair to include select juxtarenal and thoracoabdominal aneurysms.[4,5]

Concomitant iliac artery aneurysms are present in approximately 10% to 20% of all AAAs.[6] Iliac artery involvement, which usually affects the common and internal iliac vessels but preserves the external iliac, may complicate both open and endovascular aneurysm repair (EVAR).

MAGNITUDE OF THE PROBLEM

AAAs are common in developed countries. The incidence of AAAs in the United States ranges from 1.5% in autopsy series to 3.2% among unselected adult patients screened with ultrasonography.[7] Predictably, the incidence increases among patients with risk factors for AAAs and approaches 50% in patients with either femoral or popliteal artery aneurysms.[7] Interestingly, the incidence of AAAs increased through the end of the 20th century, then plateaued, and has even started to decline more recently.[8,9] These changes may be reflective of smoking trends in the United States.[9] A total of 9,928 deaths were caused by AAAs and/or dissections during 2017 and this corresponded to death rate of 3/100,000 as reported by the Centers for Disease Control and Prevention.[10] These numbers may be an underestimate due to sudden deaths in the elderly, which may be secondary to undiagnosed ruptured aneurysms. Of note, since the introduction and rise of endovascular aortic aneurysm repair (EVAR), the 30-day abdominal aneurysm-related mortality (elective repair, rupture repair, and death due to rupture without repair) has decreased by 50%.[11]

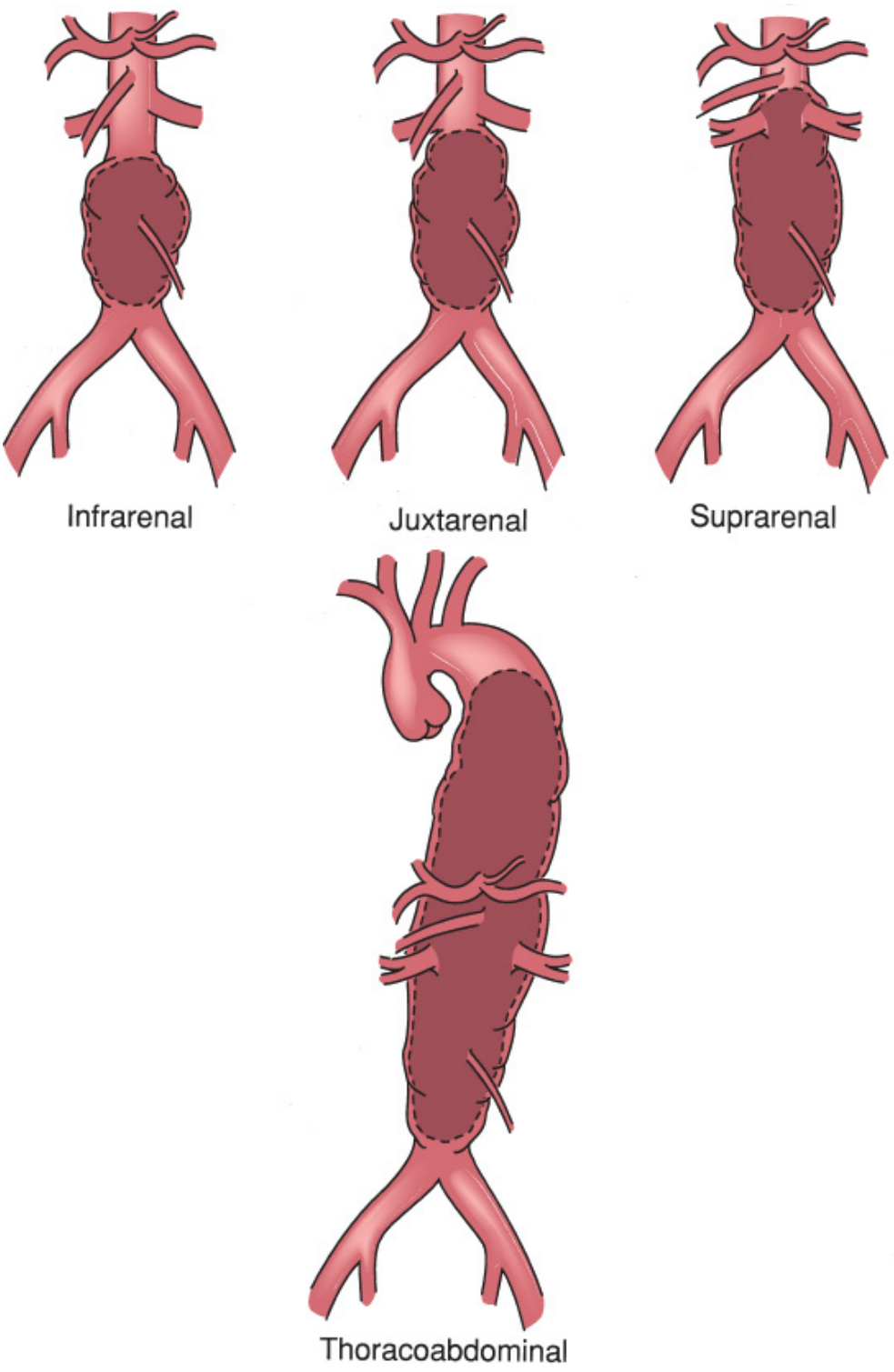


Figure 94.1 Classification of abdominal aortic aneurysms. More than 85% of all abdominal aortic aneurysms are infrarenal. Juxtarenal aneurysms extend to the level of the renal arteries, and suprarenal aneurysms to the level of the superior mesenteric. Aneurysms extending above the superior mesenteric artery and above are designated as thoracoabdominal aneurysms and are classified (Crawford extent I–V) according to how far they extend cephalad and caudal.

PATHOGENESIS AND RISK FACTORS

The pathogenesis of AAAs remains unresolved, although it is an intense area of investigation. Multiple etiologic factors have been implicated including atherosclerosis,[12] hemodynamics,[13] collagen,[14] collagenase,[15] elastin,[16] elastase,[17] metalloproteinases,[18] protease inhibitors,[19] programmed cell death (apoptosis),[20] neutrophils,[21] and inflammatory mediators.[22] The etiology is likely multifactorial with interaction between both environmental and genetic factors. Unfortunately, investigation into the potential mechanisms has not resulted in any effective biologic therapies. Elucidation of the pathogenesis has been complicated by the older age of patients at presentation and the absence of suitable animal models.

2 Multiple risk factors have been identified for the development of AAAs, including age, sex, race, smoking, hypertension, hyperlipidemia, peripheral vascular disease, myocardial infarction, and family history.[23] Identification of these risk factors is important to facilitate screening high-risk patient populations. AAAs typically affect the elderly and are rare among persons less than 50 years of age. Indeed, the mean age among patients undergoing repair across the country was 75.5 years in a Medicare population study.[11] A meta-analysis of the population-based screening studies for AAAs reported that male sex had the strongest association (odds ratio, 5.69).[24] The death rate from AAAs for men of 60 to 64 years of age is 11-fold higher than that for women of the same age, but it is only 3-fold higher for men between 85 and 90. Furthermore, men account for approximately 80% of all AAA repairs performed nationally.[11] The Aneurysm Detection and Management Veterans Affairs Cooperative Study Group (ADAM) reported that smoking was the strongest modifiable risk factor associated with AAAs >4 cm (odds ratio, 5.57) among the 73,451 veterans screened.[25] Darling et al.[26] prospectively analyzed patients undergoing repair of AAAs and reported that 15.1% had a first-degree relative with an aneurysm, in contrast to only 1.8% in the control group. Interestingly, the presence of a female family member with an aneurysm correlated with an increased risk for rupture. It is notable that the risk factors for AAA are similar to those associated with the development of atherosclerosis except for diabetes

mellitus.[27] Furthermore, atherosclerotic changes are found almost universally within degenerative aneurysms at the time of repair suggesting that the two disease processes are likely related, but it is unclear how.

The presence of an aneurysm in the aorta, iliac, femoral, or popliteal arteries increases the risk for a new or additional AAA. The incidence of aortoiliac aneurysms in patients with concomitant popliteal or femoral artery aneurysms is approximately 50%.[7] Importantly, all patients found to have one of these peripheral artery aneurysms should undergo a computed tomography (CT) scan of the entire aorta from thorax to the iliac vessels to exclude a synchronous aneurysm in addition to being screened for other peripheral aneurysms. In contrast, less than 15% of patients with AAA have a concomitant popliteal artery aneurysm and thus evaluation with proper physical examination and/or ultrasonography is typically adequate.[28]

The incidence of AAAs is increased among patients with an aortic dissection. Despite appropriate medical therapy, 20% to 40% of type B aortic dissection (TBAD) patients develop false lumen degeneration with aneurysm formation[29] and up to ~45% eventually undergo aortic-related intervention.[30]

Interestingly, the prevalence of AAAs and the rate of expansion are both increased among heart and abdominal organ transplant patients.[31,32] The responsible mechanisms remain unclear, but the obligatory chronic immunosuppression may contribute.

PRINCIPLES OF MANAGEMENT

The treatment goals for patients with AAAs are to prolong meaningful life, relieve symptoms, and reduce aortic-related mortality by preventing rupture. Because surgical treatment is the only effective means to achieve these goals, the crucial question that must be answered is whether the patient merits repair. The decision algorithm is relatively straightforward for patients with ruptured or symptomatic aneurysms, but more difficult for patients with asymptomatic, intact aneurysms. Prophylactic intervention in the elective setting is contingent on the balance between the risk of the procedure and that of expectant, nonoperative management within the context of the patient's wishes and life expectancy. Appropriate assessment of these risks requires

an understanding of the size-associated risk for rupture, the interval growth rate, and the morbidity and mortality associated with repair, as well as the natural history of a patient with the risk factors that led to aneurysm disease.

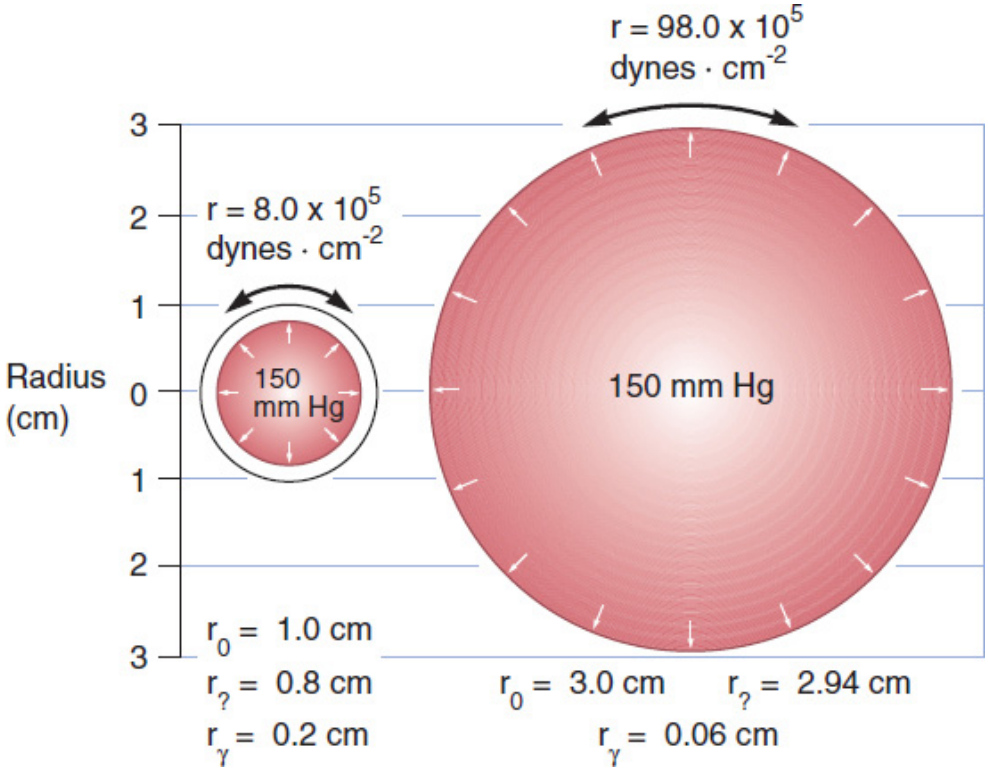


Figure 94.2 Cross-sectional view of a 2-cm-diameter cylinder that expands to a diameter of 6 cm while wall cross-sectional area remains constant. t, wall stress; d, wall thickness; r_i, inside radius; r_0, outside radius. Expansion of a 1-cm-diameter cylinder to a diameter of 3 cm with no change in wall cross-sectional area increases wall tensile stress 12-fold.

Understanding the natural history of untreated AAA requires knowledge of the physics associated with the vessel wall. The tangential stress (t) of a fluid-filled cylindrical tube is determined by the following equation:

$$t = Pr/d$$

where P is the pressure exerted by the blood (dyne/cm^2), r is the internal radius (cm), and d is the thickness (cm) of the arterial wall.[33] The tangential stress of a cylinder 0.2 cm thick with an internal radius of 0.8 cm and a fluid pressure of 150 mm Hg is 8×10^5 dyne/cm^2 (**Fig. 94.2**). An increase in the internal radius (diameter) of the cylinder to 2.94 cm and a concomitant

decrease in the wall thickness, as might occur with an aneurysm, would increase the tangential stress to 98×10^5 dyne/cm^2. Thus, a 3-fold increase in diameter would result in a 12-fold increase in the tangential stress. Aneurysms rupture when the tangential stress exceeds the tensile strength of the vessel wall. It should be emphasized that the tangential stress varies directly with the radius of the cylinder (vessel), but is independent of its length.

3 The diameter of an AAA is the greatest predictor of rupture as estimated by the tangential stress of the vessel wall. The diameter of an aneurysm is determined by measuring its greatest diameter from outer wall to outer wall, preferably using an orthogonal image, throughout the extent of the aneurysm. Orthogonal refers to a cross-sectional measurement perpendicular to the long axis, along the centerline of flow to avoid overestimation due to tortuosity of the aorta. The collective annual rupture risks per aneurysm diameter are shown (**Table 94.1**).[33] Although there is some variability in the data, it is agreed upon that the rupture risk for aneurysms less than 5 cm in diameter is very small, but increases considerably for those greater than 5.5 cm in men and 5 cm in women. These data may be simplified by using the rule of thumb that the annual rupture risk is ≤5% for a 5-cm aneurysm, ~5% for a 5.5-cm aneurysm, 10% for a 6-cm aneurysm, and 20% for a 7-cm aneurysm. These numbers correspond to an estimated 5-year rupture risk of 50% for 6-cm aneurysms and 100% for those of 7 cm. Notably, both the ADAM[25] and UK Small Aneurysm Trial[34] that randomized patients with small aneurysms (4 to 5.5 cm) to open repair or surveillance reported that the rupture risk for surveillance was ≤1%/yr.

Table 94.1 Estimated Annual Rupture Risk

AAA Diameter (cm)	Rupture Risk (%/yr)
<4	0
4–5	0.5–5
5–6	3–15
6–7	10–20
7–8	20–40
>8	30–50

Reproduced with permission from Brewster DC, Cronenwett JL, Hallett JW Jr, et al. Guidelines for the treatment of abdominal aortic aneurysms. Report of a subcommittee of the Joint Council of the American Association for Vascular Surgery and Society for Vascular Surgery? *J Vasc Surg* 2003;37(5):1106–1117.

A variety of other factors have also been reported to increase the risk of aneurysm rupture including female gender, chronic obstructive pulmonary disease (COPD), smoking, hypertension, family history, and wall stress.[34–36] The impact of the aneurysm growth rate on rupture risk remains unclear and has been difficult to separate from aneurysm diameter alone. However, an aneurysm expansion of ≥1 cm/yr is generally considered worrisome.

4 The natural history of AAAs is to grow in size over time. The reported mean rate of growth has varied from 0.2 to 0.4 cm/yr.[37] The rate of growth can be impacted by several factors including female gender, current smoking, and larger original diameter. Interestingly, coenzyme A reductase inhibitors (i.e., statins) may inhibit growth of small AAAs.[38] The growth curve may be somewhat erratic or "staccato" with no growth detected during consecutive 6-month intervals followed by a period of growth hence the need for persistent surveillance.[39]

The mortality rate associated with repair of an AAA depends on the status of the aneurysm (intact/asymptomatic, intact/symptomatic, ruptured), the physiologic state of the patient (age and medical comorbidities), and the method of repair (open vs. endovascular). Population studies from Medicare and the Nationwide Inpatient Sample (NIS) have reported that operative

mortality rates for *open repair of intact* aneurysms in the United States range from 4.2% to 5.4%.[40] Predictably, the operative mortality rate increases with age, ranging from 2.2% among persons of 50 to 59 years of age to 9.2% among those >80. Interestingly, operative mortality rate has been shown to be significantly higher among women (6.1% vs. 3.7%). The mortality rate for open repair in the randomized trials (UK Small Aneurysm Trial—5.8%, ADAM—2.7%, DREAM—4.6%, EVAR Trial—4.6%)[25,34,41,42] are within the range of nationwide series.

The operative mortality rate for *endovascular repair of intact* AAAs has been consistently lower than an open approach. Schermerhorn et al. reported that the operative mortality after EVAR was 1.2% among Medicare beneficiaries during 2001 to 2004 while mortality within the NIS through 2005 was 1.3%.[43] Results from the Dutch Randomized Endovascular Aneurysm Management (DREAM) Trial[41] and the Endovascular Aneurysm (EVAR) Trial[42] comparing open and endovascular repair have reported that the perioperative mortality rate is lower for endovascular repair and within the same range (DREAM—2% vs. 4.6%; EVAR Trial—1.7% vs. 4.7%).

The operative mortality rate for *open repair of intact/symptomatic* aneurysms among patients undergoing emergent repair exceeds that for elective repair and has ranged from 9% to 19%.[7,44] However, in more recent data, De Martino et al.[45] reported from the Vascular Study Group of Northern New England a perioperative mortality of 2.1% and 0% for open and endovascular repair for intact/symptomatic aneurysms, respectively. However, late mortality and inhospital adverse events were still higher comparable to the asymptomatic cohort. Various explanations have been proposed for this increased mortality rate relative to that for intact/asymptomatic aneurysms, including failure to maximize preoperative medical conditions and increased incidence of inadvertent venous injuries. Presumably surgeon experience would lend itself to improved outcomes in nonelective cases; however, Arnaoutakis et al. showed that more experienced surgeons had similar major complication rates as well as 1-year survival compared to early career surgeons with respect to nonelective open AAA repair.[46]

The actual mortality rate for ruptured AAAs is somewhat difficult to determine because a significant number of sudden deaths in elderly patients are likely secondary to ruptured aortic aneurysms. It has been estimated that

50% of all patients with ruptured AAAs die outside the hospital.[7] For those patients who do make it to the hospital, a meta-analysis spanning 50 years reported that the operative mortality rate for the *open repair of ruptured* aneurysms was 48%.[47] These figures correspond to an overall mortality rate of approximately 80% although this may be an underestimate. It is remarkable that the optimization of prehospital and emergency room care including a reduction in the mean transfer time from the emergency department to the operating room to 12 minutes did not appear to result in a decrease of the mortality rate of ruptured aneurysms.[48]

The mortality rate for the *endovascular repair of ruptured* AAAs is lower than the open approach, although data may be significantly skewed by selection bias.[49] Multiple meta-analyses have reported a perioperative mortality rate of 24% to 27% with improved overall outcomes compared to open repair.[50,51] The potential to treat ruptured AAAs with the endovascular approach may represent the greatest contribution or benefit of the technology. However, further validation is necessary since some reports likely reflect patient selection bias. In population data, Giles et al.[52] reported that the annual number of deaths across the country from both intact and ruptured aneurysms has decreased significantly since the introduction of EVAR.

CLINICAL PRESENTATION AND DIAGNOSIS

The overwhelming majority of AAAs are asymptomatic at the time of discovery. Most aneurysms are detected by abdominal or pelvic imaging studies, such as ultrasonography and CT, performed for other indications (e.g., chronic back pain, renal cysts) rather than on physical examination. It is difficult to palpate an AAA on physical examination because of its anatomic location in the posterior abdomen in conjunction with the national obesity epidemic. A literature review examining the accuracy of physical examination reported that the sensitivity ranged from 33% to 100%, the specificity ranged from 75% to 100%, and the positive predictive value ranged from 14% to 100%.[53] Intact abdominal aortic and iliac artery aneurysms may present with symptoms that lead to further investigation and the correct diagnosis although this is the exception rather than the rule. Rarely, enlargement of the aneurysm may cause vertebral erosion and chronic

back pain. In addition, thrombosis of an AAA may cause acute ischemia in the lower torso, and aneurysms may be a source of arterial macroemboli or microemboli leading to acute ischemia of a lower extremity or digit, respectively.

Patients with intact/symptomatic or ruptured aneurysms present with abdominal or back pain related to the aneurysm itself. The character of the pain is variable and ranges from dull to sharp. The pain is usually acute in onset and persistent. It may be superimposed on more chronic abdominal or back pain, but the presentation is usually not subtle, and the pain can be differentiated from more chronic complaints. In addition, the pain may radiate from the abdomen to the back, flank, inguinal region, or genitalia. Approximately 10% of patients with ruptured AAAs present with signs and symptoms similar to those of ureteral colic or other acute urologic problems.

Patients with a ruptured AAA may present anywhere along the spectrum from hemodynamically normal to profound shock. Their status depends on the ability of the tissues adjacent to the aorta to tamponade the bleeding. If the rupture is contained, the patient may present hemodynamically stable. However, it should be emphasized that this is usually temporary, and health care providers should not be lulled into a false sense of security. A ruptured AAA is a true medical emergency that requires immediate operative repair regardless of the patient's hemodynamic status. Furthermore, vital signs may be misleading because patients can lose up to 15% of their blood volume without any appreciable change in their pulse rate or blood pressure. If the aneurysm initially ruptures freely into the peritoneal space, patients usually exsanguinate before they can seek medical attention.

Patients with a ruptured AAA may also present with either an aortoenteric or an aortocaval fistula, although both are relatively rare. Patients with an aortoenteric fistula may present with massive intestinal bleeding, but often present with a "sentinel" bleed that is small volume. The aorta may rupture through any portion of the bowel, although the duodenum and proximal small bowel are the most common sites. The overwhelming majority of aortoenteric fistulae result from the erosion of a prosthetic graft into the adjacent bowel (secondary aortoenteric fistula) rather than from an unrepaired aneurysm (primary aortoenteric fistula). The diagnosis of an aortoenteric fistula must be ruled out in all patients with gastrointestinal bleeding who have either an AAA or a previous infrarenal aortic repair.

Patients with an aortocaval fistula generally present with high-output congestive heart failure, a continuous abdominal bruit, and edema of the lower extremities.

Several imaging studies are available to establish or confirm the diagnosis of an AAA. Indeed, the introduction of endovascular techniques for aneurysm repair has resulted in an evolution of these modalities. The generic imaging goals for patients with an AAA are to establish the diagnosis and determine the presence of rupture, the cephalad/caudal extent of the aneurysm, the feasibility of endovascular repair, the presence of other visceral pathology or anatomic variants that would complicate operative repair, such as a left-sided vena cava and/or a horseshoe kidney. Although no imaging study satisfies every objective, ultrasound has emerged as the ideal *screening* study with CT arteriography being the definitive *diagnostic* study and the preferred modality for operative planning.

Abdominal ultrasound is a safe, simple, and readily available method of detecting AAAs (**Fig. 94.3**). It is relatively inexpensive and does not require the use of ionizing radiation or intravenous contrast. The sensitivity of ultrasound for detecting AAAs is acceptable, and the technique is reproducible within 0.3 cm in experienced hands.[54] However, the technique is quite operator dependent and potentially confounded by the presence of bowel gas or extreme obesity. Ultrasound can accurately image the infrarenal aorta to its bifurcation but is less reliable for imaging the portions of the aorta proximal to the renal arteries and distal to the common iliac vessels. Furthermore, it is not as reliable as CT for differentiating a ruptured from an intact aneurysm. Further, it is a useful technique to follow patients with small aneurysms (<4 cm) when the exact measurement is not crucial.

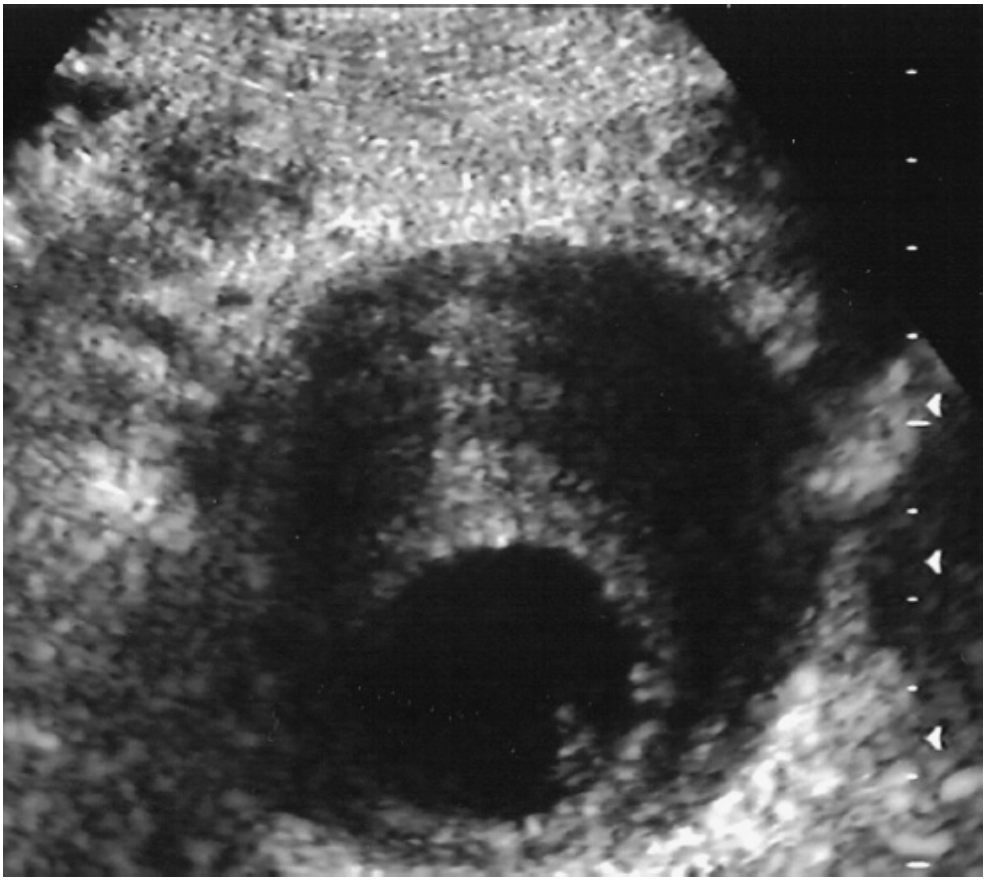


Figure 94.3 B-mode ultrasound image showing a transverse view of an infrarenal abdominal aortic aneurysm. Note the vessel wall and the large quantity of intraluminal clot surrounding the smaller, blood-filled center (*dark circle*).

5 CT arteriography overcomes many of the limitations of ultrasound and represents the current "gold standard" for imaging patients with AAAs (**Fig. 94.4**). The downside of CT is the greater expense and the potential harm that may be caused by ionizing radiation and intravenous contrast. Indeed, the evolution of EVAR and the required follow-up imaging studies have focused increased attention on the magnitude of long-term radiation injury. It is worth noting that the radiation dose associated with an abdominopelvic CT scan is 10 to 20 mGy while that for a routine chest radiograph is only 0.5 mGy. The incidence of allergic reactions to the contrast may be reduced by a steroid preparation while concerns regarding intravenous contrast-induced nephropathy remain debatable.[55] Of course, the renal risks can be avoided altogether by not using contrast. However, the quality of the noncontrast images is generally not useful for determining eligibility for endovascular repair. CT is very sensitive for detecting both

intact and ruptured aneurysms, and the images are reproducible within 0.2 cm.[56] The quality of the CT images has continued to improve with each new generation of scanners, and the image acquisition times have decreased. Given the quality and ease of imaging, CT arteriograms have essentially replaced traditional catheter-based diagnostic arteriograms for evaluation of aneurysms. Using axial CT images and 3D imaging software, a 3D image of the aorta can be obtained that allows measurements along the centerline of blood flow (**Fig. 94.5**), and dramatically improve the accuracy and consistency of sizing for EVAR.[57] CT is also helpful for detecting other intra-abdominal pathology or anatomic variants that may impact the operative approach. Specific concerns include the location of the left renal vein and other associated venous anomalies, the location and size of the kidneys, and the characteristics of the aneurysm wall. In addition, CT is the serial imaging study of choice when aneurysms exceed 4 cm and approach the threshold for intervention.

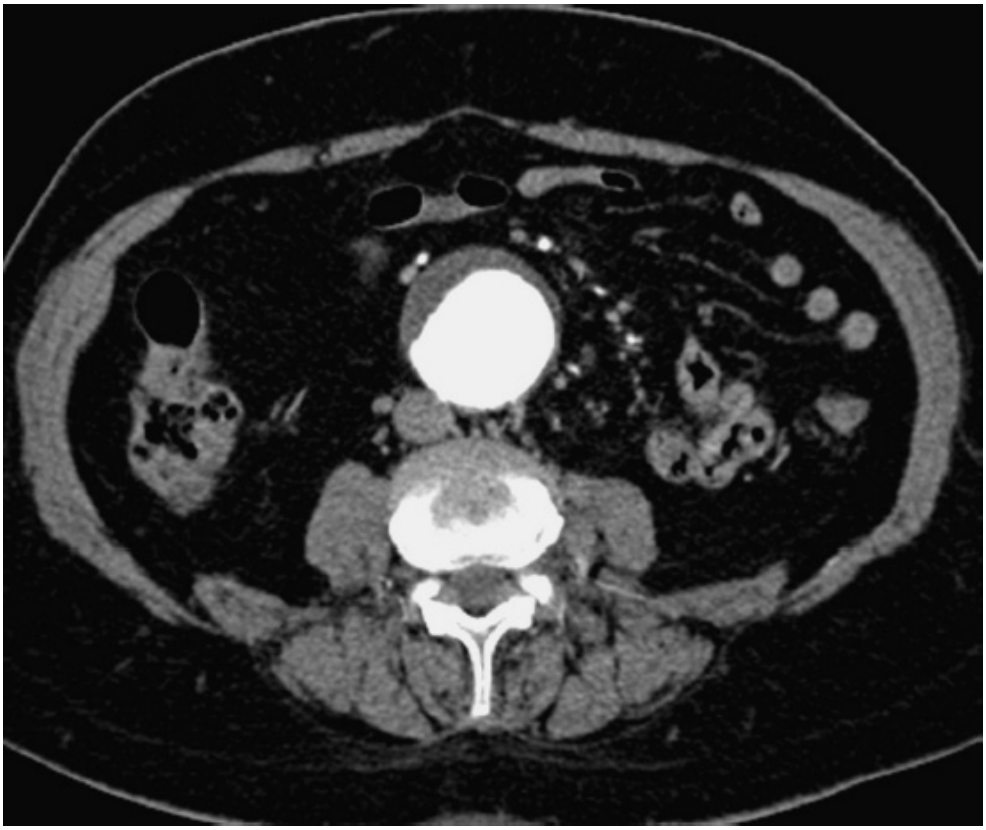


Figure 94.4 CT scan demonstrates a large abdominal aortic aneurysm. Note that the majority of the lumen is filled with contrast.

Figure 94.5 3D CT of the aorta and the iliac, femoral, and visceral arteries is shown. Note the infrarenal abdominal aortic aneurysm that extends to the aortic bifurcation.

Both magnetic resonance imaging (MRI) and catheter-based arteriography have been used as diagnostic imaging studies for patients with AAAs. The image quality and overall sensitivity of MRI is comparable to CT, but the technology is not as widely available and most surgeons are less familiar

with interpreting the images. Furthermore, the technique is relatively contraindicated for patients with ferromagnetic devices (e.g., pacemakers, joints) or renal insufficiency. Imaging of critically ill patients is also cumbersome, if not prohibitive.

Importantly, aneurysms are frequently diagnosed during catheter-based arteriography performed for other purposes, but this should not be viewed as a diagnostic test of choice for AAAs. An arteriogram only delineates the lumen of the vessels (i.e., aorta, iliac and femoral arteries), and thus gives no indication of aneurysm extent or diameter. AAAs are often filled with laminated thrombus and may have a relatively normal-appearing lumen. The "lumenogram" produced by the contrast reflects the patent lumen rather than the actual cross-sectional diameter of the aneurysm.

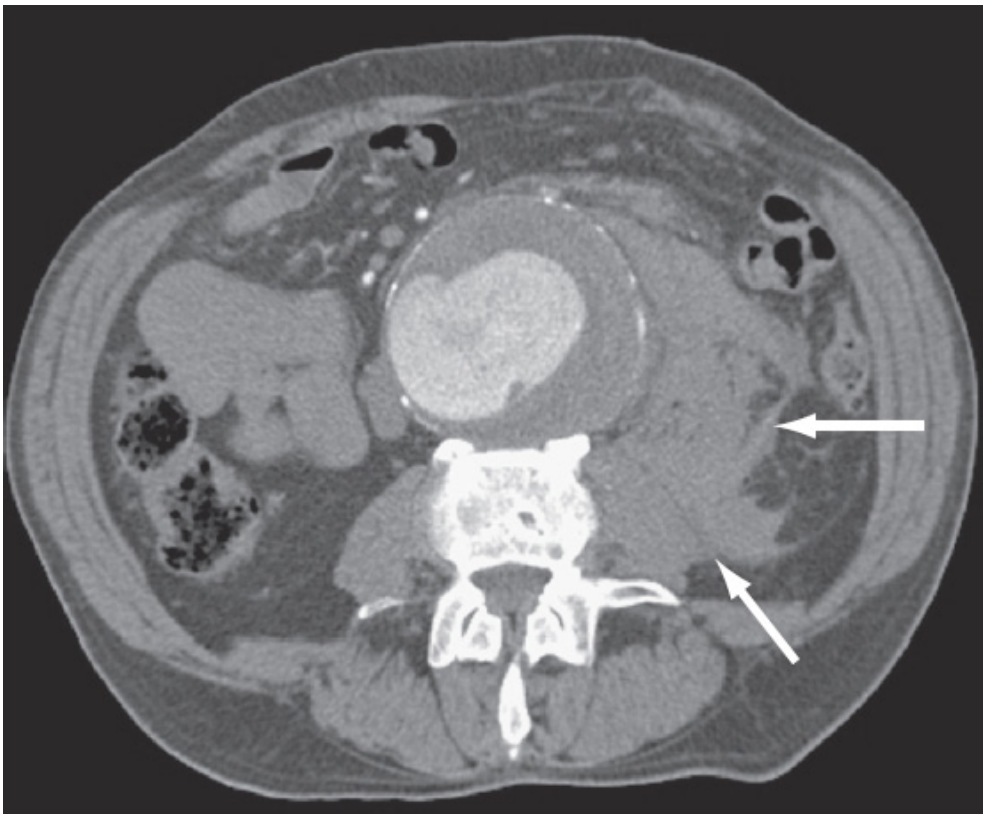


Figure 94.6 Contrast CT demonstrates a ruptured abdominal aortic aneurysm. Note the large retroperitoneal hematoma and the loss of the normal fat plane anterior and lateral to the left psoas muscle.

The diagnostic approach and initial treatment for patients with a potential ruptured aneurysm merit further comment. Because of the high attendant

mortality rate, prompt diagnosis and repair are necessary. In a study from the Cleveland Clinic Vascular Registry, the operative mortality rate associated with ruptured AAAs increased from 35% when the initial diagnosis was correct to 75% when incorrect.[58] A natural history study of patients with ruptured AAAs not offered operative repair reported that <15% of the patients died within 2 hours of hospital admission.[59] Based upon these findings, the authors concluded that most patients with ruptured aneurysms are sufficiently stable to undergo a CT scan and this opinion has been supported by improved mortality results of EVAR for ruptured aneurysms.

Several findings on CT are suggestive of a ruptured AAA including disruption of the calcium ring within the aortic wall, disruption of the aortic margins, retroperitoneal hematomas, mass lesions in the psoas region, displacement of the kidneys, abnormal soft tissues posterior to the aorta, effacement of the normal fat planes between the aorta and adjacent viscera, and abnormal retroperitoneal fluid collections (**Fig. 94.6**). Patients undergoing an emergent CT arteriogram to rule out a ruptured AAA should not receive oral contrast because of the delay associated with its administration and the confounding effects on the imaging of the vessels, especially if proceeding with an endovascular repair in short order.

The diagnosis of a ruptured AAA should be considered in elderly patients that present to the emergency room hemodynamically *stable* with abdominal or back pain. Admittedly, the differential diagnosis for abdominal or back pain in this patient population is extensive, and the incidence of a ruptured AAA is small. An expeditious history and physical examination can usually determine the cause of the pain. A pulsatile abdominal aortic mass, an unexplained low hematocrit, or hemodynamic instability before presentation are particularly worrisome and increase the level of suspicion. If ultrasound confirms the diagnosis of an aneurysm, further evaluation with CT should be obtained to rule out rupture. Alternatively, a CT may be obtained as the sole imaging study. Any findings consistent with a ruptured aneurysm on CT mandate direct transfer to the operating room for immediate repair. Aggressive fluid resuscitation should be avoided and mild hypotension (i.e., systolic pressure >80 mm Hg) tolerated in conscious patients due to the theoretical potential to cause the aneurysm to rupture into the peritoneal cavity and/or release the tamponade effect of the retroperitoneal tissue. If an intact aneurysm is found on CT without any suggestion of rupture, the next

logical question is whether the aneurysm is the source of the pain. Symptomatic aneurysms are likely associated with an increased risk of rupture although the natural history remains poorly defined. Patients with symptomatic/intact aneurysms ≥5 cm in diameter should be admitted to a monitored setting and scheduled for urgent operative repair provided no alternative causes for the pain are identified. Additional sources of the abdominal pain should be sought in patients with aneurysms smaller than 4 cm in light of the small rupture risk. The appropriate treatment for patients with aneurysms 4 to 5 cm is less clear. These aneurysms have the potential to rupture although the risk is very small. It is recommended that these patients be admitted and the source of their pain further investigated.

The role of screening for AAAs in asymptomatic patients is somewhat controversial given that screening in select populations has been shown to decrease aneurysm-related mortality yet increase the number of invasive procedures exposing patients to additional risks.[54] The United States Preventative Task Force has issued a position statement advocating a single screening ultrasound in males 65 to 75 years of age who have a smoking history and selective screening for males without smoking history.[54] These recommendations were based upon the results of a best-evidence systematic review of 50 studies, 17 of which were randomized controlled trials. Notably, the Preventative Task Force stated that the literature did not substantiate screening for women who have never smoked and have no family history of AAA and the literature was insufficient to make a recommendation for women aged 65 to 75 years who have smoked or have a family history of AAA. The American Heart Association and American College of Cardiology do not recommend screening in women[60]; however, the Society for Vascular Surgery advocates for screening in women older than 65 years who have tobacco history or family history of AAA.[61] Medicare currently pays for a single screening ultrasound as part of the Welcome to Medicare physical examination for men who have smoked sometime during their life and for both men and women with a family history of AAAs.

OPERATIVE INDICATIONS

All patients with symptomatic or ruptured AAAs should undergo operative repair unless they have an underlying medical condition that precludes long-term survival or their quality of life is not sufficient to justify the intervention. The latter situation entails a difficult decision, but not offering operative repair should be considered in certain cases (e.g., a debilitated, demented patient in a nursing home) after discussion with the patient and/or family.

6 The operative decision-making process for intact/asymptomatic AAAs is a complex one that needs to be tailored to the individual patient. Indeed, there is no single parameter that merits repair. The operative indications are contingent upon the size of the aneurysm, life expectancy, comorbidities, preference, and anatomic configuration. It is important to remember that the repair of an intact/asymptomatic AAA is a prophylactic operation that represents a balance between the operative risk and the future risk of rupture with the ultimate treatment goals to prolong life, relieve symptoms, and prevent rupture.

7 The diameter of the AAA is the best predictor of rupture as stated above and has been used as the most common indication for repair. The Joint Council of the American Association for Vascular Surgery and the Society for Vascular Surgery have released updated guidelines for the treatment of patients with AAAs.[61] They recommend that a diameter of 5.5 cm is an appropriate threshold for repair in the "average patient" with an intact infrarenal aneurysm, but emphasize the importance of individualizing each case. They state that rapid aneurysm expansion (>1 cm/yr), symptoms related to the aneurysm, and female gender merit repair at a smaller diameter, while consideration should be given to earlier repair in young patients provided that the operative mortality rate is acceptable. Furthermore, they recommend that a larger diameter threshold is appropriate in higher-risk patients and emphasize that there does not appear to be any justification to alter the operative threshold for the endovascular approach.

There is some controversy regarding the management of patients with aneurysms that are 4 to 5.5 cm. Both the UK Small Aneurysm Trial[34] and the ADAM Trial[25] concluded that it was safe to follow patients with 4 to 5.5 cm aneurysms and that early operation did not confer any long-term survival benefit. As noted above, the rupture risk for patients in the surveillance group was <1%/yr. It is important to note that more than 60% of the patients in both

studies ultimately underwent operative repair despite their initial randomization. A longer-term follow-up study from the UK Small Aneurysm Trial extending to 12 years did not demonstrate a survival benefit for the patients assigned to early surgery.[62] However, it is important to note that almost all of the patients that survived ultimately required repair since their aneurysms continued to grow and exceed the 5.5-cm threshold. Indeed, the relevant question may not be whether patients with small aneurysm need to be repaired, but rather when they need to be repaired. The proponents of smaller diameter-based thresholds for repair (i.e., <5.5 cm) have justified their approach stating that even small aneurysms rupture, aneurysms continue to increase in diameter and will likely need to be repaired, the patients' medical conditions will likely deteriorate with age, and the operative mortality/morbidity rate for small aneurysms may be less. In addition, the significant decrease in the perioperative mortality rate after EVAR have also challenged the threshold diameter for operative repair. However, Finlayson et al.[63] used a decision analysis model to determine the optimal diameter for open repair and EVAR and concluded that the endovascular approach lowers the operative threshold only for older patients in poor health. Although the level 1 evidence does not support this lower threshold, it is important to note that the size discrepancy between a 5.2-cm and a 5.5-cm aneurysm is very small and likely within the resolution of the imaging study.

The presence of medical comorbidities predictably impacts the perioperative mortality rate and threshold for repair. Steyerberg et al.[64] identified several independent risk factors for operative mortality during open repair, including renal insufficiency (creatinine >1.8 mg/dL, congestive heart failure, ECG ischemia, pulmonary dysfunction, older age, and female gender) and these have remained consistent throughout the literature. Similarly, Beck et al.[65] developed a predictive model for both open and endovascular repair using a prospective registry from the Vascular Study Group of New England. They reported that COPD, suprarenal aortic clamp, renal insufficiency, and advanced age (≥70) were predictive of mortality at 1 year after open repair with the mortality ranging from 1% to 67% depending upon the number of risk factors. Congestive heart failure and larger aneurysm diameter (≥6.5 cm) were the only predictive factors after endovascular repair with the mortality ranging from 4% to 23%. The consistent, dramatic impact of renal insufficiency was further emphasized by a national series that

reported a nine-fold increase in mortality. Notably, the estimated glomerular filtration rate may be a better index of renal function than serum creatinine and, therefore, likely a better predictor of adverse outcome. Life expectancy is inseparable from comorbidities, but it should be noted that the average life expectancy for a 60-year-old and an 85-year-old man in the United States is 18 and 5 years, respectively.

Patient preference should also be factored into the operative decision process. Patients may not be willing to accept the small, finite risk of rupture from a <5.5-cm aneurysm and thus desire to have their aneurysm repaired at a lower threshold. Indeed, patients often echo the justification for early repair proposed by surgeons.

The anatomic configuration of the aneurysm and/or the associated structures should factor into the operative decision process as well. Any technical factors that complicate the repair likely increase the perioperative mortality/morbidity including the need for suprarenal clamp application with subsequent renal/visceral ischemia, venous anomalies (e.g., left-sided vena cava), renal anomalies (e.g., horseshoe kidney), and inflammatory aneurysms. Admittedly, many of these technical concerns are relevant only to the open approach and can be overcome/avoided by endovascular repair provided that it is an option from an anatomic standpoint. Anatomic concerns relevant to endovascular repair include continued aneurysm degeneration of the aortic neck or iliac arteries that may make standard infrarenal endograft repair more difficult or impossible unless early repair is undertaken.

Patients that do not meet the threshold for operative repair should be followed closely. It is important to educate the patients about their underlying disease process and emphasize the importance of long-term follow-up. Notably, Valentine et al.[66] reported that 32% of patients with small aneurysms managed by “watchful waiting” were noncompliant with their follow-up plan. Furthermore, it is important to counsel patients about the presence of symptoms associated with rupture and the importance of seeking urgent medical attention. Guidelines have suggested that patients with aneurysms <3 cm in diameter should be reimaged at 5 years while those with between 3 and 3.4 cm should be reimaged at 3 years and those between 3.5 and 4.4 cm should be reimaged at 1 year. Aneurysms >4.5 cm should be reimaged every 6 months.[67] It is important to note that up to 50% of the patients deemed a prohibitive operative risk and not offered elective repair

will ultimately die from a ruptured aneurysm.[68] The patients who are not candidates for elective repair should not be offered emergent repair in the event that their aneurysm ruptures or becomes symptomatic and must be counseled on this matter preemptively.

CHOICE OF OPEN OR ENDOVASCULAR REPAIR

After the decision to recommend operative repair has been made, the technique for repair needs to be determined. Admittedly, these decisions are somewhat interrelated since the decision to recommend operative repair in certain subsets of patients is oftentimes contingent upon whether they are candidates for an endovascular approach. The past several decades have witnessed a rapid evolution of the endovascular technique, and, indeed, this evolution has helped define our discipline. It has been clearly demonstrated that the technical success rates for endovascular graft repair are excellent and the need for intraoperative conversion to open repair negligible. The perioperative events and long-term outcomes have been defined by level-1 evidence. Many of the technical limitations inherent to the earlier endovascular devices and anatomic limitations have been overcome. Despite a lack of long-term overall survival advantage compared to open repair, the endovascular approach for treatment of AAAs has been widely 8 applied.[69] Indeed, the endovascular approach eclipsed open repair in the United States in 2005 and data shows that more than 75% of aneurysms are repaired in this manner.[70] The choice of open or endovascular repair is complicated and contingent upon several factors including feasibility, outcome, comorbidities, compliance, cost, and preference. It is imperative that these issues, including their respective advantages/disadvantages, be addressed with patients preoperatively to ensure proper informed consent.

The initial determinant of the approach is the anatomic configuration of the aorta, the aneurysm, and the access vessels. The commercially available endovascular devices come in a finite range of sizes and, thus, are suitable only if specific anatomic conditions are satisfied. Although the number of available devices and their specific characteristics are constantly evolving,

the “generic” endograft consists of a fabric graft (i.e., polyester or ePTFE) and a metallic endo/exoskeleton (i.e., stainless steel or nitinol) that facilitates proximal/distal fixation by the radial force of the stent (**Fig. 94.7**). In some devices, proximal fixation is augmented by the presence of suprarenal hooks. The “generic” devices are modular and consist of either two (main body and contralateral iliac limb) or three (main body, contralateral iliac limb, ipsilateral iliac limb) components with a variety of additional ancillary pieces that allow proximal or distal extensions at the aortic and iliac ends, respectively. The current strategy is to seat the proximal component of the bifurcated system as close to the lowest renal artery as possible and the distal components as close to the iliac bifurcation as possible to improve immediate seal and fixation and decrease the potential for later aneurysm degeneration at or adjacent to seal sites.

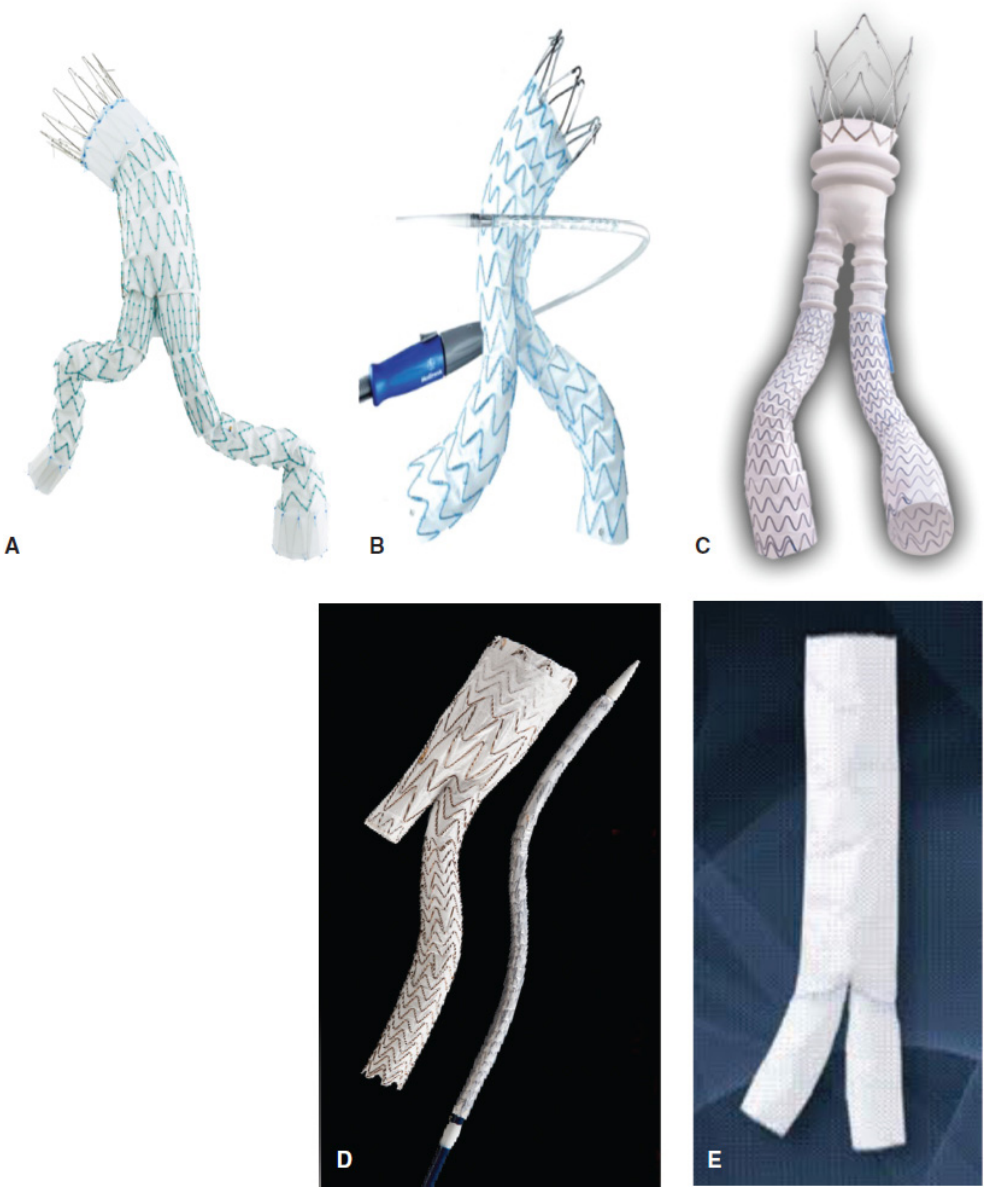


Figure 94.7 Some of the current commercially available infrarenal endografts in the United States are shown: Cook Zenith (**A**); Medtronic Endurant (**B**); Trivascular Ovation (**C**); Gore Excluder (**D**); Endologix AFX (**E**). These are modular devices consisting of a main body, iliac limbs/extensions, and main body extensions. Note the common theme of bilateral iliac limbs and a main body. There are many differences between these endografts, which make them each uniquely suited for some patients. Some devices (**A–C**) utilize a bare suprarenal stent construct to facilitate proximal fixation. Other devices do not have a suprarenal stent component but rather utilize active fixation with hooks (**D**) or anatomic fixation at the aortic bifurcation (**E**).

Although there is some variability among the commercially available devices in terms of their specific sizes and anatomic constraints, the general

anatomic requirements are somewhat similar. The infrarenal abdominal aorta must have a suitable, nonaneurysmal landing zone for the endograft that measures ≥10 to 15 mm in length and ≥17 mm but ≤32 mm in diameter (ranges reflect differences between the commercial devices). Furthermore, the proximal neck angle should be ≤60 degrees for most devices (≤75 to 90 for some newer devices), as measured by the intersection of the centerline of the infrarenal aorta at the landing zone site and the centerline of the aneurysm through the aortic bifurcation. Newer devices do allow for more neck angulation, but the operating surgeon should keep in mind that more infrarenal neck may be required in more severely angulated necks to allow for appropriate seal and fixation of the device. The infrarenal neck should be relatively free of thrombus and calcification to facilitate a seal at the implantation site. In general, a longer the infrarenal neck length equates to longer device seal zone and improved durability. The iliac artery should have a suitable landing zone ≥20 mm with an associated diameter between 7 and 20 mm to facilitate both anchoring the graft and passing the main device into the aorta. The distal landing zone for the iliac limbs is usually in the common iliac artery although the anatomic constraints with regard to the size of the access vessels and the introduction of the devices are relevant for both the common and external iliac vessels.

A variety of techniques have been described to overcome the anatomic limitations of the endovascular approach, thereby extending its feasibility. Indeed, some modification has been described to overcome almost every anatomic contraindication. Unfortunately, extending the indications for endovascular repair beyond those recommended by the manufacturers (i.e., instructions for use [IFU]) has been associated with an increase in the incidence of adverse events and a higher need for reintervention.[71] For those with short (≥4-mm) infrarenal necks, fenestrated endografts have been commercially available since 2012 with excellent midterm results.[72] Details regarding this technique/device are discussed later in the juxtarenal section of this chapter. EndoAnchor systems have been employed in those with short necks (≥4 mm and <10 mm) although long-term data using this technique is lacking.[73] Stenosis within the access vessels can be overcome by dilation (i.e., balloon angioplasty, serial dilators) or by the use of an open prosthetic conduit or endovascular stent graft conduit.[74] The open prosthetic conduit is usually anastomosed to the bifurcation of the common iliac artery and then

tunneled through the retroperitoneal space below the inguinal ligament. Alternatively, an aorto-uni-iliac endograft can be configured and a femoral–femoral bypass performed.

Aneurysm degeneration of the common iliac artery can be overcome by a variety of techniques including simply using larger-diameter graft limbs, occluding/embolizing the internal iliac artery, and seating the iliac limb in the external iliac artery, bypassing the internal iliac artery (and seating the iliac limb in the external iliac artery), or with an iliac branch endoprosthesis. Although relatively simple to perform, internal iliac artery embolization has been associated with a moderate incidence of complications including buttock/thigh claudication (30% to 40%), sexual dysfunction, neurologic deficit/paraplegia, pelvic ischemia, and gluteal compartment syndrome.[75] The claudication improves with time in the majority of patients, but can be quite debilitating. Many of the other complications, although somewhat rare, can be catastrophic. Because of these concerns, concomitant bilateral internal iliac artery occlusion/embolization should be avoided when possible. Iliac branch endoprostheses have been commercially available since 2016 and have demonstrated excellent midterm outcomes in preserving internal iliac artery flow yet providing aneurysm sac exclusion by extension into the external iliac artery.[76] Their main limitation remains somewhat stringent anatomic requirements for their application.[77] Nonetheless, this technology advancement has certainly changed the manner with which aneurysmal disease involving the common iliac artery is managed.

Consideration of the perioperative and long-term outcomes after EVAR requires introduction of the concepts of endoleak and endotension. Simply, endoleak is the perfusion of the aneurysm sac outside the lumen of the endograft while endotension is the persistent pressurization within the excluded aneurysm sac. Approximately 10% to 20% of patients develop an endoleak during the first year after endovascular repair.[78] Admittedly, not all of these require remediation. Endoleaks have been classified as types 1 through 4 based on the mechanism of the leak (**Fig. 94.8**). Type 1 leaks originate at either the proximal or distal attachment sites. Type 2 leaks come from branch vessels, such as the lumbar or inferior mesenteric arteries. Type 3 leaks are caused by fabric tears or problems at the graft interfaces of the modular devices, whereas type 4 leaks are usually transient (<24-hour) transgraft extravasations that result from the porosity of the graft and needle

holes. It should be emphasized that the entire concept of an endoleak is predicated on the ability to detect contrast or blood flow outside the lumen of the endograft and is, therefore, contingent on the sensitivity and specificity of the various imaging techniques. The major concern about both endoleaks and endotension is that the pressure transmitted to the aneurysm wall may cause the aneurysm to expand and/or rupture. The clinical significance of the various endoleak types is quite different. Both type 1 and 3 endoleaks are considered major adverse outcomes associated with an increased risk of rupture, and they merit reintervention.[79] Type 2 endoleaks are generally considered less worrisome in terms of their rupture risk although they are associated with an increased risk for reintervention. They can generally be followed with serial imaging studies, but merit evaluation/intervention if the aneurysm sac continues to enlarge. Type 4 endoleaks are self-limited and benign. The clinical significance of endotension is likewise unresolved. Indeed, the concept itself is somewhat ambiguous given the limitations of actually measuring the pressure within the aneurysm sac. It should be noted that freedom from endoleak does not necessarily mean freedom from endotension given the observation that aneurysms can continue to enlarge in the absence of an identifiable endoleak. Aneurysm-related reinterventions occurred in 3.7% of patients per year after EVAR from 2001 to 2004 in the Medicare population.[80] The majority of these remedial procedures are minor endovascular procedures, however with a risk of major open procedures of 0.4%/yr.[81] In contrast, open aneurysm repair is associated with a less than 1%/yr incidence of aneurysm-related complications that require remedial procedures in long-term follow-up. Graft-related deaths have been reported in 2% of patients at 15 years.[82]

Perioperative complication rates appear to be lower after endovascular repair. As noted above, the randomized, controlled DREAM and EVAR Trials reported a significant decrease in the perioperative mortality rate (DREAM—1.2% vs. 4.6%; EVAR Trial—1.7% vs. 4.7%).[41,42] The EVAR Trial also reported a trend toward a decrease in the combined operative mortality/*severe* complication rate (9.8% vs. 4.7%, $p = 0.10$). Multiple clinical trials have reported that the overall major complication rates after both endovascular and open repair are approximately 15% although the magnitude of the complications is less for the endovascular approach and primarily includes vascular access complications (e.g., hematoma, femoral

artery injury). These clinical trials have likewise demonstrated that the total hospital length of stay, intensive care unit length of stay, operative blood loss, and time necessary to resume normal activities are all less for the endovascular approach. Interestingly, the impact on sexual function remains unresolved. A survey of the DREAM participants demonstrated that sexual dysfunction was common after both endovascular and open repair, but returned to the baseline state at 3 months for both groups.[83] In contrast, Xenos et al. reported significantly less orgasmic and erectile dysfunction after endovascular repair.[84]

The long-term results after the EVAR and DREAM Trials have failed to document any significant benefit for the endovascular approach in terms of almost every outcome measure analyzed.[69] In the DREAM Trial, there was no difference in all-cause mortality at 12 years (survival, open—42.2%, EVAR—38.5%).[85] More concerning, the EVAR Trial showed worse overall and aneurysm-related mortality beyond 8 years for those undergoing EVAR (overall mortality: EVAR—53% vs. Open—46%; aneurysm-related mortality: EVAR—5% vs. open—1%).[86] These outcomes were presumably driven by secondary aneurysm rupture and increase cancer-related mortality in the EVAR group.

In the EVAR Trial, costs (EVAR—£13,257, open—£9,926) were significantly greater for the endovascular approach while there were negligible differences in the quality of life assessments.[87] However, the OVER Trial showed no difference in total healthcare costs between open and endovascular repair after 2 years.[88] The cost savings from a shorter length of stay and lower incidence of major perioperative complications with an endovascular approach are offset by the device costs. In fact, device costs reflect about 40% of initial hospitalization costs after endovascular repair.[89] It is important to note that most of the analyses have focused on the hospital and device-related costs, but have failed to include the associated professional fees and the costs associated with long-term follow-up and reintervention, all of which may be substantial.

These long-term results from the DREAM and EVAR Trials are somewhat sobering. It is clear that the endovascular approach is not as secure a repair as the traditional, open alternative. The endovascular repair is associated with ongoing rupture risk that likely approaches 1%/yr.[81,90] The rupture risk has been associated with poor patient selection, operator error,

unrecognized/untreated endoleaks, large aneurysms, and device migration.[81] Interestingly, the mortality rate associated with rupture after endovascular repair may be less than for de novo ruptures.[90]

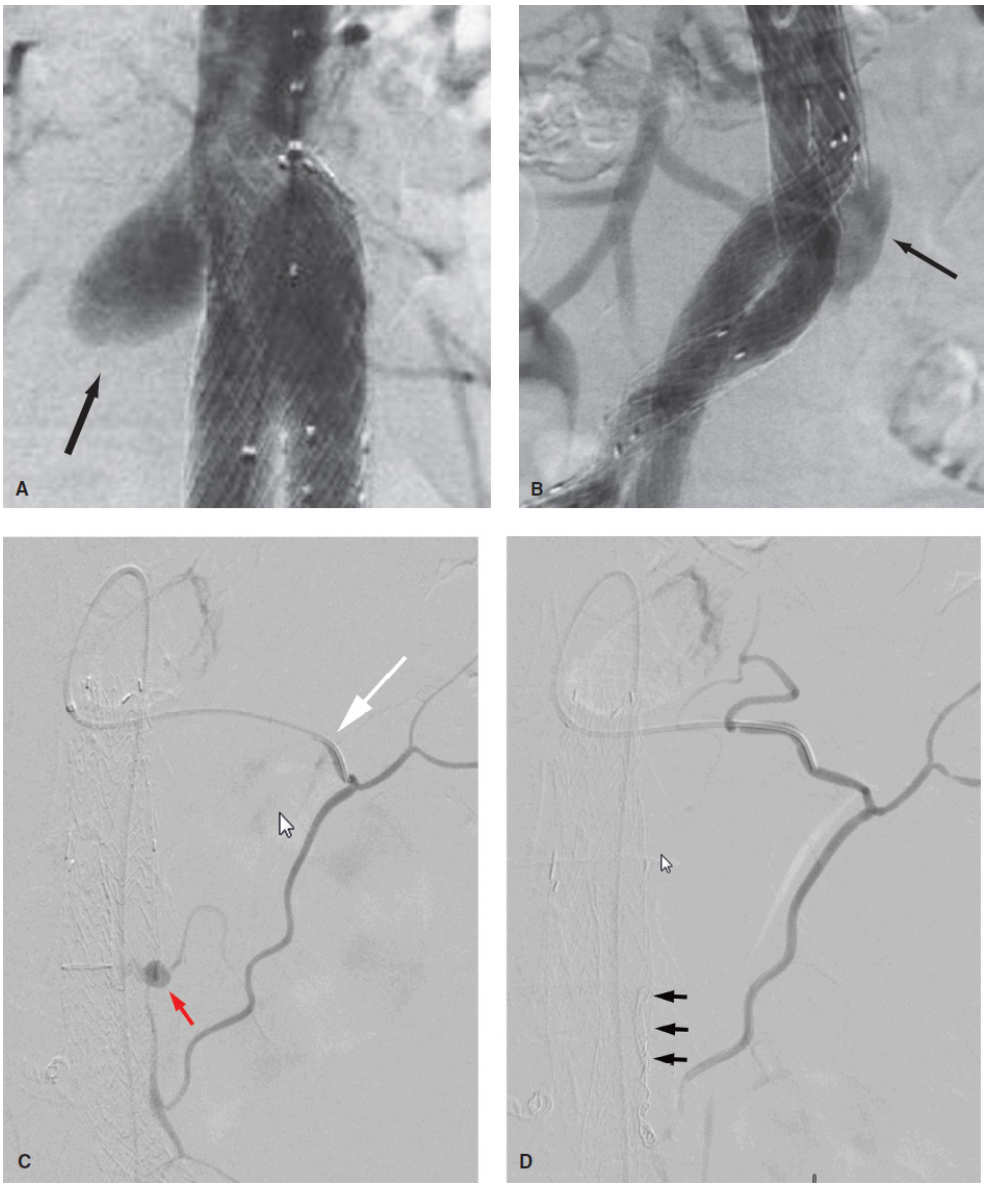


Figure 94.8 Type 1 to 4 Endoleaks. Type I and III represent the most dangerous forms of endoleaks, and represent what is essentially an unrepaired aneurysm. **A:** Type I leaks originate at either the proximal (Ia) or distal (Ib) attachment sites. Note the large blush of contrast outside of the graft lumen at the proximal fixation site, demonstrating a type Ia endoleak. **B:** Type 3 endoleaks are caused by fabric tears or problems at the graft interfaces of the modular devices. Note the contrast blush outside of the lumen of the graft at the modular interface. Type II endoleaks generally have a more benign natural history, but can cause aneurysmal growth and rupture. **C:** Demonstrates an inferior mesenteric arteriogram from a catheter (*white arrow*) in the meandering mesenteric artery. Filling of the aneurysm sac through a patent inferior mesenteric artery (*red arrow*) is evident. **D:** Demonstrates successful embolization of the IMA with coils demonstrated by *black arrows*. Note no further filling of the aneurysm sac.

The presence of significant comorbidities and advanced age favors the endovascular approach. Chronic renal insufficiency is not an absolute contraindication to endovascular repair as the procedure can be performed without contrast by using intravascular ultrasound (IVUS) or CO_2 as the contrast agent. Of note, both open and endovascular repair are associated with a long-term decrement in renal function.[91] In general, the endovascular approach may allow a subset of patients not considered suitable candidates for an open operation to have their aneurysms repaired. The EVAR Trial 2 randomized patients not fit for open repair to expectant management or endovascular repair and demonstrated no difference in aneurysm-related mortality, all-cause mortality, or quality of life.[92] Notably, the patients were truly "high risk" with a perioperative mortality rate of 9% and a 4-year mortality rate of almost 40%.

The known device-related complications and the uncertainty about the long-term outcome after endovascular repair mandate indefinite surveillance, although the intervals and type of imaging for surveillance remain controversial. Patients must agree to comply with the prescribed protocol and their ability to fulfill these expectations should be factored into the specific choice of procedure. It is important to note that although the incidence of complications declines with the number of negative postoperative CT scans, new endoleaks have been discovered many years after device implantation. Similarly, it is imperative that all surgeons that offer EVAR provide conscientious, long-term follow-up.

Despite the various advantages and disadvantages of the approaches outlined above, patients and providers seem to prefer the endovascular approach and these preferences appear to be one of the driving forces for the widespread application of the technique. Indeed, it is uncommon for patients that are candidates for either approach to elect open repair. Notably, Williamson et al. reported that 18% of all patients undergoing open repair would not undergo the procedure again.[93] The potential to perform the endovascular repair completely percutaneously (i.e., no femoral artery exposure) clearly adds to the appeal of the approach.

The proverbial "bottom line" for the open versus endovascular debate remains somewhat unresolved, but the discussion is merely academic at this point. EVAR, when anatomically possible, has essentially become the

standard of care in most practices despite all the aforementioned data suggesting equivocal results. The trend toward dominance of EVAR over open repair has increased to a point where many vascular training programs are having difficulty with finding enough open aneurysm cases to sufficiently educate their trainees.[94]

OPERATIVE REPAIR

Preoperative Evaluation

The preoperative evaluation of patients undergoing elective AAA repair is similar to that of patients undergoing any major general or vascular surgical procedure. Patients undergoing endovascular repair should likely undergo the same preoperative work-up despite the perception that associated perioperative stresses are less. All patients should receive a complete history and a physical examination, electrocardiogram, and a chest radiograph. Routine preoperative laboratory studies should be obtained and the appropriate quantity of blood products cross-matched. A thorough peripheral pulse examination should be included in the physical examination and validated with formal ankle–brachial indices. In addition, patients should be started on an aspirin and a statin (HMG Co-A reductase inhibitors). The perioperative use of beta-blockers in patients undergoing noncardiac surgery has been controversial. The most updated recommendations from the ACC/AHA in 2014 state that beta-blockers should be continued in patients who have been on these agents chronically.[95] The initiation of the beta-blockers should be *considered* in those patients who have ≥three cardiac risk factors (diabetes, heart failure, CAD, renal insufficiency, prior stroke), but these agents should *not* be started on the day of surgery as this is associated with increased adverse events. Beta-blockers have uncertain benefit in those without significant cardiac risk factors.[95]

All active medical problems should be controlled as well as possible before elective aneurysm repair. However, extensive diagnostic testing is probably unnecessary. Routine pulmonary function tests and measurement of arterial blood gases are not indicated, although they may be beneficial in selected patients with advanced COPD. The presence of COPD often

complicates postoperative ventilator management, but it is unusual for a patient's pulmonary disease to be sufficiently severe to preclude operation.[96]

The appropriate cardiac work-up before AAA repair is evolving and is somewhat institution dependent. This controversy has been further complicated by the publication of the CARP Trial that examined the role of coronary artery revascularization before major vascular surgery among patients with significant coronary artery disease.[97] Notably, the study reported that preoperative coronary artery revascularization did not reduce the incidence of either perioperative myocardial infarction or long-term mortality. It is important to emphasize that the overall objective of the preoperative cardiac work-up is to optimize the cardiovascular system and thereby reduce both the perioperative and long-term risk of myocardial infarction and death. Admittedly, the prevalence of coronary artery disease among patients undergoing AAA repair is quite high. Hertzer et al., in a landmark publication, reported that 25% of 1,000 patients undergoing evaluation for peripheral vascular surgery (cerebral vascular occlusive disease, lower extremity arterial occlusive disease, AAA) had severe, surgically correctable lesions detected during cardiac catheterization; 6% had severe, uncorrectable disease, and only 8% had no evidence of disease. Interestingly, the incidence of surgically correctable disease was highest among patients undergoing evaluation for AAA.[98] The ACC/AHA Guidelines have simplified the preoperative evaluation before elective vascular procedures for patients with risk factors for stable coronary disease.[95] Briefly, a patient's estimated perioperative risk of major adverse cardiac event should be calculated using combined clinical and surgical risk factors. The American College of Surgeons NSQIP risk calculator (https://riskcalculator.facs.org/RiskCalculator/) can be used. If elevated risk, the patient's functional capacity then determines the need for additional cardiac testing. More specifically, patients who can generate at least four metabolic equivalents (METS) can proceed without additional testing. Those patients with poor (<4 METs) or unknown functional capacity should undergo pharmacologic stress testing with coronary catheterization/revascularization as indicated before surgery. Notably, there is insufficient evidence to support a reduced cardiac work-up for patients undergoing endovascular repair.[99] It is important to emphasize that although

the cardiac risk of endovascular repair may be less, the subset of patients undergoing the procedure are often older and sicker.

Open Repair of Intact Abdominal Aortic Aneurysms

Technique

A significant amount of preparation is required in the operating room before making the incision. Adjunctive epidural anesthesia has been associated with improved survival along with reduced immediate postoperative events although the direct explanatory mechanism for this finding remains unclear.[100] Adequate intravenous access should be established to facilitate resuscitation. Central venous access is usually obtained although not necessary. Electrocardiographic leads, an arterial catheter, and a Foley catheter should be placed for continuous monitoring of the electrocardiogram, arterial pressure, and urine output, respectively. In addition, a nasogastric tube should be inserted. A Swan–Ganz pulmonary artery catheter or a transesophageal echocardiogram probe should be inserted in patients with heart failure. Peripheral arterial pulses should be interrogated with either palpation or continuous-wave Doppler ultrasound and marked to facilitate confirmation after restoration of lower extremity perfusion. Strategies to maintain core body temperature should be initiated. Bush et al. reported that hypothermia (<34.5°C) during AAA repair was associated with multiple physiologic derangements and adverse outcomes.[101] Of note, this does not pertain to thoracoabdominal aortic surgery where hypothermia has shown some benefits in spinal cord ischemia reduction.[102]

Use of an intraoperative autologous transfusion device should be considered. However, a meta-analysis reported that there is insufficient evidence to recommend its use during vascular surgery including aortic surgery.[103] These devices should likely be used when a significant amount of blood loss is anticipated, such as during suprarenal or thoracoabdominal aortic aneurysm repairs. Furthermore, they can be helpful in patients who object to blood transfusions on religious principles. A first-generation cephalosporin or vancomycin should be administered prior to the incision.

AAAs may be repaired through several different incisions or approaches including midline, retroperitoneal, or transverse/bilateral subcostal. The incisions or approaches must be viewed as complementary since neither is perfect for every clinical scenario. Indeed, surgeons should be familiar with the various approaches and select the optimal one for the clinical setting. The determinants of the incision include the cephalad/caudal extent of the aneurysm, body habitus, presence of prior abdominal incisions, presence of abdominal wall stomas, comorbidities, additional intraoperative pathology, inflammatory aneurysms, renal anomalies, requirements for concomitant procedures, urgency of aortic control, and surgeon preference. The midline approach is preferable for patients with ruptured infrarenal AAAs because aortic control at the level of the diaphragm can be obtained rapidly. The bilateral subcostal approach provides the best exposure and is the incision of choice for obese patients, those with extensive iliac artery aneurysms, those patients requiring concomitant renal artery revascularization, and those patients with juxtarenal aneurysms that require suprarenal aortic control. The retroperitoneal approach is optimal for patients with multiple previous abdominal incisions ("hostile abdomen"), abdominal wall stomas, suprarenal aneurysms, inflammatory aneurysms, and horseshoe kidneys. However, the retroperitoneal approach provides limited exposure to the right renal artery and right iliac vessels. It was previously contended that the retroperitoneal approach posed less of a physiologic insult than the transperitoneal approach and, therefore, was ideal for patients with advanced pulmonary or cardiac disease. However, this has not been supported by a prospective, randomized trial.[104] A detailed description of the retroperitoneal approach is beyond the context of this chapter, but is available in most standard vascular surgical texts.

The sequence of steps used to repair an intact, infrarenal AAA through a transperitoneal approach can be summarized (**Fig. 94.9**). The abdomen is explored after the peritoneal cavity is entered, and both the gallbladder and colon carefully examined. The small bowel is manually retracted laterally to the right, and the duodenum is mobilized by incising the ligament of Treitz. The inferior mesenteric vein may be suture ligated at this juncture to facilitate exposure. The tissue adjacent to the inferior mesenteric vein should be palpated to rule out a large, meandering mesenteric artery. This artery is an important visceral collateral and should be preserved. The

retroperitoneum over the aorta is incised with the electrocautery, and the left renal vein is exposed. Self-retaining retractors (e.g., Bookwalter, Omni retractors) are then placed to facilitate further exposure. The small bowel is retracted laterally to the right with the aid of malleable self-retaining retractors. The transverse colon and superior abdominal wall are retracted cephalad while the lower abdominal wall is further retracted caudal. The aorta immediately inferior to the renal arteries is exposed and both renal arteries visualized. The infrarenal aorta at this location is dissected to facilitate placement of an aortic clamp. It is important to identify the course of the renal vein and any venous anomalies on the preoperative CT scan to prevent inadvertently injuring these structures at this stage of the procedure. In the presence of a retroaortic renal vein or circumaortic collar, the aortic neck should not be dissected circumferentially and vascular control should be obtained with a vertical clamp. The retroperitoneum over the aorta is then incised further caudally and the incision extended along the course of the right common iliac artery. The extent of the caudal dissection depends on the anatomic configuration of the aneurysm. If the aneurysm extends to the aortic bifurcation, it is sufficient to dissect only the common iliac arteries provided a suitable site for clamp application is identified. If the aneurysm extends to the distal common iliac arteries, both the internal and external iliac vessels should be dissected free. This may be facilitated on the left side by mobilizing the sigmoid colon along its peritoneal reflection and reflecting it medially. The inferior mesenteric artery is then dissected free and vascular control obtained with a vessel loop. Patients are administered 100 units/kg of intravenous heparin, and the activated clotting time is confirmed to be twice the baseline value. Supplemental doses of heparin are administered throughout the procedure as dictated by the activated clotting time.

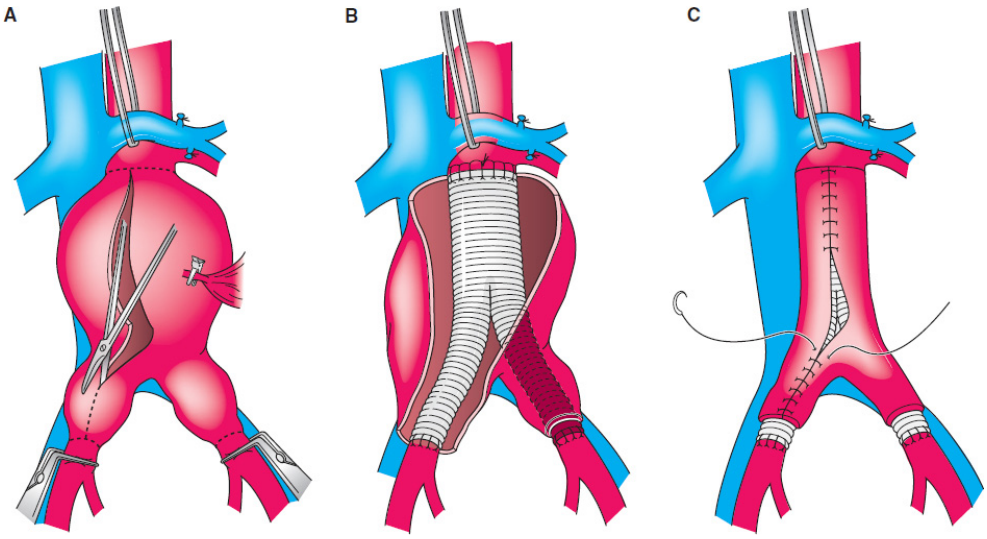


Figure 94.9 Steps involved in the standard repair of an infrarenal abdominal aortic aneurysm extending into the proximal common iliac arteries. **A:** The proximal duodenum is mobilized and the retroperitoneum overlying the aorta incised. The infrarenal aorta immediately below the renal vein is dissected. The iliac bifurcations are exposed, and vascular clamps are applied to the infrarenal aorta and distal common iliac arteries after adequate heparinization. A longitudinal arteriotomy is extended from the infrarenal aorta onto the right common iliac artery. **B:** Back bleeding from the lumbar arteries is controlled with "figure-of-eight" sutures. The proximal anastomosis is performed in an end-to-end configuration below the renal arteries. The distal anastomoses are performed at the common iliac bifurcation beyond the aneurysmal segments. The left limb of the graft is tunneled through the intact left common iliac aneurysm shell. **C:** The residual aneurysm shell is closed over the prosthetic graft, and the retroperitoneum is reapproximated to prevent erosion of the graft into the overlying bowel.

The appropriately sized prosthetic graft is selected. The graft diameter is sized according to the infrarenal aortic neck by visual inspection or with the calibrated graft rulers (i.e., "sizers"). The general "rule of thumb" is that the smaller graft should be selected when the aorta is between two graft sizes because the aorta always appears smaller after it is transected and redundant graft material at the proximal anastomosis is more difficult to correct than the opposite problem. A variety of vascular prostheses are available. Despite the contentions of the various manufacturers, there is no clear advantage for an individual graft and the choice should be determined by surgeon preference as dictated by ease of handling, cost, and availability.

The distal vascular clamps are applied to the external, internal, or common iliac vessels as indicated. Occasionally, the iliac vessels are so

calcified that they cannot be safely occluded with a clamp. Vascular control may be obtained intraluminally with the use of a balloon thromboembolectomy catheter after the aneurysm has been incised. The configuration of the aortic reconstruction (aortoaortic, aortoiliac, aortofemoral) depends on the extent of aneurysmal involvement and the degree of occlusive disease. Despite the fact that a patient may be a candidate for an aortic tube graft, it is often easier to perform an aorto-bi-iliac graft because the terminal aorta is often very calcified. Aorto-bi-femoral bypass grafts should be reserved for the small subset of patients who truly have concomitant aneurysms and severe occlusive disease since the risks of wound complications and graft infections are greater.

The proximal aortic clamp is then applied after the distal clamps. The clamp is applied immediately below the renal arteries to facilitate an anastomosis to the proximal infrarenal aorta. The length of the infrarenal aorta should be sufficient to permit a safe anastomosis. However, a long infrarenal cuff should be avoided because it may become aneurysmal over time. Either a vertical or horizontal aortic clamp may be used. The aorta is then incised longitudinally, and the incision is extended to the distal aorta and into the iliac arteries if the distal anastomosis will be to the iliac vessels. Attempts should be made to preserve the autonomic nerves overlying the distal aorta and proximal left common iliac artery in men. This can usually be achieved by incising the left common iliac artery transversely beyond the aneurysmal portion and tunneling the limb of the graft through the residual shell. The intraluminal thrombus and debris are removed from within the aorta, and all back bleeding from the lumbar arteries is controlled with suture ligatures. The atheromatous debris within the aorta has been reported to be culture positive in approximately 25% of cases although this has not been associated with long-term graft infections.[105] The infrarenal aorta at the level of the planned proximal anastomosis may be completely transected, or the back wall may be left intact. Completely transecting the aorta makes the proximal anastomoses slightly easier although leaving the back wall intact reinforces the anastomosis and provides the equivalent of an autogenous pledget. The proximal anastomosis is performed in an end–end configuration with a running 3-0 Prolene suture. All leaks in the suture line are repaired with Prolene sutures and felt pledgets as necessary. The distal anastomosis or anastomoses are performed to the aortic bifurcation, common iliac

arteries, or iliac bifurcation as dictated by the anatomy of the aneurysm. A 3-0 Prolene suture is used for anastomoses at the aortic bifurcation, and a similar 4-0 suture is used for the common iliac arteries.

All anastomoses are flushed to remove any intraluminal debris before flow is restored. Blood flow is restored to the pelvis and lower extremities in sequence. Attempts should be made to flush initially into the internal iliac circulation to prevent embolization to the lower extremities. This can be facilitated by manually compressing the common femoral arteries for tube graft configurations. The lower torso should be reperfused gradually (i.e., one extremity at a time) to prevent hypotension. It is imperative that the patient is resuscitated prior to reperfusion and it is frequently necessary to delay this process to allow the anesthesiologists, time to achieve this objective. Reperfusion of the ischemic tissue causes the release of acid, potassium, and a variety of inflammatory mediators and reactive oxygen species into the systemic circulation, all of which are potentially detrimental.

The inferior mesenteric artery may be reimplanted into either the body of the graft or the iliac limbs if it is patent. Alternatively, if there is robust back-bleeding from the inferior mesenteric artery, it is typically ligated. The colon and lower extremities should be interrogated with the Doppler ultrasound after reperfusion, and the heparin reversed with intravenous protamine sulfate after confirmation of adequate lower extremity signals. The protamine dose is estimated based on the effectiveness of protamine (1 mg of protamine/100 units of heparin). The protamine should be administered slowly to prevent any untoward hemodynamic events. The aneurysm sac and the overlying retroperitoneum are both closed with absorbable suture to provide a biologic tissue layer between the graft and the viscera. The retractors are then removed, the viscera are returned to their anatomic positions after inspecting their viability, and the abdominal wall fascia is closed with standard technique.

Patients are transferred directly from the operating room to the intensive care unit. Most of the patients are extubated in the operating room or shortly after arrival to the intensive care unit. The intensive care unit length of stay is usually 1 to 2 days, and the median total length of stay is 8 days.[40] Patients are encouraged to get out of bed and begin ambulating in the early postoperative period (i.e., 24 to 48 hours). Nasogastric decompression is continued until bowel function returns. Oral feedings are initiated after

removal of the nasogastric tube and advanced as tolerated. Patients are discharged when they are ambulatory, can tolerate a regular diet, have normal bowel function, and are sufficiently able to care for themselves. A subset of people requires transfer to rehabilitation or extended care facility. Patients are usually seen in the clinic 2 weeks after discharge and then at 6 months thereafter. Additional clinic appointments may be necessary as dictated by any ongoing postoperative problems. Furthermore, patients are discouraged from lifting heavy objects for the first 3 to 6 months to reduce the incidence of incisional hernias.

Complications and Outcome

Open repair of intact AAAs is associated with significant mortality and morbidity. The attendant mortality rates have been discussed extensively in the preceding sections. Briefly, the contemporary mortality rate across the country has consistently been 3% to 5%.[106,107] The overall morbidity rate remains about 30% in patients undergoing repair of intact AAAs across the United States.

Intraoperative complications can result from injury to the intra-abdominal structures during dissection although these technical complications are not specific to the aneurysm repair. The small bowel, colon, ureter, and major venous structures (inferior vena cava, iliac veins, left renal vein) are particularly susceptible. Iatrogenic bowel injury at the time of AAA repair is particularly problematic due to the potential to infect the prosthetic graft. If the colon is injured before the aneurysm repair, the defect in the colon should be fixed and the aneurysm repair should be aborted. If the small bowel is injured before the aneurysm repair, the same course should likely be followed although this decision requires a modicum of clinical judgment. The infectious concerns must be balanced by the fact that the small bowel contents are assumed sterile, a second procedure will be required to repair the aneurysm, and the small risk of aneurysm rupture during the intervening delay. Injury to the bowel during or after implantation of the aortic graft should be treated with repair of the defect, extensive irrigation, and prolonged antibiotics. Admittedly, these approaches are very conservative and it is noteworthy that clinical series have attested to the safety of simultaneous aortic and gastrointestinal/urologic procedures.[108] The ureter is

susceptible to injury at the point where it crosses over the iliac bifurcation. Injury can be avoided by a heightened awareness of this anatomic location and dissection in the tissue plane immediately on top of the common iliac vessels. Inadvertent venous injury can be associated with significant bleeding. This can usually be controlled by direct pressure using sponge sticks and suture repair. The left renal vein may be transected if necessary. It should be transected near its juncture with the vena cava, and the gonadal, adrenal, and lumbar branches should be preserved to maintain venous outflow from the kidney. Interestingly, division of the left renal vein does not appear to affect renal function after AAA repair.[109,136] Transecting the common iliac artery or infrarenal aorta may facilitate exposure of the common iliac or retroaortic renal veins, respectively.

Excessive intraoperative bleeding may be encountered occasionally. Patients with significant bleeding and platelet counts below 50,000/mL should receive a platelet transfusion, and it should be considered for coagulopathic bleeding and counts below 100,000/mL or for those on preoperative clopidogrel or other equivalent antiplatelet medications. Transfusions of fresh frozen plasma are indicated for both patients with either significant bleeding in conjunction with prolonged coagulation studies (>1.5 times control value) and those with coagulopathic bleeding.

Ischemia of the lower extremities has been reported to occur approximately 2% of the time after open repair.[110] The causes are multiple and include distal embolization, thrombosis, clamp injury, and technical errors. The lumen of the aneurysm is frequently filled with both thrombus and atheromatous debris that may serve as a source for both macro- and microembolization. Thrombosis may result from inadequate heparinization, hypercoagulable conditions, or poor arterial runoff. Further intervention is mandatory if the lower extremities are found to be ischemic. Anastomotic defects should be corrected. This may simply require dissembling and redoing the anastomosis, but often requires placing the anastomosis further distal on the outflow artery. If no problems are identified at the distal anastomosis, the femoral vessels should be explored and an intraluminal thrombus removed with a balloon embolectomy catheter. A transverse arteriotomy may be created in the common femoral artery if it is anticipated that only a thrombectomy will be required; a longitudinal incision should be created if a bypass (inflow or outflow) procedure is anticipated. A bypass

from the aortic graft to the femoral vessels is required if adequate inflow cannot be restored with thrombectomy alone. The popliteal artery below the knee should be explored and a thrombectomy performed if the extremity is still ischemic. This may be facilitated by creating a longitudinal arteriotomy on the below-knee popliteal artery that extends to the tibioperoneal trunk. This allows the passage of the balloon embolectomy catheter into all three tibial vessels under direct vision. A below-knee popliteal or tibial artery bypass is required if adequate perfusion to the distal extremity is not restored after patch closure of the popliteal arteriotomy. Predictably, a complex lower extremity revascularization in conjunction with an aortic reconstruction is associated with a significant degree of morbidity and dramatically increases the mortality rate.[110]

Many of the systemic complications that follow open aneurysm repair are not surprising, given the magnitude of the operation and the age/comorbidities of the patients. Cardiac complications (ischemia, infarction, arrhythmias, congestive heart failure) occur in up to 25%[111] and are the leading cause of death after open aneurysm repair in many series. Pulmonary complications (pneumonia, ventilator dependence >48 hours, acute respiratory distress syndrome) are also quite common and approximately 10% of the patients require prolonged ventilation.[111] Deterioration of renal function, defined by an increase in serum creatinine or blood urea nitrogen, occurs in approximately 5% of cases although acute renal failure requiring dialysis is rare (i.e., <1%).[111]

Ischemic colitis has been reported to occur in approximately 4% of cases after open aneurysm repair.[112] The reported incidence may vary, however, depending on the diagnostic modality (routine sigmoidoscopy vs. selective sigmoidoscopy) and is dramatically increased after ruptured aneurysm repair. Indeed, the incidence of colonic ischemia after ruptured aneurysm repair in patients undergoing routine colonoscopy is approximately 25% to 40%.[113,114] Multivariable analysis of patients undergoing both open and endovascular repair demonstrated that the duration of the procedure and preoperative renal insufficiency were also predictors of colon ischemia.[112] The sigmoid colon is affected most frequently and is usually due to inadequate resuscitation, disruption of collaterals, and/or failure to revascularize a hemodynamically significant inferior mesenteric artery. Patients usually present with bloody diarrhea in the early postoperative

period. However, the diagnosis should be considered in the absence of bloody diarrhea in patients with thrombocytopenia, multiple-organ dysfunction, increasing abdominal pain/peritonitis, and generalized "failure to thrive." The diagnosis may be confirmed by endoscopy. Treatment depends on the endoscopic findings and clinical setting. The endoscopic findings range from mucosal ischemia to transmural necrosis. In the absence of peritonitis, patients with mucosal ischemia alone can be treated with bowel rest, broad-spectrum antibiotics, total parenteral nutrition, and serial endoscopic examinations. Many of these lesions resolve spontaneously without long-term sequelae although colonic strictures may develop in a subset of patients. Patients with transmural colonic necrosis should undergo laparotomy with resection of the involved segment, a proximal diverting colostomy, and a distal Hartmann pouch. After laparotomy, they should be maintained on broad-spectrum antibiotics. The reported mortality rate in patients with transmural necrosis may range up to 85%.[112]

Several other gastrointestinal complications are common after standard infrarenal AAA repair.[115] A postoperative ileus develops in essentially all patients with bowel function usually returning within 3 to 5 days. Nasogastric decompression should be continued, narcotics minimized, electrolytes normalized, and ambulation encouraged. Either calculous or acalculous cholecystitis may develop after aneurysm repair. The mortality rates reported historically for postoperative cholecystitis were significant and served as the catalyst for simultaneous cholecystectomy and aneurysm repair. Although this approach has been found to be safe and not associated with an increased risk for graft infections, it is usually reserved for patients with small stones or evidence of chronic cholecystitis. Pancreatitis may develop after AAA repair although the incidence is surprisingly low in light of the obligatory manipulation of the pancreas during repair.

Sexual dysfunction is quite common after open AAA repair ranging from 7% to 80% depending on the series.[116] The responsible mechanisms include interruption of the pelvic perfusion and injury to the autonomic nerves that overlie the distal aorta/proximal common iliac arteries. Injury to these autonomic nerves disrupts the internal sphincter mechanism of the bladder and results in retrograde ejaculation. Care should be used during aneurysm repair to maintain pelvic perfusion and avoid nerve injury to prevent these

untoward complications. It is imperative that these potential complications be discussed with patients preoperatively.

Paraplegia after open infrarenal AAA repair occurs with an incidence of 0.25%.[117] The potential mechanisms for this devastating complication include embolization, thrombosis of the spinal artery, and disruption of the spinal blood supply. Paraplegia after aneurysm repair is usually an irreversible injury. Maintaining adequate antegrade pelvic perfusion through the internal iliac arteries may minimize this complication.

The long-term outcome after open repair is generally favorable with survival rates of approximately 80% beyond 4 years.[118] Cardiovascular events account for the leading cause of death.[119] This underscores the importance of long-term medical follow-up and the AHA/ACC Guidelines for preventing myocardial infarction and death. Prosthetic aortic grafts are associated with long-term complications with a reported incidence of approximately 10% to 15% at 15 years.[120] The long-term graft-related complications include infection, aortoenteric fistula, thrombosis, and pseudoaneurysm formation. Additional aneurysms of a sufficient size to merit intervention develop in approximately 5% to 15% of patients in either the iliac vessels or the aorta above the prosthetic graft. As such, the Society for Vascular Surgery recommends that patients undergo CT of the complete aorta and iliac vessels every 5 years postoperatively to screen for additional aneurysm disease.[61]

Endovascular Repair of Intact Abdominal Aortic Aneurysms

Technique

The preoperative preparation before endovascular AAA repair is more complicated than for the open approach. The various imaging studies must be reviewed before it can be determined whether the endovascular approach is even feasible. Appropriate measurements must be taken and the necessary devices/components selected. An operative plan must be generated including specific modifications of the standard approach to overcome the patient's anatomic limitations and, thereby, extend the feasibility of the technique.

Indeed, “preoperative planning” has facetiously been identified as the most important component of a successful repair.

CT arteriography with 3D reconstructions has emerged as the optimal approach to determine feasibility of EVAR. It is important to emphasize that no imaging technique is perfect and, consequently, a certain degree of flexibility is necessary for the operative plan. Measurements obtained from the 3D CT tend to overestimate the actual renal artery–internal iliac artery length assumed by the graft when deployed in vivo.

The various devices/components should be selected using the underlying principles that the main body of the device should sit as close to the orifices of the renal arteries as possible while the iliac limbs should extend to the orifices of the internal iliac arteries. This methodology not only provides exclusion of abnormal tissue, but also extends the length of seal and fixation of the endograft, and may provide additional column strength. Furthermore, the manufacturers’ recommendations (IFU) for sizing and device selection should be followed. The endograft is sized according to the anatomic configuration of the aneurysm and adjacent arteries, and this must be performed in advance of the procedure to ensure that the appropriate devices are available. The diameter and length of the infrarenal cuff, aneurysm, and iliac vessels must be measured precisely. In addition, the distance from the lowest renal artery to the aortic bifurcation and both renal bifurcations needs to be determined. The diameter of the proximal graft is chosen to oversize the aortic cuff and iliac arteries by approximately 10% to 20%. Oversizing the graft diameter beyond that recommended has been associated with both graft migration and aneurysm reexpansion.[121] Additional devices should be ordered for each case including two iliac limbs and an aortic extension cuff to allow for any discrepancy between the preoperative plan and the actual course of the graft in vivo. Each endograft procedure and device configuration is “custom fit” for an individual patient. Furthermore, physicians typically are required to complete a training course comprised of sizing exercises and monitored deployments.

The choice of the specific endovascular device is contingent upon the anatomic constraints of the aneurysm, device-associated outcome, and surgeon preference. There are specific differences between the various grafts that lend themselves to different clinical scenarios. The specific considerations include neck diameter, neck length/angulation, renal–internal

iliac artery distance, common iliac artery diameter, and access vessel diameter. For example, a graft with suprarenal fixation may be more suitable for a shorter neck while a lower profile system (i.e., smaller outer diameter of the delivery sheath) may be most appropriate for patients with smaller access vessels (i.e., common femoral and external iliac arteries). Despite the initial concerns about compromising renal function, suprarenal fixation has been consistently shown to be safe.[122] Deployment of the various endografts is reasonably involved from a technical standpoint; thus, it is not particularly surprising that most surgeons choose to concentrate their proficiency with one or two devices. However, a working knowledge and comfort level with all devices on the market is advised given the benefits that each graft may have over the others in certain scenarios. This permits use of a graft that best meets the individual patient's needs.

The need for adjunctive procedures to facilitate the endovascular repair is usually determined by the preoperative imaging and should be factored into the overall plan. The major concerns include stenotic access vessels and the absence of a suitable common iliac artery landing zone due to aneurysm enlargement. The remedial procedures for small access vessels or significant occlusive disease include serial dilation or a retroperitoneal prosthetic iliac conduit, as previously discussed. Repeated attempts to pass the device through a diseased native artery should be avoided as it can cause vessel rupture. Aneurysm degeneration of the common iliac artery can be overcome by extending the iliac endoprosthesis into the external iliac artery. This necessitates either embolization of the ipsilateral internal iliac artery or more preferably preserving internal iliac perfusion with the use of an iliac branch device, which has a precannulated internal iliac gate for ease of use. These devices have demonstrated satisfactory midterm results and their application to preserve internal iliac flow is strongly recommended by the Society for Vascular Surgery.[61,76]

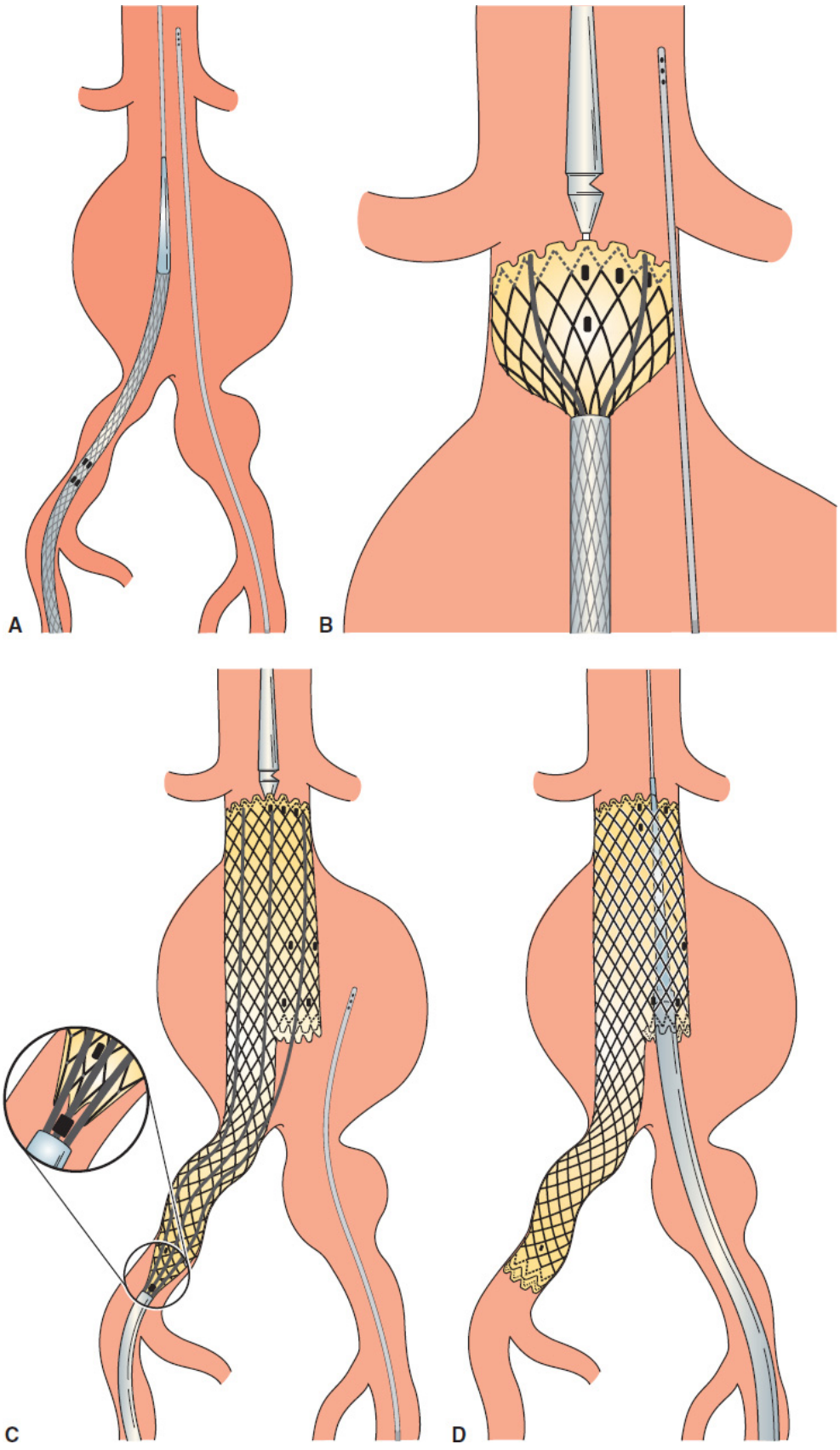
Intraoperative preparation for endovascular repair is similar to that for the open approach although there are several significant differences. The appropriate imaging equipment is mandatory. Ideally, this would entail a complete endovascular suite with a fixed fluoroscopic unit although a portable unit with the appropriate vascular software and an imaging table is adequate. General endotracheal anesthesia, local, and regional anesthesia can all be used for endovascular repair, depending on the individual patient,

the clinical scenario, the planned length/complexity of the procedure, and the comfort level of the surgeon and anesthesiologist. Indeed, the endovascular approach is well suited for these less-invasive alternatives particularly considering the feasibility of a completely percutaneous approach. For a straightforward endovascular repair, intraoperative autologous transfusion devices and a nasogastric tube are unnecessary. In the current era, it is quite rare to convert to an open repair at the time of the initial implantation. However, it should be emphasized that EVAR is a surgical procedure and most would agree that the procedure should be performed in an operating room with strict aseptic technique.

Percutaneous access to the common femoral arteries has become standard for many physicians using a "preclose" methodology that involves placing a suture-based closure system that is deployed prior to delivery of the device and closed at the conclusion of the procedure.[123] If the surgeon is uncomfortable with that approach, or the femoral artery anatomy precludes use of closure devices, an open exposure works well and can be done through transverse, longitudinal, or oblique incisions. Although the technique for implanting the various endografts is somewhat specific to the individual device, the basic steps for deploying a "generic" modular bifurcated device using an open femoral artery exposure is illustrated (**Fig. 94.10**).

Briefly, the common femoral arteries are exposed and an umbilical tape or vessel loop is wrapped circumferentially around the vessels at the level of the inguinal ligament to facilitate vascular control. Approximately 2 cm of the common femoral artery is dissected free. The common femoral artery on the side chosen to introduce the main body of the device (ipsilateral groin) is punctured using an angiographic needle and a 0.035-in standard working wire (e.g., Bentsen) is passed into the abdominal aorta using fluoroscopic guidance. A 5-Fr introducer sheath is advanced over the guidewire using a Seldinger technique and vessel entry is confirmed by manual contrast injection. The working wire is further advanced into the thoracic aorta and exchanged for a longer 0.035-in stiffened guidewire (e.g., Lunderquist, Meier) using a catheter. Attention is then directed to the contralateral groin and in a similar manner a guidewire is advanced into the aorta and an appropriate-sized introducer sheath is inserted over the guidewire into the body of the aneurysm at approximately the L3 vertebral space. An angiographic catheter is advanced to the L1 vertebral body through the

contralateral sheath and the catheter connected to the power injector. The patient is then anticoagulated with heparin using a standard protocol (100 units/kg) and therapeutic anticoagulation (ACT twice baseline) is maintained throughout the procedure. The main body delivery catheter is introduced over the stiff wire through the ipsilateral groin and the upper limit of the main body positioned between the L1–L2 vertebral bodies. Devices that do not have an integral sheath as part of their delivery system require an 18- to 22-Fr sheath to be inserted prior to introduction of the actual delivery catheter. Radiopaque markers on the graft facilitate the positioning and orientation of the main body.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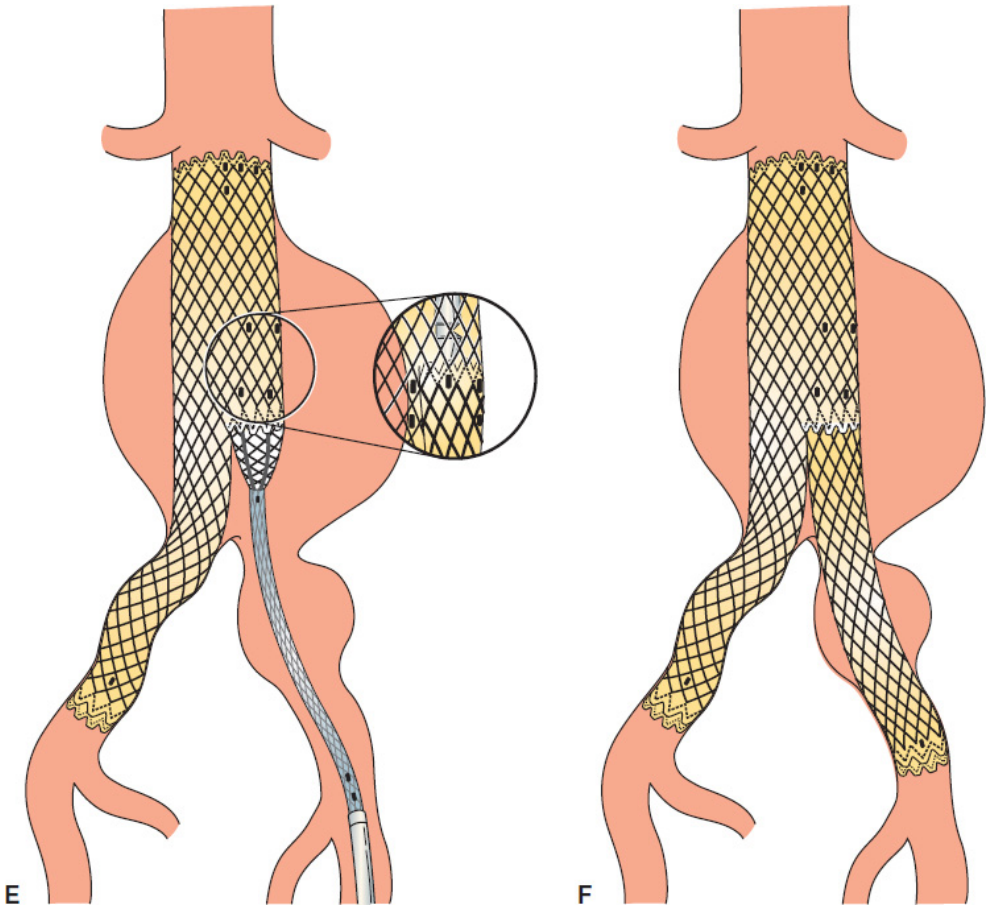

Figure 94.10 General steps involved in the endovascular repair of an abdominal aortic aneurysm. The common femoral arteries are exposed bilaterally (alternatively, and more commonly, percutaneous access is achieved and "preclose" sutures are placed) and stiff wires are introduced into the thoracic aorta under fluoroscopic guidance. An appropriate-sized large diameter introducer sheath is inserted over the stiff wire into the body of the aneurysm at approximately the L3 vertebral space on the side contralateral to the one chosen for the main device. If the device is contained within its own deployment system, a sheath may not be required. **A:** The main body delivery catheter is introduced over the stiff wire through the ipsilateral groin and the upper limit of the main body positioned between the L1 and L2 vertebral bodies. An aortogram is obtained and the location of the renal arteries identified. The location of the renal arteries is marked on the imaging screen and the position of the main body finely adjusted. **B, C:** The main body is deployed exposing the opening of the contralateral docking limb. The contralateral docking limb is cannulated and a stiff wire advanced into the thoracic aorta. After confirming successful cannulation of the docking limb, deployment of the contralateral limb is deployed after marking the origin of the hypogastric artery. The hypogastric origin can be identified by using intravascular ultrasound or by obtaining a retrograde arteriogram through the sheath in the opposite oblique projection to identify the orifice of the internal iliac artery. **D–F:** The location of the orifice is marked on the imaging screen; the contralateral limb is then introduced over the stiff wire, appropriately positioned, and deployed. A compliant aortic occlusion

balloon is advanced over the stiff wire and inflated in the region of the infrarenal neck to mold the proximal and distal attachment sites, and is used to ensure the overlapping devices are well sealed.

As imaging has improved, multiple techniques allow for determining the proper location of endograft deployment. This may involve the use of IVUS or 3D overlay imaging, both of which can decrease the use of contrast and the radiation exposure to both the patient and practitioner. In the absence of these advanced imaging techniques, an aortogram can be obtained after delivery of the endograft to the location of the renal arteries and the renal arteries marked for device deployment. A 5- to 10-degree cranial angulation is usually sufficient to account for the anterior angulation of the infrarenal neck caused by the natural lumbar lordosis of the spine and the posterior bulging of the aneurysm sac. However, the optimal angulation or orientation should be estimated based upon the preoperative 3D CT images. The location of the renal arteries is marked on the imaging screen and the position of the main body adjusted. The main body is now deployed exposing the opening of the contralateral docking limb ("gate"). Using a combination of a hydrophilic wire and a curved catheter, the contralateral docking limb is cannulated. Various maneuvers including different fluoroscopic projections, different-shaped catheters, and proper orientation of the contralateral docking limb prior to deployment of the main body device can facilitate this step. It is imperative to confirm that the cannulating guidewire is actually within the body of the main endograft. There are a number of methods to confirm entry into the main aortic graft. The most definitive way is to use IVUS. A common method is to place a reverse curve catheter, such as a SOS, or a pigtail catheter into the main body at the level of the neck and then spin the catheter. If the catheter spins freely, this confirms that it is inside the endograft and not trapped between the aortic wall and endograft. Another option is to insert a compliant aortic occlusion balloon (which will be used later in the procedure) partially into the gate and *gently* inflate giving the balloon an upside-down mushroom appearance. Alternatively, an arteriogram can be performed using a catheter within the main body, confirming that dye fills the aortic graft, but not the aneurysm on initial injection. Once the wire is confirmed to be within the endograft, the contralateral wire is advanced

into the proximal descending thoracic aorta under fluoroscopic guidance and exchanged for a stiff wire using a catheter.

Next, the contralateral internal iliac artery origin must be identified in order to select the appropriate length iliac endoprosthesis. This can be accomplished with an IVUS catheter. Alternatively, retrograde angiography can be performed through the sheath in order to visualize and mark the internal iliac artery. The optimal fluoroscopic angle to visualize this artery can be variable and is best determined using preoperative 3D imaging. However, the typical angle is in the opposite obliquity about 30 degrees from the side of the vessel (i.e., right anterior oblique for the left internal iliac artery). The location of the orifice is marked on the imaging screen and a marker catheter is used to measure the distance from the contralateral docking limb to confirm the iliac device selection. The contralateral limb is then introduced over the stiff wire, appropriately positioned relative to the docking limb and the orifice of the internal iliac artery, and then deployed.

After deployment of all the devices, a compliant aortic occlusion balloon is advanced over the ipsilateral stiff wire and inflated in the region of the infrarenal neck to mold the proximal attachment sites. The aortic balloon is then withdrawn and gently expanded at the main body/iliac limb overlap zone and both distal iliac artery fixation sites. A completion arteriogram is then obtained using an angiographic catheter placed through one of the introducer sheaths (**Fig. 94.11**). The arteriogram should adequately evaluate the proximal/distal fixation sites, the graft/graft overlap zones, and the orifices of the renal/internal iliac arteries. In addition, it should include delayed imaging to help identify any endoleaks. Problems identified on the completion study should be corrected, if possible. The potential remedial procedures include balloon dilation or aortic/iliac extension cuffs.

Figure 94.11 Completion arteriogram after an endovascular aneurysm repair is shown. The *arrow* marks the caudal extent of the stent graft. Note that the iliac limbs have been intentionally crossed to facilitate the cannulation of the contralateral gate.

All sheaths, catheters, and wires are removed after the completion of the arteriogram if using an open femoral approach and the arteriotomy is closed using purse-string suture placed at the time of the initial exposure or primary suture repair. In the case of percutaneous approach, the wire is left in during initial Perclose use to allow placement of additional closure devices as necessary. Doppler signals should be confirmed in the pedal vessels prior to removal of the wire and completion of arterial closure. Heparin is then reversed with protamine (1 mg protamine/100 units of heparin). The groin wounds are closed in layers with absorbable suture and the final skin later is closed with a subcuticular technique.

The immediate postoperative course is typically uneventful. Patients are transferred to the general care ward after recovery in the postanesthesia care unit. Patients are started on an appropriate diet the evening of the procedure and encouraged to get out of bed. However, patients should be kept supine for 4 to 6 hours after the operation when a percutaneous technique is used to ensure successful hemostasis. Most infrarenal EVAR patients are discharged home on postoperative day 1, and then seen in the outpatient clinic at 1 month with an abdominal/pelvic CT scan. It is important to note that mild fever and the finding of air around the graft on CT are common occurrences immediately after endograft repair and have not been associated with graft infection.[124]

9 It is imperative that patients are followed-up long term given the uncertainty associated with the endovascular repair and the need for remedial procedures. A variety of protocols and imaging techniques have been described. The Society for Vascular Surgery recommends an abdominal/pelvic CT scan at 1 month. In the absence of endoleak or sac enlargement, contrasted CT scan or color duplex ultrasound can be repeated in 12 months.[61] If there is no sac enlargement or endoleak at that point, the patient can be followed with annual color duplex ultrasound, or CT scan if ultrasound expertise is not available. More frequent imaging is necessary if the aneurysm continues to grow or there is evidence of an endoleak. A multicenter trial demonstrated that the absence of an endoleak at 1 and 12 months predicted favorable long-term outcome.[125] Of note, color duplex ultrasound has been shown to be very effective in detecting endoleak and minimizing patient radiation and contrast exposure, but this technique is predicated on comfort level and training of the local vascular laboratory.[126,127] Surveillance CT scans should include noncontrast and biphasic contrast views with delayed images to help identify any late endoleaks.[128]

Complications and Outcome

The mortality rates in randomized trials and national series is less than 2%,[85,86] the perioperative complication rate is <25%,[43] the rupture risk is approximately 1%/yr,[81] and the incidence of remedial procedures approximately 10%/yr.[129] Many of the same complications that can occur

after open repair can occur after endovascular repair. However, the relative incidence of the various complications is significantly different, and several complications inherent to EVAR have been identified.

A variety of potential complications may arise during insertion of the delivery catheter or introducer sheath. Indeed, access problems secondary to iliac stenosis and/or tortuosity are the most common procedure-related complication. The outer diameters of the delivery sheaths are device dependent, but can range up to 24 Fr. Excessive force during insertion of these large sheaths or delivery catheters can result in serious injury and perforation/disruption of the vessels. Predictably, this can lead to significant hemorrhage and hemodynamic changes. The diagnosis can be confirmed by arteriography and the bleeding controlled intraluminally using the device sheath or a balloon catheter. A variety of endovascular salvage techniques are possible in this setting including deployment of either the main device or a covered stent across the disrupted artery. Most major arterial disruptions can be managed with endovascular techniques, but in the event they are unsuccessful, a retroperitoneal incision with direct control of the iliac arteries must be performed expeditiously.

Safe conduct of an EVAR is predicated by sufficient knowledge of the various salvage techniques, the necessary catheter and guidewire skills to execute these techniques, and a complement of ancillary equipment. However, the adage that “prevention is better than the cure” holds true and endovascular surgeons should maintain a low threshold for constructing a retroperitoneal iliac conduit prophylactically. Besides rupture, the access vessels can be dissected from misdirection or excessive force during sheath or device insertion. If non–flow limiting, no intervention is necessary; but, if a flow limitation is present, the dissected segment typically requires stenting. Prior to doing so, confirmation that the wire is within the true lumen is critical.

Graft deployment can be associated with mechanical problems related to the delivery system or inappropriate positioning. A host of mechanical problems have been described, and the list will likely expand with widespread application of the devices and the introduction of updated systems. Many of the mechanical problems are device specific and related to the actual sequence of events and manipulations required. Troubleshooting guidelines and specific recommendations are available from the

manufacturers. Deployment of the endovascular graft below the proximal target site along the infrarenal aorta may be corrected using an aortic extension cuff. Attempting to reposition the graft more cephalad after deployment is not recommended. Deployment of the endovascular graft across the orifices of the renal arteries can potentially be corrected by displacing the graft caudally. A guidewire can be passed over the flow divider and out the contralateral groin. The entire graft can then be retracted caudally by pulling on the wires. Alternatively, a large balloon can be inflated above the flow divider and retracted. Extreme care must be exercised during these maneuvers to prevent complete dislodgement of the proximal main body from the neck. Deployment of the graft across part of the renal orifice with subsequent renal malperfusion can be corrected by placing a "chimney" or "parallel" stent within the lumen of the renal artery. This typically requires brachial artery access in order to cannulate the target vessel. Deployment of the endograft across the lumen of one internal iliac artery is usually tolerated provided the contralateral vessel is patent and relatively free of occlusive disease. With coverage of a single hypogastric artery, severe complications are rare. Occlusion of both internal iliac arteries or occlusion of one vessel in the presence of contralateral disease may render the pelvis ischemic. In the event of unintentional hypogastric artery coverage, the iliac limb can be pushed cephalad using a sheath and its dilator. It should be emphasized that many of these remedial procedures are not manufacturer approved and should only be attempted by experienced endovascular surgeons. Due to the advanced age of many of these patients and their attendant comorbidities, open surgical conversion should be contemplated only as a last resort after the endovascular options have been exhausted, again emphasizing the need for advanced endovascular skills.

It is relatively common to see an endoleak on the completion arteriogram. Treatment is contingent upon the specific type of leak and its associated natural history although the majority of these early endoleaks ultimately resolve. Type 1a/b (a-proximal, b-distal attachment site) and type 3 (fabric tear or modular component separation/leak) endoleaks are particularly concerning and every reasonable attempt to correct these defects should be made. The aneurysm sac is often exposed to systemic pressure in the presence of a type 1 or type 3 endoleak, and, therefore, the rupture risk likely approaches that associated with the untreated aneurysm. Both the type 1 and

3 endoleaks can potentially be corrected by repeat balloon angioplasty at the proximal/distal attachment sites or at the modular interface. If these measures are not successful, additional extension devices can be deployed if there is adequate length before the target vessel. With the exception of large proximal type 1 endoleaks, it is reasonable to manage most perioperative endoleaks expectantly since most resolve spontaneously after reversal of the anticoagulation or within the first 6 months. Indeed, even type 1a endoleaks often thrombose before the first postoperative imaging study, although patient selection, aneurysm diameter, and risk of rupture should be carefully considered before leaving the operating room with a persistent endoleak of this nature. Thus, the surgeon should be mindful that the inability to obtain a satisfactory exclusion of the aneurysm at the time of endograft implantation does not mandate a surgical conversion at the same setting. In situations where there is concern for a persistent endoleak, an earlier postoperative CT than the usual 1-month study may be advisable.

In the event that a significant type 1a endoleak persists on postoperative imaging, the potential options include remediation with branched/fenestrated endograft, aortic cuff extension with renal chimneys, application of EndoAnchors, embolization, or open surgical repair with endograft explant. Numerous nonrandomized series have reported relatively feasible and durable results with the above options.[130] Type 2 endoleaks have a relatively benign natural history and do not merit aggressive intervention unless the aneurysm continues to increase in size over time. Type 4 endoleaks are self-limiting, and do not merit treatment at all. They are identified as a diffuse contrast "blush" at the time of the completion arteriography. They represent a diagnosis of exclusion and mandate that the more worrisome type 1 endoleak be excluded.

The spectrum of immediate postoperative complications after EVAR is comparable to that outlined for after open repair and will not be repeated. However, the incidence of major, systemic complications after EVAR is quite uncommon. It is noteworthy that the incidence of both paraplegia and bowel ischemia are comparable after endovascular and open repair although the mechanisms are different and likely due to atheroembolism.[131]

The long-term complications after EVAR include endoleak, structural failure, need for remedial procedures, need for open conversion, and rupture. These ongoing risks further emphasize the importance of conscientious

lifelong surveillance. Device migration has been reported to cause type 1 endoleaks and has been associated with neck length, site of deployment below the renal arteries, and surgeon/center experience.[132] The treatment of late-occurring type 1 and 3 leaks is identical to that for those occurring earlier as previously described.[130] Type 2 endoleaks merit intervention and treatment if the aneurysm continues to increase in diameter, although the clinical scenario is an important deciding factor in these cases. Identification of the type 2 endoleak can be challenging and may require selective catheterization of the superior mesenteric or internal iliac arteries. A variety of approaches have been described to treat the type 2 endoleaks including coil embolization, laparoscopic ligation of the feeder vessels, and direct translumbar or transcaval injection of the aneurysm sac with glue or other thrombotic agents.[133]

Aneurysms that continue to increase in size after EVAR merit further intervention and may require open conversion due to their ongoing rupture risk. It should be emphasized that the goal of aneurysm repair is to prevent rupture/death from rupture and that endoleak and sac enlargement are surrogate markers of potential late failure of the therapy. Even more concerning is recent evidence that failure of sac regression has been associated with higher long-term mortality.[134] The clinical significance of an enlarging sac in the absence of a visible endoleak is controversial as long as a secure proximal and distal fixation of the endograft has been demonstrated. To confound the issue further, rupture of aneurysms without an endoleak or a change in sac diameter has also been reported, leading some to describe the phenomenon teleologically as endotension. A presumed endoleak that is not detected on a properly performed contrast CT scan is typically not identified on a catheter-based arteriogram. The proper diagnostic investigation of an endoleak should include interrogation of all the fixation sites and modular interfaces and selective injections of mesenteric and hypogastric arteries with sufficient contrast dose and proper acquisition techniques. It should be emphasized that open conversion and explant of the endovascular graft can be technically more challenging than a de novo open repair and usually requires suprarenal or supraceliac aortic control. In the absence of infection, it is not always possible (or necessary) to remove the entire device, particularly when the device has suprarenal fixation. It is possible to transect the endovascular graft near the usual site of the infrarenal aortic anastomosis

and incorporate the fabric/stents of the graft into the anastomosis. Temporary distal vascular control can be achieved by clamping the limbs of the endovascular graft. The limbs of a bifurcated surgical graft may be anastomosed directly to the endograft limbs if they are securely attached to the iliac artery, typically incorporating the native terminal aorta or common iliac arteries. In properly chosen elective patients, open conversion can be performed with similar outcomes to primary open juxtarenal AAA repair.[135]

A variety of device-specific complications, including strut fracture, fabric tears, and buckling of the graft, have been identified. Importantly, these may present at any time throughout the postoperative period. An extensive discussion of all the potential device-related complications and their treatment is beyond the scope of this chapter.

REPAIR OF RUPTURED ABDOMINAL AORTIC ANEURYSMS

Open Repair

The approach to the patient with a ruptured AAA is similar to the elective scenario with the exception of several points that merit further comment. Prompt communication with all operating room personnel is critical for a good outcome. The blood bank should be notified as the case may require massive transfusion of blood products. The patient should be prepared and draped before induction of anesthesia with a broad operative field from the chin to the toes. This allows access to both groins if percutaneous insertion of an aortic occlusion balloon is necessary to obtain proximal control, and the chest in the event that resuscitative thoracotomy is required. The surgeon should be ready to make the incision at the time of induction, since patients with ruptured aneurysms frequently become hypotensive at this point.

A midline incision should be made and supraceliac aortic control obtained. The aorta/esophagus can be difficult to identify, especially in a hypotensive patient. The placement of a nasogastric tube can facilitate identification of the gastroesophageal junction, and thus guide proper placement of the supraceliac clamp. The esophagus should be manually moved to the patient's left and the gastrohepatic ligament, the crus of the

diaphragm, and the connective tissue enveloping the aorta can be divided using blunt finger dissection. The aorta can be temporarily controlled manually by either occluding the aorta between the fingers and thumb or compressing it against the vertebral bodies. Definitive control should be obtained with an aortic clamp. Care should be utilized during these maneuvers to prevent injury to the esophagus or the aorta itself.

Aortic control can also be achieved through a variety of other means: thoracotomy with occlusion of the descending thoracic aorta, intraluminal control of the infrarenal aorta with a compliant balloon placed through the common femoral artery, or supraceliac control via a retroperitoneal incision. The surgeon should be familiar with these various techniques because they can be helpful in certain clinical settings, but the midline approach with supraceliac control is recommended for most ruptured *infrarenal* aneurysms. After supraceliac aortic control has been obtained, the infrarenal aorta is dissected and vascular control is achieved below the level of the renal arteries to restore visceral perfusion. The hematoma from the ruptured aneurysm often facilitates the dissection by displacing the normal tissue planes. However, the normal tissues may be obscured, and care should be taken not to injure the venous structures, particularly the left renal vein. It is imperative that these various steps are coordinated with the anesthesia team, and it is recommended that the supraceliac clamp be left in position to facilitate reapplication if necessary. Distal vascular control can be achieved with either vascular clamps or intraluminal balloons, depending on the character of the iliac vessels.

The decision to anticoagulate the patient is contingent on a variety of factors, including the quantity of blood lost, presence of coagulopathic bleeding, body temperature, and hemodynamic status. Anticoagulation potentially reduces thrombotic complications, but it exacerbates coagulopathic bleeding. It is recommended that the inferior mesenteric artery be implanted (if patent) to reduce the risk of postoperative colonic ischemia. The heparin effect can be reversed with protamine. The administration of plasma, platelets, and/or additional clotting factors should be considered at this point if indicated.

The postoperative course after repair of a ruptured aneurysm is predictably more complicated and protracted than after elective repair. Both the intensive care unit and total hospital length of stay are significantly

increased. The mortality and complication rates are likewise significantly increased. The contemporary mortality rate for patients with ruptured AAAs who make it to the operating room is approximately 41%, which is improved compared to outcomes from several decades ago.[47] The spectrum of postoperative complications after repair of a ruptured aneurysm is essentially the same as after elective repair although the incidences are increased. The incidence of bowel ischemia may be as high as 40% and routine colonoscopy may be indicated.[114] Abdominal compartment syndrome has been reported in up to 34% and merits consideration in patients that are not doing well.[136] Notably, adrenal insufficiency was identified in almost 70% of patients with unexplained postoperative hypotension after ruptured aneurysm repair.[137]

ENDOVASCULAR REPAIR FOR RUPTURE

A recent meta-analysis comprising data of ~60,000 patients showed that endovascular repair of ruptured *infrarenal* AAA has significantly improved outcomes compared to traditional open repair.[138] Randomized controlled trials and observational series report 30-day mortality rates of 31% to 33% with EVAR.[139,140] However, these studies may be subject to selection and publication bias. A study querying the NSQIP database showed that endovascular approach had significantly lower 30-day mortality for both unstable and stable ruptured AAAs compared to open repair.[141] However, a more recent risk-adjusted meta-analysis of 30-day mortality showed no significant difference between the two approaches.[142] The Society for Vascular Surgery currently recommends EVAR over open repair, if anatomically feasible, for treatment of ruptured AAA, albeit the Society acknowledges the relatively poor quality of evidence to support this guideline.[61]

An endovascular approach requires a defined protocol/program consisting of an experienced endovascular surgeon, a committed team, an available operating room with the necessary imaging equipment, and an inventory of suitable devices. Studies estimate that approximately 40% to 50% of patients with ruptured aneurysms are anatomically suitable for endovascular repair using conventional devices.[143] This number would be about 10% higher if

taking into account those patients suitable for advanced proximal fixation techniques (e.g., use of renal chimneys, etc.).[144]

The endovascular approach for the treatment of ruptured AAAs can be briefly described.[145] Oversizing of the aortic neck ≥20% and encroachment on the orifices of the renal arteries with adjunctive stenting are both tolerated in an attempt to limit the necessary inventory and increase the proximal fixation zone, respectively. Access to the common femoral arteries can be obtained using a percutaneous approach with Perclose application or directly repaired at the completion of the procedure. In the absence of severe hypotension, the remaining conduct of the procedure is essentially the same as described in the elective setting. It is not usually necessary to occlude the aorta with an intraluminal balloon although one should be readily available in the event that the patients become hemodynamically unstable. The criteria for an acceptable result are somewhat less in the emergent setting and persistent attempts to achieve a perfect radiographic result should be avoided. Further interventions including conversion to open repair may be necessary at a later date, but these can usually be performed in an elective fashion.

Notably, patients treated with EVAR are at risk of developing abdominal compartment syndrome as a result of the intra/retroperitoneal hemorrhage and/or aggressive volume resuscitation. A meta-analysis estimated this rate to be 20% with half of these patients ultimately dying.[146] The surgeon should consider prophylactic laparotomy or retroperitoneal evacuation with placement of an open abdominal vacuum dressing at the conclusion of the procedure depending on the clinical status.

ADDITIONAL CONSIDERATIONS

Isolated Iliac Artery Aneurysms

Isolated iliac artery aneurysms are rare comprising less than 2% of all aneurysms.[147] The common iliac artery is involved in approximately 70% of the cases, and the internal iliac artery in the remainder. Aneurysmal involvement of the external iliac artery, either in combination with the common iliac artery or alone, is distinctly rare. These isolated iliac artery

aneurysms should be differentiated from the common iliac artery aneurysms that occur concomitantly with AAAs. Simultaneous aneurysmal involvement of the aorta and common iliac arteries occurs in about 10% to 20% of all AAAs[6] and should be considered as one disease process.

The natural history of isolated iliac artery aneurysms is poorly defined because of their low incidence. The clinical risk factors appear to be similar to those for AAAs with the highest incidence seen among elderly men. Unlike patients with AAAs, a significant proportion of patients with isolated iliac artery aneurysms present with symptoms. These symptoms may result from either rupture or compression of adjacent structures including the bowel, ureters, iliac veins, and nerves. The clinical presentation of patients with a ruptured iliac artery aneurysm is similar to that of ruptured AAAs, and the diagnosis should be included in the differential for patients with genitourinary symptoms and normal findings on urinalysis and testicular examination. CT arteriography is optimal for confirming the diagnosis of an isolated iliac artery aneurysm. The utility of ultrasonography is limited by the posterior course of the iliac vessels and the overlying bowel.

The principles of treatment for asymptomatic, isolated iliac artery aneurysms are similar to those for AAAs, and operative repair is justified when the risk for rupture offsets the risk of repair. Unfortunately, the natural history of isolated iliac artery aneurysms and the appropriate threshold for repair remain unresolved. Although rupture has been reported for aneurysms smaller than 2 cm, it is incredibly rare for aneurysms smaller than 3 cm to rupture. Consequently, operative repair is generally recommended for good-risk patients with isolated iliac artery aneurysms ≥3.5 cm.[147]

The treatment or repair of isolated iliac artery aneurysms depends on the specific vessel involved and the extent of the aneurysm. Theoretically, common iliac artery aneurysms can be repaired with an interposition graft or a covered stent provided that there is a sufficient proximal and/or distal neck to sew the anastomosis or seat the graft. However, this is rarely an option because the aneurysm involvement of the vessel usually extends over its whole length. Therefore, open repair necessitates replacing the whole common iliac artery with a bifurcated graft similar to the approach for patients with combined aortoiliac disease. Likewise, an endovascular approach should adhere to the same principles outlined for treatment of an

infrarenal AAA and may require the use of a iliac branch device to achieve distal seal and maintain internal iliac perfusion, as previously discussed.

The treatment of internal iliac artery aneurysms is typically exclusion. This can be performed using either an endovascular or open approach although the former is likely preferred due to its simplicity. Bypass of an internal iliac artery aneurysm is often not possible because there is rarely a proximal or distal neck. Indeed, the aneurysmal involvement usually extends to the common iliac bifurcation and the distal aspect usually arborizes into multiple smaller vessels. An alternative to open bypass is to ligate the origin of the internal iliac artery and oversew its distal branches from within the aneurysm although this is feasible only if the aneurysmal degeneration does not involve the origin of the vessel. Obtaining the necessary distal control for this approach can be challenging. It is certainly important to assess the status of the contralateral internal iliac artery and overall pelvic circulation before ligating this artery. The principles of an endovascular approach include obliterating both the inflow and outflow of the aneurysm along with complete sac thrombosis. The inflow of the vessel can be occluded by placing a covered stent across the origin of the internal iliac artery and the outflow can be occluded using selective embolization of the various branches using a variety of other agents including coils, plugs, glues, or gelfoam. Alternatively, an iliac branch device may be used to fully exclude the aneurysm sac and maintain internal iliac perfusion but this option depends on the size and quality of the posterior and anterior divisions of the internal iliac artery. The 1-year patency with this technique is 95%, but additional long-term data is necessary to determine its efficacy.[148]

INFLAMMATORY ABDOMINAL AORTIC ANEURYSMS

Approximately 5% of all AAAs are described or considered inflammatory.[149] These aneurysms are characterized by a dense inflammatory response encasing the anterior and lateral walls of the infrarenal aorta with sparing of the posterior aspect. The inflammatory response consists of a dense cellular infiltrate that has a white, glistening appearance on inspection.

The inflammation results in an increase in wall thickness with the difference between the inner and outer diameters of the aorta ranging from 1 to 5 cm. The cause of this inflammatory process remains unresolved, but it is likely an autoimmune phenomenon. Indeed, some type of autoimmune disorder has been identified in up to 20% of patients with inflammatory aneurysms.[150]

Patients with an inflammatory abdominal aneurysm are predominantly male and frequently present with symptoms of back or abdominal pain. The triad of a pulsatile abdominal aortic mass, abdominal pain, and an elevated erythrocyte sedimentation rate (ESR) has been described. CT findings are characteristic and include a thick, contrast-enhancing wall in the distribution described. An inexperienced observer may confuse the CT findings with those of a ruptured AAA. Hydronephrosis with *medial* displacement of the ureters is frequently seen in contradistinction to the lateral displacement seen with noninflammatory aneurysms. Indeed, this entity may share some pathophysiologic pathways with retroperitoneal fibrosis.

The treatment of inflammatory AAAs is essentially the same as that for the more common, noninflammatory variety. Nonoperative treatment with corticosteroids has been advocated in the past, although this approach is likely ineffective and has largely been abandoned. It has been suggested that the rupture risk of inflammatory aneurysms is less than that for noninflammatory variety because the wall thickness is increased. However, this is likely untrue, and patients should not be lulled into a false sense of security. It should be emphasized that most aneurysms rupture through their posterior or posterolateral aspect, which is not involved in the inflammatory process. The open repair of an inflammatory AAA is complicated by the fact that the adjacent structures, including the duodenum, colon, and ureters, may be involved in the process and densely adherent to the aortic wall. No attempt should be made to mobilize the adherent structures, specifically the duodenum, because of the potential for accidental injury. Proximal aortic control can be achieved either immediately above the renal arteries or above the visceral vessels. A retroperitoneal approach can reduce the technical difficulties associated with the open repair. The preoperative placement of ureteral catheters may facilitate their identification intraoperatively and can be helpful in patients with hydronephrosis. Perioperative complications, length of stay, and most notably graft infections were greater with open repair of inflammatory AAAs compared to the more conventional bland AAA.[151]

If anatomically feasible, EVAR has been shown to be the optimal treatment for inflammatory AAAs given its reduced morbidity and mortality compared to open repair.[149,152] In Stone's series of inflammatory aneurysms, there were no aneurysm-related deaths or major morbidity in those undergoing EVAR.[149] Kakkos showed a decreased operative time, transfusion requirement, and length of stay.[152] Puchner et al. performed a meta-analysis of patients undergoing endovascular repair for inflammatory aneurysms and reported that the inflammatory process resolved in approximately 50% of the cases.[153]

Juxtarenal and Suprarenal Abdominal Aortic Aneurysms

The management of aneurysms extending to the level of the renal arteries or more cephalad is more complicated, and, predictably, the morbidity rates associated with open repair are increased.[106] Interestingly, reports from centers of excellence have documented mortality rates comparable to those reported for infrarenal repairs although it is unlikely that these findings are applicable nationwide.[154] Repair of these complex aneurysms is complicated by the obligatory period of renal and visceral ischemia associated with aortic occlusion during the proximal anastomosis. Indeed, the renal complication rates range from 15% to 20% even from these select centers of excellence.[106,154] These increased morbidity and mortality rates should be factored into the decision algorithm and threshold for open operative repair. Elective open operative repair is usually recommended for patients with aneurysms 6 cm or larger in diameter in this setting although the 5.5-cm criterion may be appropriate for low good-risk patients and those with juxtarenal aneurysms who will require only a short period of suprarenal aortic occlusion.

The open operative approach for AAAs extending to the renal arteries or more cephalad may be repaired achieved through either a retroperitoneal or a transperitoneal exposure although the former is optimal, especially with more cephalad disease. The *retroperitoneal* approach, with anterior reflection of the left kidney, obviates the concerns about the left renal vein (except when a retroaortic renal vein is present) and simplifies exposure of the abdominal aorta. The distal descending thoracic aorta is easily exposed

by incising the diaphragm and its crus. Of note, the right renal artery and right common iliac artery are more difficult to expose via the retroperitoneal approach because of their trajectory, but this is not prohibitive in most cases. The proximal anastomosis may be fashioned as a beveled anastomosis incorporating the orifices of the renal and visceral arteries, or a Carrel patch can be fashioned from the aortic segment with reimplantation or bypass of the left renal artery in situations where the aneurysm involves the entire visceral segment.

For juxtarenal aneurysms repaired through the *transperitoneal* approach, the aorta can be clamped in the supraceliac or suprarenal position, depending on the extent of the disease and the patient's body habitus. Suprarenal clamp is preferred to avoid unnecessary visceral ischemia. Of course, if the aneurysmal tissue extends above the renal arteries, a supraceliac clamp may be required. The supraceliac exposure is similar to that described above for a ruptured infrarenal AAA, but performed in a more controlled fashion. After mobilization of the left lobe of the liver, the esophagus should be reflected left laterally. Placement of a nasogastric tube facilitates identification of the esophagus/gastroesophageal junction. The gastrohepatic ligament should be divided making note of aberrant hepatic arterial anatomy to avoid dividing a replaced hepatic vessel during this portion of the dissection. The crus of the diaphragm can be divided bluntly or sharply followed by division of the dense connective tissue surrounding the aorta for placement of the clamp. If a clamp is to be placed in the suprarenal position, this is facilitated by retracting the left renal vein superiorly or inferiorly after ligating its adrenal, gonadal, and lumbar branches. As noted previously, the left renal vein may be ligated near its confluence with the vena cava without adverse sequelae provided that its branches are preserved. The anterior surface of the aorta at the level of the visceral vessels is encased by dense neural tissue, which can be incised. Incising the crus of the diaphragm that envelops the lateral aspect of the aorta further facilitates clamp application. The configuration of the proximal anastomosis in the setting of the transperitoneal approach depends on the extent of the aneurysm and the vessels involved.

EVAR for juxtarenal AAAs has become widely available with the FDA approval of the Zenith Fenestrated Endovascular Graft (Cook Medical) in 2012.[72] The approach is based upon constructing a suitable landing zone for the more traditional endograft in patients with an inadequate or short

infrarenal neck (<4 mm). This is accomplished using a custom-designed fenestrated endograft that contains a combination of fenestrations and/or scallop that correspond to the renal and superior mesenteric arteries (SMAs). There are, however, several restrictions as to where the fenestrations/scallop can be placed on the endograft. The typical combination is two small fenestrations for the renal vessels and a scallop or large fenestration for the SMA. The fenestrations permit the introduction of individual covered stents into the side branch vessels once they are selected from within the endograft. For aneurysms that extend further cephalad on the aorta (i.e., outside of the IFU for the ZFEN device), fenestrations and/or branches are necessary for all visceral and renal vessels in order to obtain adequate proximal seal. Such a configuration requires more complex device designs that are accomplished through physician modifications of an endograft (PMEG) on the back table under sterile conditions, ordered through company-manufactured custom-made device (CMD) programs, off-the-shelf devices that are in an ongoing clinical trial, or with chimney/parallel grafts. It is important to note that access to CMDs is limited to a select number of centers in the United States. Additional details regarding these complex devices are beyond the scope of this chapter.

The worldwide experience with fenestrated EVAR (FEVAR) for juxtarenal aneurysms is vast, and the technique has been shown to be safe and effective. Oderich et al. reported a 100% technical success rate with a 1.5% 30-day mortality in the prospective Zenith Fenestrated trial.[155] A nationwide series using NSQIP data reported 30-mortality rate of 0.8% for FEVAR with 19% sustaining any complication.[156,157] In this series, these outcomes were significantly better than traditional open repair. Similarly, a recent meta-analysis comparing the two approaches for juxtarenal AAAs demonstrated significantly better 30-day mortality and complication (acute renal failure, spinal cord ischemia, bowel ischemia) rates for FEVAR compared to open repair.[158] Data regarding long-term survival and reintervention is somewhat lacking. In general, most studies have reported similar overall survival rates for FEVAR and open repair. For instance, Freyrie et al. reported 4-year overall survival of 81% and 87% for open repair and FEVAR, respectively.[159] The 4-year outcomes are lacking, however. As with more conventional EVAR, durability after FEVAR remains a concern. Maeda et al.

reported the 7-year secondary intervention rate after FEVAR to be as high as 40%, notably different than open repair.[160]

Combined endovascular and open (i.e., "hybrid") approaches have also been used to treat the juxtarenal and more complex proximal aneurysms. These techniques are based upon constructing a suitable aortic neck to land a traditional endograft by "debranching" the renal or visceral vessels. For example, a suitable landing zone below the SMA could be created for a juxtarenal aneurysm by performing bilateral iliorenal bypasses. These debranching procedures, however, are typically reserved for those who have a true thoracoabdominal aortic aneurysm as opposed to a juxtarenal aneurysm.

Infected Abdominal Aortic Aneurysms

Infected AAAs comprise a small subset of all AAAs, accounting for less than 1% of all repairs.[161] The term *mycotic aneurysm* coined by William Osler to describe aneurysms that developed after septic cardiac emboli caused an arterial infection has often been used to refer to all infectious etiologies for aneurysms. Unfortunately, "mycotic" is a misnomer that has led to a significant amount of confusion. A more specific classification system consists of four groups based on the underlying mechanism: (a) classic "mycotic aneurysm" caused by embolus from the heart infecting an artery; (b) microbial arteritis, in which bacteria infects an atherosclerotic but nonaneurysmal artery and leads to aneurysmal degeneration; (c) an existing aneurysm that becomes infected; (d) traumatic pseudoaneurysm with concomitant bacterial inoculation. Microbial arteritis resulting from hematogenous bacterial spread currently accounts for approximately 80% of all cases of infected aortic aneurysms.[162] *Salmonella* causes approximately 40% of all aneurysmal infections in contemporary series with the remainder caused by *Staphylococcus, Streptococcus, Bacteroides, Arizona hinshawii, Escherichia coli,* and *Pseudomonas aeruginosa.*[162]

The diagnosis of infected aortic aneurysm is often difficult and the clinical presentation insidious. Patients may present with fever, back/abdominal pain, or both. The physical examination is often remarkable for a palpable abdominal mass and the presence of peripheral emboli. Laboratory studies are notable for an elevated leukocyte count and positive blood cultures

although the latter are present only 50% of the time and negative blood cultures do not exclude the diagnosis. CT is the most useful diagnostic study, and the features suggestive of an infected aneurysm include a periaortic mass, an aneurysm in an atypical location, periaortic fluid or gas, retroperitoneal inflammation, and frank rupture. The angiographic finding of a saccular or eccentric/irregularly shaped aneurysm in an atypical location is also suggestive of an infected aneurysm.

The treatment of an infected aneurysm requires control of hemorrhage in the presence of rupture, aggressive debridement of all infected tissues, and restoration of perfusion to the viscera and lower torso. Indeed, these treatment concerns and the management options are identical to those for patients with infected aortic grafts. Patients should be started on broad-spectrum antibiotics when the diagnosis is suspected although antibiotic therapy alone is not sufficient and the operative intervention should not be delayed in an attempt to sterilize the retroperitoneum. Patients with suspected rupture should undergo emergent exploration through either a transperitoneal or retroperitoneal approach. After vascular control has been obtained, the retroperitoneum should be explored, and intraoperative cultures along with stat Gram stain should be obtained. Several options for arterial reconstruction are available, depending on the clinical scenario and the individual patient's anatomy. These options include in situ replacement with autogenous femoral vein or a prosthetic or cadaveric graft, ligation of the infrarenal aorta with extra-anatomic bypass (axillofemoral, femoral–femoral configuration), or in situ replacement with staged extra-anatomic bypass and subsequent removal of the in situ graft. The choice is contingent on the character of the aorta, degree of inflammation in the retroperitoneum, suspected organism, and hemodynamic status. In situ replacement of the infected aneurysm with a prosthetic or cadaveric graft is a reasonable option if retroperitoneal inflammation is minimal and the Gram stain is negative. The integrity of the aortic stump at the time of ligation and the potential for dehiscence or breakdown of the suture line are major concerns. The aorta should be debrided back to grossly uninvolved tissue and sutured in two layers with a running horizontal mattress and a simple continuous technique using nonabsorbable monofilament suture. A pedicle of omentum can be mobilized and approximated next to the aortic stump to help control the retroperitoneal inflammation and minimize the risk for stump dehiscence.

When the diagnosis is suspected preoperatively and no evidence of rupture is found, a staged approach with extra-anatomic bypass followed by graft removal may decrease the physiologic impact of any one procedure. The procedures are usually performed 2 to 3 days apart to allow the patients a period of recovery. Patients should be anticoagulated between procedures to prevent thrombosis of the extra-anatomic bypass resulting from competitive flow. Fortunately, the risk of graft thrombosis and graft infection during the intervening period is small.

Endovascular repair of infected aortic aneurysm can be considered an additional alternative. Although the long-term safety of EVAR in this clinical scenario remains unclear, it may serve as a temporizing approach that converts an urgent problem to an elective one. A meta-analysis by Kan et al.[163] reported that the endovascular approach was reasonable, but the incidence of subsequent endograft infection was significant in patients with ruptured aneurysms and those with fevers. They concluded that endovascular repair could be used as a bridge in this setting (i.e., ruptured aneurysm, febrile) prior to definitive open repair.

Infected aneurysms involving the suprarenal aorta pose a particularly challenging problem, but fortunately are uncommon. In situ replacement with a prosthetic or cadaveric graft is frequently the only available option. This can be accomplished in a number of ways, but the principle of aggressive removal of all infected tissue should be adhered to in order to prevent recurrent infection, typically a fatal event. If the thoracic aorta is of good quality, an antegrade debranching of the visceral segment can be performed to limit the ischemia time to the visceral/renal vessels. If there is a contained rupture of the aorta or the tissues are particularly inflamed, it may be best to obtain proximal and distal control above and below the disrupted/infected segment before attempting to dissect the visceral/renal vessels from the inflammatory mass. After obtaining sites for proximal and distal aortic control, a branched prosthetic graft soaked in Rifampin is sewn to the aorta in an end-to-side manner using a partial-occluding, side-biting clamp on the thoracic aorta to allow antegrade perfusion during the anastomosis. It is important to leave enough good aorta below this bypass to allow a cross-clamp and separate end-to-end anastomosis. The left renal, superior mesenteric, and celiac arteries can be bypassed individually in some cases and then a cross-clamp placed on the aorta distal to the end-to-side graft. The

aorta is then transected and aggressively debrided as dictated by the extent of the infection. A separate tube or bifurcated graft can then be sewn from the distal thoracic aorta to the bifurcation of the abdominal aorta, or to the iliac/femoral arteries, as indicated. This technique limits the ischemia time on the individual viscera/renal arteries, and allows full removal of all atherosclerotic material and infected aorta along with the infected periaortic tissues after complete revascularization of the visceral vessels.

Patients with infected aneurysms, regardless of the arterial reconstruction, require long-term antibiotics with tailoring of the medications based on culture results. If culture-directed therapy is not possible, broad-spectrum antibiotics for 6 weeks are indicated. The patient should then be placed on oral antibiotics although the duration of treatment remains unresolved and many surgeons will treat the patient with lifelong suppressive antibiotics. In addition, patients should undergo serial CT scans to assess the retroperitoneum and the status of the in situ graft as applicable. In the event that stable imaging is obtained over the first few CT scans, later imaging may not be warranted. Predictably, the morbidity and mortality rates associated with infected AAAs are significant with a 40% mortality rate.[164]

Aortoenteric Fistulae

An aortoenteric fistula is a communication between the aorta and the bowel. The duodenum is involved most commonly at the site where it crosses anterior to the aorta, but the communication can develop between almost any portion of the intestine. Primary aortic fistulae result when an aortic aneurysm erodes into the bowel and are distinctly rare with a reported incidence of 0.04% to 0.07% in autopsy series.[165] Secondary aortic fistulae result from the erosion of a prosthetic aortic graft into the bowel; are significantly more common, with a reported incidence of 0.1% to 2.0% after either open[166] or endovascular[167] aortic reconstruction. The management of both primary and secondary aortic fistulae is the same.

The diagnosis of an aortoenteric fistula is often difficult and mandates a high index of suspicion. Patients usually present with gastrointestinal bleeding manifested as either hematemesis or melena. The initial episode of gastrointestinal bleeding is often self-limited and has been described as a “herald” bleed. The diagnosis of aortoenteric fistula should be foremost

among the differential when a patient with a known aneurysm or prior aortic reconstruction presents with intestinal bleeding. Patients should undergo endoscopic evaluation of the upper and lower intestinal tract to determine the source of bleeding. It is imperative that the clinical suspicion of an aortoenteric fistula be communicated to the endoscopist to ensure that the third and fourth portions of the duodenum are adequately examined. The endoscopic findings of erosion, thrombus, active bleeding, or visible prosthetic graft in third or fourth portion of the duodenum are diagnostic of an aortoenteric fistula and mandate emergent treatment due to the risk of massive hemorrhage. Mild duodenitis and gastritis without frank erosion are frequently seen at the time of endoscopy and do not exclude the diagnosis of an aortoenteric fistula. Notably, the findings during upper endoscopy are normal in up to 30% of patients. A CT should be performed if the results of endoscopy are inconclusive. The findings on CT that suggest an aortoenteric fistula include inflammation within the retroperitoneum, an anastomotic pseudoaneurysm, close approximation of the bowel, and the prosthetic aortic graft or aneurysm, and loss of the normal tissue planes between the duodenum (or any other bowel segment) and the aorta or prosthetic graft. Occasionally, both endoscopy and CT are nondiagnostic despite the clinical suspicion of an aortoenteric fistula. Exploratory laparotomy is recommended in this setting for both diagnosis and treatment. Adherence of the bowel to the aorta at the time of the initial exploration suggests an aortoenteric fistula and mandates obtaining suitable proximal and distal control of the aorta, iliac vessels, or prosthetic graft before further dissection. The diagnosis cannot be excluded until the bowel is entirely separated from the retroperitoneum and graft.

The treatment of an aortoenteric fistula requires repair of the defect in the gastrointestinal tract in addition to repair of the aneurysm or treatment of the infected prosthetic graft. Treatment of the gastrointestinal defect is usually straightforward and is based on standard surgical principles. After the fistula is disassembled, the edges of the bowel can be debrided and a primary closure performed. A limited bowel resection or enteral diversion may be necessary. The intraoperative and longer-term management of the aortic aneurysm or prosthetic graft is the same as that outlined above for infected aortic aneurysms. In situ replacement of the prosthetic graft or infrarenal aorta using autogenous femoral vein or cryopreserved aortic allograft,

ligation of the infrarenal aorta with excision of the prosthetic graft and extra-anatomic bypass, or temporary in situ aortic replacement with staged extra-anatomic bypass and subsequent graft excision are all reasonable options. The decision algorithm is based upon the hemodynamic stability of the patient, their baseline physiologic state, and the anatomy and involvement of the aorta. In older/sicker patients, the most expeditious procedure is best. Replacement of the infected graft using autogenous femoral vein (neo-aorto-iliac system [NAIS]) is reasonably well tolerated in younger/healthier patients, and may be a better option that obviates the risk of aortic stump blow-out. If the visceral segment is involved, ligation of the aorta may not be possible without sacrifice of the renal arteries. In any case, these patients should be maintained on long-term antibiotics and undergo serial imaging studies, as outlined for infected aneurysm patients.

Venous Anomalies Relevant to Aortic Surgery

Anomalies of the vena cava and renal veins are occasionally encountered at the time of aortic reconstruction. The common anomalies are related to the embryologic development of the iliac veins and vena cava. The four most clinically relevant anomalies include duplication of the inferior vena cava (0.2% to 3.0%), left-sided vena cava (0.2% to 0.5%), circumaortic left renal vein (1.5% to 8.7%), and retroaortic renal vein (1.2% to 2.4%).[168] Patients with a duplicated inferior vena cava have large veins that run parallel to the infrarenal aorta and join together either anterior or posterior to the aorta at the level of the renal vein. In the case of a left-sided inferior vena cava, the cava runs parallel to the left side of the aorta, and the normally located right-sided vena cava is absent. The left-sided vena cava typically crosses the aorta at the level of the renal vein to become the suprarenal inferior vena cava, and the gonadal and adrenal veins on the right drain directly into the renal vein in a mirror image of the normal anatomy. The circumaortic left renal vein forms a collar of veins that surrounds the aorta at the normal level. In the case of a retroaortic left renal vein, a single vein runs posterior to the aorta at a slightly more caudal location. Notably, both duplication of the

inferior vena cava and left-sided vena cava can be associated with other venous anomalies, including a circumaortic or retroaortic renal vein.

The diagnosis of the various venous anomalies can usually be made preoperatively on CT. Identification of the vena cava and left renal vein should be part of the mental checklist used when the preoperative CT scans are reviewed. The various anomalies may not become evident immediately in the operating room if missed on the preoperative imaging studies. A very prominent left renal vein at the usual location or slightly inferior is suggestive of a left-sided vena cava, whereas the absence of a left renal vein despite dissection along the anterior aspect of the aorta at the level of the SMA is suggestive of a retroaortic renal vein.

Open repair of an infrarenal AAA in a patient with a venous anomaly is essentially the same as the standard approach although additional care should be exercised to prevent inadvertent injury of the aberrant vein. Exposure of the infrarenal neck is more difficult in the presence of a duplicated or left-sided vena cava. However, sufficient exposure can usually be obtained by gentle dissection and mobilization of the venous structures. The presence of a duplicated or left-sided vena cava is a relative contraindication to the left retroperitoneal approach. A circumaortic left renal collar or retroaortic left renal vein presents a potential hazard when the proximal aortic clamp is applied. A vertical aortic clamp is recommended and obviates the dissection on the posterior aspect of the aorta. Transecting the aorta may facilitate exposure of a retroaortic renal vein when significant bleeding is encountered.

Renal Anomalies

Congenital variations in the kidney anatomy may complicate the repair of an AAA. Specifically, aberrant kidney anatomy may complicate the dissection during open repair because they are frequently associated with multiple renal arteries, aberrant venous return, and abnormally positioned ureters. The various congenital anomalies of the upper urinary system have been classified in an attempt to standardize the approach for vascular surgeons.[169] The anomalies have been broken down into abnormalities of position, including simple ectopia, and abnormalities of both form and fusion, including horseshoe kidney, crossed renal ectopia without fusion, and crossed renal ectopia with fusion. An ectopic kidney may be positioned

anywhere from the pelvis to the thorax. Common forms of ectopic kidney include the pelvic kidney, located opposite the sacrum and below the aortic bifurcation; the lumbar kidney, located opposite the sacral promontory in the iliac fossa and anterior to the iliac vessels; the abdominal kidney, located above the iliac crest adjacent to the second lumbar vertebra; and the thoracic kidney, which can be located above the diaphragm in the posterior mediastinum. In a horseshoe kidney, two distinct renal masses are fused together by either a bridge of renal parenchyma or fibrous tissue; in the overwhelming majority, the lower poles are fused. In crossed renal ectopia, the kidney mass is located on the side opposite to its insertion in the bladder. Multiple configurations of crossed ectopia with and without fusion have been described.

The preoperative objective for the various renal anomalies is to image the renal mass adequately, delineate the course of the ureter, and establish the arterial and venous supply. The approach is simplified by the fact that most patients undergo abdominal/pelvic CT as part of the preoperative evaluation. The location and position of both the kidneys and ureters, like the position of the left renal vein, should be established as part of the review of every CT scan for patients with aneurysms. Formerly, it was recommended that patients with renal anomalies undergo preoperative arteriography to confirm the location and number of renal arteries. However, this information can now be obtained from the CT arteriogram, which is now part of the routine preoperative evaluation.

Patients with renal anomalies can safely undergo repair of an AAA using either an open or endovascular approach. The specific operative approach depends on the location of the renal mass, blood supply, course of the ureters, and presence of fusion. A left-sided retroperitoneal or transperitoneal approach with medial visceral rotation is the most helpful for open repair, particularly in patients with a horseshoe kidney. A standard transperitoneal approach with transection of the fused parenchyma can be used in patients with a horseshoe kidney although this may be associated with both significant bleeding and a urine leak and, therefore, is discouraged. The multiple renal arteries can be handled most expeditiously by using a Carrel patch technique, in which a cuff of aorta including the renal artery orifices is reimplanted into the aortic graft after completion of the proximal anastomosis. Endovascular repair is possible in many cases with the

feasibility dictated by the location of the renal arteries in addition to the other standard anatomic considerations.

Coexistent Renal or Visceral Artery Occlusive Disease

Coexistent renal or visceral artery occlusive disease is frequently found in patients undergoing AAA repair. The optimal management of patients with coexistent lesions remains unresolved. The options include repair of the aneurysm alone, simultaneous repair of the aneurysm and revascularization of the renal or visceral vessels, and staged repair, with either aneurysm repair or revascularization performed first. Furthermore, the specific treatment options include both open and endovascular alternatives for the aneurysm repair and visceral/renal revascularization (i.e., angioplasty/stent). The rapid expansion of the endovascular technologies has afforded effective, safe approaches that have replaced open surgical revascularization for both renal and visceral artery lesions to a great degree. Regardless, the optimal approach represents a balance between the indications for the procedure and the associated added risk.

Renal/visceral revascularization is mandatory at the time of open aneurysm repair if the affected vessels are involved in the aneurysm, as in a suprarenal aneurysm or a horseshoe kidney. More commonly, a lower pole or accessory renal artery may arise from the aneurysm. The decision to perform a concomitant revascularization with either reimplantation or a bypass graft in this setting depends on the size of the vessel and the quantity of kidney parenchyma perfused. Revascularization is recommended for larger vessels (>3 mm) that supply a significant portion of the renal mass. The presence of any accessory renal arteries should factor into the operative plan and the general feasibility for endovascular repair. Covering small, accessory renal arteries with an endograft has been reported to be safe with no significant decline in renal function.[170]

Combined aneurysm repair with renal or visceral artery revascularization may be justified if the indications for renal or visceral artery revascularization are satisfied. The traditional indications for renal revascularization included poorly controlled hypertension in a patient with a

significant renal artery stenosis and rapidly progressive renal insufficiency in a patient with adequate renal mass and bilateral renal artery stenosis. However, the antihypertensive agents have improved to the point that renal revascularization is currently reserved for patients with poor blood pressure control despite optimal medical therapy with at least three separate medications, including a diuretic.[171] Endovascular treatment of the renal artery stenosis (when indicated) can be performed prior to open aneurysm repair or simultaneous with the endovascular approach.

The traditional indications for mesenteric revascularization include symptoms of chronic mesenteric ischemia and critical stenosis of either the SMA alone or two of the three visceral vessels. Patients with chronic mesenteric ischemia and AAAs should have their visceral occlusive disease corrected prior to aneurysm repair when possible. Repairing the aneurysm first potentially increases the risk of developing acute mesenteric ischemia in the perioperative period, and performing concomitant mesenteric revascularization with AAA repair carries significant morbidity/mortality over and above that seen with open mesenteric revascularization alone.[172] Endovascular treatment with stent placement is probably the optimal treatment for the visceral lesions but long-term surveillance is necessary given reintervention rates.[173]

The optimal treatment for patients with aneurysms and *asymptomatic* renal or visceral artery lesions remains poorly defined. Analysis of patients with asymptomatic renal artery stenosis who underwent aortic reconstruction found that the natural history of the renal artery lesions is fairly benign when untreated and is associated only with an increase in the antihypertensive requirements.[174] Little is known about the natural history of asymptomatic mesenteric occlusive lesions with concomitant abdominal aneurysms. Ultimately, consideration should be given to mesenteric revascularization prior to aneurysm repair in patients with severe visceral artery occlusive disease due to the potential risk of mesenteric infarction at the time of aneurysm repair as noted above.

Additional Concurrent Intra-Abdominal Disease

The finding of an AAA and an additional intra-abdominal process that may require operative repair is a frequent event. A second surgical problem may be identified as part of the preoperative evaluation or discovered at the time of the exploratory laparotomy during open aneurysm repair. Alternatively, an AAA may be identified during the surgical treatment of another problem. No algorithms have been defined for the management of such concurrent problems, and the overall approach certainly requires sound clinical judgment. Options include simultaneous performance of the necessary operations, or a staged operation with repair of the AAA as either the first or second procedure. The approach depends on the risk for aneurysm rupture, natural history of the second surgical problem, and potential for infection of the prosthetic graft during simultaneous repair. Notably, both the laparoscopic and endovascular approaches have impacted the approach to patients with combined problems due to their reduced morbidity and mortality facilitates a more rapid, definitive treatment.

The generic recommendation for patients with an AAA and an additional intra-abdominal surgical problem is that the most life-threatening problem be addressed first. The natural history of untreated AAA has been defined reasonably well and has been outlined extensively earlier in this chapter. It has been suggested that the risk for aneurysm rupture is increased after major intra-abdominal surgery and that it is potentially related to an increase in collagenase activity.[175] However, this reported increased rupture risk is speculative and should not necessarily be factored into the decision algorithm. The management of concurrent colon cancer and AAA is a frequent treatment dilemma that provides an excellent illustration of the approach to these problems. Indeed, the reported incidence of colon cancer and an AAA occurring simultaneously ranges from 0.5% to 2.1%.[108] The treatment principles include the following: (a) aneurysm repair first in the presence of rupture; (b) colon resection first in the presence of hemorrhage, perforation, or obstruction; (c) aneurysm repair first in the presence of a large aneurysm and a small colon cancer; (d) colon resection first in the presence of a large colon cancer and a small aneurysm.[176]

Simultaneous AAA repair and cholecystectomy is probably safe for patients with cholelithiasis or evidence of chronic cholecystitis. The safety of these simultaneous procedures has been documented in several series, and the concerns about an increased incidence of aortic graft infection have not

been substantiated.[177] Regardless, the cholecystectomy and other simultaneous procedures should not be performed until after the aneurysm repair is completed and the retroperitoneum closed in an attempt to reduce the hypothetical risk for graft infection. Again, the exponential rise in EVAR has made some of the above concerns somewhat obsolete.

The safety and utility of other simultaneous procedures remain poorly defined although a wide range of procedures have been combined with open aneurysm repair. The repair of ventral hernias is often mandatory to achieve a tension-free abdominal closure and should be viewed more as an extension of the aneurysm repair than as a simultaneous procedure.

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95

Lower Extremity Aneurysms

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Key Points

1 Femoral artery aneurysms are the most common peripheral aneurysm if both true and false aneurysms are considered together. Popliteal artery aneurysms are the most common true peripheral aneurysm.

2 Femoral and popliteal aneurysms are often incidental findings on imaging or routine physical examination.

3 Extremity aneurysms are potentially limb threatening and frequently associated with other aneurysmal disease, including life-threatening abdominal aortic aneurysms.

4 Screening imaging studies should be done to evaluate for concurrent abdominal aortic aneurysms or contralateral femoral or popliteal artery aneurysms.

5 Femoral artery aneurysms should be repaired at a size ≥3.5 cm, if intraluminal thrombus is present, or if symptomatic.

6 Popliteal artery aneurysms should be repaired at a size of 2 to 3 cm or if symptomatic, to prevent limb-threatening complications.

7 Anastomotic aneurysms result from a disrupted suture line between a graft and the host artery.

8 Pseudoaneurysms after percutaneous intervention result from failed hemostasis.

9 Thrombolytic therapy is a useful adjuvant in patients presenting with acute limb ischemia secondary to thrombosis of a popliteal artery aneurysm.

PERIPHERAL ANEURYSMS

1 The significance of peripheral aneurysms comes from their potential for limb-threatening complications, more so than rupture, and their association with abdominal aortic aneurysms. Popliteal artery aneurysms are the most frequently encountered peripheral true aneurysm. True femoral artery

aneurysms are rare, with iatrogenic and anastomotic pseudoaneurysms being more common.

Incidence

An aging population, increased arterial trauma, more common use of invasive therapies for vascular disease, and increased use of imaging modalities all contribute to the rise in number of peripheral aneurysms being diagnosed. In a screening study of men between the ages of 65 and 74 years, abdominal aortic aneurysms were identified in 4.9% of patients.[1] In patients with abdominal aortic aneurysms, 6.8% had femoral artery aneurysms and 9.6% had popliteal artery aneurysms.[2] Screening of men between the ages of 65 and 80 years identified popliteal artery aneurysms in 1%.[3]

An increasing number of false aneurysms—"pseudoaneurysms"—are occurring coincident with the increased use of catheter-based diagnostic and therapeutic interventions in addition to lower extremity bypass surgery. Pseudoaneurysms can be iatrogenic, infectious, or traumatic in nature and are identified by their lack of involvement of all three vessel wall layers, as compared to true aneurysms. Femoral pseudoaneurysms most commonly develop after cannulation with arterial sheaths used for coronary or arterial interventions and may vary based on patient anatomy and habitus.[4]

Degenerative (often called atherosclerotic) femoral and popliteal artery aneurysms are encountered far more frequently in men than women. The male to female ratio in patients with femoral and popliteal aneurysms is about 30:1.[5,6] This predilection for men is markedly different from aortic aneurysms, where male to female patient ratio is approximately 4:1.[2]

Pathogenesis

The cause of femoral and popliteal aneurysms has changed significantly since they were first recognized centuries ago. Once primarily infectious in origin, most true aneurysms in the 21st century have a degenerative cause, commonly called *atherosclerotic aneurysms*. Peripheral pseudoaneurysms usually follow surgery or trauma. Rarely, peripheral aneurysms develop secondary to connective tissue disorders, such as Marfan syndrome or Behçet syndrome. Notably, tibial and pedal artery aneurysms are rare.

The cause of degenerative aneurysms of the femoral and popliteal vessels is not clear. One factor believed to contribute to aneurysm formation is turbulent flow beyond a relative stenosis resulting in poststenotic dilatation beyond the inguinal ligament at the groin or beyond the tendinous hiatus of the adductor magnus or the arcuate popliteal ligament and the heads of the gastrocnemius muscle at the popliteal level. Arterial wall fatigue resulting from vibration and turbulence proximal to a major branching or caused by stress during hip and knee flexion may also contribute to aneurysm formation.

The frequent occurrence of multiple peripheral aneurysms in the same patient suggests a systemic abnormality in the arterial wall, which promotes aneurysmal degeneration at locations where hemodynamic or mechanical factors put unusual stress on the arterial wall. There are multiple factors that contribute to aneurysmal degeneration and are felt to contribute to degenerative femoral and popliteal aneurysms, as well as aortic aneurysms. The presence of an inflammatory infiltrate has been noted in the wall of femoral and popliteal aneurysms, similar to aortic aneurysms.[7] The exact role of this inflammatory process, with potential release of reactive oxygen species and matrix metalloproteinases, is unknown. Apoptosis of smooth muscle cells may also play a role in the formation of aneurysms by limiting the ability of the arterial wall to respond to the degenerative process.[8] These factors, however, do not explain the male predilection for femoral and popliteal aneurysm formation. X-linked genetic abnormalities for aneurysm formation in popliteal artery aneurysms have not been noted in humans.

Clinical Manifestations

Femoral and popliteal aneurysms are often asymptomatic. They may be detected on routine physical examination by a bounding, expansile pulse, or discovered incidentally on imaging. When symptomatic, femoral and popliteal artery aneurysms may be accompanied by sensations of local fullness, pain caused by pressure on the adjacent nerve, limb edema, and venous distention or thrombosis caused by compression of the adjacent vein. Secondary complications from thrombosis or distal embolization include lower extremity ischemia with intermittent claudication, rest pain, or gangrene. Because the natural history and complication rate in femoral and popliteal aneurysms differ, they are considered separately here.

FEMORAL ARTERY ANEURYSMS

2 Femoral artery aneurysms are the most common peripheral aneurysm if both true and false aneurysms are considered together, with the vast majority being pseudoaneurysms. Their clinical significance is related to limb-threatening complications from thrombosis, embolization, or rupture. True aneurysms are predominantly degenerative from atherosclerosis, whereas femoral pseudoaneurysms include anastomotic, traumatic, and mycotic lesions.

Degenerative (Atherosclerotic) Aneurysms

Incidence

The exact incidence of degenerative (atherosclerotic) common femoral artery aneurysms in the general population remains undefined; one study suggests 5 in 100,000 patients may be affected.[6] Femoral aneurysms are found in 6.8% of all patients with abdominal aortic aneurysms; conversely, 85% of patients with femoral artery aneurysms have abdominal aortic aneurysms.[2,5]

Pattern of Disease

As with all aneurysms, femoral artery aneurysms are defined as being greater than 1.5 times the diameter of the disease-free proximal adjacent arterial segment. The average size of the common femoral artery is approximately 8 to 10 mm, with variations based on age and sex; an average of 9.8 mm in males and 8.2 mm in females was demonstrated in healthy volunteers.[9] Femoral aneurysms most frequently affect the common femoral artery. They may be classified as *type I,* those limited to the common femoral artery, or *type II,* those involving the orifice of the profunda femoris artery.[10] Type I and type II aneurysms occur with nearly equal frequency. This classification becomes important in reference to vascular reconstructive procedures, with type II aneurysms requiring more complex reconstructions to ensure continued patency of both the superficial and profunda femoris arteries. Isolated lesions of the profunda femoris artery are rare (2% of femoral artery aneurysms), and are prone to rupture because they are difficult to diagnose at

the asymptomatic stage. Isolated superficial femoral artery aneurysms are also uncommon, but one-third of patients present with rupture and one-quarter with thrombosis.[11]

Multiple aneurysms are common in patients with femoral artery aneurysms. In a series of 100 patients with degenerative femoral artery aneurysms seen at a single institution, 72% of patients had bilateral femoral artery aneurysms.[5] In addition, aortoiliac aneurysms were detected in 85% of patients, thoracic aortic aneurysms in 6%, and popliteal aneurysms in 44%, of which 55% were bilateral.

Clinical Manifestations

The typical patient with a degenerative femoral artery aneurysm is a male in his 60s or 70s with the usual risk factors for atherosclerosis. Of these patients, 86% are cigarette smokers, 36% have hypertension, and 14% have diabetes mellitus.[5] Associated cardiovascular disease is common, with clinical manifestations of coronary artery disease and cerebrovascular disease present in 34% and 7%, respectively.

As with aneurysms in other locations, femoral artery aneurysms may be complicated by embolization, thrombosis, or rarely rupture. Peripheral embolization may be identified incidentally on angiography or produce signs as mild as spotty discoloration of the toes to as severe as peripheral gangrene. Although embolization is reported in about 10% of aneurysms, the femoral artery aneurysm is not necessarily the source of these emboli because many patients have a concomitant popliteal aneurysm.[5] In larger clinical series, approximately 30% of patients are symptomatic, with thrombotic or embolic events developing in 2.5% to 15% of patients and rupture in 4% to 14%.[6,12,13]

Compression symptoms are present in 34% of patients. Lower extremity venous disease is present in 8%, being attributable to venous obstruction by the femoral artery aneurysm in 4%. A palpable mass is found in 23% of patients, and localized pain in just under 10% of patients with femoral aneurysms.[6,12]

Natural History

The natural history of degenerative femoral artery aneurysms is poorly defined. One study of 236 isolated femoral artery aneurysms found that 66% were asymptomatic on presentation. 114 patients were initially managed nonoperatively, with 64% later undergoing repair, but only 10% of the initial cohort doing so for acute complications. The authors found that the femoral artery aneurysms rarely developed complications unless >3.5 cm in size or if intraluminal thrombus was present.[5,6]

Diagnosis

In most cases the diagnosis of femoral artery aneurysm is suspected by the finding of a pulsatile groin mass on routine physical examination or during evaluation for vascular disease. If the femoral artery aneurysm is small or thrombosed, detection on physical examination may be difficult. Although a radiograph of the region may occasionally demonstrate the calcified rim of the aneurysm, only ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) can reliably establish the diagnosis of the femoral aneurysm. In addition, these modalities are useful in accurately defining the size of the lesion and evaluating associated aneurysmal disease in the distal aorta and popliteal regions. The diagnostic accuracy of arteriography is limited because it demonstrates only the residual lumen and an aneurysm filled with smooth mural thrombus may be missed, but the definition of the vascular anatomy of the lower extremity provided by angiography is helpful in planning the appropriate operative procedure (**Fig. 95.1**).

Treatment

Operative treatment of femoral aneurysms is indicated for asymptomatic aneurysms >3.5 cm in size, or for any size causing local symptoms or presenting with limb-threatening complications. In patients with small, asymptomatic aneurysms, observation may be appropriate. When nonoperative management is selected, the size of the aneurysm should be documented by ultrasonography. The patient should be followed at regular intervals with ultrasound scans and careful examination for complications; no consensus guidelines exist for follow-up intervals. Operative treatment should be undertaken without undue delay if the femoral aneurysm enlarges,

produces symptoms, or is complicated by embolization, thrombosis, or rupture.

Figure 95.1 Arteriogram demonstrating bilateral femoral artery aneurysms that extend into the superficial femoral arteries. Unlike many patients with femoral artery aneurysms, this patient did not have an associated aortic aneurysm or popliteal aneurysms.

Surgical Strategy

The operative approach is individualized based on associated aneurysmal disease. In patients with multiple asymptomatic aneurysms, treatment is staged. Generally, aortic aneurysm repair precedes extremity repairs, and popliteal aneurysms are repaired prior to femoral aneurysms. Aortic lesions are treated before femoropopliteal lesions, based on the rationale of life-versus-limb threat. If an aortofemoral bypass is necessary, the femoral aneurysm should be treated at the same time, to avoid later anastomotic

aneurysm formation. The graft limb can be anastomosed into an interposition graft that has replaced the femoral aneurysm. Similarly, if a stent graft is placed for treatment of an abdominal aortic aneurysm in a patient with femoral artery aneurysms, the aneurysm should be repaired with an interposition graft. In patients with severe lower extremity ischemia, the femoral aneurysm is treated with an interposition graft, from which the proximal anastomosis of the required femoropopliteal or femorotibial bypass is based.

Technique

The operative procedure for treatment of an isolated femoral artery aneurysm is determined by aneurysmal involvement of the superficial and deep femoral arteries as well as by the existence of lower extremity occlusive disease. The femoral artery aneurysm is usually approached through a longitudinal groin incision. As a special consideration when addressing an unusually large aneurysm or a ruptured aneurysm, however, initial proximal control of the external iliac artery through a retroperitoneal approach is advisable. After proximal and distal arterial control is obtained, the aneurysm sac is opened and the atheromatous debris is removed. Small aneurysms may be excised, but routine excision of large aneurysms is not recommended as these lesions can often be adherent to the adjacent vein and nerve.

For type I aneurysms, the preferred treatment is reconstruction with an interposition graft of Dacron or expanded polytetrafluoroethylene, with the proximal anastomosis at the distal external iliac artery or proximal common femoral artery and the distal anastomosis at the femoral bifurcation.

For type II aneurysms with patent superficial and profunda femoris arteries, an interposition graft to the profunda femoris artery with reimplantation of the superficial femoral artery is one standard configuration. If the superficial femoral artery is chronically occluded and the patient has minimal symptoms, an interposition graft to the profunda femoris artery alone is sufficient. If the patient has severe lower extremity ischemia, this is typically followed by a standard distal reconstruction. If recent emboli or in situ thrombosis has occluded the outflow tract, percutaneous mechanical thromboembolectomy or catheter-directed thrombolytic therapy is useful before open arterial reconstruction is undertaken.

Results

Results of surgical therapy depend upon the patency of the distal vasculature. More than 80% of asymptomatic patients have excellent long-term results, whereas 68% of those presenting with lower extremity ischemia achieve satisfactory long-term outcomes.[5]

Anastomotic Pseudoaneurysms

Incidence

3 Anastomotic pseudoaneurysms result from a disrupted suture line between a graft and the host artery. The incidence varies with the location of the anastomosis and the type of graft that is used. Involvement of the femoral artery accounts for nearly 80% of these lesions, and 3% of all femoral anastomoses.[14,15] After infrainguinal bypass procedures, the incidence is higher with prosthetic grafts than with autogenous vein grafts; 6% of femoral anastomoses develop aneurysms when Dacron is used, compared with 0.9% when a vein graft is placed.[14] Anastomotic pseudoaneurysms are a late complication of bypass procedures; the mean interval from primary procedure to recognition is more than 6 years.[16,17] A notable subset exists in aortofemoral bypass; 6% of femoral anastomoses after aortofemoral bypass develop this complication compared with 0.2% of the proximal aortic anastomoses.[14] Patient factors that are associated with increased likelihood of developing a femoral anastomotic aneurysm after aortofemoral bypass include chronic obstructive pulmonary disease, current smoking, and postoperative groin wound infection.[18]

Pathogenesis

Several factors contributing to anastomotic pseudoaneurysm formation have been identified: weakness of the arterial wall, the type of graft material and suture utilized, the presence of infection, the method of construction of the anastomosis, and the stress on the suture line from hypertension, leg motion, or excess tension on the graft limb.[14,16,17] Progressive degeneration of the recipient artery accounts for most anastomotic pseudoaneurysms, and an increased incidence has been noted following endarterectomy of the artery at

the anastomosis. False aneurysms occur less frequently with saphenous vein grafts than synthetic vascular grafts, a reflection of more complete healing of autogenous tissue. With the use of monofilament synthetic suture, anastomotic pseudoaneurysms rarely result from a loss of suture integrity, although occasionally a broken suture is a factor in pseudoaneurysm formation. Although most anastomotic aneurysms are not accompanied by overt graft infection, occult infections with coagulase-negative *Staphylococcus* species may be an important factor in development of anastomotic aneurysms.[17] A higher incidence is noted in patients with wound-healing complications, and the use of anticoagulants may increase such complications.

Clinical Manifestations

Femoral anastomotic pseudoaneurysms usually present as a pulsatile groin mass, which may or may not be accompanied by pain, redness, or symptoms of venous obstruction. Acute complications include hemorrhage, embolization, and occlusion with acute limb ischemia.

Diagnosis

The diagnosis of an anastomotic pseudoaneurysm is usually made on physical examination by the presence of a pulsatile groin mass in a patient who has undergone a femoral arterial reconstructive procedure. The differential diagnosis includes nonpulsatile groin masses, such as hernia, lymphocele, or abscess, through which pulsation is transmitted from an underlying normal femoral artery. Diagnosis of an anastomotic disruption in one region should raise suspicion of other anastomotic pseudoaneurysms as multiple lesions are found in at least 30% of patients.[16] The presence of multiple anastomotic pseudoaneurysms suggests infection. Evaluation of an anastomotic aneurysm includes ultrasonography, CT, or angiography to define all anastomoses of the graft (**Fig. 95.2**).

Treatment

Because of the progressive nature of anastomotic pseudoaneurysms, surgical treatment is generally undertaken for all lesions >2 cm except those in high-risk patients. Principles of surgical therapy are those of primary aneurysms: obtain proximal and distal control and replace the aneurysmal segment.

Securing proximal control often requires dividing the inguinal ligament to isolate the graft limb. Distal control is most easily obtained using intraluminal balloon catheters. If intrinsic arterial disease requires extension of the graft distally on the profunda femoris or superficial femoral artery, these arteries can be identified by dissection through unscarred tissue distal to the previous exposure. After débridement of the degenerated artery, an interposition graft is placed between the prosthetic graft limb and the healthy native artery. Cultures of the graft and vessel wall are essential to exclude infection as an etiologic factor in the development of the anastomotic aneurysm. If infection is obvious at the time of surgery, the approach is the same as that of any infected graft with removal of infected prosthetic material and reestablishment of blood flow, if necessary, with a bypass through an uninfected tissue route, such as an obturator, lateral femoral, or axillofemoral bypass.

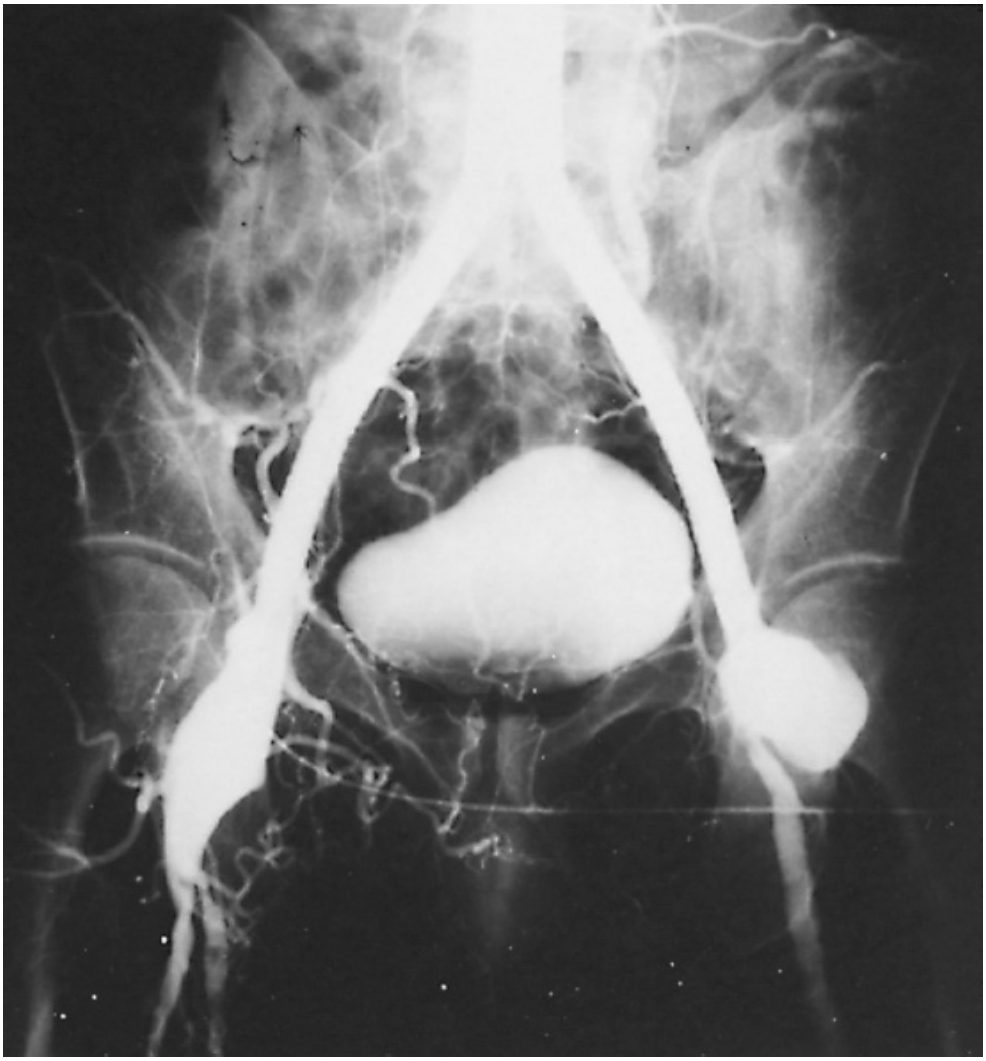


Figure 95.2 Arteriogram demonstrating bilateral femoral anastomotic aneurysms after an aortofemoral bypass and a left femoropopliteal bypass.

Results

Results of elective operations on femoral anastomotic pseudoaneurysms are excellent with 2% operative mortality, 97.5% graft patency at 2 years, and 2% amputation within 2 years of surgery.[16] Recurrence is reported in less than 16% of cases.[14,15] Patients presenting with aneurysms complicated by hemorrhage, occlusion, or embolization have significantly increased operative morbidity and mortality.

Femoral Pseudoaneurysms

Incidence

Femoral pseudoaneurysm incidence has increased as a result of diagnostic and therapeutic angiography. Therapeutic angiography often requires prolonged arterial cannulation, large-bore sheaths, and anticoagulation, which are associated with a higher rate of arterial complications than diagnostic studies. One study with routine ultrasound surveillance following 254 therapeutic interventions via femoral access in patients with known arterial disease showed a pseudoaneurysm development rate of 2.75%.[19] A meta-analysis of 7,889 femoral arterial access procedures demonstrated an increase in pseudoaneurysm formation with arterial closure devices (odds ratio 3.8) versus surgical cutdown, albeit with fewer other complications including seroma, surgical site infection, and wound dehiscence.[20] A registry analysis of 12,937 patients undergoing percutaneous interventions through the femoral artery showed pseudoaneurysm rates of 0.6% with manual compression versus 0.1% with arterial closure devices ($p < 0.5$).[21] The overall reported rate of pseudoaneurysm formation after percutaneous procedures is reported to be anywhere between 0.05% and 8%.[22]

Pathogenesis

Pseudoaneurysms from iatrogenic catheter trauma are defined as collections of blood in continuity with the arterial system, and not enclosed by all three layers of the arterial wall.[4] These lesions form because of failed hemostasis at the arterial wall defect created by sheath insertion. Normally hemostasis seals the defect promptly, aided by direct focal application of pressure or hemostatic devices, and the arterial wall repairs itself. When hemostasis is not successfully obtained, blood under arterial pressure leaks from the artery, dissects surrounding tissue planes, and forms what is perceived on physical examination to be a pulsatile mass. The gross findings at surgery are a blood-filled cavity surrounded by a capsule. As pseudoaneurysms, these lesions can cause symptoms by rupture or compression of surrounding structures.

Diagnosis

The diagnosis of femoral pseudoaneurysm is suspected when a pulsatile groin mass is noted after arterial catheterization. The differential diagnosis includes hematoma, lymphadenopathy, and abscess. Duplex ultrasound with

color flow or CT is typically used to establish the diagnosis, differentiate pseudoaneurysm from hematoma, and aid in defining the communication between the mass and the arterial lumen. Color-flow duplex scanning is the diagnostic test of choice, providing accurate diagnosis with a characteristic to-and-fro waveform and a "yin-yang" pattern of color swirling, along with localization and sizing of the false aneurysm (**Fig. 95.3**).[23]

Natural History

Color-flow duplex scanning has been used to define the incidence and natural history of pseudoaneurysms after percutaneous transluminal coronary angioplasty.[24] Many pseudoaneurysms smaller than 2.0 cm in diameter will thrombose spontaneously within 4 weeks; anticoagulation and size greater than 2.0 cm are predictors of failure of spontaneous thrombosis. About 30% of patients with pseudoaneurysms will require intervention.[25]

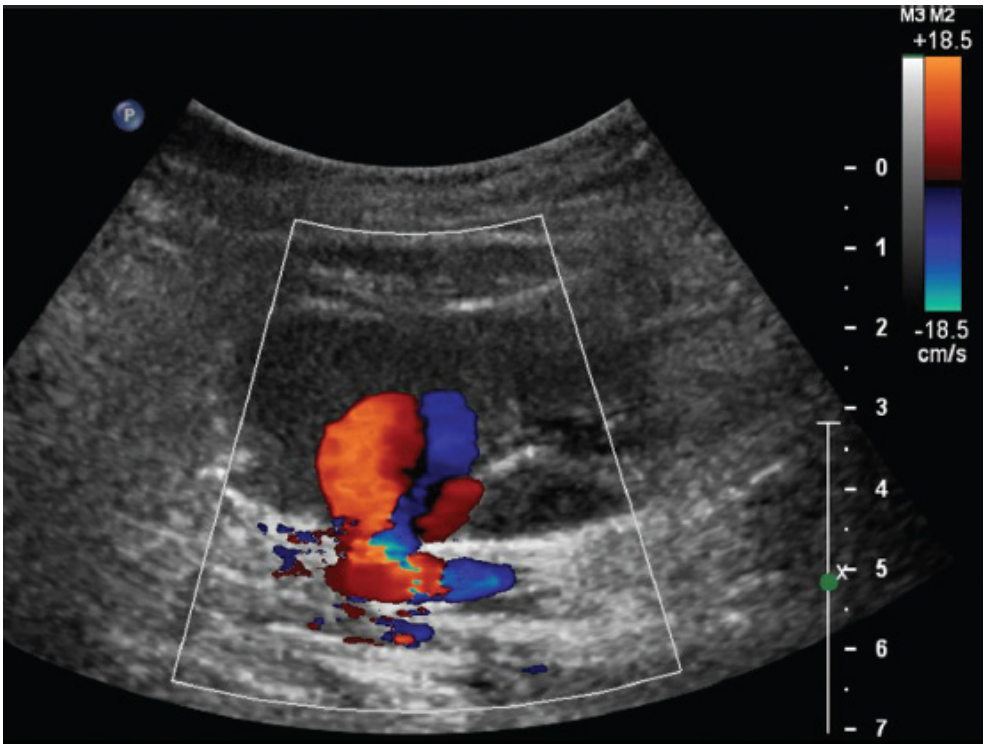


Figure 95.3 Ultrasound findings with a to-and-fro flow pattern in a femoral pseudoaneurysm.

Treatment

Therapy of femoral pseudoaneurysms is influenced by aneurysm size and symptoms, and whether the patient requires continuous anticoagulation (**Algorithm 95.1**). Surgical intervention is mandatory for all pseudoaneurysms that are acutely expanding, compressing adjacent nerves, or compromising the overlying skin. Proximal and distal arterial control is obtained, and the arterial defect is repaired directly, rarely requiring placement of more than one or two sutures.

Ultrasound-guided compression and ultrasound-guided thrombin injections are alternative treatment strategies when urgent evacuation of the hematoma and arterial repair are not required. Compression therapy entails identification with a color-flow ultrasound probe and directed intermittent compression of the pseudoaneurysm with the transducer, allowing the visualization and documentation of flow cessation when effective. This technique may be limited by body habitus, patient discomfort, and requires up to 30 minutes of compression by the ultrasonographer.

Another nonoperative treatment option of femoral pseudoaneurysms is percutaneous ultrasound-guided injection of 0.5 to 1.0 mL thrombin (1,000 U/mL) into the pseudoaneurysm sac, at a site away from the neck of the aneurysm.[26–28] Thrombin injection avoids the discomfort of prolonged compression and is effective in anticoagulated patients. Continuous ultrasonographic imaging is used to monitor thrombosis of the pseudoaneurysm.

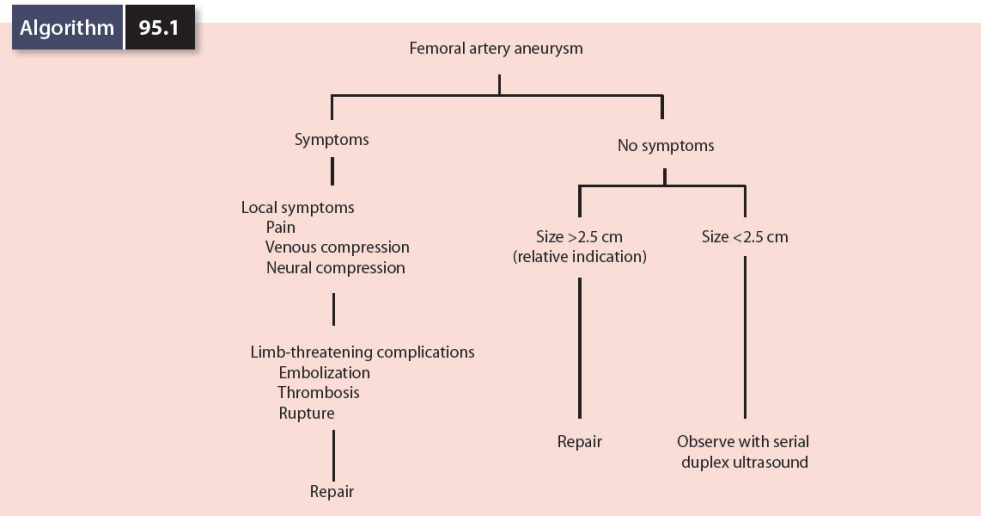
Results

A meta-analysis of studies involving 992 patients treated with ultrasound-guided compression versus ultrasound-guided thrombin injection showed pooled success rates of 69.3 versus 97.4%, respectively, without significant difference in the rate of complications.[22]

In one of the largest series of pseudoaneurysms treated with ultrasound-guided compression, thrombosis was achieved in 86% of anticoagulated patients, and in 98% of those not anticoagulated, with a 20% recurrence rate in less than 24 hours in anticoagulated patients.[29] Success using this therapeutic modality requires a knowledgeable ultrasonographer and meticulous postcompression follow-up, though patient discomfort from

prolonged compression often renders the technique unsuccessful in achieving hemostasis.

Thrombin injection to induce thrombosis of pseudoaneurysms is successful in 94% to 98% of patients, with thrombosis occurring in less than 1 minute.[26–28] This technique can be complicated by arterial thrombosis if an excessive volume of thrombin is used and may not be appropriate for pseudoaneurysms with large necks. Remote thromboembolic events are rare and probably are not a result of a systemic effect of the thrombin. Allergic reactions to bovine thrombin occasionally occur. Large pseudoaneurysms, greater than 8 cm in diameter, and an associated arteriovenous fistula (AVF) are predictors of failure with thrombin injection.[30]



Algorithm 95.1 Management of femoral pseudoaneurysm.

Mycotic Aneurysms

The term *mycotic aneurysm* is currently used to refer to any infected aneurysm. Mycotic aneurysms today are often a complication of parenteral drug abuse, but can follow arterial trauma of any form and have been associated with iatrogenic injury, osteomyelitis, endocarditis, or idiopathic etiologies. Historically, septic emboli from bacterial endocarditis were a major cause of mycotic aneurysmal degeneration, as were tuberculosis and late-stage syphilis. With the change in cause, the location of mycotic aneurysms has shifted from central to peripheral arteries, with the femoral

artery being the most common site.[31,32] The importance of mycotic aneurysms comes from their propensity to rupture.

Pathogenesis

The pathogenesis of mycotic aneurysms can be divided into four major categories, although other less common causes also exist.[31] First, septic emboli from bacterial endocarditis may lodge in normal arteries, causing infection that weakens the arterial wall, resulting in aneurysm formation. These lesions are often multiple. Second, during an episode of bacteremia, microorganisms may lodge in a pre-existing atherosclerotic plaque or aneurysm and begin to multiply with the same result. A third cause of mycotic aneurysms is the contiguous spread of bacteria from a local abscess. The inflammatory process destroys the arterial wall, leading to pseudoaneurysm formation. Finally, trauma to the artery with concomitant contamination may result in formation of an infected pseudoaneurysm. Bacteria may be introduced concomitantly with needle puncture or by migration during prolonged arterial catheterization. Mycotic aneurysms accompanying drug abuse may be secondary to direct contamination of the arterial wall, or they may result from destruction of the vessel wall by a local abscess.

A contemporary case series of 29 patients with mycotic peripheral aneurysms found *Staphylococcus aureus* in 38.5%, *Streptococcus* sp. in 11.5%, other *Staphylococcus* spp. in 7.7%, and gram-negative rods (*Serratia* and *Pseudomonas* spp.) in 7.7% of patients.[33] Staphylococcal species, *Salmonella* sp., *Escherichia coli*, and *Proteus* sp. have also been cultured.

Clinical Manifestations

The typical patient with a mycotic femoral aneurysm presents with a history of chills and fever, and a tender, enlarging, pulsatile groin mass. The patient may have a history of intravenous drug use, recent arterial catheterization, penetrating trauma, or bacterial endocarditis. Local signs of infection, including tenderness, erythema, and warmth are noted on physical examination. Lower extremity edema may occur secondary to venous or lymphatic obstruction. Petechial skin lesions, splinter hemorrhages, cutaneous abscesses, and septic arthritis may occur as a result of emboli

originating from a mycotic aneurysm. A “sentinel bleed” may occur and signals impending rupture and life-threatening hemorrhage. Urgent or emergent surgical intervention is indicated for these aneurysms.

Diagnosis

The diagnosis of a mycotic aneurysm is usually straightforward, but distinguishing an abscess adjacent to the femoral artery from a femoral mycotic aneurysm may be difficult. In the patient with a pulsatile groin mass, laboratory findings including a leukocytosis, elevated erythrocyte sedimentation rate, and positive blood cultures are suggestive, but not specific, for a mycotic aneurysm. Multiple blood cultures or downstream arterial blood cultures may be necessary to yield positive results. Ultrasonography and CT angiography are helpful in establishing the diagnosis of an aneurysm (**Fig. 95.4**), but lack precision in distinguishing infected from bland aneurysms. The diagnosis of a mycotic aneurysm is confirmed at operation by demonstration of organisms on Gram stain or by positive cultures of the aneurysm wall.

Figure 95.4 Computed tomography scan of an infected femoral anastomotic aneurysm that was diagnosed 5 years after aortofemoral graft placement.

Treatment

Mycotic aneurysms represent a serious life- and limb-threatening disease because their natural history is one of expansion and rupture, and should therefore be treated when discovered. The goal of treatment is eradication of the infection. Before operative intervention is performed, the patient is started on antibiotics that are subsequently modified based on sensitivity testing of intraoperative cultures. The complexity of the operative procedure varies with the location and extent of the mycotic aneurysm, with excision, tissue débridement, and staged revascularization through noninfected tissue planes the main goals of treatment.

Stent grafts have been used in selected cases of mycotic aneurysms when other approaches were not feasible; however, concern about latent infection of the stent graft oftentimes renders this more of a bridging technique than a long-term solution.

Although a direct approach to the femoral artery may be taken, a retroperitoneal exposure of the distal external iliac artery for proximal control is often safest for large or proximal femoral lesions to avoid excessive hemorrhage. In more than 50% of cases, the mycotic aneurysm involves the femoral artery bifurcation, and treatment requires resection of the femoral bifurcation to afford débridement to healthy arterial wall. Three options for repair exist: ligation, immediate revascularization, or selective revascularization. (1) The distal external iliac or proximal common femoral artery, as well as the superficial and deep femoral arteries, are oversewn with nonabsorbable monofilament suture. This results in significant ischemia in most patients, but with the patient heparinized, symptoms gradually improve as collateral circulation increases. The majority of patients will not need revascularization for limb salvage, but up to one-third of patients will have limb-threatening ischemia.[34,35] (2) In patients in whom sepsis can be adequately controlled at the initial procedure, aggressive débridement may be followed by immediate revascularization using autogenous vein graft as the conduit and covering the graft with a muscle flap.[35] This technique is most effectively utilized when the area of arterial infection is limited. If the field was significantly contaminated, immediate revascularization will frequently be met with blowout. (3) Another option is to observe patients for 24 hours after arterial ligation and selectively revascularize only those patients in whom limb-threatening ischemia persists. Use of prosthetic material through the original infected tissue planes is avoided because of the high incidence of early and late septic complications. If necessary, synthetic graft may be tunneled through uninfected tissue such as the obturator canal or via the lateral femoral route. Antibiotics are begun preoperatively and continued for at least 4 to 6 weeks postoperatively.

POPLITEAL ARTERY ANEURYSMS

5 Popliteal aneurysms are limb-threatening lesions, the vast majority of which are degenerative in etiology. Rarely, anastomotic, traumatic, or mycotic popliteal aneurysms are encountered in contemporary practice. The remainder of this section addresses only popliteal aneurysms that are degenerative in etiology. The average popliteal artery size is approximately

4 to 7 mm; one study identified a mean diameter of 5.2 mm in healthy male subjects.[36] Again, aneurysmal dilatation is defined as being greater than 1.5 times the diameter of the disease-free proximal adjacent arterial segment.

Incidence

Popliteal artery aneurysms are the most common degenerative true peripheral aneurysm. They occur slightly more frequently than femoral artery lesions; however, popliteal aneurysms are relatively unusual compared to abdominal aortic aneurysms. Aortic aneurysms are diagnosed with about 10 times the frequency of popliteal aneurysms.[37,38]

Pattern of Disease

Like patients with femoral artery aneurysms, multiple aneurysms occur frequently in patients with popliteal aneurysms. About 50% of patients have bilateral popliteal aneurysms, and 55% have extrapopliteal aneurysms.[39,40] Of patients with popliteal artery aneurysms, 40% have femoral artery aneurysms; 40% to 50% have abdominal aortic aneurysms; and bilateral popliteal artery aneurysms are associated with aortic aneurysms in 70% of cases. The association with other aneurysms has resulted in the recommendation that patients discovered to have femoral or popliteal aneurysms should have completion imaging to exclude contralateral limb aneurysms and abdominal aortic aneurysms.[41] Even when popliteal aneurysms are initially asymptomatic, patients will develop symptoms at a mean rate of 14% per year, and one-third will develop complications requiring emergent intervention within 5 years, resulting in poorer outcomes for both life and limb.[42,43]

Clinical Manifestations

The typical patient with a popliteal aneurysm is a male in his 60s or 70s with the usual risk factors for atherosclerosis. Of patients with popliteal aneurysms, 50% to 75% are smokers, 40% to 60% have hypertension, and about 15% have diabetes mellitus.[44–47] Other manifestations of cardiovascular disease are also common, with 10% of patients having

manifestations of cerebrovascular disease and more than 40% having evidence of significant cardiac disease.[46]

The clinical manifestations of popliteal artery aneurysms range from an asymptomatic pulsatile mass to severe lower extremity ischemia. About 40% of patients are asymptomatic at diagnosis.[5] More than 50% of patients present with symptoms of limb ischemia, usually claudication, but the ischemia may be more advanced and manifested as rest pain or gangrene. Local symptoms, including sensation of a mass, local pain, and leg swelling or phlebitis secondary to compression of the adjacent vein, account for the remainder of symptoms. A popliteal artery aneurysm may be complicated by thrombosis, embolization, or rarely rupture. Thrombosis is reported in approximately 40% of patients, and embolization occurs in about 25% of cases. This may result in isolated digital embolic occlusion, the "blue toe syndrome," or occlusion of multiple tibial outflow vessels. Rupture occurs in fewer than 5% of popliteal aneurysms; in these cases, the hemorrhage is usually confined to the popliteal space, thus permitting surgical intervention and arterial reconstruction in a timely fashion.[44,45]

Natural History

The natural history of popliteal aneurysms is not well defined because most series are composed primarily of aneurysms that have been treated surgically. Additionally, there is not a clear predictive relationship between aneurysm size and risk of thrombosis, embolization, and compression, all of which are more common complications than rupture in popliteal aneurysms.[41] In a review of 29 reports in the English literature published between 1980 and 1994, patients whose aneurysms were observed rather than intervened upon showed that a mean of 35% of patients with nonoperative follow-up developed ischemic complications, and 25% of these required amputation even with modern therapy.[5] Thus, a significant percentage of popliteal aneurysms will develop a complication if left untreated, and although this is not synonymous with limb loss, the amputation rate is high. Rupture of popliteal artery aneurysms is reported in only 2% to 4% of cases.[40]

Diagnosis

Palpation of the popliteal space with the knee flexed reveals a pulsatile mass in approximately two-thirds of patients. Small aneurysms may not be palpable, and if thrombosis has occurred, the mass may be nonpulsatile. Radiographs of the knee demonstrating a calcified arterial wall occasionally suggest the diagnosis of a popliteal artery aneurysm, but it must be confirmed by duplex ultrasonography, CT (**Fig. 95.5**), or MRI. These diagnostic modalities can establish diagnosis of popliteal artery aneurysms and exclude other etiologies of a popliteal fossa mass (such as tumors or Baker cyst). Angiography can be misleading in the diagnosis of aneurysms because intraluminal thrombus may obscure the true size of the vessel (**Fig. 95.6**); however, it is essential for visualization of the inflow and outflow vessels necessary for revascularization. CT angiography can be a noninvasive way to provide this information (**Fig. 95.7**).

Treatment

Indications

Surgical treatment is indicated for all symptomatic popliteal aneurysms. Controversy exists regarding management of asymptomatic aneurysms, with size of 2 to 3 cm generally regarded as an indication for treatment.[48] In some reports, the average diameter of symptomatic aneurysms is smaller than asymptomatic lesions, and the degree of tortuosity or distortion of the aneurysm and the amount of mural thrombus have also been correlated to risk of complications.[39,47,49] Proponents of early repair at smaller sizes cite greater 5-year patency and limb salvage rates with elective aneurysm repair.[39]

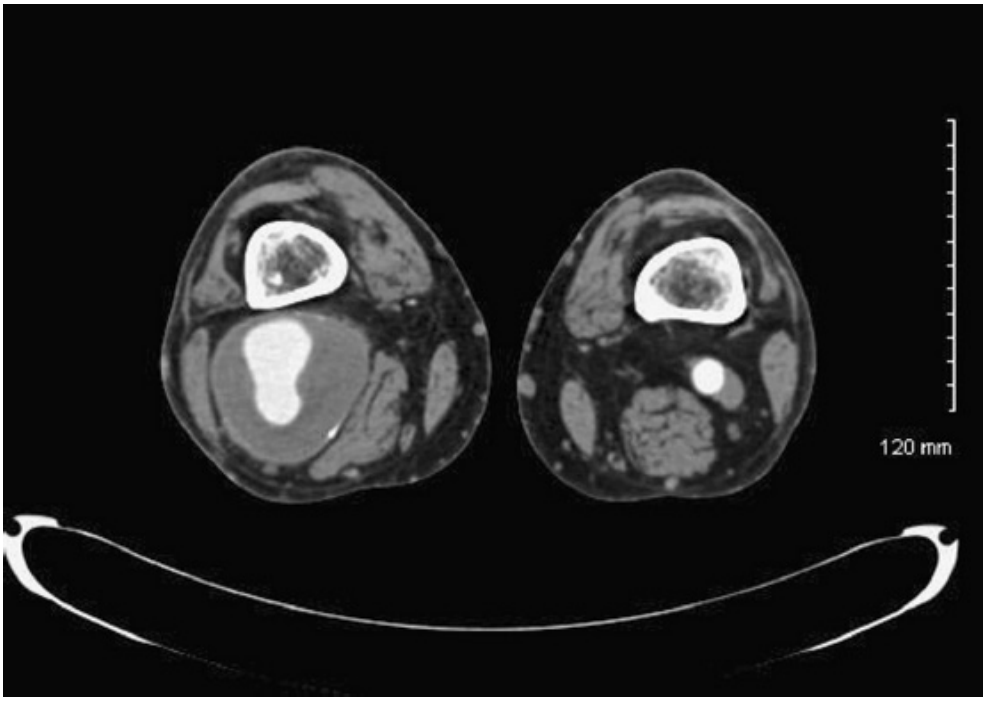


Figure 95.5 Computed tomography of a large right popliteal aneurysm with significant laminar thrombus present.

Figure 95.6 Arteriogram demonstrating a popliteal aneurysm associated with occlusion of the outflow tract presumably from repeated episodes of embolization. A bypass to the distal posterior tibial artery was successful.

Figure 95.7 Computed tomography arteriogram demonstrating right popliteal artery aneurysm and associated inflow and outflow.

The goals of surgical treatment are to eliminate the potential for complications and to preserve or restore adequate blood flow to the limb.

Surgical Technique

Most popliteal aneurysms are easily approached through standard medial thigh and calf incisions for exposure of the distal superficial femoral artery and the distal popliteal artery, respectively. The proximal anastomosis will need to originate from the common femoral artery if the entire superficial femoral artery is aneurysmal. Occasionally, the posterior approach is preferred for lesions confined to the popliteal fossa, especially when accompanied by symptoms due to compression of adjacent structures. Most aneurysms are left in situ, bypassed using a segment of saphenous vein, and ligated proximally and distally. The conduit of choice for bypass is autologous saphenous vein, which is harvested from the thigh, reversed, and tunneled along the course of popliteal artery. The proximal and distal anastomosis may be either end to end or end to side in configuration, with the aneurysm excluded from the circulation by proximal and distal ligatures. Ligation should be adjacent to the aneurysm to minimize the number of patent collaterals that are in continuity with the aneurysm.[49] Late expansion and rupture of a bypassed and ligated popliteal aneurysm can occur when patent geniculate arteries continue to perfuse and pressurize the aneurysm sac.

Tibial outflow is a concern in the management of popliteal artery aneurysms. When the distal popliteal and proximal tibial vessels are occluded with recent emboli, preliminary catheter-directed thrombolytic therapy is indicated prior to bypass.[41] Alternatively, balloon catheter embolectomy may be attempted. Frequently, bypass grafts must be carried to the distal tibial arteries. Extensive, combined femoral and popliteal aneurysms may require a femoral-popliteal or femoral-tibial bypass using in situ saphenous vein with a prosthetic graft segment replacing a common femoral artery aneurysm.

Popliteal aneurysms have been treated by an endovascular approach with stent-graft placement to exclude the aneurysm sac. Small series show a primary patency rate of about 50% at 14 to 18 months, and a cumulative patency of 74%, suggesting that this approach should be reserved for the more high-risk patient who requires intervention.[50–52]

The patient who presents with an acutely ischemic extremity secondary to popliteal aneurysm thrombosis is a management challenge. Popliteal aneurysms often thrombose because of repeated episodes of emboli to the

outflow vessels, which result in their occlusion. An expeditious arteriogram may identify a suitable outflow vessel for the bypass graft. If no target vessel is identified, intra-arterial thrombolytic therapy should be initiated with the goal of lysing thrombus in the tibial arteries to identify a suitable outflow vessel for vascular reconstruction. Although the embolic process may be chronic, results with thrombolytic therapy followed by bypass of the aneurysm have been much better than surgical therapy alone for the patient with an acutely occluded aneurysm and severe leg ischemia.

Results

Excellent results are obtained in asymptomatic aneurysms with intact distal vasculature. Patients with thrombosed aneurysms, or those in whom multiple episodes of embolization have occluded the tibial arteries, have less optimal results. Operative mortality is in the 0% to 2% range, with asymptomatic patients faring better than those presenting with acutely symptomatic lesions.[53,54] In patients undergoing revascularization before ischemic complications occur, 5- and 10-year graft patency rates are greater than 80% and limb salvage is 93% to 98%.[44,55] Graft patency rates in patients undergoing surgery after developing complications of their aneurysms are 60% and 48% at 5 and 10 years, respectively, and limb salvage rates are 60% to 80%.[40,44,55,56] Thrombolytic therapy, when successful, improves primary graft patency in patients presenting with acute limb ischemia.[57]

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Venous Disease

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Key Points

1. New drug therapies are impacting the treatment of acute deep venous thrombosis (DVT) and pulmonary embolism (PE).
2. Characterization of the disease is being scrutinized to allow for a better understanding of how treatment truly impacts patient outcomes.
3. The diagnosis and treatment of acute and chronic venous disease have made significant advances in the last decade.
4. The care of venous disease is an active and maturing discipline within the realm of the surgical disciplines.
5. Chronic venous disease treatment has experienced a resurgence of interest in the United States with new endoluminal and surgical interventions being investigated and utilized clinically.

VENOUS THROMBOEMBOLISM

Incidence, Risk Factors, and Categories

Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is a national healthcare concern. DVT affects greater than 250,000 patients annually, whereas PE affects greater than 200,000 patients per year. The incidence has remained constant since 1980 and increases with age. The cost of treatment for both DVT and PE (termed VTE) is in the billions of dollars per year. Although Virchow triad of stasis, vessel wall injury, and hypercoagulability have defined the events that predispose to DVT formation for the past 150 years, today the understanding of events that occur at the level of the vein wall including the influence of the inflammatory response on thrombogenesis is increasingly being recognized.[1–3]

Acquired risk factors for VTE include increasing age, malignancy, immobilization, surgery and trauma, oral contraceptive use, hormone replacement therapy, pregnancy and the puerperium, neurologic disease, cardiac disease, obesity, and antiphospholipid antibodies. Genetic risk factors include deficiencies of antithrombin, protein C and protein S, factor V Leiden, prothrombin 20210A, blood group non-O, dysfibrinogenemia, dysplasminogenemia, hyperhomocystinemia, reduced heparin cofactor II activity, elevated levels of clotting factors (e.g., factors II, VII, VIII, IX, X, and XI), and elevations in plasminogen activator inhibitor-1 (PAI-1). When a patient presents with an idiopathic VTE, there is family history of VTE, there is recurrent thrombosis, or there is thrombosis in unusual locations, workup for a hypercoagulable state may be indicated. Hematologic diseases associated with VTE include heparin-induced thrombocytopenia (HIT) and thrombosis syndrome, disseminated intravascular coagulation, antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, and myeloproliferative disorders. Risk assessment that takes all of these factors into consideration, such as the Caprini score, has been validated in many different clinical settings.[4]

Most DVTs affect the iliac, femoral, or popliteal lower limb veins. Presenting symptoms include unilateral leg pain and swelling, but some DVTs are silent, with the first manifestation of a PE. Some of the more common comorbidites include hypertension, surgery within 3 months, immobility within 30 days, cancer and obesity.

Venous Thromboembolism Diagnosis

Venous color duplex imaging is now standard, although D-dimer may be considered in low probability settings. The positive and negative predictive values for gray-scale imaging are inferior to color imaging. A meta-analysis of 13 studies comparing CT with ultrasound for proximal DVT found a sensitivity of 71% to 100% and specificity between 93% and 100%.[5] In symptomatic patients, sensitivity is approximately 93%, specificity 98%, accuracy 97%, with approximately 30% of studies indeterminate in the calf.[6] Data from the Prospective Investigation of Pulmonary Embolism Diagnosis II, a multicenter study of 711 patients, were used to compare the clinical value of CT venography (CTV) after multidetector CT angiography (CTA) with venous compression ultrasonography for the diagnosis of VTE. There was 95.5% concordance between CTV and ultrasonography for the diagnosis or exclusion of DVT ($\kappa = 0.809$). Attesting to the accuracy of ultrasound, the sensitivity and specificity of combined CTA and CTV were equivalent to combined CTA and ultrasonography.[7]

The biomarker D-dimer is a useful test to rule out, not rule in DVT. In a patient with a low pretest probability for DVT (such as with a negative Wells score), if a D-dimer biomarker test is negative, no further testing is necessary and ultrasound imaging may be omitted in this situation. D-Dimer requires that a high-sensitivity D-dimer assay (such as the advanced turbidimetric method or ELISA) is used. On the contrary, if the D-dimer is positive, then duplex must be performed even if the pretest probability is high, as a positive D-dimer and a positive risk assessment is associated with DVT in only approximately 70% of cases.[8] A highly soluble P-selectin, along with a positive Wells score, may allow for the diagnosis of DVT in greater than 90% of cases, although this biomarker is research based and is not clinically available.[9]

The high negative predictive value (NPV) of color duplex Doppler ultrasound both above and below the knee supports withholding anticoagulation on the basis of a good-quality negative study alone, and clinical data also support that strategy.[10] A single good-quality color duplex Doppler study is sufficient (NPV >99.5%) to exclude proximal DVT; repeat scanning is seldom indicated unless the initial study was technically

suboptimal. A truly negative study means that all the segments of the leg, including the external iliac, common femoral, femoral, popliteal, and calf veins, are negative by ultrasound imaging and clear by Doppler flow. While duplex ultrasound has a high accuracy for proximal DVT, it is less accurate for the diagnosis of distal DVT and it is highly operator dependent in this location. During pregnancy the aforementioned recommendations remain, but it is very important to attempt to assess for iliac vein thrombosis at the time of ultrasound evaluation. For the future, other biomarkers in addition to D-dimer for the diagnosis of DVT are under investigation, as a means to augment venous imaging.[11]

For the diagnosis of superficial vein thrombophlebitis (SVT), duplex ultrasound is also important.[12] In a prospective epidemiologic study, including 844 patients with symptomatic SVT, 210 (24.9%) had concomitant DVT at the time of diagnosis of SVT. Of the 600 patients without DVT, over the next 3 months, 58 (10.2%) developed thromboembolic complications, including 3 (0.5%) with PE, 15 (2.8%) with DVT, 18 (3.3%) with extension, and 10 (1.9%) with recurrence of SVT. These events occurred despite the use of anticoagulant treatment. Thus, it is important to perform good duplex imaging in patients diagnosed with SVT.

For pediatric DVT, as symptom development is often subtle, the diagnosis again is usually made with compression color duplex imaging.[13] Magnetic resonance venography (MRV) and computed tomography venography may also be useful in evaluating upper extremity DVT as well as iliocaval DVT, balancing the risk of anesthesia (when it is required in this age group), radiation, and contrast usage.

Other conditions may be confused with DVT and include lymphedema, muscle strains, and muscle contusion. Iliac vein obstruction may lead to unilateral leg edema (May–Thurner syndrome), while the presence of a cyst behind the knee may produce unilateral lower leg pain and edema. Other causes of leg swelling include systematic problems such as cardiac, renal, or hepatic abnormalities. These systemic problems usually lead to bilateral edema.

Pulmonary Embolism

Testing for PE begins with prior probability estimation for all patients. Two of the most widely known and validated diagnostic scoring systems are the Wells criteria (or modified/dichotomous Wells criteria) and Geneva score.[14–16] They use a combination of physical examination, history, and vital signs to predict the likelihood of PE. D-Dimer testing is used to exclude PE for patients with low prior probability for DVT. D-Dimer testing has no role in diagnosis if prior probability is not low. Use of D-dimer testing in PE diagnosis requires that a high-sensitivity D-dimer assay (such as the advanced turbidimetric method or ELISA) validated at the local institution be used. Patients with both low probability and negative D-dimer require no further investigation as the NPV is 99%.[17]

The diagnosis of PE has involved ventilation-perfusion (V/Q) scanning and pulmonary angiography. However, newer techniques include spiral computed tomographic scanning and magnetic resonance imaging. The sensitivity of V/Q scanning was defined in PIOPED I at 98%, but specificity was low at 10%.[18] By combining clinical factors with V/Q scan, levels of sensitivity and specificity greater than 95% were achieved. With a high-probability V/Q scan, two risk factors positive for PE, the sensitivity was 97%; with one risk factor, 84%; and with no risk factors, 82%. Similarly, with a normal V/Q scan, the chance of PE was essentially 0, irrespective of the risk factor status. Thus, a normal V/Q scan or a high-probability scan provided good diagnostic information that could be used to base treatment on. However, only a small portion of V/Q scans are in one of these two categories, leaving many patients needing further testing.

Multidetector helical CTA is the primary imaging modality, although V/Q scanning remains viable (particularly for patients with otherwise normal lungs in whom interpretability of the test is optimal), and a positive lower-extremity color duplex Doppler study in a high-probability patient can establish the diagnosis of VTE without lung imaging. However, the problem with using only lower extremity duplex imaging is that a baseline study in the chest is not obtained for later comparisons and as such, we do not favor using lower extremity duplex imaging as a substitute for the diagnosis of PE. Additionally, the accuracy for lower extremity imaging as a surrogate for PE is relatively low. Multidetector scanners have significantly improved the sensitivity and specificity, as well as the positive and negative predictive

value of CTA. Outcome studies have found the sensitivity and specificity of CTA to be greater than 95%, and a negative CTA carries a 3-month risk of VTE of 1% to 2%. CTA establishes the diagnosis of PE if it is positive in an intermediate- or high-probability patient, or in a low-probability patient with findings of a mainstem or lobar embolus. It excludes the diagnosis of PE in low-probability patients with negative scans. Discordance between prior probability and CTA findings requires further investigation, as well as technically inadequate studies.[7] Other diagnostic tests may include V/Q imaging or pulmonary angiography.

Outcome studies have found comparable results between pulmonary angiography and CTA; a negative result with either study confers approximately a 1% VTE rate within 6 months. However, because angiography is invasive, it carries a greater risk of complications and mortality. The mortality from angiography has been estimated at 0.5%, while 1% may experience major complications, including arrhythmias, hypotension, bleeding, and nephrotoxicity.[19] Without a higher standard to appeal to, one cannot discuss specificity and sensitivity of pulmonary angiography using commonly accepted definitions of these terms. Instead, the accuracy of pulmonary angiography is discussed in terms of interobserver variability in the reading of pulmonary angiograms obtained in the context of large multicenter trials. Studies demonstrate that the larger the embolus, the better the interobserver agreement. For segmental and larger emboli, agreement exceeds 95%. For subsegmental emboli, agreement is considerably less. We do not recommend pulmonary angiography, except in certain circumstances, such as with inadequacy of V/Q imaging or when catheter-directed thrombolysis (CDT) is recommended.

Recently, the efficacy of magnetic resonance angiography (MRA), MRV, or the combination of the two in the diagnosis of acute PE has been studied.[20] The gold standard used for comparison was a composite end-point of CTA, CTA-CTV, V/Q scan, lower extremity ultrasonography, D-dimer assay, and clinical assessment. Overall, MRA and MRA-MRV were found to be poor tests for the diagnosis of PE. Approximately 25% of the 371 patients enrolled in a large multicenter study had a technically inadequate MRA, and 48% had either an inadequate MRV or MRA. Considering all patients enrolled, MRA alone identified only 57% of PEs and had a sensitivity of

78% when only patients with adequate studies were considered. The combined MRA-MRV studies had a sensitivity of 92%, but only about half of the patients had technically adequate studies. These poor results are generally felt related to the technical difficulties of MRA in identifying abrupt vessel termination and capturing adequate images of the chest vessels secondary to motion artifact. At this time, MRA-MRV is not generally recommended and only considered in centers with a great deal of experience. Because of its low sensitivity and specificity, transthoracic or transesophageal echocardiography has limited diagnostic value for PE.[21]

For critically ill patients too unstable for transport, echocardiography can suggest the diagnosis of PE by showing dilatation of the RV or hypokinesis. Commonly, acute changes in the RV pressure, size, and function are seen, indicating increased RV strain and pulmonary arterial pressures. These changes suggest PE in the absence of alternative diagnoses. Although of limited value in the diagnosis of PE, echocardiography is of great prognostic use in stratifying risk for patients with acute PE. Right ventricular dysfunction or dilatation in acute PE is associated with worse outcomes, including increased mortality rate.

Biomarkers include B-type natriuretic peptide (BNP), released by ventricular myocardial cells in response to wall stretch and volume overload. BNP is a prognostic (not diagnostic) biomarker for PE. BNP levels generally indicate RV strain due to elevated pulmonary vascular resistance in the lungs. If measured early (within 4 hours of admission for PE), elevated BNP levels (>90 pg/mL) demonstrate a sensitivity of 85% and a specificity of 75% in predicting PE-related outcomes. Conversely, normal BNP values in the setting of acute PE carry a 97% to 100% NPV for in-hospital death. Another biomarker is troponin released from damaged myocardial cells. When elevated in acute PE, troponins represent myocyte ischemia and microinfarction due to acute cardiac strain of the right ventricle. Approximately 30% to 50% of patients with large PE will have elevations in troponins I and T that are mild and short lived. They correlate with worse RV function and a high incidence of complications. Normal troponin T levels have a 97% to 100% NPV for in-hospital death. These two biomarkers are not part of routine algorithms.[17]

Axillary/Subclavian Vein Thrombosis

Thrombosis of the axillary/subclavian vein accounts for less than 5% of all cases of acute DVT. However, it may be associated with PE in up to 10% to 15% of cases and additionally can also be the source of significant disability. Primary axillary/subclavian vein thrombosis results from obstruction of the axillary vein in the thoracic outlet, the so-called Paget–Schroetter syndrome, noted especially in healthy muscular athletic individuals. Such thrombosis may also occur in patients with hypercoagulable states. Secondary axillary/subclavian vein thrombosis results from mediastinal tumors, congestive heart failure, and nephrotic syndrome. Patients with axillary–subclavian venous thrombosis often present with arm pain, edema, and cyanosis. Superficial venous distention may be apparent over the arm, forearm, shoulder, and even the anterior chest wall.[22]

Upper extremity venous duplex ultrasound is used to diagnose suspected axillary–subclavian vein thrombosis. Thrombolysis and phlebography are often considered next. If phlebography is performed, it is important that the patient undergo positional phlebography with arm abduction to 120 degrees to confirm extrinsic subclavian vein compression at the thoracic outlet. Venous compromise is further evidenced by prominent collateral veins. Since a cervical rib may be the cause of such obstruction, chest x-ray film should be obtained to exclude its presence.[23]

Standard Therapy for VTE

Treatment

The traditional treatment of VTE is systemic anticoagulation, which reduces the risk of PE, extension of thrombosis, and thrombus recurrence. Immediate anticoagulation should be undertaken as the recurrence rate for VTE is higher if anticoagulation is not therapeutic in the first 24 hours. For DVT, since duplex imaging is rapidly obtained, usually testing precedes anticoagulation while for PE, anticoagulation is recommended either simultaneous with or before testing. Recurrent DVT can still occur in up to one-third of patients over an 8-year period, even with appropriate anticoagulant therapy.

As a result of the evidence demonstrating the effectiveness and safety of DOACs, they are now recommended as first-line treatment of acute VTE over VKAs in patients whom do not have an associated cancer (grade 2B).[24] Currently, the direct Xa inhibitors apixaban, rivaroxaban, and edoxaban have been FDA approved for the treatment of VTE, while dabigatran is the sole-approved direct thrombin inhibitor. The DOACs are all administered orally, have fixed doses that do not need to be weight based adjusted, and do not need monitoring. One of the appealing aspects of VKAs (and to a lesser extent LMWH), is the ability to be quickly reversed by protamine (for heparin and to a lesser degree LMWH), fresh frozen plasma (FFP), or prothrombin complex concentrate (PCC) if indicated. In addition, there are available laboratory tests to monitor reversal. Until recently, DOAC reversal was limited to supportive measures, PCC or selective dialysis. The FDA recently approved idarucizumab (Praxbind™), a monoclonal antibody, that binds to dabigatran and can reverse its anticoagulant effects within minutes[25] and andexanet alfa, a recombinant factor Xa decoy, for all factor Xa inhibitors, including DOACs, LMWHs, and fondaparinux.[26] Clinical trials have shown the andexanet alfa can effectively reverse DOACs anticoagulant effect without any known thrombotic events in healthy patients.[27] The final reversal agent progressing in development with FDA fast track designation for hemorrhage is Aripazine (PER-977, ciraparantag, Perosphere Inc.), a water-soluble, catatonic molecule available in intravenous formulation. This agent noncovalently binds to and reverses the anticoagulation of all anticoagulation agents (LMWH, UFH, FXa inhibitors, dabigatran) in animal models and healthy volunteers.[27]

There are several scenarios which would preclude the use of DOACs; for example, patients with mechanical heart valves, patients who cannot afford the cost of the medication, and patients with impaired renal function. Given that all of the comparison studies showed noninferiority, in many cases either a DOAC or VKA is acceptable. However, certain patients are at much higher risk of treatment failure with VKAs than others defined by a scoring system SAMe-TT_2R_2.[28]

Unfractionated heparin or low–molecular-weight heparin (LMWH) is given along with oral anticoagulation with vitamin K antagonists (usually warfarin [Coumadin]). It is recommended that the international normalized

ratio (INR) be therapeutic for 2 consecutive days before stopping heparin or LMWH.[29] LMWH has become the standard for treatment because it is administered subcutaneously, requires no monitoring (except in certain circumstances, such as renal insufficiency or morbid obesity), and is associated with a decrease in bleeding potential.[30]

Compared to standard unfractionated heparin, LMWH has significantly improved bioavailability, less endothelial cell binding and protein binding, and improved pharmacokinetics.[31] The half-life of LMWH is dose independent and it is administered in a weight-based fashion. LMWHs may decrease indices of chronic venous insufficiency (CVI) compared with standard therapy when used over an extended period. Warfarin should be started after heparinization is therapeutic to prevent warfarin-induced skin necrosis, as warfarin causes inhibition of protein C and S before factors II, IX, and X, leading to paradoxical hypercoagulability at the initiation of therapy. For standard unfractionated heparin, this requires a therapeutic activated partial thromboplastin time; for LMWH, warfarin is administered after an appropriate weight-based dose of LMWH is administered and allowed to circulate.

Complications

Bleeding is the most common complication of anticoagulation. All currently approved VTE treatment agents carry the risk of significant bleeding complications, as they all target various aspects of the coagulation cascade. When treating VTE, the incidence of major bleeding at 3 months using unfractionated heparin or enoxaparin is approximately 4.3% and 2.9%, respectively. The rate of major bleeding using warfarin for the treatment of VTE is also approximately 2% during the initial 3 months of anticoagulation. Apixaban and rivaroxaban have a major bleeding incidence of approximately 0.5% (at 3 months) and 0.8% (during treatment follow-up period), respectively.[32,33]

HIT occurs in 0.6% to 30% of patients. Although historically morbidity and mortality rates have been high, it has been found that early diagnosis and appropriate treatment have decreased these rates.[34] HIT usually begins 3 to 14 days after heparin is begun, although it can occur earlier if there has been exposure to heparin in the past. A heparin-dependent antibody binds to

platelets, activates them with the release of procoagulant microparticles leading to an increase in thrombocytopenia, resulting in thrombosis.[35] Both bovine and porcine unfractionated heparin and LMWH have been associated with HIT, although the incidence and severity of the thrombosis are less with LMWH. Even small exposures to heparin can cause the syndrome. The diagnosis should be suspected with a 50% or greater drop in platelet count, when the platelet count falls less than 100,000/mL or when thrombosis occurs during heparin or LMWH therapy.[36] A highly sensitive but poorly specific ELISA test detects the antiheparin antibody in the plasma. The serotonin release assay is another test that is more specific but less sensitive.[37]

When the diagnosis is made, heparin must be stopped and warfarin should not be given until an adequate alternative anticoagulant has been established and the platelet count has normalized. LMWHs cannot be used as substitutes as studies demonstrate high cross-reactivity with standard heparin antibodies. Agents that have been approved by the Food and Drug Administration (FDA) as alternatives include the direct thrombin inhibitor argatroban and bivalirudin (Table 96.1). Fondaparinux has also been found effective for treatment of HIT, but it is not FDA approved for this indication. The use of these alternative agents is given 2C and 1C evidence.[38]

Duration of Anticoagulation

The recommended duration of anticoagulation for the treatment of provoked proximal and symptomatic distal VTE is 3 months (Grade 1B). Extended therapy is considered under the following circumstances: Previous VTE event, thrombophilias associated with a high risk of recurrence, and unprovoked VTE. Virtually all agree that for a second unprovoked VTE, anticoagulation should be continued due to the high recurrence risk well past 3 months in those patients with low/moderate bleeding risks (grades 1B, 2B).[24] For patients with diagnosed hereditary thrombophilias, those that are associated with a higher risk of VTE recurrence (protein C/protein S deficiency [especially with a family history], antithrombin deficiency, homozygous factor V Leiden and homozygous prothrombin 20210 gene mutation, and multiple thrombophilias in the same patient), prolonged therapy is recommended. Although Factor V Leiden heterozygous mutation alone

does not confer an increased risk of recurrence, when combined with prothrombin 20210 gene mutation, recurrence is increased and prolonged anticoagulant therapy is recommended. Among acquired thrombophilias, antiphospholipid antibodies and active cancer mandate extended therapy.[39]

Unprovoked first-time VTE remains a difficult clinical scenario, as one must balance the competing risks and implications of recurrent VTE and major bleeding. D-dimer and repeat duplex testing have both been advocated to determine risk of recurrence with cessation of anticoagulation. D-dimer is measured approximately 1 month after stopping oral anticoagulation. Elevation of D-dimer suggests that active thrombosis is occurring and the rate of recurrence is higher (15%) compared to 6.2% with a normal D-dimer. This risk can be mitigated with resumption of anticoagulation which reduces the VTE rate down to 2.9%.[24,40] The use of repeat serial lower extremity ultrasound to determine the state of the thrombosed veins has been studied, with the assumption that if the veins are occluded with fibrotic scar tissue, flow will be sluggish and the risk of recurrent VTE elevated. The usefulness of this test is less certain, as it is difficult to reproduce in day to day clinical practice.

Table 96.1 Elements of a Complete Hypercoagulability Evaluation

Hypercoagulability Evaluation
Activated Protein C Resistance
Antithrombin III Activity
Antithrombin III Antigen
Cardiolipin Antibody
D-dimer
Dilute Russell's Viper Venom Test
Factor VIII Assay
Fibrinogen (Clottable)
Fibrinogen Antigen
Hexagonal Phospholipid Neutralization
Plasma Homocysteine Plasminogen Activity
Protein C Activity
Protein C Antigen
Protein S Antigen (Free)
Prothrombin 20210 Mutation Detection
PT (Prothrombin Time)
PTT (Partial Thromboplastin Time)

Not all tests for every evaluation are recommended.

Adapted from https://www.pathology.med.umich.edu/handbook. Accessed February 7, 2020.

Emerging Medical Treatments and Trends in VTE Managements

1 In patients with cancer who develop acute VTE, LMWH has been considered definitive first-line treatment. However, meta-analysis of cancer patients enrolled in phase 3 DOAC trials demonstrates the feasibility and safety in cancer patients, although this analysis was hampered by lack of comparison to LMWHs as the standard of care.[41] Recently, the DOACs rivaroxaban and edoxaban have been studied in patients with active malignancy. The Hokusai-VTE cancer trial enrolled 1,050 patients with cancer-associated VTE who were then randomized to edoxaban compared to LMWH. Results from this trial demonstrated that the primary event (recurrent DVT or major bleeding) occurred in 12.8% with edoxaban and 13.5% with LMWH, meeting the endpoint of noninferiority for DOAC compared to LMWH.[42] Overall, a reduction in recurrent VTE events in the edoxaban group was offset by an increase in bleeding complications, higher in patients with primary GI malignancy.[42] A smaller RCT, SELECT-D, evaluated rivaroxaban compared to LMWH in patients with cancer-associated VTE with similar findings: recurrent VTE was 4% with rivaroxaban and 11% with dalteparin, but with an increased rate of major bleeding in patients treated with rivaroxaban.[43] As a result of this new information, the International Society of Thrombosis and Haemostasis has recommended the use of DOACs in patients with cancer-associated VTE but without GI cancer and with low bleeding risk.[44]

One new advance is the validation of the HERDOO2 score, which was developed and prospectively validated. This score identifies women at low risk of recurrence following unprovoked VTE who may safely discontinue anticoagulation following short-term (standard) treatment. In this score, women receive a point for (a) hyperpigmentation, edema, or redness in either leg, (b) VIDAS D-dimer ≥250 μg/L, (c) Obesity (BMI ≥ 30), and (d) Older age (≥65 years). Patients with 0 or 1 point are at low risk for recurrent VTE and may discontinued long-term anticoagulation therapy. Women who were defined as both low risk and discontinued therapy have a 3.0% risk of recurrent VTE per patient year, compared to an 8.1% risk in high-risk women who discontinue anticoagulants.[45]

The advent of the DOACs has reinvigorated the use of low-dose anticoagulation to improve the risk–benefit profile of extended therapy via decreased bleeding risk. Historically, low-dose VKAs resulted in similar

bleeding profile to standard therapy.[46] More recently, both treatment and thromboprophylaxic doses of rivaroxaban and apixaban have been shown to be more effective in prevention of VTE recurrence with no increased risk of bleeding compared to placebo or ASA.[47,48] The WARFASA and ASPIRE trials have also demonstrated a reduced risk of VTE recurrence in patients treated with aspirin compared to placebo.[49,50] However, this decrease in VTE recurrence with ASA was much less than with low-dose DOAC. Indeed, network meta-analysis has shown that some DOACs have the most favorable profiles compared to warfarin, and aspirin.[51,52]

Calf Vein DVT

There is clinical equipoise to the treatment of calf vein DVT. Withholding anticoagulation in outpatients with suspected calf vein DVT, if serial compression ultrasound is negative for proximal DVT at baseline, and if again negative 1 week later results in 3-month pooled estimate thromboembolic risk of 0.6%.[53] Given these findings, the recently completed Compression Alone Versus Anticoagulation for Symptomatic Calf Vein Thrombosis Diagnosed by Ultrasonography (CACTUS) trial was performed with the goal of assessing the safety of withholding anticoagulant treatment in patients with isolated symptomatic calf vein DVT at low risk for proximal extension/VTE, as defined by no personal VTE history or active malignancy.[54] LMWH did not reduce proximal extension or VTE and resulted in increased bleeding complications. A limitation of this study is that it was underpowered for its endpoints, as only 259 patients were enrolled and the calculated power calculation for the study was 572 patients. Despite poor enrollment, the CACTUS trial signifies progress in one of VTE's most debated topics: it represents the first effort to rigorously study treatment algorithms for calf vein DVT and adds to accumulating data suggesting that avoiding anticoagulation may be safer and more cost effective for low-risk patients. Data from smaller studies evaluating low-risk patients with calf vein DVT suggests that shorter duration (1 month) and intensity (full-dose LMWH ×1 week and ½ dose for 3 weeks) had a low recurrence and VTE complication rate, raising the provocative question as to whether patients at high risk need to be treated in the same manner as proximal DVT.[55]

For pediatric DVT, the two mainstays of treatment are either anticoagulation with continued monitoring or thrombolysis. Recently LMWH has been FDA approved for the treatment of pediatric DVT. Current recommendations are to use LMWH for 3 to 6 months, with subsequent continuation of therapy based on the persistence or absence of clinically significant prothrombotic risk factors. Recurrence of DVT in children carries a lower risk than in adults, with cumulative incidences of 6% to 11% versus 12% to 22%, respectively. The risk of PTS appears as great in children as in adults, although severe PTS is uncommon. Compression stockings are indicated in children to treat PTS. For neonatal DVT, standard LMWH is indicated, with a shortened duration compared to older children.[13]

Nonpharmacologic Treatments

Postthrombotic syndrome (PTS) results from loss of competence of the venous valves as a result of DVT and vein wall fibrosis or persistent venous obstruction, or a combination of both. It can cause significant morbidity in the form of pain, swelling, skin breakdown, and ulcerations. A Cochrane meta-analysis found a strong effect (OR 0.31) for prevention of PTS using graduated compression stockings beginning within 2 weeks of onset of DVT, with important data highlighted from two open-labeled randomized single-center studies that utilized stockings of 30 to 40 mm Hg for 2 years after DVT.[56]

From these data, stockings of 30 to 40 mm Hg gradient should be recommended to most patients with DVT, for a minimum of 2 years post-DVT, and longer if they have symptoms of PTS. There is a new study (the SOX trial) that would suggest that stockings may not prevent PTS after a first proximal DVT.[57] In addition, ambulation with good compression does not increase the risk of PE, while significantly decreasing the incidence and severity of the PTS.[58,59] Based on the SOX trial results, the most recent ACCP guidelines suggest not using compression stockings to prevent PTS (grade 2B evidence). It must be remembered that the use of strong compression and early ambulation after DVT treatment can significantly reduce the symptoms of pain and swelling resulting from the DVT, even if the development of PTS is not prevented, and a new study suggests that immediate application of compression (rather than the more liberal criteria

in the SOX trial) after DVT diagnosis may result in a small decrease in PTS and residual vein obstruction.[60] Early ambulation has the potential to decrease PTS and improve patients' quality of life (QOL). Thus, patients should be encouraged to ambulate as part of their post-DVT care recommendations and use stockings, especially if they have pain and swelling from their DVT.[24]

IVC Filters

The traditional indications for the use of IVC filters include a complication of anticoagulation, a contraindication to anticoagulation, and failure of anticoagulation. Protection from PE has been greater than 95% using cone-shaped wire-based permanent IVC filters.[61] Cone-shaped filters have a lower incidence of IVC thrombosis compared with basket-shaped filters, and a recent study between the two filter types was stopped early because of the high rate of IVC thrombosis with the basket-shaped device.[62]

The success achieved with filters has expanded the indications, including free-floating thrombus longer than 5 cm, when bleeding risk with anticoagulation is excessive, when the risk of PE is felt to be very high, and to allow for the use of perioperative epidural anesthesia.[63–65] Filters can be permanent or optional (retrievable). If a retrievable filter is left in to become a permanent filter, the long-term fate of that filter has yet been defined.

Filters are usually placed in an infrarenal location. However, they may also be placed in the suprarenal location or in the superior vena cava. Indications for suprarenal placement include high-lying clot, pregnancy, women of childbearing potential, or a previous device that has failed or become filled with clot. Sepsis is not a contraindication to the use of wire-based filters since the trapped material can be sterilized with antibiotics. Although filters have been placed under x-ray guidance, percutaneous techniques for filter insertion using bedside external ultrasound or intravascular ultrasound are now being recommended. Transabdominal external ultrasound is difficult in the face of morbid obesity, overlying bowel gas, or open abdominal wounds. In these instances, intravascular ultrasound has been found to be more successful.[66]

Other than one randomized prospective study on the use of filters as treatment of DVT (which is not how filters are traditionally used), evidence

for the use of filters is given a 2C level of evidence.[24]

Thrombolytic and Surgical Procedures for Deep VTE

For DVT treatment, the goals are to prevent extension or recurrence of DVT, prevent PE, and minimize the late squeal of thrombosis, namely CVI. Standard anticoagulants accomplish the first two goals but not the third goal. The PTS (venous insufficiency related to venous thrombosis) occurs in up to 30% of patients after DVT and even greater with more proximal iliofemoral DVT. Experimentally, prolonged contact of the thrombus with the vein wall increases damage.[67] The thrombus initiates an inflammatory response in the vein wall that can lead to vein wall fibrosis and valvular dysfunction. Some patients with proximal DVT may also be candidates for thrombus removal, if they meet specific criteria, or if they have venous ischemia, as described below. Early thrombus removal may be performed for patients with all of the following: First episode of acute iliofemoral DVT, symptoms less than 14 days in duration, low risk of bleeding, ambulatory patient with good functional capacity and acceptable life expectancy, and moderate to severe symptoms (which can be determined by a Villalta score ≥10 after a trial of anticoagulation).[68–75]

While not currently endorsed by major society guidelines, CDT has been shown to decrease symptoms of pain and swelling at 30 days and may decrease development of PTS in highly selected patients. Following initial symptoms, CDT is ideally performed within 2 weeks but may be performed up to 4 weeks. CDT has been employed in many nonrandomized studies and, in small randomized trials, was more effective than standard therapy in patients with acute proximal lower extremity DVT, improving QOL. Results are optimized by combining CDT with mechanical devices.[69,71] These devices hasten thrombolysis, decrease the amount of thrombolytic agent needed, and decrease bleeding potential. The Attrack trial, while not showing a benefit in PTS overall, did results in improvements in patients with specific iliofemoral DVT.[76] Importantly, this multicenter NIH sponsored trial demonstrated that there is no benefit in performing aggressive thrombus removal in the femoropopliteal location alone.

Phlegmasia and venous gangrene is a rare clinical phenomenon that places the affected limb at risk of ischemia. Phlegmasia cerulea dolens (PCD) is an uncommon form of DVT characterized by severe pain, swelling, cyanosis, and edema. This is preceded by phlegmasia alba dolens, which is characterized by the same clinical signs except the limb is pale and white due to early ischemia, and not yet cyanotic. Venous gangrene is defined as skin necrosis, discoloration, and documented VTE. Treatment for PCD or venous gangrene is the same as for proximal DVT, with an emphasis on immediate anticoagulation. Early thrombus removal is the treatment of choice in patients with limb-threatening venous ischemia due to iliofemoral venous thrombosis, with or without associated femoropopliteal venous thrombosis.[68,77,78] These patients require CDT with pharmacomechanical assist. Surgical venous thrombectomy is reserved for patients who have contraindications to thrombolysis[79] or when thrombolysis is not indicated or effective, although the number of times surgical venous thrombectomy is actually necessary and used in quite small.

Thrombolytic therapy for PE remains controversial. Although agents lyse thrombus effectively, recurrence rates and patient mortality rate were not reduced. However, the original studies were not powered to address this outcome. Results are best if patients are young, the embolus is less than 48 hours old, and the embolus is large. Streptokinase, urokinase, and tissue plasminogen activator have all been used.[80]

All agents rapidly dissolve clot, but by 7 days, the advantages for all three agents decrease. The benefit of thrombolytic agents for PE thus appears to be greatest in patients who would die as a result of massive PE in the first hour after the PE occurs, which can occur in up to 10% of cases. However, more recent data suggest that thrombolysis may be useful in patients with right ventricular dysfunction without hemodynamic instability and it has been suggested that thrombolysis will improve outcomes if patients have evidence of right-sided heart changes.[81–86] In addition, thrombolysis therapy has been recommended in patients without hypertension who are judged to have a low risk of bleeding.[24] The development of multidisciplinary teams for the aggressive treatment of patients with significant PE is a national trend which appears to be having a positive effect on the morbidity and mortality of PE.

Contraindications to thrombolytic therapy include:

Allergies

- Alteplase (recombinant tissue plasminogen activator); Heparin; Iodinated contrast

Anatomic criteria

- DVT not involving the iliac system (i.e., distal DVT, isolated femoral-popliteal DVT; Symptoms lasting > 28 days)

Bleeding risk

- Active bleeding; Bleeding diathesis; Recent (<10 days) history of surgery, CPR, trauma, obstetrical delivery, cataract surgery, major invasive procedure; Recent (<3 months) internal eye surgery, hemorrhagic retinopathy, gastrointestinal bleed; Recent history of stroke or intracranial lesion; Severe liver dysfunction

Comorbidities:

- Active cancer (except nonmelanoma primary skin cancer); Pregnancy; Severe hypertension; Severe renal impairment

Functional status:

- Chronic nonambulatory status; Inability to provide consent; Inability to tolerate catheter-directed therapy (strict bedrest 24–72 hours); Life-expectancy <2 years[87]

Pulmonary Embolectomy

Surgical approaches for PE are indicated for patients with massive PE with hypotension who require large doses of vasopressors. These are often patients in whom thrombolytic agents have been unsuccessful. Open pulmonary embolectomy is associated with high rates of morbidity and mortality. Today, open pulmonary embolectomy is limited to those who require manual cardiac massage for hypotension or those in whom catheter pulmonary embolectomy fails. However, there may be a more expanded role for pulmonary embolectomy in the future.[88]

Superficial Thrombophlebitis

SVT is a well-recognized clinical entity, characterized by a painful erythematous and palpable cord-liked structure, usually compromising the lower extremities but capable of affecting any superficial vein in the body. Thrombophlebitis is believed to have a multifactorial etiology, in which Virchow triad of altered blood flow, changes in the vessel wall, and abnormal coagulation are recognized to play a significant role. SVT has been considered a benign disease requiring only conservative management with compression, nonsteroidal anti-inflammatory medications, and lower extremity elevation. Recently SVT, especially above-the-knee superficial thrombophlebitis, has been reported to coexist with DVT, to propagate to popliteal or femoral level and to even cause PE.[89] A medical approach using anticoagulant therapy appears as the treatment of choice when there is above-knee SVT with deep venous system involvement.

The incidence of SVT occurs in approximately 125,000 people in the United States per year. However, the actual incidence is likely far greater as these statistics may be outdated and many cases go unreported. Approximately 54% to 65% of the reported cases affect females with an average age of 58 years. The most frequent predisposing risk factor for SVT is varicose veins, occurring in 62% of patients. Other risk factors include immobilization, trauma, postoperative states, age >60 years, obesity, tobacco use, history of DVT or SVT, pregnancy, puerperium, autoimmune disease, use of oral contraceptives or hormonal replacement therapy, and hypercoagulable state. Hypercoagulable screening should be considered in patients with ascending or worsening thrombophlebitis despite initial treatment.[90,91] Malignancy has been reported as a risk factor for developing SVT, affecting 13% to 18% of patients.

The overall recurrence of SVT was described as 18% over 15 months, equally frequent in varicose and nonvaricose phlebitis. Deep venous reflux increases the recurrence rate to 33%, while hypercoagulable states increase the recurrence rate to 42% over the same period of time. The clinical symptoms and signs for SVT are overt. Duplex ultrasound imaging of the affected extremity should be performed to rule out extension of the process into the deep venous system or concomitant DVT.[90]

Duplex ultrasound shows the extent of the SVT, its relation to the veins connecting with the deep vein system, and the presence of concomitant DVT. In addition, duplex ultrasound allows checking the competence of the valves

in the superficial and deep veins. Complete thrombophilia workup is not routinely recommended. However, it may be indicated in selected patients with recurrent primary thrombophlebitis or aggressive thrombophlebitis. Screening for underlying diseases, including malignancy or vasculitis, is performed if signs or symptoms suggest the presence of such a problem.

Treatment

Several therapeutic approaches have been proposed for patients with SVT. These include ligation or vein stripping of the affected vein, elastic stockings, NSAIDs to reduce pain and inflammation, and variable doses of unfractionated heparin or LMWH followed by oral anticoagulant therapy. There is no consensus on the optimal treatment of SVT in clinical practice.

The course of treatment for SVT should be tailored accordingly to its location and concomitant DVT if there is any associated infectious process. Thrombus location in trunks of either the great saphenous vein (GSV) or small saphenous vein (SSV) may have the highest risk of extension into the deep vein system and thus require more aggressive treatment than other locations. The treatment for primary SVT localized in the distal GSV and tributaries veins consists of ambulation, warm soaks, compression, and NSAID agents. If the patient presents risk factors for DVT, pharmacologic prophylaxis should be considered seriously.

In a large prospective randomized study (CALISTO), fondaparinux was found effective in limiting a series of endpoints including death, PE, DVT, and extension or recurrence at days 47 and 77 after SVT diagnosis. This was in patients with axial vein SVT of at least 5-cm length with the thrombus at least 3 cm from the SFJ. Less extensive SVT requires only symptom control with oral or topical NSAIDs.[92] Both fondaparinux and LMWHs are administered subcutaneously, which can be inconvenient, painful and lead to decreased compliance. In recent years, the rapid adoption of direct oral anticoagulants (DOACs) for a variety of indications has led to the question as to whether DOACs may offer comparable results for patients with SVT. This hypothesis was tested recently in the SURPRISE trial, a randomized, open-label trial enrolling 472 patients. A departure from CALISTO which had excluded patients with history of malignancy treated within the last 6 months, the SURPRISE trial was designed to include patients at highest risk

for VTE, including those with cancer. In SURPRISE, patients were included only if they had a supragenual location and one of the following risk factors associated with a higher rate of thromboembolic complications: age >65 years, male sex, previous cancer, history of VTE, and absence of varicose veins.[93] When comparing 6 weeks of prophylactic fondaparinux to daily rivaroxaban (10 mg qday), rivaroxaban was noninferior to fondaparinux in the prevention of DVT, PE, and progression or recurrence of SVT. Rivaroxaban therapy was postulated to be a less expensive and a more patient-friendly treatment for SVT. In the "high-risk" SVT patients in this study thromboembolic events increased after the end of the active treatment in both treatment groups.[94]

Septic thrombophlebitis requires treatment with broad-spectrum IV antibiotics. If rapid resolution of the cellulitis occurs, no treatment beyond a short course of antibiotics and standard treatment for the superficial thrombophlebitis are required. However, if the patient becomes septic, excision of the infected vein is required. With positive blood cultures, an extended course of antibiotics specific for the identified organism is indicated additionally. The majority of episodes of uncomplicated superficial thrombophlebitis respond to conservative management. However, the recurrence rate for superficial thrombophlebitis has been estimated between 15% and 20%.[95–97]

CHRONIC VENOUS DISEASE

Normal Venous Anatomy

The lower extremity venous system is composed of deep, perforating, and superficial veins.[98] The common femoral, femoral, deep femoral veins in addition to the popliteal, sural and tibial/peroneal veins make up the deep system. The deep veins lie beneath the investing fascia of the muscles of the leg and thigh (the deep compartment) while the superficial veins lie above this muscular fascia. The GSV and SSV lie within the subcutaneous tissue and are surrounded by a separate saphenous compartment formed by the muscular fascia below and the saphenous fascia above. The saphenous nerve lies within the GSV compartment below the knee, which places the nerve at

risk of injury during surgery or percutaneous intervention. Similarly, the sural nerve lies in close proximity to the SSV and within its compartment.

In the past, various terminology and eponyms abounded but modern nomenclature prefers more descriptive terms designating location.[98] The names of other typical veins found in the lower extremity include the term of "accessory saphenous veins" for those superficial veins that lie outside the saphenous compartment, but parallel to the GSV or SSV, while "*communicating* veins" connect veins of the same system and "*perforating* veins" penetrate the muscular fascia to connect the superficial and deep systems.

The variability of the lower extremity venous system is well recognized with certain anatomic variations of clinical importance. The popliteal and femoral veins have variable anatomy and are often double much like the tibial veins. The deep femoral vein commonly connects directly or through tributaries to the popliteal vein. Complete duplication of the GSV in the thigh may occur in 8% of cases with some partial duplication in another 25%.[99] The saphenofemoral junction (SFJ) generally has at least four branches in addition to the GSV, but the configuration of the branches is quite variable.[100] The most cephalic branch is generally the superficial epigastric vein which acts as a landmark for percutaneous interventions and ideally remains patent following the procedure. The SSV is usually singular, dives under a thickened fascia in the upper calf (bringing it in proximity to the deep muscles), in less than two-thirds of cases actually ends in the popliteal creases and can travel well above the knee before diving to meet the deep system.[101] The varied location of perforating veins especially in the lower leg is important when deep to superficial reflux is a concern.

With the exception of foot veins, the valves promote blood flow from superficial to deep and from caudal to cephalad. The valves are made of a fine connective tissue skeleton covered by endothelium and are generally bicuspid, delicate, and extremely strong. Each tibial and peroneal vein contains about 7 to 19 valves. The popliteal vein contains one or two valves and the femoral vein generally three. Approximately 70% of common femoral veins have a valve located within 1 cm of the inguinal ligament while only 25% of external iliac and 10% of the internal iliac veins have a valve.[102] The common iliac vein generally has no valves. The GSV commonly has more than six valves (range, 4 to 25) with at least one valve

within a few centimeters of the SFJ and the SSV has an average of 7 to 10 valves (range, 4 to 13).[103] Perforating veins and even larger venules have venous valves.[102]

The veins of the abdomen and pelvis begin at the inguinal ligament as the external iliac vein that is joined medially by the internal iliac to form the common iliac vein. The internal iliac vein drains the pelvis via connections such as the obturator, gluteal, and internal pudendal veins and their interconnections. To the right of the fifth lumbar vertebrae and aorta, the common iliac veins join to form the IVC. Compression of the left iliac vein by the right common iliac artery can lead to a venous obstructive condition called May–Thurner syndrome. The IVC typically ascends to the right of the aorta and vertebral column terminating in the right atrium. Its direct tributaries are the lumbar veins, the right gonadal vein, the renal veins, the right suprarenal vein, the right inferior phrenic vein, and the hepatic veins. Other named veins generally join one of these tributaries to empty into the IVC. Because of the embryonic evolutions that lead to the "normal" IVC and its branches, variations are common. Duplication of the IVC occurs in 0.2% to 0.3% of cases, transposition or a left-sided IVC can occur in 0.2% to 0.5%, a retroaortic left renal in 1.2% to 2.4%, and circumaortic left renal vein in 1.5% to 8.7% of cases.[104] In the face of IVC occlusion, veins of the chest and abdominal wall, the azygos and hemiazygos systems, and vertebral plexuses may play a prominent role in venous drainage of the lower extremities, abdomen and retroperitoneum.

Normal Venous Physiology

Morphologically veins have a thin wall and lack external support. Small intramuscular veins are extremely compliant such that increasing the venous volume (VV) by over 1½ times results in a minimal increase in pressure (0 to 15 mm Hg).[105] This allows a significant volume of blood (at least 500 mL in the standing position) to become sequestered in the lower limb without a significant rise in intraluminal pressure. However, once the full capacitance of the venous system is reached, further increases in VV result in a proportional increase in intraluminal pressure and changes the vein from an elliptical to a circular configuration. In general, this forgiving design can compensate for much pathology but when overstressed sustained venous

hypertension results in decompensation at the cellular level with resulting edema in the lower leg tissues. The many factors that can affect peripheral venous pressure including arterial inflow are addressed in a recent experimental model.[106]

In contrast to intramuscular veins, the compliance of large axial veins (e.g., femoral, popliteal) mimics that of an artery in that pressure changes are more reflective of volume changes. They are conduit rather than compliance vessels.

The calf and possibly the thigh muscles act as a pump, the "peripheral heart," which can generate pressures of up to 300 mm Hg in the deep system and 100 to 150 mm Hg in superficial veins during exercise.[102] Normally, modest exercise of the muscles will expel the contained blood volume present in the veins and reset the capacitance of the venous system maintaining a homeostatic environment.

The venous valves (superficial, deep, and perforating) play a key role because they allow blood to move forward in response to an increased distal pressure gradient (muscle pumps) and by preventing reflux, protects the capacitance vessels from overload and, thereby, the superficial structures (i.e., skin, soft tissues) from the high pressures generated in the deep system.

Prevalence and Impact

Chronic venous disease (CVD) is a common, costly malady in Western countries. CVI is defined as venous pathology that results in advanced clinical symptoms (edema to venous ulceration). If one considers the entire spectrum of the disease based on modern methods of classification, approximately 21.7% have reticular veins/telangiectasia, 18% varicose veins, 15% edema, 7% hyperpigmentation, 1.4% healed ulcers, and 0.7% active ulcers.[107,108] A population-based study in San Diego that included Duplex imaging demonstrated that 5.8% of those studied presented with edema while 6.2% had skin changes and/or prior or active venous ulcers.[107] The estimated cost of venous ulcer care to the healthcare system is 1.5 to 3 billion annually and significantly more if actual patient cost is considered.[109,110] The negative impact on QOL for other less severe forms of venous pathology would greatly surpass this cost to the healthcare system.

Relevant risk factors for varicose veins are advanced age, a positive family history, female gender, multiparity, and obesity, while the risk factors for CVI are advanced age, positive family history, and obesity.[111]

Pathophysiology and Etiology

Three pathophysiologic states exist: obstruction, valvular insufficiency, and calf muscle pump malfunction. These conditions reflect a failure of one or more of the components of the normal venous system and are not mutually exclusive.

Venous obstruction causes an increased resistance to blood exiting the lower extremity. Once thought to be an uncommon etiology of treatable lower leg venous pathology, venous occlusive disease in combination with venous insufficiency was evident in over 50% of patients with CVI in one study, especially noted in those with the most severe symptoms. The result is elevated intravenous pressure noted clinically as pain especially after exercise as one added manifestation of the disease.[112]

Asymptomatic primary iliac venous compression is quite common, one study of 50 patients without symptoms of CVI demonstrated that 24% had greater than 50% narrowing (compression) of the left common iliac vein by the right common iliac artery.[113] It has been suggested that this type of nonthrombotic stenosis (compression with potential for intramural fibrosis) is a "permissive lesion" not clinically significant until other components of the lower extremity venous circulation fail or the occlusive disease progresses.[114] Less common causes of obstruction include intraluminal webs from repetitive trauma as well as extrinsic compression of the iliac and pelvic veins by tumor, fibrosis, infection, femoral hernias, or arterial aneurysms.

Postthrombotic obstruction is also a common cause of venous occlusive disease due to the rather high prevalence of DVT and can impact any part of the venous system. Acute thrombosis is associated with inflammation and remodeling during resolution and results in external vein wall scarring with stiffening and thickening, as well as intraluminal recannulation with webs and bands. The venous valves are generally incorporated into the scarring process leading to valve malfunction.

In one of the largest experiences treating iliofemoral venous occlusive disease involving nearly 1,000 patients, compression of the common iliac vein was observed in 36%, external iliac vein in 18%, and both sites in 46% of limbs. Of these patients, 53% of limbs had nonthrombotic compressive lesions (absent history of DVT, no venographic or ultrasound findings indicating previous DVT); 40% had postthrombotic obstruction; and 7% had a combined etiology. Furthermore, 20% of the patients were men and 25% of the symptomatic lower limbs were on the right side.[114]

Valvular insufficiency occurs throughout the lower extremity veins and is estimated to account for 80% of symptomatic CVD cases.[115,116] While superficial reflux is most common, deep venous insufficiency frequently coexists with superficial and perforator disease[107,117] and duplex imaging studies suggest that patients with minimal symptoms tend to have isolated superficial reflux while those with edema, skin changes, and past or present ulcers have an increasing presence of perforator and deep disease as well as a postthrombotic etiology.[115] The presence of both obstructive and reflux pathology denotes more risk for the development of skin changes[118] and the degree to which combined obstructive and insufficient venous pathology contribute to CVD is likely underestimated.[114,119] No matter the clinical stage, the superficial system is most commonly affected (90%) with GSV involvement in 70% to 80%, SSV in 15% to 20%, and nonsaphenous veins in approximately 10%. The deep veins are involved in about 30% and perforator veins in about 20% of cases in one series.[115]

Reflux allows the transmission of high venous pressures to the lower leg when standing and is not relieved by exercise. Primary valvular insufficiency is rare but can be a consequence of congenital valve absence.[120] There are predisposing genetic factors that can lead to primary venous reflux including Klippel–Trenaunay syndrome, FOXC2 gene mutation, desmulin dysregulation, the Ehlers–Danlos syndrome, and a CADASIL gene mutation, to name a few, but these do not reflect the typical patient.[121] The muscle cell–dilating effect of estrogens may explain the genesis of varicose veins noted in the first trimester of pregnancy. Prolonged exposure to high venous pressures can cause vein dilation as occurs from an arteriovenous fistula or occupations requiring prolonged periods of standing. For our standard patient, venous valve prolapse (elongated, floppy valves) and defects in the vein wall that cause the valve ring to dilate results in malfunctioning valve

cusps with retained valve architecture.[122] Whether the vein wall changes precede valve insufficiency or the valve insufficiency causes wall distention and wall changes is less clear.[123]

Roughly 50% of deep vein valvular dysfunction occurs secondary to DVT whereas the remainder appears to be of a primary etiology.[124–126] Inflammation and thrombosis associated with DVT tend to cause valve scarring, whether or not recanalization is complete, leaving a damaged valve in most cases. Sometimes, however, whether due to rapid resolution of thrombi or lack of actual involvement of the valve, the valve may escape damage remaining architecturally intact, and can be repaired surgically.[127]

CVD can result from failure of calf muscle pump function. The pump becomes unable to generate the force needed to eject blood from the leg while standing, resulted in sustained venous hypertension. Patients with muscle disuse (e.g., paraplegia, traumatic injury, elderly or bedridden patients) may not have sufficient muscle for effective exercise. Pathologic conditions that result in muscle fibrosis (e.g., muscular dystrophy, multiple sclerosis) can destroy the calf muscle pump. Thrombus and scarring in the gastrocnemius and soleal veins can prevent blood from entering the pump chamber resulting in a deficient volume for ejection with contraction. Calf pump function and ankle range of motion progressively diminish with increasing severity of CVI.[128,129] Physical conditioning can improve the metrics of pump function, however, evidence regarding improved clinical outcomes is lacking.[130–132]

Regardless of the etiology, the sequelae of venous hypertension/stasis are changes observed in the lower leg skin and subcutaneous tissues, the end organ. The current belief holds that the fundamental basis for CVD and ulceration is inflammation within the venous microcirculation when subjected to increased hydrostatic pressure. Research remains active in this component of venous pathophysiology and excellent reviews are available for further information on the current understanding of basis venous pathophysiology.[133,134]

Clinical Signs and Symptoms

Venous disease presents in many ways. A telangiectasia, spider vein, is a confluence of dilated intradermal venules less than 1 mm in caliber. A

reticular vein is a dilated bluish subdermal vein, 1 mm to less than 3 mm in diameter and usually tortuous. These venous abnormalities may be associated with a larger, more deeply located, pathologic vein but not always. Hereditary varicose veins usually appear during the second decade of life. If the varicosities are due to a secondary etiology (e.g., thrombosis, trauma), presentation can be several years after the inciting event. These veins appear alone or in clusters as dilated, often bluish, serpentine, and palpable protrusions of branches of the GSV, SSV, or collateral veins lying beneath the skin in the subcutaneous tissues. Varicose veins measure 3 or more millimeters in diameter when measured in the upright position.[135] One finding thought to be an early sign of advanced disease is corona phlebectatica, a fan-shaped pattern of small intradermal veins located around the ankle or dorsal foot (also called ankle flare or malleolar flare). If the varicose veins observed are the result of proximal disease, such as pelvic reflux or obstruction; the location of the varicosities may be scrotal, perineal, vulvar or posterior/lateral in the lower extremity.[103]

Symptoms may be those associated with any type of CVD and are noted as pain, edema, hyperpigmentation, stasis dermatitis/eczema, and/or venous ulcers. These changes often occur in the "gaiter" area just above the medial malleolus. Important perforating veins lay in this area. The observed hyperpigmentation is thought to result from extruded red blood cells that are degraded by macrophages leaving hemosiderin deposits. Less definable but described symptoms of CVD include tingling, burning, muscle cramping, a sensation of throbbing or heaviness, itching, restless or tiredness of the legs, and fatigue.[136] They are more specific for venous disease if made worse with standing and heat and if relieved by rest and leg elevation.

Venous claudication is a pain syndrome experienced when walking and is associated with cyanosis, a sensation of increased swelling, and increased prominence of the superficial veins, which is relieved with rest in combination with elevation of the extremity.[137]

2 Critical to patient management and treatment evaluation is an accurate classification of the disease at any given time. Each patient is stratified according to the *c*linical picture, the *e*tiology, the *a*natomic distribution, and the *p*athophysiology (CEAP) classification system (Table 96.2).[135] This classification system helps the physician define the venous disease and then formulate an appropriate management strategy. An extension of the clinical

classification, the Venous Clinical Severity Score, is available to quantify the extent of venous disease and, therefore, to evaluate the patient's clinical response to treatment (Table 96.3).[138,139] The anatomic and pathophysiologic improvement following a treatment of venous disease can be scored using the Venous Segmental Disease Score, while the Venous Disability Score provides some information of what a person can do when afflicted with venous disease.[139] QOL surveys developed specifically for patients with venous disease help to determine the impact of the disease on the patient's life and the effect therapy has on the patient's overall well-being.[140,141] Consistent application of these treatment outcome tools is imperative to improve our ability to precisely determine the effect and benefit of a given intervention.

Table 96.2 Clinical Classification of Chronic Venous Disease

Class	Description
0	No visible or palpable signs of venous disease
1	Telangiectasias and/or reticular veins
2	Varicose veins
3	Edema
4a	Skin changes (pigmentation and/or eczema)
4b	Skin changes (lipodermatosclerosis and/or atrophie blanche)
5	Healed venous ulcer
6	Active venous ulcer
S (in addition to the class)	Symptoms including ache, pain, tightness, skin irritation, heaviness, muscle cramps as well as other complaints attributable to venous dysfunction
A (in addition to the class)	Asymptomatic

Diagnostic Evaluation

The diagnosis of CVD begins with a thorough history and physical examination. Prior DVT, pregnancies, a family history of varicosities, obesity, or the presence of other factors associated with CDV will add support to the presence of venous disease. When performing the physical examination: the location, distribution and size of varicosities, skin changes,

and/or presence or indication of past ulcers should be noted. Swelling should be quantified, the location specified, and a determination made as to whether it is pitting or nonpitting in nature. Inspection, palpation, and auscultation (presence of a bruit) may be keys to the presence of a vascular malformation or arteriovenous fistula. Utilization of the CEAP clinical classification will provide a snapshot of the patient being examined, whereas the use of the more detailed Venous Clinical Severity Score and the other measurement tools mentioned above will allow for some impression of how any patient therapy is performing.

In addition to determining and classifying the signs and symptoms of venous disease, the history and physical examination should exclude other potential causes for the patient's complaints such as arterial occlusive disease, collagen vascular disorders, allergic reactions, infection, or malignancy. Appropriate confirmatory diagnostic studies may be required to confirm the clinical suspicion, such as a lower extremity arterial Doppler study, biopsy, or specific blood analyses when the diagnosis is unclear. Such studies become most pertinent during the evaluation of advanced venous disease, especially in patients with venous ulcers.[142] Only in selected patients, such as those with recurrent, early, or unusual sites of DVT or recurrent venous ulcers, is evaluation for thrombophilia recommended.[103,142]

Venous duplex ultrasonography provides a B-mode picture of the vein, as well as spectral analysis of the blood flow within. It is recommended as the first diagnostic test for all patients with suspected CVD.[143] To provide an accurate impression of the venous disease present, a standardized technique is mandatory.[143,144] Venous duplex imaging clearly visualizes deep, superficial, and perforator veins and often the valves that lie within the veins. The venous duplex study can help to clarify the etiology, better define the anatomic location, and aid in determining the pathophysiology of the venous problem (EAP of CEAP). While once considered unnecessary in the evaluation of patients with simple varicose veins, it has become common practice prior to treating superficial reflux due to the known anatomic variability present and the need for precise targeting of veins during endoluminal intervention.[144–146]

Valvular insufficiency is defined as prolonged reflux time through a valve following a provocative test when duplex imaging is the diagnostic modality. To aid in the standardization of the test, a rapidly deflating distal cuff

technique is used in some vascular laboratories, while others use manual compression of the distal leg after which valve reflux is determined by duplex imaging. An abnormal reverse venous flow (reflux) in the saphenous, tibial, and deep femoral veins is ≥ 0.5 seconds while the femoral and popliteal veins have a cutoff value of 1 second.[147] Since perforating vein reflux can also be associated with venous pathology, significant work has gone into determining how to define abnormal reflux. Current consensus and available data suggest that a "pathologic" perforating vein is defined as a vein with an outward flow of ≥0.5 seconds with a diameter of >3.5 mm, which is located beneath a healed or open venous ulcer.[103,142,143] The duplex examination for reflux is performed in the upright position but many other provocative maneuvers to generate venous reflux exist (Valsalva, standardized Valsalva, etc.) in addition to performing the test in different positions (e.g., 15% Trendelenburg, sitting) and are used in many laboratories for particular patients who have difficulty standing.[148] Each may be acceptable if standardized and validated for an individual laboratory.

Venous obstruction is seen as thickened, scarred, and constricted veins with poor flow and diminished augmentation following distal and/or proximal compression. Respiratory variation is lost as a result of local occlusive disease or proximal occlusion. Disease within the SSV should not be ignored because it can have a significant clinical impact as an isolated finding.[149] By imaging the entire lower leg venous system, the surgeon possesses a detailed roadmap of all veins with determination of obstruction or reflux within segments separated by valves. This is often the only diagnostic tool needed for the evaluation of superficial and even perforator disease requiring treatment.

A difficult area of investigation from a noninvasive perspective is the pelvic, abdominal, and chest veins. CT and MRI can provide details of anatomy and the effect of surrounding structures and can be particularly useful in evaluating for the pelvic congestion syndrome.[150–152]

Plethysmography assesses the overall hemodynamics of the lower extremity venous system. Air plethysmography (APG) can measure several venous hemodynamic parameters. A plastic cylinder filled with air is fitted over the calf and foot and changes in leg volume with positional change or exercise are detected by pressure changes in the cylinder. Calculated parameters include venous filling index (<2 mL/s is normal) which assesses

the competency of the venous system, ejection fraction (>60% is normal) and residual volume fraction (<35% is normal) which suggest that the calf pump is working well.[153] In current clinical practice, it is being used only in complex cases or for research purposes. Current consensus encourages the use of plethysmography in the patient with advanced CVD if duplex scanning cannot provide a definitive diagnosis regarding the underlying pathophysiology.[103]

As in acute venous disease, venography has no significant role in the initial evaluation of patients with CVD. Unfortunately, ascending venography can suggest venous occlusion when duplex imaging clearly demonstrates an open system.[154] The absence of significant collaterals on transfemoral venography may underestimate the degree of venous occlusion as documented by intravascular ultrasound.[155] The use of ascending venography is selectively used in specific cases to complement noninvasive studies when considering intervention in the deep venous system or in research protocols.

DIAGNOSIS

Table 96.3 Venous Clinical Severity Score

Attribute	Absent 0	Mild 1	Moderate 2	Severe 3
Pain	None	Occasional, not restricting activity or requiring analgesics	Daily, moderate activity limitation, occasional analgesics	Daily, severe limiting activities, regular use of analgesics
Varicose veins[a]	None	Few, scattered: branch VVs with competent GS/SS	Multiple: single-segment GS/SS reflux	Extensive: multisegment GS/SS reflux
Venous edema[b]	None	Evening ankle edema only	Afternoon edema, above ankle	Morning edema above ankle and requiring activity change, elevation
Skin pigmentation[c]	None or focal, low intensity (tan)	Diffuse, but limited in area and old (brown)	Diffuse over gaiter distribution (lower 1/3) or recent pigmentation (purple)	Wider distribution (above lower 1/3) and recent pigmentation
Inflammation	None	Mild cellulitis, limited to marginal area around ulcer	Moderate cellulitis, involves most of gaiter area	Severe cellulitis (lower 1/3 and above) or venous eczema
Induration	None	Focal, circummalleolar (<5 cm)	Medial or lateral, less than lower third	Entire lower third of leg or more
No. of active ulcers	0	1	2–4	>4
Active ulceration, duration	None	<3 mo	>3 mo and <1 y	Not healed >1 y
Active ulcer, size[d]	None	<2-cm diameter	2- to 4-cm diameter	>4-cm diameter
Compressive therapy[e]	Not used or not compliant	Intermittent use of stockings	Wears elastic stockings most days	Full compliance: stockings + elevation

[a]Varicose veins must be >4-mm diameter to qualify so that differentiation is ensured between C1 and C2 venous pathology. Occasional or mild edema and focal pigmentation over varicose veins does not qualify for C3 or C4.
[b]Presumes venous origin by characteristics (e.g., brawny [not pitting or spongy] edema), with significant effect of standing/limb elevation and/or other clinical evidence of venous etiology (i.e., varicose veins, history of DVT). Edema must be regular finding (e.g., daily occurrence). Occasional or mild edema does not qualify.
[c]Focal pigmentation over varicose veins does not qualify.
[d]Largest dimension/diameter of largest ulcer.
[e]Sliding scale to adjust for background differences in the use of compressive therapy.
GS, great saphenous; SS, small saphenous; VV, varicose vein.
From Rutherford RB, Padberg FT Jr, Comerota AJ, et al. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg* 2000;31(6):1307–1312.

Descending venography is used to determine valve leaflet integrity and anatomic location and demonstrate the extent of reflux.[156] Assessment of the competence of the profunda femoris venous system in addition to the femoral system is imperative prior to valve transposition or isolated proximal femoral vein repair.[157–159] And while descending venography is not infallible in determining the presence or absence of a normal valve,[127] when combined with a careful venous duplex examination, it is currently the best method available to determine preoperatively if an in situ reconstruction will be possible.

Intravenous pressure measurements can aid in the diagnosis of venous disease but is invasive and generally used only when invasive surgery of the deep system is being considered. This study can help to determine the overall

magnitude of reflux and can be correlated with the incidence of venous ulceration.[160] Although IV pressure measurements and venography were once 3 the gold standard for evaluating venous disease, duplex scanning—with the addition of intravascular ultrasonographic techniques when required—is the anatomic and functional test of choice in current medical practice.

4 Treatment Options and Results

Medical Therapy

Compression has been the mainstay of the medical treatment for all stages of CVI for centuries. The goals are to manage clinical symptoms and to control venous hypertension. Roughly speaking, there are two types of compression: elastic (e.g., support stockings or long stretch bandages) and inelastic (e.g. Unna's paste boot, short stretch bandages, multilayer [four-layer] bandage, or Velcro band devices). In general, the more layers the less elastic and more stiff the compression. The degree to which any particular bandaging is one or the other will depend on the care provider who applies the compression along with other factors. The mechanical effect is dependent on the level and type of compression and the desired amount of compression is influenced by the underlying venous pathology being treated.

Consistent narrowing of superficial and calf veins occurs at a median of 30 to 40 mm Hg pressure on standing while complete occlusion occurs at a median pressure of 70 mm Hg.[161] Complete occlusion is not the goal. Therapeutic calf compression improves calf muscle pump function expressed as a reduction in residual volume fraction during walking[162] and even compression <20 mm Hg results in improved symptoms and QOL data when used to treat mild disease.[163,164]

It is interesting that an elastic stocking maintains a rather constant pressure during exercise and at rest. Alternatively, inelastic wraps demonstrate a more dramatic increase in pressure during exercise since they do not stretch but have decreasing pressure with recumbence as the edema exits the leg and the bandage maintains its shape.[165] Inelastic wraps are much better tolerated when left on for days and especially when recumbent at night when compression is not required to contra-act gravity. Constant compression at night can be perceived as discomfort/pain. Further, inelastic compression has

been found to result in a greater improvement in venous hemodynamics when applied at the same pressure as elastic compression[166–168] and maintains greater effect despite loss in pressure over time[169] (pressure loss likely related to the decreased volume of the leg). The significant decrease in swelling noted early in compression treatment explains why compression stocking often need to be changed more frequently during the early stages of care.

Although there has been concern that compression may impede microcirculatory flow and thereby jeopardize tissue viability, it is known that compression, when used to treat edema, has favorable effects on extracellular fluid balance, capillary density, and transcutaneous oxygen tension.[170] Compression therapy also decreased levels of endothelial growth factor and tumor necrosis factor which correlated with ulcer healing[171] and actually increases microcirculatory flow.[172]

Patients with concomitant arterial occlusive disease pose a unique challenge. In one center, 15% of those presenting with leg ulceration and venous reflux had an ankle to brachial artery index (ABI) <0.85.[173] There is some suggestion that standard compression can actually increase arterial blood flow in certain circumstances.[165,174] Overall, data suggest that improvement in tissue level perfusion is likely related to improvement in the microangiopathy of CVD, offloading of the outflow system, and through a decreased burden on the lymphatic system (often damaged in patients with CVI).[175]

In patients with concomitant arterial occlusive disease with ABI of ≥0.80, the use of standard compression is safe and effective.[176]

In those with more advanced arterial occlusive disease defined as an ABI ≥0.50 (but <0.80) or an ankle systolic pressure ≥ 60 mm Hg or toe pressure ≥30 mm Hg as a minimum; modified compression dressings with lower pressure ratings not to exceed the tissue perfusion pressure can improve tissue perfusion and aid in healing ulcers of mixed etiology.[176,177] These data support the current SVS/AVF practice guideline suggesting that in a patient with a venous leg ulcer and underlying arterial disease, compression bandages or stockings are not indicated if ABI is ≤0.5 or if the absolute ankle pressure is <60 mm Hg.[142]

Evidence-based medicine confirms our clinical impression and basic science findings regarding the potential benefits of compression garments for

the treatment of CVI. Substantial evidence exists to demonstrate that compression is statistically beneficial for most clinical stages of symptomatic venous disease ($C_{2–6}$). Whether compression stockings should be the primary treatment for symptomatic varicose veins is challenged by data from the United Kingdom. The randomized trial (REACTIV) demonstrated that in 246 patients with class C_2 disease, surgical intervention resulted in a statistically significant benefit in quality-adjusted life-years and in symptomatic and anatomic measurements compared to conservative management.[178] Likewise, cost-effective analysis demonstrated a benefit for the surgical intervention.[179] Therefore, in contradistinction to current third-payer policies, and based on available statistical data, the SVS/AVF Guidelines Committee recommends against compression therapy as the primary treatment of symptomatic varicose veins in those patients who are candidates for saphenous vein ablation (grade 1B recommendation).[103] Certainly in those who do not desire interventional options or are not candidates for superficial venous ablation, the Guidelines Committee suggests compression therapy (20 to 30 mm Hg) for symptomatic benefits (grade 2C).

Compression is the standard of care for patients with advanced CVD ($C_{3–6}$) and the majority of the evidence-based data investigate the benefits of treating venous ulcers since the rate and degree of healing are measurable. The evidence suggests that venous ulcers heal more quickly with compression therapy than without compression[180] and that noncompliance with therapy is associated with both nonhealing of the ulcer as well as increased risk of recurrence.[181] Compression also decreases the risk of recurrence following surgical intervention.[182] The modality of the compression therapy is also a factor and there is some evidence to support multicomponent compression over single component compression[180] and high compression over medium compression to treat venous ulcers.[183] However, these results are not consistently reproducible[184] and both the skill of those applying the dressing[185] as well as patient compliance likely remain significant confounding factors.[181] The SVS/AVF Guidelines Committee recommends that compression be used to heal venous ulcers (grade 1A), to decrease recurrence (grade 2B), and it is suggested that multicomponent compression bandages be used to treat venous ulcers (grade 2B).[103]

As a general approach, multilayer relatively inelastic wraps are preferred for the therapy phase of venous disease (ulcer healing). With ulcer healing, elastic wraps, such as compression stockings, are used to maintain a stable clinical condition (maintenance phase). In addition, elevating the legs when possible during the day, avoiding prolonged periods of standing or sitting, and elevating the foot of the bed 4 to 6 in above the heart while sleeping are adjuvant components of conservative therapy.[186,187]

Intermittent pneumatic compression (IPC) provides pulsatile emptying of the venous system via compressive bladder(s) that inflate and deflate. A Cochrane review suggests that there is advantage in using IPC compared to no compression, but little evidence to support that it adds to compression therapy alone.[188] Currently it is recommended that IPC be employed when compression has failed, is unavailable, or cannot be used.[142]

Other forms of conservative therapy for CVI include lifestyle changes such as exercise as well as pharmacologic agents, which are generally not available in the United States. Structured exercise can improve dynamic muscle strength and calf muscle pump function in patients with essentially all levels of CVI from varicose veins to venous ulceration.[130,132] A meta-analysis of five RCTs found that exercise was as associated with healing of venous ulcers at 12 weeks[189] and the use of supervised active exercise to improve muscle pump function and to reduce pain and edema in patients with leg ulcers is a guideline recommendation (grade 2B).[142]

In Europe and other countries, various oral agents (e.g., rutosides, hidrosmin/diosmine, dobesilate) are used to improve the feeling of heaviness, fatigue, and even edema associated with CVD but these agents are not available in the United States.[103,142] A Cochrane review of 53 studies of such agents concluded that there was possible benefit regarding edema control and other signs and symptoms of venous disease (cramps, restless legs, paresthesias), however, there was no improvement in ulcer healing and many phlebotonic agents were poorly tolerated.[190] A drug which is potentially useful in treating patients with venous ulcers and is available in the United States is pentoxifylline. A review of 12 trials indicated that pentoxifylline does provide an incremental benefit in ulcer healing when used as an adjunct to compression and may also have some effect in the absence of compression but the trade-off is more gastrointestinal adverse effects.[191] This is currently an off-label use of this medicine, originally

prescribed for patients with claudication. For long-term effects and as an adjunct to compressive therapy when treating large venous ulcers, pentoxifylline, in combination with compression therapy, is recommended (grade 1B).[142] Current practice is to prescribe 400 mg of pentoxifylline three times per day and, if tolerated, 800 mg three times per day may accelerate ulcer healing.[192] Prophylactic use of systemic antibiotics in the treatment of venous ulcers does not improve healing and may only select resistant organisms.[193] Certainly, an established infection (cellulitis or deeper) must be treated as it would be at any site and is recommended best care by the SVS/AVF Guidelines Committee. In addition, the recommendation is for oral agent use for 2 weeks unless evidence of clinical infection continues (grade 1C).[142] Limb cellulitis with or without a venous ulcer generally requires systemic gram-positive antibiotic coverage and is a grade 1B recommendation for patient care.[142,194]

5 Surgical Therapy

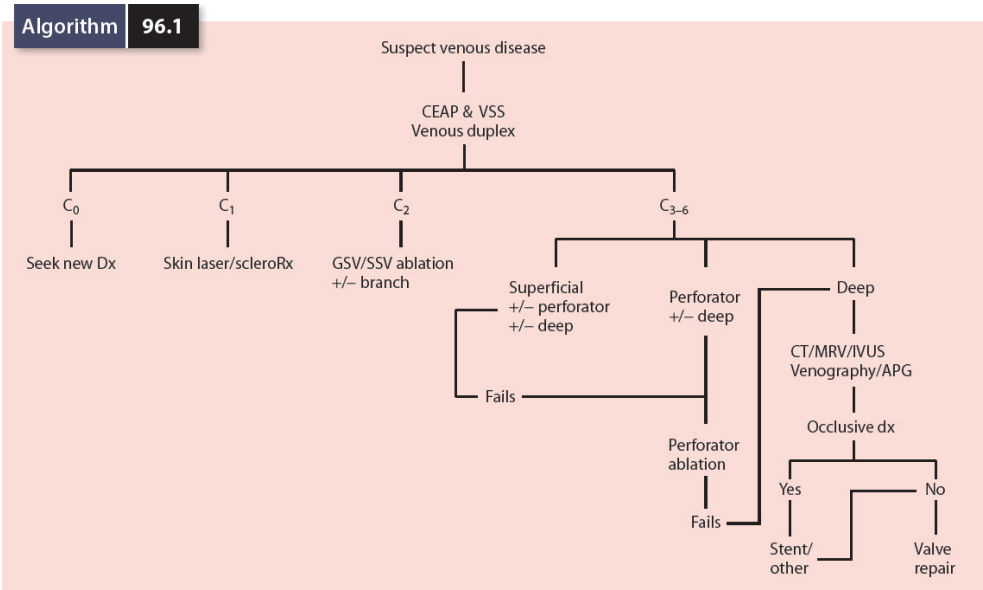
The use of surgical intervention in the realm of venous disease as in all areas of vascular surgery is driven by the documented presence of disease, the risk of the intervention, and the expected outcome (Algorithm 96.1).

Telangiectasia, Reticular Veins, and Branch Varicose Veins

Laser or intense pulsed light (IPL) ablates telangiectasias with reasonable success, inducing vessel destruction by targeting the absorption peaks of hemoglobin. Various devices exist with selection based on the wavelength and pulse duration most appropriate for the size and location of the lesion.[195] In general, shorter wavelengths work best for smaller diameter vessels. Dyspigmentation can occur and tanned skin is a contraindication to treatment because melanin is a strong competing chromophore that absorbs the light energy and causes a tattoo.[196]

Sclerotherapy (needle injection of detergents, hypertonic solutions, or chemical irritants directly into superficial veins with or without ultrasound guidance) is used to treat varicosities most often remaining after saphenous ablation, small isolated varicosities, telangiectasias, and reticular veins. Sclerotherapy alone appears an effective treatment for branch varicosities in patients without major saphenous reflux or when combined with techniques to treat major saphenous reflux when present.[197,198] The FDA-approved

sclerosing agents are sodium tetradecyl sulfate, sodium morrhuate, polidocanol, and glycerine. Hypertonic saline (23.4%), although not approved for sclerotherapy in the United States, is used and has been for many years. All act to damage the vein endothelium, inducing inflammation and scarring with ultimate lumen collapse.[199] Polidocanol has rapidly been adopted as the workhorse for venous sclerotherapy because of a very low allergic and anaphylactic reaction rates, a low risk of tissue necrosis, in addition to being essentially painless. Foam sclerotherapy is the addition of air, carbon dioxide or other gases to a sclerosants such as polidocanol to allow a more protracted contact of the sclerosing agent to the vein wall. The most popular technique uses two syringes and a three-way stopcock to allow the gas to be aspirated into one of the syringes, while the other syringe contains a detergent sclerosant, which results in a one part of drug to four parts of gas mixture. Aggressive agitation of the mixture between the syringes allows for a more stable, microbubble containing foam.[200] Now there are commercially available products. The exact concentration of sclerosant, liquid or foam, used for sclerotherapy is dependent on vein size and agent used.[199] These interventions are generally outpatient procedures with low complication rates. Transient local discomfort is common and rarely extravasation of the agent, especially if ultrasound guidance is not used, can cause fat or skin necrosis with ulceration.[201] Hyperpigmentation can occur and is reduced by microthrombectomy of clotted blood trapped in treated veins especially in veins 1 mm or less in diameter.[202] Other potential complications of sclerotherapy include allergic reactions and systemic toxicity if too much agent is used at one sitting.[199,201,203] Rarely neurologic events including visual disturbance, migraine, and stroke are reported and this possibility must be discussed with the patient prior to its use.[201,204] The presence of a patent foramen ovale is associated with a higher frequency of transient neurologic events[201,205] while the use of CO_2 as the mixing gas used for foam sclerotherapy appears to decrease the risk of such adverse events.[206] On the basis of the available data, the SVS/AVF Guidelines Committee recommends that liquid or foam sclerotherapy be used to treat telangiectasia, reticular veins, and varicose veins (grade 1B).[103]



Algorithm 96.1 Treatment of chronic venous insufficiency.

Phlebectomy (ambulatory phlebectomy, stab avulsion, stab phlebectomy, microphlebectomy, and microextraction are synonymous terms) is a technique in which varicose veins are removed through small skin stab incisions with hooks or small mosquito clamps used to pull the vein from its bed.[207] It can be performed in an ambulatory setting with local anesthesia or in conjunction with a more invasive procedure. There is evidence that phlebectomy has fewer recurrences than sclerotherapy but is still associated with risks (blisters, telangiectatic matting, scar formation, and bruising).[208] Tumescent anesthesia has allowed for extensive interventions with little pain and on an ambulatory basis.[209]

Saphenous Vein Stripping/Ablation

Saphenous preservation or conservative hemodynamic management of varicose veins (e.g., CHIVA) can lead to good results in the hands of skilled interventionalist willing to interpret detailed preoperative imaging (proper patient selection) and a meticulous technical approach. It involves removal of only selected branch varicosities resulting in improved saphenous function and preservation of saphenous drainage with a reported lower rate of recurrence when compared to saphenous stripping in selected series.[210] Because of limited data available and the technical nuances, treating saphenous veins reflux and associated varicose veins in this manner is only

suggested for those with experience (grade 2B/C) by the SVS/AVF Guidelines Committee.[103]

If axial and extensive saphenous insufficiency is present, some method of eliminating reflux is required for best results. Entirely removing the refluxing vein from the venous system is the current best and most studied solution. Lower leg deep venous occlusive disease is not an absolute contraindication to removal of the saphenous system and may actually be indicated in patients with mixed obstruction/reflux disease. It is often the first step in cases of combined deep and superficial insufficiency.[211,212]

There are several methods available to accomplish this task. Open surgical removal involves preoperative marking of the dilated veins while standing so that apparent varicose veins can be removed during operation. The operation includes ligation and disconnection of the GSV at the SFJ via open incision followed by complete removal of the vein to the knee by one or more distal incisions centered over the vein. If the below-knee GSV is incompetent based on preoperative diagnostic studies, it may be excised. The method of vein removal may involve the introduction of long metal or plastic stripping wires with removable heads of varying size or various other tools to facilitate pulling the vein from the distal leg incision.[213] Both the GSV and SSV can be treated by these methods with proper patient positioning and knowledge of existing anatomic variability especially of concern in the case of the SSV. In particular, protection of the sural nerve by limited deep dissection is critical. More technical details are found in a recent review and description of technique.[214]

In addition to classic ligation and stripping, either saphenous vein may be removed from the venous circulation via endovenous ablative techniques. These include thermal methods such as radiofrequency ablation (RFA) or laser ablation as well as sclerotherapy with the common premise of scarring the vein such that it does not act as the conduit for venous blood. In addition, there are nonthermal methods of endovenous ablation: mechanochemical and cyanoacrylate embolization. These techniques also cause intravenous scarring, fibrosis, and occlusion.

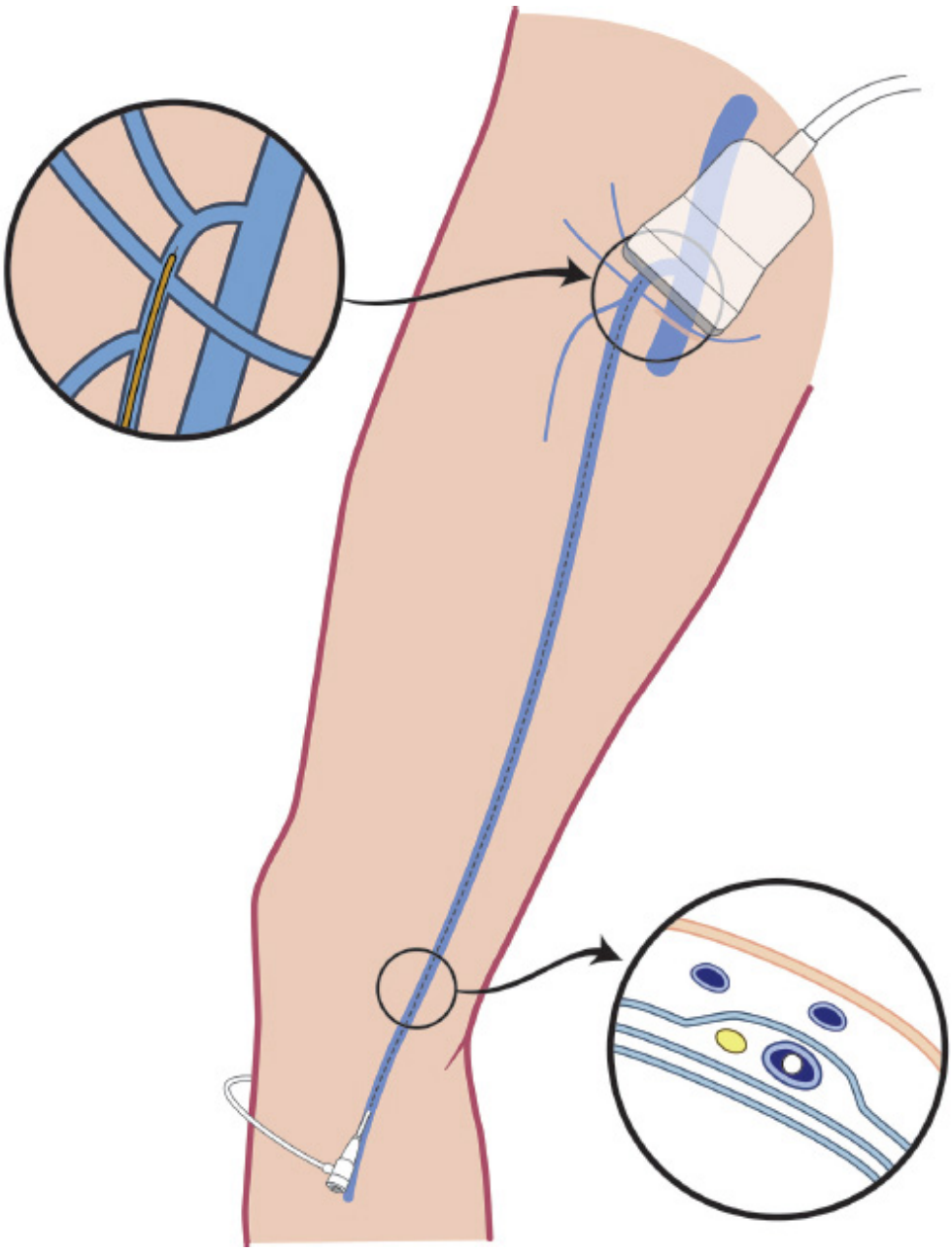


Figure 96.1 An artist depiction of percutaneous radiofrequency ablation of the great saphenous vein. Note percutaneous access of the vein around the knee and advancement of the device to about 2 cm below the CFV. The vein is serially treated with the RFA probe (or laser, glue, sclerosant in other methods) to result in ablation. Pulling the sheath and applying pressure is sufficient to prevent bleeding from the access site. Note the close location of the saphenous nerve near the GSV at the knee and below. (Lower magnification demonstrates saphenous nerve in saphenous tunnel [yellow structure] near the great saphenous vein and is protected somewhat by tumescent anesthesia. Outside the saphenous compartment can be one or more accessory saphenous veins.) Note that the superficial epigastric vein generally maintains flow after ablation. (Upper magnification demonstrates typical

side branches, RFA device ~2 cm below the common femoral vein and somewhat below the superficial epigastric vein.)

For laser or RFA interventions, access is gained either percutaneously or rarely by venous cut down and the respective device is advanced into the vein to about 2 cm below the SFJ using duplex imaging for proper positioning (Fig. 96.1). The saphenous vein is sequentially heated throughout its length as the heating probe (laser fiber or RFA device) is pulled back to the entrance site. Tumescent anesthesia is administered within the saphenous compartment providing anesthesia, a heat sink, and some venous compression during the procedure. The precise parameters for heating the RFA probe is standardized for each pullback length and treatment cycle (e.g., 7-cm sections and 20-second cycles) and usually two treatment cycles are used in the more proximal segment of the vein to ensure proximal ablation at the point of maximal reflux from the deep system.[215]

Laser energy of various wavelengths (810 to 1,470 nm) delivered via bare-tipped fiber will cause a localized thermal injury to the vein wall. The laser probe technique is more physician directed and involves a slow, continuous withdrawal as opposed to the stepwise removal of the RFA probe (generally 1 to 2 mm/s at 10 W with a desired 60 to 100 J/cm). The exact rate and energy delivered depends on the device used but like RFA typically more ablative effort is applied to the first 10 cm of the vein.[215] One of the best technical description of RFA, laser and hybrid (surgical excision of residual disease) to treat saphenous reflux is included in a recent atlas.[216]

The nonthermal methods generally do not require tumescent anesthesia (no need for a heat sink or anesthesia) and so are potentially better tolerated by patients. These are the newest of the ablation methods which do not rely on local heat so may have less issues with nerve/skin injury. The mechanical occlusion chemical-assisted (MOCA) ablation technique (ClariVein) requires distal percutaneous saphenous access and positioning of the rotating wire 2 cm below the SFJ or at the fascial curve of the SPJ. Only the wire is activated for the first centimeter (induces spasm), for the remainder of the 1.5 mm/s pull pack of the rotating wire sclerosant (8 to 12 mL of 1.5% sodium tetradecyl sulfate [STS] or polidocanol [PLD]) is injected from the tip. The cyanoacrylate closure (CAC) technique (VenaSeal) involves percutaneous distal access with 7-Fr sheath placed 5 cm distal to the SFJ then within the

sheath is placed a 5-Fr catheter through which is extruded cyanoacrylate by a specially designed delivery gun. 0.1 mL is delivered every 3 cm after 30 seconds of ultrasound-guided pressure and the catheter is pulled down 3 cm. In general, 1.3 to 1.5 mL of adhesive is required for completion. An excellent review of the techniques and results expected is available in a recent review.[217] There are other techniques continually being studied but currently these are mature representations of the options.

Sclerotherapy can be applied to large vein ablation (great or small saphenous). Percutaneous access above the knee if proximal and below the knee if distal saphenous involvement is present, allows placement of a 4- or 5-Fr sheath or 18-gauge angiocatheter into the vein. The foam is injected until it is seen nearing the SFJ at which time duplex-guided compression (usually by a second person) is applied for 3 to 5 minutes and the injection is stopped. A polidocanol propriety foam (Varithena) mixes nitrogen gas and 1% polidocanol liquid in a cannister to produce the consistent foam superior to physician-compounded foam.[217,218] Other agents previously noted (sodium morrhuate, sodium tetradecyl sulfate, etc.) are available for use.[215] Ultrasonography-guided foam sclerotherapy (UGFS) was found superior to liquid preparations and is effective in elimination saphenous vein reflux at least initially.[219]

Efforts to evaluate and compare the outcomes of these various techniques provide useful generalizations. Direct comparisons between surgical and endovenous modalities support that RFA and laser have comparable results to open surgery and to each other but that UGFS may have a lower technical success rate and a higher rate of recurrent reflux at 5 years.[220,221] Furthermore, a recent meta-analysis comparing nonthermal to thermal saphenous ablation found that nonthermal were as effective as thermal techniques initially and at 1 year with potentially less procedural pain but no difference in paresthesia, phlebitis, or skin pigmentation.[222]

Clinically recurrent varicose veins after GSV high ligation and stripping are observed in less than 25% of cases at 2 years,[223] around 55% at 5 years,[224,225] and in one study reached 62% at 11 years.[226] It should be noted, however, that recurrent varicosities do not indicate recurrent reflux at the SFJ; in a meta-analysis, following high ligation and stripping only 12% of 549 legs developed recurrent reflux at the SFJ at 5 years.[221] Rather other sites of reflux (perforators, neovascularization of parallel veins, etc.) result

in the recurrences noted.[224] Recurrences occur with all techniques used for saphenous ablation.

Complications of GSV interventions are rare but include wound infection, DVT, nerve damage, and hematoma formation.[214,215,217,227] Saphenous nerve injury can result in an area of numbness around the knee or foot (may be clinically unrecognized)[228] but does highlight that surrounding structures must be protected from thermal injury during RFA or laser ablation by appropriate use of tumescent. Complications from SSV interventions although rare include bleeding, hematoma formation, sural nerve damage, DVT, and wound infection.[229] Potential complications of sclerotherapy have been mentioned previously with embolization to local arteries or the systemic circulation as specific risks.[214,215,217]

The following guidelines are proposed regarding the treatment of C_2 (patients with varicose veins) to improve QOL and to prevent recurrence: high ligation and stripping of the GSV to the knee are suggested for incompetent GSVs (grade 2B) with a 1-week period of postoperative compression (grade 1B). For the incompetent SSV, the recommendation is high ligation of the vein at the knee crease about 3 to 5 cm distal to the saphenopopliteal junction with selective stripping of the incompetent portion (grade 1B). In addition, the consensus was that endovenous thermal ablation (RFA and laser) was recommended over surgery for saphenous incompetence treatment based on reduced convalescence, pain, and morbidity (grade 1B) and over foam sclerotherapy due to improved efficacy (grade 1B).[103]

The elimination of saphenous reflux is useful in treating more advance stages of CVD in the patient with a venous ulcer (C_6). A randomized controlled trial comparing compression alone versus compression plus saphenous surgery in patients with active or recently healed venous ulcers found a significant decrease in ulcer recurrence in the surgery group, 31% versus 56% at 4 years but there was no difference in ulcer-healing rates, 89% versus 93% at 3 years.[182] A meta-analysis conducted in 2014 also failed to find more than low-quality evidence favoring ablation over compression therapy alone to improve ulcer healing.[230] However, a recent RCT compared early endovenous ablation of superficial venous reflux with late intervention (after ulcer healing or greater 6 months after enrollment) in

450 patients with leg ulcers and found faster healing in the early intervention group with a median time to healing of 56 versus 82 days.[231] Extrapolating these results to the patients with a healed ulcer, ablation in addition to standard compression therapy is recommended to prevent recurrence (grade 1C). In patient with skin changes at risk of venous ulceration, the same treatment is suggested (grade 2C).[142]

Perforator Vein Ablation

Perforator vein reflux is amenable to open or percutaneous ablative methods. Open methods of perforator ablation, subfascial endoscopic perforator surgery (SEPS) or the "Linton's procedure," although successful[232] have been replaced by less invasive methods of treatment.

Methods of percutaneous perforator ablation include RFA, laser and UGFS. No matter the ablating energy delivered (radiofrequency, laser or chemical) during percutaneous perforator vein ablation, ultrasonographic access, operative monitoring, and confirmation of results are routine and the procedure is accomplished under local anesthesia. The ablating device is inserted into the pathologic perforator and is serially pulled back during activation to burn the perforator for its length or the sclerosant injected into it with a similar result. Prevention of energy delivery to the deep system prevents unwanted thrombosis, accomplished by positioning the ablation device (when used) away from the deep system or by properly compressing the vein at or just slightly below the fascia when using sclerotherapy.[233] All percutaneous methods have a high initial technical success rate.[234,235] One series studying sclerotherapy reports 75% obliteration of perforators through 20 months.[234] RFA results in an 80% occlusion rate at 1 year while laser ablation results in a >85% occlusion rate at 6 months.[235] A recent retrospective review of 296 ablations comparing all three modalities reported differing closure rates: 57% for UGFS, 73% for RFA, and 61% for laser at 2 weeks, and found that thermal ablation was statistically superior to UGFS. Thermal ablation was used with success after failed UGFS.[236] Data on ulcer healing following percutaneous methods are scarce. One study of sclerotherapy in 37 limbs demonstrated a 67% rate of ulcers healing but with a 32% recurrent rate,[234] consistent with the findings of a recent systematic review.[237] Complications are rare but there is risk of DVT, phlebitis, local necrosis, and other risks associated with thermal and chemical ablations.

The available data allowed the SVS/AVF Guidelines Committee to provide four basic recommendations.[142] In patients with active ulcers and both superficial and perforator incompetence to the pertinent ulcer bed, it is suggested that both are ablated to aid in ulcer healing and to prevent recurrence (grade 2C) and in patients without active ulcers the addition of perforation ablation can be simultaneous or staged on the basis of outcome (grade 2C). It is suggested that isolated "pathologic" perforators are ablated (grade 2C). It is recommended that "pathologic" perforation ablation be percutaneous rather than an open procedure to eliminate the need for incisions in areas of compromised skin (grade 1C). The pertinent available data have resulted in an SVS/AVF guideline which recommends that incompetent perforator veins in patients with varicose veins should not be treated (grade 1B).[103]

Iliac Stenting and Venous Bypass

Endovascular stenting of iliac vein stenosis/obstruction involves percutaneous access of a disease-free caudal vein (popliteal, femoral, common femoral vein) with guidewire/catheter advancement across the lesion under fluoroscopic guidance and generally intravascular ultrasonographic confirmation of stenosis >50%. If confirmed, dilation with a 12- to 18-mm diameter percutaneous balloon, depending on the vein involved from common femoral to common iliac, is undertaken with subsequent self-expanding stent deployment to maintain the dilation. This is accomplished from normal outflow (generally distal IVC without impinging the contralateral common iliac vein) to distal normal vein even to the area of lesser trochanter within the common femoral vein if needed to ensure good inflow.[238] The procedure may include recanalization of an obstructed inferior vena cava.[239,240] Eliminating significant outflow obstruction in symptomatic patients has decreased edema, pain symptoms, and improved QOL parameters.[112,117,239–243] It will often result in venous ulcers healing, many of which have associated untreated lower leg venous insufficiency.[112,117,241] In one study, 133 patients with active ulcers had an initial healing rate of 65% at 6 months and 54% at 5 years following venous stenting[117] and rates may be even higher when complete obstruction is relieved.[239,240] Parameters of venous reflux are not worsened following resolution of the iliac vein occlusive disease.[112,117,241] The primary and assisted primary stent patency

rates at 3 years are 75% and 92% and at 6 years 67% and 89%, respectively,[241] and patency is in general higher for nonthrombotic than thrombotic obstructions (Fig. 96.2).[241,244]

Potential complications include major bleeding, pulmonary embolism, early thrombosis, access site complications, retroperitoneal hematoma, and other catheter- and balloon-related problems. Overall, however, complications are rare with essentially no mortality associated with the procedure.[244]

When technically feasible, endovascular intervention has replaced more invasive approaches. As a result of accumulating data, the SVS/AVF Guidelines Committee has recommended venous angioplasty and stent recanalization in addition to standard compression therapy to aid in venous ulcer healing and prevention of ulcer recurrence in patients with proximal venous occlusion/severe stenosis and C_{4b}, C_5, and C_6 disease (grade 1C).

The open surgical procedures used to relieve proximal IVC or iliac vein occlusions utilize the native saphenous vein or polytetrafluoroethylene (PTFE) graft material as the conduit to bypass from a nondiseased distal vein to a disease-free proximal or collateral axial vein. Vena cava or bilateral iliac veins occlusion reconstructions often use PTFE grafts to allow a proper size match. If a single iliac vein is severely stenosed or occluded and percutaneous methods have failed, cross-femoral venous bypass or direct repair of the iliac vein provides therapeutic options.[245,246] Overall, patient survival is considered prior to aggressive intervention if iliac vein compression is due to cancerous encroachment. The cross-femoral venous bypass (Palma procedure) involves passing a vein graft or synthetic conduit via a suprapubic subcutaneous tunnel from the common femoral vein on the affected side to contralateral femoral vein and normal outflow system. The saphenous vein or prosthetic graft is connected to the unaffected femoral vein by an end-to-side technique after anastomosis on the affected side. The key to success of this surgery may be graft diameter. If the native vein is less than 4.5 mm in diameter, better success may be achieved with a 10-mm diameter PTFE graft, although in retrospective studies PTFE does have lower patency.[246]

In one series of 64 open surgical or hybrid reconstructions for iliofemoral venous or IVC obstructions, the overall 5-year secondary patency was 59%.

For the femoroiliac and ilio-infrahepatic IVC reconstructions, the 5-year secondary patency was 86% while it was 78% for the Palma procedure while longer bypasses, complex or hybrid procedures had lower patency rates.[245] The use of an adjunctive AVF to improve conduit flow and thereby patency remains controversial due to the observation that it has been associated with decreased patency[245] but this finding is likely confounded by its use as an adjunct when the risk of failure is thought to be excessively high.

Based on the limited current available data, the guidelines for treating bilateral proximal venous occlusion/stenosis in patients with recalcitrant venous ulceration and no endovascular option is an open intervention using externally supported PTFE graft in addition to standard compression therapy (grade 2C). In the same scenario, but with unilateral iliofemoral venous disease, the suggested therapy is an open surgical bypass using saphenous vein if available and sufficiently large with the alternative being a synthetic graft (grade 2C). When inflow is an issue during open operation, a distal adjunctive arteriovenous fistula (4 to 6 mm in diameter) is suggested (grade 2C).[103]

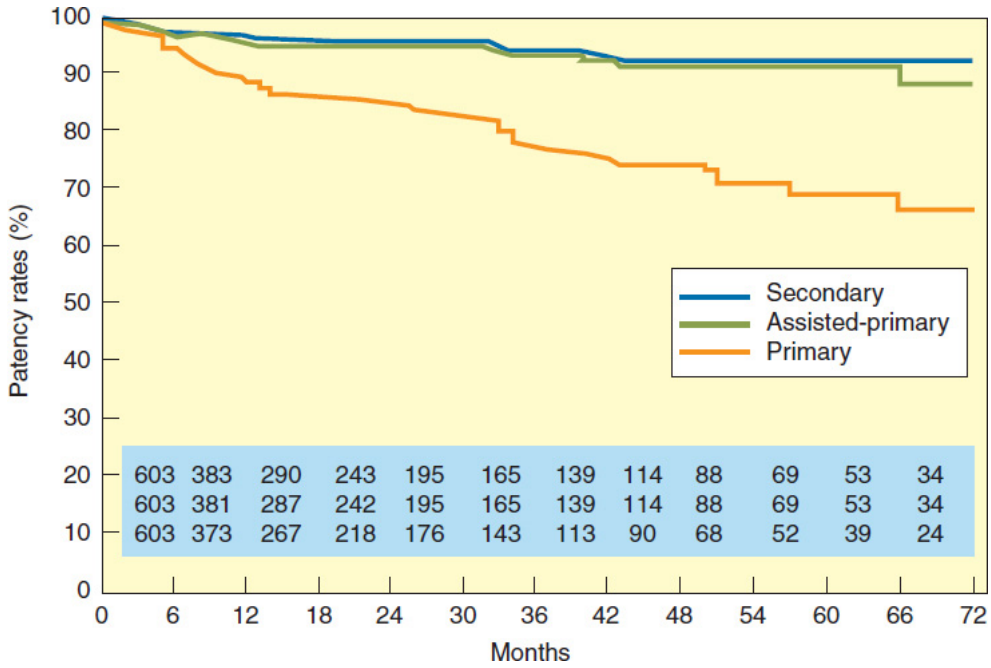


Figure 96.2 Life-table presentation demonstrates the patency rates of iliac venous stents placed for symptomatic occlusive venous disease. (After Neglen P, Hollis KC, Olivier J, et al. Stenting of the venous outflow in chronic venous disease: long-term stent-related outcome, clinical, and hemodynamic result. *J Vasc Surg* 2007;46(5):979–990.)

In the case of more distal venous obstruction, venous bypass, endophlebectomy and patch venoplasty or hybrid open and endovenous procedures have been used.

In patients with chronic symptomatic occlusion of the femoral or proximal popliteal vein, saphenopopliteal vein bypass may be considered if conservative therapy has failed. The patient's distal GSV is transected and anastomosed end to side to the deep system at a site distal to the obstruction allowing venous drainage to bypass the obstruction. This procedure is relatively rare, however, as it necessitates that the patient has a patent proximal common femoral and iliocaval systems as well as a competent GSV. In a series of 17 patients with a median follow-up of 103 months, secondary patency was 75%.[247]

For occlusion of the common femoral vein or distal iliac disease, a hybrid approach involving endophlebectomy and patch angioplasty in combination with angioplasty and stenting of the iliac vein has been explored. In one small series, endophlebectomy sites in 10 patients had a primary patency rate of 77% at 12 months and in the 6 patients who had hybrid procedures the primary and secondary patency rates of iliac vein stents at 15 months were 83% and 100%.[248] However in the experience of other investigators, the 2-year secondary patency in 12 patients was just 30% and this approach is currently not recommended except as a last resort.[245]

Venous Valve Repair or Replacement

The goal of venous valve repair or replacement is the prevention of deep venous reflux and, consequently, a decrease in sustained distal venous hypertension. These interventions are considered only after all other more easily treated venous pathology has been addressed. In planning and during these operations, several observations influence what the surgeon can offer a patient. Preoperative planning helps to determine if a valve is present locally or remotely, and if the recipient conduit is sufficiently disease free to allow a valve repair or replacement. If operative handling of the suspect valve results in vasoconstriction and secondary competence (often determined by a standard "strip test"), an external valvuloplasty or a prosthetic sleeve technique may be viable options. The later simply involves using an external synthetic sleeve wrapped circumferentially around the vein at the valve and tightened to diminish the size of the vein lumen until the valve is competent.

The sleeve is then anchored in place to the adventitia by sutures to avoid slippage.[249,250] In one series of 42 limbs, valvular competence was maintained in 90% of patients with a mean follow-up of 86 months and 80% of venous ulcers healed.[250]

Valves which are architecturally intact but incompetent due to redundancy of the valve leaflets may benefit from valvuloplasty and numerous techniques exist to restore valve competence. If an absence of valve attachment lines are noted during surgery this may signify the destruction of the valve as a consequence of the PTS, prevent valvuloplasty and prompting other than an in-situ repair.[125] The technical aspects and results of the various methods of repair have been recently reviewed.[251–254]

An internal valvuloplasty or an open direct valve repair has been the mainstay for the repair of primary venous valvular reflux for decades. This technique involves venotomy and suturing of the elongated valve leaflets under direct visualization with fine polypropylene suture (7 or 6 to 0) to tighten the valve cusps. The type of venotomy used to expose the valve leaflets varies between practitioners and those described include a single longitudinal,[255] single supravalvular transverse,[256] a T incision,[257] and a trapdoor incision (Fig. 96.3).[258]

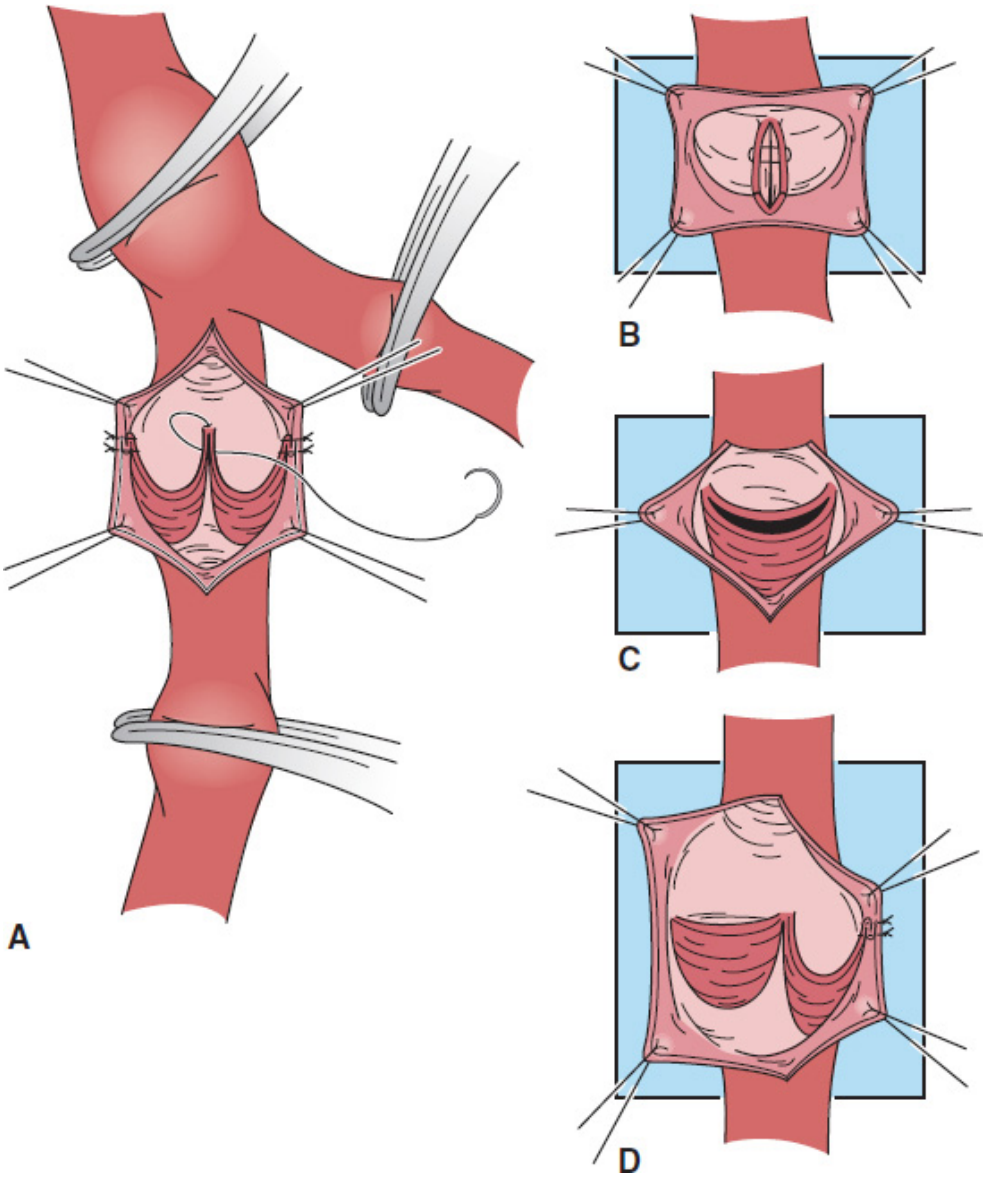


Figure 96.3 Open valvuloplasty to repair an insufficient valve can be accomplished by various venotomy incisions. **A:** Single longitudinal (Kistner). **B:** Single supravalvular transverse (Raju). **C:** T-shaped (Sottiurai). **D:** Trapdoor (Tripathi et al.).

Each approach has a different balance between adequacy of exposure, potential for iatrogenic valve injury and complexity of the closure. Regardless of initial venotomy, once the valve has been visualized the redundant cusps are reefed by suturing their lateral edges to the apices of the respective commissures[255–258] or by excising the excess and reimplanting the cusp.[259] In either case, plication of approximately 20% of the valve leaflet length tends to restore valve competency in the majority of cases.[260] Internal

valvuloplasty has a documented clinical success rate of ~70% at 5 years with ulcer recurrence or ulcer nonhealing occurring in <30% of patients.[251–253] In general, a patent and competent valve translates into clinical improvement and a healed ulcer, while the reverse is true with recurrent reflux. This is true for all types of single-station venous valvular reconstructions.

The technique of external valvuloplasty offers the advantage of valve repair without venotomy. It is performed by placing sutures transmurally through the valve attachment lines and, when tied, reduces the commissural angle and vein diameter, resulting in a competent valve. At 5 years, one can expect a 50% overall success of valve competence and clinical success. The valve leaflets are generally not captured or reefed by this method. In a "transcommissural" modification of the technique, the venous valve cusps are actually engaged with the suture and the cusps are tightened directly much like in the open method of repair.[251–253] The results can approach those noted for open valvuloplasty after significant experience. This approach is either performed blindly (limited anterior plication) which involves only anterior vein dissection and then reefing of the cusps using a running mattress suture[261] or under direct visualization by the use of an angioscope.[262]

Venous valve transplantation is an option when the valve is absent or destroyed. The incompetent femoral vein is clamped and opened below the takeoff of the profunda femoris vein, and the donor vein segment (with valve inside) is sutured into place following the removal of an appropriate length of the recipient vein. The donor vein containing valve segment is often harvested from the axillary vein. If the femoral location does not control all axial reflux into the leg, such as if the profunda femoral vein system is also incompetent, then the popliteal location may be the more appropriate recipient site. For the anastomoses, interrupted sutures are preferred to avoid suture line stenosis.[260] The proximal connection may be accomplished first to confirm the competence of the newly transplanted valve and to allow distention and lengthening of the vein/valve to facilitate the distal anastomosis.[251,252,254]

Reported outcomes of valve transplantation series are highly variable but about a 50% clinical improvement at 5 years was noted in several studies.[251,252,254] There is some evidence that transplantation to the popliteal location may have better outcomes.[263]

A less common option for venous insufficiency is valve transposition.[251,252,254] If a venous valve is competent in one of the major thigh venous systems, then a transposition procedure can be performed placing the incompetent venous system below a competent valve in an adjacent system, effectively shunting the incompetent system into a competent one. Most commonly, the femoral system is incompetent and can be transected and reimplanted distal to a competent valve in either the profunda femoris vein or the GSV. Analogously, if the profunda femoris venous system is incompetent, it may be placed distal to a competent valve in either the femoral vein or the GSV.

A technique has also been described for transposition of the ipsilateral valve competent GSV to the femoral vein with proximal ligation of the femoral vein just distal to the takeoff of the profunda femoris vein thereby escaping problems with diameter mismatch.[264]

Clinical series of vein transposition are few, with small patient accrual and with variable follow-up; outcomes are not as favorable as noted with primary valve repair. Overall, the 3- to 5-year favorable clinical results are about 40% to 50% of cases with similar valve competency.[251,252,254]

Whether valvuloplasty, transplant or transposition; aggressive venous valve surgery requires appropriate consideration of perioperative adjunctive care. This care includes prophylactic antibiotics, intraoperative heparinization especially if the vein is opened, the use of pneumatic compression devices postoperatively, and the use of LMWH or IV heparin in the postoperative period. Some use closed-suction drainage of wounds to avoid hematoma and seroma formation. Warfarin should have an initial target INR range of 2.0 to 2.5 for the first 6 weeks and some would advocate a subsequent decrease to 1.7 to 2.0 until 4 months when it is discontinued. Adjustments are made to accommodate those with an increased risk of thrombosis.

Valve repair procedures are well tolerated by most patients and have a low morbidity, as well as essentially zero mortality in most series. Hematoma and seroma formation are noted in less than 15% of cases, depending on the level of anticoagulation used. DVT occurs in less than 10% of cases in most series, while the pulmonary emboli risk is well less than 1%. Wound infections have been seen in 2% to 7% of cases.[251,252,254]

In general, patients with postthrombotic reflux tend to have more problems maintaining healed ulcers than those with a primary etiology of reflux, as noted from the results of internal valvuloplasty (generally a primary etiology) versus those requiring transplantation or a transposition operative approach.[126,265] Review of pertinent data has resulted in guidelines as to when and how to treat patients with C_{4b}, C_5, and C_6 disease.[142] It is suggested that in such patients with structurally preserved deep venous valves, individual valve repair can be offered (grade 2C). If no structurally intact exists, then valve transposition or transplantation is a suggested treatment (grade 2C).

Valve Substitutes

Autogenous tissues appear to be the only material that currently can act as a substitute valve with some hope of success in the clinical arena. Using a thin-walled donor vein such as the GSV, after trimming adventitia and part of the media, to fashion semilunar cusps within the deficient recipient vein, rapid ulcer healing was reported in five of seven patients and all were patent at 1 year.[125] A recent innovation has been to use an ophthalmic knife or other fine tool to dissect the intima/media wall of the thickened postthrombotic vein wall (or even normal wall) into one or two sheets and thereby fashion the valve cusp(s).[266,267] Adding two sutures on the cusp(s) to hold the valve in the semi-open position and prevent valve collapse, 21 operations resulted in a 95% ulcer-healing rate and late two recurrences (9.5%).[251,254,266,267] The SVS/AVF Guidelines Committee suggests consideration of autogenous valve substitutes in addition to standard compression therapy to aid in venous ulcer healing and recurrence prevention (grade 2C).[142]

Venous Ulcer Wound Care

The quest to heal venous ulcers has generated a myriad of potential topical agents to aid in ulcer healing. Topical antibiotics and dressings containing antimicrobials may retard wound healing and cause allergic reactions and are not recommended for the treatment of venous ulcers.[142,193,268] Growth factors and cytokines demonstrate inconsistent results or studies with insufficient data to determine with any certainty the efficacy of such adjuvants.[269] A number of topical dressings applied on the ulcer bed and beneath the compression dressing have been investigated. A recent meta-

analysis of 78 trials found low-quality evidence that silver may be superior to foam (397 patients in 4 trials) and hydrocolloid (58 patients in 1 trial) and that sucralfate may be superior to hydrogel (100 patients in 1 trial).[270] Insufficient data are available to make firm conclusions, but it is recommended that the nature and amount of the exudates present may provide a rationale for dressing selection as an absorbent dressing should be applied to wet wounds to decrease the risk of surrounding skin maceration and infection while dry wounds should be treated with dressing that will keep them moist to accelerate healing.[270] The SVS/AVF Guidelines Committee suggests that the wound dressing be selected, which absorbs wound exudates and protects the periulcer skin from damage (grade 2B).[142]

Surgical debridement to healthy tissue, when required, benefits the rate of ulcer healing and does not lead to a higher risk of systemic infection.[268,271] The use of local anesthetic (EMLA) during debridement of venous leg ulcers has been found statistically beneficial in lowering pain scores in a Cochrane analysis of six trials.[272] Surgical debridement is recommended to remove slough, nonviable tissue and eschar (grade 1B) using local anesthesia to minimize discomfort (grade 1B).[142]

Autolytic or enzymatic ulcer debridement has also been studied, but has failed to demonstrate increased healing on meta-analysis.[273] Current guidelines suggest each as a potential alternative to surgical debridement when a trained practitioner is not available to provide surgical debridement (grade 2B/C).[142]

For resistant venous ulcers, defined as those that fail to demonstrate improvement in a minimum of 4 to 6 weeks of standard wound therapy, adjuvant wound therapy options should be considered.[274] Skin grafting allows for coverage of raw surfaces to speed the healing process and there are reports on improved healing with skin grafting for chronic venous ulceration.[275,276] A number of skin substitutes have been used to aid in venous ulcer healing and two have shown promise. A bioengineered bilayered human skin equivalent with an allogenic epidermal and dermal layer statistically improved the time to complete healing[277] and an extracellular matrix graft derived from porcine small intestinal submucosa also significantly increased wound healing.[278] The use of these skin substitutes is suggested as guideline adjuvant therapy in recalcitrant venous ulcer care (grade 2 A/B).[142]

Miscellaneous Pelvic Disorders

The complex interconnections of the renal, ovarian, common and internal iliac and lower extremity veins can explain how distention in one or more of the proximal veins can result in distal distention and symptoms. The May–Thurner syndrome has already been discussed. Compression of the left renal vein between the superior mesenteric artery and aorta can result in the "nutcracker syndrome" so called because the renal vein is being crushed like a nut between the respective arteries.[279] The most common symptoms are left flank pain and microscopic or gross hematuria but as the disease progresses the pelvic veins are more affected resulting in symptoms related to the "pelvic congestion syndrome." Upper thigh and pelvic varicosities may be noted. Duplex imaging followed by CT or MRI confirms the clinical suspicion with often venography demonstrating renal vein compression and a pressure gradient. Open surgical vein repositioning or endovascular stenting can relieve the compression.[280] Reflux in the ovarian and internal iliac veins overload the distal veins resulting in pelvic pain as a rather constant complaint which can be disabling and may be associated with dyspareunia, dysuria, dysmenorrhea, and postcoital pain. Varicosities may be noted in the pelvis or upper thigh. Duplex, CT, or MRI can help confirm the diagnosis but venography provides venous detail and potential therapeutic options. Gonadal vein excision is described but has been supplanted by endovascular techniques using coils, sclerosants, or a combination thereof. Hypogastric vein reflux may be best managed by percutaneous embolization.[281] When the elimination of proximal reflux does not resolve superficial varicosities, the management involves techniques used for saphenous vein branch varicosities.

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Section N: PEDIATRIC SURGERY

97

Fetal, Pediatric, and Neonatal Physiology

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Key Points

1. A knowledge of embryology is essential as alterations in fetal development lead to congenital surgical disorders.
2. Persistence of fetal circulation may have clinical significance and affect postnatal hemodynamics.
3. Children compensate well for shock and hypotension is a late finding. Bradycardia is more ominous than tachycardia.
4. Septic shock in neonates and infants manifests as low cardiac output syndrome or "cold" shock, which is preferentially treated with inotropic agents such as dopamine, versus vasodilatory "warm" shock in older children and adults, which is treated primarily with vasoconstrictive agents such as norepinephrine.
5. Children have a higher metabolic rate and lower functional reserve capacity than adults and therefore develop hypoxemia and respiratory distress quicker.
6. Fluid and energy requirements are greatest for neonates and gradually decrease over time until they reach adult levels.
7. Neonatal sepsis may present with subtle signs and will progress to septic shock if not recognized and treated.

INTRODUCTION

Caring for pediatric patients requires an understanding and knowledge of the unique embryologic, anatomic, physiologic, and behavioral characteristics of neonates and children that differ from adults. Furthermore, providers that may need to care for pregnant patients also need a fundamental understanding of fetal development and physiology. The purpose of this chapter is to provide the reader with a fundamental understanding of the unique aspects of fetal, neonatal, and pediatric physiology that differ from those of adults. Physiologic attributes change with development, as such, we have organized this chapter into fetal and transitional, neonatal, and pediatric sections to further exemplify the unique physiologic characteristics of children.

This chapter is intentionally not an exhaustive overview of human physiology, as that content is covered in the foundational chapters found in the Scientific Principles section of this textbook. Many disease- and technology-specific aspects of pediatric care are presented in other sections of this text (see Chapters on Congenital Heart Disease, Pediatric Chest, Fetal Intervention, and Mechanical Circulatory Support).

Fetal and Transitional Physiology

Introduction

An understanding of fetal and neonatal development is an asset to surgeons providing perioperative care of the neonate and infant. Many of the surgical disease processes with which these patients present are a result of fetal development gone awry. The physiologic details discussed below may not seem directly related to surgical 1 pathology, but an understanding of these unique physiologic aspects of development enables a surgeon to appreciate aspects of neonatal care that impact treatment options.

Early Fetal Development and Organogenesis

During the first week after conception, the fertilized egg undergoes a series of divisions, forming a blastocyst, which becomes implanted in the uterine wall. This is followed by the establishment of uteroplacental circulation. The formation of the ectoderm, mesoderm, and endoderm occurs during week 3 and then further differentiation into derivative organs and tissues occurs during the embryonic period, which continues up through week 8.[1] Key events include the diaphragm separating the body into the thoracic and peritoneal cavities, the gut tube differentiation into the gastrointestinal (GI) tract, limb formation, and central nervous system development. During this period, the developing embryo is sensitive to various insults that may lead to congenital defects.[1] For example, from the 6th to the 10th week of gestation, the intestines undergo a process of rapid growth, so that they are no longer contained within the fetus but herniate through the umbilicus.[1] At that time, they also undergo rotation 270 degrees counterclockwise prior to returning to the abdomen. Failure of the complete rotation and fixation upon return to the

abdomen (or if the intestines do not return to the abdomen as is the case in abdominal wall defects and diaphragmatic hernia) results in intestinal malrotation and places infants at risk for volvulus. Failure of complete formation of the lateral pleuroperitoneal folds of the abdominal wall leads to an omphalocele. Gastroschisis occurs if the herniation does not occur through the umbilical ring, but through part of the abdominal wall immediately to the right of the umbilicus and then fails to return to the abdomen. Any of the above processes can compromise intestinal blood flow, resulting in an intestinal atresia. By week 9, the fetus enters a period of rapid growth and continued development and maturation of organs, which continues until 40 weeks' gestation, which is considered full term.[1]

The Placenta and Placental Function

The placenta is a specialized organ that develops between the maternal and fetal circulations that functions in gas and nutrient exchange, filtering of waste products, and trafficking of immunologic mediators. Early in the first trimester, nutrients are obtained directly from the uterine environment, with the role of the mature placenta in supporting the fetus becoming more pronounced at the transition from the first to the second trimester.[2] While not mature for several weeks, placental development begins soon after implantation. In the second week, villi from the chorionic plate (fetus) and maternal spiral arteries from the decidual plate (uterus) meet at the junctional zone where intervillous "lakes" filled with maternal blood form, creating the initial mechanism for blood, nutrient, and gas exchange between the mother and fetus. The chorionic vessels mature, propagate, and coalesce into the umbilical vessels. A majority of the population has two umbilical arteries and one umbilical vein, but 0.5% of the population is born with a "two-vessel cord" that contains only one umbilical artery.[1] Particular attention to this examination finding is essential on the newborn examination, as up to 20% of infants with this finding may have an associated cardiovascular anomaly and may have other noncardiac anomalies.[3]

The placenta is mature by 14 weeks' gestation and continues to grow with the fetus, increasing the surface area for filtration and exchange until 40 weeks. It is at 14 weeks' gestation that passive immunity to the fetus occurs by transmission of immunoglobulin G from the mother.[1] For reasons that are

not completely clear, a placenta may not adequately provide nutrients to the fetus (placental insufficiency)—potentially related to inadequate perfusion of the placenta and/or an increased demand by the fetus, such as in multiple pregnancies.[4] Placental insufficiency can lead to intrauterine growth restriction, maternal preeclampsia, and/or preterm birth. Infection of the placenta (i.e., chorioamnionitis) can also induce preterm birth, and can place the neonate at risk for perinatal sepsis and cardiorespiratory failure.[4]

Amniotic Fluid Production and Resorption

A key component of the neonatal history is the identification of any prior abnormality in the amount of amniotic fluid seen on prenatal ultrasound, as this can provide clues as to possible surgical lesions to be addressed postnatally. The fetus is normally surrounded in the amniotic cavity by amniotic fluid. The amount of fluid increases over time as the fetus grows, and can exceed 1 L of fluid at term.[1] Fluid initially originates from maternal blood and is diffused along an osmotic gradient into the fetal environment by cells of the amniotic sac.[5] During the second trimester, most of the production of amniotic fluid shifts to the fetus through swallowing and absorbing fluid through the enteral route and by excreting fluid through urine and respiratory secretions.[5] Alterations in the normal levels of fluid may be an indicator of underlying congenital abnormality. Oligohydramnios is a decreased amount of fluid and can originate from either placental insufficiency or from anomalies leading to decreased urine production, such as renal dysgenesis or urinary obstruction. Adequate amniotic fluid volume is essential in maintaining alveolar back pressure to promote lung development and in maintaining adequate space for fetal development; severe oligohydramnios due to renal abnormalities can be associated with pulmonary hypoplasia, limb development anomalies, and craniofacial anomalies (Potter sequence).[6] Polyhydramnios refers to more fluid present than expected and usually results from proximal GI obstruction (e.g., esophageal or duodenal atresia) that keep the fetus from swallowing and absorbing amniotic fluid. Additionally, cardiac high-output states can also result in polyhydramnios.

Fetal Circulation and Transitional Physiology

2 A knowledge of the fetal circulation is essential in understanding anatomic vascular remnants that one may encounter even while caring for adult patients. There are three fetal shunts that work to ensure maximum distribution of oxygenated blood to the fetus—one shunt to bypass the hepatic portal circulation and two shunts to bypass the pulmonary vascular bed. Oxygenated blood (typically at 80% saturation) enters the fetus from the placenta via the umbilical vein, passes through the liver, flows into the inferior vena cava, and then to the right atrium. The first shunt encountered is the ductus venosus (Fig. 97.1), which diverts blood away from the hepatic sinusoids and into the inferior vena cava, preventing the immediate consumption of oxygen and nutrients prior to blood reaching the brain and remainder of the systemic circulation. A majority of blood flow into the right atrium is then diverted through a second shunt—the foramen ovale. The foramen ovale is an intracardiac shunt through the atrial septum between the right and left atria that bypasses the right ventricle to allow flow of oxygenated blood directly to the left heart. The remainder of the blood (<10%) from the right atrium follows the normal pathway into the right ventricle, where it encounters the third shunt—the ductus arteriosus. This last shunt connects the pulmonary artery to the aorta just distal to the arch, feeding into the systemic circulation and allowing the remaining oxygenated blood to bypass the pulmonary vascular bed and to flow directly into the systemic circulation. The lungs do not play a role in gas exchange in the uterine environment and the vascular resistance in the pulmonary vascular bed is high, which maintains a right-to-left shunt through the patent ductus arteriosus (PDA) and minimizes unnecessary pulmonary blood flow. This shunting ensures the brain and heart receive more oxygenated blood and minimizes energy expenditure of the right heart pumping blood through a dormant pulmonary vascular tree.[1,7] Despite these shunts, systemic blood remains quite deoxygenated due to mixing at the level of the IVC (<60% saturation). Blood flow back to the placenta is derived from the systemic circulation, with blood flow returning to the placenta via the paired umbilical arteries arising from the iliac arteries bilaterally.

The fetus develops in an oxygen-poor environment, relying on a partial-pressure gradient of oxygen from the maternal circulation to provide adequate transplacental oxygen delivery to the fetus. To augment oxygen extraction from the placenta, fetal red blood cells contain primarily fetal

hemoglobin (α2γ2) chains, which have a higher affinity for binding oxygen than normal adult hemoglobin chains (α2β2) (Fig. 97.2), facilitating transfer of oxygen from maternal blood to the fetus. As the fetus transitions to postnatal life, oxygen demands increase, but the fetal hemoglobin chain preponderance impairs oxygen delivery to the neonatal tissues. During the 1- to 2-month transition period of fetal to adult hemoglobin, higher levels of 2,3 diphosphoglycerate (2,3 DPG) and the resulting mild acidosis decrease oxygen affinity and increase oxygen delivery.[8]

Immediately at birth a number of anatomic and physiologic triggers occur that lead to the transition from fetal circulation to postnatal circulation. Initiation of respiration causes a resultant decrease in hypoxic pulmonary vasoconstriction resulting in a drop in pulmonary vascular resistance (PVR) and an increase in pulmonary blood flow.[1,9] Around the time of birth, pulmonary pneumocytes cease producing fluid and start to absorb the fluid into the interstitial space and into the fetal circulation, thereby clearing fluid from the alveolar spaces.[1,9] A delay in this process can lead to transient tachypnea of the newborn (TTN), which should start to improve within 2 hours and usually resolves completely within 48 hours.[1,9] Due to the fact it is transient in nature, the diagnosis is usually made retrospectively and is often a diagnosis of exclusion. Treatment is supportive care.

Changes in blood flow through the pulmonary, systemic, and mesenteric vascular beds at the time of delivery promote closure of the three shunts of the fetal circulation. Upon clamping of the umbilical cord, the newborn's separation from the placental blood flow causes a drop in mesenteric blood return resulting in closure of the ductus venosus, and increases the systemic vascular resistance due to decreased runoff from the iliac arteries to the placenta. After initiation of respiration, the resultant decrease in PVR and increase in systemic vascular resistance leads to decreased right heart pressures and increased left heart pressures. These changes in pressures result in reversal of the directionality of flow through the foramen ovale, leading to closure of the valve of the foramen ovale (developed by the growth of the septum primum and secundum). Persistent patency of the foramen ovale is a result of incomplete septal fusion and occurs in 20% of the population.[1,8] Closure of the ductus arteriosus occurs secondary to vasoconstriction of the vessel in response to increasing oxygenation of the blood and decreasing levels of prostaglandins (PGE). The ensuing ischemic

changes to the inner muscular layer render it resistant to the vasodilatory effects of PGE and cause tissue remodeling that obliterates the lumen of the ductus in term infants. In premature neonates, however, blood oxygen levels within the ductus do not drop to the same level of hypoxemia needed to promote the remodeling process, resulting in an increased risk for PDA.[10]

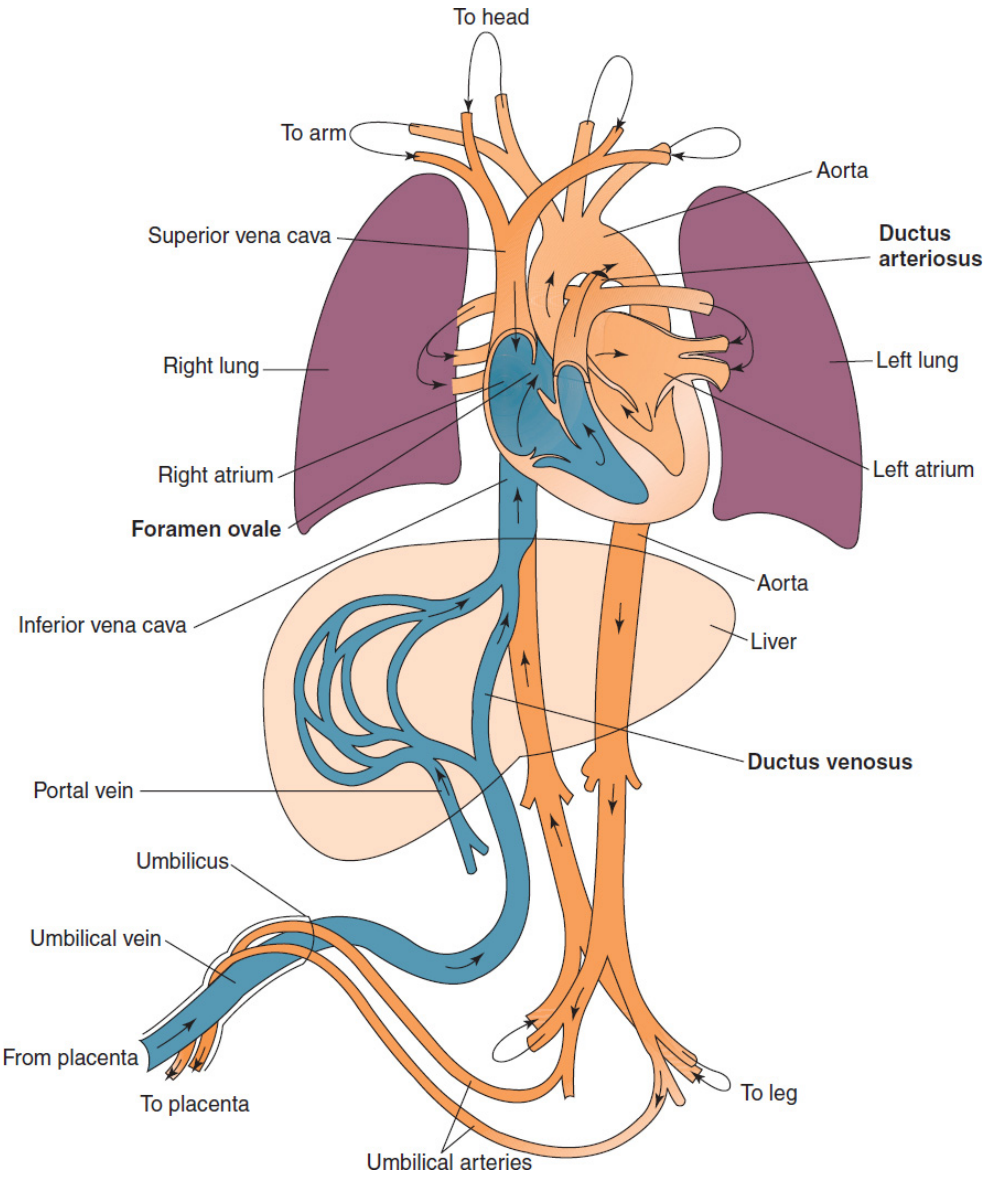

Figure 97.1 Fetal circulation. (From Rosdahl CB, Kowalski MT, eds. *Textbook of Basic Nursing*. Philadelphia, PA: Wolters Kluwer Health; 2012.)

Persistent elevations in PVR (persistent pulmonary hypertension of the newborn; PPHN) can lead to persistence of the PFO and PDA. In the presence of persistent elevation of PVR, shunts through the PDA and PFO

remain right to left, with deoxygenated blood from the right heart passing through the patent foramen ovale and from the main pulmonary artery through the ductus arteriosus, leading to lower oxygen saturation measured in the left arm and bilateral legs (postductal saturation) compared to that measured in the right arm or head (preductal saturation).[7]

In the absence of elevated PVR, the ductus arteriosus is expected to close within the first 48 hours in 96% of term neonates without other cardiac anomaly and who are otherwise healthy.[11] Failure of closure leads to a PDA, which has been reported in 56.7 per 100,000 live births, not including those incidentally found on echocardiogram.[12] In premature neonates, younger gestational age and lower birth weight are associated with lower rates of closure by 1 week of life.[13] Left-to-right shunting through persistent large PDAs results in pulmonary overcirculation, and can lead to heart failure and an increased risk of chronic lung disease.[14,15] When PDA closure is desired, medical treatment options include indomethacin, ibuprofen, or acetaminophen.[16] Operative PDA ligation was first reported by pediatric surgeon Robert Gross in 1939[17,18] and remains an option for treatment of PDAs that fail attempts at medical therapy. In the last decade, enthusiasm for surgical PDA ligation and pharmacologic treatment has waned with evidence emerging for "watchful waiting" being associated with no increase in adverse outcomes.[19–23]

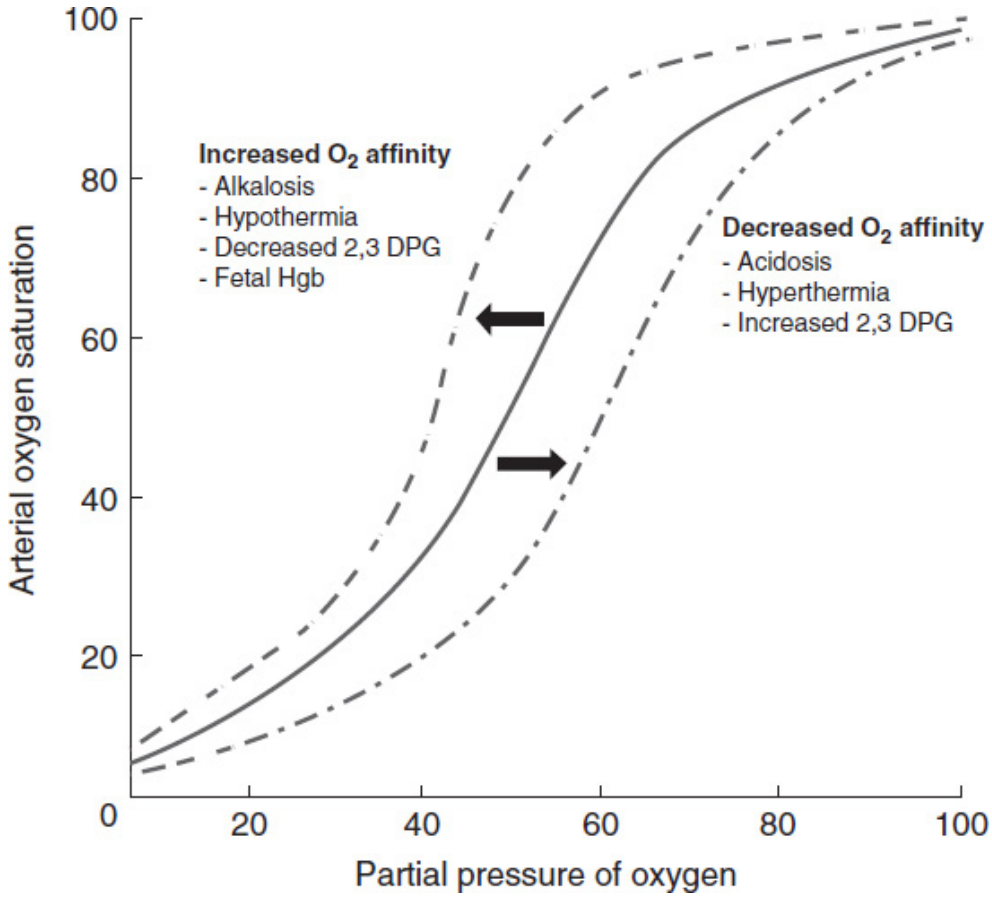

Figure 97.2 The oxygen dissociation curve shows the percent of oxygenated hemoglobin at various partial pressure of oxygen levels, and demonstrates factors that alter the affinity for oxygen.

Fetal Lung Development

The respiratory system has its beginnings in the fourth week of gestation when the respiratory diverticulum first appears as an outpouching of the foregut. The tracheoesophageal septum subsequently forms, dividing the respiratory tract from the GI tract. Failure of this septum to completely close results in variations of tracheoesophageal fistula (with or without esophageal atresia).[1] At week 5, the pseudoglandular phase of respiratory development begins, in which lung buds enlarge and begin to divide into main and secondary bronchi, ultimately forming terminal bronchioles by 16 weeks. In the following 10 weeks, the canalicular phase sees the further division of the terminal bronchioles into respiratory bronchioles and alveolar ducts. During the terminal sac phase (week 26 until birth), the early alveoli develop and come in close contact with the capillaries. In addition, type I pneumocytes

(gas exchange cells) and type II pneumocytes (cells that produce surfactant) are first identified in this phase. The final stage is the alveolar phase that starts in utero during the last few weeks of gestation but is not completed until early childhood. This time is allotted for further increase in alveoli number and final maturation of the relationship between the alveoli and the capillaries to allow for adequate gas exchange.[1] Fetal lung development has profound implications on the viability of extremely premature infants, as only in the late canalicular phase is the lung functional for gas exchange, with surfactant production (see below) beginning in the saccular phase. Though current American Academy of Pediatrics guidelines define the lower limits of viability at 22 weeks,[24] the generally accepted practice is to recommend resuscitation of premature infants delivered at 25 weeks or later, with resuscitation of premature infants between 22 and 24 weeks remaining controversial.[25]

Surfactant is an essential lipoprotein that is produced and secreted by type II pneumocytes starting during the saccular phase of development. The surfactant lines the alveolus and protects it from complete collapse during expiration by lowering the surface tension between the air and alveolar surface interface. Lack of an adequate amount of surfactant in premature neonates is the cause of respiratory distress syndrome (RDS), a major cause of morbidity and mortality in infants who fail to make it to term. The respiratory consequences of preterm birth can be potentially mitigated by the administration of corticosteroids (typically betamethasone) to any woman who is at risk for preterm labor. A complete course of steroids given to women who are less than 34 weeks' gestation (but greater than 24 weeks) prior to preterm delivery can stimulate fetal production of surfactant, as well as hasten fetal lung maturity, decreasing the risk of developing RDS.[26] Once the neonate is born, treatment includes supplemental oxygen and respiratory support (continuous positive airway pressure [CPAP] or mechanical ventilation) as needed. Postnatal administration of exogenous surfactant has also been successful in prevention and treatment of RDS, though in rare cases it can cause pulmonary hemorrhage.[26]

Neonatal Physiology

Prematurity and Physiologic Implications

Gestational age at birth plays a role in the prognosis of the child and the complications they may be susceptible to at birth or shortly thereafter. Neonates born at full term (37-0/7 weeks' up to 42 weeks' gestation) have typically completed intrauterine development, while infants born prior to completing 36 weeks of gestation are considered preterm. Infants born after 42 weeks are considered postterm and have an increased risk of delivery-related complications. The most recent data estimates 10.6% of all live births worldwide are preterm infants.[27] Further classification of preterm infants into "very preterm," "moderate preterm," and "late preterm" has been proposed due to differences in complication rates and outcomes by these strata, though there is no clear consensus on what gestational ages fall within each group. Prematurity disposes infants to a number of physiologic consequences of incomplete development, discussed briefly by systems in the following sections.

Neurologic Considerations

The central nervous system in an adult is a fragile system and prone to insult, but the developing nervous system in neonates—particularly premature neonates—is particularly prone to injury. The immature brain is most vulnerable at the germinal matrix. This area has a high concentration of thin-walled vessels that develop during fetal life between 24 and 34 weeks of gestation.[28,29] These vessels are poorly tolerant to changes in systemic blood pressure and are prone to rupture leading to intracranial hemorrhage. Preterm infants are unable to adequately regulate cerebral blood flow, and any hemodynamic instability increases the risk of vascular injury and intraventricular hemorrhage.[29] The risk of bleeding is particularly increased in conditions leading to prematurity with hemodynamic instability, such as placental abruption, chorioamnionitis leading to sepsis, birth trauma, temperature instability, or perinatal hypoxia.[28] Routine screening cranial ultrasounds are recommended in premature infants <33 weeks to evaluate for potential bleeding in the setting of any these risks.[30]

As an extension of the central nervous system, the neonatal retina is particularly susceptible in premature infants. Normal development of the retina involves angiogenesis that starts at the optic nerve and progresses

peripherally and is dependent on the hypoxic fetal environment triggering production of vascular endothelial growth factor (VEGF). The process begins at 16 weeks and is typically complete by 40 weeks, with migration completion on the medial side of the eye occurring prior to the lateral side (by 36 weeks). In retinopathy of prematurity (ROP), VEGF is inhibited by the introduction of oxygen that occurs upon the neonate's first breath. During this first stage of ROP pathogenesis, the systemic hyperoxia-induced VEGF inhibition halts the normal development of the retinal vasculature. However, since normal angiogenesis did not occur, the retina is avascular and therefore hypoxic during the second stage. This local retinal hypoxia abnormally reestablishes VEGF production and results in abnormal vascular proliferation in the retina that extends into the normally avascular vitreous. The ensuing destructive process can eventually lead to blindness secondary to retinal detachment.[31,32]

As indicated by its name, prematurity with associated low birth weight is the greatest risk factor for ROP,[33] with an incidence of 84% in neonates less than 28 weeks.[34] Other risk factors include oxygen exposure, need for ionotropic support, intraventricular hemorrhage, and need for mechanical ventilation.[31] The longest recognized and greatest modifiable risk factor is oxygen exposure that can cause hyperoxia. Efforts to limit supplemental oxygen exposure in premature neonates must be carefully balanced with the increased mortality risk for when lower oxygen saturation goals are used—as hypoxia can contribute to neurologic injury and increased rates of cerebral palsy. The ideal balance is not yet known.[33–35] Patients should undergo regular retinal examination screening by specialized ophthalmologists to identify ROP early and continue to monitor until retinal maturation or resolution in patients developing ROP.[36] Traditional treatment options include laser photocoagulation, cryotherapy, and in severe cases, retinal reattachment.[31] Newer medical management options include bevacizumab, propranolol, and caffeine.[32,37,38]

Cardiovascular Considerations

Evaluation and management of a neonate or infant with a surgical condition requires a fundamental understanding of normal and abnormal cardiovascular function in this age group with additional consideration of whether or not the

heart is structurally normal. This chapter will not cover congenital heart disease in detail—for this we will refer the reader to the chapter in the textbook (Congenital Heart Disease), but will point out that an increased index of suspicion of structural heart disease should be raised in patients presenting with cyanosis, presence of a heart murmur, or evidence of fluid overload. Additionally, several pediatric general surgical conditions (VACTERL association, duodenal atresia, congenital diaphragmatic hernia, omphalocele, and intestinal rotational anomalies) are known to be associated with structural heart disease, and these patients should be evaluated with echocardiogram prior to undergoing general anesthesia. Some cardiac lesions are not apparent until the ductus arteriosus begins closing, which results in the loss of persistent fetal circulation that allowed the child to compensate; in these cases, prostaglandins may be used to open or maintain patency of the ductus arteriosus.

In the absence of structural heart disease, there are still a number of unique physiologic characteristics in neonates and infants that warrant attention. Of paramount importance for the surgeon is an understanding of normal vital signs in infants and children—and the implications of abnormal vital signs (Table 97.1). An important distinction to note in neonates is that the cardiac output is highly dependent on heart rate; they compensate solely by increasing their heart rate as infants are not able to substantially increase stroke volume. Bradycardia is a sign of myocardial ischemia and 3 impending cardiac arrest if untreated. The myocardium is less compliant in neonates and therefore less tolerant to rapid changes in volume, so providers must be careful to avoid excessive fluid resuscitation in times of illness.[7] Fluid overload can lead to right heart failure and reopening of a ductus arteriosus. Premature neonates are often treated with smaller (10 mL/kg) fluid boluses and earlier initiation of inotropes to account for the decreased tolerance of volume overload. Infants in septic shock typically present with tachycardia and signs of increased systemic vascular resistance: weak pulses, delayed capillary 4 refill, and decreased urinary output (i.e., cold shock). Resuscitation should be with sequential fluid boluses of 10 mL/kg at a time (up to 40 to 60 mL/kg), while watching for evidence of fluid overload on examination (Fig. 97.3).[39] If pharmacologic support is needed, dopamine is usually initiated first (Fig. 97.3) for increased chronotropy and inotropy, as children in fluid-refractory septic shock generally have a hypodynamic shock

state with low cardiac output and high systemic vascular resistance.[40] Epinephrine is generally used as a second-line agent over norepinephrine due to its preferential inotropic profile. Milrinone is an inodilator that is often used as an adjunct due to its inotropic and vasodilatory effects to improve the dynamic state, as well as lusitropic effects that improve cardiac relaxation and diastolic function.[7,41]

Neonates and infants have a reactive pulmonary vascular bed. Pulmonary hypertension can result from sepsis, meconium aspiration, pulmonary hypoplasia associated with congenital diaphragmatic hernia, and a number of other disease processes. Clinical indicators include differential oxygen saturation at pre- and postductal measurements and hypoxemia that does not sufficiently improve with increasing supplemental oxygen support. Treatment involves mechanical ventilation, pulmonary vasodilation (supplemental oxygen, milrinone, inhaled nitric oxide), and avoidance of hypotension and acidosis. If these initial measures fail, extracorporeal membrane oxygenation can be utilized for cardiopulmonary support.[42]

Respiratory Considerations

There are a number of key physiologic characteristics of neonates and infants that impact management. Compliance is a major determinant of how well a patient ventilates and is based on both lung compliance and chest wall compliance. Neonates have a very compliant chest wall due to the fact that the rib cage is cartilaginous and the musculature is underdeveloped as compared to the bony and muscular adult chest wall. Though intrinsic lung compliance is similar in infants and adults,[43] the difference in the negative pressure due to chest wall compliance makes infant lungs more likely to collapse.[8] The ability to sustain functional reserve capacity (FRC) in the setting of increased tendency for lung collapse is enabled by the narrower glottic openings and shorter expiratory times.[44] “Grunting” with respiration (expiring against a closed larynx to increase FRC) in an infant is a compensatory mechanism and a telltale sign of impending respiratory failure.

Table 97.1 Normal Heart Rate and Blood Pressure Ranges for Infants and Children

Age	Awake Heart Rate (BPM)	Sleeping Heart Rate (BPM)	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
Neonate	100–190	80–160	50–70	25–45
Infant	100–180	75–160	70–100	50–70
Toddler	80–140	60–90	80–110	50–80
Preschooler	70–120	60–90	80–115	50–80
School age	65–110	60–90	80–120	55–80
Adolescent	60–100	60–90	90–130	60–80

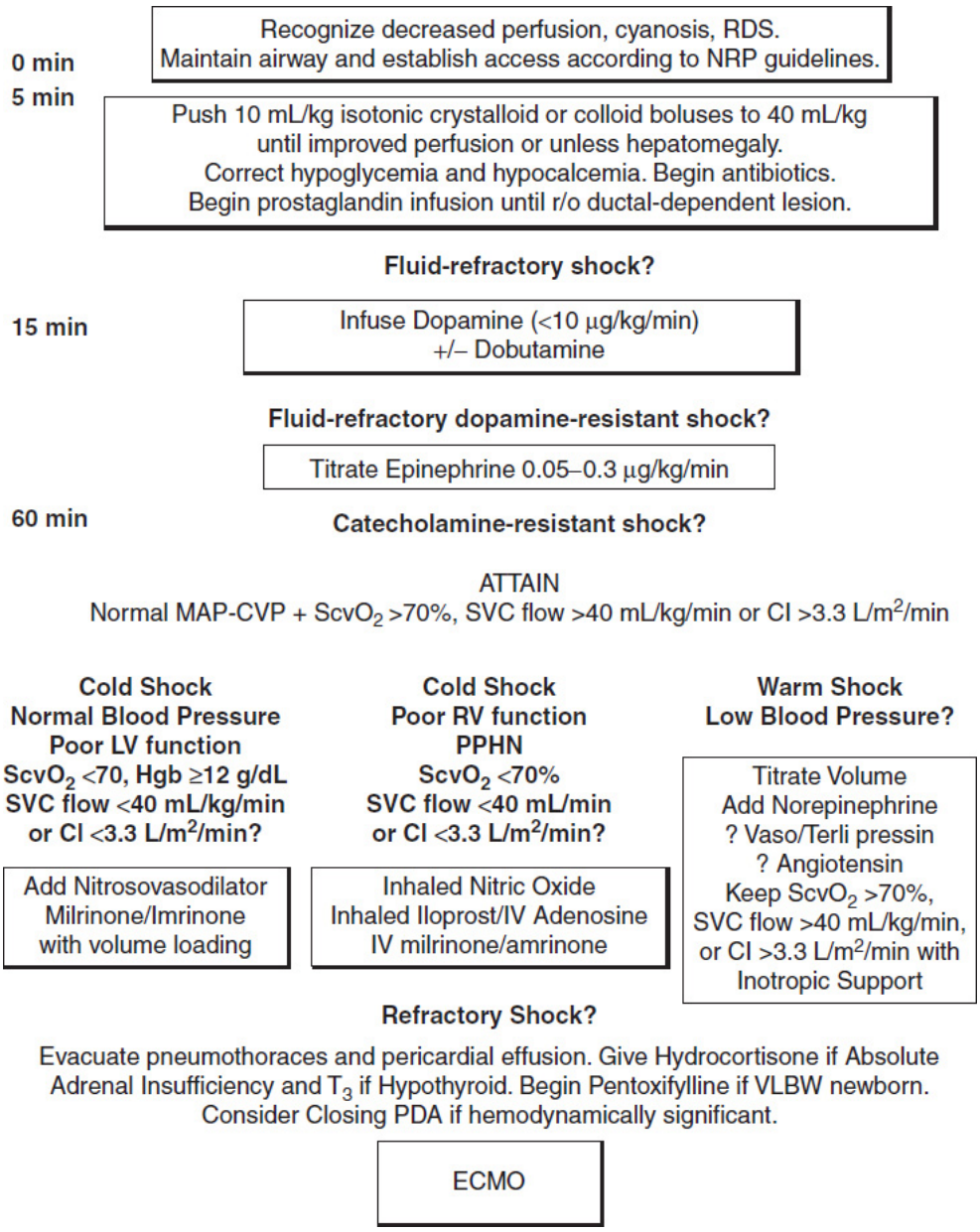

Figure 97.3 Neonatal algorithm—goal-directed therapy for sepsis algorithm. (From Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. *Crit Care Med* 2017;45[6]:1061–1093. Wolters Kluwer Health, Inc.)

5 High metabolic demand predisposes infants to a high risk of respiratory decline, hypoxemia, and inadequate oxygen delivery. Neonatal indications for respiratory support include apnea, airway obstruction, pulmonary effects of congenital heart defects, poor respiratory drive in premature infants, and other disease-specific reasons, such as congenital diaphragmatic hernia.[45]

Noninvasive measures, including CPAP and noninvasive positive-pressure ventilation (NIPPV) are preferred if sufficient to sustain adequate oxygenation and ventilation due to a decreased risk of developing ventilator-induced damage to already fragile premature lungs.[46] If endotracheal intubation and mechanical ventilation are required, neonatal-specific ventilators have been designed to provide adequate tidal volumes and take into account factors related to neonatal respiratory mechanics.[46] High-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV) are nonconventional modes often used in the neonatal period. These modes rapidly deliver small "subtidal" volumes on the order of hundreds of breaths per minute, thereby using relatively constant pressure and volume to maintain lung expansion. The use of high-frequency ventilation in neonates with bronchopulmonary dysplasia is often recommended though the benefits compared to conventional ventilation are less clear as previously thought.[45,47]

Apnea of prematurity is one of the most common respiratory disorders in premature neonates. Most preterm infants less than 28 weeks' gestational age have some level of apnea, with decreasing incidence at increasing gestational age.[48] Apnea may be obstructive or central nervous system mediated, but is often a result of both. Treatment includes initiation of methylxanthines, most commonly caffeine, and noninvasive positive airway pressure. Transfusion of anemic patients may also decrease apneic episodes.[48] Resolution of apnea spells usually occurs by the time the child has reached term.[48] Postoperative apnea may occur in 25% of preterm infants up to 44 weeks' gestational age,[49] with the risk decreasing to <1% only after postconceptual age of 56 weeks.[50] As a result, current accepted practice is to avoid elective operations in preterm infants until they reach 55 to 60 weeks' total gestational age, or to admit them for 24 hours of apnea and bradycardia monitoring after undergoing general anesthesia if it is necessary to proceed with surgery prior to 55 to 60 weeks.

Chronic lung disease of prematurity, previously referred to as bronchopulmonary dysplasia (BPD), is the need for supplemental oxygen in a premature (<32 weeks) infant for more than 28 days. The severity of chronic lung disease is determined by the level of oxygen support required at 36 weeks' postmenstrual age, with the most severe cases seen in patients still supported by mechanical ventilation or positive airway pressure and

supplemental oxygen levels at 30% or greater.[51] Development of chronic lung disease is multifactorial, but one mechanism is ventilator-induced inflammatory injury to premature lungs.[51] Dexamethasone administered within the first week of life decreased rates of chronic lung disease at 28 days and 36 weeks, but was also associated with hyperglycemia, hypertension, GI bleeding and/or perforation, and development of cerebral palsy.[52] Waiting until after the seventh day of life had a decreased risk of GI complications and was associated with lower mortality at 28 days, lower need for home oxygen and higher rates of earlier extubation, in addition to the overall decrease in chronic lung disease of prematurity rates.[52] Due to the concerning side effect profile, dexamethasone is only recommended in select neonates, but ongoing studies are evaluating more directed steroid administration. Prevention of chronic lung disease is targeted at neonatal lung protection. The mainstay of this preventative strategy is minimization or avoidance of mechanical ventilation if possible by using various methods including CPAP, noninvasive surfactant treatment, temporary intubation for administration of surfactant, or NIPPV, all of which have shown some benefit against mechanical ventilation in decreasing the odds of chronic lung disease or death in preterm infants.[53]

Gastrointestinal Considerations

Development of the upper and lower esophageal sphincters and coordinated peristalsis are mature by 31 weeks' gestation.[54] Gastroesophageal reflux (GER) itself is a common occurrence in neonates and infants, in which gastric contents pass retrograde into and through the esophagus after a feed that may result in the "spit up" but has no other serious consequences. Transient relaxation of the lower esophageal sphincter has been shown to be the primary cause of reflux in premature infants.[54] Increased gastric volume from feedings may trigger relaxation, making these events more common after a meal.[55] This phenomenon is separate from gastroesophageal reflux disease (GERD), which is defined as reflux episodes that result in "troublesome symptoms and/or complications."[56] Though these are somewhat difficult to define in infants, they may include aspiration events with subsequent pneumonia and poor weight gain.[57] No treatment is needed for pure uncomplicated reflux episodes in infants as they typically resolve with time;

88% of infants have resolution by 1 year,[58] and treatment options for GERD include diet modification such as thickening feeds and/or behavioral pacing of feeds by the caretaker, positional changes after feeds (head of bed elevation), medical treatment with prokinetics and acid suppression, nasojejunal feeding, and Nissen fundoplication for refractory cases.

The GI tract develops with contributions from the endoderm, mesoderm, and ectoderm and is separated into foregut, midgut, and hindgut. Although a full discussion of gut embryology will not be undertaken at this time, a few notable events of intestinal development will be mentioned. Intestinal villi with their columnar epithelium first develop at 10 weeks, followed by formation of Paneth (enzyme secretion) and goblet cells (mucin production).[59] Digestive enzymes begin to appear as early as 10 weeks, but some may not reach normal levels until up to 34 weeks' gestation, while mucin production does not reach postnatal levels until infant is term.[60,61] Lymphoid tissue congregates in the ileum to form Peyer patches by week 14, and both T and B lymphocytes are identified within these patches by week 18.[59,60] The lamina propria also develops at the time but lies mostly dormant due to the lack of antigen presentation and inability to produce immunoglobulin A, which normally acts to bind antigens, preventing their translocation across the gut wall.[59] Gastric motility is seen as early as 20 weeks, but intestinal motility can take up to 34 weeks for full development of factors associated with intestinal mobility (e.g., motilin, migrating myoelectric complexes).[60,62] The ability for coordinated suck and swallow is fully developed usually by 34 weeks.[62] Due to the incomplete development of these (and many other) anatomic and functional aspects, feeding of premature infants should be initiated slowly.

In addition to the lack of gut development, prematurity brings added consequences that may affect intestinal barrier function and increase the risks of necrotizing enterocolitis. Hypotension and associated vasopressor requirement can cause visceral ischemia and mucosal sloughing, while withholding or delaying feeding can lead to atrophy of intestinal villi and prevent normal colonization of gut bacteria. Gastric acid acts as a primary defense against bacteria, and acid-suppressive medications can therefore increase the risk of necrotizing enterocolitis and pneumonia.[63] Decreased mucin production and peristaltic action also make the intestinal mucosa vulnerable to invasion. Premature infants lack the ability to mount an

appropriate anti-inflammatory response as evidenced by increase in proinflammatory markers and cytokines in premature infants with necrotizing enterocolitis.[63]

Total energy requirements for neonates and infants range from 80 to 120 kcal/kg/d,[64] and up to one-third of this energy is used for growth. The expected daily growth rate for weight is based on age, while babies up to 3 months old are expected to grow in length at a rate of 0.15 cm/d, followed by up to 0.075 cm/d until a year of age.[65] 6 The basic metabolic rate is higher in premature infants and neonates than in older children, which is in turn higher than in adults. Fats provide most of the energy for the growing infant and are the most common way that energy is stored.

Though carbohydrates cease being the main mode of energy at birth, glucose metabolism is a key concern during the perinatal period. After being separated from the maternal circulation, infants only have enough glucose stores (glycogen) for at most 24 hours and with a high turnover rate (up to 5 mg/kg/min in neonates compared to 2 to 3 mg/kg/min in adults), stores can be quickly depleted. It is therefore imperative for infants who are not able to feed to be started on dextrose-containing fluids as soon as possible. Most infants require a glucose infusion rate (GIR) of 4 to 9 mg/kg/min at birth to keep up with glucose metabolism; the GIR is increased slowly over subsequent days to a maximum rate of up to 14 mg/kg/min.[65,66] The majority (90%) of glucose is used by the brain, so hypoglycemia (glucose <45 mg/dL) can affect early neurodevelopment if left untreated.[67]

If there is no contraindication, enteral feeding is the preferred method of providing nutrition to neonates and infants. Very premature infants may not developmentally be able to take feeds by mouth due to the lack of oral coordination that usually develops at 32 to 34 weeks of gestation, and usually require nasogastric access for feeding. Oral aversion is a concern for infants who have need to be nil per os for an extended period of time (e.g., prolonged intubation, long-gap esophageal atresia). Breastmilk (20 kcal/oz) is recommended due to immunologic benefits, but formula may be augmented/substituted if breastmilk is insufficient/unavailable or not tolerated (i.e., milk protein allergy). Fortification may be utilized for additional calories, but can increase the risk of necrotizing enterocolitis, especially in premature infants.

If unable to proceed with enteral nutrition, parenteral nutrition (PN) can be initiated. PN is recommended in very low-birth-weight/extreme preterm infants as their intestinal immaturity puts them at high risk for necrotizing enterocolitis with early initiation of full feeds. Since they are unable to immediately tolerate full enteral feeds, have high protein turnover rates, and require supplemental protein to maintain a positive nitrogen balance and prevent starvation, premature infants are started on PN as soon as possible after birth.[66] PN is also useful for infants with bowel obstruction or in the postoperative state. Some infants who have lost a large portion of small bowel secondary to midgut volvulus (anatomically) or gastroschisis (functionally) may be dependent on PN for a long period of time and are at risk of the development of PN-associated cholestatic liver disease.[65] Recent advances in alternative lipids have been show to decrease the risk of PN-related cholestasis with the use of fish oil–based lipid formulations (as opposed to the standard soy-based lipids) containing omega-3 fatty acids.[68,69] Infants receiving PN must have their electrolytes and glucose levels monitored closely to avoid metabolic derangements. While lifesaving and sustaining, prolonged PN use places infants at risk for complications, including catheter-related complications (central line–associated bloodstream infections, thrombosis) and cholestasis, and therefore transition to enteral nutrition whenever possible is preferred.

Hyperbilirubinemia is common in infants and an understanding of the natural progression of bilirubin levels is needed in the approach to the evaluation of the GI surgical neonate. Bilirubin levels in the blood are determined by the amount created from the breakdown of heme, primarily from red blood cells, and the amount reabsorbed from the enterohepatic circulation. The normal level of bilirubin in infants is higher because neonates produce two to three times the amount of bilirubin as adults, in part because of the increased turnover of red blood cells.[70] Unconjugated hyperbilirubinemia is a result of decreased ability to conjugate due to deficiency of the conjugating enzyme uridine diphosphogluconurate glucuronosyltransferase (UGT). Additionally, absorption of unconjugated bilirubin from the GI tract can occur if the conjugated bilirubin normally excreted in stool is instead unconjugated by β-glucuronidase. This GI resorption can be increased in diseases that result in prolonged retention of stool, such as Hirschsprung disease or distal atresias. Typically, during the

first 1 to 2 weeks, unconjugated bilirubin levels transiently rise to 6 to 12 mg/dL, depending on gestational age of child (full-term infants have lower levels) before returning to normal levels of <2 mg/dL.[70,71] Neurotoxic effects of hyperbilirubinemia can be avoided by clearing bilirubin with phototherapy (first-line therapy) or exchange transfusions. Established nomograms that incorporate postnatal age and rate of rise can be helpful in determining the proper threshold at which to initiate phototherapy.

Fluid, Electrolyte, and Genitourinary Considerations

As mentioned previously, fetal fluid balance is influenced by placental factors and fetal factors. Fetal kidneys regulate amniotic fluid levels, but after birth, they assume control of the electrolyte and fluid maintenance. Renal blood flow starts around 5% of cardiac output and rises over the first few weeks to adult levels of 25% as systemic (and renal) vascular pressure decreases. Glomerular filtration rate (GFR) likewise increases over time from 40 mL/min/1.73 m^2 at birth to goal rate of 125 mL/min/1.73 m^2 by age 2 in term neonates and later in childhood for preterm infants. Delay in the first urine output up to 24 hours is not uncommon in neonates, though premature infants seem to be more likely to urinate earlier (within the first 8 hours) than term or postterm infants.[72] The urine that is passed is quite dilute because their concentrating ability is poor, though it doubles over the first 30 days of life and continues to increase over the first year.[73] Once urination begins, minimal adequate urine output is 1 mL/kg/hr, but should ideally be 2 to 3 mL/kg/hr. The use of creatinine to measure renal function in the early neonatal period must be interpreted with care, as neonatal levels mirror maternal creatinine and reflect maternal renal function. This false alteration in creatinine usually clears by 2 weeks of life in term infants (by 4 weeks in premature infants) when levels are more reflective of the child's own renal function.[73]

Neonatal body composition is 80% water compared to 55% to 60% for adults. The excess body water is primarily intracellular, and migrates into the extracellular space and is subsequently excreted—leading to the typical weight loss seen during the first few days of life. Typical fluid requirements for a term neonate start at 60 to 80 mL/kg/d and gradually increase to 150 to 160 mL/kg/d but may be higher for very low–birth-weight and premature

neonates or neonates with conditions that lead to excessive fluid losses (e.g., gastroschisis).[67] Neonates do not excrete sodium in their urine for the first few days due to low GFR, so supplemental sodium during this time frame is not required. Normal sodium requirements thereafter are 2 to 4 mEq/kg/d. Similarly, potassium is not initially added to fluids as levels are elevated at birth due to shifts into the extracellular space. After the first void and subsequent excretion of potassium, supplemental potassium may be added for goal of 1 to 3 mEq/kg/d. Transient hypercalcemia and hypermagnesia can occur in neonates immediately after birth due to passage from the mother via the placenta.[67,73] Otherwise, electrolyte abnormalities and management of them are similar to the adult population as has been discussed in the foundational chapters in this textbook.

Hematologic Considerations

Coagulation factor measurement studies of fetal and newborn coagulation reveal longer clotting times before 30 weeks' gestation, followed by an increase in the amount of clotting factors between 30 and 38 weeks.[74] There were significantly lower coagulation factor levels in late preterm fetuses than levels of full-term neonates, possibly indicating some trigger for further rapid maturation at the time of birth.[74] Lower coagulation levels in preterm infants may be related to hepatic synthetic immaturity.[75] In the absence of an underlying coagulation disorder, these levels will improve over time to adult levels. If the child does have a bleeding disorder, it may manifest in a number of ways. Bleeding following circumcision is the most common presentation of hemophilia overall, followed by spontaneous hemorrhage (subgaleal hematoma, cephalohematoma, and intracranial hemorrhage).[76]

Vitamin K levels in the fetus and neonate are low, and decrease further over the first 48 to 72 hours. A lack of bacterial production from the mostly sterile GI tract and low levels of dietary vitamin K consumed leads to deficiency until about 7 to 10 days after birth.[77] Vitamin K is a cofactor for coagulation factors II, VII, IX, and X and for proteins C and S; carboxylation of these factors by vitamin K activates them in the coagulation cascade. Because of this transient vitamin K deficiency, neonates are at increased risk of hemorrhage, which may manifest as intra- or extracranial hemorrhage, GI bleed, or, in males, bleeding at the time of circumcision. Diagnosis can be

made in patients with prolonged PT and PTT and elevated PIVKA (proteins induced by vitamin K absence) levels.[77] Complications can be prevented by administration of exogenous intramuscular vitamin K at birth.[78] Surgeons must be aware of this entity in perioperative planning of neonates, especially as there have been increasing reports of parental refusal of vitamin K treatment.[79,80] In these instances, operations should be delayed if possible.

Infectious Disease Considerations

Neonates can become quite ill without many of the typical signs seen in older children and adults. 7 They may not have any specific symptoms, but may present with unexplained respiratory distress, apnea, or bradycardic episodes, even with nonrespiratory causes of illness. Temperature instability usually manifests itself as hypothermia instead of febrile illness. Because of their poor physiologic reserve, clinical deterioration can occur quickly if signs are not recognized and appropriate treatment initiated. Within the first 3 days of life, illness is thought to be a result of maternal–fetal transmission as a result of early and/or prolonged rupture of membranes or maternal infection (chorioamnionitis, colonization with group B streptococcus). Conversely, late-onset sepsis usually occurs after 1 week of life and is more likely a result of some environmental insult or exposure (ventilator-associated pneumonia, catheter-related bloodstream infection). Premature infants are at risk for either type of sepsis due to their weaker immune systems.[81]

Positive cultures of body fluid (blood, urine, sputum, cerebrospinal fluid) are preferred for diagnosis of sepsis in the appropriate clinical context. Ancillary studies may be used in conjunction with cultures (or in instances of culture-negative illness) for the workup of sepsis. Though leukocytosis on a standard complete blood cell count (CBC) is concerning for infection in older children and adults, leukopenia is of greater concern in neonates. The ratio of immature neutrophils to total neutrophils (I/T ratio) is a more sensitive indicator of sepsis (ratio ≥ 0.2) and is commonly used in neonates to help identify those with infection. C-reactive protein (CRP) increases in response to an inflammatory process and is one of the most common trended laboratory values in neonates. It has a high specificity and positive predictive value (both >90%) for neonatal infection.[81] A benefit of the CRP, I/T ratio, and the absolute neutrophil count (another commonly used lab test)

is that normal results have a high negative predictive value (>95%).[82] Thrombocytopenia is also associated with neonatal sepsis, though the mechanism is not entirely clear. Neonates with gram-negative sepsis are more likely to consume platelets compared to those with gram-positive sepsis (42% vs. 17%) and experience a greater drop in platelet levels.[83] Additionally, severe thrombocytopenia ($\leq 50 \times 10^9$/L) is associated with higher rates of mortality.[83]

Temperature instability can be an early sign of neonatal sepsis, presenting as low temperatures. Neonates lose heat more easily than adults for a variety of reasons, including increased relative body surface area and thin skin, through which evaporative losses may occur. They lack the ability to generate heat through shivering, instead creating heat by the breakdown of stores of brown fat. Premature infants have more pronounced issues with heat loss because of their skin immaturity, and they also have less brown fat, making them even more prone to hypothermia. Environmental measures (blankets, increasing room temperature, and radiant warmers) are vital in temperature maintenance; these measures are key to perioperative temperature management. Surgeons should be mindful and try to limit the time a neonate is uncovered on the operating table; use forced-air heating units and maintain higher operating room temperatures to keep the child normothermic.[84]

Pediatric Physiology

Normal physiology of children continues to change as children grow and mature, and mimics that of adults as children enter into adolescence. A fundamental understanding of normal age-adjusted vital signs is imperative in caring for children (Table 97.1) in order to recognize impending shock states and respiratory failure. This section will highlight important aspects of pediatric physiology that differ from adults and that impact the care of a child.

Cardiovascular Considerations

As with neonates, an awareness of any pre-existing congenital cardiac lesion (repaired or unrepaired) is imperative in treating general surgical conditions.

Survival of children with congenital heart defects is increasing and encounters with patients with a history of congenital cardiac lesions are becoming more common—even into adulthood.[85] We refer the reader to the chapter on congenital heart disease for a detailed discussion, but will point out here the specific implication of single-ventricle physiology on laparoscopy. Children having undergone Fontan palliation of single-ventricle congenital heart disease have passive perfusion of the pulmonary vasculature and are therefore sensitive to changes in preload and may not tolerate standard pressure pneumoperitoneum for laparoscopy, which compresses the IVC and may lead to decreased venous return to the pulmonary vascular bed and consequently to the heart. Laparoscopy, carefully performed, has been shown to be safe in children with single-ventricle physiology in the context of an experience multidisciplinary team.[86] Close attention to volume status is essential in these children, as children with single-ventricle physiology are also sensitive to changes in vascular tone and can become unstable with the induction of general anesthesia if induced in a hypovolemic state, while children with unrepaired septal defects may be sensitive to volume resuscitation and are prone to pulmonary edema if aggressively resuscitated. Arrhythmias are uncommon in children overall, but have an increased incidence in children with congenital heart disease, or may be secondary to acid–base disturbances, medications, central venous catheters, or electrolyte imbalances.[87,88]

Shock states in children are generally classified as "warm" or "cold" shock. Septic shock in young children tends to mimic the physiology of neonates ("cold shock") with predominantly low cardiac output and high systemic vascular resistance. Septic shock in older children and adolescents more commonly mimics the physiology of adults ("warm shock") with peripheral vasodilation and a high cardiac output state. Resuscitation of children with septic shock begins with fluid resuscitation and should then follow the algorithm in Figure 97.4 to guide initiation of inotropic and vasoconstrictor support, with a key branch point in determining vasodilatory ("warm") shock or a low cardiac output ("cold") shock state based on physical examination findings.[89] Central venous pressure monitoring in children can be utilized, but physical examination of the abdomen to assess for hepatomegaly (congestive hepatopathy) is a useful adjunct in assessing volume status. Cardiogenic, neurogenic, obstructive, and hypovolemic shock

states in children mimic the physiology of adults and should be managed in a similar fashion with attention paid to weight-based dosing of fluids, blood products, and vasoactive agents.

Respiratory Considerations

Young children, like neonates, have a diminished respiratory reserve due to high metabolic rate and low FRC and can decompensate rapidly. It is important to recognize compensatory physical examination findings associated with respiratory distress such as tachypnea, nasal flaring, subcostal and supraclavicular retractions, expiratory grunting (to maintain recruitment and higher FRC), and head bobbing. Young children have large heads in relation to the torso, leading to flexion at the neck and relative airway obstruction when lying supine. A blanket or roll can be placed behind the shoulders to extend the neck to neutral and improve airway positioning.

An important consideration when caring for a pediatric patient in respiratory distress is the contribution of small airway size to limitation in laminar airflow. As detailed in the respiratory physiology chapter, airway flow is primarily limited by airway resistance, which in turn is proportional to the radius of the airway to the fourth power. Therefore, very small changes in airway diameter can lead to substantial increases in airway resistance in young children. Airway mucosal edema, mucus plugging, and foreign bodies can all lead to significant respiratory compromise.

Respiratory failure in children can be managed with noninvasive ventilation or may be escalated to endotracheal intubation and mechanical ventilation. Pediatric airway sizes are age dependent; therefore, a working knowledge of tube sizes or an easily available resource such as a length-based color-coded tape is needed. Appropriate endotracheal tube size can be estimated using the formula (age in years + 4)/4 (for an uncuffed tube) or by referring to a length-based color-coded tape. Mechanical ventilation is generally initiated targeting tidal volumes of 6 to 8 mL/kg of predicted body weight (based on length, age, and sex).[90] Tidal volumes in mechanically ventilated young children can be challenging to measure at the level of the ventilator as the dead-space volume of the ventilator tubing far exceeds the tidal volume of the patient. For this reason, inline flow sensors at the level of the endotracheal tube are used to more precisely measure actual tidal

volumes.[91] Compliance is highly variable across ages and disease processes; therefore, initial ventilator pressures are generally estimated using bag ventilation with a handheld manometer and visual inspection of chest rise to determine the pressure needed to deliver adequate volume. Pediatric minute ventilation is higher than in adults, and younger children generally require higher respiratory rates (15 to 30 breaths/min) that need to be titrated to maintain adequate CO_2 clearance. Tracheostomy timing in children remains a controversial issue. The incidence of subglottic stenosis with prolonged intubation in children is much higher (11%, mean length of mechanical ventilation 9 days, range 3 to 33 days) than previously thought, and increases with duration of intubation (50% increased risk for every 5 days of endotracheal intubation).[92] The incidence of tracheostomy-related complications, however, is much higher than in adults with a 2-year tracheostomy-related complication rate of 39% and in-hospital mortality rate of 9%, which decreases the enthusiasm for tracheostomy in young children unless deemed absolutely necessary.[93] Within the specific population of pediatric traumatic brain injury, tracheostomy at 14 days is associated with faster time to discharge and lower complication rates without significantly increasing the number of unnecessary tracheostomies performed.[94]

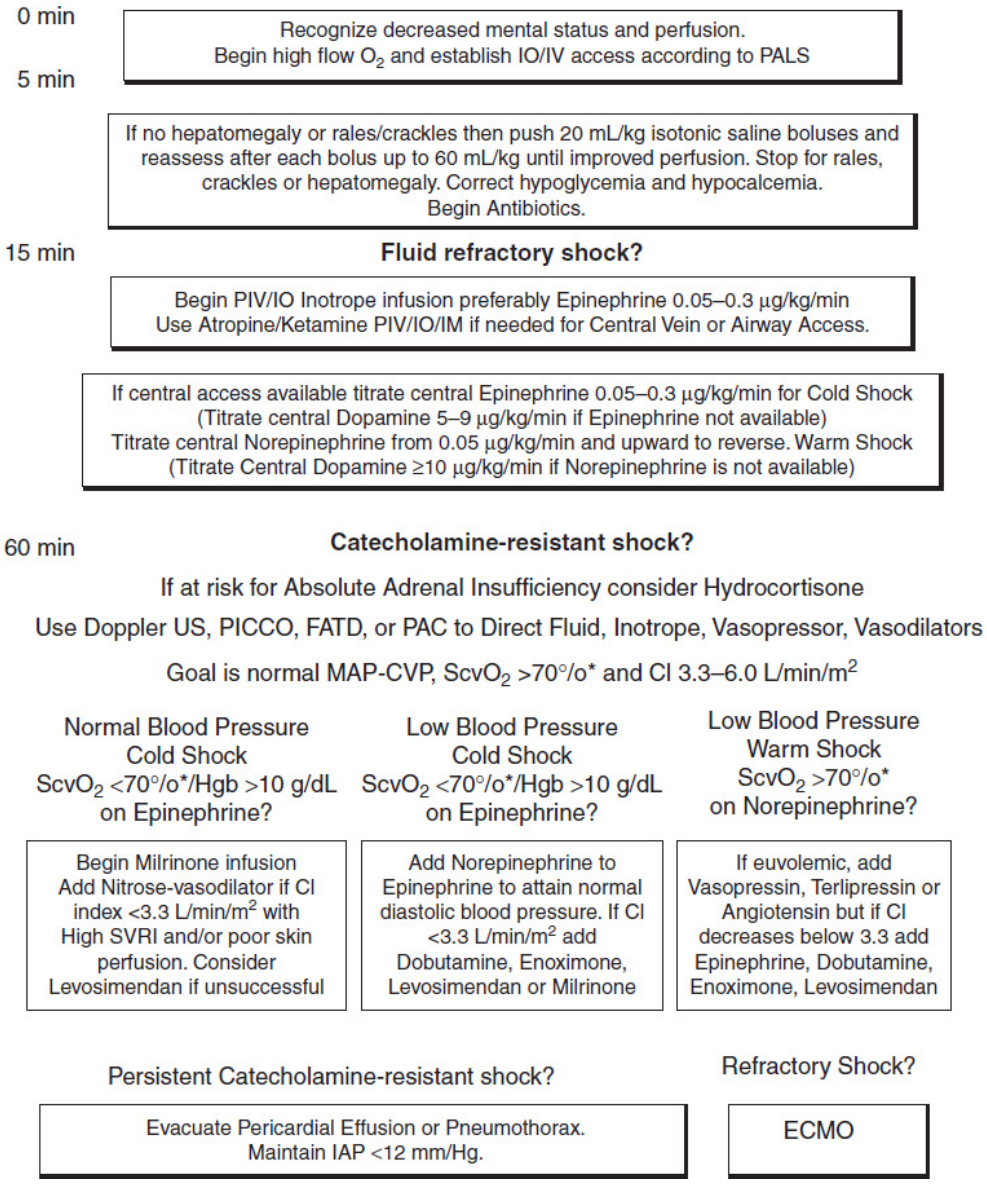

Figure 97.4 Pediatric algorithm—goal-directed therapy for sepsis. (From Davis AL, Carcillo JA, Aneja RK, et al. American College of Critical Care Medicine clinical practice parameters for hemodynamic support of pediatric and neonatal septic shock. *Crit Care Med* 2017;45[6]:1061–1093. Wolters Kluwer Health, Inc.)

Gastrointestinal and Nutritional Considerations

Outside of the neonatal period, GI physiology mimics that of adults. Growing children do have higher metabolic needs, and daily baseline caloric requirements are higher in younger children (Table 97.2).[64] PN is commonly used in pediatric patients with prolonged inability to tolerate adequate

enteral nutrition, with the recommended timing of initiation generally similar to adult patients at 7 days in the absence of pre-existing malnutrition.[95]

Genitourinary, Fluid, and Electrolyte Considerations

Renal function is not mature at birth and does not mature until 2 years of age. Normal urine output is higher in infants and younger children (1 to 2 mL/kg/hr) and approaches adult levels (0.5 to 1 mL/kg/hr) by adolescence. Children have a higher body surface-to-mass ratio and higher minute ventilation, leading to greater insensible losses. Daily maintenance fluid requirements in children per unit body weight are higher than in adults and the hourly fluid requirements can be calculated using the 4-2-1 rule initially described by Holiday and Seger in 1957 or daily fluid requirements similarly referenced in Table 97.3.[64,96] Outside of infancy, daily electrolyte requirements mimic those of adults.

Table 97.2 Parenteral Nutrition Baseline Caloric and Protein Needs by Age

Age Group	Daily Caloric Needs (kcal/kg/d)	Daily Protein Needs (g/kg/d)
Premature Neonate	90–120	3–4
<6 mo	85–105	2–3
6–12 mo	80–100	2–3
1–7 yrs	75–90	1–2
7–12 yrs	50–75	1–2
>12 yrs	30–50	0.8–1.5

Adapted from Mirtallo J, Canada T, Johnson D, et al; Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2004;28(6):S39–S70.

Hematologic Considerations

Pediatric blood volumes are relatively higher in infants (90 mL/kg) and young children (80 mL/kg) and approach adult levels (65 to 70 mL/kg) by adolescence.[97,98] In general, transfusion of 5 mL/kg of red blood cells should result in an expected 1 g/dL increase in hemoglobin.[99] Massive transfusion in children is generally defined as more than 40 mL/kg/24 hrs of combined blood product (red blood cells, plasma, platelets, and cryoprecipitate), with improved outcomes demonstrated with high ratio RBC:plasma transfusion—similar to adults.[100,101] Venous thromboembolic disease (VTE) is less common in children, but does occur—often in critically ill or injured patients and in association with indwelling central venous catheters, oncology diagnoses, oral contraceptive use, postpubescence, and obesity.[102] While the efficacy of pharmacologic VTE prophylaxis likely mimics that of adults in adolescents, it is unclear if pharmacologic chemoprophylaxis is effective in decreasing VTE rates in younger children.[103]

Infectious Disease Considerations

Evaluation of febrile infants—particularly under 3 months of age—involves complex algorithmic decision making and is beyond the scope of this chapter. It is important to understand that young infants are susceptible to central nervous system seeding from bacterial bloodstream infections due to the immature meninges. Risk factors such as young age (<60 days), appearance on physical examination, presence of alternative etiology of fever (otitis media or positive urinalysis), hematologic abnormalities (sickle cell or asplenia), and degree of laboratory abnormality (white blood cell count and CRP) have all been used to risk stratify patients and guide decision making around the necessity for lumbar puncture and admission for empiric intravenous antibiotics.[104]

Table 97.3 Pediatric Fluid Requirements by Weight

Body Weight (kg)	Daily Fluid Requirement
<1.5	130–150 cc/kg/d
1.5–2	110–130 cc/kg/d
2–10	100 cc/kg/d
11–20	1,000 cc/d (for first 10 kg) + 50 cc/kg/d for every kg over 10 kg
>20	1,500 cc/d (for first 20 kg) + 20 cc/kg/d for every kg over 20 kg

Adapted from Mirtallo J, Canada T, Johnson D, et al; Task Force for the Revision of Safe Practices for Parenteral Nutrition. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr* 2004;28(6):S39–S70.

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Fetal Intervention

Diana L. Farmer and Tippi MacKenzie

Key Points

1. There are seven fetal conditions currently treated with fetal intervention: twin-to-twin syndrome (TTTS), myelomeningocele (MMC)/spina bifida, congenital diaphragmatic hernia (CDH), congenital heart defects (CHDs), congenital lung lesions (CLLs), lower urinary tract obstructions (LUTO), and sacrococcygeal teratomas (SCTs), all of which are dependent on the severity in utero.
2. Fetal surgery will only occur if (a) there is significant chance of the procedure being lifesaving or preventing serious or irreversible disability in the fetus, (b) the procedure involved low mortality and morbidity risk to the fetus, and (c) the operation has low mortality and morbidity risk to the pregnant woman, including impact on future pregnancies.
3. Fetal surgery originally was only recommended when the fetus would not survive without it, and thus the risk–benefit ratio was favorable.
4. The first fetal surgery for a nonlethal defect was for MMC.
5. *Ex utero*intrapartum treatment (EXIT) procedure is most often used for fetuses with predicted compromised airway access at birth.
6. Fetal molecular therapies allow potential treatment of fetuses with numerous stem cells, proteins, or viral vectors.
7. In utero gene therapies show promise in treating genetic abnormalities.

INTRODUCTION

The Development of a New Surgical Subspecialty

Fetal surgery is a multidisciplinary subspecialty that emerged at the crossroads of pediatric surgery and maternal–fetal medicine.[1] During initial stages of development, the idea of surgically operating on a human fetus within the womb was considered impossible, radical and questionably unethical. Nevertheless, pioneers took on the task of confronting and overcoming numerous obstacles in pursuit of an innovative concept that would eventually become the accepted standard of care for many congenital conditions.

Modern fetal surgery was envisioned and established in the late 1970s as a multidisciplinary translational program by Doctors Alfred de Lorimier and Michael Harrison at the University of California, San Francisco.[1] In 1981, Dr. Harrison performed the first open surgical intervention on a fetus with obstructive uropathy.[1] Prior to this landmark case, intrauterine interventions were limited to diagnostic procedures such as amniocentesis and chorionic villus sampling, or limited procedures such as intrauterine transfusion for Rh incompatibility. Harrison's success proved that surgeons could accomplish an operation on a pregnant uterus, return the fetus to the womb, and maintain the pregnancy.

CORE PRINCIPLES

In 1982, pediatric surgeons, neonatologists, perinatologists, radiologists, and anesthesiologists from 13 centers and five different countries attended a collaborative conference in Santa Ynez, CA, to review and discuss the potential benefits and liabilities of various interventions in fetal treatment.[2] The group, now recognized as the International Fetal Medicine and Surgical Society (IFMSS), reached a medical consensus by the end of the conference and established the following principles which have been updated and remain in place today (Table 98.1).

In the last 40 years, the field of fetal surgical intervention has advanced tremendously and will continue to do so with evolving techniques and clinical improvements in safety for both women and the unborn patient.

FETAL SURGERY—KEY ELEMENTS LEADING TO SUCCESS OF FETAL SURGERY

Fetal Imaging

Technologic advancement in fetal imaging not only furthered medical insight but also led to the evolution of surgical techniques and conceptual innovation. With the development of 3D and 4D ultrasound, diagnoses of facial, neural tube, and skeletal abnormalities can be made with increasing accuracy. Real-time spatiotemporal resolution is used in surgical intervention to guide instrument placement.[3] Moreover, magnetic resonance imaging (MRI) provides improved soft tissue contrast for imaging of central nervous system, lungs, kidneys, and placenta to overcome some limitations of ultrasound.[3] Fetal MRI provides significant benefits of gaining additional anatomical information, demonstrating complex structural relationships and studying these relationships from alternative angles, and allowing preparation of a more detailed surgical plan.[3]

Prenatal Genetic Diagnosis

The advances made in prenatal diagnosis with analysis of fetal DNA circulating in maternal blood has improved and eased the ability to diagnose genetic abnormalities in the fetus.

Table 98.1 Criteria for the Advancement of Fetal Therapy

Topic	Principles
Most fetal abnormalities are now detectable	
Best treatment for most abnormalities	Remains after birth. Prenatal diagnosis allows patient, family, and physician to discuss and develop a delivery and treatment plan for optimal outcome.
Nature of the disorder in the fetus (i.e., fatal or disabling); fetal natural history	The natural history of the fetal condition must be understood; appropriate animal models should be employed to test potential efficacy of intended therapies.
Reporting requirements	Voluntary reporting is a moral obligation in the field. Self-imposed registry efforts are in progress, mandatory reporting is not established as reporting largely lacks funding and resources.
Appropriate use of therapies' criteria	Effective therapies for multiple pregnancies with or without an "innocent bystander" (e.g., TTTS, selective reduction of an anomalous twin) may be considered if therapy will prolong and/or improve outcome of that pregnancy
Candidate diseases	Improvements in prenatal diagnosis have enhanced diagnosis of fetal conditions and understanding of fetal physiology and pathophysiology. Predictive measures of morbidity and mortality help providers weigh risks and benefits for mother and fetus. Candidate diseases will continue to change and evolve.
Center infrastructure	Levels of care for newborn and for pregnant woman have been refined and

	redefined.
Checks and balances	Multidisciplinary teams should be tailored to the defect(s) being treated and include a variety of disciplines. Procedures for informed consent and formal reporting must be in place. Any experimental or innovative procedure must have ethical oversight, participation in registries, and transparent counseling and reporting. Parents must be counseled regarding any alternative therapies, and the options of pregnancy termination and neonatal palliative care where appropriate.
Goals of treatment	There is increasing focus on short- and long-term effects of fetal therapy on maternal reproductive health. Issues are becoming increasingly complex as the goals of fetal treatment move from primarily achieving survival, to decreasing morbidity and improving the functional and neurodevelopmental outcome of the child.
Maternal safety and autonomy	Maternal expectations have evolved. Fetal abnormalities are expected to be prenatally diagnosed, and for some abnormalities the option for fetal treatment (where available and evidence based) will be available. As fetal therapy becomes more available, uptake has become greater. In addition, some are willing to incur greater personal risk to improve the prognosis for their fetus. Care must be taken to avoid the pitfalls in perception—just because a procedure

is offered within or outside a research protocol does not imply proven efficacy.

MATERNAL–FETAL RISKS

Unlike standard operations, fetal surgery involves two patients simultaneously. This reality presents challenging moral and ethical conflicts that must be considered and balanced in each circumstance. Chervenak and McCullough[4] and others have helped to provide an ethical framework within which fetal surgery should exist. The keys to this framework are that (a) the fetal operation has significant chance of being lifesaving or of preventing serious or irreversible disease in the fetus; (b) the procedure involves low mortality and morbidity risk to the fetus; and (c) the operation has very low mortality and morbidity risk to the pregnant woman, including risks to future pregnancies. In light of these considerations, several contraindications to fetal intervention exist, including chromosomal abnormalities, the presence of other major anomalies, and significant maternal comorbidities.

The significant maternal and fetal risks associated with fetal surgery must be weighed for each patient. For the fetus, there is risk of preterm delivery, fetal death, or survival with poor outcome. Most indications for fetal surgery, however, are ones in which the fetus would not survive without it, and therefore the risk-benefit ratio is very favorable. For interventions aimed at improving the outcome of fetuses with nonlethal conditions, the risk–benefit ratio is more difficult to assess.

The risks and benefits to the mother depend on the invasiveness of the fetal surgical operation. In any intervention, benefits to the mother include the psychological reward from doing everything possible to improve the condition of the unborn baby. In selected cases, there is physiologic benefit in preventing the possibility of "mirror syndrome," a preeclampsia like condition in which the mother's condition "mirrors" that of a sick or dying fetus.[5] In the presence of this syndrome, fetal surgery is contraindicated and urgent fetal delivery is important to ensure maternal health. For all women having open fetal surgery, there are theoretical risks to subsequent pregnancies and future fertility. When maternal fertility following fetal surgery was studied, it was found that 32 of 35 mothers were able to achieve

successful subsequent pregnancies and 31 live births resulted.[6] However, after open fetal surgery, all subsequent deliveries must be performed by cesarean section, and labor in the index pregnancy and ALL future pregnancies must be avoided to prevent uterine rupture.[7] As with all obstetric surgery, blood loss may be significant and mothers undergoing fetal surgery occasionally require blood transfusion.[8] Chorioamniotic membrane separation and preterm labor remain the Achilles heel of fetal interventions.[9,10] Surgical approaches that involve a smaller hysterotomy and more minimally invasive techniques appear to lower these risks.[10] Specifically, fetoscopic and percutaneous approaches appear to lessen the maternal and fetal risks.[11] These techniques allow vaginal delivery after fetal surgery and appear to decrease the incidence of preterm delivery.[12] Overall the maternal risk profile has been quite favorable with NO maternal deaths from open fetal surgery occurring at major fetal surgery centers in the United States or Europe in the past 30 years.

CURRENT FETAL CONDITIONS AMENABLE TO FETAL INTERVENTION

Originally, fetal interventions were carried out only for conditions that were deemed lethal, as only saving the life of the fetus was thought to be of enough benefit to warrant the surgical risks to the mother. Once techniques of fetal access were standardized, open, fetoscopic, or needle-based procedures were developed based on the anatomy and subsequent physiology of each anomaly.

Twin-to-Twin Transfusion Syndrome

Twin-to-twin transfusion syndrome (TTTS) is a complication occurring in twin pregnancies as a result of aberrant vascular connections formed between twins sharing one placenta. Although all monochorionic (one placenta) pregnancies are considered high risk, TTTS is only present in 9% to 15% of pregnancies.[13] Diagnosis occurs during early-to-mid second trimester when unequal vascular utilization results in a “donor” twin

providing vascular flow to a “recipient” twin. This causes oligohydramnios in the donor twin and polyhydramnios in the recipient twin. The risk of discordant growth, cardiac failure, and hydrops often leads to fetal demise in both twins.

Rationale for Prenatal Treatment

Fetal intervention for TTTS is a minimally invasive procedure in which a fetoscope is introduced through the mother’s uterus (Fig. 98.1). A laser is used to ablate the offending communicating vessel across the shared placenta. Fetal laser ablation can be performed from 16 to 26 weeks of gestation. Randomized controlled trials of laser ablation in advanced TTTS have demonstrated a significantly higher likelihood of survival of at least one twin and decreased neurologic complications, although the risk of premature rupture of membranes and preterm delivery has increased.[14] This treatment converted a disease that previously had a near 80% mortality into one that has a greater than 80% survival and is now the standard of care for this condition today.

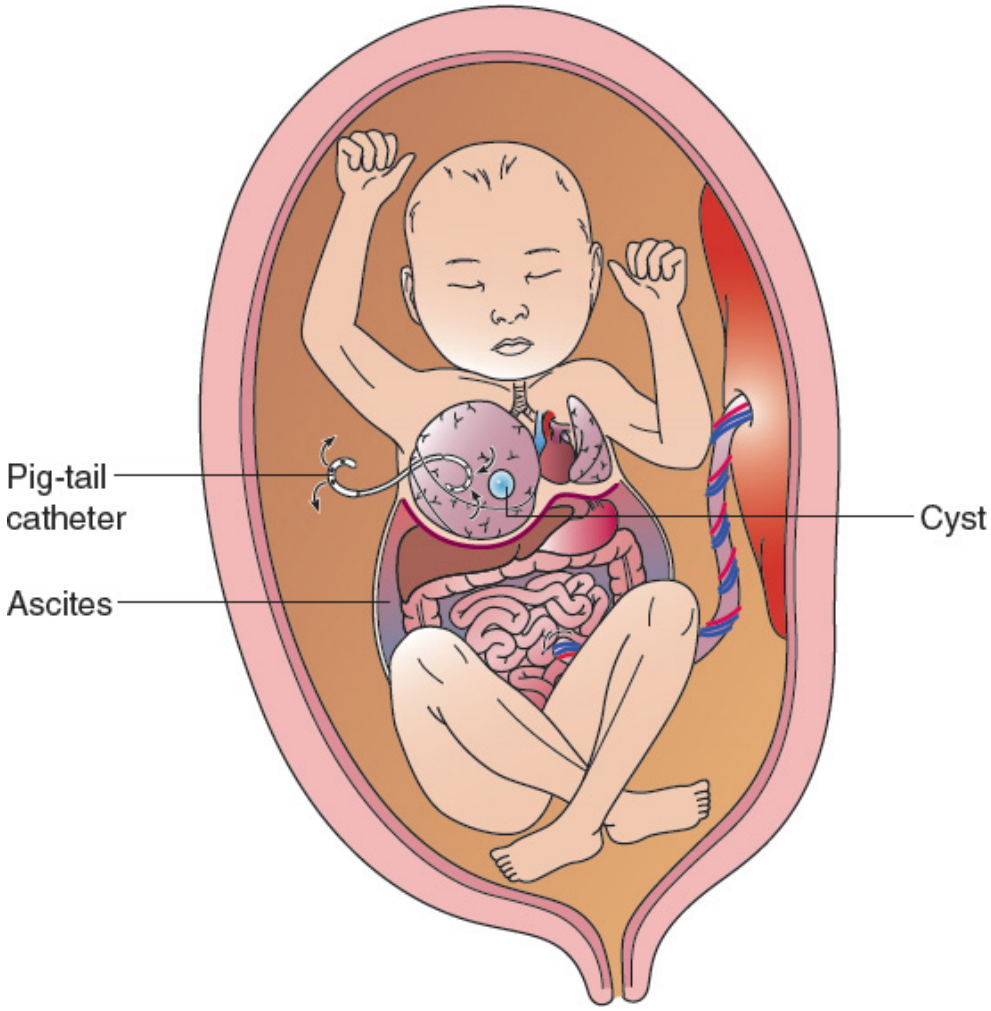

Figure 98.1 Treatment of twin-to-twin transfusion syndrome using fetoscopic laser ablation.

Myelomeningocele aka Spina Bifida

In the United States, roughly four children are born daily with MMC, making it one of the most common congenital defects resulting in paralysis.[6] Myelomeningocele (MMC) or spina bifida is a neurologic defect characterized by incomplete closure of the neural tube during early embryonic development, resulting in exposed neural tissue and leakage of cerebrospinal fluid (CSF). Depending on the vertebral level of the spinal defect, patients with MMC display a wide range of lifelong clinical consequences, which include paralysis, bowel and bladder incontinence, musculoskeletal deformities, hindbrain herniation, hydrocephalus, and cognitive disabilities.[15]

Until the late 1950s, surgical treatment was only offered to MMC patients who survived at least 2 years after birth. Survival rates were 10% to 12% until the groundbreaking development of ventriculoperitoneal shunts.[6] Shunt procedures managed CSF build-up and associated hydrocephalus.[5,6] Survival rates in the mid-1960s improved as treatment provided within 12 to 48 hours post delivery became standardized.[15] Still, shunts required constant revision; urinary tract infections and subsequent renal failure were still unresolved; and paralysis was not improved.[16]

Rationale for Prenatal Surgery

Neurologic deficits of MMC are explained by the "two-hit hypothesis," in which the neural tube fails to close, enabling CSF leakage and neural placode exposure (first hit), thereby allowing direct trauma by uterine wall contact and chemical trauma from amniotic fluid toxicity (second hit).[4,5] Fetal MMC intervention was hypothesized to potentially avert acquired injury of the second hit.

The hypothesis was tested in fetal lamb models with study results showing (1) reversal of hindbrain herniation in fetal lambs that received MMC surgical repair,[7] and (2) that distal neurologic function could be improved by prenatal coverage of the exposed placode.[17]

These promising animal studies led surgeons to begin fetal surgery for the first nonlethal fetal defect, MMC. Eventually a three-center, randomized controlled clinical trial that examined the efficacy of surgical repair in fetal patients with MMC compared to standard postnatal repair, known as the Management of Myelomeningocele (MOMS) trial, was performed. Study outcomes showed a 50% decrease in need for ventriculoperitoneal shunting and decreased occurrence of Chiari neurologic malformations.[8] Moreover, follow-up observed 42% of infants walking at 30 months as compared to 21% of infants in the control group, with complications primarily related to maternal outcomes.[8,9] For the first time, a fetal intervention definitively provided superior outcomes to postnatal repair. The MOMS trial results are one of the most important milestones in the clinical success of fetal surgery. Current work in the fetal treatment of MMC includes expansion of the inclusion criteria, modifications of surgical technology including fetoscopic approaches to hopefully lessen maternal morbidity, and scientific

investigation into further ways to improve the distal neurologic functioning for patients.

In 2020, the first in-human clinical trial for fetal intervention of MMC with placental derived stem cells was FDA approved. The cellular therapy for in utero repair of myelomeningocele (CuRE) study will examine the safety and preliminary efficacy of placental mesenchymal stem cells (PMSCs) seeded on a commercially available dural graft extracellular matrix (ECM) used for dural closure during standard fetal MMC repair. Other technologies are under preclinical investigation to help ameliorate the consequences of this devastating disease (Fig. 98.2).

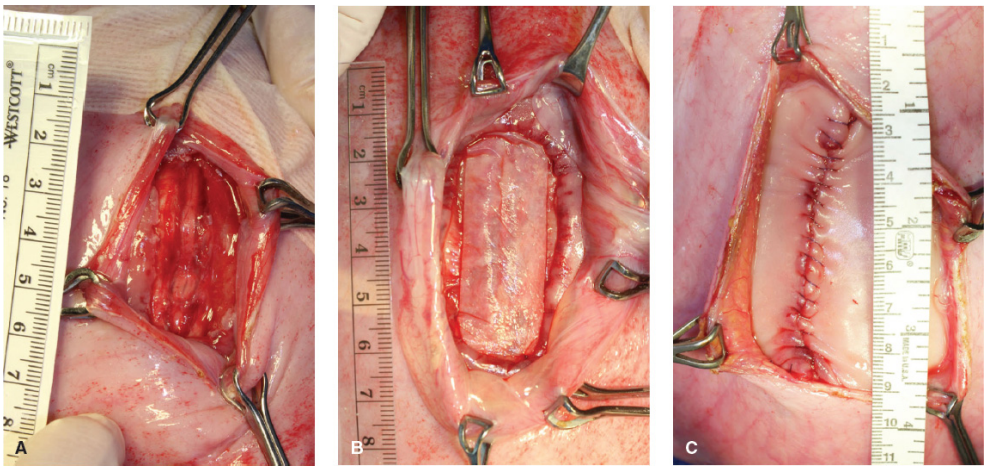

Figure 98.2 PMSC-ECM application for MMC in utero—representative images. **A**: The MMC defect in the fetal sheep model. **B**: The PMSC-ECM patch applied during repair surgery. **C:** The closure of the overall repair. *MMC*, myelomeningocele; *PMSC*-ECM, placenta mesenchymal stem cell–extracellular matrix.

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernias (CDHs) are congenital defects in the diaphragm that allow abdominal contents to herniate into the fetal chest and may cause fetal or neonatal death due to pulmonary hypoplasia and pulmonary hypertension.[10] CDH is observed in one to four cases for every 10,000 births and survival rates in this country range from 69% to 93%. Unlike conditions of MMC and sacrococcygeal teratomas (SCTs) where defects are typically isolated, high CDH mortality rates may be attributed to

a wide variety of associated anomalies such as congenital heart disease or chromosomal abnormalities.[10]

Treatment Methods

Establishing fundamental criteria for CDH fetal intervention remains controversial in the absence of confidence in the condition's natural history. Poor outcomes in initial attempts to treat CDH with open fetal surgery led to an increased use of tracheal occlusion as primary treatment to address the underlying lung growth failure. Tracheal occlusion reversibly blocks the trachea of the fetus, causing fluid build-up that stretches fetal lung and enables a pathway for airway and pulmonary vessel growth.[11] Tracheal occlusion studies of pulmonary hyperplasia in fetal lamb models with CDH showed accelerated lung growth and improvement in pulmonary function. Persistent efforts in Europe to develop fetoscopic tracheal occlusion (FETO), and the results of a randomized control trial, have revived investigative research in the United States (Fig. 98.3).[12]

Congenital Cardiac Lesions/Congenital Heart Defects

Congenital heart defects (CHDs) are structural abnormalities of the heart or intrathoracic vessels with functional significance. Occurring in approximately 5 to 10 cases for every 1,000 live births, an estimated 25% of infants with CHDs will require surgery within 1 year after birth.[18] CHD malformations are detected using fetal echocardiography and remain relatively unvaried throughout gestation except for the following three lesions:

1. Severe aortic stenosis with evolving hypoplastic left heart syndrome (AS/eHLS)
2. Pulmonary atresia with intact ventricular septum with evolving hypoplastic right heart syndrome (PA/IVS)
3. Hypoplastic left heart syndrome with intact or severely restrictive atrial septum (HLS/IAS)

Rationale for Prenatal Intervention—Treatment Methods

Fetal cardiac intervention (FCI) intends to alter in utero anatomy and physiology for the three lesions listed above. AS/eHLS and PA/IVS FCI can result in biventricular circulation which avoids single-ventricular palliation and associated complications.[19] HLHS/IAS FCI can improve in utero left atrial hypertension and decrease the need for emergent postnatal intervention; although overall survival benefit is less apparent. FCI limitations that lead to the inability to demonstrate long-term survival benefit include restricted patient eligibility, late patient referrals for specialized fetal cardiac centers, and lack of providers with technical expertise.[19] The lack of good animal models for robust preclinical investigations also limits progress with fetal cardiac diseases. Open fetal interventions for cardiac lesions have been limited to fetal cardiac tumors (teratomas) resulting in fetal hydrops.

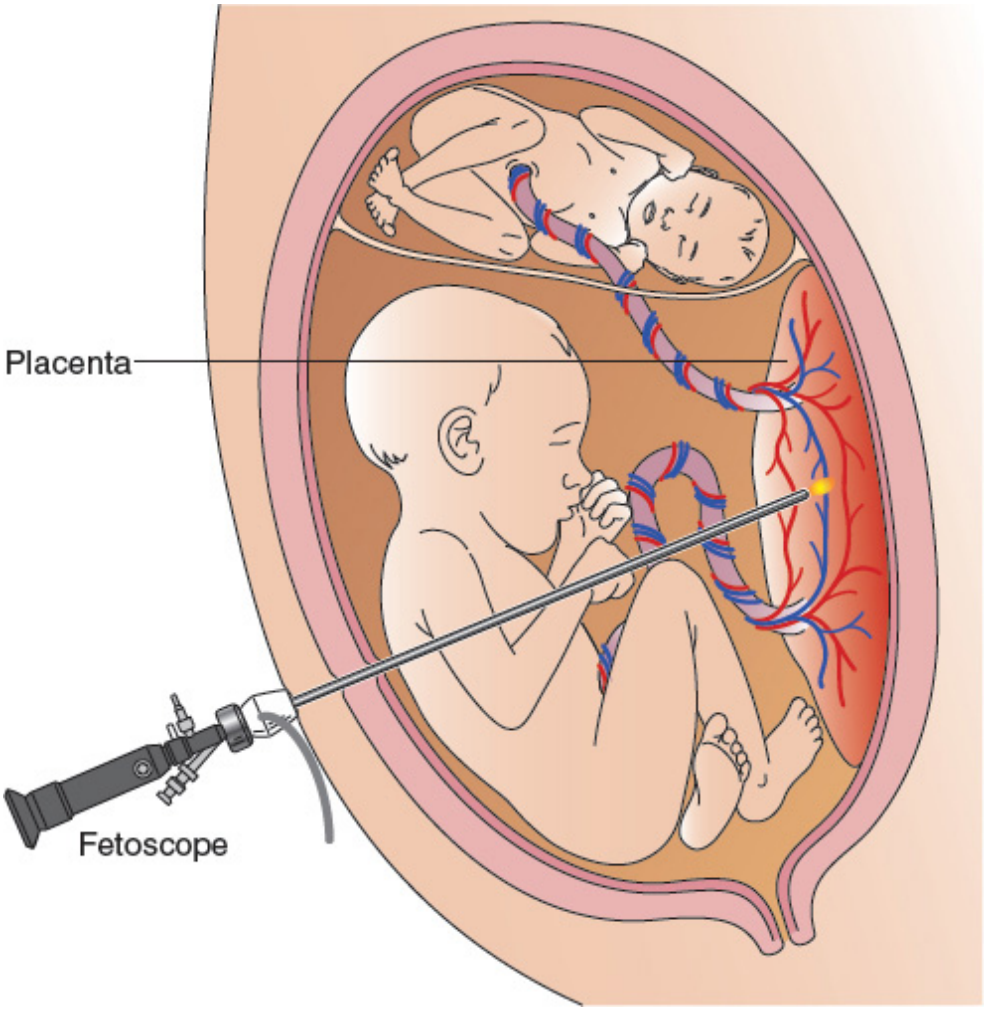

Figure 98.3 Fetal endoscopic tracheal occlusion.

Congenital Lung Lesions

Congenital lung lesions (CLLs) comprise a group of prenatal pathologies occurring at a rare incidence of 1 in 10,000 to 35,000 pregnancies.[20] Ultrasound imaging between 18 and 20 weeks of gestation is used to detect and diagnose CLLs ranging from relatively small asymptomatic lung cysts to large congenital pulmonary airway malformations (CPAMs) that can lead to fetal demise.[21] Early diagnosis is critical in CLLs because lesions exhibit fetal growth variability ranging from third trimester regression to rapid expansion with hydrops development and fetal demise.

Serial ultrasonography is a useful tool in defining the natural history of CLLs, identifying pathophysiologic features, and formulating course of

treatment based on prognostic information. A fetal echocardiogram detects abnormalities of increased/decreased cardiac output, ventricular hypertrophy, atrial or ventricular chamber dictation, cardiomegaly, significant valvular regurgitation, and diastolic dysfunction.[22,23] Through fetal imaging, including fetal MRI, prognoses are predicted based on the size of the lung mass and associated pathophysiologic effects.

Treatment Methods

Various options for fetal management are available for CLLs. Administration of maternal steroids can reverse early hydrops and is primarily used in cases of microcystic CPAM.[14] Cyst aspiration is an option allowing decompression in large macrocystic lesions.[14] Thoracoamniotic shunting is a method used to reverse hydrops when a CLL is composed of a dominant cyst and no large solid components.[24] Complications associated with this approach include shunt dislodgement, fetal distress, and consequential repeat procedure to correct shunt maladjustment (Fig. 98.4).[18]

Finally, open fetal surgery with surgical fetal lobectomy is required only rarely for select CPAMs with impending fetal demise. Alternative methods, such as laser ablation in solid CPAMs, have been limited by high mortality. A third procedure reserved for fetal patients of at least 30 weeks in gestational age is an EXIT-resection surgery. This procedure attempts to provide a more stable transition for fetuses when CLLs associated with hydrops are diagnoses late in gestation.

Sacrococcygeal Teratoma

Fetal SCTs, although rare, is the most common prenatally diagnosed congenital tumor occurring at approximately 1:35,000 to 1:40,000 births.[25] Most SCTs are diagnosed before birth through routine fetal screening and do not typically require treatment until after birth.[26] Conversely, diagnosis of large fetal SCTs requires active clinical attention due to associated obstetric complications and high rates of fetal mortality.[27] Detrimental effects of large SCTs can include rapid growth rate, hydrops development caused by high-output fetal heart failure, preterm delivery, erratic hemorrhaging and tumor rupture, and maternal mirror syndrome.[26]

The causes of death in fetal SCT are multifactorial, but primarily involve tumor rupture and bleeding at the time of delivery, or high-output cardiac failure and hydrops from high blood flow within the mass.[28] The development of high-output cardiac failure and hydrops in a fetus with SCT is the sole indication for fetal surgical intervention.

Rationale for Prenatal Surgery—Treatment Methods

Fetal surgical intervention for SCT treatment is only considered when a fetus shows rapid decline in cardiovascular function prior to 26 weeks of gestation, when the alternative outcome is prenatal fatality.[29] Fetal echocardiographic markers include increased aortic velocity, cardiac output, a dilated inferior vena cava, or reversed end-diastolic umbilical blood flow. These markers appear to be sensitive early predictors of impending hydrops and fetal demise.[13] For fetuses greater than 27 weeks of gestation, these findings are an indication for emergency cesarean delivery and postnatal resection. For fetuses less than 27 weeks, open fetal surgery and resection is the treatment of choice. Minimally invasive approaches to interrupt the tumor's blood supply with radiofrequency ablation have had limited success, but may warrant further investigation as an alternative for a fetus that is a poor candidate for open fetal resection.

Gastroschisis

Gastroschisis is a congenital defect of abdominal wall that involves herniation of the intestine and other intra-abdominal organs. Despite decreasing mortality in recent decades, gastroschisis occurs worldwide in 1 of 4,000 live births and the considerable impact of morbidity remains at the forefront of clinical concern.[18] Following gastroschisis repair, poor intestinal peristalsis and absorption impairs the speed of recovery in gut function leading to prolonged requirement of total parenteral nutrition (TPN). Early detection and diagnosis during the first trimester are key factors for indicating risk and predicting prognostic severity.[30] Unfortunately,

inconsistencies in current predictors of prognosis impose clinical limitations for counseling patients on outcome severity.

At present, because survival outcomes of gastroschisis with postnatal treatment is quite good in developed countries, fetal surgical considerations remain in the preclinical/experimental domain. Investigational studies of fetal lamb models are still in early stages.[31] High mortality in low- and middle-income countries has driven renewed interest in potential fetal interventions.

Lower Urinary Tract Obstruction

Lower urinary tract obstruction (LUTO) is a congenital defect obstructing fetal bladder outflow resulting in upstream urinary congestion. This often results in renal failure and pulmonary hypoplasia since amniotic fluid is formed by fetal urine and is necessary for normal lung development. LUTO occurs in approximately 2.2 to 3.3 cases per 10,000 with devastating impacts of fetal morbidity and mortality.[32] LUTO is caused by a variety of pathophysiologic processes resulting in distal urinary tract obstruction, decreased urinary flow, and regionalized urinary congestion.

Fetal ultrasound remains the primary tool for diagnosing LUTO by detecting megacystis or bladder enlargement with bilateral hydronephrosis. Although the use of ultrasound imaging is problematic when differentiating underlying etiology, it remains important in determining treatment options because it can detect renal parenchymal abnormalities.[32] Recent studies also indicate fetal MRI may provide additional diagnostic information.

Rationale for Fetal Treatment

While it seems logical that relieving the blockage of fetal urine would be ideal, not all fetuses with LUTO have favorable urinary biochemistry to benefit from fetal intervention. Different treatments are determined by severity of the disease in addition to diagnostic criteria. When indicated, fetal intervention is recommended as treatment in order to restore amniotic fluid (fetal urine) and enable normal lung development and preserve renal functioning. This can be accomplished by several means, but placement of a fetal vesicle (bladder) amniotic shunt is currently most common.

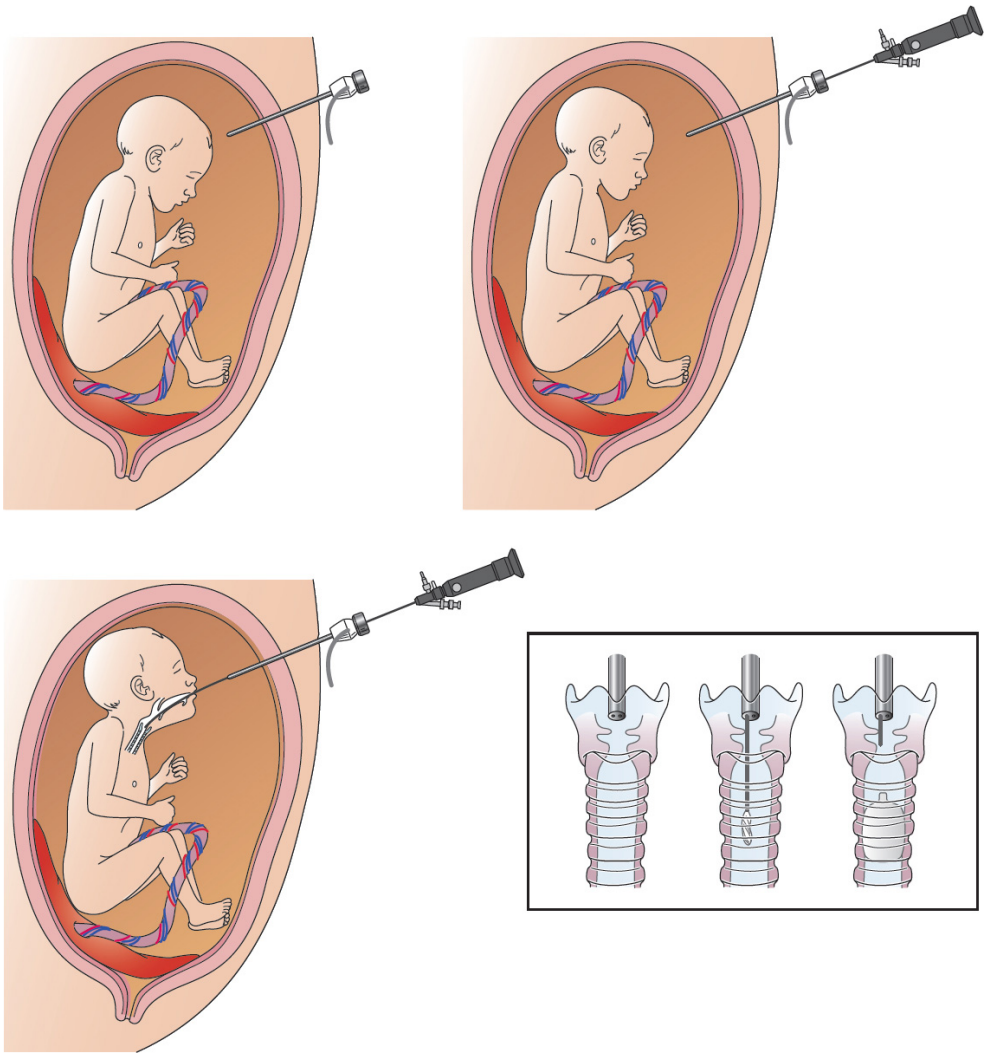

Figure 98.4 Thoracoamniotic shunting for a congenital lung lesion.

Cervical Teratoma, Airways Masses, and EXIT Procedures

Ex-utero intrapartum treatment (EXIT) is a surgical procedure similar to fetal surgery that allows time to stabilize the obstructed airway in a fetus, prior to delivery. EXIT-to-airway operations partially deliver the head and neck of a fetus to attempt direct endotracheal intubation through laryngoscopy, bronchoscopy, or tracheostomy.[33] Complete resection may be necessary in large teratomas, placing the mother under deep anesthesia to maintain maternal–fetal uteroplacental circulation as is required in open fetal surgery

to maintain the pregnancy. Following resection, the umbilical cord is cut, and the baby can be completely delivered.[34]

FUTURE DIRECTIONS

Although the past for fetal surgery has been marked by extraordinary progress for an entirely new field of medicine, it is the future that shines most brightly. From discoveries on the fetal origins of adult diseases, to ever increasing applications for fetal gene and stem cell therapies, or the induction of tolerance for future transplants, the promise of fetal medicine and surgery is extraordinary and holds a lifetime of investigative promise for young scientists. As fetal surgery is evolving, promising animal work is underway, exploring the technical feasibility and pathophysiologic rationale for in utero interventions.

Fetal Molecular Therapies

Fetal molecular therapies represent the newest frontier of prenatal therapy for genetic diseases. The ability to access the fetal umbilical vein, a procedure performed frequently for in utero transfusions, allows potential treatment of fetuses with numerous stem cells, proteins, or viral vectors. For example, in utero hematopoietic stem cell (HSC) transplantation can be performed to treat fetuses with blood disorders such as thalassemia. This concept has been demonstrated well in animal models and in patients with immunodeficiencies. There is now an ongoing phase 1 clinical trial of in utero transplantation in patients with alpha thalassemia major.

Other potential therapies include in utero enzyme replacement therapy for fetuses with lysosomal storage disorders. Fetuses with MPS7 (Sly syndrome) often have hydrops, a sign of impending demise. Infusion of the missing recombinant enzyme has improved outcomes in mouse models of MPS7 and has potential implementation in clinical trials.

In Utero Gene Therapy

In utero gene therapy takes an inward approach to fetal intervention by using stem cells to regenerate normal function in genetic abnormalities. Anticipated benefits associated with gene therapy are optimistic as immature development in fetal immune systems increase the likelihood of successful stem-cell receptivity. The procedure is relatively less invasive than alternative methods of fetal intervention and capitalizes on accessible stem cells located in amniotic fluid or pathologic states.[35]

In utero gene therapy could improve outcomes in multiple disorders for which postnatal gene therapy has been tested, such as spinal muscular atrophy or hemophilia. The specific benefits of these strategies include (a) inducing tolerance to the missing protein, as the fetal immune system is more prone to tolerance; (b) ability to cross the blood–brain barrier before it is formed, potentially addressing the neurologic aspects of diseases; and (c) low costs of enzymes or viral vectors due to the small size of the fetus.

Gene editing tools play a vital role in the feasibility of gene therapy by enabling manipulation of genes into a variety of target cells and organisms. Among available gene editing tools, clustered regularly interspaced short palindromic repeats (CRISPRs)/CRISPR-associated protein-9 nuclease (Cas9) (CRISPRs/Cas9) is the most widely used. CRISPR/Cas9 binds synthetic gRNAs to chromosomal DNA sites specified by Cas9 enzyme.[35]

As with other fetal interventions, maternal safety is the paramount concern when embarking on fetal molecular therapies. While preclinical studies do not indicate significant risk to the mother from in utero administration of stem cells enzyme replacement or gene therapy, clinical implementation requires careful attention for any unanticipated adverse events.

The extent of research for in utero gene therapy remains in the preliminary stages of animal studies, and human clinical trials are just beginning. Several issues in fetal gene therapy require attention and are mostly related to moral and ethical disagreements.

In Utero Stem Cell Transplantation

In utero stem cell transplantation emerged as a highly anticipated treatment when fetal imaging technology enabled access to the fetus and further understanding of fetal development. During early gestation, fetuses exhibit immunologic immaturity and plasticity meaning that differentiation in cell

function occurs gradually. As a result, expectations for successful fetal stem cell receptivity are greater than those of adults with fully matured immune systems.[32] Stem cells used for fetal transplantation are sourced from bone marrow, placenta, and two forms of amniotic fluid. Overall, HSCs are the most widely investigated due to effective transplant abilities with potential blood cell differentiation, suggesting clinical benefits of HSC transplantation as possible cures for prenatal hemoglobinopathies requiring bone marrow transplants.[28]

Other directions of in utero stem cell transplantation focus on mesenchymal stem cells (MSCs). MSCs exhibit migratory responses to sites of injury where they engraft to target tissues, suggesting possible involvement in site repair. Reported cases of bone injury strongly indicate MSCs engraft as reparative course of action to repopulate regional damage with healthy cells.[36] Compared to adult derived MSCs, fetal MSCs hold higher prevalence during fetal life and are more frequently in tissues of fetal liver, umbilical cord, blood, amnion, placenta, and amniotic fluid as early as 15 weeks of gestation. The FDA has recently approved a phase I clinical trial of placental derived MMC's in the treatment of spina bifida in utero.

Osteogenesis imperfecta (OI) is a common disorder of abnormal skeletal, osteopenia, numerous painful fractures, and short stature. Postnatal treatments thus far decrease the severity of associated morbidity but do not offer a cure. Pre-clinical mouse studies comprise the majority of research in OI, however, two cases of MSC stem cell intervention performed in Singapore, demonstrated remarkable benefit for each patient.

Tissue Engineering

Tissue engineering approaches often combine the use of a matrix with stem cells aimed at regenerating missing or malformed structural organs.

In alignment with normal fetal biology, stem cells enable transplanted cells to piggyback on natural processes of migration, engraftment, differentiation, and expansion. Early tissue engineering studies demonstrate sustained release of basic fibroblast growth factor (bFGF) using gelatin-based hydrogel on fetal rats with MMC. Other investigators are exploring amniotic fluid derived MSCs to provide a skin-like covering to the MMC lesion,

while others are using placental derived engineered MSCs to augment existing fetal surgery repairs.

Just as the early pioneers in open fetal surgery had to persevere despite grave doubts as to the feasibility, ethics, and efficacy, so do the current fetal gene and cell therapy pioneers. It is only with persistence that science advances and diseases are vanquished.

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99

Pediatric Head and Neck

Nikolaus E. Wolter and Reza Rahbar

Key Points

1. The site of the neck mass is important (midline vs. lateral) for narrowing the differential diagnoses.
2. Benign cervical lymphadenopathy is the most common neck mass in the pediatric population.
3. Although rare, always consider malignancy to avoid delay in diagnosis.
4. Infants are obligate nasal breathers for the first 3 to 6 months of life; therefore, any nasal obstruction can cause respiratory distress.
5. History is important in the workup and treatment of an airway foreign body.

INTRODUCTION

The differential diagnosis of pediatric head and neck lesions includes a broad range of congenital and acquired etiologies. In contrast to the adult population, the majority of pediatric neck masses are benign with only 11% of neck masses demonstrating a malignancy on biopsy.[1] In pediatrics, neck

masses can be congenital, infectious, inflammatory, traumatic, lymphovascular, or neoplastic. Neck masses can range in presentation from an asymptomatic lesion to acute respiratory distress, depending on their size and location. Inflammatory cervical lymphadenitis is the most common cause of pediatric neck masses found in children. Congenital masses, such branchial cleft cysts and thyroglossal duct cysts (TGDC), often become clinically apparent when infected. Malignant processes are rare in children, and the most common malignancy seen in the pediatric neck is lymphoma. This chapter will focus on the most common head and neck pathologies found in the pediatric population along with their clinical presentation and treatment.

Imaging

Imaging is not always required for the diagnosis of a pediatric neck mass, but can be helpful in clarifying extent and size, location, and radiologic characteristics of a lesion. Ultrasound (US), computed tomography (CT), or magnetic resonance imaging (MRI) can be helpful in narrowing the differential, but often a biopsy or excision is still required for diagnosis.

Ultrasound

US is a good first choice for imaging in children. US has the advantages of being portable, fast, does not require sedation, and does not expose the pediatric patient to ionizing radiation. Disadvantages of US include variability of the technician's skill/experience as well as lower resolution images. The pediatric neck often has less subcutaneous adipose tissue, which lends to better imaging with US.[2] Moreover, US offers the ability to differentiate solid from cystic lesions, and color Doppler can determine the presence and characteristics of vascular flow within a mass.[3] US can be very helpful in determining the stage of an abscess, helping to differentiate early lymphadenopathy (LAD) that can be treated with antibiotic therapy from a mature abscess that requires surgical drainage.

Computed Tomography

CT scans and MRI provide a more detailed study of the anatomy of the neck. CT scans are readily available in emergent situations with scans completed quickly for patients who are critically ill. This speed can also help to eliminate the need for sedation and help to minimize artifact from movement. CT scans offer more osseous detail such as remodeling or erosion, as well as calcifications. The main disadvantage of CT scans is the exposure to ionizing radiation, which could potentially have carcinogenic effects in the long term.[4–6] Newer techniques offer reduced exposure with CT scans, but MRI and US should be utilized when appropriate.

Magnetic Resonance Imaging

MRI is the scan of choice for neck masses due to excellent soft tissue detail and avoidance of ionizing radiation. Details of the margins and possible neural spread or intracranial extension of a mass can be noted with the use of a contrast-enhanced MRI. The longer length of time required to obtain an MRI often requires sedation due to concerns of movement artifact in the pediatric population, which is the main disadvantage of the MRI.

Congenital

Congenital lesions of the head and neck are diverse and often the location of the lesion can greatly assist in narrowing the diagnosis (Table 99.1).

Branchial Anomalies

The branchial apparatus in the fetus eventually develops into head and neck structures. Any deviation in the development of these structures can result in an anomaly that can present as a mass in the neck. Sinus tracts and fistulas tend to present at a younger age due to their physical appearance, whereas cysts usually present when they get infected and enlarge. A sinus tract has an external opening to the neck, whereas a fistula has an external and internal opening. The location of the lesion is predicted by the portion of the branchial apparatus that is involved. Broadly speaking, remnants of the branchial clefts run deep to the structures derived from the corresponding arch but superficial to the structures derived from the next arch.

These lesions often present with infection. It is best to settle inflammation and infection with antibiotics prior to excision, making the dissection and identification of important structures easier. Abscesses can be treated with minimal intervention, such as needle aspiration or if needed, incision and drainage. During the procedure, it is important to communicate with anaesthetist to avoid paralysis for proper nerve monitoring. Radiologic imaging with CT or MRI can be helpful (Fig. 99.1). Rate of recurrence for branchial cleft cysts is quoted around 3%, but this increases to 20% in cases that have undergone a prior attempt at excision.[7]

Table 99.1 Benign Congenital Pediatric Neck Masses Based on Location

Location		Diagnosis		
		Developmental	Inflammatory/Reactive	Neoplastic
Lateral	Anterior to sternocleidomastoid (anterior triangle)	Branchial cleft cyst, vascular malformation, thymic cyst	Reactive LAD, lymphadenitis, sternocleidomastoid tumor of infancy	Lymphoma, rhabdomyosarcoma, metastatic lesion
	Posterior to sternocleidomastoid (posterior triangle)	Vascular malformation, thymic cyst	Reactive LAD, lymphadenitis	Lymphoma, metastatic lesion
	Preauricular	Hemangioma, vascular malformation, type I branchial cleft cyst, preauricular cyst	Reactive LAD, lymphadenitis, parotitis, atypical mycobacterium	Pilomatrixoma, salivary gland tumor
	Submandibular	Branchial cleft cyst, vascular malformation	Reactive LAD, lymphadenitis, atypical mycobacterium	Salivary gland tumor
	Supraclavicular	Vascular malformation, bronchogenic cysts	Reactive LAD, lymphadenitis	Lymphoma, metastatic lesion
Midline	Anterior neck	Thyroglossal duct cyst, dermoid cyst, teratoma, ectopic thymus, external laryngocele	Reactive LAD, lymphadenitis	Thyroid tumor, metastatic lesion (e.g., delphian node)
	Submental	Thyroglossal duct cyst, dermoid cyst, plunging ranula	Reactive LAD, lymphadenitis, Ludwig angina	—
	Occipital	Vascular malformation	Reactive LAD, lymphadenitis	Metastatic lesion

Anatomy and Embryology

The branchial arches form during the fourth to eighth week of gestation as four pairs of well-developed ridges with associated clefts. Each has a cartilaginous center (mesoderm), a cleft (ectoderm), an internal pouch (endoderm), and an associated artery and nerve (Table 99.2). These structures mature into the major structures of the head and neck (Fig. 99.2).

First branchial cleft anomalies, which comprise 8% of branchial cleft anomalies, are divided into type 1 and type 2.[8] Type 1 branchial cysts often present as a fistula around the conchal cartilage. The tract can follow the course of the external auditory canal and is lined by squamous epithelium.[9] Type 2 branchial lesions are found near the angle of the mandible and are composed of both epithelium and mesoderm (as opposed to only epithelial elements in type 1). Both type 1 and type 2 first branchial cleft anomalies can be closely associated with the facial nerve, although type 2 lesions are more likely to be intimately involved with the nerve. Type 2 branchial lesions can loop under the facial nerve, pushing it laterally and inferiorly.[10] The tract for a first branchial cleft usually extends from the opening near the mandible, near the posterior aspect of the parotid, and toward the external auditory canal. One should monitor the facial nerve at all times, with visualization of the face during the entire excision and avoidance of paralysis with anesthesia.

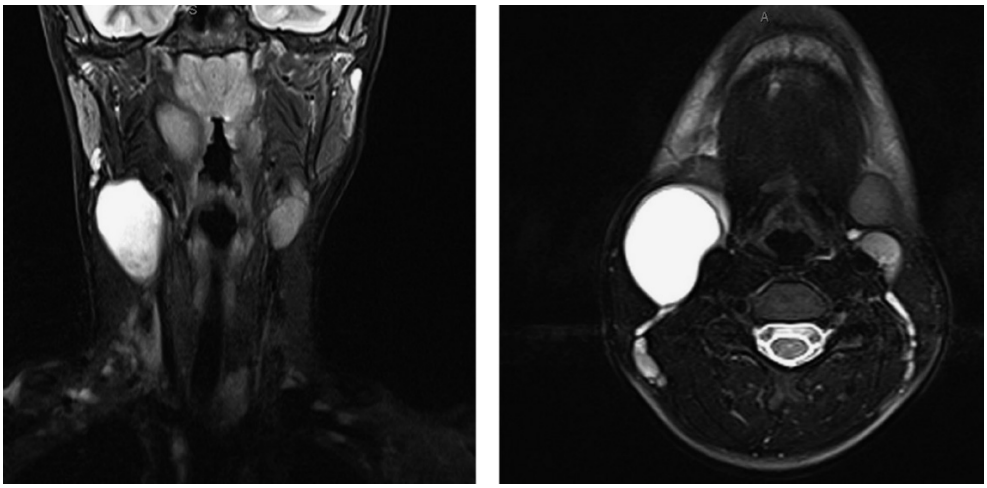

Figure 99.1 Coronal and axial view of MRI for second branchial cleft cysts.

Table 99.2 Pharyngeal Arch Structures

Arch	Nerve	Artery	Muscular Contributions	Skeletal Contributions
1st	Trigeminal nerve (V2 and V3)	Maxillary artery	Muscles of mastication, anterior belly of the digastric, mylohyoid, tensor tympani, tensor veli palatini	Premaxilla, maxilla, zygomatic bone, part of the temporal bone, mandible (only as a model for mandible not actual formation of mandible), incus, malleus. Meckel cartilage and the sphenomandibular ligament
	Pouch	Pharyngotympanic tube, middle ear cleft, part of mastoid air cells		
	Cleft	External auditory canal		
2nd	Facial nerve	Stapedial artery	Muscles of facial expression, buccinator, platysma, stapedius, stylohyoid, posterior belly of the digastric, auricular muscles	Stapes, temporal styloid process, hyoid (lesser horn and upper part of body), stylohyoid ligament, Reichert cartilage
	Pouch	Tonsillar fossa		
	Cleft	Obliterates		
3rd	Glossopharyngeal nerve	Common carotid, proximal internal carotid	Stylopharyngeus	Hyoid (greater horn and lower part of body)
	Pouch	Ventral: thymus; Dorsal: inferior parathyroid glands		
	Cleft	Obliterates		
4th	Vagus nerve (X), superior laryngeal nerve	Right: proximal subclavian artery Left: aortic arch	Cricothyroid muscle, all intrinsic muscles of soft palate (including levator veli palatini) *except* tensor veli palatini	Thyroid cartilage, superior parathyroids, epiglottic cartilage
	Pouch	Ventral: ultimobranchial body; Dorsal: superior parathyroid glands		
	Cleft	Obliterates		
6th	Vagus nerve (X), recurrent laryngeal nerve	Right: pulmonary artery Left: pulmonary artery and ductus arteriosus	All intrinsic muscles of larynx except the cricothyroid muscle	Cricoid cartilage, arytenoid cartilages, corniculate cartilage, cuneiform cartilages

The most common branchial anomaly is derived from the second branchial cleft, representing 90% of branchial cleft anomalies.[11] It can occur as an isolated cyst or as a sinus tract/fistula that extends from the cervical skin to the tonsillar fossa. The cysts will often present at the time of an upper respiratory tract infection as an enlarging, tender mass. If a fistula is present, it will course between the internal and external carotid arteries, over the hypoglossal and glossopharyngeal nerves to end in the tonsillar fossa. A cyst can occur anywhere along this tract, but most commonly occurs in the anterior triangle of the neck below the hyoid.

Third and fourth branchial cleft lesions are rare. Third branchial cleft cysts present low and anterior in the neck. Fistulas can course from the

piriform fossa and drain to the anterior cervical skin. This tract pierces the thyrohyoid membrane and tracks under the glossopharyngeal nerve and internal carotid artery, but stays above the vagus nerve. These lesions can be intimately involved with the thyroid, and sometimes a hemithyroidectomy is required for repeated recurrences. An infected TGDC or third branchial cleft cyst may be the cause of suppurative thyroiditis in children.[12] The external location for a fourth branchial cleft is the same as the second and third, but the internal opening is near the apex of the piriform sinus. Fourth arch masses are extremely rare but reports do exist. Third and fourth branchial sinus/tract dissections are similar to a second branchial cleft. Endoscopy at the beginning of the case can greatly assist in locating and resecting the tract. One promising surgical option for third or fourth sinus tracts is cauterization or sclerotherapy.[13]

The standard treatment for all types of branchial anomalies is complete surgical excision. The surgery is performed under general anesthesia and the patient is positioned with the neck slightly extended with a shoulder roll. If there is a sinus tract or fistula present, a small ellipse is made around this opening after it has been cannulated with a small lacrimal probe. The tract is then dissected cephalad until the end of the sinus tract or until the internal opening of the fistula is reached. The dissection for the most common branchial cleft anomaly, the second branchial cleft, penetrates the platysma, rises along the carotid sheath and turns medially near the branches of the internal carotid artery and courses between the posterior belly of the digastric muscle and stylohyoid muscle, and over the hypoglossal nerve before ending near or in the tonsillar fossa. The tract is then ligated with absorbable suture. Often a direct laryngoscopy or simply a finger placed in the oropharynx can help to visualize the course of the tract and assist with dissection. Some patients might require a “stepladder” incision to trace the tract superiorly.

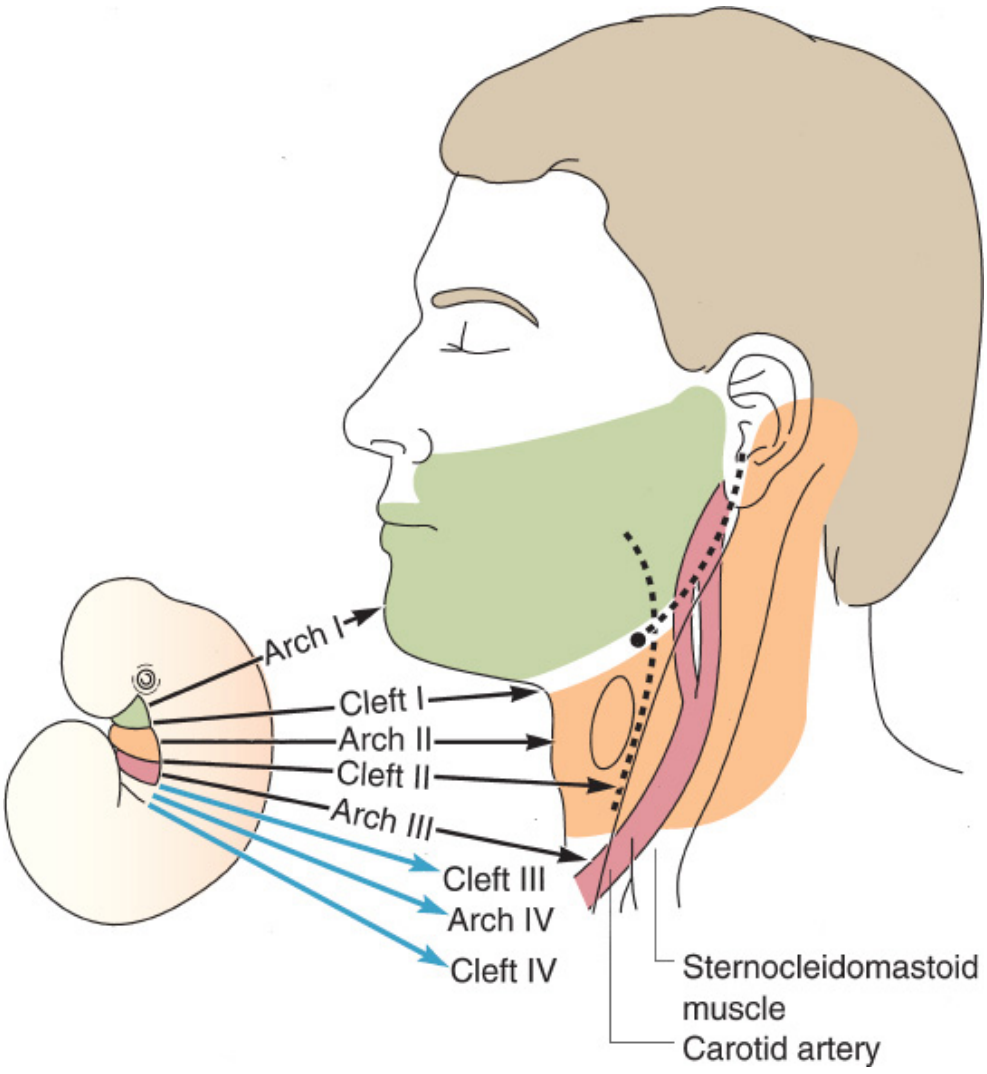

Figure 99.2 Derivation of various areas of the head and neck from the branchial arches and clefts of the embryo.

Preauricular cysts, pits, and sinuses are common in children and are thought to develop from the ectodermal hillocks of His which are found along the first two branchial arches. They are more common and more often bilateral in comparison to first branchial cleft cysts. The tracts extend from the skin down to the helical cartilage of the auricle and are lined with squamous epithelium. Treatment is surgical excision and the recurrence rate ranges from 19% to 40%.[14]

Thyroglossal Duct Cysts

TGDCs are congenital lesions that develop from the thyroglossal duct tract that occurs during the descent of the thyroid from the foramen cecum at the sixth week of gestation. The duct descends along the anterior neck in close association with the developing hyoid bone. This tract usually involutes, but if it persists the tract can present as a TGDC at any point from the foramen cecum to the thyroid (Fig. 99.3). TGDCs are the most common neck mass besides benign LAD in the pediatric population.[15] Physical presentation reveals a midline neck mass that may move with protrusion of the tongue (Fig. 99.4). US is useful to look at the characteristics of the cyst, but is most important to determine if there is a normal thyroid gland present (Table 99.3). In rare cases, the TGDC could be the sole functioning thyroid tissue in the patient.

Treatment is surgical excision and removing the entire tract with a core of tissue and the central portion of the hyoid bone can minimize recurrence. Rarely, papillary thyroid carcinoma can be found in the specimen.[18] The procedure is performed under general anesthesia with the neck extended and placement of a shoulder roll. A horizontal skin incision is made over the cyst, with no need to excise skin unless a fistulous tract or infection has involved the dermis. Careful dissection around the cyst then allows continued dissection superiorly toward the hyoid bone. Muscular attachments to the central hyoid bone are removed with cautery and the hyoid is removed en bloc with the cyst and tract. A core of tissue is then removed above the hyoid bone toward the base of tongue. The tract is then ligated with absorbable suture. Placing a gloved finger at the base of tongue can sometimes facilitate this maneuver. The wound should then be irrigated copiously and closed in a layered fashion but the hyoid should not be sutured back together. A drain is often used. Complete excision is considered curative and TGDCs have a recurrence rate of less than 10% when using this method.[17]

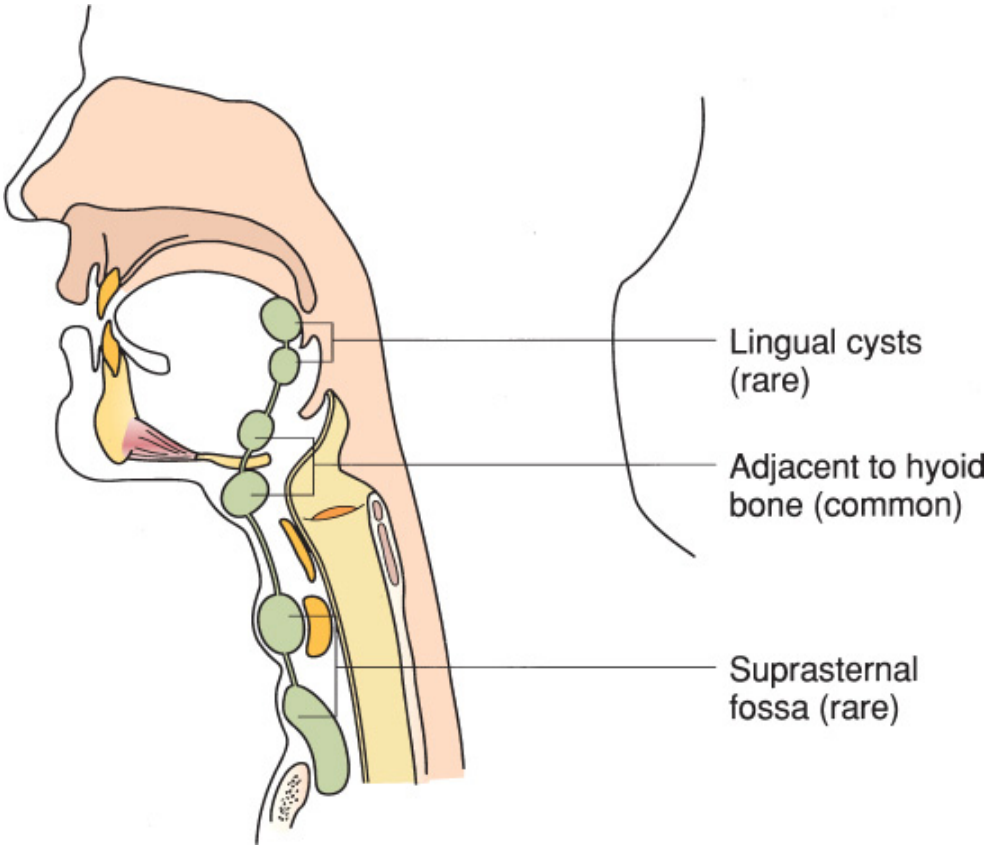

Figure 99.3 Locations of thyroglossal duct cysts.

Figure 99.4 Thyroglossal duct cyst.

Table 99.3 Ultrasonographic Features of Thyroglossal Duct Cysts[16,17]

Feature	Description
Internal septae	An internal septum is a hyperechoic linear structure in two places coursing between the walls of a cystic structure. They are usually thin
Irregular wall	The inner contour of the cyst is not well defined
Solid	Iso- or hypoechoic nodular lesions that have internal flow and no evidence of posterior acoustic shadowing
Tract	Presence of an abnormal connection between the cyst and tongue along the embryologic path of descent

Dermoid Cysts

Dermoid cysts should be considered in the differential of any midline lesion, although they can be off midline as well. On examination, dermoid cysts present as firm masses that are soft, mobile, nontender, and grow slowly. While epidermoids only include epidermal tissue, dermoid cysts contain hair follicles, sweat glands, and sebaceous glands within the wall of the cyst. Endoderm is never found within a dermoid. Treatment is total surgical excision.

Thymic Cysts

Lesions of the thymus usually occur in the lower neck, but can present anywhere from the piriform sinus to the chest along the path of the thymopharyngeal duct.[19] They can be solid, cystic, or mixed. Histologically they are identical to their thoracic counterparts and are characterized by the presence of Hassall's corpuscles. Biopsy is the gold standard for diagnosis but typical US and MRI features are useful for diagnosis as well.[20] The differential includes thymic cysts, thymic hyperplasia, or thymoma.

Infectious

2 The most common cause of a neck mass in the pediatric population is benign cervical LAD. Cervical lymph nodes are palpable in 40% of infants and 55% of pediatric patients.[21,22] Lymph nodes that are <1 cm in size and asymptomatic are considered normal in children under 12 years old.[12] Infectious LAD is most commonly seen in the submandibular region and cervical nodes, and the source of infection can be viral, bacterial, fungal, or neoplastic. Bacterial and viral infections causing upper respiratory infections are the most common cause of cervical LAD. Other possible sources of infectious LAD include, cat scratch disease, mononucleosis, atypical mycobacterium, and tuberculosis. Malignancy must always be included on the differential diagnosis in a child with cervical LAD. Biopsy should be considered if: (1) suspicion of malignancy, (2) no resolution of LAD over 4 to 6 weeks, (3) LAD steadily increases in size over 2 to 3 weeks, (4) LAD greater than 2 cm, or (5) concerning features on imaging.[23,24] Although rare, one should also consider Kawasaki disease, sarcoidosis, Rosai–Dorfman syndrome, and histiocytosis X.

Suppurative Lymphadenitis

Acute suppurative lymphadenitis is most common in the 6-month to 3-year range, with lymph node enlargement associated with an upper respiratory tract infection. The most common etiologies include *Staphylococcus aureus* and group A beta-hemolytic streptococci. There are commonly cellulitic changes in the overlying skin, leukocytosis, and fever. The lymph node enlarges and eventually outgrows the blood supply, resulting in central necrosis. Management can sometimes include needle aspiration of purulence, but often requires an incision and drainage with placement of a drain or packing under anesthesia. An incision is made in the area of fluctuance and blunt dissection should break up all loculations. It is important to place the incision in a place that minimizes risk to vital structures, such as the facial nerve, and allows for the best cosmesis. Antibiotics are geared toward *Staphylococcus* and *Streptococcus*, but cultures should be taken with a change in antibiotic therapy if necessary. The induration from the abscess can take several weeks to resolve, but recurrence is rare. If the abscess recurs, it

should prompt investigation of a possible underlying anomaly. Viral infections rarely cause suppurative adenitis.

Atypical Mycobacterial Infections

Atypical mycobacterial infections, usually caused by the *Mycobacterium avium-intracellulare-scrofulaceum* (MAIS) complex, can be very challenging to manage. The pathogens are usually acquired through the mucous membranes during the eruption of teeth, not through person-to-person transmission. The organisms can also be found in soil and nonpasteurized milk products. These lesions often cause discoloration of the skin and can fistulize over time (Fig. 99.5). Antibiotic therapy is not always curative. It most commonly occurs in children 1 to 5 years of age with a mean age of 3 years and often has associated asymptomatic LAD but no fever or leukocytosis.[25,26] The response to antibiotic therapy is variable and sometimes surgery excision of curettage is required. Long-term adjuvant treatment with clarithromycin or Rifabutin is often indicated, as is a consultation with the infectious disease team. In contrast, children with *Mycobacterium tuberculo*sis usually have fever and respiratory symptoms along with positive findings on chest x-ray and the purified protein derivative skin test.

Cat Scratch Disease

Cat scratch disease, caused by *Bartonella henselae,* can cause tender cervical lymph node enlargement in 25% of cases. Usually there is a history of contact with a cat within 2 weeks of the development of tender LAD. The site of inoculation is usually an extremity. The diagnosis can be made using *B. henselae*–based serologic indirect fluorescent antibody test or enzyme immunoassays. The disease is usually self-limited with resolution in 2 to 8 weeks and no antibiotic therapy is necessary; however, rarely patients can suffer disseminated disease.[27]

Figure 99.5 Atypical mycobacterium infection.

Vascular Malformations

Infantile Hemangioma

Infantile hemangiomas (IHs) are the most common tumor of infancy. IHs are endothelial tumors characterized by an increased proliferation and turnover of endothelial cells, which differentiate this from other vascular malformations. IH is not present at birth and then grows rapidly during the first 9 months (proliferative phase) and then slowly regresses (involuting phase). Regression is usually complete by 4 to 5 years of age.[28] They can occur anywhere in the body, with frequent involvement of the tongue and parotid gland. Usually hemangiomas occur as a solitary lesion, but 20% of

patients can have multiple affected sites. On examination, hemangiomas are a well-demarcated, raised, red mass that blanches with pressure (Fig. 99.6). Known risk factors include female sex, Caucasian race, preterm birth, and low birth weight. Most hemangiomas are not visible at birth but become apparent in the first few months of life and 90% are noticeable by 6 months of age.[29] Hemangiomas can occur in the subglottic region and present with biphasic stridor, presenting between 1 and 3 months of age. Similarly, parotid hemangiomas present as an enlarging mass within the parotid gland at age 1 to 3 months. Evaluation by Doppler US showing fast flow is diagnostic.

Treatment for most IH is conservative, as 90% are small, localized, and not problematic. IH can ulcerate, bleed, and cause deformities and in these cases local wound care can help.[30] Injection with steroids can stabilize the growth of IH in 95% of patients and decrease the size in 75% of patients.[31] Systemic corticosteroids were the mainstay of treatment for large or complicated lesions that become symptomatic. Topical and systemic beta-blocker therapy has also been used in the treatment of IH with varying results. Patients must be monitored closely while on propranolol therapy due to possible serious side effects.[32]

Figure 99.6 Hemangioma.

Figure 99.7 Picture of a patient with lymphatic malformation.

Lymphatic Malformation

Lymphatic malformations (LMs) are slow-flow vascular anomalies and 75% of LMs present in the head and neck. The incidence ranges from 1 in 2,000 to 4,000 births. The lymphatic system develops around week 5 of gestation and although the mechanism for the development of an LM is not completely

understood, it is generally thought to occur due to parts of the lymphatic system that fail to establish connections with the main lymphatic system or venous channels (Fig. 99.7). Histopathology of LMs shows progressive dilation of abnormal vessels, and LMs are composed of vascular spaces filled with eosinophilic and protein-rich fluid. LMs are present at birth, but sometimes are not apparent until enlargement due to infection or trauma with hemorrhage. Some patients are diagnosed with LM when found on prenatal US, and can potentially obstruct the airway and may require an ex utero intrapartum treatment procedure (EXIT procedure).

LMs are divided in microcystic, macrocystic, and mixed lesions. Microcystic lesions are usually above the mylohyoid and can involve the floor of mouth, tongue, parotid, and lip. These lesions have poorly defined borders and infiltrate nearby muscle and fatty planes. Macrocystic lesions are usually below the mylohyoid and have multiple large, loculated cysts in varying size and shape. LMs can enlarge with infection or trauma, which can lead to airway obstruction, functional issues (swallowing, speech), or deformity. Imaging can be helpful to determine the extent of the lesion as well as involvement of surrounding structures.

Treatment for these lesions is challenging and the main options include observation, sclerotherapy, or surgery. LMs are benign lesions and this must be kept in mind when planning treatment. Macrocystic lesions are more amenable to both sclerotherapy and surgical excision, whereas complete removal of microcystic lesions would often result in unacceptable morbidity due to their infiltrative nature. Subtotal resection leads to a high recurrence rate and surgery can be difficult due to previous inflammation and scarring from sclerotherapy. Radiofrequency ablation can be useful in relief of ulceration tongue lesions or oral mucosa.[33] The CO_2 laser can help with symptomatic lesions of the airway or oral cavity, which can reduce bleeding and ulceration. Recently, rapamycin has been investigated as a possible oral medication for LMs with variable results.[34]

Airway

Airway obstruction can occur from congenital or acquired lesions at any level from the nose to distal airway. Children can present with tachypnea,

dyspnea, and chest-wall retractions and it is imperative to establish an airway while investigating the potential causes with history and physical, chest radiograph, and arterial blood gas if appropriate. Laryngoscopy and bronchoscopy are often warranted.

Nasal Airway Obstruction

4 Infants are obligate nasal breathers and nasal obstruction, especially bilateral obstruction, can cause acute respiratory distress at birth.[35] Choanal atresia or stenosis, piriform aperture stenosis, or nasal septal deviation can cause significant obstruction. Piriform aperture stenosis is a narrowing of the anterior nasal passageway that can also cause similar symptoms to choanal atresia. Nasal obstruction can also result from lesions such as a nasolacrimal duct cyst, encephalocele, or nasal glioma. Nasal examination and sometimes a CT scan can help to determine the diagnosis.

Oral Airway Obstruction

Macroglossia or retrognathia/micrognathia may also cause obstruction of the oral cavity in the infant. In the oropharynx, a TGDC, a vallecular cyst, or lingual thyroid can cause airway obstruction.

Supraglottic Airway Obstruction

In the supraglottic region, laryngomalacia can affect the larynx in newborns. Laryngomalacia results from immature cartilage in the larynx and discoordination of the arytenoids and epiglottis. The diagnosis is made using a flexible laryngoscope and viewing the larynx while the patient is awake. High-pitched inspiratory stridor that is worsened with exertion, crying, or excitement is the classic description. In the absence of respiratory distress or failure to thrive, most children do not require any intervention. Supraglottoplasty can be performed when laryngomalacia causes breathing or feeding difficulties and is tailored to each airway to address the redundant or malacic tissue.

Glottic Airway Obstruction

At the level of the glottis, obstruction can occur for several reasons, including vocal cord paralysis and glottis webs. Bilateral vocal cord

paralysis can present with a normal cry but biphasic stridor, whereas unilateral vocal cord paralysis usually presents with a weakened cry and no respiratory distress. Iatrogenic injury is the most common etiology followed by idiopathic causes. In the absence of an obvious etiology, the entire path of the recurrent laryngeal nerve must be assessed from the brain to the mediastinum.[36] In bilateral vocal cord paralysis, a neurologic assessment for possible Arnold–Chiari malformation or hydrocephalus is required. A tracheotomy may be necessary for patients with bilateral vocal cord paralysis if they are in respiratory distress.

Glottic webs usually affect the anterior portion of the vocal cords and can range from a thin membrane to a thick web that can extend inferiorly to the subglottis. Patients present with dysphonia and sometimes respiratory distress. Treatment is dependent on the extent of the glottis web, which can be divided endoscopically in the majority of cases.[37]

Subglottic Airway Obstruction

The subglottis is the narrowest part of the airway in an infant due to the cricoid cartilage. Stenosis can occur congenitally or can be acquired after long-term intubation. Subglottic hemangiomas are another source of airway obstruction that enlarge after birth and are associated with segmental cutaneous hemangiomas typically in the "beard" distribution. They can be found as part of the PHACES syndrome (posterior fossa malformation, arteriovenous malformations, cardiac/aortic defects, eye anomalies, and sternal defect). Treatment can be beta blockers, systemic or intralesional corticosteroids, laser therapy via endoscopic approach, or open excision.

In patients with a prior intubation, one or multiple subglottic cysts may form and cause airway obstruction. Treatment entails endoscopic evaluation with marsupialization or removal with a laser or laryngeal microdebrider.

Tracheal Airway Obstruction

Tracheomalacia can occur in a primary or secondary form. Primary tracheomalacia is a rare congenital disease in which the tracheal cartilages collapse on expiration. Most cases of primary tracheomalacia are mild and no intervention is required, although if severe, a tracheostomy may be required. Secondary tracheomalacia occurs when an extrinsic compression

causes collapse of the trachea on expiration. Treatment is then tailored to the source of compression, whether a vascular anomaly or mass.

Tracheal stenosis can occur due to congenital complete tracheal rings and can involve a segment or the entire trachea. Depending on the extent of the stenosis, a tracheal resection or a slide tracheoplasty may be performed.

Acquired obstruction of the airway includes infectious sources, such as epiglottitis, and foreign-body aspiration. Although rare, epiglottitis is a life-threatening disease caused by *Haemophilus influenzae* type B (90% of cases) that occurs most commonly in children ages 2 to 4 years. The *H. influenzae* vaccination has reduced the number of cases, but pneumococci and beta-hemolytic streptococci can also cause epiglottitis. The disease presents rapidly, with stridor, airway obstruction, drooling, odynophagia, fever, tachypnea, and tachycardia. As the disease progresses, the child will often assume the "tripod" position by leaning forward, drooling, and suffering from air hunger. It is important not to agitate the patient and obtain an airway in the operating room with a tracheostomy set available. Depending on the stability of the patient, a lateral neck film can confirm the diagnosis with the "thumbprint" sign demonstrating an edematous epiglottis. The patient should be started on antibiotic therapy and laryngoscopies performed until the patient's epiglottis/airway edema allows for a safe extubation.

Airway foreign bodies can be life threatening and the history is of utmost importance. Combining the convincing history of a coughing/choking episode with an abnormal chest radiograph warrants a bronchoscopy. Sometimes a bronchoscopy is warranted on the history alone, as less than half of the patients with an airway foreign body have an abnormal chest radiograph.[38] If it was a witnessed aspiration, obtaining a detailed description of the object and practicing with the bronchoscopy foreign-body forceps on a similar object can be helpful if the patient is stable.

SUMMARY

Pediatric disorders of the head and neck range broadly from masses arising within the neck to anomalies of the aerodigestive tract from the nose to lungs and the lips to the stomach. The differential diagnosis of pediatric head and neck lesions includes congenital and acquired etiologies. History, physical examination, and appropriate imaging in addition to a low level of suspicion are of the utmost importance. Knowledge of the embryology and physiology of the head and neck as well as commonly encountered entities are critical to anticipating issues that children may develop.

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Pediatric Chest

Robert E. Cilley and Mary Catherine Santos

Key Points

1 Pectus excavatum is repaired in late childhood or adolescence. Repair is most frequently performed with a rigid transversely oriented pectus excavatum bar that pushes the deformity back into place. Improved pain management has shortened hospital stay.

2 Pectus carinatum is less common than pectus excavatum and does not cause physiologic impairment; external compression bracing has become the method of choice for treatment.

3 Pulmonary sequestrations (PSs) are abnormal lung tissue with anomalous systemic blood supply that can be either intralobar or extralobar based on their relationship with the investing visceral pleura and adjacent lung tissue. They do not communicate normally with the trachea or a bronchus.

4 Congenital cystic adenomatoid malformations (CCAMs) have a normal vascular supply and communicate with the normal tracheobronchial tree. They result from excessive proliferation of bronchial structures without the development of the corresponding alveoli. Management of asymptomatic CCAMs remains controversial. Thoracoscopic lobectomy is commonly performed.

5 Benign cysts of the mediastinum are relatively common and include thymic cysts, enterogenous cysts, dermoid cysts, lymphatic malformations (cystic hygromas), and pericardial cysts. Resection is usually recommended because of the possibility of progressive enlargement with compression, hemorrhage, or infection.

6 Primary lung tumors in children are rare and include bronchial adenoma, pleuropulmonary blastoma, inflammatory pseudotumor, hamartoma, and rarely bronchoalveolar carcinoma. Resection is usually required.

7 Metastasectomy for many solid embryonal neoplasms can improve survival if the primary disease is controlled by resection.

8 Tracheoesophageal fistula (TEF) can occur as esophageal atresia with proximal pouch and distal TEF (most common, 85% to 95%), esophageal atresia without fistula (“pure esophageal atresia,” 5% to

7%), TEF without esophageal atresia ("H-type fistula," 2% to 6%), and rarer forms of this anomaly including esophageal atresia with proximal TEF and esophageal atresia with both proximal and distal TEF.

9 Approximately 75 children die from foreign-body aspiration or ingestion each year. Bronchoscopic evaluation and foreign-body removal are performed in the operating room under general anesthesia, where the rigid bronchoscope with optical forceps can be used to remove most aspirated foreign bodies safely. "Button battery" ingestion has emerged as a cause of serious injury and death. Emergent endoscopic removal from the esophagus is required.

10 Congenital diaphragmatic hernia (CDH) is a physiologic emergency and not a surgical emergency. The newborn with CDH should be stabilized by nonsurgical means and delayed, well-planned surgical repair undertaken subsequently. Pulmonary hypertension and lung hypoplasia determine outcome.

CHEST WALL DEFORMITIES

Deformities of the chest wall may be obvious at birth but often become more noticeable at the time of preadolescent and adolescent growth. The physical appearance may vary from barely detectable to severely deforming. Although there may be some physiologic benefit from surgical correction of these deformities, restoration of a more normal appearance is equally important in the decision to treat. The impact of these deformities on normal psychosocial development, as well as evidence of cardiorespiratory impairment, justifies correction.

Embryology, Development, and Etiology of Chest Wall Deformities

Ribs are derived from individual somites as mesoderm differentiates into cartilage and advances ventrally toward the developing sternum. Rib cartilage eventually approaches the sternum. The sternum is derived independently from two parallel bands of mesoderm that develop away from the midline. The two sternal bands fuse cranial to caudal and become progressively chondrified. Transverse divisions of the cartilaginous sternum differentiate into segments opposite each end of the rib pairs. At birth, small ossification centers are present in the sternum; the ribs have largely ossified. Final ossification is usually complete by mid adolescence. The timing of sternal ossification is sufficiently predictable to be a reliable method of determining bone age. There is a sharp demarcation in each rib between the ossified portion and the cartilaginous portion, with the latter becoming ossified only much later in life. The etiology of chest wall deformities is uncertain.[1] Abnormal intrauterine pressure applied to the chest, abnormalities of diaphragmatic development, connective tissue abnormalities, and genetic predisposition may contribute. Abnormal, excessive, or asymmetric growth of the costal cartilages associated with the 3rd to 10th ribs is most implicated.[2] Sternal clefts result from a failure of fusion of portions of the sternal bands.

Pectus Excavatum

Pectus excavatum from the Latin “hollowed chest” is the most common deformity of the anterior chest wall occurring in 1 in 400 to 1 in 1,000 children, accounting for the majority of chest wall deformities. A family history is present in half.[2,3] There is male predominance. Pectus excavatum results from abnormal regulation of the growth of the costal cartilages. There is a corresponding posterior curve in the body of the sternum beginning at the manubrium and extending to the xiphoid. The deformity is rarely precisely symmetric, with one side (usually the right) slightly more curved in than the other. Asymmetry may be pronounced with the sternum rotated nearly to the sagittal plane. The deformity may be apparent at birth but often becomes more apparent during adolescence. Scoliosis is increased in this population although rarely needs surgical correction. Patients often have an asthenic build and stoop-shouldered posture. Connective tissue disorders are

associated with pectus excavatum. The diagnosis of Marfan syndrome should be considered.

Concerns about cardiopulmonary implications are often paramount in the mind of the referring physician as well as the family. Many patients will have complaints of chest pain and/or shortness of breath. Most patients are disturbed by the appearance of the deformity, and some may be profoundly depressed and dysfunctional. The physiologic consequences of the deformity are less certain. Invasive and echocardiographic assessment of cardiovascular performance has demonstrated improvement in cardiac function and resolution of mitral valve prolapse in some patients following surgical correction of pectus excavatum. Studies have also demonstrated improved body image and subjective physical ability.[2–9] The cardiorespiratory benefits of the repair remain controversial with more recent studies demonstrating improvement after bar removal especially with dynamic testing.[9] Multiple studies confirm patient and parent satisfaction.[2–12] Clinical assessment of the severity of the deformity has included chest radiographs, computerized tomography (CT), caliper measurements, contrast volume measurements of the cavity, and more recently 3-dimensional image scanning. Indices, including the "Haller Index," the Compression Index, and the Depression Index help quantitate the deformity.[7] An echocardiogram is usually indicated. Pulmonary function testing may be helpful.

Surgical Correction of the Pectus Excavatum

1 Although pectus excavatum may be present in infants and young children, repair should be deferred to adolescence to avoid recurrence and acquired thoracic dystrophy.

"Open" Operations

Traditional "open" surgical correction was performed through an inframammary incision (Fig. 100.1). The operation requires the exposure of costal cartilage by elevation of the pectoral muscles from the chest wall. The involved cartilages usually from 3 to 7 and parts of 8, 9 and 10 are removed by subperichondrial excision, with careful preservation of the perichondrial sheaths. The xiphoid is detached from the sternum and the rectus muscles are

detached inferiorly. The undersurface of the sternum is dissected free of the pericardium and pleura. A transverse wedge osteotomy is created in the sternum at the point where the sternum deflects posteriorly and the posterior surface is gently fractured. A strut is usually placed beneath the sternum to maintain the position of the sternum. The strut, typically a stainless steel bar, is removed in 6 months to 1 year.[2] The pectoral and rectus muscles are reapproximated. Closed suction drains are usually left in place in the submuscular layer. Pain is controlled using multimodal techniques. Complications may include pneumothorax, wound seromas, pleural effusions, and recurrence. Migration of implanted struts and bars has caused the most serious problems, including cardiac injury.

Minimally Invasive Repair/Nuss Procedure

Since its description in 1998 by Nuss, the minimally invasive repair has gained widespread popularity. Conspicuous incisions, resection and osteotomies are avoided. Using small lateral incisions, one or two rigid U-shaped bar is inserted transversely across the chest and then "flipped." The sternum is pushed back into a normal position (Fig. 100.2).[13] Modifications of the technique including the use of stabilizers, and routine use of thoracoscopy to guide bar insertion[2,11,14] reported complications include pneumothorax, cardiac injury, bar displacement, chronic pain, pericarditis, allergic metal reactions and extraosseous bone formation.[14] Multimodal postoperative pain management and intercostal nerve cryoablation shorten hospital stay.[15,16] The bar is left in for up to 3 years during a period of development when most children are active and may engage in contact sports. Graded activity restrictions allow return to normal activity while the bar is in place. Recent studies have demonstrated that the early-to-late teenage years are the appropriate time for repair.[10,17] Older teenagers and young adults can also be repaired.[18]

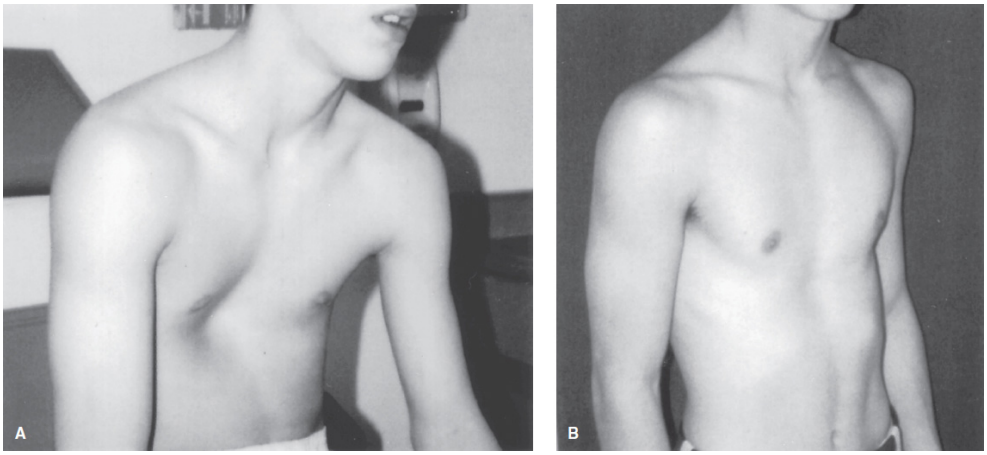


Figure 100.1 Pectus excavatum. **A:** Appearance of an adolescent male with a typical depression deformity. Note "stoop-shouldered" posture. **B:** Postoperative appearance at 6 months. Erect posture and subpectoral incision give a good cosmetic result.

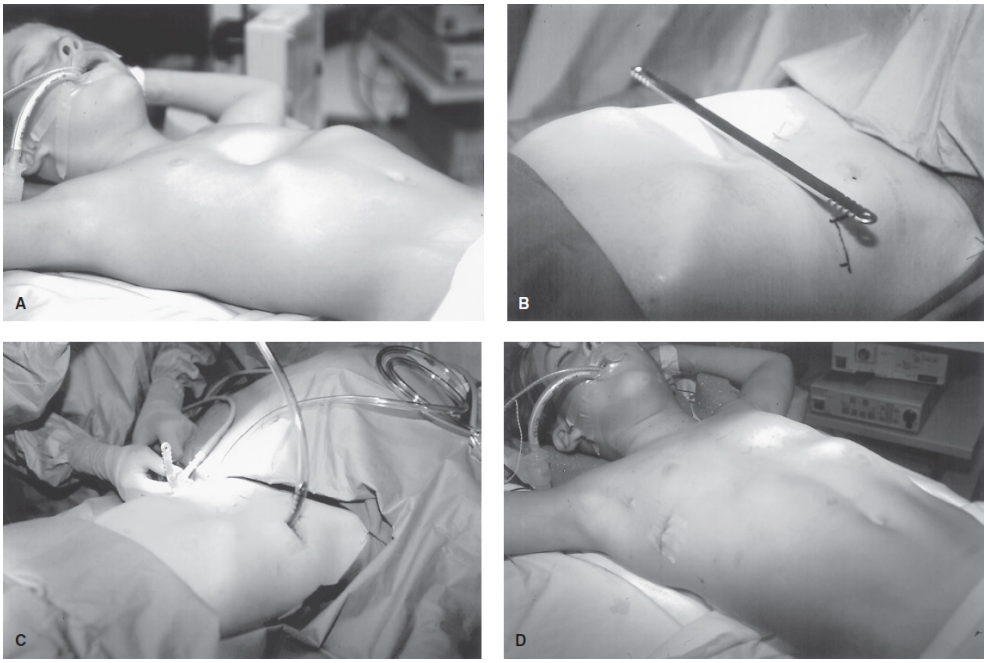


Figure 100.2 Thoracoscopically assisted Lorenz Bar insertion (Nuss procedure). **A:** Preoperative appearance with symmetrical depression deformity. **B:** Lorenz bar. **C:** Pectus excavatum bar inserted with thoracoscopic guidance. **D:** Immediate postoperative appearance. (Digital images provided by William Hardin, MD, University of Alabama, used with permission.)

Other Techniques

Implantation of submuscular silastic molds to alter the chest contour may result in a very acceptable appearance.[19] This technique does not address any of the potential physiologic problems associated with pectus excavatum and has not been used widely.

Externally applied suction may also be used to treat depression deformities of the chest wall and implanted devices that use magnetic forces to pull the sternum forward show promise in correcting the pectus excavatum defects.[20,21]

Pectus Carinatum

2 Pectus carinatum, from the Latin word for "keel," is a chest wall defect where there is a protrusion of the sternum and ribs. This type of defect occurs less commonly than pectus excavatum and is present in 1 in 1,000 to 1,500 teenagers. Physiologic impairment is absent; however, the concern for appearance may be even greater than with depression deformities of the chest wall. Protrusion deformities may be very difficult to hide even when fully clothed. Rapid growth of the costal cartilages occurring during puberty makes the deformity more pronounced at that time. Compression bracing is the first choice for correction of most pectus carinatum deformities, with surgery reserved for failures of therapy.[22,23] Bracing is most successful when performed for more than 16 hours per day. Surgical correction involves costal cartilage resection and sternal osteotomies. Minimally invasive techniques use a bar passed anterior to the sternum.[24]

Poland Syndrome

Named after the English surgeon Sir Alfred Poland, this rare congenital syndrome occurs in 1 in 30,000 births and includes a hypoplasia or aplasia of the thoracic wall components. These features may include absence of the sternal portions of the pectoralis major muscle; absence of the pectoralis minor muscle; absence of portions of the serratus anterior and external oblique muscles; forearm and hand deformities; ipsilateral hypoplasia of the nipple, breast, and chest wall subcutaneous tissues; absence or deformity of the second to fifth costal cartilages; and absence of axillary hair on the affected side. Surgical treatment includes correction of any deformed ribs,

formation of the anterior axillary fold using the latissimus dorsi muscle, and creation of the ipsilateral breast in females.[25,26] Minor forms of this developmental abnormality are more common.

Sternal Clefts

Congenital sternal clefts result from failure of midline fusion of the paired sternal bands. The cleft is usually in the superior portion of the sternum and may extend to but not include the xiphoid. The defects are rare and are usually repaired in the neonatal period when the chest is more pliable.[27] The purpose of the correction is to protect the underlying mediastinal structures. After subcutaneous and substernal mobilization, the fibrocartilaginous sternal bars are approximated in the midline. If the cardiac structures are at risk, more elaborate repairs are required. Typically, the cleft is incomplete and a V-shaped excision of the sternum at the most inferior aspect of the cleft may be required to avoid buckling of the sternum.[27] Pentalogy of Cantrell refers to a distal sternal cleft, omphalocele, diaphragmatic defect, pericardial defect, and intracardiac defect. Thoracic ectopia cordis (exstrophy of the heart) may occur as a part of this abnormality and this spectrum continues to have a high mortality.[27]

Jeune Asphyxiating Thoracic Dystrophy

Jeune asphyxiating thoracic dystrophy is a rare developmental abnormality that results in the failure of chest wall growth. Traditional surgical procedures have involved sternotomies with placement of graft material to expand the chest. More recently, a vertically expandable prosthetic titanium rib (VEPTR) device has been used. The posterior aspect of the ribs (typically 3–9) is divided along with the costochondral junction. The rib plate is then elevated to the curved VEPTR strut by wires, thus expanding the chest. This is done for both chests, and the device is serially expanded to promote chest enlargement.[28,29]

The “Slipping Rib” Syndrome

Slipping rib syndrome is an unusual cause for recurrent lower chest and upper abdominal pain. The cause is likely an inadequacy or rupture of interchondral fibrous attachments of the 9th or 10th rib. The symptoms tend to be a popping or clicking sensation with truncal movement associated with pain. Pain is usually reproducible with manipulation of the rib cartilage anteriorly. Surgical therapy involves excision of the affected rib and cartilage relieving pressure on the involved intercostal nerve.[30,31]

"Flaring" of the Costal Margin

Patients are sometimes referred for surgical opinions regarding unusual prominence of the costal margin. The "flaring" is most pronounced when the patient is supine. This finding represents a variation of the normal development of the chest wall. Surgical correction is usually unnecessary.

Costochondral "Tumor"

Prominence of a single costal cartilage may raise a concern of a tumor of cartilage or bone. This abnormality is usually found in preadolescents and adolescents. Patients may have undergone a diagnostic workup that includes chest radiographs, ultrasound, CT, or magnetic resonance imaging (MRI) prior to surgical consultation. This abnormality most likely represents a minor variation of a chest wall deformity, such as a pectus carinatum. The area of enlargement is rarely tender so that costochondritis is an unlikely explanation. Excision of the involved cartilage is rarely helpful. Plain radiographs or thoracic imaging are usually sufficient to exclude a tumor.[32]

CONGENITAL LUNG LESIONS

Congenital lung lesions have been characterized as lesions of defective budding, differentiation and separation of the foregut, as well as airway maldevelopment with resultant obstruction.[33,34] These lesions include pulmonary sequestration (PS), congenital pulmonary airway malformation (CPAM; formerly CCAM), bronchogenic cyst (BC), and congenital lobar overinflation (CLO). The first three are in the family of bronchopulmonary

foregut malformations. PS is characterized by aberrant blood supply, CPAM by hamartomatous lung parenchyma, and BC by an isolated cyst. There is overlap among the types; many lesions are found to be hybrid.[33,34] CLO is likely a secondary response to abnormal compression or obstruction of a bronchus during lung development.

Pulmonary Sequestration

3 PSs consist of nonfunctioning pulmonary tissue without a normal bronchial communication with the tracheobronchial tree. The blood supply is from an aberrant systemic vessel often originating from the descending aorta. The lesions are most commonly found in the lower lobes, more commonly on the left. They are characterized as intralobar or extralobar based on pleural lining.

Intralobar sequestrations are incorporated into the surrounding lung and are invested by its visceral pleura. They are most common in the left medial or posterior basal segment of the lower lobe. The arterial supply is from the descending aorta and the venous return is usually into a pulmonary vein. Usually asymptomatic at birth, but aberrant air space connections can result in recurrent pneumonia.

Extralobar sequestrations occur outside of the pleura of the normal lung. They are most common in the lower left side of the chest but have been reported in a variety of locations including the retroperitoneum.[33–35] In the retroperitoneum, they may be difficult to distinguish from neuroblastoma. These have occasionally been associated with congenital diaphragmatic hernia (CDH). In 20% of cases, the blood supply originates from the infradiaphragmatic aorta. Arteriovenous shunting in rare cases can lead to high output heart failure.

Radiographic evaluation of PS involves chest radiographs, ultrasound, and CT scans with contrast enhancement to identify the vascular supply. Intralobar sequestrations are treated with lobectomy. Extralobar sequestrations may be removed by excision of the sequestration. The lesions may be removed with thoracotomy or thoracoscopy with attention to safe ligation of the vascular supply (Fig. 100.3).[33–39]

Congenital Pulmonary Airway Malformations

4 CPAMs result from overgrowth of bronchial structures at the expense of the associated alveoli associated with an abnormal supplying airway affecting a single lobe in 95% of cases. This group of anomalies represents 30% to 40% of the developmental lung bud anomalies. On gross appearance, they can be solid, cystic, or both. The malformations have a normal blood supply and communicate with the normal tracheobronchial tree. The common classification separates these lesions into three main types. Type I CPAMs consist of cysts with large, irregular widely dispersed spaces larger than 2 cm or a single large cyst with multiple small surrounding cysts and represent 50% to 65% of postnatal cases. Type II CPAM is described as numerous smaller cysts (0.5 to 2 cm) and account for 10% to 40% of cases. Type III CPAMs are made of small cystic lesions (generally 0.2 cm) or solid lesions appearing similar to immature lung devoid of cartilage and make up of 5% to 10% of cases. CPAMs generally affect one lobe but multilobar and bilateral involvement occurs. Most commonly, the lesions are left sided and affect the lower lobes. Prenatal diagnosis is common and has led to an increase in diagnosis of lung lesions.[44] CPAMs may compromise fetal cardiac function leading to hydrops that can be life-threatening. Fetal surgery has included open resection and thoracoamniotic shunting with survival of some of the affected fetuses.[33,42] The natural history of prenatally diagnosed CPAMs is variable and even large lesions may regress. Growth tends to plateau at 26 to 28 weeks of gestation.[35,40]

The incidence is reported to be between 1:25,000 and 1:35,000 live births which likely underrepresent the incidence. Although 80% are asymptomatic at birth, many will have respiratory symptoms within the first month of life.[35] Less commonly, patients may present with pneumonia later in life (Fig. 100.4).

Symptomatic lesions require resection of the involved lobe. Those with severe respiratory compromise may require resection on extracorporeal membrane oxygenation (ECMO) with excellent results. Other infants may benefit from an ex utero intrapartum treatment (EXIT) to ECMO approach when gas exchange is predicted to be compromised at delivery[40,41] Best treatment for asymptomatic lesions is less certain as the natural history of the lesion is unknown. There is concern for future infection and the possibility of

malignancy.[33,34,40–42] Those who recommend resection favor timing between 2 and 10 months of age. With antenatal diagnosis, a CT is used to assess resolution and to aid preoperative planning. Thoracoscopic resection has become the standard. With multilobar and bilateral disease, CT scans assist in planning lung-preserving resections. Bilateral and multilobar lesions are associated with the development of pleuropulmonary blastoma.[33]

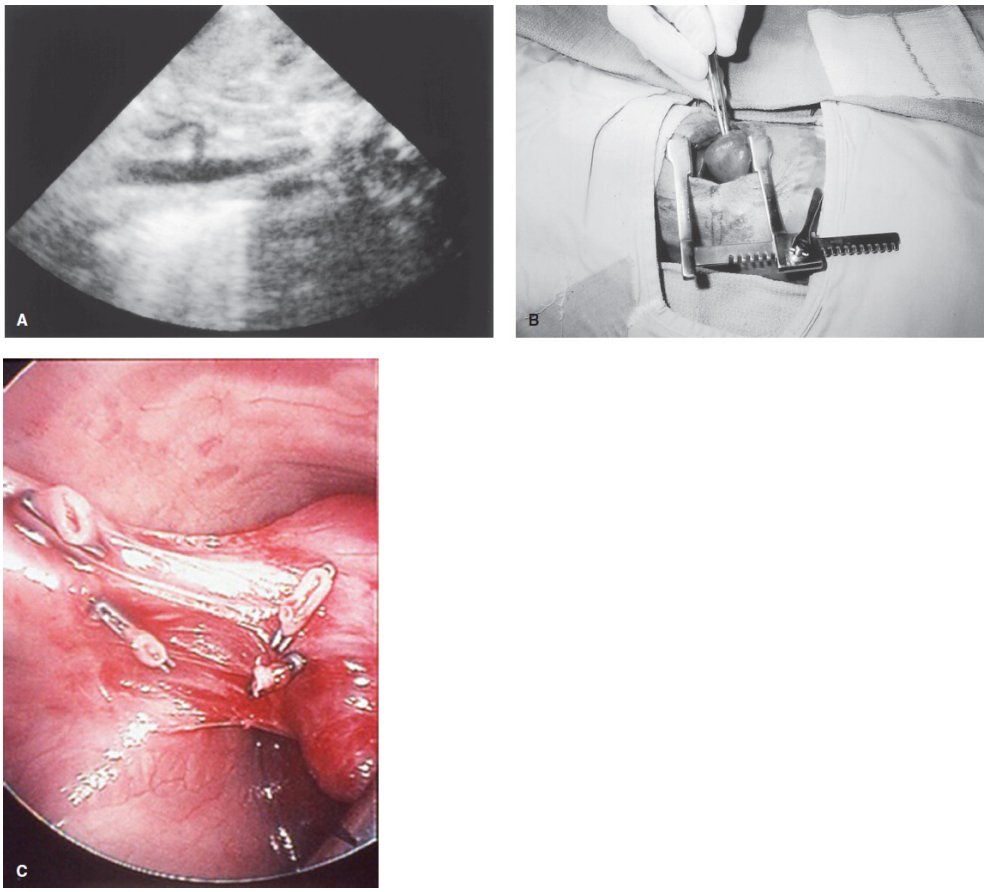


Figure 100.3 Pulmonary sequestration (PS). **A:** Sagittal ultrasound view of the aortic branch supplying an extralobar PS. **B:** Left-sided extralobar PS excised via a muscle-sparing thoracotomy. **C:** Intraoperative view of extralobar sequestration removed thoracoscopically. Note the main blood supply with clips.

Bronchogenic Cysts

BCs are uncommon anomalies arising from defective foregut development. They can be mediastinal or intrapulmonary and cause symptoms of cough as well as recurrent and chronic infection. These cysts appear as discrete masses and develop associated with the esophagus or large airways. They

are usually extrapulmonary and do not communicate with the normal tracheobronchial tree. Resection via thoracotomy or thoracoscopy is recommended due to the risk of bleeding, infection, or enlargement with compression of adjacent structures (Fig. 100.5).[33,43,44]

Congenital Lobar Overinflation

CLO (previously called congenital lobar emphysema) is caused by abnormal development or compression of a lobar bronchus resulting in retention of fluid during fetal lung development and subsequent air trapping and overinflation after birth. The cause ranges from a deficiency of bronchial cartilage to compression from an extrinsic mass. They usually involve the upper lobe of either lung and are rarely multilobar. A definitive cause is rarely identified. Lobar overinflation may present as worsening respiratory distress caused by enlargement of the overinflated segment with compression of the normal surrounding lung (Fig. 100.6). Symptomatic infants should undergo complete resection of the lobe. Care must be taken at resection as positive-pressure ventilation may worsen symptoms and require immediate thoracotomy. With relatively asymptomatic patients, symptoms may improve and surgery avoided.[33,34,45]

Diagnosis

Due to the routine use of prenatal ultrasound, many cystic lesions of the lung are now detected and followed prior to birth.[33–35,46–48] Patients with these lesions may be asymptomatic in the perinatal period. Standard chest radiographs remain the standard for diagnosis and follow-up. Rapid thoracic CT scanning with contrast provides definitive mapping of the lesions including demonstration of aberrant vessels. Contrast esophagograms are indicated for children with dysphagia and suspicion of connection with the GI tract. In lesions with suspected aberrant blood supply, MRI angiography can be helpful if the CT is not definitive.

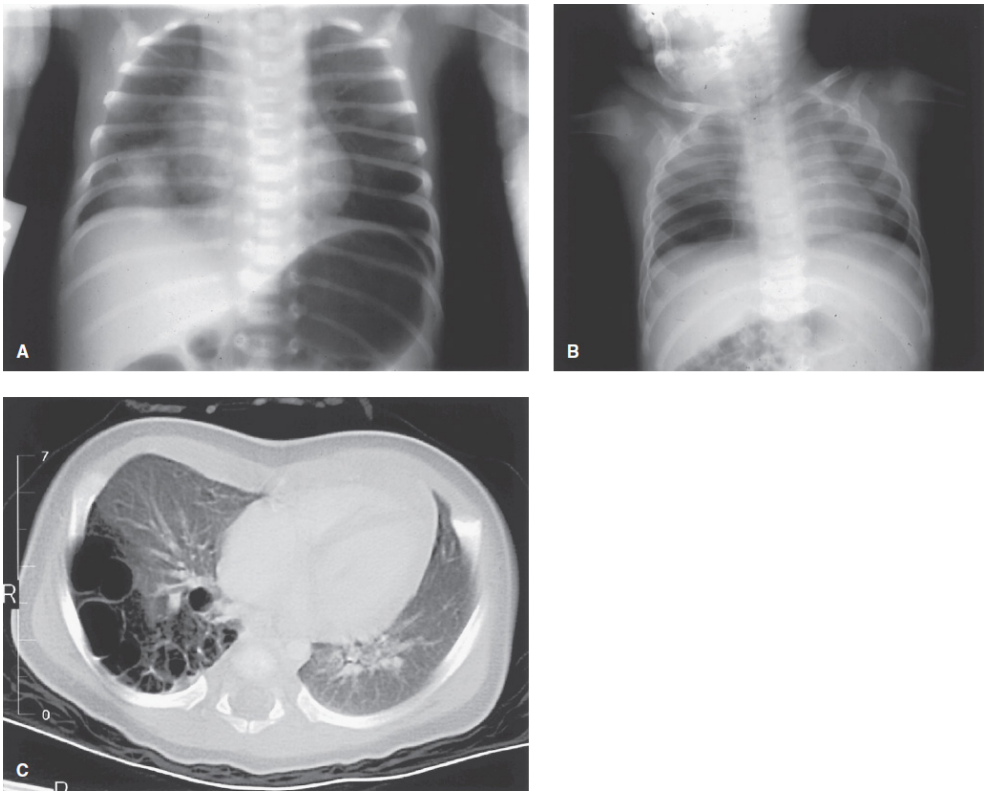


Figure 100.4 Congenital cystic adenomatoid malformation (CCAM). **A:** Newborn chest x-ray of a patient with prenatal diagnosis of CCAM. Note that immediately after birth, the mass is fluid filled and appears as a density in the right hemithorax. **B:** Chest x-ray of the same child at 5 months of age prior to surgical excision. Note the air-filled cystic appearance of CCAM. **C:** Transverse thoracic computerized tomographic view of CCAM.

Cysts of the Mediastinum

5 Benign cysts of the mediastinum are relatively common in the pediatric population. Most of these are relatively asymptomatic but surgery is usually recommended due to the possibility of enlargement with symptoms related to compression, hemorrhage, or infection. The symptoms which occur include cough, chest pain, stridor, hemoptysis, or dysphagia. The common lesions include thymic cysts, enterogenous cysts, lymphatic malformations (cystic hygromas), and pericardial cysts.

Thymic Cysts

Thymic cysts present in the neck and mediastinum and are usually unilocular but may be multilocular. They are most commonly seen in the anterosuperior mediastinum. They are benign lesions with presence of cholesterol granulomas. Symptoms may arise from rapid expansion due to infection. Resection is recommended.[47,48]

Enteric Duplication Cysts/Enterogenous Cysts

Enteric duplication cysts are usually located in the posterior mediastinum with microscopic evidence of double-layer smooth muscle and esophageal or gastric mucosa. They are from the same spectrum as bronchopulmonary cysts. These may communicate with the stomach or esophagus and may transverse the diaphragm. The cysts may also extend into the spinal canal.[47,48] The lesions may have gastric mucosa leading to bleeding. Other symptoms may include airway compression or dysphagia (Fig. 100.7). Resection is indicated for all symptomatic lesions and is favored for asymptomatic lesions.

Lymphatic Malformations

Lymphatic malformations (cystic hygromas) are unilocular or multilocular cysts which are thin walled and derived from failure of adequate drainage of embryonic lymph sacs. These may occur in the head, neck, and mediastinum. The lesions insinuate around great vessels and nerves in the superior mediastinum. The incidence is 1 in 6,000 live births. Symptoms if present are related to enlargement (frequently due to hemorrhage) or infection. Treatment options include resection and intralesional sclerotherapy. Immunomodulating drugs such as sirolimus may have a role in some cases.[49] The most frequent complications are recurrence and accumulation of lymph in the resection bed.[46–48]

Pericardial Cysts

Pericardial cysts are asymptomatic usually found incidentally on chest radiograph. The cysts are found in the cardiophrenic sulcus as a discrete mass. They are thin walled with a flat mesothelial lining and contain clear fluid. Resection can be performed with thoracotomy or thoracoscopy.[46,48]

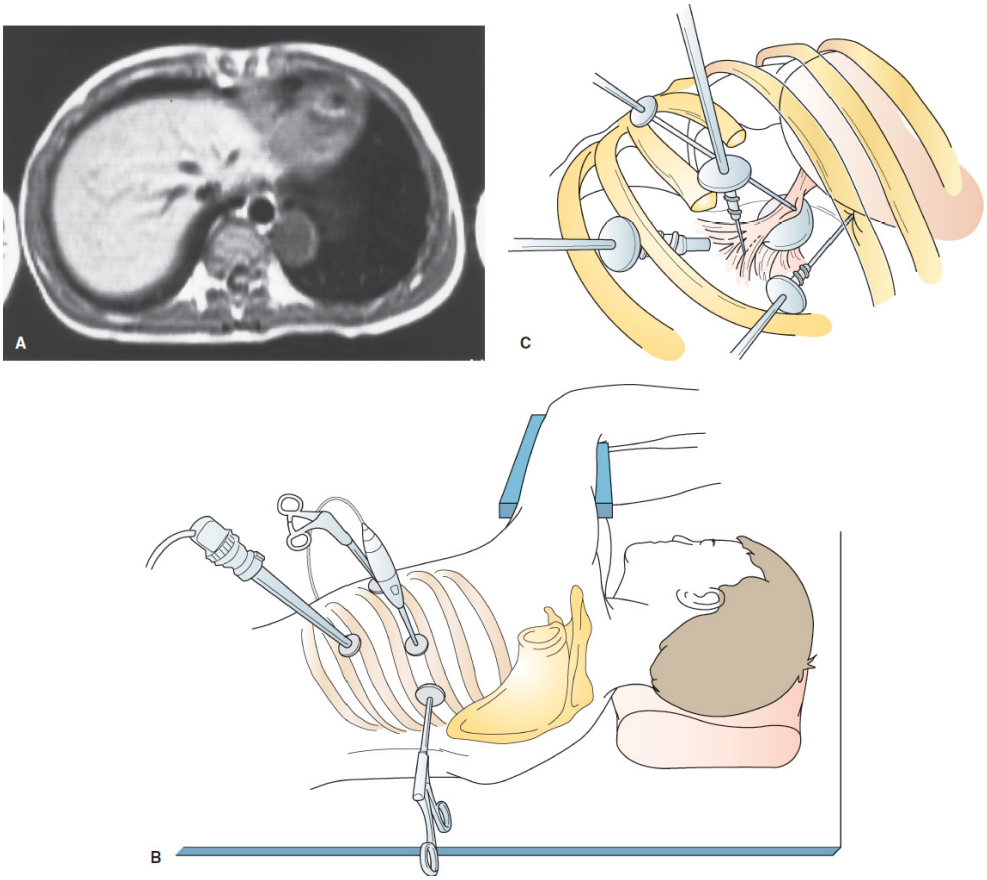


Figure 100.5 Bronchogenic cyst (BC). **A:** Transverse thoracic computerized tomographic view of a BC located in the inferior pulmonary ligament. **B:** Illustrative representation of thoracoscopic instrumentation for excision of a BC. **C:** Operative detail.

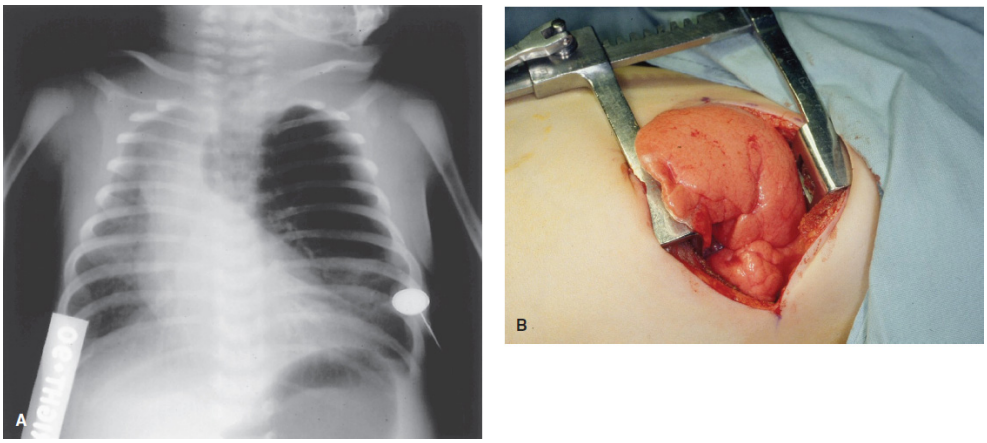


Figure 100.6 Congenital lobar overinflation. **A:** Chest radiograph demonstrating overinflation of the left upper lobe in an infant. Note the mediastinal shift. **B:** Operative photograph demonstrating an overexpanded left upper lobe decompressing through the incision.

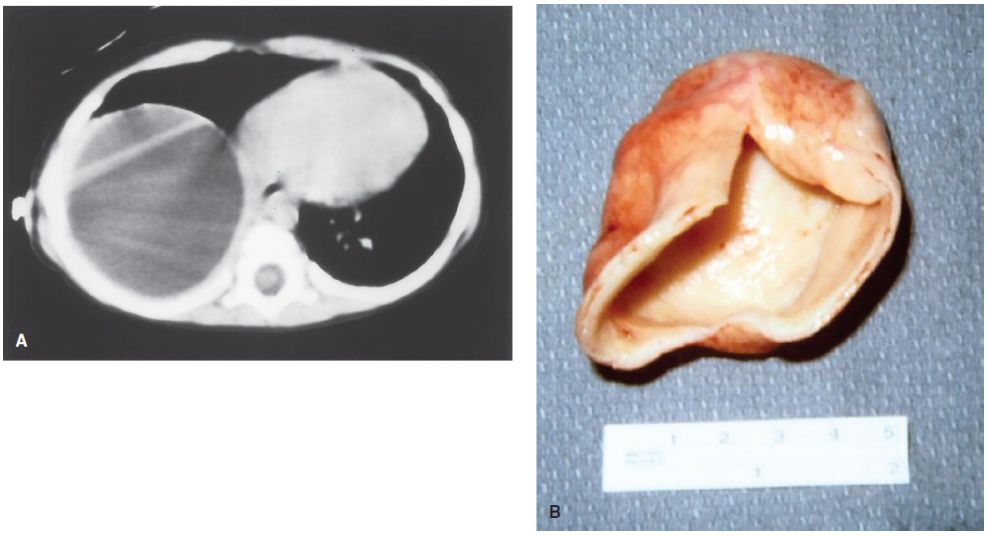


Figure 100.7 Enterogenous cyst. This represents another abnormality in the spectrum of bronchopulmonary foregut malformations. **A:** Computerized tomography demonstrating a large mass occupying the right hemithorax. **B:** Surgical specimen.

THORACIC TUMORS IN CHILDREN

6 Thoracic tumors are rare in children and diagnostic evaluation must include evaluation for both primary and metastatic conditions. Tumors may occur in the lung or the mediastinum.[50] Primary lung neoplasms in children are extremely rare.[50,51] Metastatic lung lesions are more common in the

pediatric population.[50,51] Mediastinal tumors reflect the nature of the section of the mediastinum in which they arise. Diagnostic evaluation begins with routine radiographs with CT scans and MRIs for further evaluation.[50–52]

Metastatic Lung Tumors

7 Resection of metastases in the pediatric population has been proven to be beneficial for pediatric cancers. Eradication of the primary tumor and absence of other metastases are necessary for improvement in survival.[58] Resection is considered most frequently for osteogenic sarcoma, soft tissue sarcoma, and Wilms tumor.[53,54]

Osteogenic Sarcoma

There is good evidence that resection of metastases in osteogenic sarcoma improves survival if a complete resection can be performed. The factors which improve survival are ipsilateral involvement, smaller tumor size, and longer disease-free survival between diagnosis and occurrence of metastasis.[55,56] Metastases which are more peripheral have a better outcome compared with centrally located metastases.[55,56] In addition to metastectomy, chemotherapy is required for elimination of micrometastatic disease. Metastases become calcified and therefore are palpable aiding with resection. There are some data that the outcomes are comparable between initial resection of metastases and resection of a second recurrence.[55,56] Improved survival is seen with tumor necrosis greater than 98% and disease-free interval of greater than 1 year. Thoracoscopy is inferior to thoracotomy since CT scans underestimate the number of lesions which can be directly palpated at thoracotomy.[55,56] Bilateral lesions can be identified even when CT scans demonstrate only unilateral lesions leading some authors to recommend prophylactic contralateral thoracotomy.[57]

Soft Tissue Sarcomas

Nonrhabdomyosarcomas such as synovial sarcoma respond poorly to chemotherapy and radiation therapy. In these tumors, complete resection of pulmonary metastases, but not debulking, improves survival.[58–61] Lung

metastasis in rhabdomyosarcoma responded to chemotherapeutic regimens but local treatment of the metastases did not improve survival.[60] Ewing sarcoma has a high rate of pulmonary metastases which have traditionally been treated with radiation therapy. More recent data suggest that metastectomy after irradiation leads to improved survival.[61] Delayed surgery after neoadjuvant therapy with resection of the chest wall lesion leads to decreased extent of excision and a higher rate of negative margins in tumors less than 8 cm.[61]

Wilms Tumor

Pulmonary metastectomy in Wilms tumor is only indicated for persistent lesions after chemotherapy and radiation therapy.[62] Thoracoscopy with resection of lesions is indicated for diagnostic purposes.[63]

Primary Lung Tumors

Pediatric primary tumors are rare (Table 100.1). The majority of primary neoplasms are malignant but benign lesions also have significant morbidity due to location of the lesions. Operative exploration with total resection of all involved tissues is recommended.[64]

Bronchial Adenomas

Bronchial adenomas are the most common of the malignant lung lesions (40%) in the pediatric population and include several different histologies including carcinoid tumor (85%), mucoepidermoid carcinoma (10%), and adenoid cystic carcinoma (5%). Cough, pneumonitis, fever, respiratory distress, and hemoptysis are the most common presenting symptoms. Delay in diagnosis is common due to the nonspecific symptomatology. The disease is diagnosed with chest radiograph followed by CT scan. Bronchoscopy is required for diagnosis and biopsy can be performed but there is a high risk of hemorrhage. Treatment is by surgical resection which can include lobectomy, bilobectomy, pneumonectomy, or sleeve resection with regional lymphadenectomy. Intraoperative frozen section is useful to assure complete resection and to limit lung resection. Endobronchial cryoablation may reduce

tumor size, permitting less extensive resection. Carcinoid syndrome is rare and a sign of extrapulmonary disease.[65]

Table 100.1 Primary Pulmonary Neoplasms

Type of Tumor	CT Findings
Benign	
Inflammatory myofibroblastic tumor	Well-defined solitary masses, peripheral and lower lobe, amorphous or dystrophic calcification
Pulmonary hamartoma	Well-circumcised, peripheral, intralesion fat and calcifications
Primary sclerosing hemangioma	Well-defined smooth round or oval enhancing mass adjacent to pleura
Subglottic hemangioma	Mass in subglottic trachea with early intense contrast enhancement
Recurrent respiratory papillomatosis	Numerous nodular lesions within the airway
Malignant	
Pleuropulmonary blastoma	Varied appearance, peripherally located, often multiple lobes, usually right
Adenocarcinoma	Solitary nodule to complete opacification of lung, ground glass to solid
Kaposi sarcoma	Bilateral perihilar opacities and large pleural effusions
Carcinoid and other neurendocrine	Well-defined lobulated endobronchial mass with marked enhancement, calcification 30%
Mucoepidermoid carcinoma	Central mass or endobronchial nodule, calcification 50%

Bronchogenic Carcinoma

Bronchogenic carcinoma is the second most common malignant lung tumor in children. Bronchogenic carcinoma consists of adenocarcinoma and undifferentiated carcinomas in the pediatric population. These tumors have been associated with CPAMs but have been reported in normal lung as well.[56,70] Human papilloma virus has been associated with the squamous cell variant. Resection with ipsilateral lymphadenectomy is the treatment of choice. Prognosis for bronchogenic carcinoma is poor as the presentation tends to be with advanced stages. Symptoms are related to metastases with bone pain or tumor burden with weight loss.[52,64]

Pleuropulmonary Blastoma

Pleuropulmonary blastoma is the third most frequent lung tumor in children and is most common in children under 4 years of age.[52,66,67] The lesion consists of mesenchymal elements and embryonal stroma without epithelial neoplasia. The tumor is known to be part of the spectrum of tumors related to the mutation of the DICER1 gene.[68] The tumor usually presents peripherally. These tumors are associated with CPAMs. There are three types: type I consisting of multilocular cysts, type II consisting of a combination of cystic and solid components, and type III having proliferating mesenchyme without cysts.[66,67] Treatment is with resection and adjuvant chemotherapy. Survival in type I has been reported at 91% while type II/III have survivals of 43%.[66,67] A Pleuropulmonary blastoma registry has expanded understanding of this tumor.[67]

Other Malignant Tumors

Sarcomas, including fibrosarcoma, rhabdomyosarcoma, and leiomyosarcoma, are the next most common primary malignant lung neoplasm in children. These have been reported to arise in documented cystic disease.[50,52,69] Inflammatory pseudotumor is considered to be the most common “benign” tumor in children. The tumor is a myofibroblastic spindle cell soft tissue tumor with infiltrative plasma cells, lymphocytes, and eosinophils. Recently these have been classified as intermediary lesions with

a molecular rearrangement involving the tyrosine kinase receptor anaplastic lymphoma kinase. Symptoms are nonspecific such as fever, chest pain, cough, and recurrent pneumonias.[50,52,69] They may present as an endobronchial lesion but are more often peripherally located. The lesion may invade local structures and be aggressive locally and may recur locally but spontaneous regression has been reported. Complete resection is recommended as no adjuvant regimen has gained widespread acceptance. Nonsteroidal anti-inflammatory agents have been utilized with some success (Fig. 100.8).

Hamartoma

Hamartomas are lung nodules composed of cartilage and gland-like formations in an irregular and haphazard orientation. They grow slowly and are the most common benign lesion in adults but the second most common in children.[50,53,69] Radiographically, they have a "popcorn" calcification in 10% to 25% of cases. The majority are located in the periphery of the lung. Conservative surgical resection is recommended. These may be associated with gastric smooth muscle tumors and extra-adrenal paragangliomas (Carney triad) in adolescent females; and in this age group, a workup should be performed to exclude these diagnoses.

Mediastinal Tumors

Mediastinal tumors in the pediatric population can be benign (63%) or malignant (37%).[51,71,72] Neurogenic tumors are the most common, arising in the posterior mediastinum from the sympathetic ganglia, intercostal nerves, and paraganglia cells.[51,70–72] They may grow very large before detection and may manifest with Horner syndrome or opsoclonus–myoclonus syndrome. Malignant neurogenic tumors include neuroblastoma and ganglioneuroblastoma. Benign tumors include ganglioneuroma, schwannoma, or neurofibroma.[51,70] Neuroblastoma originating in the mediastinum has a better prognosis than other sites. These tumors have more favorable biology and lower rates of N-myc amplification as well as improved rates of event-free and overall survival.[71] Diagnosis is by CT and MRI with MRI allowing improved assessment of extension into the spinal foramina.[51,70,71] Tumors

may be resected by a thoracoscopic approach or via thoracotomy (Fig. 100.9).[73,74]

Neurofibromas and schwannomas arise from intercostal nerves or sympathetic nerves. The schwannomas are encapsulated without nerve fibers within the tissue. Neurofibromas are unencapsulated, have nerve fibers running through the mass, and are common in patients with neurofibromatosis.[73] Isolated tumors may be removed but tumors associated with neurofibromatosis tend to extend over nerve sheaths precluding complete removal. These are associated with malignant degeneration.

Lymphomas arise in the anterior and middle mediastinum and are the most common anterior mediastinal mass in children.[51,70,72] They are usually inhomogeneous and resection is not required. Both Hodgkin and non–Hodgkin lymphoma arise in the mediastinum. Diagnostic workup involves biopsy for tissue diagnosis as the diagnosis often requires tissue subtyping.[75] Due to risk of airway compromise, the most accessible tissue, such as supraclavicular lymph nodes, should be biopsied and special care is required for biopsy of the mediastinum including partial upright positioning, spontaneous ventilation, availability of rigid bronchoscope, and avoidance of muscle relaxants. Risk of airway compromise is increased in patients with greater than 50% reduction in tracheal cross-sectional area, or those with dyspnea and orthopnea. Treatment is chemotherapy.

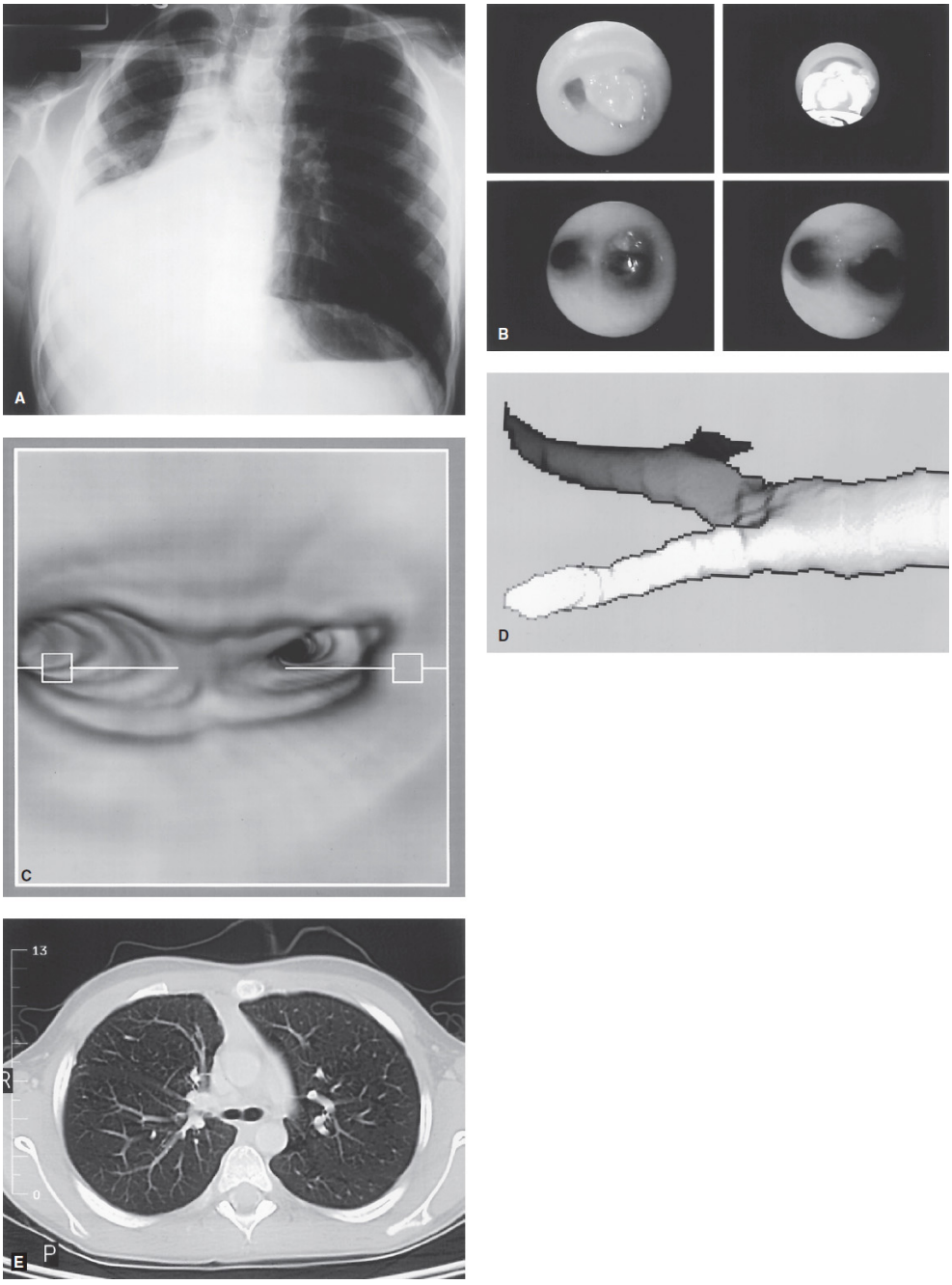
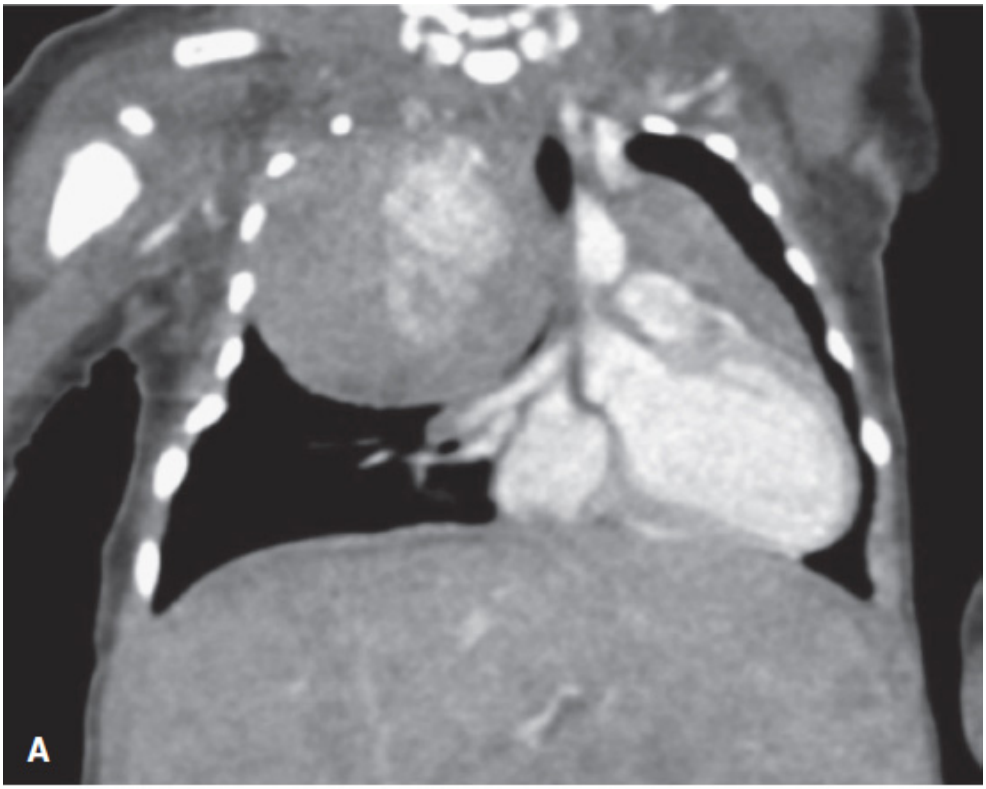


Figure 100.8 Lung neoplasm in an 8-year-old child: inflammatory pseudotumor. **A:** Presenting chest radiograph with right lung collapse. **B:** Biopsy of an obstructing endobronchial mass demonstrates inflammatory pseudotumor (inflammatory myofibroblastic tumor). **C:** Computerized tomographic "virtual bronchoscopy" image after initial biopsy demonstrates deformation of the right main stem bronchus and carina due to tumor infiltration. **D:** Computerized tomography reconstruction of the external appearance of airways demonstrating the deformation of the carina and right main stem bronchus. The child underwent excision of the right main stem bronchus and carina and tracheobronchial

reconstruction. **E:** Postoperative transverse thoracic computerized tomography at the level of the reconstruction of the carina.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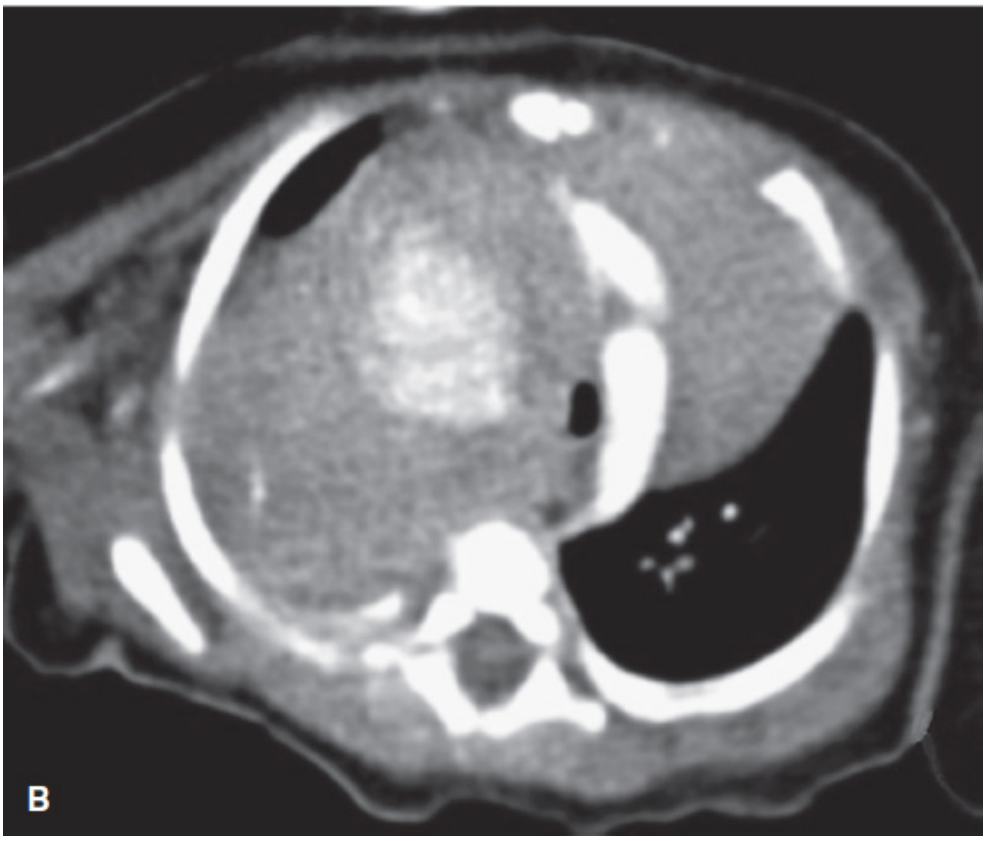
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Figure 100.9 **A:** Large neural tumor in coronal view CT scan with calcifications (neuroblastoma). **B:** Same mass on transverse view.

Teratomas are the most common mediastinal germ cell tumor and are composed of all three germinal cell layers.[51,70,72] They are typically benign, usually cystic and encapsulated. They frequently contain calcification on radiography (Fig. 100.10). Most are asymptomatic but symptoms can include stridor, tachypnea, and respiratory distress especially when lying supine.[70,72] The cysts frequently contain mature ectodermal elements such as hair, skin, and neuroglial elements and may contain bone, teeth, and fat. The tumors may be large and tend to displace rather than invade surrounding tissue.[51,72] Workup includes preoperative measurement of α-fetoprotein and β-HCG. Resection is the treatment of choice and confirms the diagnosis. Treatment of mature teratomas is resection. Immature teratomas which contain malignant elements are treated with chemotherapy and radiation in addition to surgery.

Other mediastinal tumors are very rare but often require surgical biopsy or extirpation. These include neurolemmoma, pheochromocytoma germ cell tumors, rhabdomyosarcomas, and thymic tumors.

Chest Wall Tumors

Ewing sarcoma, chondrosarcoma, and liposarcoma are malignant tumors which may arise from the chest wall. Local resection may require extensive chest wall excision and prosthetic reconstruction.[76] Primitive neurectodermal tumors are malignant small cell tumors carrying a poor prognosis. Improvement in survival is accomplished with multimodal therapy which includes chemotherapy, radiation, and surgery with aggressive management of pulmonary metastases.[76]

Respiratory Papillomatosis

Recurrent respiratory papillomatosis is caused by neoplastic proliferation associated with acquisition of papillomavirus during delivery. It is usually confined to the larynx and upper tracheal airway with spread in less than 1% of cases. Treatment is with laser ablation and may require multiple treatments. Prognosis is poor due to the recurrence of the disease.[50,65,69]

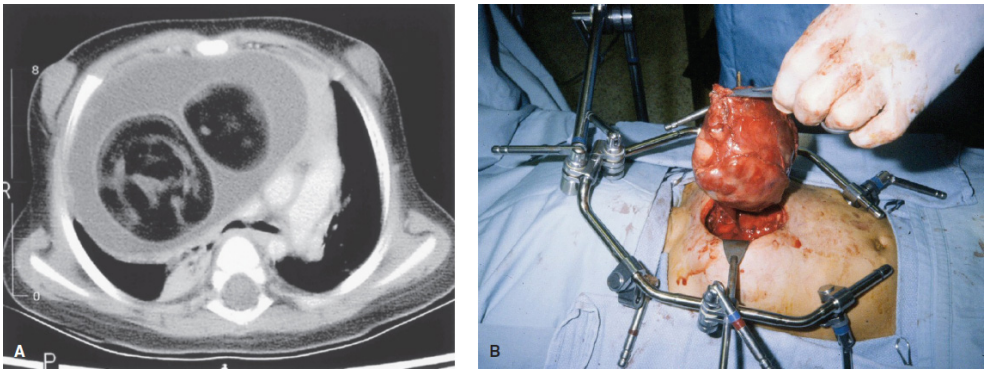

Figure 100.10 Mediastinal teratoma. **A:** Transverse thoracic computerized tomography of a large anterior mediastinal teratoma presenting with airway compression symptoms in a 9-month-old female. **B:** Tumor removal via a median sternotomy.

ESOPHAGEAL ATRESIA/TRACHEOESOPHAGEAL FISTULA

The first description of esophageal atresia was by Durston in 1670 who found a blind esophageal pouch in one pair of thoracopagus conjoined twins.[77] The first description of the classic proximal esophageal atresia with distal fistula was by Thomas Gibson in 1697. Initial attempts at repair or palliation were unsuccessful. Leven and Ladd reported survivors but only after staged reconstruction. The first successful primary repair was reported by Cameron Haight in 1941.[78,79] Outcomes have improved related to refinements in surgical technique and postoperative care.[77,80–84] In the modern era, survival is related to the degree of prematurity and the presence of cardiac disease.

Embryology

The development of the human respiratory system begins as a folding of the flat endodermal layer into the primitive gut tube. The respiratory system is derived from the foregut endoderm with the appearance of the laryngotracheal groove in the ventral floor just caudal to the level of the pharynx. The precise morphogenic events that follow are not well understood. The respiratory system may develop as a rapid outgrowth from

the original foregut tube. The fusion of the lateral foregut walls separating the trachea from the esophagus may also contribute.[85,86] TEF is caused by failure of tracheal growth and failure of the active separation of the trachea and esophagus. Sonic hedgehog patterning gene has been implicated in the development of esophageal atresia/TEF based on adriamycin-induced malformations in rats.

Classification

8 Descriptive terminology is used to indicate the anatomic configuration of a patient with esophageal atresia. The most common type of lesion is a proximal atresia with a distal TEF which accounts for 76% to 85% of all cases in recent series.[80–84] Esophageal atresia without fistula occurs in 3% to 17% (referred to as "pure esophageal atresia") and TEF without esophageal atresia in 4% to 6% ("H-type fistula"). Proximal fistula and both proximal and distal fistula occur in approximately 1% of cases each. Initially alphabetic classification schemes were devised and the most common variety of esophageal atresia/TEF is still commonly referred to as "Gross type C" (Fig. 100.11).

Incidence and Epidemiology

Esophageal atresia is relatively common occurring in 1:2,500 to 1:4,500 live births. There is a slight preponderance of males.[77,84,87] Chromosomal anomalies, congenital heart disease, and other anomalies are more common than expected.

Clinical Findings, Diagnosis, and Pathophysiology

Diagnosis of esophageal atresia is suspected with a history of choking with feeding and is confirmed by the inability to pass an NG tube into the stomach. Excessive drooling may be noted. Maternal polyhydramnios should raise suspicion for the diagnosis. If not diagnosed early, respiratory distress and aspiration may occur. Confirmation of the diagnosis is with radiograph

identifying a tube in a proximal pouch in most cases. Occasionally injection of air to outline the pouch will be necessary for confirmation. Presence of a scaphoid abdomen with no intragastric air on radiograph taken several hours after birth confirms the diagnosis of pure esophageal atresia.[88,89] Reflux of gastric contents through the fistula can enter the lungs which becomes more problematic in the face of respiratory compromise and is less of an issue with spontaneous ventilation.

Associated Anomalies

Associated anomalies are present in approximately one-half of the neonates with esophageal atresia. The most common associated anomalies are cardiovascular defects which occur in 17% to 50% of infants. Genitourinary, other gastrointestinal, skeletal neurologic, and craniofacial defects are also found. The occurrence of *v*ertebral anomalies, *a*norectal malformations, *c*ardiac, *t*racheo*e*sophageal *r*enal, and *l*imb (usually radial) anomalies is known as the VACTERL association. Two or more of the defects must occur to be denoted as VACTERL, occurring in 10% to 21% of cases.

Preoperative Management

Attempts at feeding are discontinued and sump tube is placed in the upper esophageal pouch. Precautions such as head-up position are advocated to decrease reflux via the fistula into the lung. Intubation is avoided as it increases the risk of reflux into the lungs via the fistula. Ventilatory support is more likely to be needed for low birth weight or prematurity. Preoperative antibiotics are given in the majority of patients.[82] Emergent bedside gastric decompression may be necessary before definitive surgery. If gastrostomy decompression does not improve ventilation, emergency operative ligation or placing an occluding distal esophageal balloon may allow for ventilation.[82–84,90]

In addition to chest radiograph, echocardiography is performed to determine the side of the aortic arch as well as to evaluate for major cardiac anomalies. In patients with a right-sided arch, the operative approach may be modified.[90] Radiographs of the spine are also commonly performed. The genitourinary system is evaluated by ultrasound.

In an attempt to stratify infants into groups to determine outcomes, Waterston developed criteria based on birth weight, pneumonia, and associated anomalies. With improvements in neonatal critical care, the criteria have been revised to with the current Spitz classification which uses a 1,500 g weight as the cutoff, with or without major cardiac disease. Currently survival for greater than 1,500 g infants without cardiac disease is approximately 97%, survival for either cardiac disease or less than 1,500 g approaches 82% and for both birth weight less than 1,500 g and cardiac anomaly survival is approximately 50%.[81–84]

Surgical Technique

In most patients, gastrostomy is unnecessary. A right extrapleural posterolateral or auscultatory triangle thoracotomy is used (Fig. 100.12). There is no need to divide the serratus or the latissimus muscles. The extrapleural plane is established at the fourth intercostal space and developed sufficiently to allow control of the fistula and mobilization of the proximal pouch. The fistula is divided and closed. Anastomosis is performed in a single layer with an absorbable suture. If needed there are various techniques for elongation and the esophagus may be mobilized both proximally and distally. Myotomies on the upper pouch, either circular or spiral and flap tubularization have been described. In situ stretching of both the proximal and distal esophagus facilitates repair of longer gaps. A transesophageal tube may increase stricture. A postoperative esophagram is performed 5 to 10 days after repair.[82,83,90–95]

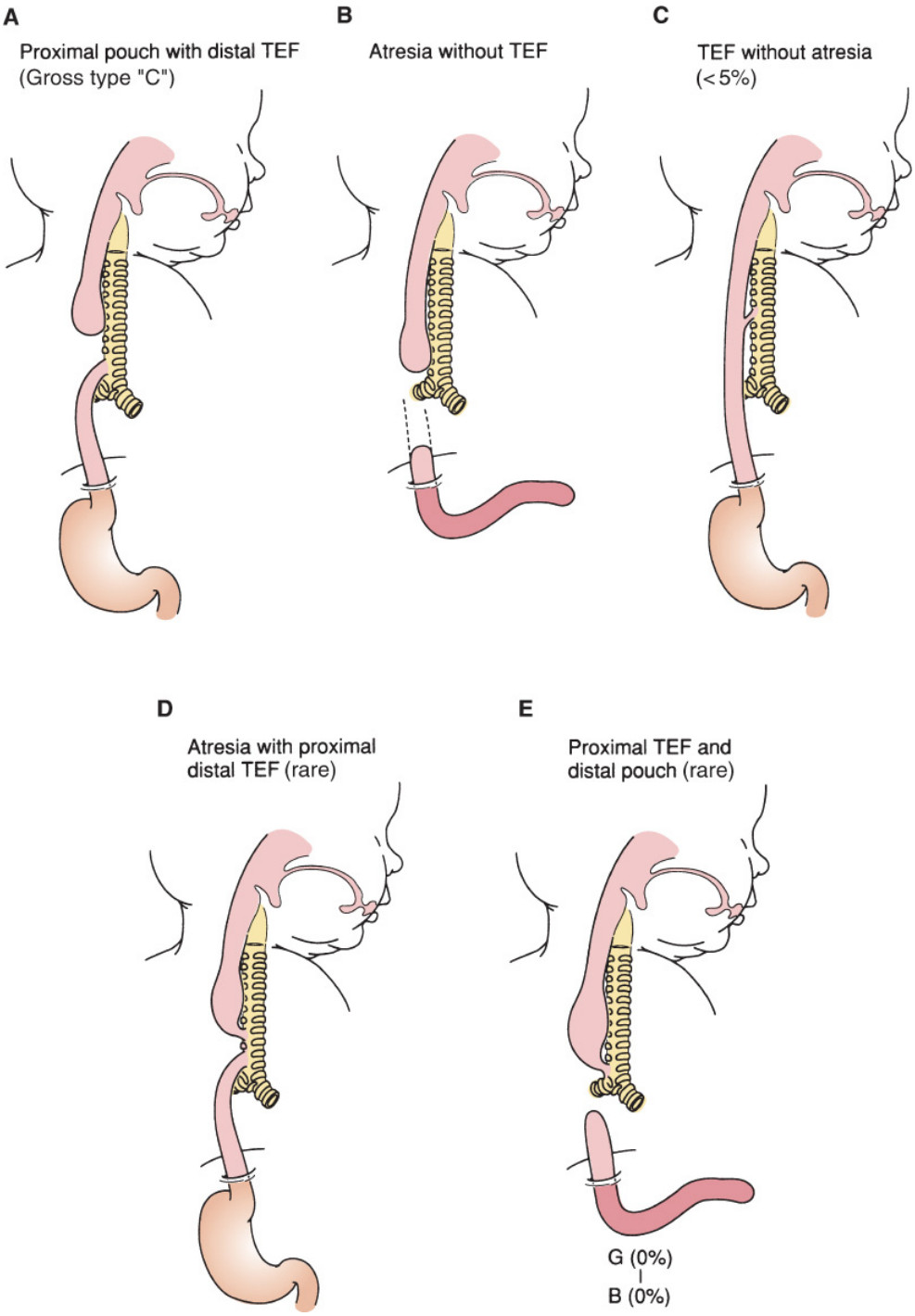

Figure 100.11 The anatomy of the variants of esophageal atresia and tracheoesophageal fistula (TEF). **A:** Proximal pouch with distal TEF (most common type occurring in 85% of patients; gross type "C"). **B:** Esophageal atresia without TEF (5%). **C:** TEF without esophageal atresia (<5%). **D:** Esophageal atresia with proximal and distal TEF (rare). **E:** Proximal TEF and distal pouch (rare).

High-risk infants who cannot safely undergo surgical correction of their esophageal abnormality may be treated with delayed repair. A decompressive gastrostomy, proximal pouch suctioning, and parenteral nutrition are used until the infant is ready for operation. Severe respiratory failure (usually from prematurity) and structural heart disease are the most common reasons to delay esophageal surgery. A staged repair that employs gastrostomy, surgical division of the TEF, followed by esophageal anastomosis as a second thoracic operation is rarely used except as a lifesaving approach.

In the case of pure esophageal atresia without fistula, a prolonged period before definitive repair may be used to improve the likelihood of completing a primary repair. A feeding gastrostomy is the initial operative management and may be technically challenging due to microgastria. Using bouginage the ends of the esophagus are elongated and once the ends are close, a thoracotomy is performed to repair the esophagus (Fig. 100.13). Other methods of elongation have been described with staged repair using traction sutures in the upper and lower esophagus (Fig. 100.14). Daily tensioning results in lengthening of the esophagus over a few weeks.[94] Alternatively, extrathoracic elongation may be utilized.[92]

Esophageal replacement is reserved for the worst cases of long-gap atresia, pure atresia, or failed initial operations. The esophagus may be replaced later using stomach, gastric tube, or colon. These cases may be temporized with a cervical esophagostomy ("spit fistula") and sham feeds. Esophageal replacement for esophageal atresia is rarely if ever required.

TEF without esophageal atresia is referred to as H-type or N-type fistula. The orientation is such that the opening into the trachea is always proximal to the esophageal entry site. Repair is performed via a cervical approach after bronchoscopically stenting the fistula with a small catheter. The catheter aids in dissection and care must be taken to stay in the plane of the esophagus to avoid recurrent laryngeal nerve injury.

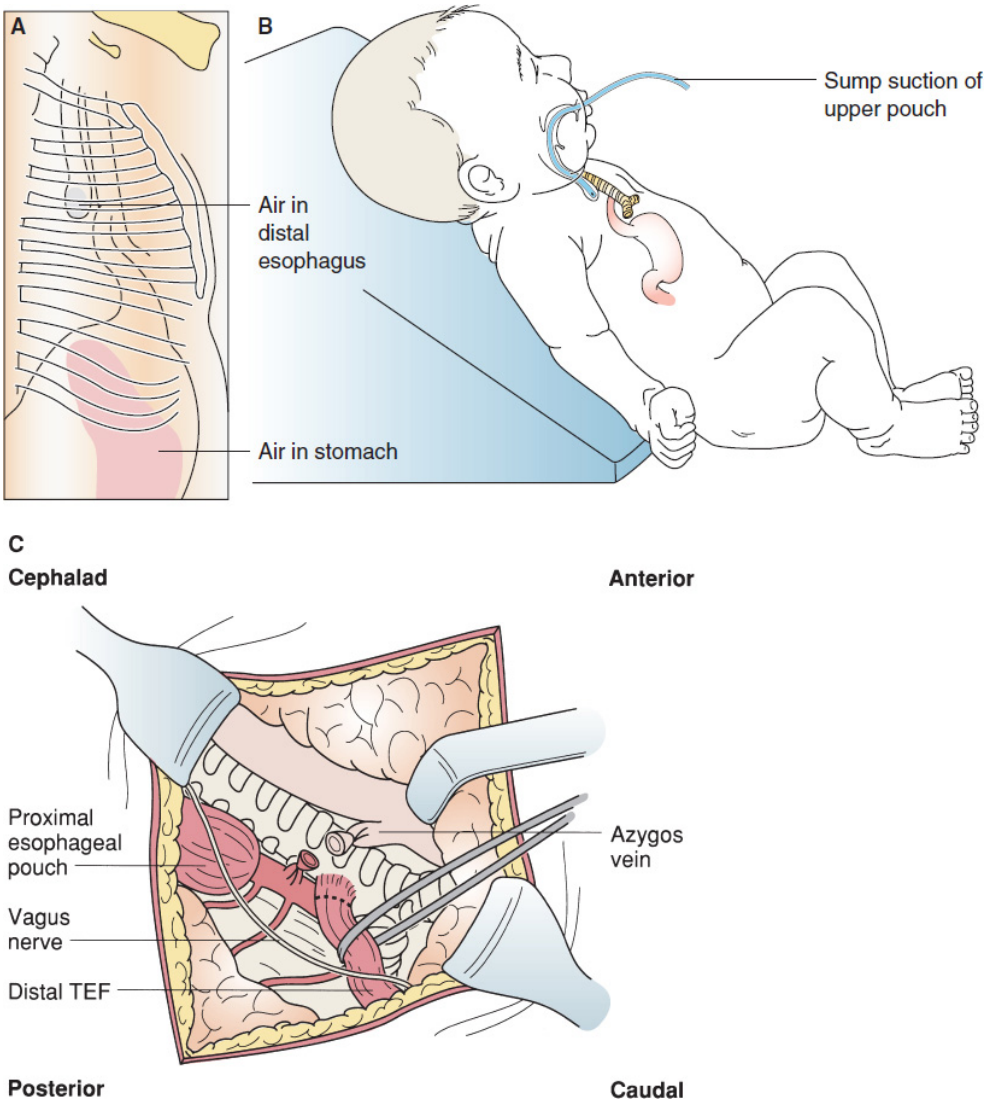

Figure 100.12 **A:** Schematic illustration of esophageal atresia with distal tracheoesophageal fistula. **B:** The initial management of this anomaly includes upright or prone posture, sump suction of the blind esophageal pouch. **C:** The right extrapleural operative approach. After division and closure of the fistula, primary esophagoesophagostomy is performed.

Thoracoscopic approaches to the repair of esophageal atresia have been described with results demonstrating equivalent outcomes to open repair.[93,94] Thoracoscopic techniques for esophageal lengthening in long-gap atresia have also been described.[95]

Results, Complications, and Outcomes

Technical mishaps may occur during the procedure when anatomy is misidentified or dissection is carried out improperly. Injury to the vagus nerves, recurrent laryngeal nerves, posterior trachea, and adjacent vessels must be avoided.

Anastomotic leak occurs in approximately 10% to 20% of cases and most may be treated nonoperatively. The presence of a leak prolongs hospitalization.[82–84,89] When detected, the retropleural tube is left in place, the infant is not fed, and antibiotics are administered. Repeat contrast radiographs are employed to document healing prior to initiation of oral feeds.

Esophageal stricture is seen in up to 40% of infants after repair. These usually respond to a few sessions of dilation performed in the operating room with endoscopic and fluoroscopic assistance as necessary to assure the safe traverse of dilators or placement of balloon dilators.[96] More recalcitrant strictures require more frequent dilation sessions, medical and/or surgical control of gastroesophageal reflux, and occasionally reoperation with stricture resection and reanastomosis.

Recurrent TEF is reported in up to 10% of patients. These may respond to endoscopic ablation, a construct placed into the fistula or may require operative division placing tissue between the esophagus and trachea to separate the suture lines.[96,97]

Gastroesophageal reflux is present in nearly all patients with esophageal atresia but is asymptomatic in many. When symptomatic, it may lead to respiratory symptoms and stricture formation. Medical management with thickened feeds, acid reduction, and prokinetics is the first line of therapy. Refractory reflux may require surgical control of reflux. Routine use of acid reduction medication is not recommended.[83]

Esophageal dysmotility is present in the majority or patients and may be responsible for dysphagia and recurrent respiratory problems.

Tracheomalacia occurs in approximately 10% of patients and may be diagnosed after the repair of esophageal atresia. On bronchoscopy, the trachea appears oval in shape rather than round and the anterior and posterior walls coapt during the respiratory cycle. Patients may develop tracheomalacia “fits” when agitated and the condition may deteriorate with complete inspiratory block and unconsciousness. Intubation and resuscitation may be required. The symptoms are completely relieved by intubation.

Patients with less severe symptoms may improve over time as the trachea grows. Severe symptoms require either tracheostomy or a tracheal suspension with an aortopexy under bronchoscopic guidance. It may be difficult to determine whether the symptoms are from gastroesophageal reflux or tracheomalacia and sometimes both an antireflux procedure and a tracheomalacia procedure may be required.[98,99]

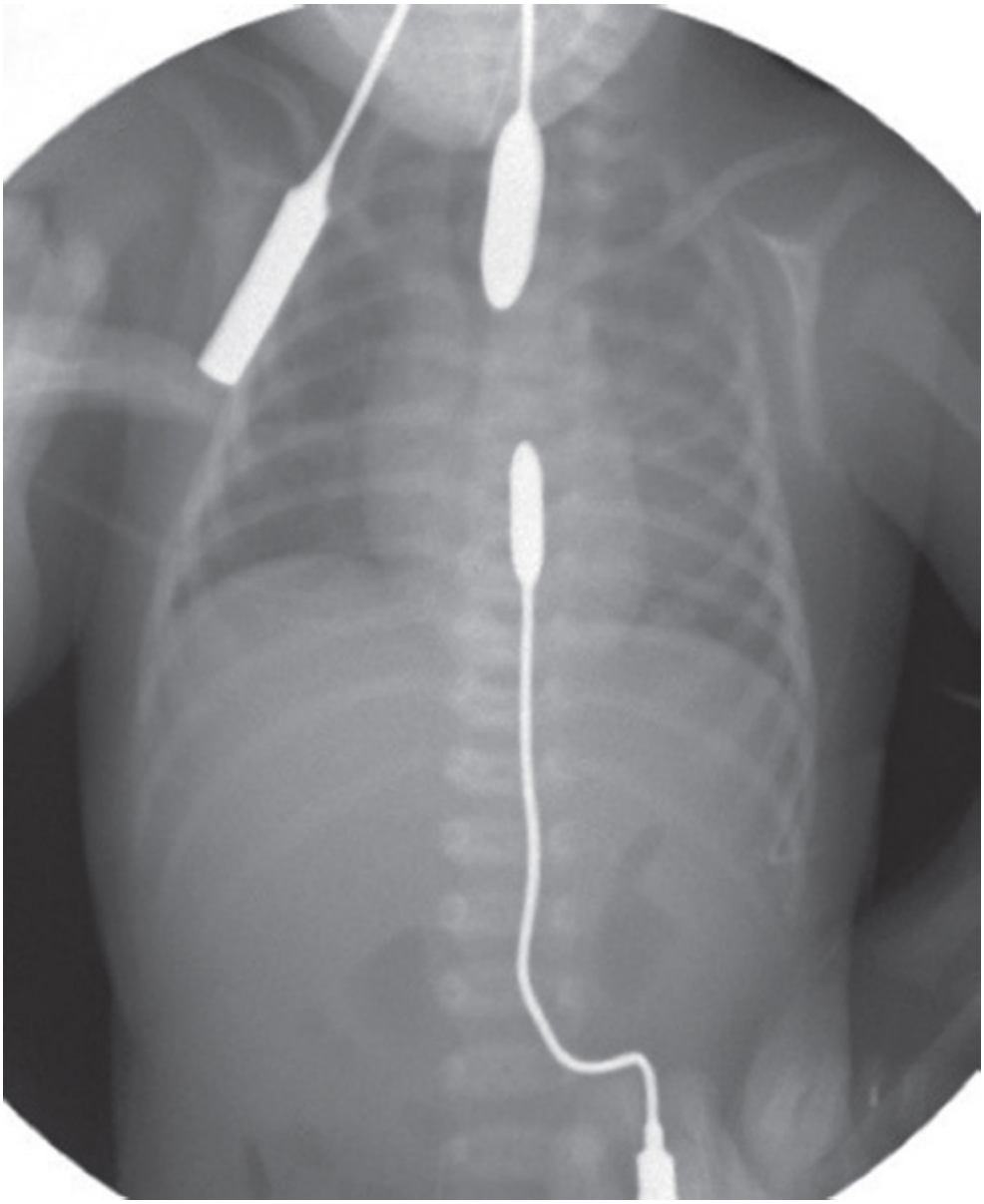

Figure 100.13 Patient with pure esophageal atresia treated initially with feeding gastrostomy, and proximal pouch stretching. This "gap-o-gram" demonstrates close approximation of a dilator in the proximal pouch and a probe placed in the distal esophagus via the gastrostomy. The child subsequently underwent primary repair of the esophagus.

Long-term results have improved and most children can look forward to normal existence. Although growth may be slow in the first 5 years of life, by 20 years of age less than one-third of the children have heights or weights below the 25th percentile.[99,100] Mortality remains high for infants with severe congenital heart defects and chromosomal anomalies. Late deaths may occur

related to respiratory disease (tracheomalacia, reactive airway disease, gastroesophageal reflux, and aspiration). Adult survivors of esophageal atresia repair have a normal quality of life with the exception of morbidity from esophageal, functional, and respiratory disorders.[100] The very long-term effects are unknown but Barrett esophagus and esophagitis have been reported.[101] The incidence is low and further studies are required to determine the need for long-term surveillance.

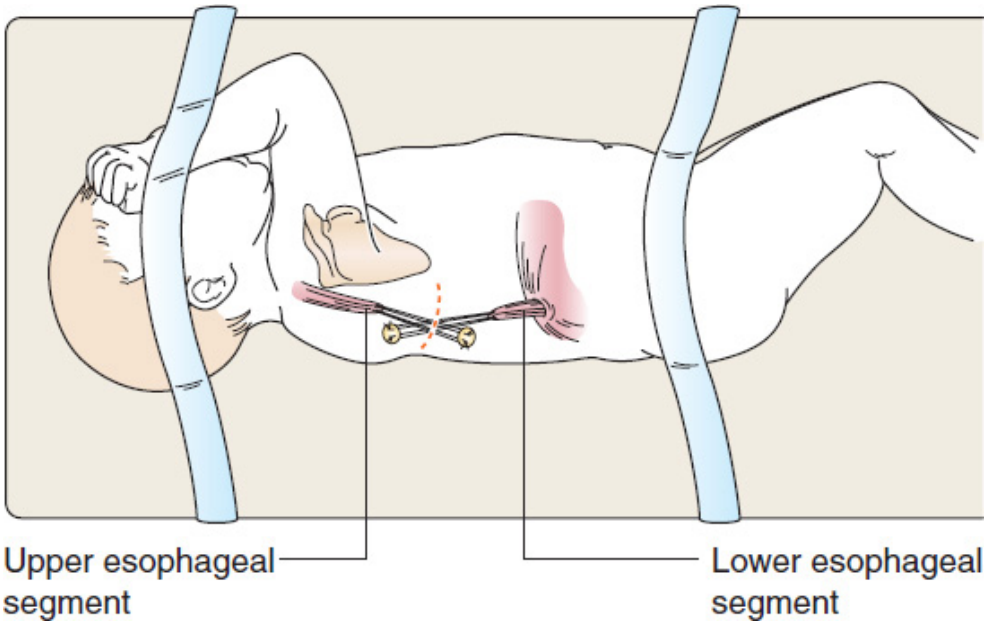

Figure 100.14 In patients with ultra-long-gap esophageal atresia, traction sutures are placed on the upper pouch and lower segment. Tension is increased daily until the segments lengthen, allowing primary repair.

OTHER CONGENITAL ANOMALIES OF THE TRACHEA AND ESOPHAGUS

Laryngotracheoesophageal Cleft and Tracheal Agenesis

Laryngotracheoesophageal clefts are rare anomalies resulting from the failure of normal separation of the esophagus and trachea. These are the most severe anomalies and the presence of the common aerodigestive channel plus the association of gastroesophageal reflux leads to aspiration with respiratory

damage and a high mortality rate. The lesions are classified by the length of the common channel. Type I clefts involve the supraglottic larynx. Type II defects extend beyond the carina to the cervical trachea. Type III clefts involve the entire trachea and type IV defects extend onto one or both bronchi. Type III and IV clefts are frequently associated with other anomalies such as esophageal atresia, microgastria, and congenital heart disease.

Type I clefts may be repaired via an endoscopic or translaryngeal approach and do not require tracheostomy. Type II clefts require cervical exposure either laterally or via the anterior wall of the larynx and trachea. The anterior approach provides good exposure and decreases the risk of damage to neurovascular structures. The approach to type III and IV defects is via a right thoracotomy and a right neck incision. However reports of midline exposure have been described. The common channel is divided and repaired with interrupted sutures with tracheostomy.[102] Oromotor function and chronic aspiration are problems and most children require gastrostomy and many require operative control of gastroesophageal reflux.

Tracheal agenesis (TA) is a rare and fatal congenital malformation that occurs in less than 1 in 50,000 live births. Approximately 150 cases have been reported with near universal lethality. At birth cyanosis, respiratory distress, and aphonia are noted. Survival requires the presence of an adequate TEF to permit lifesaving esophageal intubation. TA is classified into three anatomical variations, originally defined by Floyd.[103]

The etiology of this rare anomaly remains unknown. No genetic pattern has been implicated. However, associated congenital malformations are present in 90% of cases. All long-term survivors (older than 1 year of age) have undergone airway reconstruction with external scaffolding and use of the esophagus to create an airway. ("trachealization" of the esophagus). Survival is rare.[104] We have recently **successfully created a "neotrachea" in a patient with Type I TA using a 3D-printed scaffold and the esophagus. Colonic esophageal replacement has been performed with 3-year survival.**[105]

Congenital Esophageal Stenosis

Congenital esophageal stenosis is a rare condition. The stenosis is frequently within 2 cm of the gastroesophageal junction. The true incidence is unknown

but is reported to be 1:25,000 to 1:50,000 live births. The narrowing of the lumen is present at birth but may not present with clinical symptoms immediately. There are three histologic subtypes: ectopic tracheobronchial remnants, segmental fibromuscular hypertrophy, and a membranous diaphragm or stenosis. Esophageal stenosis has been associated with esophageal atresia. Symptoms may only occur when solids are started. Diagnosis is by esophagograms. CT scans may confirm the diagnosis. Esophagoscopy confirms the diagnosis. Initial management is esophageal dilation. If the stenosis is due to respiratory tract remnants, need for surgery is more common. Surgery consists of resection of the stenotic segment with end-to-end anastomosis.[106]

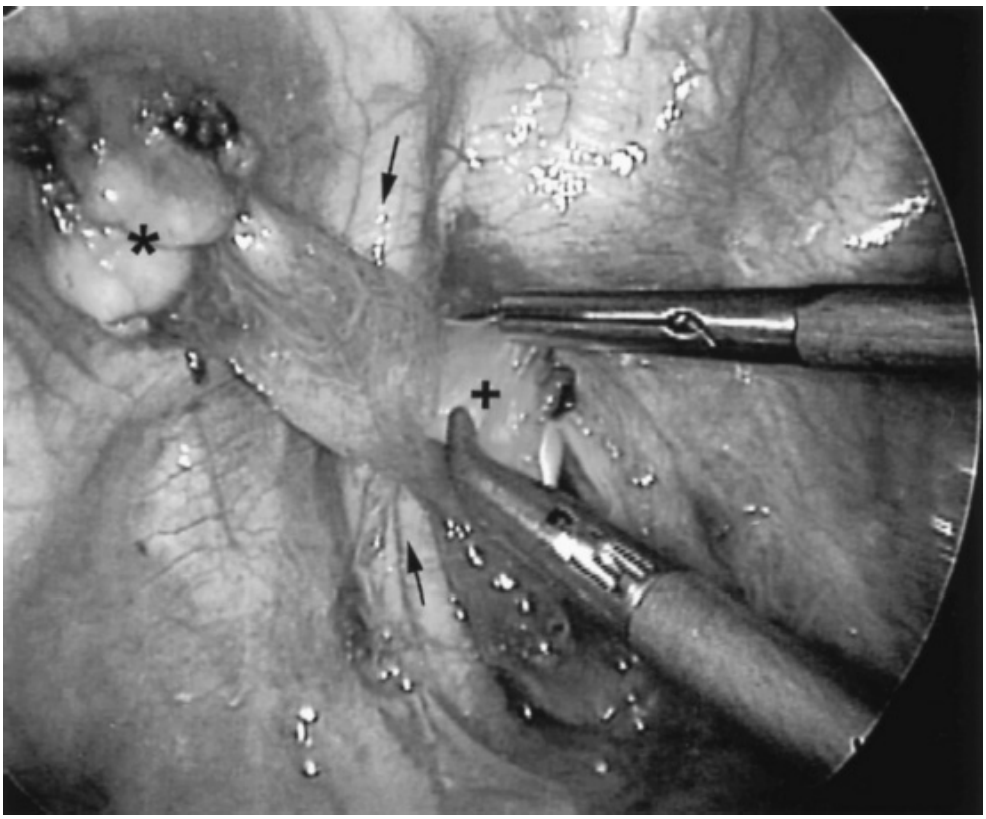

Figure 100.15 Thoracoscopic excision of an esophageal duplication cyst in a patient presenting with dysphagia. Video endoscopic view of the left superior hemithorax. (+) indicates site of original esophageal duplication cyst. Light from the intraesophageal endoscope can be seen. *Arrows* demonstrate the subclavian artery. The mass (*) is nearly excised.

Esophageal Duplication

Esophageal duplications are found in the posterior mediastinum and are covered by a muscular wall. Most are attached to the wall of the esophagus. Approximately 10% communicate with the lumen of the esophagus. Although many are asymptomatic, they may present with airway or esophageal compression. In older children and adults, the presentation may be dysphagia, retrosternal pain, and epigastric discomfort. There are reports of bleeding from acid dyspepsia. Excision is recommended and is usually accomplished by thoracoscopy (Fig. 100.15).[46,47] Neurenteric cysts are anatomically similar but communicate with the spinal canal.

Vascular Rings

Vascular rings are a set of congenital defects in which the trachea or esophagus are encircled and compressed by vascular structures associated with the development of the aorta and great vessels. These account for approximately 1% of all congenital cardiovascular anomalies. Vascular rings may lead to tracheal narrowing with associated tracheomalacia. Symptoms may include stridor, respiratory distress, or dysphagia. Barium swallow may be suggestive of the lesion. CT scan and MRI are utilized to demonstrate the anomaly. Echocardiography is performed to rule out structural cardiac anomalies. Bronchoscopy may also be useful to determine the degree of tracheal narrowing. The most common type of abnormality is the double aortic arch resulting from persistence of both the right and left embryologic aortic arches. The ascending aorta bifurcates, surrounding the trachea and esophagus. Other causes of complete or incomplete rings include pulmonary artery sling and aberrant right subclavian artery. When the vascular ring is symptomatic, the patient should be treated by the appropriate division of the ring and lysis of the fibrous bands surrounding the trachea and esophagus.[107]

Congenital Tracheal Stenosis

Congenital tracheal stenosis represents a spectrum of obstructive lesions most commonly treated with operative repair. The etiologies include complete tracheal rings, compression from anomalous cardiovascular anatomy, and tracheomalacia. Short stenosis may respond to resection and anastomosis. Longer lengths of stenosis can be managed by patch

tracheoplasty and slide tracheoplasty. Use of cardiopulmonary bypass during repair may improve outcomes.[108,109]

FOREIGN BODIES OF THE TRACHEOBRONCHIAL TREE

9 Foreign-body aspiration occurs commonly in infants and young children and is a potentially life-threatening event. A report in 2001 found that nonfood choking was a cause of death for 449 persons under the age of 14 with 65% of the deaths in children under 3 over a 20-year period. Choking on food causes death of approximately 75 children per year.[110–112]

Pathophysiology

Complete airway obstruction can occur at the level of the pharynx, hypopharynx, or trachea. Back blows, abdominal thrust, or the Heimlich maneuver may dislodge the obstruction and save a life. An inhaled foreign body which reaches the bronchial level may cause a ball-valve phenomenon allowing bi-directional but unequal flow of air. Air trapping and hyperinflation of the affected lobe lead to mediastinal shift. Complete blockage results in loss of volume due to atelectasis.

Foods are the most common aspirated items and include peanuts, carrots, popcorn, hotdogs, and grapes. Toy parts are the most common nonfood items aspirated.

Clinical Presentation

Most affected children are less than 3 years of age. History of choking crisis is present in the majority of children. Other symptoms include cough, wheezing, dyspnea, and fever. The most common signs are unilateral decreased breath sounds, unilateral wheezing, and rhonchi.

Management

Chest radiographs, including bilateral lateral decubitus films, are performed unless the patient is in respiratory distress. Radiographs demonstrate hyperinflation on the affected side. In case of questionable foreign-body aspiration, CT imaging may be performed. Alternatively, radiographs may show pneumonia or atelectasis with a completely occluding foreign body.

Bronchoscopic evaluation and foreign-body removal is performed in the operating room under general anesthesia. The rigid bronchoscope and Hopkins rod-lens system with optical forceps can be used to retrieve most aspirated foreign bodies (Fig. 100.16). Flexible graspers, Fogarty balloon catheters, and baskets can be useful especially if the foreign body has migrated distally or has a smooth or round surface. Fluoroscopic assistance can be useful with radiopaque objects which have migrated into the peripheral airways.

Over time, pneumonia or atelectasis may develop and a foreign body presenting with chronic lung infection may require surgical resection of the associated potion of the lung.

CONGENITAL ABNORMALITIES OF THE DIAPHRAGM

Advances in management of neonatal respiratory failure, fetal surgery, and lung developmental biology have arisen from the clinical and laboratory evaluation of CDH (CDH, Bochdalek, or posterolateral hernia). CDH, which is relatively rare, occurring in 1 in 3,000 neonates has led to a significant amount of clinical and basic science research.

In 1754, McCauley described the clinical course and postmortem anatomy of an infant with CDH.[113] Although Bochdalek's[114] understanding of the embryology of CDH was incorrect, this congenital defect continues to carry his name. Prior to 1940, the successful repair of this defect was rare.[115] In 1946, Gross[116] reported the postoperative survival of an infant less than 24 hours of age. From that time until the 1980s the standard of care was emergent operative repair. At that time, CDH was considered to be an anatomic derangement treated by an anatomic correction (the thought was that

by getting the bowel out of the chest, lung compression would improve and outcomes would improve).

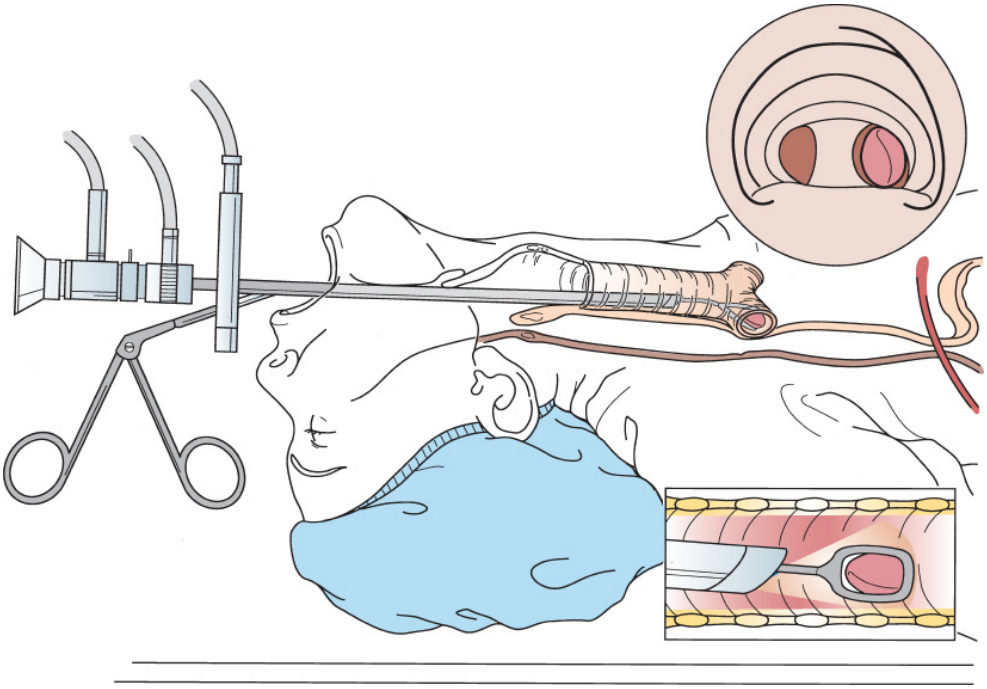

Figure 100.16 Schematic illustration of a peanut foreign body being extracted from the right main stem bronchus under direct vision.

Until the 1980s, emergency surgery was considered the primary therapeutic goal based on mechanical concept of providing space for growth of lungs. The overall published survival rates in the 1980s were 50% with ranges from 20% to 70% based on case selection. In the late 1980s, there was a change in management from emergency surgery to initial stabilization.[117] Management in the postnatal period is directed at decreasing pulmonary hypertension while maintaining adequate oxygen saturations.[117,118] Surgical repair is deferred until after physiologic stabilization. This has led to improved survival of infants with CDH.

Embryology of the Diaphragm

Mammalian lung development occurs in vivo as a coordinated developmental process that includes (a) airway and acinar development, (b) cellular differentiation, (c) biochemical maturation, (d) interstitial development including vasculature and extracellular matrix, and (e) physical

growth or enlargement. These parallel developmental processes occur in such a fashion that at any one time during development, there are characteristic relationships among each component that define the so-called, "stages of lung development."[119–121] Hormones such as the glucocorticoids, thyroid hormone, and retinoic acid have been shown to regulate several of the crucial cellular interactions required for proper pulmonary organogenesis and differentiation. In the human embryo, respiratory tract development begins in the fourth week of gestation as a ventral out pouching of the foregut that soon has bifurcated and begun branching into the surrounding mesenchyme. The primitive, pluripotent epithelial cells differentiate into both bronchial and alveolar cell lines, under the control of the surrounding mesenchyme. By a process of asymmetric branching, the divisions are complete by the 16th week of gestation. Lung at this phase has columnar epithelium with thick mesenchyme giving rise to the descriptive term *pseudoglandular phase* of development because of its histologic appearance. The *canalicular phase* that follows and continues up to about the 24th gestational week is characterized by flattening of the epithelium of the distal airways, thinning of the mesenchyme, and the growth of the capillary network that surrounds the terminal airways. Gas exchange becomes functionally possible at the end of this phase. The *terminal sac period* that follows refers to the appearance of a thin respiratory epithelium in apposition to a capillary network capable of supporting gas exchange. The *alveolar phase* of development in humans begins shortly before or around the time of birth. Alveolar maturation and multiplication takes place after birth and may continue up to 8 years of age.

The precursors of the mesoderm-derived diaphragm begin to form during the fourth week of gestation with the appearance of the peritoneal folds from lateral mesenchymal tissue. At the same time, the septum transversum forms from the inferior portion of the pericardial cavity and serves to delineate the thoracic from the abdominal cavities. Eventually, the septum transversum leads to the formation of the central tendinous area of the fully developed diaphragm. The pleuroperitoneal folds extend from the lateral body wall and grow medially and ventrally until they fuse with the septum transversum and dorsal mesentery of the esophagus during the sixth gestational week. Complete closure of the canal takes place during the eighth week of gestation, with the right side closing before the left.[122] Muscularization of the

diaphragm appears to develop from the innermost layer of thoracic mesoderm, although other mechanisms have been proposed (Fig. 100.17).[123]

Congenital Diaphragmatic Hernia Pathology and Pathophysiology

CDH occurs in 1:3,000 to 2:4,000 live births. Approximately one-third of antenatally diagnosed infants with CDH are stillborn, with most of the deaths ascribed to other fatal anomalies. Defects are more common on the left side.[124] CDH represents a sporadic developmental anomaly with some familial cases reported. One-third of patients have associated major defects. CDH associated with an abnormal karyotype or cardiac defect is associated with a poor outcome.[125]

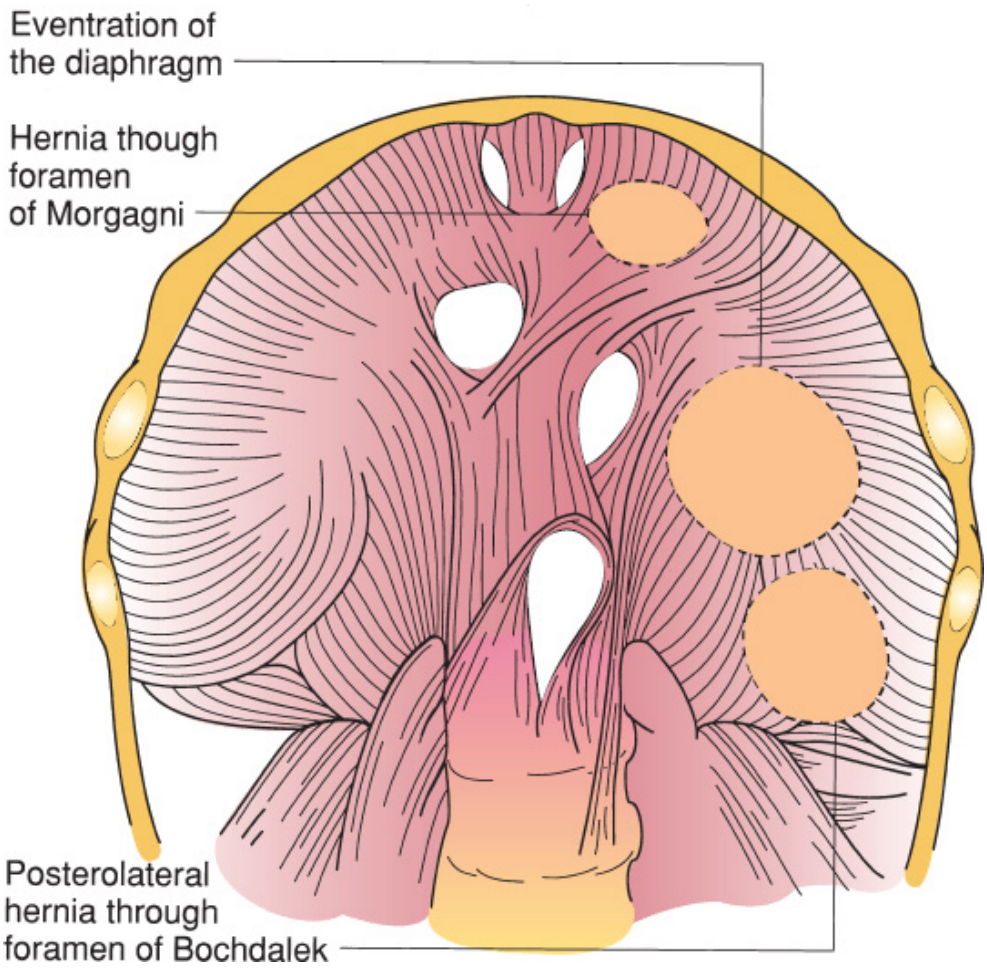

Figure 100.17 Anatomy of the diaphragm showing the location of congenital diaphragmatic defects.

The cause of CDH is unknown but is presumed that some combination of intrinsic predisposition (genetic factors) and environmental factors (teratogen or deficiency) results in abnormal diaphragm and lung development.[122] A nitrofen-induced model of CDH also inhibits retinal dehydrogenase leading to decreased retinoic acid, which has also been found in human infants with CDH.

During the early development of the diaphragm, the midgut is largely extracoelomic. If closure of the pleuroperitoneal canal has not occurred by the time the midgut returns to the abdomen during the 9th and 10th weeks of gestation, the abdominal viscera herniate through the lumbocostal trigone into the ipsilateral thoracic cavity. The resulting abnormal position of the bowel prevents its normal counterclockwise rotation and fixation. No hernia sac is present if the event occurs before complete closure of the pleuroperitoneal

canal, however a nonmuscularized membrane forms a hernia sac in 10% to 15% of CDH patients. In addition to the small bowel, other intra-abdominal organs such as the spleen, stomach, colon, and liver may also herniate through the diaphragmatic defect.

Left-sided CDH is characterized by a 2- to 4-cm posterolateral defect in the diaphragm through which the abdominal viscera have translocated into the ipsilateral thoracic cavity. On a right-sided defect, the large right lobe of the liver can occupy most of the hemithorax. The hepatic veins may drain ectopically into the right atrium, and the liver and lung may be fused.[123]

The pathophysiology of CDH has been attributed to pulmonary parenchymal compression by the herniated organs and its effect on growth and maturation of the lung. An emerging school of thought attributes the pulmonary hypoplasia to an early mesenchymal developmental insult to the lung and diaphragm. Unilateral diaphragmatic hernia is associated with both ipsilateral and contralateral abnormal pulmonary development, although hypoplasia is more severe on the ipsilateral side. The lung on the side of the hernia is much smaller than its contralateral counterpart, and both are smaller than normal lungs (Fig. 100.18). The pulmonary vascular disease associated with CDH is characterized by abnormal pulmonary vascular development, abnormal vasoreactivity, and a disorganization of vascular remodeling. There are fewer capillaries which are unevenly distributed. Both the media and the adventitia have structural abnormalities consistent with increased muscularization in utero. Sonic hedgehog signaling which is involved in the development of respiratory bronchioles is delayed in CDH. Levels of several regulatory proteins are changed compared to controls but no causative relationship has been demonstrated.[120,123]

Figure 100.18 Autopsy specimen of an infant with severe pulmonary hypoplasia secondary to congenital diaphragmatic hernia. Pulmonary hypoplasia is bilateral, but the left lung is most severely affected.

Pulmonary blood flow accounts for only 7% of cardiac output during normal fetal development. Pulmonary vascular resistance is high. The fetus preferentially shunts oxygenated blood from the placenta through the foramen ovale and ductus arteriosus in a right-to-left direction into the systemic circulation. With the institution of breathing at birth, oxygen levels rise

causing pulmonary vascular resistance to fall, which in turn allows an increase in pulmonary blood flow. Increased arterial oxygen tension induces spontaneous closure of the ductus arteriosus. Persistent fetal circulation may develop if this process is interrupted. Elevated pulmonary vascular resistance results in right-to-left shunting of blood at either the atrial or ductal levels with the delivery of unsaturated blood into the systemic circulation. As shunting increases, the oxygen saturation in the systemic circulation falls. The resulting hypoxia further increases pulmonary vascular resistance and compromises pulmonary blood flow while increasing the right-to-left shunt flow. Factors that contribute to the persistence of high pulmonary vascular resistance in CDH lungs are thought to be the structural changes of decreased total arteriolar cross-sectional area in the involved lungs and the increased muscularization of the arterial structures that are present. Additional exacerbations of pulmonary vascular resistance may be induced by the known stimulators of pulmonary hypertension, which include hypoxia, acidosis, hypothermia, and stress. Alternations in the levels of prostaglandins, leukotrienes, catecholamines, and the renin angiotensin system had been implicated as mediators of this complex process. The combination of hypoplastic lungs and lungs prone toward increased vascular resistance often proves deadly; a vicious cycle may ensue in which hypoplastic lungs and associated hypoxia leads to pulmonary hypertension in a lung vasculature already prone toward reactive vasospasm. The increase in pulmonary pressures results in a greater shunt, which in turn further reduces oxygen levels.

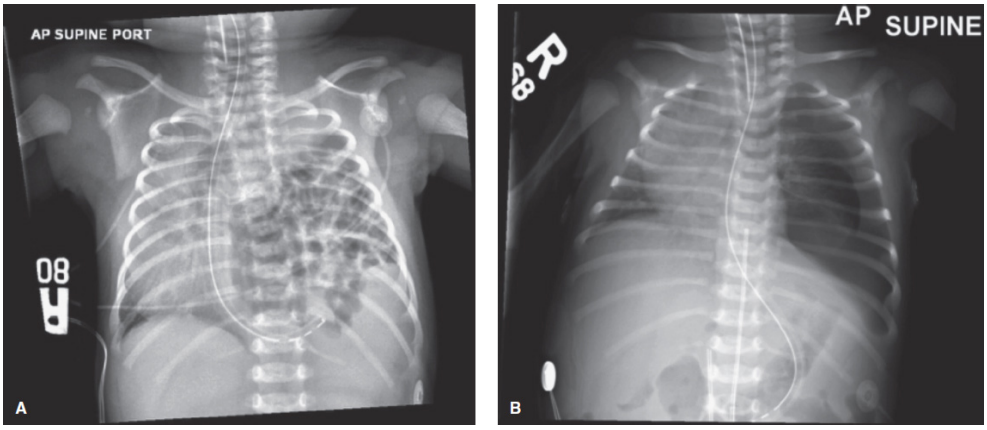

Figure 100.19 **A:** Chest radiograph of a newborn with a left congenital diaphragmatic hernia. Mediastinal structures are shifted to the right. Abdominal viscera occupy the left hemithorax. The nasogastric tube locates the stomach. The child underwent repair of the congenital diaphragmatic hernia after treatment and resolution of pulmonary hypertension. **B:** Immediate postoperative photograph demonstrates hypoplastic lung, flattening of diaphragm, and return of abdominal viscera to normal position.

Diagnosis

Diagnosis of CDH is typically made on prenatal ultrasound examination.[124,125] Polyhydramnios is common. Prenatal MRI is utilized for more accurate delineation of the defect.[124–126] Postnatal presentation includes cyanosis and respiratory distress shortly after birth in severely affected neonates. On physical examination, the patients have a scaphoid abdomen. A plain chest radiograph with loops of intestine in the chest confirms the diagnosis of CDH with an NG tube in place to confirm the position of the stomach (Fig. 100.19). After confirmation of diagnosis, echocardiography should be performed to evaluate pulmonary hypertension and to determine presence of cardiac defects. Differential diagnosis includes eventration of the diaphragm, anterior diaphragmatic hernia (Morgagni), congenital pulmonary malformations, unilateral pulmonary effusion, and primary agenesis of the lung.[127]

Prognostic Factors

Poor prognosis is associated with low lung-to-head ratio (LHR) is determined by sonographic measurements of the size of the contralateral lung

in an anteroposterior and lateromedial direction, and the head circumference. Ratios less than 1 have been associated with poor outcome. Because the LHR increases with age, the percent of predicted value for gestational age has been used with no survivors below 15% of predicted.[124,128,129] Liver above the diaphragm ("liver up") is also associated with decreased survival. The combination of a low LHR with "liver up" has a very poor prognosis. The size of the defect, presence of a major cardiac anomaly, and 1-minute Apgar sores of ≤4 are also associated with increased mortality.[124,128,129] Physiologic parameters have also been used to predict survival based on birth weight, 5-minute Apgar, SNAP-II scores, gestational age, and blood gas values in first 24 hours.[130] The Congenital Diaphragmatic Hernia Study Group and the Canadian Neonatal Network have published predictors of survival.[131,132]

Treatment

At the time of antenatal diagnosis, the mother and fetus should be referred to an appropriate tertiary care perinatal center with the availability of the full array of respiratory care strategies.

Resuscitation should begin with standard neonatal resuscitation guidelines and then proceed with endotracheal intubation and nasogastric tube insertion. Bag–valve mask should be avoided. Careful management of temperature regulation, glucose homeostasis, and volume status should be performed. Fluid resuscitation should be performed with crystalloid, blood products, and colloid. Inotropes such as dopamine or dobutamine are utilized if needed. Most infants can be managed with simple pressure-cycled ventilation with a goal of maintaining a preductal PaO_2 greater than 60 correlating with saturation between 85% and 95%. Keeping peak pressures below 25 and accepting CO_2 between 45 and 65 decreases barotrauma. For failure of "gentle ventilation strategies," the jet ventilator or oscillator ventilator may be uses.[124,127]

In addition to ventilatory methods, a variety of agents are utilized to modify pulmonary vascular resistance, including inhaled nitric oxide, phosphodiesterase-5 inhibition with sildenafil, Milrinone (a phosphodiesterase-3 inhibitor), prostacyclin and prostaglandin E1. Other

medications such as tyrosine kinase inhibitors and endothelin receptor antagonists may show promise.[133,134] Surfactant has been demonstrated to be reduced in CDH infants. However, surfactant has not been demonstrated to improve survival.[124,127,133]

Failure to improve with ventilatory and pulmonary hypertension management strategies should prompt consideration of ECMO. ECMO can be used for an extended period of time when ventilator therapy has failed. Indication for the use of ECMO is the failure to improve in the setting of severe pulmonary hypertension. In recent years the use of ECMO has decreased but still ranges from 15% to 40% of diaphragmatic hernias; with survival following ECMO of 51%.[127] There is no consensus on repair on ECMO or after ECMO.[135]

Surgery

10 Delayed surgery has been demonstrated to improve survival in some studies. The diaphragm defect is usually approached through a subcostal incision, although the repair can be performed through a thoracotomy incision (Fig. 100.20). Both thoracoscopic and laparoscopic approaches have been described. The abdominal organs are returned to the abdomen. The defect in the diaphragm is repaired. Primary repair with nonabsorbable suture is preferred. If the defect cannot be repaired primarily due to size, a prosthetic patch such as Gore-Tex may be utilized. The major drawback of the use of a patch, either inert or bioactive is recurrent herniation which may occur in up to 50% of infants.[136] There may have been loss of intra-abdominal domain and difficulty with closing the abdomen. In these cases, a silo may be used.[137] Tube thoracostomy is used at the surgeon preference. A recent meta-analysis of minimally invasive versus open repairs demonstrated that recurrence rate is higher after MIS and operative time is longer.[138] Postoperative ventilator time and postoperative mortality were higher after open surgery but none of the studies were randomized and this may have represented selection bias.[138]

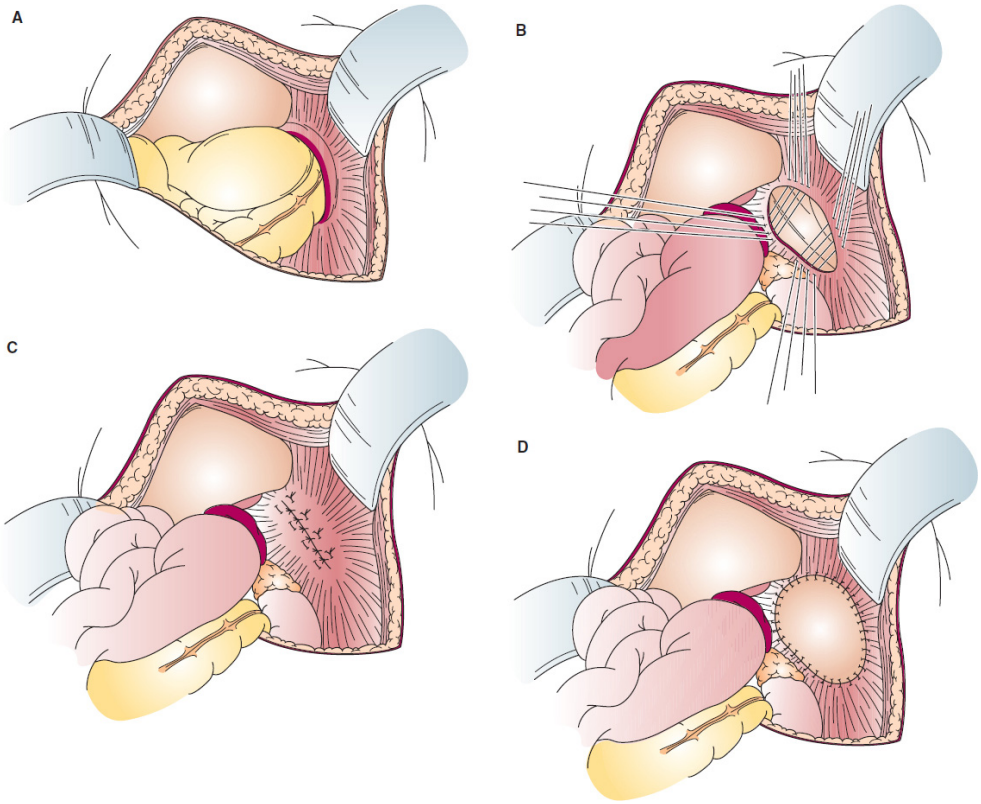

Figure 100.20 Repair of a congenital diaphragmatic hernia (CDH). **A:** Operative appearance of CDH. **B:** Placement of sutures for repair of a typical left posterolateral diaphragmatic defect. **C:** Completed repair. **D:** Prosthetic material may be used for large defects to avoid tension.

Postoperative management should continue the goals set before surgery. Continued attention to fluid status is important in the postoperative period. Weaning from the ventilator should be slow and deliberate. Refractory postoperative pulmonary hypertension is relatively common in those who required ECMO and is often treated with iNO and prostacyclin in conjunction with frequent echocardiography.

Outcome

Survival rates have been reported at 60% to 80% improved from 50% in the past. As survival has improved, other morbidities have been demonstrated including long-term use of bronchodilators, need for gastrostomy for nutritional support, and increased rate of gastroesophageal reflux disease (GERD) requiring surgery. Musculoskeletal deformities also occur with scoliosis, pectus excavatum, pectus carinatum, and chest wall asymmetry

described.[139] Adult survivors of CDH have demonstrated higher incidence of GERD, recurrent intestinal obstruction, and recurrent abdominal pain. Scores in the Gastrointestinal Quality of Life Index and the Health-related Quality of Life Survey are good or satisfactory.[140]

Evolving Therapies

Open fetal repair of diaphragmatic hernia has been performed but there was no survival benefit and there was an increase in preterm delivery so this is not currently offered. Tracheal occlusion in utero has been developed as a strategy to promote lung development based on observations that the lungs of neonates with congenital high airway obstruction developed hyperplastic lungs. Fetal tracheal occlusion improved lung volume but there was still impairment in the lung. Fetal endoscopic tracheal occlusion has been trialed with fewer premature deliveries. In the U.S. trial there was no improvement in survival in a randomized trial. The European trials added a second fetal surgery to remove the balloon to allow for improvement in the development and function of type II pneumocytes and to increase surfactant production. With the European trial, vaginal delivery is possible but with the U.S. trial, the infants were delivered by EXIT procedure, using the placenta to maintain oxygenation until an airway is secured.[124,126]

Foramen of Morgagni Hernia

The anterior CDH is rare and accounts for 3% to 5% of all CDHs. It is typically diagnosed during childhood from chest or abdominal radiographs being performed for presumed pneumonia or gastrointestinal symptoms (Fig. 100.21).[141] This is an anteromedial hernia at the junction of the septum transversum and the thoracic wall with contents being seen in a retrosternal position. There is a hernia sac present and the sac may contain colon, small intestine, or liver. The hernias are repaired due to the risk of segmental intestinal volvulus or obstruction. Laparoscopy has been demonstrated to be an effective method for repair of this type of hernia. The sac is excised and the diaphragm is sutured to the undersurface of the posterior rectus sheath at the costal margin.[141–143]

A

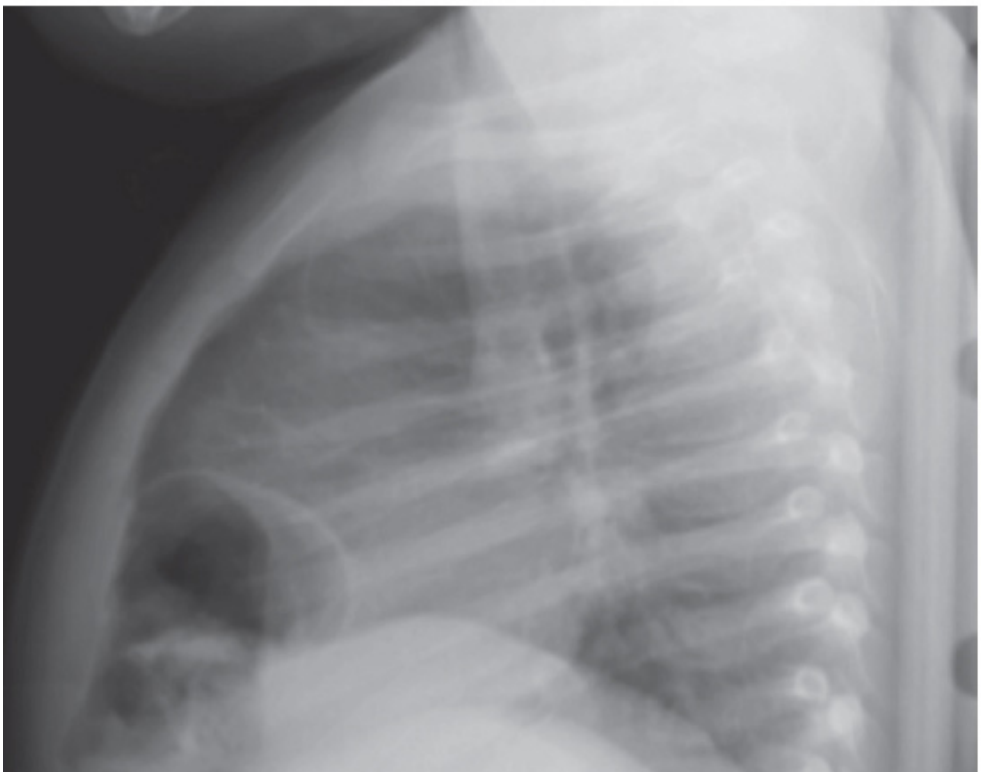

Figure 100.21 Morgagni hernia. (**A**), Anteroposterior and (**B**), lateral radiographs of patient with Morgagni hernia.

Eventration of the Diaphragm

Eventration of the diaphragm is diagnosed by the abnormal elevation of one or both hemidiaphragms and can be congenital or acquired. The congenital form may appear very similar to a diaphragmatic hernia with a sac. The cause of the congenital form is unknown although infectious causes have been implicated. The acquired form is a consequence of injury to the phrenic nerve. Asymptomatic patients may be observed. Surgical management in symptomatic patients involves plication of the diaphragm. The repair may be performed through the abdomen or the chest and both thoracoscopic and laparoscopic techniques are applicable.[143,144]

Diaphragmatic Pacing

Ventilator-dependent children with spinal cord injury or central hypoventilation syndromes may benefit from diaphragm pacing.[145] The application of repetitive stimulus patterns to the phrenic nerves causes rhythmic contractions of the diaphragm. Phrenic nerve pacing wires are implanted at the cervical or intrathoracic level. Receivers are implanted in subcutaneous pockets, while an external microprocessor-controlled transmitter/antenna assembly activates the receiver. Patients with injured phrenic nerves (high spinal cord injury) may benefit from diaphragm pacing after intercostal-to-phrenic nerve transfer.[146]

PLEURAL DISEASES

Empyema

Empyema is the accumulation of purulent material in the pleural space. In children, empyema is most often the sequelae of bacterial pneumonia. Empyema develops when a parapneumonic effusion becomes infected or when a necrotizing pneumonia erodes into the pleural space. Empyema may also be caused by penetrating thoracic trauma, intrathoracic, or cervical esophageal perforation or as a complication from surgery on the chest. The American Thoracic Society divides the empyema process into 3 stages:

1. Exudative: Thin free-flowing fluid with a low cell count.
2. Fibrinopurulent: Frank pus is present and fibrin formation begins to cover the pleura with development of loculations.
3. Organizing: Thick peel with fibroblasts.[147]

The most common organism responsible for empyema is *Streptococcus pneumoniae*. Other common organisms are *Staphylococcus aureus* and *Haemophilus influenzae*.[147] The signs and symptoms include worsening pneumonia with fever, tachypnea, dyspnea, and sometimes cyanosis. Abdominal pain may be present. Chest radiograph demonstrates the presence of fluid and loculation. CT imaging is the best method of determining the extent of loculated fluid versus underlying pulmonary pathology (Fig. 100.22).

With a small amount of fluid, the empyema may resolve with antibiotics alone. When the collection becomes larger, the treatment is drainage of the collection. Several trials have compared fibrinolytics to video-assisted thoracoscopy (VATS). Both VATS and chest tube with fibrinolytics have been shown to be effective with a systematic review demonstrating no superiority of VATS. Other studies have demonstrated improvement after VATS.[147,148]

Pneumothorax

Spontaneous pneumothorax is relatively uncommon. The etiology seems to be lung connective tissue changes predisposing to leaks into the pleural space. Apical lung blebs are associated with the disease. The presentation is usually with chest pain and shortness of breath but may also be associated with cough. The pain may be pleuritic in nature. Diagnosis is best confirmed

with chest radiograph.[149] Chest CT has been utilized for identification of blebs but a negative examination does not predict freedom from recurrence.[150]

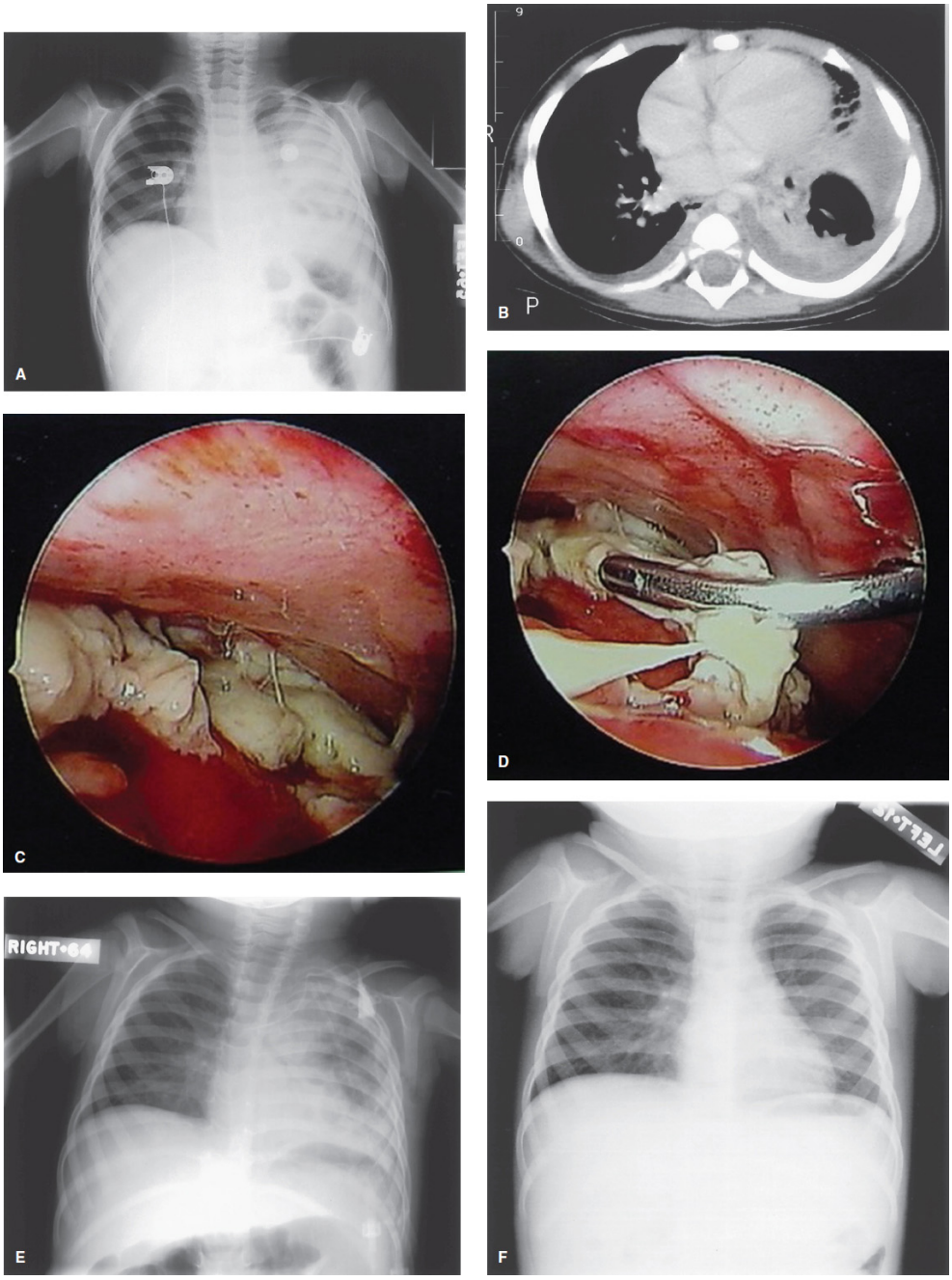

Figure 100.22 Video-assisted thoracoscopic treatment of complicated empyema in children. **A:** Chest radiograph of a 2-year-old child presenting with pneumonia and pleural effusion. **B:** Computerized tomography demonstrates complicated pneumonia with loculated empyema. **C:** Video endoscopic view of organized empyema debris. **D:** "Decortication" procedure includes removal of all loculated, organized debris from the hemithorax. All surfaces of the visceral and parietal pleura are accessible using video endoscopic techniques. **E:** Immediate postoperative chest x-ray shows the expected residual parenchymal lung disease. **F:** One month later, the chest radiograph findings have resolved.

Treatment of pneumothorax depends on the patient. Observation with or without high-flow oxygen is appropriate for the relatively asymptomatic patient. Chest tube placement is the next stage of treatment. VATS with bleb resection and pleurodesis has also been described with good results.[149] For recurrent pneumothoraces, intrapleural sclerosing agents can be used.

Chylothorax

Chylothorax, the accumulation of chyle in the pleural space, is a rare cause of effusion in children but is the most common cause in the neonate.[151] Chylothorax is associated with pulmonary lymphangiomas and lymphangiectasia. Chylothorax may also be a manifestation of Down, Turner, and Noonan syndromes. Chylothorax may occur due to trauma to the thoracic duct either iatrogenic or due to blunt trauma. Malignancy and granulomatous diseases may cause obstruction of the thoracic duct leading to chylothorax.

The initial symptoms are related to accumulation of fluid in the pleural space with dyspnea, cough, and chest discomfort. Pleuritic pain and fever are rare. Diagnosis is by chest radiograph combined with findings on thoracentesis. The fluid is usually milky in appearance with triglycerides greater than 1.1 mmol/L, total cell count greater than 1,000 cells per mL, and lymphocyte predominance greater than 80%.[151]

Management consists of expansion of the lung with thoracentesis or tube thoracostomy. Minimization of lymph flow is managed by either parenteral nutrition or diet manipulation using medium-chain fatty acids. Long-term loss of lymphatic fluid can lead to life-threatening immunologic problems. Surgical management includes thoracic duct ligation, performed either via thoracotomy or thoracoscopy. Administration of cream via a nasogastric tube in the hours before surgery may facilitate identification of the leak. Pleurectomy and pleurodesis or pleuroperitoneal shunting may also be used.

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101

Pediatric Abdomen

Andrea Hayes-Jordan and Michael Phillips

Key Points

1 Gastroschisis occurs with an incidence rate of 1 in 2,000 live births and is characterized by exposed intestine herniating through a defect to the right of the umbilicus. In contrast, omphalocele is a midline abdominal wall defect characterized by herniated visceral contents contained within the umbilical cord covering and has a high incidence rate of associated congenital anomalies.

2 A congenital, indirect inguinal hernia is an abnormal, patent continuation of the peritoneum through the internal inguinal ring; inguinal hernia repair is the most common elective procedure in pediatric surgery.

3 Neonatal bilious emesis should be considered the result of an acute mechanical intestinal obstruction until proven otherwise; emergent surgical evaluation is warranted to determine whether intestinal malrotation with midgut volvulus is present.

4 Necrotizing enterocolitis (NEC) is a progressive, inflammatory intestinal condition of the surviving premature neonate. Perforated NEC is the most common neonatal surgical emergency.

5 Hirschsprung disease is caused by aganglionosis of the myenteric nervous system in the rectum. Most commonly, the rectosigmoid colon is involved, but the length of contiguous aganglionosis varies in length proximally. Both propulsion and reflexive relaxation may be disordered or absent in the rectum, leading to functional bowel obstruction in the neonate and chronic constipation in the older child or adolescent. Enterocolitis associated with Hirschsprung disease is a potentially life-threatening condition.

6 Intussusception is the invagination or telescoping of a proximal segment of intestine into an adjacent distal segment and is the most common cause of intestinal obstruction in infants and children 3 months to 3 years of age.

7 The incidence of biliary atresia is 1 in 8,000 to 12,000 live births and is the most common cause of chronic cholestasis in infants and children as well as the most frequent indication for pediatric liver

transplantation. Early diagnosis and management is necessary for optimal outcome.

ABDOMINAL WALL DEFECTS

Gastroschisis

1 Gastroschisis occurs with an incidence of about 1 in 2,000 to 4,000 live births. Infants with gastroschisis tend to be born to mothers who are younger (teenage), white, and consumed alcohol or tobacco during pregnancy.[1–3] Familial cases of gastroschisis are distinctly rare.[4] Associated congenital anomalies are uncommon. However, in about 10% of cases, intestinal atresia or stenosis can be seen and is thought to be a result of mechanical or vascular compromise to the herniated bowel. Rarely, infants with gastroschisis have complete loss of small bowel secondary to volvulus in utero.

The pathophysiology of gastroschisis remains unknown. In normal fetal development, two umbilical veins are initially present. As the intestine returns to the abdominal cavity through the umbilicus, the right umbilical vein undergoes resorption, leaving the left umbilical vein intact. Weakness of the umbilical membrane at the site of umbilical vein resorption may allow the evisceration of the intestine through the defect. This explanation is consistent with the clinical observation that the gastroschisis defect is almost always located to the right of the umbilicus. Routine antenatal ultrasonography has documented the sequential development of gastroschisis as a consequence of a ruptured hernia of the umbilical cord in utero.[5] Therefore, gastroschisis should be considered an isolated mechanical defect of the developing umbilical cord rather than a global defect in embryogenesis.

The amount of bowel eviscerated in gastroschisis can be extensive because the bowel has not undergone complete mesenteric rotation and fixation at this particular time in embryogenesis. The bowel may be thickened and the mesentery may be foreshortened secondary to the inflammatory response induced by direct exposure to amniotic fluid. In gastroschisis, herniation of the liver is distinctly unusual (Fig. 101.1).

Figure 101.1 Gastroschisis. The defect is to the right of the normal umbilicus, and the bowel is thickened and inflamed.

Figure 101.2 Omphalocele. The herniated intestines and liver are visible inside the sac. The umbilical cord attaches to the sac.

Omphalocele

Anatomy, Embryology, and Pathophysiology

The incidence rate of omphalocele is approximately 1 in 6,000 to 10,000 live births and has been stable over the past several decades. *Omphalocele* is a midline abdominal wall defect of varying size characterized by the presence of herniated visceral contents into the translucent sac of the umbilicus. The sac is composed of amniotic membrane, mesenchymal tissue known as *Wharton jelly,* and peritoneum. The umbilical cord attaches to the sac and may be eccentric in origin (Fig. 101.2). The sac may be inadvertently ruptured before or during delivery but it is always present. Similar to gastroschisis, intestinal malrotation is usually present. Unlike gastroschisis, the bowel is typically normal in appearance because it has not been directly exposed to the amniotic fluid. Small omphaloceles are defined as 2 to 3 cm in diameter and have only a small amount of herniated bowel within the sac. Closure of small omphaloceles is typically performed without significant physiologic complications. In contrast, giant omphaloceles defined as greater than 4 cm in diameter can lead to extensive herniation of the stomach, bowel, liver, and spleen with subsequent underdevelopment of the abdominal cavity (Fig. 101.3).

Omphalocele results from incomplete closure of the anterior abdominal wall at the umbilicus during embryogenesis. During week 4 of gestation, the midgut undergoes progressive elongation in the yolk sac outside the embryonic coelomic cavity. The midgut returns to the abdominal cavity during week 10, where it undergoes normal rotation and fixation of the mesentery to the posterior abdominal wall. Normal closure of the anterior abdominal wall requires return of the midgut to the abdominal cavity, along with growth and fusion of the anterior body folds (cephalic, caudal, and two lateral) at the base of the umbilicus. Failure of growth, migration, or fusion of the lateral body folds leads to omphalocele. Failure of growth and fusion of the cephalic folds may lead to either a supraumbilical omphalocele associated with a midline sternal defect (Fig. 101.4) and a herniated heart, termed *ectopia cordis,* or a constellation of defects known as the *pentalogy of Cantrell.*[6] This sequence includes a sternal cleft, an absence of the septum transversum of the diaphragm, a pericardial defect, a cardiac defect, and an epigastric

omphalocele. Infants born with either ectopia cordis or pentalogy of Cantrell have significant morbidity and often, these conditions are lethal.

Figure 101.3 Ruptured omphalocele. Although the bowel is relatively normal in appearance, the abdominal cavity is extremely underdeveloped.

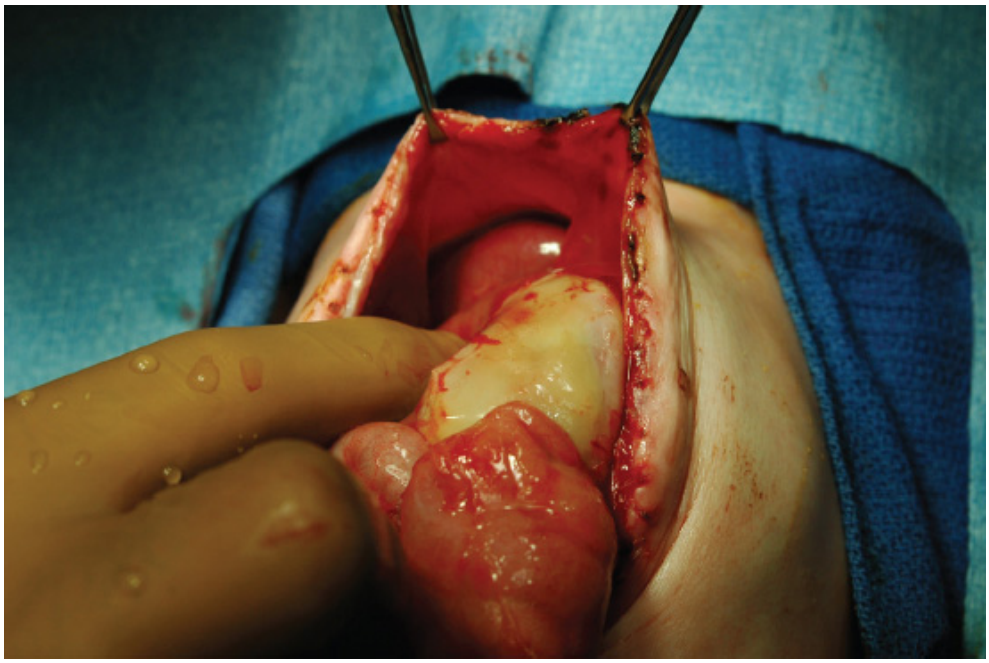


Figure 101.4 Operative exploration of giant omphalocele with abdominal wall defect, absence of the septum transversum of the diaphragm, pericardial defect, and cardiac defect.

Associated anomalies are more common in infants with omphalocele than with gastroschisis, reflecting the more global abnormality of embryogenesis in omphalocele. About 50% to 60% of infants with omphalocele have at least one associated congenital anomaly involving the skeleton, gastrointestinal tract, nervous system, genitourinary system, and cardiopulmonary system.[7,8] In addition, infants with omphalocele have a higher incidence of chromosomal abnormalities and other conditions such as Beckwith–Wiedemann syndrome. A comparison of gastroschisis and omphalocele is summarized in Table 101.1.

Perioperative Management for Gastroschisis and Omphalocele

In contemporary practice, infants with gastroschisis can be safely delivered vaginally.[8,9] Studies comparing vaginal delivery with elective cesarean section for infants with gastroschisis demonstrated no significant differences in outcome.[10,11] Early delivery to minimize intestinal damage in gastroschisis patients has not been proved to be efficacious.[12,13] Fetal well-being has been advocated to be the primary determinant for gastroschisis. To prevent birth-related hepatic injury, cesarean section is preferable for prenatally diagnosed infants with giant omphaloceles.

After delivery, infants with either gastroschisis or omphalocele have similar initial management priorities. If necessary, an adequate airway with effective ventilation and oxygenation is established. The infant should be maintained under either an external warmer or a humidified incubator. An orogastric sump tube should be inserted early and placed on suction to prevent intestinal distention. In gastroschisis, the herniated viscera should be examined to make certain that the mesentery is not twisted. In addition, the tightness of the opening of the abdominal wall should be assessed to ensure that there is sufficient perfusion of the bowel. The infant's entire lower torso can be placed inside a plastic bowel bag, or the viscera can be covered with moisten gauze, to prevent further contamination, hypothermia, and volume depletion. The initial therapeutic goal is to provide rapid, effective temporary coverage of the viscera. Adequate support of the herniated viscera must be provided to prevent intestinal ischemia. This can be done by placing the baby on his or her side, and placing support under the intestines. With large

omphaloceles, the position of the infant's liver and viscera may impair venous return from the inferior vena cava when the infant is supine, and these infants may preferentially require a left-side-down position to maintain normal hemodynamics. Intravenous dextrose and broad-spectrum antibiotics are administered. Infants with gastroschisis will have higher intravenous fluid requirements to maintain euvolemia. If the infant is not delivered at a center where definitive surgical care can be provided, urgent transport should be arranged.

DIAGNOSIS

Table 101.1 Comparison of Gastroschisis and Omphalocele

Characteristic	Gastroschisis	Omphalocele
Defect size (diameter)	2–3 cm	2–15 cm
Sac	Never	Always, may be ruptured
Gestational age	Prematurity	Term
Umbilical cord	Adjacent (left side) of defect	Attached to sac
Herniated viscera	Small bowel, stomach, colon	Small bowel, stomach, colon, liver
Malrotation	Yes	Yes
Bowel character	Inflammatory, edematous	Normal
Enteral nutrition	Delayed	Normal
Associated anomalies	Uncommon (10% atresia)	Common (50%)

Gastroschisis

Once the infant with gastroschisis has been stabilized, measures are taken to secure the viscera and, if possible, correct the abdominal wall defect. One option is to take the infant to the operating room, where reduction of the herniated viscera with primary fascial closure of the abdominal wall is an achievable goal in approximately 60% to 70% of infants with either gastroschisis. Gentle but definitive stretching of the abdominal wall is performed, and proximal decompression of the bowel is maintained with orogastric decompression. The defect may need to be enlarged to evaluate the intestinal tract fully and/or reduce the viscera into the abdominal cavity. The limiting factor in primary closure of a congenital abdominal wall defect is the increased intra-abdominal pressure generated by the reduction of the herniated viscera. Increased intra-abdominal pressure can lead to abdominal compartment syndrome. Features of neonatal abdominal compartment syndrome include impaired venous return caused by compression of the inferior vena cava, reduction of splanchnic blood flow leading to mesenteric ischemia, and respiratory compromise secondary to impaired diaphragmatic excursion. Intraoperative measurement of intragastric or intravesical pressure, end-tidal CO_2, central venous pressure, or regional oximetry may be helpful in determining the safety of primary abdominal wall closure. If the herniated viscera cannot be reduced primarily, the viscera is placed in a constructed Silastic pouch or preformed spring-loaded silo. Daily partial reduction of the viscera within the silo is performed. This technique allows gradual reduction of the herniated viscera into the abdominal cavity, and complete reduction is usually obtained within 3 to 7 days. The infant is returned to the operating room for removal of the temporary silo with delayed primary closure of the abdominal wall defect (Fig. 101.5). Alternatively, a large abdominal wall defect may be effectively covered with abdominal skin flaps, or biologic mesh, with delayed repair of the ventral hernia months to years later (gross closure).

Figure 101.5 Silastic chimney or silo for temporary coverage and staged reduction of giant omphalocele.

In some centers, all babies with gastroschisis are managed by placing a preformed silo at the bedside after the baby is born. Thereafter, the viscera is slowly reduced into the abdomen and eventual fascial closure is attained.[14] Some studies caution that this practice may lead to longer ventilator and fluid requirements.[14,15] Another method that has been described in gastroschisis patients with noninflamed pliable intestines is to reduce the viscera with some sedation at the bedside, fold the umbilical cord stump over the skin closure, and place a pressure dressing over the defect.[16] The use of the umbilical stump has been described even for patients requiring staged or silo closure.[17] In some retrospective studies, this method of closure has been shown to effect fewer days of mechanical ventilation, decreased antibiotic and opioid utilization, but with a higher rate of umbilical hernia at follow-up.[17–21] A wound vacuum closure can be used to augment this technique.

Omphaloceles

Given the high incidence of associated anomalies, infants with omphalocele should undergo diagnostic investigation, guided by the clinical presentation and physical examination. These studies include chest radiography, echocardiogram, and renal ultrasound, in addition to baseline blood work. Chromosomal analysis may be necessary. Until the decision is made with

respect to the timing and method of repair, the omphalocele should remain covered and protected with a gauze dressing. If the omphalocele is ruptured or torn, immediate closure or coverage is necessary.

Closure of omphaloceles is dictated by the size of the defect, the amount of viscera extruded into the sac, and the abdominal domain. There is no standard definition of what constitutes a regular versus a giant omphalocele. Practically, a giant omphalocele has an abdominal wall defect larger than 4 cm, containing a portion of liver, and is difficult to close primarily in the first days of life without physiologic compromise.

Omphaloceles with a small abdominal wall defect typically would have operative fascial closure with sac excision in the newborn period. Many techniques have been described to close giant omphaloceles including sac excision and temporary coverage with grafts, use of intraperitoneal tissue expanders,[22,23] and allowing the omphalocele sac to scar and then epithelialize in the latter technique.

The sac can be physically supported and left undisturbed, allowing epithelialization of the sac over several weeks to months. Antibiotic solutions or ointments are usually applied to control desiccation.[23–26] Delayed repair of the ventral hernia is required. This delay is particularly useful in the infant with a giant omphalocele and a small, underdeveloped abdominal cavity that prohibits primary closure.

Infants with repaired omphalocele usually have relatively prompt return of bowel function after definitive repair, while infants with gastroschisis may require up to 4 weeks after repair to have bowel function normalize. The time to achieve full enteral feeding is not affected by the use of erythromycin as a prokinetic agent.[27] Approximately 15% of infants with gastroschisis develop necrotizing enterocolitis (NEC), a diffuse, often life-threatening inflammatory complication of the neonatal intestinal tract.[28] In addition, infants with gastroschisis are at risk for nutrient malabsorption and intestinal dysmotility with inability to tolerate full enteral feeding. In particular, infants with gastroschisis and associated intestinal atresia may have pronounced intestinal dysmotility and may require long-term, sometimes lifelong, dependence on TPN for caloric intake.[29]

Long-term outcome of infants operated on for gastroschisis or omphalocele is usually dependent on the morbidity and mortality of associated conditions rather than the abdominal wall defect itself. Surgical conditions such as

undescended testicles, Meckel diverticulum, and adhesive small bowel obstruction are encountered with moderate frequency. Adhesive small bowel obstruction most commonly occurs in the first year of life and requires operative management in the majority.[30] Most children with repaired abdominal wall defects enjoy satisfactory health and quality of life, although they have been reported to have a lower degree of physical fitness measured by exercise time and maximal oxygen consumption.[31]

Umbilical Hernia

Anatomy and Embryology

Congenital umbilical hernia is the most common abdominal wall defect in infants and children. The umbilical ring begins to contract circumferentially after birth and normally is reinforced by the paired lateral umbilical ligaments (the obliterated umbilical arteries), the singular round ligament (the obliterated umbilical vein), the urachal remnant, and the transversalis fascia. Incomplete growth or impaired development of any one of these structures can lead to weakness at the umbilical ring and cause a congenital umbilical hernia.

Clinical Issues and Management

Congenital umbilical hernias generally do not pose significant problems during childhood, with incarceration of intra-abdominal contents within the sac occurring about 1:1,500 cases.[32] Infants and children may also present with infection or drainage at the umbilicus from associated urachal or vitelline duct remnants. The incidence rate of congenital umbilical hernia has been reported to be 25% to 50% in black infants and 4% to 9% in white infants in the first few months of life.[33] There is an increased incidence of umbilical hernia in premature infants, and there is a tendency for familial inheritance.

Diagnosis of umbilical hernia is usually made after separation of the umbilical cord remnant from the umbilicus and is often initially noted by parents or pediatrician. The size of the defect may vary from a few millimeters to several centimeters and is typically reducible and asymptomatic. Age and size of the defect are the most important factors

determining spontaneous closure rates.[34] Many umbilical hernias spontaneously close within the first 2 to 3 years of life. Given the high rate of spontaneous closure and the relatively asymptomatic nature of most umbilical hernias, operative repair is generally not performed during the first 2 years of life. Skin ulceration or an episode of incarceration should prompt earlier repair. Large defects with significant protrusion may necessitate surgery, and parents may desire repair if an older child appears to be self-conscious about the hernia.

Nearly all umbilical hernia repairs can be performed as outpatient surgical procedures. An incision is made along the umbilicus and the hernia sac is dissected free circumferentially. The sac is completely excised and primary fascial closure is performed. The umbilical skin is typically preserved and sutured to the fascial closure, and an acceptable cosmetic result is almost always achievable. Large umbilical hernias with redundant skin may require umbilicoplasty. The incidence of complications such as wound infection and recurrence is low.

Inguinal Hernia and Hydrocele

Anatomy, Embryology, and Pathophysiology

2 Inguinal hernia repair is the most common elective general surgical procedure performed by pediatric surgeons. Three distinct anatomic types of inguinal hernias are observed in children: congenital indirect (99% of infants and children), direct (0.5%), and femoral (<0.5%). An *indirect inguinal hernia* is an abnormal, patent continuation of the peritoneum through the internal inguinal ring. The hernia sac originates lateral to the deep inferior epigastric vessels and descends along the spermatic cord within the cremasteric fascia. The sac can reside completely within the inguinal canal or descend through the external inguinal ring into the scrotum. A *direct inguinal hernia* originates medial to the deep inferior epigastric vessels and is external to the cremasteric fascia. The hernia sac protrudes directly through the posterior wall of the inguinal canal and can descend through the external inguinal ring and into the scrotum. A *femoral hernia* originates medial to the femoral vein and descends inferior to the inguinal ligament along the femoral canal. A femoral hernia never enters the scrotum or the labia.

The developing testicle is initially adjacent to the mesonephros and subsequently descends to the scrotum during the third trimester of gestation. The peritoneal extension that descends alongside the chorda gubernaculum of the testicle is called the processus vaginalis. A slightly higher incidence rate of right-sided indirect inguinal hernia is thought to reflect delay of right-sided testicular descent from the developing inferior vena cava and right external iliac vein. As the testicle descends into the scrotum, the processus vaginalis forms a serous covering around the testicle known as the tunica vaginalis. Normally, the patent processus vaginalis undergoes obliteration, closing the communication between the peritoneal cavity and the inguinal canal. A patent processus vaginalis can lead to a variety of anatomic conditions of the inguinal region (Fig. 101.6).

The incidence of patent processus vaginalis has been reported to be as high as 80% to 94% in newborn infants undergoing autopsy,[35] whereas in adulthood, the incidence is 20% to 30%. Infants with unilateral inguinal hernias have been found to have a patent contralateral processus vaginalis in 60% during the first few months of life. By the age of 2 years, 20% of these hernias were obliterated, and half of the remaining 40% became clinical hernias.[36] At least 30% of infants requiring placement of a ventriculoperitoneal shunt for hydrocephalus have been observed to have a patent processus vaginalis in the first few months of life, with a rapid decline in patency in older children.[37] These studies, along with contemporary use of laparoscopic exploration of the contralateral internal ring, demonstrate that although a patent processus vaginalis is common in infancy, there is some degree of obliteration that occurs with increasing age, and a patent processus vaginalis by itself does not constitute a clinical inguinal hernia.

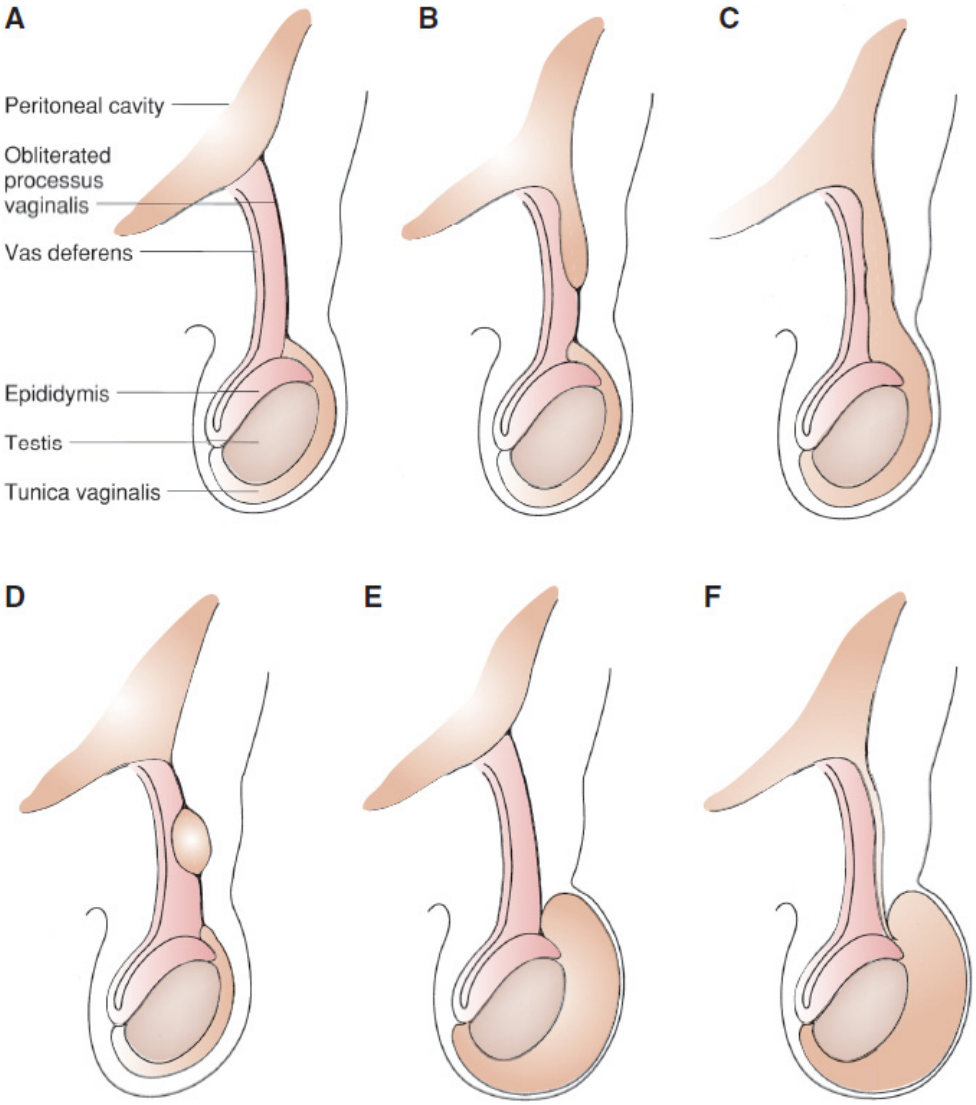


Figure 101.6 Anatomic variations that occur with different degrees of obliteration of the processus vaginalis. **A:** Normal; obliterated processus vaginalis. **B:** Proximal hernia sac; distal obliterated processus. **C:** Hernia sac extending into scrotum; no obliteration. **D:** Proximal and distal obliteration with hydrocele of the cord. **E:** Hydrocele of the scrotum, obliterated processus. **F:** Patent processus with communicating hydrocele.

Clinical Issues

Inguinal hernias occur in 1% to 3% of all children and in 3% to 5% of premature infants. There is no known inheritance pattern, but there is an increased incidence of inguinal hernia in children with connective tissue disorders such as Ehlers–Danlos syndrome and Marfan syndrome. There is a 6:1 predominance of males to females. At least 30% of children are younger

than 6 months at the time of operative repair. Inguinal hernia more commonly presents as right-sided (56.2%) compared with left-sided (27.5%) or bilateral (16.2%).[38]

Most infants and children with an inguinal hernia have a history of an intermittent inguinal mass or bulge that may descend into the scrotum or labia. The hernia may become more pronounced during times of increased intra-abdominal pressure, such as crying or defecating. Most inguinal hernias in children reduce spontaneously or are reducible with gentle, manual pressure along the inguinal canal. Female infants may have an ovary and fallopian tube in the hernia sac, identified clinically as a firm, slightly mobile, nontender mass in the labia or the inguinal canal. Most parents or pediatricians give a characteristic history that is sufficient to warrant inguinal exploration, even in children in whom the hernia cannot be clinically demonstrated at the time of examination. Depending on institution and surgeon preference, infants and children with a strong history consistent with inguinal hernia and an equivocal clinical examination may be offered ultrasound or diagnostic laparoscopy to effectively confirm the diagnosis before groin exploration.[39]

Incarceration is a common consequence of untreated inguinal hernia and presents as a nonreducible mass in the inguinal canal, scrotum, or labia.[40] Clinical symptoms and signs are related to the duration of incarceration. If the incarceration has been present for several hours, the infant may be inconsolable and have feeding intolerance, pain, abdominal distention, vomiting, and lack of flatus or stool, signaling complete intestinal obstruction. The affected groin may become quite edematous, and a reactive scrotal hydrocele may evolve. Elevation of the infant's lower extremities with a pillow may help encourage spontaneous reduction. Attempts at manually reducing an incarcerated inguinal hernia should be performed by an experienced surgeon. If necessary, sedation to calm the infant before attempting manual reduction may be cautiously used. Ice packs should be avoided in infants and children. Following successful reduction of an incarcerated hernia, expedient elective repair of the hernia should be performed after the edema has subsided. This may be up to 48 hours later. If reduction of an incarcerated hernia requires several attempts and is difficult, overnight inpatient observation is warranted to rule out reduction of strangulated bowel; fortunately, this is an uncommon occurrence in the pediatric population. Inability to reduce an incarcerated hernia is a clear

indication for urgent operative exploration and repair. Incarcerated inguinal hernia must be differentiated from an acute, noncommunicating hydrocele, or inguinal lymphadenitis. With acute hydrocele, it is usually possible to transilluminate the hydrocele and palpate normal cord structures above the scrotal mass. In addition, symptoms of bowel obstruction are absent with acute hydrocele. Acute lymphadenitis typically is associated with fever, erythema, and tenderness, and there may be a history of lower extremity infection on the ipsilateral side. If the inguinal mass is not reducible and an incarcerated hernia cannot be excluded, urgent groin exploration is required.

Operative Considerations and Outcome

The diagnosis of inguinal hernia in an infant or a child is an indication for operative repair. The rationale for elective repair is to prevent the complications associated with incarceration. At least 71% of infants who require operative reduction of incarcerated inguinal hernia are younger than 11 months.[41] Therefore, an approach emphasizing timely elective repair of inguinal hernia is warranted, particularly during infancy. Delay of elective repair may be necessary in premature, extremely low–birth-weight (<1,500 g) infants and in children with other conditions such as congenital heart disease, pulmonary disease, infection, or metabolic disease.

Elective inguinal hernia repair in the pediatric age group is usually performed as an outpatient surgical procedure using general anesthesia, although spinal anesthesia is an effective alternative in selected high-risk infants.[42] A regional caudal block or local inguinal nerve block using local anesthetic is useful to diminish perioperative pain and increase patient comfort. These techniques, along with the use of rapid-acting general anesthetics, allow the vast majority of children to be discharged home within hours of operation. Overnight observation and monitoring are required for high-risk infants and children with disorders that increase anesthetic risk for postoperative apnea.

Repair of pediatric inguinal hernia relies on high ligation of the hernia sac at the internal inguinal ring. Sensory nerves deep to the external oblique aponeurosis should be identified and preserved. Careful identification and dissection of the hernia sac from the vas deferens and the testicular blood supply must be performed. The vas deferens must be carefully dissected free

from the sac, and direct handling or pinching of the vas with forceps is avoided. The absence of a vas deferens or a blind-ending vas may be observed in children with cystic fibrosis (CF). In female infants, opening the hernia sac to visualize the ovary and fallopian tube may help avoid inadvertent injury to these structures during suture ligation of the sac. The distal component of the hernia sac is opened widely, and any fluid in the sac is evacuated. If the internal inguinal ring is attenuated or enlarged, it can be repaired with a few sutures. Experience with laparoscopic inguinal hernia repair using purse-string suture closure of the patent internal ring without direct inguinal exploration has been described.[43] The testicle is returned to its scrotal position by gentle traction on the gubernaculum, and the spermatic cord is carefully aligned along the inguinal canal. Postoperative pain is managed with oral acetaminophen for 24 to 48 hours; older children may require postoperative narcotics. In addition, abnormalities of the vas deferens may be associated with genitourinary anomalies. A renal ultrasound should be performed to rule out kidney malformations.

Operative exploration of the asymptomatic contralateral groin remains controversial but is often performed in infants younger than 2 years because of the reported 60% to 70% incidence of a patent processus vaginalis on the opposite side.[44] In a survey of the surgical section of the American Academy of Pediatrics, 65% of the respondents perform contralateral exploration in male patients younger than 2 years, and 84% perform exploration for female infants up to 4 years of age.[45] Direct visualization of the contralateral groin can be performed using a laparoscope inserted either through the umbilicus or through a side-viewing laparoscope inserted through the hernia sac. Experience with diagnostic laparoscopy demonstrates that approximately one-third to one-half of children have a patent processus vaginalis on the contralateral, asymptomatic groin, with higher rates in infants younger than 1 year.[46,47] This approach avoids unnecessary contralateral groin exploration in about half of all children who undergo surgery for unilateral inguinal hernia. However, the presence of a patent processus alone does not necessarily translate into a clinically significant hernia, and via systematic review, the reported risk of developing a metachronous contralateral inguinal hernia following open unilateral hernia repair in children is 7.2%.[48]

The major risk of inguinal hernia repair in infants and children is related to general anesthesia. Complications in pediatric inguinal hernia repair include

wound infection, injury to the vas deferens or testicular vessels, injury or displacement of the testicle, and recurrence. Fortunately, all these complications are infrequent. The overall complication rate is higher for children requiring emergent operation for incarcerated or strangulated hernia. Recurrent inguinal hernia following elective repair is unusual and may be an indication of an underlying connective tissue disorder such as Ehlers–Danlos syndrome.

Hydrocele

A *hydrocele* is a fluid collection that resides in the tunica vaginalis in the scrotum or the processus vaginalis in the inguinal canal. A hydrocele may be present at birth, or it may occur acutely as a result of an incarcerated hernia or torsion of the appendix testis. On examination, a hydrocele transilluminates with a bright handheld light. A hydrocele is described as either *communicating* or *noncommunicating* depending on whether there is direct patency between the hydrocele and the peritoneal cavity. A history of intermittent fluctuation in the size of the hydrocele is generally diagnostic for communicating hydrocele. A communicating hydrocele is synonymous with a patent processus vaginalis, and, therefore, a communicating hydrocele is treated operatively in the same fashion. In male patients, a hydrocele of the cord is a collection of fluid in the processus vaginalis separate from the tunica vaginalis. In female patients, fluid trapped in the processus vaginalis is considered a hydrocele of the canal of Nuck. In noncommunicating hydrocele, the isolated fluid collection is typically asymptomatic and tends to spontaneously resolve before age 12 months. Operative management of noncommunicating hydrocele is usually reserved for lesions that persist after this age, acute enlargement of the hydrocele, or if there is any question of communication.

GASTROINTESTINAL DISORDERS

Neonatal Intestinal Obstruction

3 A variety of congenital anatomic defects, inherited metabolic diseases, and acquired physiologic disorders may present as intestinal obstruction in a newborn. Neonatal intestinal obstruction is characterized clinically by bilious emesis and is often associated with abdominal distention. Bilious emesis in a neonate must be considered to be acute mechanical intestinal obstruction until proven otherwise. Emergent surgical evaluation is warranted for any newborn with bilious emesis. Table 101.2 provides differential diagnoses for neonatal intestinal obstruction along with salient features of the history, physical examination, and diagnostic studies.

The clinical presentation of neonatal intestinal obstruction depends, in part, on the site of obstruction and the age of the infant. Clinical examination of the infant typically provides the surgeon with a preliminary diagnosis and helps guide further diagnostic studies. Abdominal distention is a characteristic physical finding with distal bowel obstruction, whereas the abdomen may be flat in proximal obstruction. The presence of bile in the gastric contents or stool provides clinical evidence of the location of an obstruction relative to the ampulla of Vater. Bilious emesis in an infant or child should be considered an anatomic obstruction requiring emergent surgical evaluation. An infant with bilious emesis who has already passed meconium and has tolerated feeding is unlikely to have intestinal atresia and more likely to have intestinal malrotation with midgut volvulus. If volvulus is suspected, emergent evaluation must be performed to diagnose and prevent catastrophic bowel injury or death.

Definitive diagnosis of neonatal intestinal obstruction may often be made by physical examination and readily available radiologic studies. Incarcerated inguinal hernia is an important cause of neonatal bowel obstruction, and examination leads to a straightforward diagnosis. Some congenital conditions have clearly recognizable features and may be associated with anatomic intestinal obstruction. For example, infants with trisomy 21 have a higher probability of having duodenal atresia or Hirschsprung disease than the general population. An approach to imaging the neonate suspected of having an intestinal obstruction is to obtain a plain abdominal radiograph, followed by either a contrast enema or an upper gastrointestinal series. Plain films of the newborn abdomen can be extremely useful because swallowed gas acts as a contrast agent. For example, duodenal atresia gives rise to a dilated, gas-filled stomach and duodenum

proximal to the obstruction; the remainder of the bowel remains gasless, giving rise to the “double-bubble” appearance on plain films. Other causes of proximal intestinal obstruction may lead to a microcolon on contrast enema, which is a small, unused but otherwise normal colon. If a retrograde contrast enema does not pass into the dilated segment of bowel, an upper gastrointestinal series may be useful to identify a more proximal obstruction. Upper gastrointestinal series is also the most useful diagnostic test for intestinal malrotation.

Table 101.2 Neonatal Intestinal Obstruction

Diagnosis	History	Physical Examination	Diagnostic Studies
Intestinal atresia or stenosis	Bilious emesis Failure to pass meconium	Abdominal distention	Plain abdominal film Contrast enema
Duodenal atresia or stenosis	Bilious or nonbilious emesis Feeding intolerance	Gastric distention Trisomy 21	Plain abdominal film Upper GI contrast study
Imperforate anus	Failure to pass meconium Bilious emesis (late)	Absent anus or visible fistula Abdominal distention VACTERL association	Plain chest, abdominal film Ultrasound kidneys, sacrum, rectum Echocardiogram
Necrotizing enterocolitis	High-risk, premature infant Bilious emesis	Abdominal distention Abdominal wall erythema Hematochezia, guaiac positive stool	Plain abdominal film
Meconium ileus	Cystic fibrosis (10%) Bilious emesis	Acholic meconium Abdominal distention	Plain abdominal film Contrast enema
Malrotation	Bilious	No abdominal	Plain abdominal

	emesis Term, healthy infant	distention	film Upper GI contrast study
Hirschsprung disease	Delayed passage of meconium Bilious emesis	Abdominal distention Trisomy 21	Plain abdominal film Contrast enema
Uncommon causes of obstruction (intussusception, Meckel diverticulum, duplication)		Abdominal mass, incarcerated hernia	Variable
Medical conditions associated with ileus	Bilious emesis	Sepsis, hypothyroidism, etc.	Plain abdominal film

GI, gastrointestinal; VACTERL, vertebral, anal, cardiac, tracheal, esophageal, renal, and limb anomalies.

Several medical conditions of the newborn appear clinically similar to mechanical intestinal obstruction (see Table 101.2). In particular, bilious emesis from ileus secondary to neonatal sepsis is not uncommon. Congenital hypothyroidism is an infrequent and medically treatable condition that can produce delayed intestinal motility that mimics mechanical intestinal obstruction.

Intestinal Atresia or Stenosis

Embryology and Anatomy

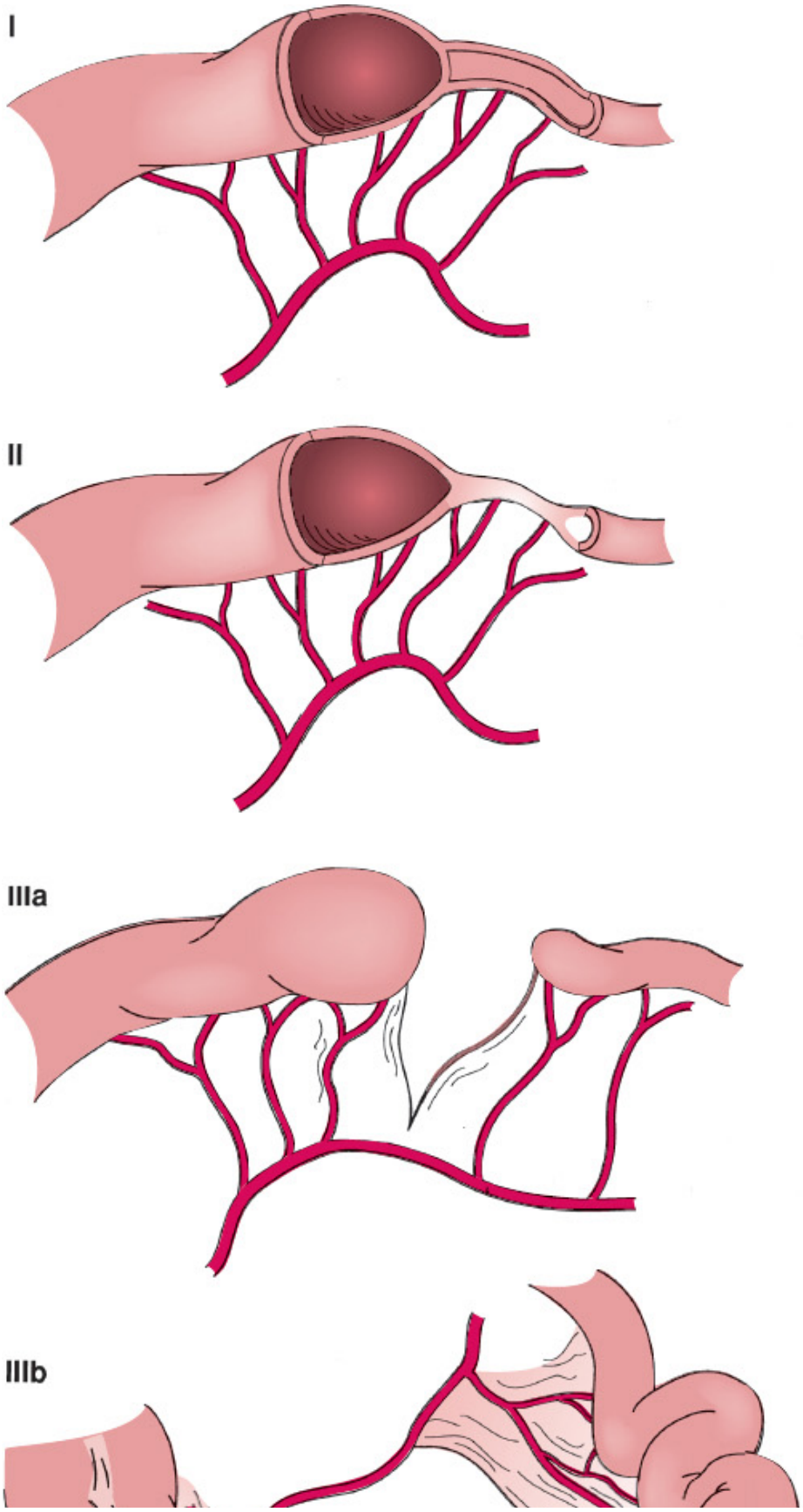
The embryonic intestine undergoes segmental development during the third week of gestation. The septum transversum demarcates the developing foregut from the midgut. The midgut can be considered a tubular structure that

progressively undergoes several predictable, developmental stages: (a) elongation; (b) herniation from and reduction into the coelomic cavity; (c) rotation; and (d) fixation of the mesentery to the posterior body wall.

Several different types of intestinal atresia are clinically observed (Fig. 101.7). *Type I* atresia is an intraluminal web or diaphragm that can either be complete or fenestrated with intact seromuscular layers of bowel. *Type II* and *IIIa* atresia are believed to be a result of in utero mesenteric vascular accidents. Experimental interruption of the fetal mesenteric blood supply in utero leads to this type of atresia.[49,50] *Type IIIb* atresia, also known as the *apple-peel* or *Christmas tree deformity,* has complete mesenteric discontinuity, with the distal bowel concentrically surrounding a singular mesenteric blood supply. *Type IV* atresia has multiple segmental areas of discontinuous bowel. Type IIIb and IV atresia are thought to be consequences of major and multiple fetal mesenteric vascular interruption.

At least 90% of infants with congenital intestinal obstruction of the small bowel have complete atresia, whereas the remaining children have either stenoses or fenestrated intraluminal webs. The most common location is the distal ileum, and multiple areas of atresia are discovered in 3.6% to 20% of these infants.[39] Infants with a fenestrated intraluminal web may have a small, often eccentric, opening that is only millimeters in diameter. These infants may not have obstructive symptoms until the introduction of solid food at 6 to 12 months of age and present with feeding intolerance, failure to thrive, or abdominal pain.

Congenital colonic atresia is a distinctly unusual condition. In a contemporary series of 277 infants treated with intestinal atresia, only 21 children had colonic atresia.[51] Similar to small bowel atresia, colonic atresia is believed to reflect fetal mesenteric vascular injury. Given the distal nature of colonic atresia, initial feeding may be well tolerated and definitive diagnosis may be delayed for several days. The diagnostic evaluation and surgical treatment of colonic atresia is identical to the approach used for small bowel atresia. Colonic atresia may be associated with abdominal wall defects, skeletal or cardiac defects, congenital aganglionosis (Hirschsprung disease), or coexisting intestinal atresia.


I
II
IIIa
IIIb

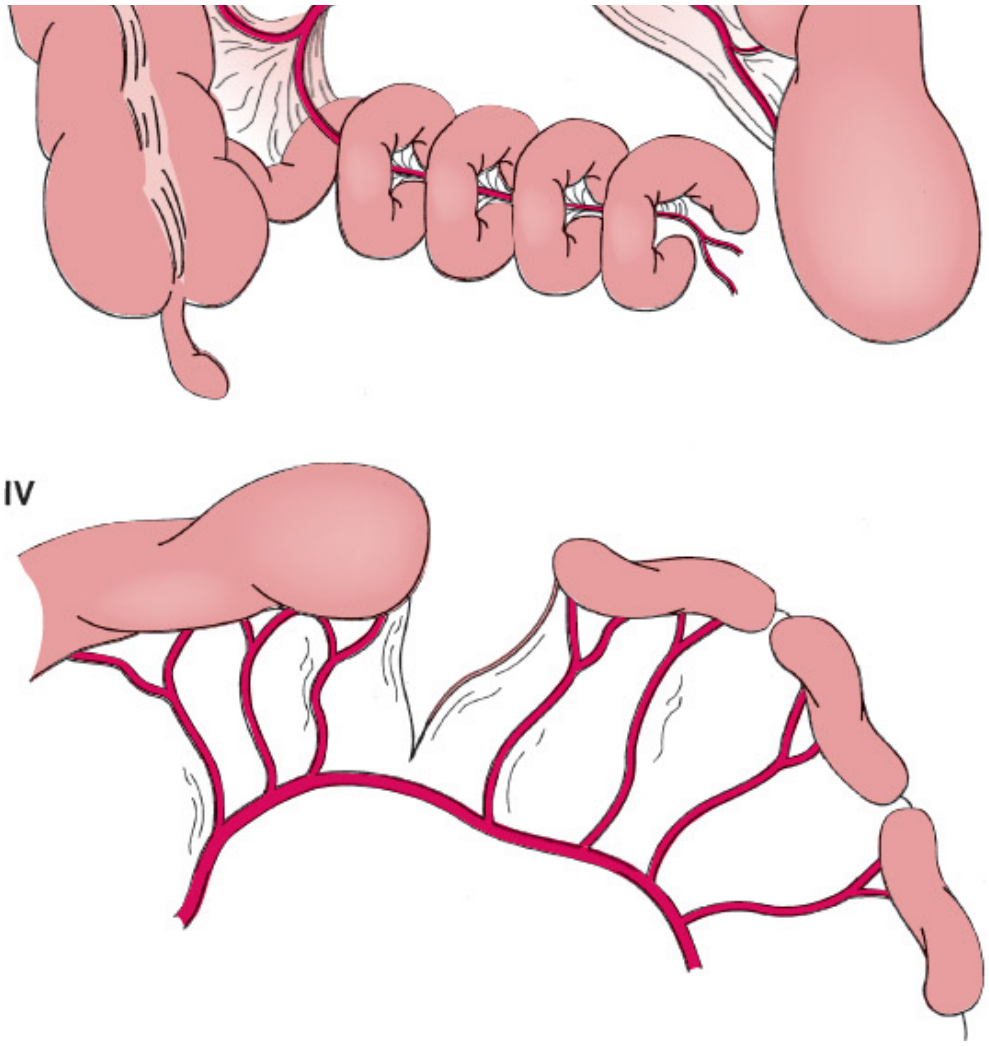


Figure 101.7 Classification of intestinal atresia. Type I, muscular continuity with a complete web. Type II, mesentery intact, fibrous cord. Type IIIa, muscular and mesenteric discontinuous. Type IIIb, apple-peel deformity. Type IV, multiple atresias.[57]

Clinical Presentation

Estimated incidence of intestinal atresia in the United States are 3.5 to 3.75 cases per 10,000 total births.[52] Infants with jejunal or ileal atresia have a low incidence rate of significant associated anomalies. Approximately 10% of infants with gastroschisis have intestinal atresia or stenosis secondary to mechanical interruption of the mesenteric vascular supply.

Detection of maternal polyhydramnios on routine prenatal ultrasound screening can be an indication of proximal bowel obstruction caused by the interruption of normal amniotic fluid absorption in the fetal gut.[53] Following

delivery, the classic clinical presentation of intestinal atresia is bilious emesis, abdominal distention, and failure to pass meconium. The degree of abdominal distention depends on the site of obstruction, the infant's age, and the efficacy of proximal decompression. Abdominal distention may be absent with proximal intestinal atresia. Distal intestinal atresia may lead to abdominal distention with visible or palpable intestinal loops on examination. Rectal examination and evaluation of stool character remains important when intestinal obstruction is suspected.

Diagnosis

Following history and physical examination, plain radiographic abdominal films should be obtained. Plain films in jejunal or ileal atresia demonstrate marked gaseous distention of the proximal intestine with gasless distal small bowel and colon. Haustral markings are normally not apparent in the neonatal colon, and, therefore, discrimination between small bowel and colon in the newborn is difficult without intraluminal contrast. A contrast enema is can be obtained to confirm the diagnosis of jejunoileal atresia and to rule out distal obstructions. A diminutive, unused but otherwise normal microcolon is typical, and the inability to reflux contrast into the proximal, dilated small bowel segment is diagnostic for congenital intestinal obstruction. This radiographic finding, in conjunction with the clinical setting, warrants operative exploration. An upper gastrointestinal series is unnecessary and may increase the risk of further emesis and aspiration in the newborn with obstruction. Incomplete obstruction from a fenestrated intraluminal web may require more sophisticated imaging techniques such as catheter-directed enteroclysis.

Treatment

Anatomic lesions causing neonatal intestinal obstruction require operative treatment. Whereas malrotation with midgut volvulus requires emergent diagnostic workup and operative intervention, obstruction resulting from intestinal atresia is generally not associated with life-threatening physiologic disturbances. Therefore, initial treatment is aimed at treating any other associated problems, confirming diagnosis, and preparing the infant for an operation. During this period, the infant should always have an orogastric or

nasogastric tube in place to provide proximal decompression of the obstructed bowel.

The operative strategy in treating intestinal atresia is to restore gastrointestinal tract continuity while preserving as much intestinal length as possible. The operation is straightforward and an end-to-end or end-to-oblique (end-to-back) anastomosis is typically performed (Fig. 101.8). Short-segmental bowel resection and excision of an intraluminal web or diaphragm are done when necessary. Visual inspection and instillation of intraluminal saline or air to exclude distal atresia or web prior to anastomosis is important to evaluate patency of the downstream bowel. The size discrepancy between the proximal and distal bowel is usually considerable, and delayed postoperative bowel motility is common. Some surgeons advocate the use of technical procedures to improve emptying of the proximal bowel by reducing overall bowel diameter. These procedures include resection of 4 to 5 cm of proximal jejunum or ileum, plication, and tapering enteroplasty. Complex atresia associated with apple-peel deformity or multiple segmental atresias may require multiple serial anastomoses to preserve as much bowel length as possible. The ileocecal valve is preserved whenever possible, allowing improved tolerance of enteral nutrition in infants with limited small bowel length. It is estimated that approximately 40 cm of small bowel without an ileocecal valve, compared with 15 to 20 cm with an ileocecal valve, is sufficient for long-term enteral feeding tolerance in the neonate.[54] Contemporary management of colonic atresia includes primary anastomosis when technically possible.

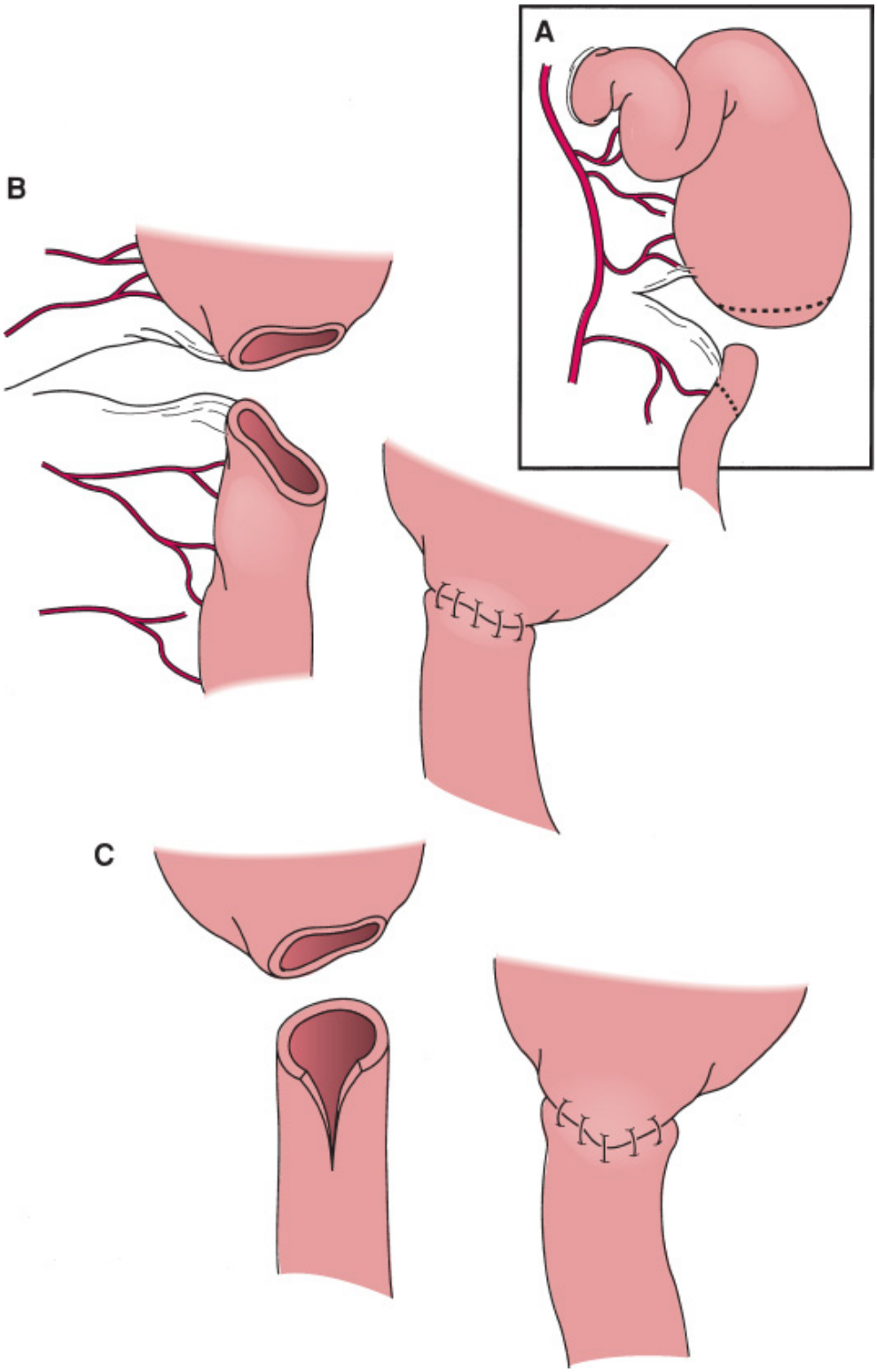


Figure 101.8 **A, B:** The end-to-oblique anastomosis for small bowel atresia. **C:** An extension of the distal enterostomy along the antimesenteric border may be used to create proximal and distal lumens of equal size for anastomosis.

Results and Outcome

Currently, the overall survival rate for infants treated for intestinal atresia or stenosis (including duodenal atresia) exceeds 93% in most large series.[51,55] Mortality in these infants is generally related to cardiac anomalies, birth weight less than 2 kg, and associated congenital anomalies.[56] Infants with a limited amount of intestinal length for nutritional absorption (short bowel syndrome with less than 40 cm) usually require long-term TPN and are at moderate to high risk for sepsis and liver injury. Infants with normal gastrointestinal length may still have prolonged intestinal dysfunction and dysmotility for several weeks.

Congenital Duodenal Obstruction

Causes of duodenal obstruction in the newborn include duodenal atresia or stenosis, duodenal intraluminal web, and annular pancreas. Because of the common embryologic basis, clinical presentation, and treatment, these entities are considered jointly.

Embryology and Anatomy

The duodenum is derived from both the caudal segment of the foregut and the cranial segment of the midgut. Duodenal development is intimately related to the developing pancreaticobiliary system. The fetal pancreas arises from paired dorsal and ventral foregut diverticula during week 6 of gestation. The dorsal anlage gives rise to the body and tail of the pancreas as well as the main pancreatic duct. The ventral anlage migrates 180 degrees to fuse with the dorsal gland, forming the uncinate process and the distal portion of the duct of Wirsung (Fig. 101.9). An annular pancreas is characterized by glandular persistence surrounding the duodenum at the site of the embryonic ventral anlage. It is invariably associated with intrinsic duodenal obstruction, and a patent accessory pancreatic duct is common (Fig. 101.10).[58]

It is believed that congenital duodenal obstruction results from abnormalities of pancreatic development, failure of duodenal recanalization, or vascular compromise to the duodenum. Duodenal atresia may occur with or without seromuscular continuity, and an intraluminal duodenal web may occur with or without fenestration. The most frequent location for duodenal

atresia is in the descending duodenum distal to the ampulla of Vater. Most series report a 5% to 10% incidence of duodenal atresia proximal to the ampulla, giving rise to nonbilious gastric contents and emesis. Another important variant is a periampullary web projecting distally into the duodenal or jejunal lumen, forming a "wind-sock" deformity (Fig. 101.11). In this instance, the ampulla must be clearly identified before excision and repair because of the proximity of the ampulla to the web.

Clinical Presentation

The incidence rate of congenital duodenal obstruction is estimated to be about 1 in 6,000 to 10,000 births.[59] About 30% of these infants have trisomy 21.[60] Infants born with duodenal atresia should be examined with a high degree of suspicion for trisomy 21 and undergo routine karyotype analysis. Other associated anomalies such as congenital heart disease, genitourinary tract malformations, and musculoskeletal disorders are common in these infants, and appropriate preoperative workup is necessary.

Congenital duodenal obstruction most commonly presents in the first 24 to 48 hours of life with feeding intolerance and bilious emesis; duodenal obstruction proximal to the ampulla of Vater results in nonbilious emesis. On physical examination, infants with untreated duodenal obstruction may have a palpable epigastric mass, and gastric peristaltic waves may be visible. The collapsed and unused distal small intestine typically does not produce diffuse abdominal distention. Partial duodenal obstruction from a fenestrated web may not produce symptoms in the newborn period, and delayed diagnosis is common.

Diagnosis

Prenatal diagnosis of duodenal atresia is possible given contemporary fetal ultrasound techniques. Following birth, infants with suspected duodenal atresia should obtain plain abdominal radiographs. The classic radiographic finding of duodenal atresia is a double bubble from the air-filled stomach and duodenum (Fig. 101.12). In complete duodenal obstruction, no gas is seen distal to the duodenum; in this setting, the plain film is sufficiently diagnostic that no further imaging of the gastrointestinal tract is necessary. If there is incomplete obstruction, gas may be seen distally in the small or large

intestine. Infants with suspected incomplete obstruction at the duodenal level may have either a fenestrated web or volvulus secondary to malrotation. Given the need for emergent operative intervention in malrotation with acute volvulus, an urgent upper gastrointestinal series with contrast should be strongly considered to exclude a neonatal surgical emergency. Importantly, all anatomic lesions causing neonatal duodenal obstruction require operative repair using a similar approach.

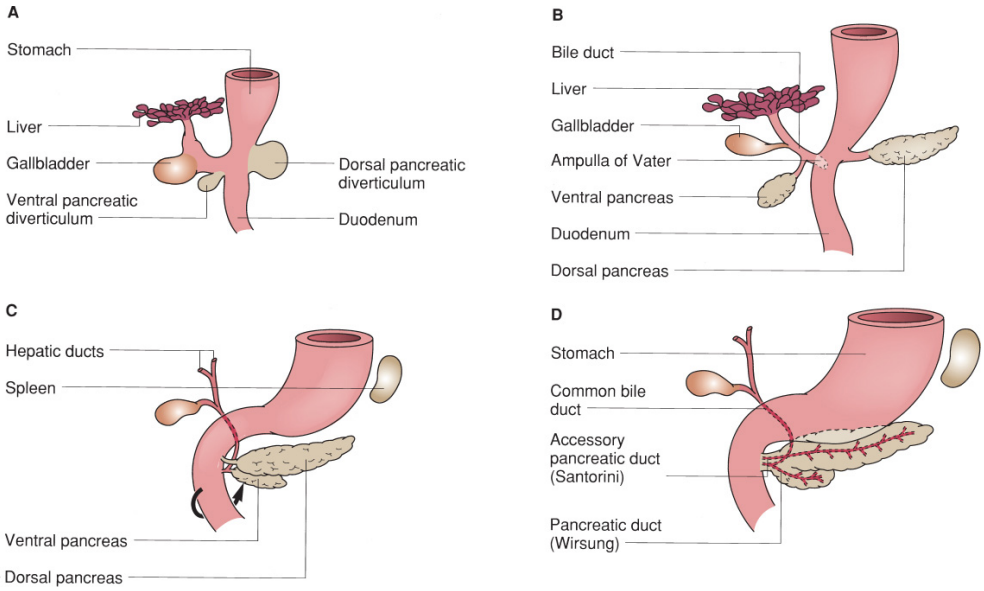


Figure 101.9 Normal embryologic development of the duodenum, pancreas, and bile ducts. **A:** Fifth gestational week. **B:** Sixth week. **C:** Seventh week. **D:** Eighth week.

Treatment

Following expedient treatment of any associated life-threatening medical conditions and preoperative evaluation, the operative goals are to restore gastrointestinal continuity without sacrificing intestinal length or absorptive surface area. Because most lesions causing congenital duodenal obstruction are near the ampulla of Vater, great care must be exercised in treatment to avoid inadvertent injury to the ampulla or the pancreas.

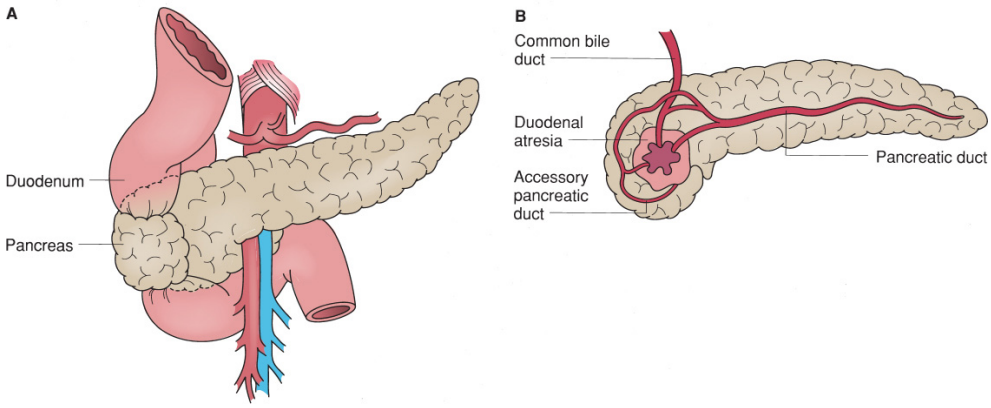


Figure 101.10 Annular pancreas. **A:** The associated duodenal atresia is shown. **B:** The relationships of the annular pancreas to the common bile duct and main and accessory pancreatic ducts are shown in cross section.

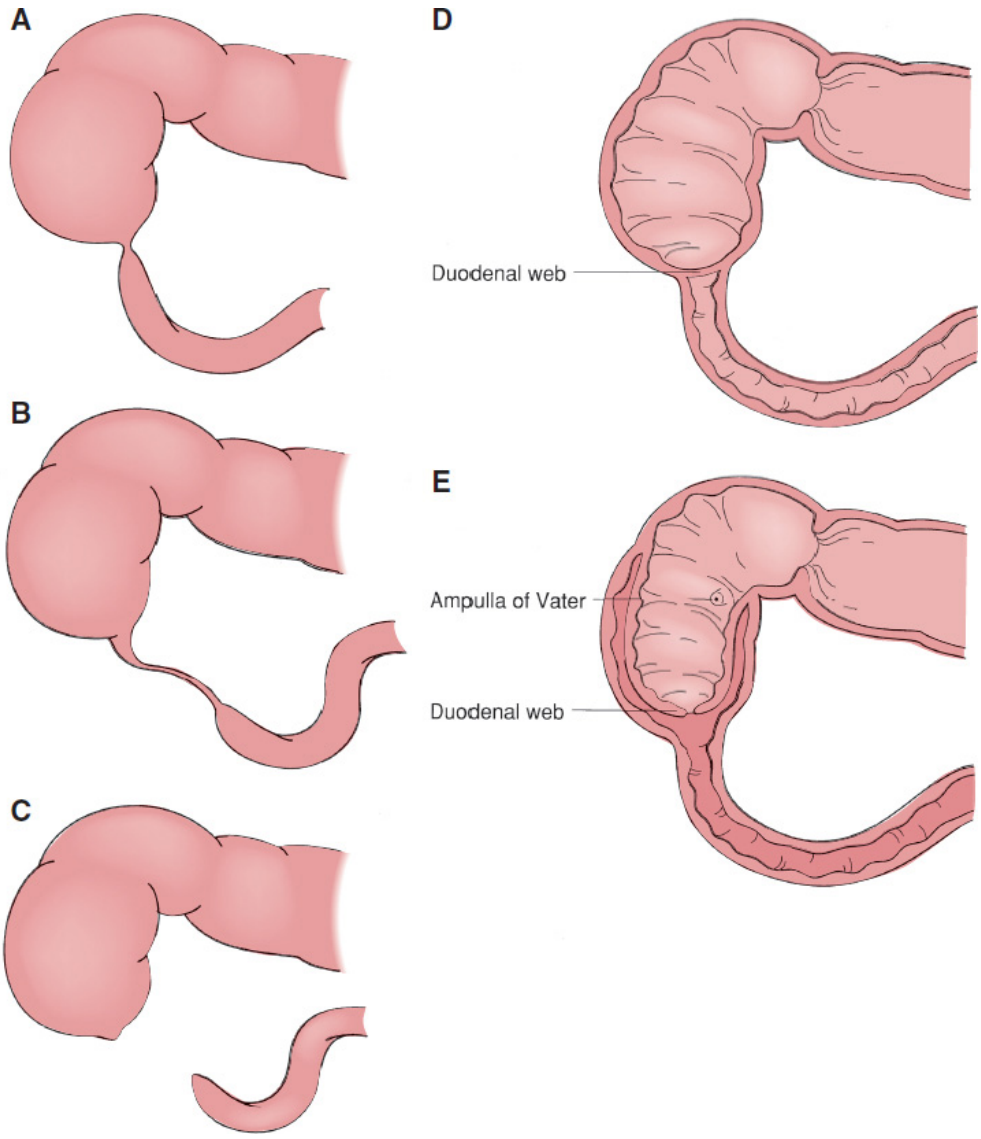


Figure 101.11 Anatomic forms of duodenal atresia (**A–C**) and webs (**D, E**). In particular, (**E**) demonstrates the unique wind-sock deformity. This lesion is important and potentially confusing because the point of obstruction is not at the apparent point of change in luminal diameter.

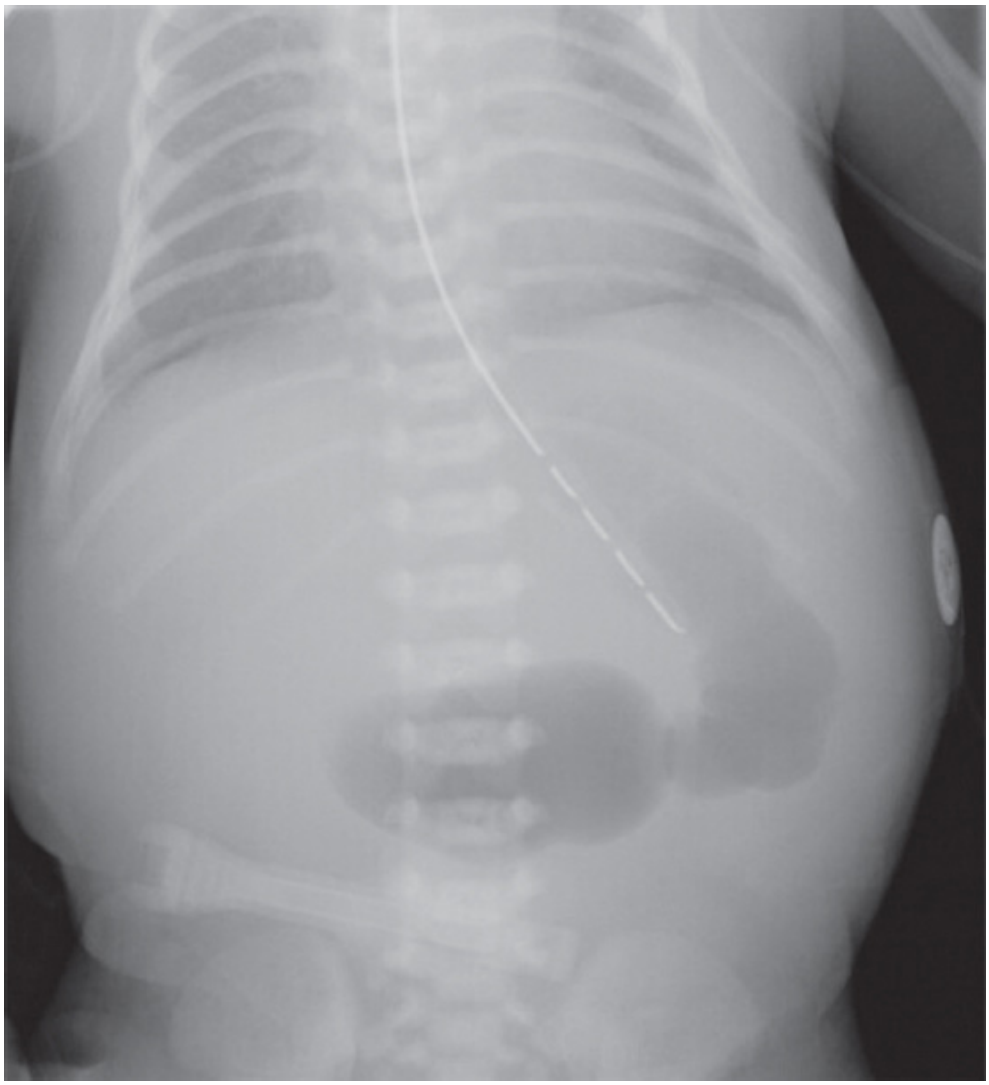


Figure 101.12 Classic radiographic appearance of duodenal atresia. There is a double bubble of gas in the stomach and the proximal duodenum, with no gas in the distal intestinal tract.

Congenital duodenal atresia is treated by duodenoduodenostomy. Duodenal obstruction secondary to annular pancreas is also treated by duodenoduodenostomy. Direct division of annular pancreas is not performed because this does not address the underlying intraluminal duodenal obstruction, and there is significant risk of injury to the accessory pancreatic duct (see Fig. 101.10).

Duodenoduodenostomy is performed by making a transverse incision in the dilated, proximal duodenum and a longitudinal incision in the unused, downstream duodenum. The lumens are sutured together to form a diamond-shaped anastomosis (Fig. 101.13).[61] Downstream duodenal patency should be

demonstrated by passing a catheter or infusing saline or air distally to avoid overlooking synchronous distal intestinal atresia. Successful and efficacious laparoscopic duodenal atresia repair has also been reported.[62]

Duodenal webs are excised through a longitudinal duodenotomy. The wind-sock duodenal web must be clearly identified because the visible transition from the distended, proximal duodenum to the small, downstream duodenum may be several centimeters distal to the base of the web. The ampulla of Vater must be unequivocally identified before duodenal web excision to avoid injury. Closure of the longitudinal duodenotomy is performed transversely to avoid narrowing of the duodenum.

There is usually great size discrepancy between the dilated, proximal pouch and the distal duodenal lumen, leading some surgeons to advocate procedures designed to reduce the diameter of the proximal duodenum in an effort to facilitate improved postoperative bowel motility. The efficacy of these procedures, which include tapering duodenoplasty and duodenal plication, has been described in anecdotal fashion without randomized comparison.

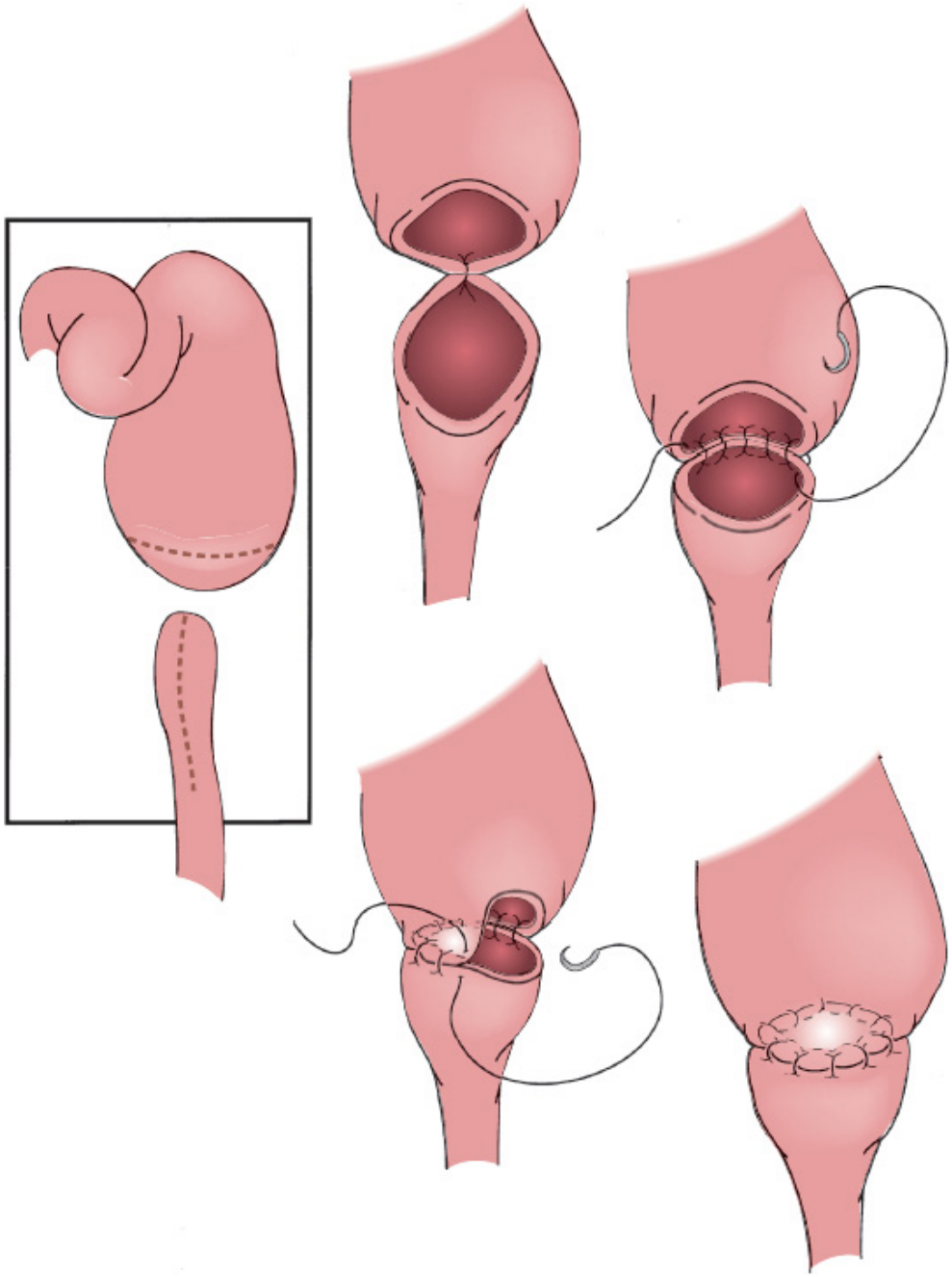


Figure 101.13 Diamond-shaped duodenoduodenostomy for repair of duodenal atresia.

Results and Outcome

After successful operative repair of duodenal atresia or stenosis, delayed gastric emptying is common and typically manifests as enteral feeding intolerance. Patience and persistence are essential during the postoperative period as recovery of bowel function may take up to 10 days post op.

Surgical outcomes after repair of congenital duodenal obstruction are excellent,[60–63] with perioperative survival exceeding 95%. Perioperative mortality is generally related to other congenital anomalies and, in particular, congenital heart disease in infants with trisomy 21. Other late problems may be encountered that reflect gastroduodenal motility issues such as poor gastric emptying, gastroesophageal reflux, and duodenal dilatation. These symptoms may appear several months to years following repair and, therefore, long-term surgical follow-up remains important.

Anorectal Malformations (Imperforate Anus)

Embryology

By week 5 of gestation, the fetal cloaca is identifiable with the adjacent hindgut, allantois, and vestigial tailgut (Fig. 101.14). The mesoderm of the urorectal septum extends caudally to fuse with the cloacal closing plate. Fusion of the lateral cloacal ridges completes division of the cloaca into the rectum and the urogenital sinus. The caudal aspect of the urorectal septum forms the perineal body. The anal membrane normally ruptures during week 8 of gestation, completing the patency of the distal rectum to the skin. Further development of the urogenital sinus leads to the formation of the urethra and the bladder. In female infants, the uterus and the proximal vagina develop from the müllerian ducts. The diverse anatomic variation observed with anorectal malformations is thought to reflect anomalous or interrupted development of these structures during normal embryogenesis.

Anatomy and Classification

The normal anatomy of the anus and the rectum is reviewed in previous chapters. Normally, the rectum descends to the perineum and ultimately to the anal orifice through a striated muscle complex in the pelvis resembling a funnel. The striated muscle complex is under voluntary control and is responsible for providing fecal continence (Fig. 101.15). Contiguous portions of the *levator ani,* the *external sphincter,* and the *puborectalis* muscles compose the *striated muscle complex.* These anatomically indistinct components of the muscle complex act together to provide control of defecation. The concept of the striated muscle complex and anatomic

relationships leading to normal fecal continence with respect to anorectal malformations has evolved from both clinical and anatomic data as described by Peña.[64]

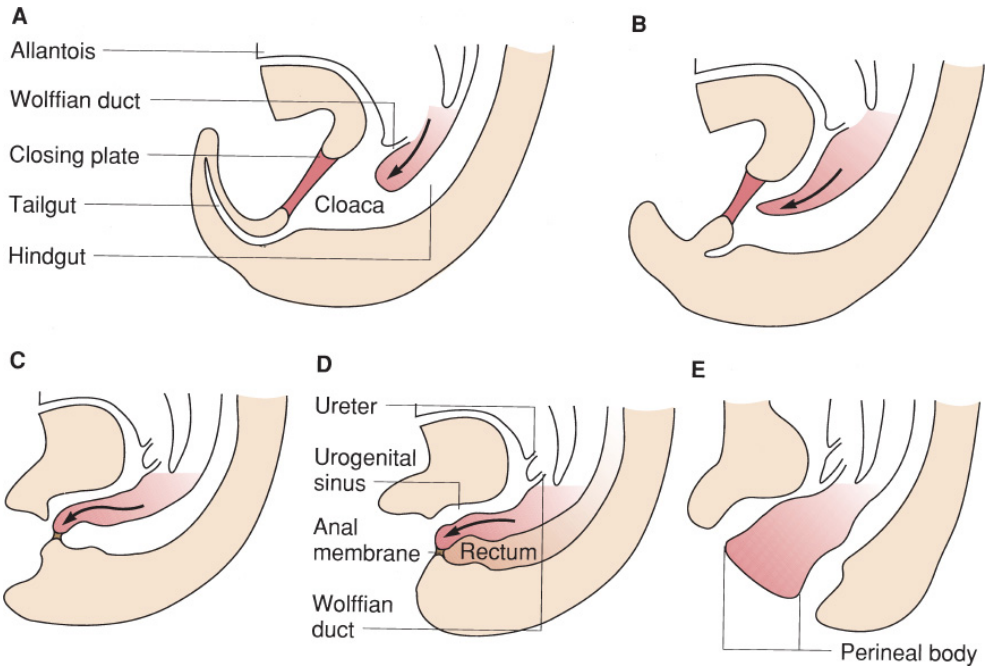


Figure 101.14 Normal embryologic division of the cloaca by the urorectal septum into the ventral urinary tract and the dorsal rectum. This process is normally completed by the ninth or tenth week of gestation.

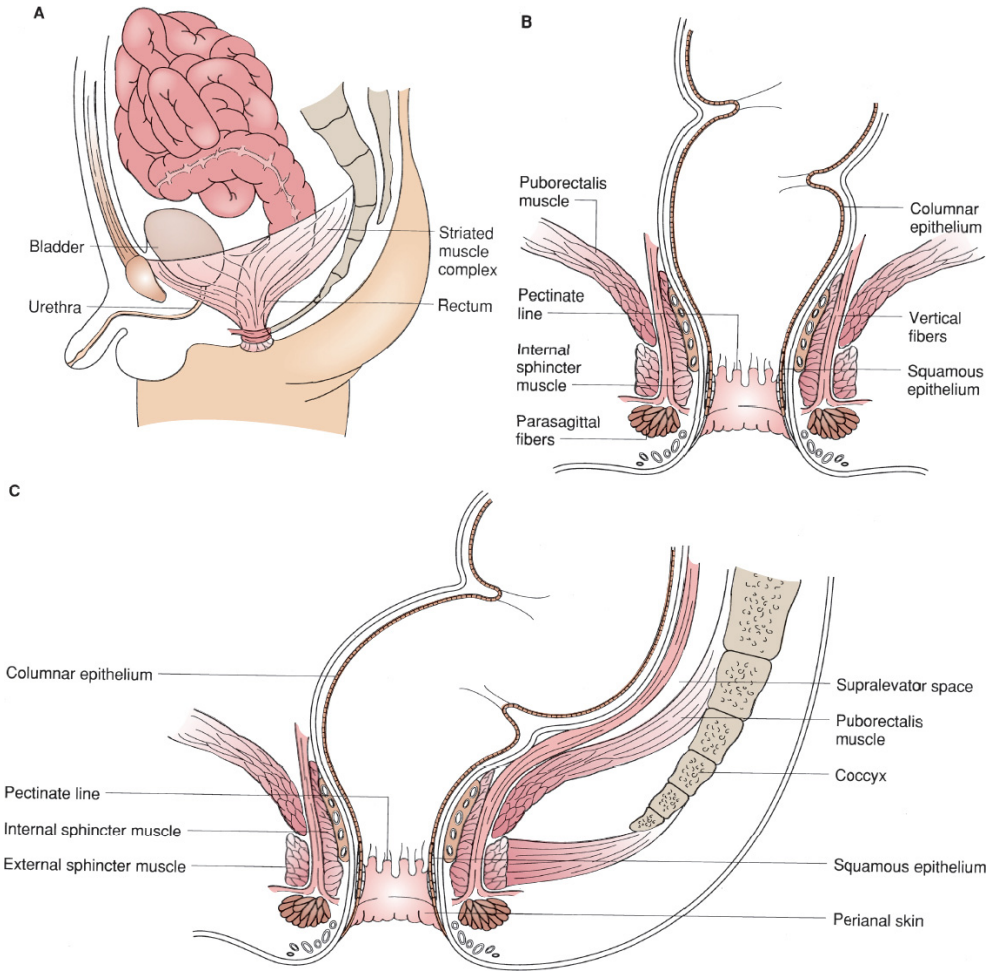


Figure 101.15 The normal relations of the pelvic striated muscle complex and the rectum. **A:** Normal male anatomy. **B:** Coronal view showing individual components of the striated muscle complex. **C:** Sagittal view of normal anatomy.

Because of the variety of anorectal malformations observed, different classification systems have been proposed in an attempt to characterize the defects. A summary of the Wingspread Classification is provided in Table 101.3. This anatomically descriptive classification scheme is useful in planning the operative management of anorectal malformations.

In male subjects, the two most common anorectal malformations observed are low imperforate anus with a perineal fistula (Fig. 101.16) and high anorectal agenesis with a rectoprostatic urethral fistula (Fig. 101.17). Male patients without a visible perineal fistula are assumed to have high imperforate anus with a rectourethral fistula until proven otherwise. In female subjects, the most common malformation encountered is low imperforate anus with a fistula from the rectum to either the perineal body or the vaginal

vestibule (Fig. 101.18). As these malformations result from developmental arrest at various times during migration of the urogenital septum, considerable anatomic variability exists in both male and female subjects.

A common anatomic feature of imperforate anus is incomplete rectal descent to the perineum. Consequently, the rectum is not completely within the striated muscle complex. The caudal portion of the striated muscle complex remains a solid mass of striated muscle, whereas the cephalad portion may be normally positioned circumferentially around the rectal pouch. In low imperforate anus, the rectum nearly reaches the perineum, and the configuration of the striated muscle complex surrounding the rectum more closely approximates normal. With high imperforate anus, less striated muscle surrounds the rectal pouch. All anorectal malformations are considered to have some component of striated muscle complex hypoplasia and dysfunction, although the physiologic effects are variable. Low anorectal lesions have a more favorable prognosis for fecal continence than intermediate or high lesions.

CLASSIFICATION

Table 101.3 Anatomic Classification of Anorectal Malformations

Female	Male
High	
Anorectal agenesis with rectovaginal fistula without fistula	Anorectal agenesis with rectoprostatic urethral or rectocystic fistula or without fistula
Rectal atresia	Rectal atresia
Intermediate	
Rectovestibular fistula	Rectobulbar urethral fistula
Rectovaginal fistula	Anal agenesis without fistula
Anal agenesis without fistula	
Low	
Anovestibular fistula[a]	Anocutaneous fistula[a]
Anocutaneous fistula[a,b]	Anal stenosis[a,c]
Anal stenosis[c]	Rare malformations
Cloacal malformations[d]	
Rare malformations	

[a]Relatively common lesion.

[b]Includes fistulas occurring at the posterior junction of the labia minora, often called *fourchette fistulas* or *vulvar fistulas.*

[c]Previously called *covered anus.*

[d]Previously called *rectocloacal fistulas.* Entry of the rectal fistula into the cloaca may be high or intermediate, depending on the length of the cloacal canal.

Classic delineation between low and high anorectal malformations is made anatomically at the pubococcygeal line. The vast majority of low lesions have

associated perineal or vestibular fistulas. High imperforate anus has a blind-ending rectal pouch above the pubococcygeal line and, therefore, above the striated muscle complex (or levator ani).

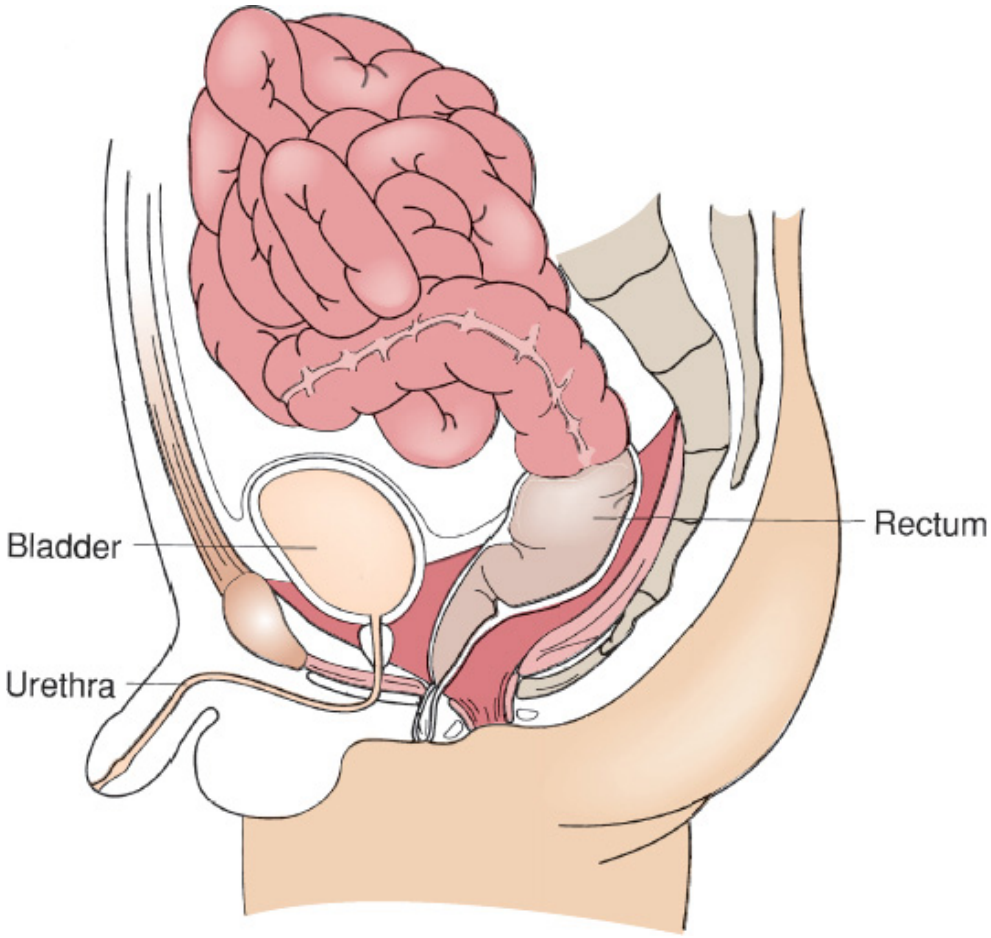


Figure 101.16 Male infant with low imperforate anus and perineal fistula. Note that the fistula is anterior to the striated muscle complex.

Associated Anomalies

Associated anomalies in infants with anorectal malformations are common and may be found in more than 70% of patients. The VACTERL (vertebral, anal, cardiac, tracheal, esophageal, renal, and limb) association is important and requires consideration in any infant with imperforate anus. *Vertebral anomalies* are common and include sacral dysplasia and agenesis. Infants with sacral anomalies commonly have high imperforate anus and sacral nerve dysfunction that can lead to poor long-term fecal continence and neurogenic bladder. A variety of spinal cord malformations can also be observed in these

infants, including tethered spinal cord syndromes and some myelodysplastic syndromes. During the neonatal period, these spinal lesions may be detected by using ultrasound or magnetic resonance imaging (MRI), and surgical treatment may be necessary within the first 8 to 18 months of life. *Tracheoesophageal* fistula with or without esophageal atresia is estimated to occur in about 10% of infants with anorectal malformations. *Renal anomalies* are the most common associated abnormalities with anorectal malformations and include both upper and lower tract conditions. Genitourinary screening in the form of a renal ultrasound and voiding cystourethrogram is routinely performed. *Cardiac* anomalies are common and screening echocardiography is clinically indicated. *Limb abnormalities,* in particular, involvement of the radius, complete the associated anomalies defined by the acronym.

Clinical Presentation

The incidence rate of anorectal malformations is estimated at 1 in 2,524 to 5,000 live births,[65] with a slightly higher rate in males. Careful examination of the neonatal perineum reveals the diagnosis. If unrecognized and left untreated, high imperforate anus eventually leads to signs and symptoms of complete bowel obstruction characterized by abdominal distention, feeding intolerance, and bilious emesis. Because of the nearly uniform rectourethral or rectovesicular fistula in males with high lesions, some of these infants will pass meconium or gas through the urethra during urination. In contrast, infants with low malformations typically pass meconium through a perineal or vestibular fistula within the first 24 hours of life. Occasionally, infants with large perineal fistulas are not diagnosed with an anorectal malformation until progressive constipation is noted weeks to months after birth.

In male infants, more than 95% of low malformations are associated with either a thin anal membrane or a fistula to the perineum or the scrotal raphe. The presence of a “bucket-handle” skin deformity at the presumptive anal dimple is also diagnostic of a low lesion. Infants with high malformations typically lack anal skin dimpling, have a flat gluteal contour, and may have little or absent contraction of the external sphincter with cutaneous stimulation. In female infants, 90% to 95% of low malformations have a perineal or vestibular fistula. In both male and female infants, a perineal

fistula may not become apparent in the first 12 to 24 hours of life until meconium progresses distally through the rectum into the fistula.

Diagnosis

Because surgical treatment of a high or intermediate anorectal malformation is different from that of low lesion, a primary diagnostic goal is to determine whether an infant with imperforate anus has a high or low malformation. A secondary diagnostic goal is to determine the specific anorectal malformation as it relates to the rectourethral or rectovesicular fistula.

Clinical examination of an infant with low imperforate anus almost always reveals an external fistula to the perineum or the vestibule. The classic radiographic study of newborns with imperforate anus is the Wangensteen–Rice invertogram, with a lateral view of the pelvis obtained 12 to 24 hours after birth with the infant in a head-down position. This technique has been largely replaced by ultrasound-directed imaging.[66] Real-time ultrasound is currently well accepted as an accurate method of determining the distal extent of the rectal pouch. Computed tomography (CT) imaging and MRI can be useful in evaluating the pelvic striated muscle complex in difficult cases and, in particular, cloacal malformations. MRI is also useful in evaluation of the distal spinal cord in these infants.

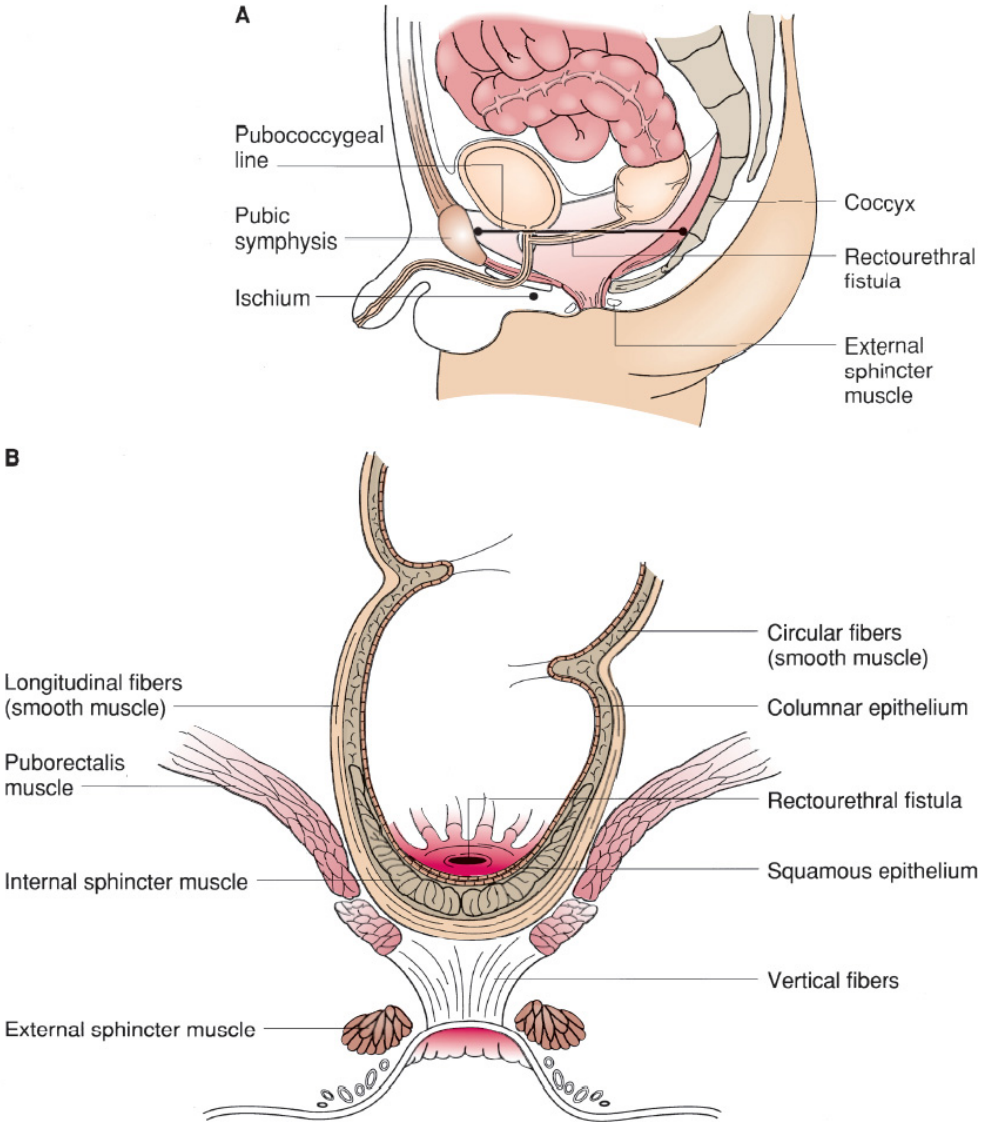


Figure 101.17 Male infant with high imperforate anus, showing the pubococcygeal line, ischium, and striated muscle complex. **A:** The rectal pouch ends cephalad to the pubococcygeal line. This location of the rectourethral fistula is typical. **B:** Coronal view showing incomplete development of the rectal pouch within the striated muscle complex. The rectourethral fistula is shown.

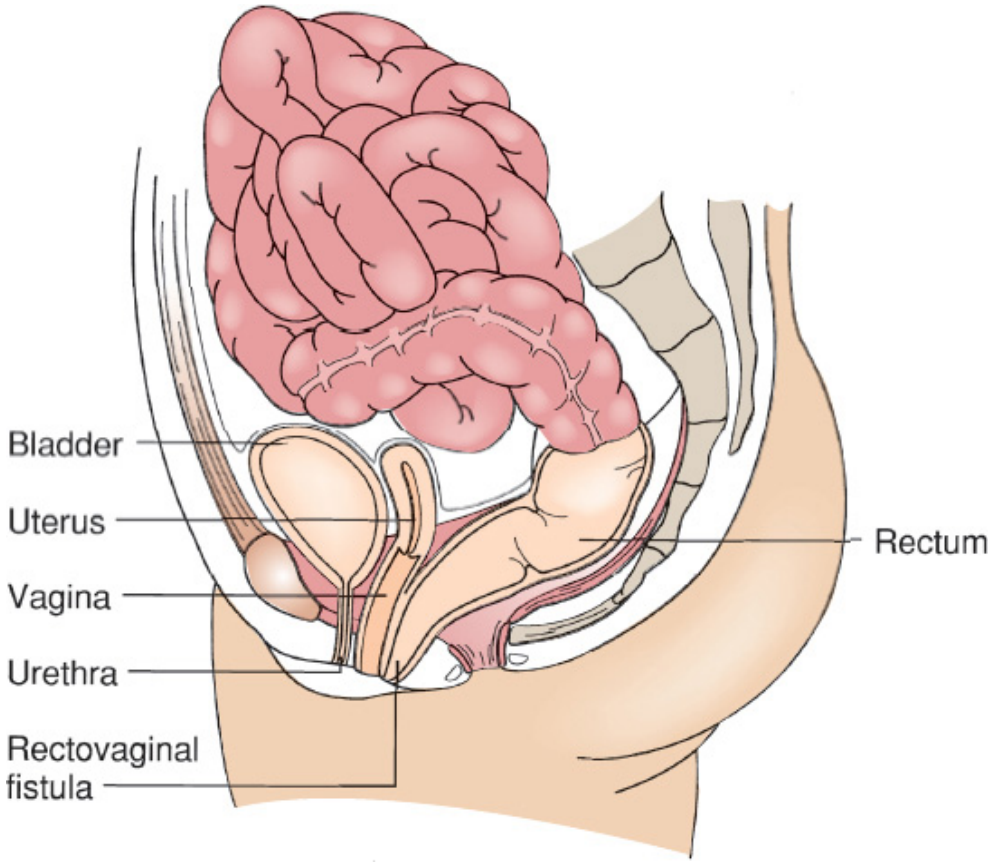


Figure 101.18 Female infant with low imperforate anus and vestibular fistula.

If there is a suspected perineal fistula or covered anus, diagnostic needle aspiration under anesthesia may be useful. Aspiration of meconium not only localizes the rectum or fistula but can also provide an estimation of the distance between the perineum and the rectum or the fistula. In general, low lesions are within 1 cm of the perineum. An infant not clearly found to have a low lesion by physical examination, radiographic studies, or examination under anesthesia should be considered to have a high anorectal malformation and treated accordingly.

Treatment

Imperforate anus by itself is not a life-threatening condition, and, in many instances, observation for 12 to 24 hours may help delineate the presence or absence of a fistula. The surgical management of anorectal malformations has been well described elsewhere[64] and a brief summary follows below.

Low Malformations

Definitive repair of most low anorectal malformations can be performed in the newborn period with perineal procedures that do not require diverting colostomy. Simple dilatation of the fistula or unroofing of a covered anus may relieve the anatomic obstruction. For more complex anal stenoses or anterior perineal fistulas, a formal perineal anoplasty may be required. A common perineal procedure performed is cutback anoplasty, in which the anterior fistula or anal orifice is opened posteriorly by dividing the perineum to the external sphincter. More complex alternative approaches may be preferred in female infants with low vaginal or anterior perineal fistulas. These lesions generally require circumferential mobilization of the anterior fistula with transposition to the center of the external sphincter. Anterior reconstruction of the perineal body is then performed. Transposition anoplasty is designed to position the neoanus within the center of the external sphincter and separate the neoanus from the vaginal introitus.

Intermediate and High Malformations

Infants determined to have an intermediate, high, or indeterminate anorectal malformation generally require diverting divided colostomy as initial surgical management. Care must be taken to ensure that the proximal diverting colostomy provides adequate length and mobility of the distal colon in anticipation of eventual anorectoplasty. A divided colostomy is preferred over a loop colostomy by many surgeons to provide maximal fecal diversion from the downstream rectourinary fistula. Following diverting colostomy, a distal contrast study into the rectal pouch can also define the fistula and delineate the position of the rectum relative to the perineum.

Anorectoplasty is generally performed when the infant is approximately 8 to 12 months of age. Many different approaches have been described, and considerable personal and institutional variation is common. No single approach has superior results, and all have technical merits and difficulties. The common surgical objectives in the treatment of anorectal malformations include (a) relief of the rectal obstruction; (b) creation of a new anus; (c) position the rectum as normally as possible within the striated muscle complex; and (d) divide the rectourinary fistula. In addition, preservation of the surrounding structures (prostate, urethra, seminal vesicles, vaginal wall) is essential.

For repair of high and intermediate anorectal malformations, the most widely used procedure in the United States is the posterior sagittal anorectoplasty described in detail by Peña.[64] The infant is placed prone and a posterior sagittal incision following the gluteal crease is used. The external sphincter and the striated muscle complex are divided posteriorly along the midline to expose the rectal pouch. A muscle stimulator is used to define and map the striated muscle complex and to confirm symmetric dissection along the midline. Typically, the rectal pouch can be adequately dissected by this approach to allow enough length to reach the perineum. Infrequently, a combined abdominoperineal approach is required. The mobilized rectal pouch is opened and the rectourinary fistula identified and closed directly. The rectal pouch is placed centrally within the striated muscle complex, which is reconstructed circumferentially around the rectum. The neoanus is centered within the external sphincter and the mucosa is sutured to the perineum.

Other accepted and practiced surgical approaches to imperforate anus include a sacroperineal approach as proposed by Stephens,[67] and an approach that uses components of endorectal dissection as attributed to Rehbein.[68] Both these surgical procedures are characterized by blind pull-through of the distal rectum to the perineum without direct visualization of the striated muscle complex. Experience with laparoscopic dissection and division of the rectourinary fistula with perineal pull-through reconstruction has been reported, but is only needed in approximately 10% of cases.[69,70] It appears that personal preference, experience, and familiarity rather than differences in outcome dictate the selection of procedure. In general, diverting colostomy in all of these procedures is maintained until the anorectoplasty has completely healed, after which the colostomy is closed electively.

Results, Complications, and Outcome

Mortality following anorectoplasty is related to the presence of associated congenital anomalies other than imperforate anus. A careful review of 284 infants undergoing repair of anorectal malformations observed an 18.7% mortality,[71] suggesting that this group is at moderate to high risk for complications and death secondary to coexisting congenital anomalies.

Complications are similar to other gastrointestinal surgical procedures and include infection, leak, recurrent fistula, or anastomotic stricture. Leak or stricture formation is observed in 5% to 10% of infants undergoing tapering rectoplasty during posterior sagittal anorectoplasty. Anorectal strictures are treated by gradual postoperative anal dilatation for weeks to months. Recurrent rectourethral fistula or urethral stricture is uncommon.

Long-term functional outcome in infants with low malformations is generally good given the relatively normal descent of the distal rectum within the striated muscle complex. Infants with higher lesions have a less predictable prognosis and are much more likely to have difficulty with fecal continence. Currently, the outcomes appear to be independent of the type of surgical reconstruction performed and more related to anatomic patient factors, including degree of rectal descent, integrity of the striated muscle complex, and sacral innervation. However, there are no established accurate predictors of long-term fecal continence, and as such these children should be followed until at least 4 years of age.[72] Few or perhaps none of these children have completely normal bowel habits after operation. About half of the infants have acceptable to good results with episodic fecal soilage that can be improved with bowel management programs enemas and cathartics.[73–75] A comprehensive bowel management program is essential in preventing fecal impaction and subsequent motility dysfunction in the rectum. The remaining children require major adjustments in lifestyle secondary to fecal incontinence, chronic constipation, or fecal smearing and odor. In some instances, socially acceptable continence can be assisted by the use of daily antegrade enemas via a cecostomy or appendicostomy. In other situations, a permanent diverting colostomy may be desirable.

Necrotizing Enterocolitis

Pathophysiology

4 NEC is a neonatal disease characterized by an initial intestinal mucosal injury that may ultimately progress to transmural bowel necrosis. NEC is the most frequently encountered neonatal surgical emergency and a major cause of morbidity and mortality in the premature infant. Despite its frequency and extensive study, the pathogenesis remains obscure, and surgical treatment is

directed largely at controlling the complications of intestinal necrosis. The development of NEC occurs in association with a variety of associated conditions, including perinatal stress, sepsis, respiratory failure, hypoxemia, hypotension, and congenital cardiac defects. In general, NEC is observed in the premature infant with multiple risk factors and potential etiologic events and conditions. To create a murine model of NEC, the necessary factors are hypoxemia and to formula (not breast milk) feed the animals.[76–78] Current clinical and experimental data support the concept that the pathophysiology of NEC remains enigmatic and multifactorial.

The intestinal mucosal injury observed in NEC is likely to be the end result of an ischemic insult in a susceptible host. Normally, the neonatal pulmonary and systemic vascular smooth muscle undergoes rapid structural and physiologic changes shortly after birth. The premature infant appears to be particularly vulnerable to vasoconstriction. With regard to NEC, it is hypothesized that hypoperfusion and ischemia of the premature neonatal intestinal tract may be the result of uncontrolled splanchnic vasoconstriction. This situation may be worsened in critically ill premature infants with low cardiac output states impairing oxygen delivery to the intestines.

A common characteristic of NEC is the host inflammatory response to the initiating mucosal injury. Experimental data are consistent with an important role for inflammatory mediators in the propagation of intestinal injury in NEC.[79] More than 90% of cases of NEC occur after the initiation of enteral feeding, and several studies document that the osmolarity or rate of initial feeding may be important. Although controversy exists, most neonatal centers now avoid rapid advancement of hyperosmolar enteral feedings and attempt to prevent excessive fluid volume in premature infants.[80,81] A multicenter, randomized controlled clinical trial using *Bifidobacterium* and *Lactobacillus* as a probiotic given with initial feeding demonstrated significant reduction in death from NEC in very low–birth-weight premature infants.[82]

The most common site of involvement of NEC is the terminal ileum and right colon. NEC may be localized, segmental, or it may involve the entire gastrointestinal tract. Histopathologic examination of intestinal tissue from infants with NEC demonstrates submucosal edema, hemorrhage, and microvascular thrombosis leading to transmural necrosis. The histopathology of NEC resembles that of experimental intestinal ischemia, with areas of reversible mucosal injury adjacent to areas of transmural necrosis. Dissection

of intraluminal gas through the injured mucosa leads to gas within the bowel wall, known as *Pneumatosis intestinalis*. The finding of pneumatosis intestinalis is a classic radiographic and pathologic feature of NEC. Initially, the gas may be localized in the submucosa or lymphatic vessels, but it may dissect into the muscularis, the portal venous tract, or into the subserosa. Intestinal perforation, inflammatory phlegmon, and diffuse peritonitis are common with advanced NEC.

Clinical Presentation

NEC is estimated to occur in 1 to 3 of 1,000 live births and 30 per 1,000 low–birth-weight births.[83] NEC may also occur in term infants, and in this group, it has a tendency to involve the colon and may present without classic signs.[84] The actual incidence of NEC remains difficult to determine because the diagnosis is subjective; classic signs on physical examination and diagnostic imaging are not always uniformly present. The classic clinical signs of NEC include abdominal distention, feeding intolerance, bilious emesis, and either occult or gross blood in the stool. Gastrointestinal mucosal bleeding is present in the vast majority of cases (80% to 90%) but is rarely significant from a hemodynamic standpoint. On physical examination, abdominal tenderness with distention is common, and individual loops of thickened or fixed bowel may be palpable. Edema, erythema, crepitus, or discoloration of the abdominal wall suggests intestinal necrosis, perforation, or intra-abdominal abscess (Fig. 101.19). Hematochezia or guaiac-positive stool is typical. Systemic signs of inflammation and sepsis such as temperature instability, apnea, bradycardia, hypoxemia, acidosis, and thrombocytopenia are also common. The primary diagnostic goal during initial clinical evaluation is to determine whether irreversible, transmural intestinal necrosis is present. There is no single physical finding or laboratory test that makes this distinction.

Diagnosis

The diagnosis of NEC relies on clinical evaluation and judgment based on symptoms and signs in the appropriate setting. Table 101.4 summarizes diagnostic criteria and a staging system for NEC most commonly used in the United States.[85] Radiographic confirmation of NEC requires only plain

abdominal films. During the acute inflammatory phase, contrast studies may be hazardous and are contraindicated. The classic radiographic finding of pneumatosis intestinalis (Fig. 101.20) confirms the diagnosis in the appropriate clinical setting but is variably present. Other radiographic findings consistent with NEC include thickened bowel loops, ascites, and portal venous gas. Serial abdominal films, including a left lateral decubitus or upright film, should be obtained every 6 to 8 hours during the early course of the disease. These sequential studies help document the progression or resolution of the inflammatory process and, importantly, evaluate for the presence of intestinal perforation presenting as free intraperitoneal gas or pneumoperitoneum. The presence of pneumoperitoneum mandates operative intervention; however, up to half of infants with perforated NEC do not have discernible pneumoperitoneum on plain films.

Figure 101.19 Clinical presentation of diffuse staining of abdominal wall in an extremely low–birth-weight infant with perforated necrotizing enterocolitis.

Table 101.4 Necrotizing Enterocolitis

Stage I NEC (Suspected)

Any one or more historical factors producing perinatal stress

Systemic manifestations

- Temperature instability
- Lethargy
- Apnea
- Bradycardia

Gastrointestinal manifestations

- Poor feeding
- Increasing pregavage residuals
- Emesis
- Mild abdominal distention
- Occult blood in stool

Abdominal radiographs showing distention with mild ileus

Stage II NEC (Definite)

Any one or more historical factors

Above signs and symptoms, plus

- Persistent occult or gross gastrointestinal bleeding
- Marked abdominal distention

Abdominal radiographs showing significant intestinal distention with

- Ileus
- Small bowel edema
- Pneumatosis intestinalis
- Portal venous gas

Stage III NEC (Advanced)

Any one or more historical factors

Above signs and symptoms, plus: Deterioration of vital signs

- Evidence of septic shock
- Marked gastrointestinal hemorrhage
- Abdominal radiographs showing pneumoperitoneum in addition to findings listed for stage II

From Bell MJ, Kosloske AM, Benton C, et al. Neonatal necrotizing enterocolitis: prevention of perforation. *J Pediatr Surg* 1973;8:601–605, with permission.

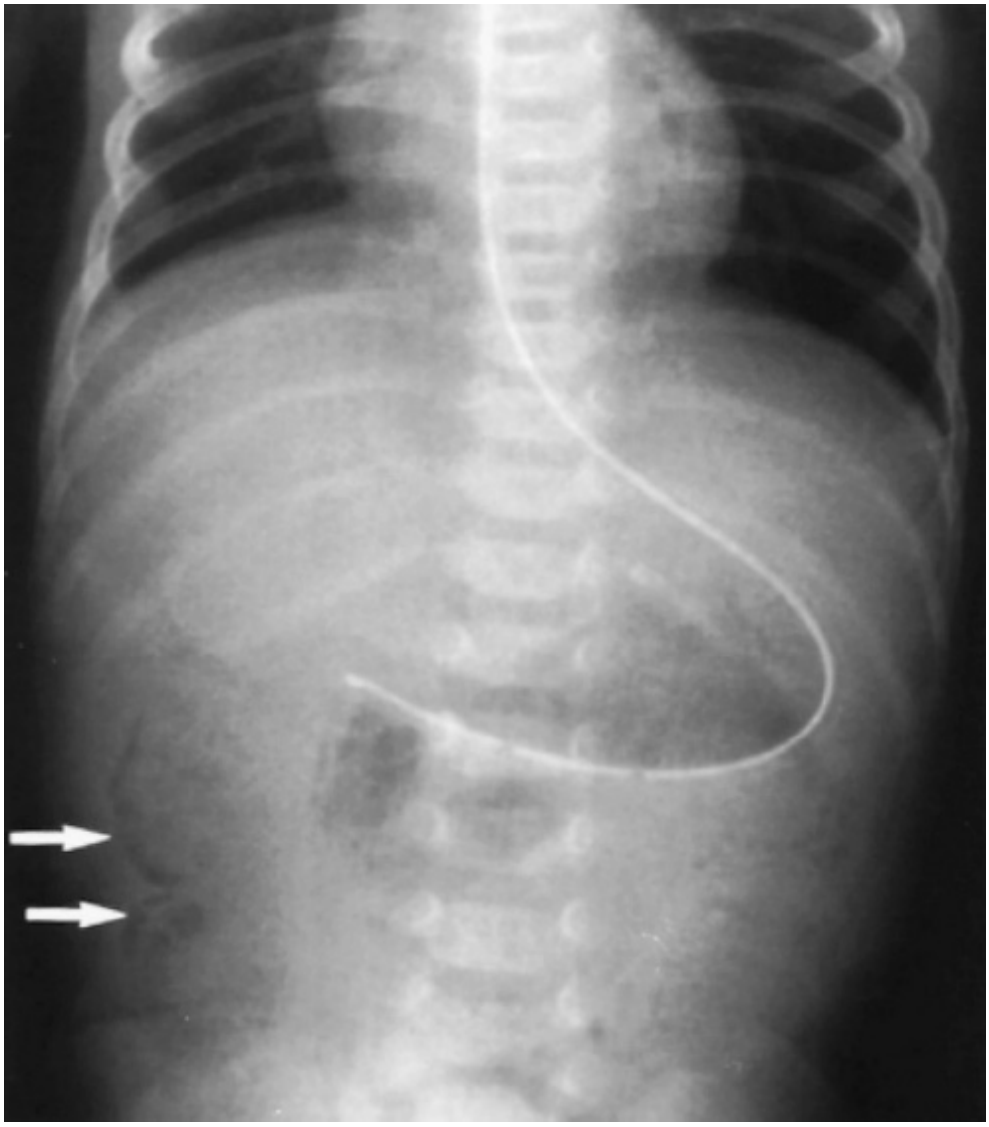


Figure 101.20 Plain abdominal film demonstrating *pneumatosis intestinalis* (*arrows*) in an infant with necrotizing enterocolitis.

Treatment

Nonoperative

The vast majority of infants with NEC can be managed medically. Initial management of NEC includes proximal decompression with a nasogastric or orogastric tube, bowel rest, and broad-spectrum intravenous antibiotics. Prompt correction of hypotension, hypoxemia, and inadequate ventilation must be undertaken. Intravenous fluid management, with particular attention to electrolytes and acid–base status, is essential. Central venous access is secured and TPN is initiated. Oxygen delivery and cardiac performance must

be maintained, which in a premature neonate may require operative closure of a patent ductus arteriosus; this approach is preferable over the use of indomethacin in the setting of NEC.[86] Serial physical examinations and blood work are useful in monitoring disease progress.

Most infants with NEC improve with medical management. Typically, reversal of the systemic inflammatory response occurs rapidly, and the abdominal distention and ileus resolve over a period of days. Nasogastric tube decompression and intravenous antibiotics are usually continued for 7 to 14 days. Enteral feeding usually is resumed once antibiotics have been discontinued and there has been return of gastrointestinal function. The usual course of medically treated NEC is rapid clinical response and stabilization in the first 24 to 36 hours. Infants with significant intestinal necrosis typically have signs of either pneumoperitoneum or clinical deterioration during the initial 24 to 72 hours of treatment.

Indications to abandon medical management and escalate surgical therapy include evidence of intestinal perforation or clinical deterioration with persistent or progressive systemic illness despite maximal medical therapy. Evidence of persistent or progressive systemic sepsis includes temperature instability, refractory hypotension, acidosis, hypoglycemia, neutropenia, and thrombocytopenia. Local findings such as portal venous gas, abdominal wall cellulitis, or crepitus also may signal intestinal necrosis and the need for operative intervention. A palpable, fixed abdominal mass consistent with intestinal perforation with an inflammatory phlegmon or abscess also may be a relative indication for operation. Because there is not complete agreement on what constitutes clinical deterioration, some controversy exists regarding operative indications for NEC in the absence of pneumoperitoneum. Because the interpretation of clinical deterioration criteria remains subjective, the decision to operate remains a multifactorial clinical judgment. In equivocal situations, abdominal paracentesis of ascitic fluid may be helpful in diagnosing intestinal necrosis with perforation in the absence of pneumoperitoneum if the aspirate contains bacteria or stool.[87]

Operative

Operative indications in NEC include the presence of intestinal necrosis with or without frank intestinal perforation. Conventional operative intervention is aimed at treating the complications of NEC (i.e., intestinal necrosis). In

general, resection of intestine involved with NEC does not prevent further extension of disease in other involved areas of the bowel. For isolated segmental disease, the traditional surgical treatment of NEC is resection of necrotic bowel with proximal enterostomy and distal mucous fistula placement. In infants with diffuse NEC, multiple resections with several enterostomies may be required. The primary operative goal is an expedient operation with preservation of as much intestinal length as possible, including the ileocecal valve. Because the risk of developing short-gut syndrome is substantial in infants with diffuse disease, preservation of marginal areas of involved intestine with a planned second-look operation to reevaluate intestinal viability may be useful. Accurate measurement of the remaining bowel length is important from a diagnostic and prognostic standpoint, with the length of bowel resected determined by the extent of transmural intestinal necrosis. Resection with primary anastomosis in selected infants with NEC has been reported,[88] with a recent study observing recurrent NEC in 22% and strictures in 17% of 18 treated infants following primary anastomosis.[89] Complete intestinal necrosis of the small intestine and the colon is uncommon and is not compatible with long-term survival without the sequelae of short-gut syndrome and the potential need for chronic TPN dependence and ultimately intestinal transplantation (Fig. 101.21).

Infants with NEC are typically fragile and premature, and complications in this population are not well tolerated. Survival in this situation may be more dependent upon disease severity and coexisting medical problems than the operative approach. For the high-risk, low–birth-weight infant, initial management with primary bedside peritoneal drainage rather than laparotomy and bowel resection may be useful as either a temporizing measure or, in some instances, a definitive procedure.[90] A multicenter, randomized controlled surgical trial comparing laparotomy with primary peritoneal drainage in premature infants with perforated NEC found that overall survival, dependence upon TPN, and length of stay were independent of the type of operation performed.[91] However, 18-month follow-up of neurodevelopmental outcomes demonstrates worse neurodevelopmental scores in prospective cohort studies.[92]

Complications, Results, and Outcome

Most infants with NEC are treated successfully without operative intervention. Morbidity and mortality for this group are related primarily to problems associated with prematurity. Given the delay of bowel function and the need for TPN, cholestatic jaundice commonly occurs but is generally reversible. Infants placed on broad-spectrum antibiotics for an extended period are at risk for developing fungal sepsis. For infants with intestinal necrosis from NEC, infectious complications including wound sepsis, central venous catheter infections, and pneumonia with respiratory failure may occur.

Figure 101.21 Fulminant necrotizing enterocolitis involving the entire gastrointestinal tract in a premature infant. Note the presence of pneumatosis intestinalis.

The overall surgical complication rate in infants with NEC is at least 20% to 40%. Immediate technical complications in treating NEC include intestinal leak, fistula formation, stoma necrosis, bleeding, and liver injury during exploration (Table 101.5). These complications are obviously magnified in the extremely low–birth-weight infant with preexisting intestinal injury. Fluid and electrolyte losses from proximal diverting enterostomies can be significant and even life-threatening in extremely low–birth-weight infants whose circulating blood volume is less than 50 to 100 mL. A review of 68

infants treated surgically for NEC observed a 26% mortality rate and a 68% complication rate related to the stoma or its closure in the perioperative survivors.[93] Complications included intestinal stricture, incisional or parastomal hernia, stoma prolapse, intussusception, wound dehiscence or infection, small bowel obstruction, and anastomotic failure. The complications associated with diverting enterostomy in this unique population provide a compelling rationale for early enterostomy closure once the inflammation from peritonitis has resolved. A prospective, randomized trial comparing resection and enterostomy with resection and primary anastomosis in the treatment of NEC has not been reported; however meta-analysis of retrospective outcomes has shown decreased odds of mortality in primary anastomosis. There is some concern that these retrospective studies are biased toward ostomy placement in the most critically ill patients.

COMPLICATIONS

Table 101.5 Operations for Necrotizing Enterocolitis

Infection (wound, intra-abdominal, central venous catheter, pneumonia)
Bleeding
Stoma-related complications (stenosis, retraction, prolapse)
Electrolyte or nutritional disturbances from enterostomy output
Enterocutaneous fistula
Anastomotic leak, stenosis, failure
Adhesive small bowel obstruction
TPN-associated cholestasis
Short-bowel syndrome, malabsorption
Sepsis, cardiopulmonary failure
Intraventricular hemorrhage

Intestinal stricture formation following NEC, whether managed operatively or nonoperatively, is not uncommon. This consequence usually results from a normal host inflammatory response to transmural intestinal injury. The degree of fibrosis and subsequent stricture formation are clearly related to the severity and extent of disease. Less frequently, mesenteric vascular compromise secondary to an intra-abdominal adhesion may lead to stricture formation. Although stricture can develop anywhere in the gastrointestinal tract involved with NEC, a higher rate of demonstrable stricture is observed in the left colon, occurring in as many as 36% of medically treated infants.[94] Routine contrast enema 4 to 6 weeks after clinical resolution of NEC treated operatively or nonoperatively has been advocated in some institutions. Symptomatic strictures generally require segmental resection with anastomosis, although fluoroscopically guided balloon catheter dilatation has been reported.

Overall survival rates for infants with NEC have improved significantly over the past three decades and are currently about 60% to 80% for both operative and nonoperative groups.[95] The observed improvement in survival is thought to reflect improved neonatal intensive care, the use of TPN, and early, aggressive treatment of suspected NEC. Most neonatal intensive care units initiate aggressive medical treatment in any infant with suspected NEC. Whether surgical interventions such as resection with primary anastomosis or limited primary peritoneal drainage can improve morbidity and mortality in these critically ill infants remains to be fully determined. Long-term outcome for NEC survivors generally reflects associated problems of prematurity. In particular, many of these infants have persisting neurodevelopmental, ophthalmologic, and pulmonary diseases, but morbidity from the gastrointestinal system generally is limited to infants with short-gut syndrome following extensive bowel resection. These infants present complex ethical and management issues beyond the scope of this review. Most NEC survivors (75%) enjoy a good to excellent quality of life, suggesting that the treatment cost relative to the potential benefit for these infants is worthwhile.[96]

Meconium Ileus

Meconium ileus is a descriptive term for small bowel obstruction in a newborn infant with CF. About 10% to 20% of infants with CF initially

present with meconium ileus. A review of CF is useful to understand the pathophysiology and treatment of meconium ileus.

CF is the most common fatal hereditary disease in Europe and North America. It is an autosomal recessive disorder found with a heterozygous carrier incidence rate of 1 in 20 to 25 in white populations. The estimated incidence rate of homozygous gene expression and phenotypic manifestation of CF is about 1 in 2,000 to 2,500 in this population.[97] Screening of at-risk couples with a family history of CF is recommended, however, and in this setting, carrier discovery approaches 100% so that appropriate genetic counseling can be provided. Molecular genetic screening should also be offered to parents and infants with clinically suspected CF as well as asymptomatic infants born to at-risk couples. This approach allows rapid identification and confirmation of virtually all infants homozygous for CF.

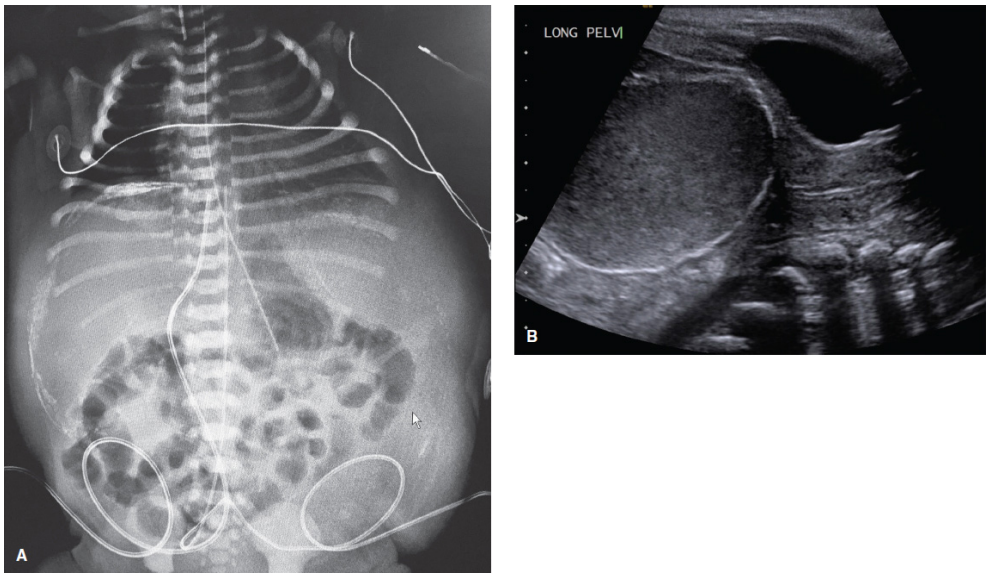


Figure 101.22 **A:** Plain film radiograph of calcified pseudocyst in complicated meconium ileus. **B:** In utero ultrasound demonstrating calcified pseudocyst.

Pathophysiology

Table with CF manifestations

Cystic Fibrosis Clinical Manifestations	
Organ System	**Clinical Manifestation**
Apocrine sweat glands	Increased loss of sodium chloride in sweat
Tracheobronchial tree	Diminished volume and increased viscosity of airway secretions leading to decreased clearance
Pancreas	Deficiency of pancreatic proteinases, impaired chloride resorption, and abnormally thick meconium
Gastrointestinal tract	Abnormal thick inspissated stool, can lead to appendicitis, rectal prolapse, and intussusception
Liver	Chronic hepatic inflammation, fibrosis, and cirrhosis

In utero events such as proximal volvulus of the dilated segment of ileum, perforation from distention, or atresia occur in approximately one-third to one-half of fetuses with meconium ileus. These clinical entities are characterized together as *complicated meconium ileus*. A classic clinical presentation of complicated meconium ileus is in utero intestinal perforation with sterile meconium peritonitis and formation of a calcified pseudocyst (Fig. 101.22). Gastrointestinal conditions presenting later in life occur in 10% of children with CF and include acute appendicitis, recurrent rectal prolapse, and intussusception. These conditions reflect abnormal transit of thick, inspissated stool causing proximal distention or obstruction of the bowel lumen. Small bowel obstruction in CF outside the neonatal period was historically called *meconium ileus equivalent,* and is now termed *distal intestinal obstruction syndrome* (DIOS). Treatment of DIOS is similar to initial nonoperative management of uncomplicated meconium ileus in the newborn discussed later. Prevention of DIOS relies on conscientious pancreatic enzyme replacement. Finally, children with CF are at risk to cholestasis secondary to obstruction of small intrahepatic bile ducts. Chronic hepatic inflammation can occur with subsequent fibrosis and cirrhosis,

causing hepatic failure and portal hypertension in approximately 5% of CF patients.

Diagnostic Evaluation

In nearly all newborns with CF, the diagnosis is clinically apparent by the presence of meconium ileus, a family history of CF in a sibling, or a positive newborn screening test. Laboratory confirmation of *CFTR* gene dysfunction is performed in several ways. The historical standard for the detection of CF has been analysis of the sodium chloride content of the sweat. The most commonly used and reliable technique uses pilocarpine iontophoresis, with positive sweat test results showing sodium and chloride concentrations exceeding 60 mEq/L.[99] This test is less useful during the first 4 to 6 weeks of age because normal neonates do not reliably conserve sodium chloride in sweat. Generally, abnormal *CFTR* gene is documented by two elevated sweat chloride tests obtained on separate days. With the emergence of genetic technology capable of providing accurate assessment of *CFTR* gene mutations, the sweat test is now largely used to provide clinical confirmation of *CFTR* gene dysfunction along with molecular diagnosis of CF.

Clinical Presentation

With routine prenatal ultrasound practices along with selected fetal DNA screening, the prenatal diagnosis of CF or meconium ileus is feasible, potentially allowing for improved management of anticipated clinical problems following delivery.[100] Initial signs of meconium ileus include neonatal bowel obstruction with abdominal distention, bilious emesis, and failure to pass meconium. On examination, the neonate may have palpable loops of meconium-filled intestine with a texture on palpation described as "doughy." Similar to other causes of proximal neonatal intestinal obstruction, rectal examination and evaluation of the meconium typically reveals clear white mucus or thick gray meconium. In utero intestinal perforation with pseudocyst formation in complicated meconium ileus may cause a palpable abdominal mass that is not particularly tender. On plain films or ultrasound, calcification is visible in the pseudocyst wall. In contrast, volvulus or intestinal perforation secondary to meconium ileus following birth generally

results in diffuse peritonitis and sepsis. Intestinal atresia may also be seen as a consequence of complicated meconium ileus.

Diagnosis

Abdominal plain films may be diagnostic in meconium ileus, demonstrating multiple, distended loops of bowel. Fluid- or meconium-filled loops of bowel mixed with gas give a characteristic "soap bubble" or "ground glass" appearance. Classic air–fluid levels seen in other causes of intestinal obstruction are not expected because of the tenacious, sticky intraluminal meconium. The presence of intraperitoneal calcifications or a calcified cyst is consistent with prenatal intestinal perforation of sterile meconium.

A water-soluble contrast enema is useful in the evaluation and treatment of simple meconium ileus. This study usually demonstrates an unused but functionally normal microcolon. Reflux of contrast into the terminal ileum may confirm the presence of inspissated meconium pellets. In conjunction with a family history and plain films, this finding is sufficient evidence to confirm the diagnosis of neonatal meconium ileus. Upper gastrointestinal contrast studies are generally unnecessary and may complicate further therapeutic efforts.

Treatment

Nonoperative

Nonoperative management of simple meconium ileus is achieved in about 60% to 70% of newborns. Once the diagnosis of meconium ileus is confirmed, the initial treatment of choice is to perform retrograde irrigation of the terminal ileum with one of several solutions designed to dissipate the obstructing meconium. In the United States, several different enema techniques and a variety of contrast media have been described, including normal saline, hyperosmolar contrast agents, and dilute *N*-acetylcysteine. Initially, it was believed that using hyperosmolar contrast material was necessary to create an osmolar gradient. The resultant influx of fluid into the intestinal lumen was thought to solubilize the inspissated meconium. Recent data suggest that successful meconium clearance is not necessarily related to the osmolality of the contrast agent; however, a significantly higher overall success rate is reported with the use of Gastrografin (sodium and meglumine

amidotrizoate) and the use of other solubilizing agents such as Tween-80 and *N*-acetylcysteine.[101] As long as clinical progress is being made, sequential enemas may be required to disimpact the inspissated meconium from the terminal ileum. In similar fashion, children and older patients presenting with DIOS are treated with retrograde enemas until the obstruction resolves. The distinct advantage of this treatment approach is the avoidance of general anesthesia and exploratory laparotomy. Reported complications with this approach include rare intestinal perforation, intestinal mucosal injury, and persistent obstruction resulting from meconium concretions.

Operative

The major indications for operative intervention are either failure to clear the obstruction by retrograde enema or complicated meconium ileus with cyst formation, volvulus, atresia, or perforation. For simple meconium ileus with persistent obstruction despite contrast enemas, the operative goals are meconium disimpaction from the ileum and evacuation of the remaining stool from the small intestine. These steps can be accomplished by either milking the meconium downstream into the colon or solubilizing the meconium by transmural needle instillation of irrigant. However, enterotomy or enterostomy and direct irrigation of the bowel lumen are usually required to completely clear the inspissated meconium. Simple closure of the enterotomy is preferred, but segmental resection may be required if marginal or compromised intestine is found. End-to-end anastomosis is the appropriate reconstruction technique following segmental bowel resection. A temporary enterostomy may be required, and several historical techniques have been described. Another surgical option is the placement of a T-tube into the ileum for continued irrigation with dilute *N*-acetylcysteine. Following clearance of meconium from the intestine and the return of bowel function, the T-tube can be safely and simply removed.[102]

Complicated meconium ileus occurs in about one-third of patients. The surgical management of this entity is individualized. Intestinal atresia is not uncommon in meconium ileus, and the entire length of the intestine must be inspected for patency. When possible, resection of nonviable, stenotic, or perforated intestine is performed with immediate reconstruction via primary anastomosis. Patency of the downstream bowel must be confirmed to prevent anastomotic leak resulting from distal obstruction. If the infant is critically ill

or has diffuse peritonitis, a safe primary anastomosis may not be possible and a diverting enterostomy is required. Stoma closure may be performed promptly after resolution of peritonitis and inflammation.

Postoperative Care and Results

If the meconium has been successfully cleared without opening the intestine, dilute *N*-acetylcysteine may be given through the nasogastric tube or by enema. Alternatively, if a T-tube has been placed, dilute *N*-acetylcysteine or other irrigant can be used directly into the ileum. These efforts are aimed at keeping the meconium soluble and preventing recurrent ileal obstruction. Following return of bowel function, enteral feeding using breast milk or an elemental formula is started along with oral pancreatic enzyme replacement. Vigilant pulmonary therapy is routine and includes mucolytics and antibiotics when indicated. Nutritional assessment and support are essential in long-term management.

Successful nonoperative management of simple meconium ileus historically was associated with a more favorable outcome; however, the operative mortality rates of infants with meconium ileus have improved dramatically over the past several decades, and current short-term operative survival rates of 70% to 100% are reported.[103,104] Long-term survival following meconium ileus is generally determined by the course of the underlying pulmonary disease. Contemporary management of CF has produced a mean survival age that approaches 30 years in most centers. With the exception of the development of portal hypertension in about 5% of patients, intestinal manifestations of the CF are treatable. Future medical and surgical efforts to improve the long-term outcome in these patients include direct replacement of the diseased pulmonary system by lung transplantation, manipulation of the epithelial chloride transport defect with pharmacologic agents, and gene therapy directed at *CFTR* gene transfer into respiratory epithelial cells.

Meconium Plug Syndrome

Meconium plug syndrome is characterized by functional obstruction of the colon or the rectum by a meconium plug. It affects both normal and premature infants with immature gastrointestinal motility and must be differentiated from

other causes of neonatal intestinal obstruction. Unlike meconium ileus, in meconium plug syndrome the colon is of normal caliber and the meconium is not inspissated. The infant's symptoms within the first few days of life are abdominal distention and bilious emesis. Spontaneous passage of meconium is often absent. On examination, the infant is normal with a patent anus and a distended abdomen. Digital rectal examination may deliver the meconium plug. Plain films of the abdomen demonstrate dilated loops of bowel consistent with distal bowel obstruction. The diagnosis is confirmed by contrast enema, which is also therapeutic in helping the meconium plug pass. The meconium plug is followed by bile-stained meconium of normal consistency. Importantly, although the vast majority of these infants are normal, a few have Hirschsprung disease or CF. Therefore, infants presenting with meconium plug syndrome may require rectal suction biopsy and have CF screening tests performed.

Malrotation

Embryology

Normal midgut fixation requires sequential growth, elongation, and rotation of the intestine beginning as early as week 5 of gestation as illustrated in Figure 101.23. Three distinct events occur during normal midgut fixation. The first stage involves herniation of the primary midgut loop into the base of the umbilical cord, where it remains until week 10 of gestation. The axis of the midgut loop is the superior mesenteric artery (SMA), with the omphalomesenteric duct at the apex of the midgut loop. The midgut loop rotates 180 degrees counterclockwise so that the proximal half passes posterior to the SMA. The proximal portion gives rise to the proximal duodenum, which lies to the right of midline. A portion of this segment becomes the third and fourth portions of the duodenum. The distal duodenum is normally fixed to the left of the aorta at the ligament of Treitz, having rotated 270 degrees counterclockwise from its original position. The jejunoileal segment undergoes dramatic elongation, forming about six primary intestinal loops. The distal midgut loop gives rise to the cecum and the right colon, which also undergoes growth and elongation with concomitant rotation 270 degrees counterclockwise. Therefore, the cecum is initially positioned to

the left, then anterior, and finally to the right of the SMA before reaching its final location.[105]

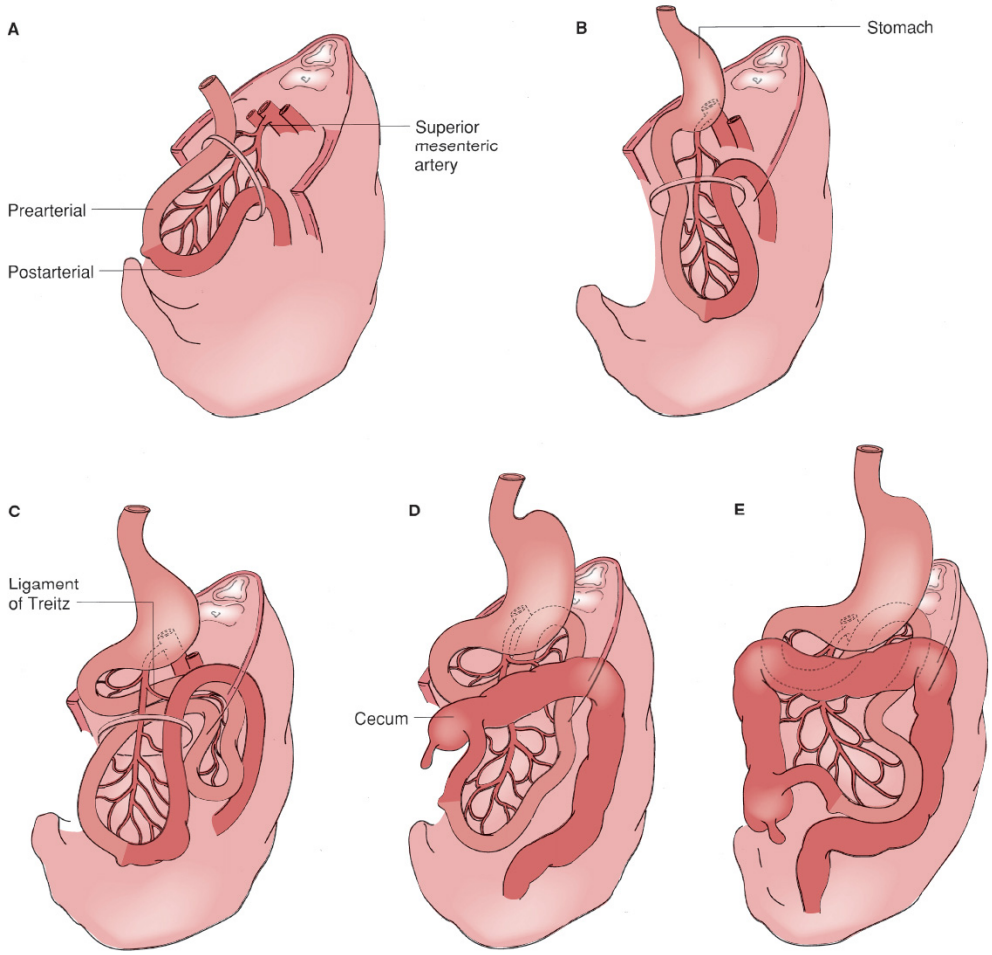


Figure 101.23 Normal midgut rotation is shown with appropriate positioning of the stomach, duodenum, small intestine, and cecum from the fifth gestational week (**A**) through completion by the 12th week (**E**).

Reduction of the extracoelomic gut is the second stage of midgut development and fixation, occurring between weeks 10 and 12 of gestation. By this time, the duodenojejunal junction has passed posterior to the SMA and the midgut has rotated 180 degrees counterclockwise; however, the small intestine initially remains to the right side of midline, and the cecum and ascending colon are anterior to the SMA after return of the gut into the abdomen. Many common abnormalities of intestinal fixation occur as a result of arrested development during this 2-week period.

The final stage of midgut development is fixation of the intestine to the posterior body wall, occurring after week 12 of gestation. Cecal descent occurs at this time. Normal points of fixation include the cecum in the right iliac fossa and the duodenojejunal junction at the ligament of Treitz just to the left of the aorta and anterior to the left renal vein (Fig. 101.24). Therefore, the normal intestinal mesentery is fixed with a broad base extending from the ligament of Treitz to the cecum. This broad-based mesenteric attachment prevents volvulus from occurring. In contrast, in disorders of intestinal rotation, the base of the mesentery is neither fixed nor broad, placing the entire midgut at risk for volvulus.

Anatomy

The normal sequence required for intestinal positioning and fixation can be interrupted at any developmental stage, producing a diverse spectrum of rotational abnormalities. Some neonatal surgical conditions are nearly always associated with abnormal intestinal rotation or fixation resulting from displacement of the midgut from the abdominal cavity during embryologic development. These anomalies include omphalocele, gastroschisis, and congenital diaphragmatic hernia. The term *malrotation* has been applied generically to describe disorders of intestinal rotation and fixation, although specific definitions of the more commonly encountered lesions are provided in the following sections.

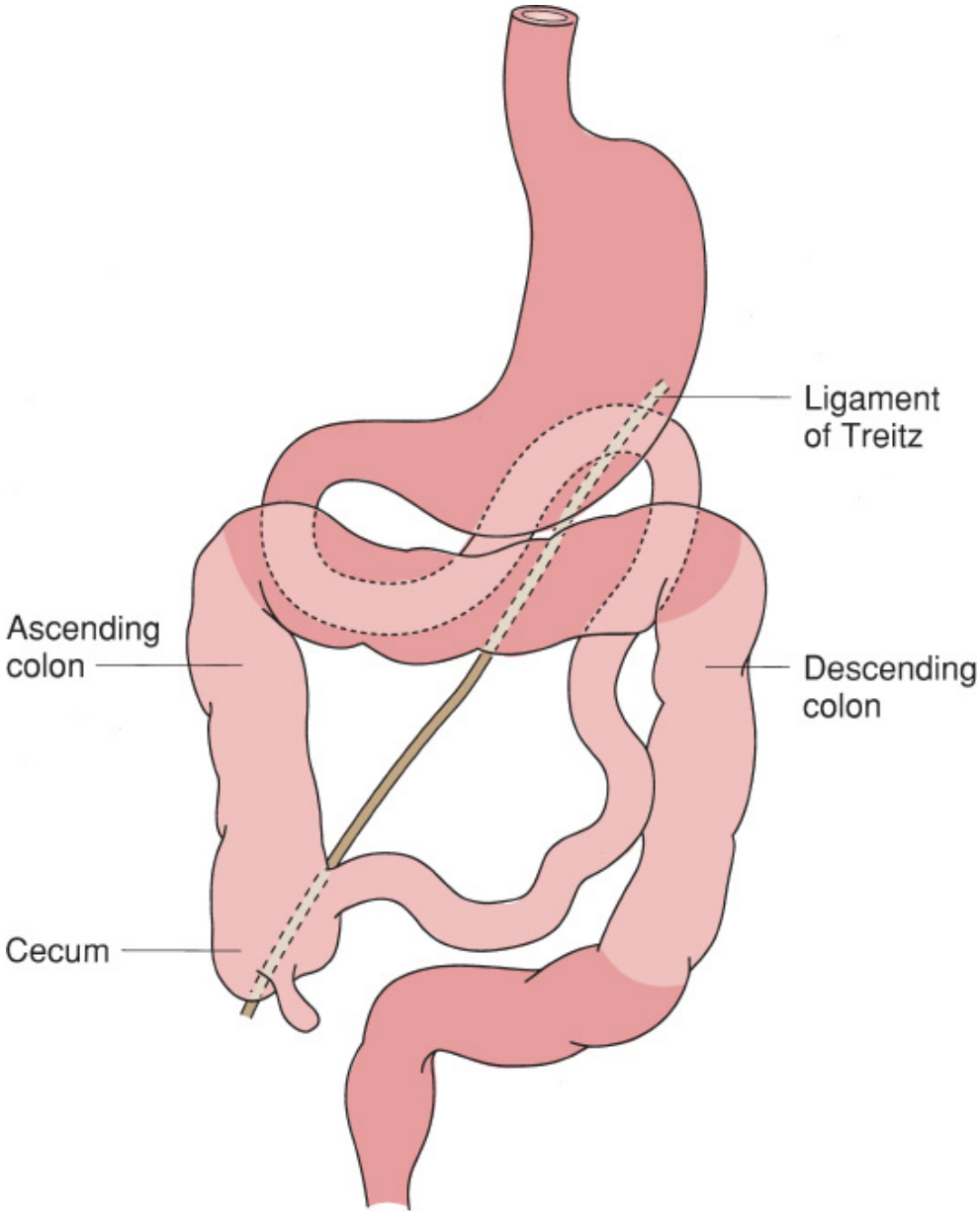


Figure 101.24 Normal oblique fixation of the midgut mesentery at the ligament of Treitz and in the right lower quadrant. The blue portions of the colon are extraperitoneal.

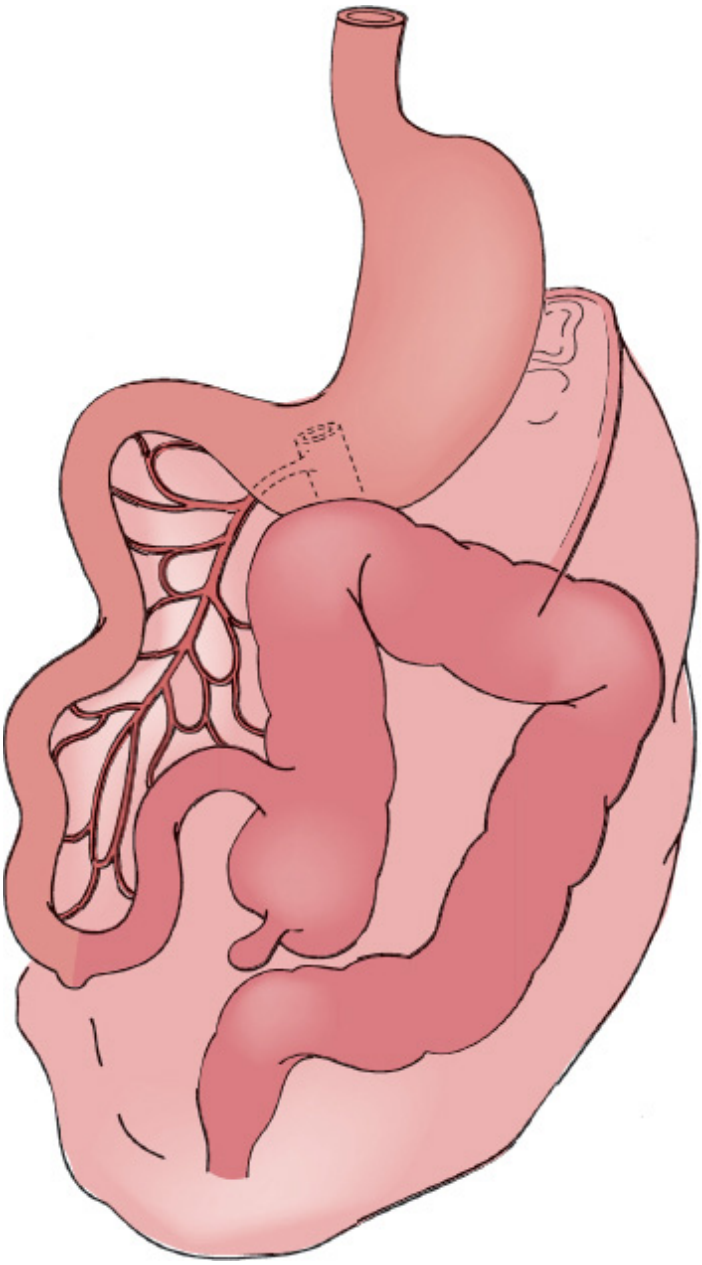


Figure 101.25 Nonrotation. The proximal segment of the small intestine resides on the right side of the abdomen, and the distal segment (*colon*) is on the left. Neither has rotated normally.

Nonrotation

This common anomaly is characterized by inadequate counterclockwise rotation of the midgut around the SMA. Instead of the normal 270-degree arc, rotation is either absent or arrested before exceeding 90 degrees (Fig. 101.25). The small intestine resides on the right side of midline, the colon resides on the left, and the cecum is anterior and near the midline. The

duodenojejunal junction is to the right of midline and more caudal and anterior in position. Nonrotation carries a significant clinical risk of midgut volvulus because the mesenteric vascular pedicle is narrow. Duodenal obstruction also may occur as a result of peritoneal attachments known as *Ladd bands*. These peritoneal bands fix the cecum to the posterior body wall by passing anterior and lateral to the distal duodenum.

Mixed or Incomplete Rotation

This rotational abnormality is characterized by arrest of the normal rotation at or near 180 degrees rather than the normal 270 degrees (Fig. 101.26). Instead of rotating posterior and to the left of the SMA, incomplete or arrested rotation of the prearterial segment leaves the duodenojejunal junction to the right of midline. The cecum also does not complete its counterclockwise passage anterior to the SMA; it usually resides in the upper abdomen just to the left of the SMA. Similar to nonrotation, fixation of the cecum to the posterior body wall by Ladd bands places the duodenum at risk for compression or obstruction. In addition, the SMA pedicle is narrow and places the midgut at risk for volvulus.

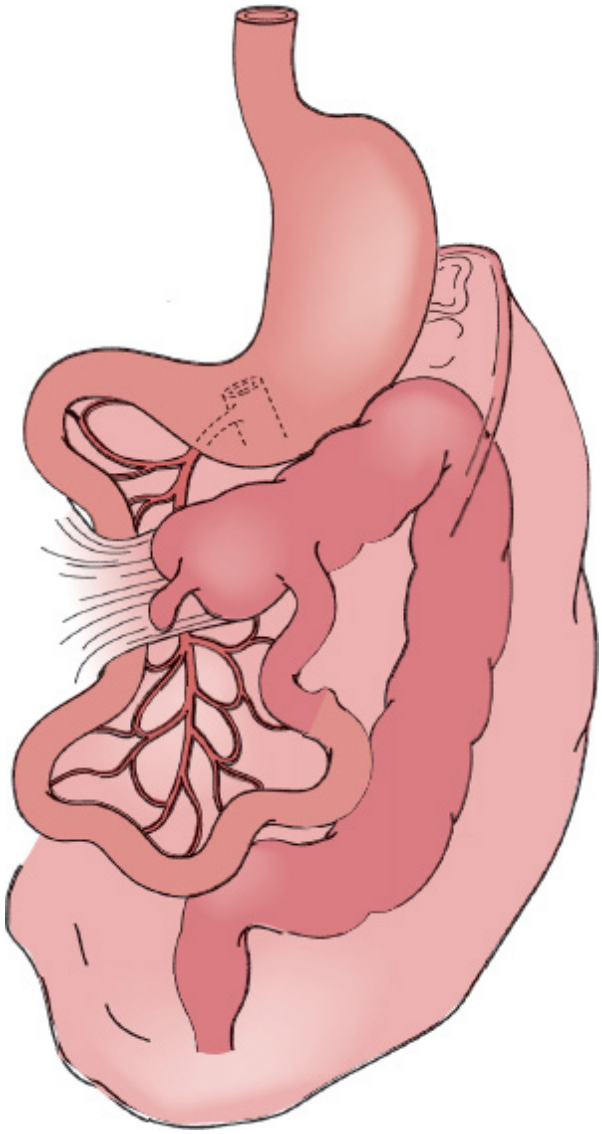


Figure 101.26 Incomplete rotation. The proximal segment has failed to rotate and is on the right. The distal segment has rotated to reside anterior to the duodenum so that cecal bands to the posterior abdominal wall may compress and obstruct the duodenum.

Mesocolic Hernias

Mesocolic hernias are rare but important anomalies characterized by failure of fixation of either the right or left mesocolon to the posterior body wall. Small bowel can become entrapped in the resulting potential cavities on either side of the abdomen. A right-sided mesocolic defect (paraduodenal hernia) is associated with nonrotation of the proximal midgut segment. Small bowel entrapment posterior to the right colon and cecum may occur. Similar entrapment of small bowel may occur from an incompletely fixed left

mesocolon but is associated with normal colonic and cecal position. Entrapped small bowel in a left mesocolic hernia usually is contained within a hernia sac with the neck composed of the inferior mesenteric vein and peritoneal bands extending to the posterior body wall. Both left and right mesocolic hernias carry the potential risks of obstruction, incarceration, and strangulation of bowel.

Clinical Presentation

Abnormalities of intestinal rotation are estimated to be present in about 1% of the population. Most persons with intestinal rotational anomalies are clinically asymptomatic; therefore, some children are found to have malrotation incidentally by upper gastrointestinal contrast studies conducted for other reasons. Symptomatic malrotation is usually encountered clinically in the setting of duodenal obstruction or midgut volvulus. Duodenal obstruction may occur as a result of Ladd bands fixing the abnormally positioned cecum to the posterior body wall. These peritoneal bands cause duodenal obstruction by extrinsic compression. Children with symptomatic duodenal obstruction typically present with bilious emesis and distention of the stomach and the proximal duodenum. Similar to proximal neonatal intestinal obstruction, newborn infants may present with bilious emesis without abdominal distention secondary to partial duodenal obstruction. A paucity of small bowel gas may be seen on plain abdominal films.

A potential consequence of intestinal malrotation is midgut volvulus. Midgut volvulus should be considered in any infant or child presenting with bilious emesis. The clinical outcome of midgut volvulus is time dependent, which is the fundamental reason that signs and symptoms of acute intestinal obstruction in an infant or a child must be pursued aggressively until a clear diagnosis is made. The devastating, life-threatening consequence of midgut volvulus is vascular insufficiency, gut ischemia, and, if untreated, infarction of the entire bowel supplied by the SMA. The initial symptoms may be subtle and limited to feeding intolerance, abdominal pain, and irritability, followed by bilious emesis. Guaiac-positive stool from mucosal injury is a common early finding. Late findings include progressive abdominal distention, hematemesis, and hypotension. Metabolic acidosis, coagulopathy, and shock

may become prominent clinical features. If unrecognized or left untreated, transmural necrosis of the entire midgut will occur.

At least 50% to 75% of intestinal rotational abnormalities are discovered within the first week to month of life, and about 90% occur in children younger than 1 year.[106,107] Symptomatic infants and children require emergent surgical exploration and correction. Older children and adults initially may present with acute volvulus but also may have a history of vague symptoms of episodic intestinal obstruction and chronic abdominal pain. It is essential to recognize that, regardless of age or chronicity of symptoms, midgut volvulus from malrotation occurs in a completely unpredictable manner.[108] Therefore, it is generally recommended that patients with incidentally discovered, asymptomatic malrotation undergo operative management to reduce the risk of volvulus.

Diagnosis

As with other forms of neonatal intestinal obstruction, the diagnostic evaluation begins with a plain abdominal radiograph. Classic findings with malrotation include gastric and proximal duodenal distention with a paucity or absence of distal small bowel gas (Fig. 101.27**A**). The plain film alone may not differentiate malrotation from duodenal atresia or stenosis. In most cases of suspected duodenal obstruction with concern of malrotation, an upper gastrointestinal series is a conclusive imaging study (Fig. 101.27**B**). Malrotation with volvulus typically produces incomplete duodenal obstruction with a corkscrew or coiled appearance in the distal duodenum. Extrinsic compression of the duodenum by Ladd bands may be visible on contrast study. Duodenal atresia and stenosis may occur anywhere within the duodenum but tends to be more proximal. Complete absence of small bowel gas is typical of duodenal atresia, whereas diminished but discernible distal gas is characteristic of duodenal stenosis or malrotation with volvulus.

Other radiographic findings in malrotation include incorrect position of the duodenojejunal junction, particularly to the right of midline. Failure to achieve normal cephalad and posterior fixation is typical in malrotation and may be best appreciated on lateral views. The small bowel resides in the right side of the abdomen, the colon, and cecum on the left (Fig. 101.27**C**). In a symptomatic infant or child, radiographic evidence of malrotation alone is

enough to warrant emergent exploration. A contrast enema is helpful in the evaluation of neonatal intestinal obstruction, although it may not be the initial study of choice if malrotation is suspected. The classic finding on contrast enema for malrotation is cecal malposition, usually in the left abdomen or near the midline. Finally, the relative position of the SMA to the superior mesenteric vein may be assessed by ultrasound. Normally, the superior mesenteric vein is to the right of the SMA on transverse sonograms. Abnormal position of the superior mesenteric vein either ventral or to the left of the SMA is associated with malrotation.[109]

Treatment

The management of bowel obstruction from malrotation or an internal hernia is operative. Initial assessment, resuscitation, and preoperative preparation in a symptomatic newborn should be conducted simultaneously so that confirmation of malrotation can be followed immediately by laparotomy. Urgent laparotomy is required to reduce the ischemic injury to the intestine. Shock, if present, must be treated aggressively by insuring adequate gas exchange and establishing restoration of intravascular volume prior to the induction of general anesthesia. Volvulus with complete infarction of the midgut, if not immediately lethal, is survivable only with enterectomy, followed by permanent or long-term TPN support. In older, asymptomatic children with incidentally discovered malrotation, operative repair remains controversial. Given the devastating consequences of midgut volvulus, however, elective surgical correction appears warranted in most asymptomatic individuals as well.

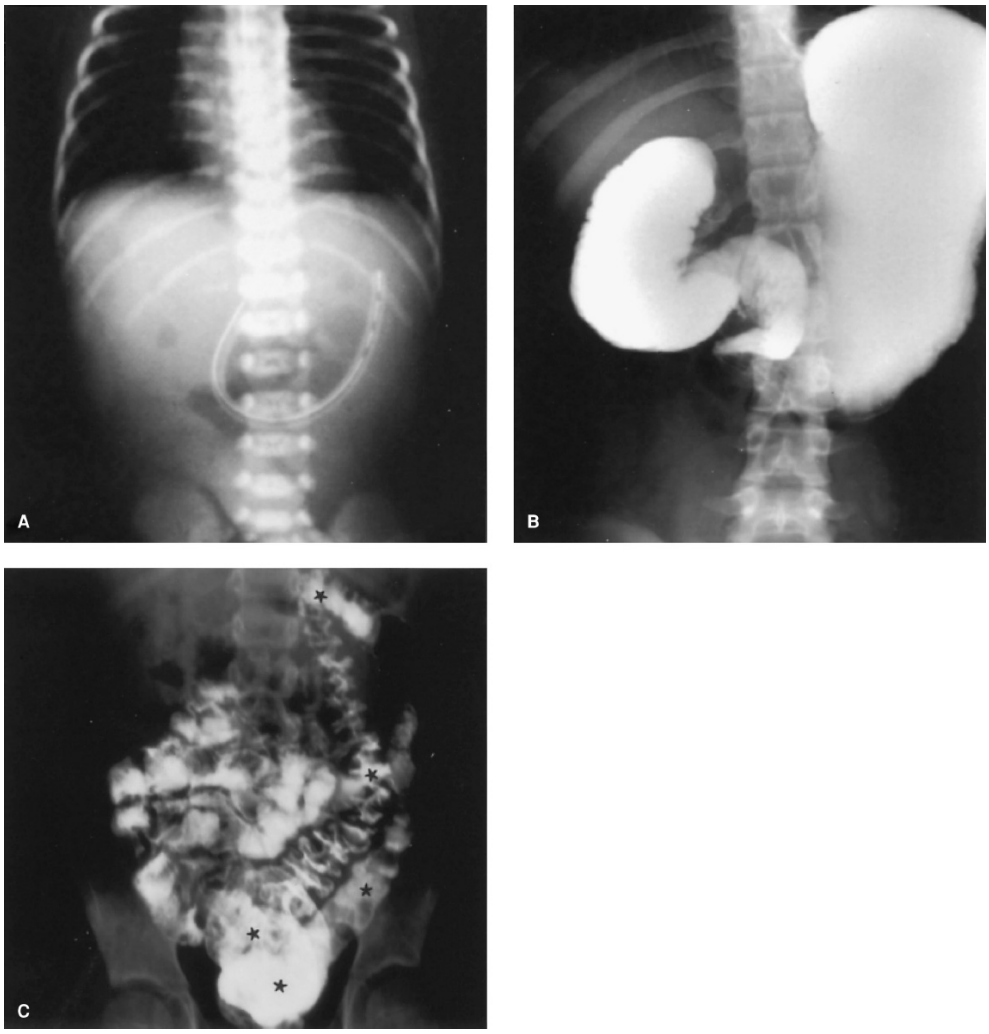


Figure 101.27 **A:** Plain radiograph of an infant with malrotation. There is a paucity of small bowel gas. **B:** Upper gastrointestinal contrast study demonstrating malrotation with midgut volvulus and duodenal obstruction. The position of the duodenojejunal junction is abnormal. **C:** Plain film showing a contrast-filled colon and cecum on the patient's left (*asterisks*). The entire small bowel is to the right of midline. These are typical radiographic findings of malrotation.

Operative repair of malrotation is performed by Ladd procedure.[110] The first objective is to relieve the midgut volvulus, if present. This is accomplished by delivery and detorsion of the affected midgut, usually in a counterclockwise direction. Recurrent volvulus is prevented by broadening the base of the mesenteric vascular pedicle by dividing the peritoneal bands that tether the cecum, small bowel mesentery, mesocolon, and duodenum around the base of the SMA (Fig. 101.28). Once completed, the mesentery

and the mesocolon open widely and the mesenteric pedicle is at low risk for recurrent volvulus.

The second objective of Ladd procedure is to divide the abnormal peritoneal attachments between the cecum and the abdominal wall. A modified Kocher maneuver involving meticulous and complete mobilization of the entire duodenum with division of all anterior, lateral, and posterior attachments is performed. Duodenal and distal small bowel patency should be demonstrated using intraluminal air or saline because synchronous intestinal webs and atresia have been reported. An appendectomy is performed to eliminate potential confusion from acute appendicitis developing in an abnormally positioned appendix. Performance of laparoscopic Ladd procedure has been demonstrated to be feasible and may help reduce time to enteral feeding and hospital length of stay; however, the long-term efficacy of this approach has been debated.[111] Fixation of the mesentery by cecal or duodenal plication to the body wall has been abandoned for lack of data supporting efficacy. Postoperative small bowel obstruction secondary to adhesions is reported in about 10% of patients.

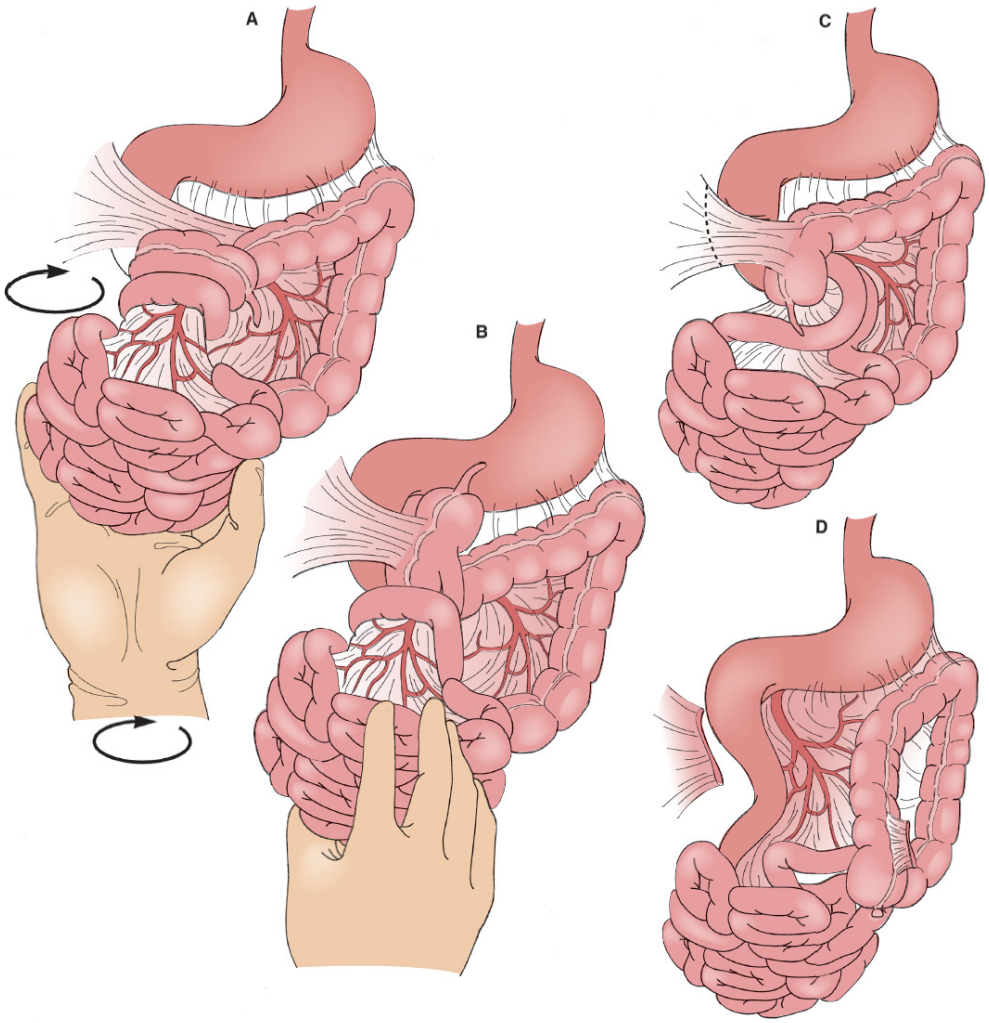


Figure 101.28 Correction of malrotation. **A, B:** Detorsion of midgut. **C, D:** Division of peritoneal attachments (Ladd bands) of cecum to abdominal cavity.

Volvulus with intestinal necrosis is treated by preserving as much bowel length as possible. If bowel viability is unclear during initial exploration, a second-look procedure may be helpful to delineate reversible from irreversible injury. The management of nonviable bowel from volvulus is not different from other situations in which intestinal necrosis is encountered, and clinical decisions regarding resection and anastomosis are individualized. In situations in which the entire small intestine is lost and long-term survival is doubtful, treatment decisions must be made with the family.

Surgical management of right mesocolic hernia is directed at dividing the lateral peritoneal attachments of the cecum and right colon to eliminate the hernia. In addition, given the associated nonrotation of the proximal bowel, the vascular pedicle should be broadened as much as possible. Left

mesocolic hernia is treated by mobilization of the inferior mesenteric vein, reduction of the small bowel from the hernia sac, and closure of the neck of the hernia sac to eliminate the potential space.

Results and Complications

Results following surgical correction of intestinal rotational abnormalities should be excellent, and life expectancy should be normal in the absence of intestinal necrosis. Recurrent volvulus and recurrent duodenal obstruction are distinctly unusual if the initial procedure is technically complete. Adhesive small bowel obstruction following Ladd procedure is reported in 1% to 10% of patients. Long-term outcome is obviously less favorable in patients with intestinal necrosis at the time of exploration.

Congenital Aganglionosis (Hirschsprung Disease)

Embryology

5 Congenital aganglionosis of the intestine (Hirschsprung disease) is characterized by the absence of intestinal ganglion cells. The pathogenesis of aganglionosis remains unknown. In normal development, neuroblasts derived from neural crest precursors become evident by week 5 of gestation. The neuroblasts begin maturation and caudal migration along with vagal nerve fibers. The initial caudal migration in an intermuscular plane is followed by intramural dispersal into both superficial and deep submucosal nerve plexuses. Ultimately, the neuroblasts give rise to the ganglion cells of the myenteric nervous system, with functional maturation continuing well into infancy. The orderly migration pathway of myenteric innervation has been documented in human embryos; normally, ganglion cells can be identified in the esophagus at week 6 of gestation, in the transverse colon at week 8 of gestation, and in the rectum by week 12 of gestation.[112]

Anatomy

Hirschsprung disease is characterized by a lack of ganglion cells in the distal intestine. The length of aganglionosis is variable but most commonly involves

the distal rectosigmoid colon in 75% to 80% of affected infants. In about 5% of cases, the transition zone between the normal, proximal bowel and the distal, aganglionic segment occurs in the small intestine.[113] Discontinuous aganglionosis has been reported but should be considered distinctly unusual. Therefore, in virtually all cases, the aganglionic intestinal segment is continuous with the distal rectum to the anal verge and also includes the internal sphincter. Because of this distribution, the pathogenesis of congenital aganglionosis is often attributed to failure of neuroblast migration. The characteristic lesion in the distal bowel is the aganglionosis in the intermuscular and submucosal plexuses. Large, hypertrophied, nonmyelinated nerve fibers are present within the muscularis mucosa, lamina propria, submucosa, and Auerbach intermuscular plexus. Both adrenergic and cholinergic fibers are prominent in the aganglionic segment, and acetylcholinesterase staining is useful diagnostically. Abnormalities in the peptidergic nervous system, including vasoactive intestinal peptide, substance P, and neurotensin immunoreactive fibers, are also described in the aganglionic bowel segment.[114] Deficient neuronal nitric oxide synthase mRNA and subsequent decreased local nitric oxide synthase activity in the aganglionic bowel have also been described.[115] These experimental data are consistent with the concept that a defect in nitric oxide–mediated smooth-muscle relaxation may account for some of the characteristic clinical features of Hirschsprung disease.

The transition zone between the normal, proximal bowel and the aganglionic distal bowel is distinguished grossly by distention of the proximal bowel with histologic evidence of muscular hypertrophy. The transition zone often becomes evident to direct inspection or on contrast enema during the first few weeks of life as functional obstruction leads to progressive proximal dilatation. On gross inspection, the transition zone may appear as a short funnel or cone-shaped colonic segment. The discrepancy in bowel lumen diameter is somewhat age dependent and may be subtle in a newborn or in a child with total colonic aganglionosis. Therefore, it may be difficult for the surgeon or the radiologist to define the exact transition zone site based on gross inspection or contrast enema. Gross examination alone is not sufficient for surgical decision making, and histologic confirmation of the level of ganglion cell transition is required. Given the continuous nature of

aganglionosis, a rectal biopsy performed 1.5 to 2 cm above the dentate line demonstrating ganglion cells effectively excludes Hirschsprung disease.

Neuronal intestinal dysplasia is a clinically described entity similar to or associated with Hirschsprung disease.[116,117] Despite the presence of ganglion cells, dysplastic changes in the myenteric nervous system affect bowel motility in similar fashion to aganglionosis. Clinical presentation and treatment are similar to those of classic Hirschsprung disease. There is considerable controversy regarding neuronal intestinal dysplasia, but it is reasonable to suggest that this represents an entity within the spectrum of abnormalities found in the intestinal myenteric nervous system.

Pathophysiology

Normal intestinal motility depends on coordinated propagation of segmental contraction waves immediately preceded by relaxation of the enteric smooth muscle. Patients with Hirschsprung disease lack a functional myenteric nervous system in the aganglionic segment; therefore, both propulsion and reflexive relaxation are disordered or absent in the distal bowel. Loss of neuronal nitric oxide synthase activity appears to play an important role. The internal sphincter is aganglionic and lacks the normal reflexive relaxation following rectal distention. In fact, patients with Hirschsprung disease may exhibit a paradoxical increase in sphincter tone in response to rectal distention. The functional result is tonic contraction of the aganglionic segment of bowel with ineffective peristalsis. Clinically, this presents as incomplete, distal intestinal obstruction in the newborn or as chronic constipation in the older child or adult.

Hirschsprung disease has been associated with mutations in at least three specific genes: the *RET* protooncogene, the endothelin B receptor (*EDNRB*) gene,[118] and the endothelin 3 (*EDN3*) gene. In addition, several other candidate genes are under investigation. In mice, natural and in vitro induced mutations affecting the *RET, EDNRB,* and *EDN3* genes generate intestinal aganglionosis identical to Hirschsprung disease.[119,120] Although widely accepted, it is still unknown whether the primary event in aganglionosis is failure of neuroblast migration to the distal bowel. Alternatively, ineffective microenvironmental support of neuroblasts that have already migrated may fail to promote normal neuroblast development and survival.[121]

Clinical Features

Incidence and Associations

The incidence rate of Hirschsprung disease is estimated at 1 per 5,000 live births with a marked male-to-female (4:1) preponderance. Most cases are sporadic, but long-segment, total colonic aganglionosis and female gender are strongly associated with familial inheritance. Genetic chromosomal analysis suggests that multiple loci may be involved, including chromosomes 13q22, 21q22, and 10q, among others.[122] Familial Hirschsprung disease has been clearly associated with *RET* protooncogene mutations. From a clinical standpoint, mutations of the *RET* protooncogene are associated with disorders of neural crest development, namely, multiple endocrine neoplasia (MEN) types IIA and IIB as well as familial medullary thyroid carcinoma, and patients with familial Hirschsprung disease associated with RET mutation are at risk for the development of medullary thyroid carcinoma.[123] Congenital cardiac defects are present in 2% to 5% of patients with Hirschsprung disease. Other rare congenital anomalies have been reported, but a consistent and important association is a 5% to 15% incidence of trisomy 21.[111] Infants presenting with meconium plug syndrome should undergo rectal suction biopsy to exclude aganglionosis.

Presentation

Most infants with Hirschsprung disease fail to pass meconium within the first 24 to 48 hours of life. Nonspecific signs of neonatal intestinal obstruction (feeding intolerance, abdominal distention, and bilious emesis) may develop. About half of the patients with Hirschsprung disease are diagnosed as neonates. Infrequently, older children or adults are diagnosed with aganglionosis during evaluation for chronic constipation. In this setting, symptoms may be minimal to disabling, and parents or patients often develop elaborate strategies to deal with chronic constipation. Abdominal distention is characteristic, and sometimes failure to thrive and malnutrition may occur. Digital rectal examination may demonstrate spasm, and, in the presence of enterocolitis, forceful expulsion of foul-smelling, liquid stool may occur.

Enterocolitis occurs in about 10% to 30% of infants and children with Hirschsprung disease and may be the presenting clinical manifestation. Enterocolitis associated with Hirschsprung disease has an unknown

pathophysiology, but obstructive stasis and bacterial overgrowth are thought to be important factors. *Clostridium difficile* and rotavirus have been implicated as important pathogenic organisms; diagnostic and treatment plans should consider these possibilities. The early presenting symptoms and signs of enterocolitis include fever, abdominal distention, and diarrhea, which may be explosive, foul smelling, and bloody. Systemic sepsis, transmural intestinal necrosis, and perforation are all possible later findings. The clinical progression can be rapid, with death occurring in as few as 12 to 24 hours if treatment is not initiated. Infants are particularly vulnerable to this complication and enterocolitis accounts for virtually all mortality directly related to Hirschsprung disease in modern pediatric surgical practice. Infants with known Hirschsprung disease and suspected enterocolitis should be treated aggressively. Initial treatment includes resuscitation, broad-spectrum antibiotics, cessation of feeding, and rectal irrigation. If the enterocolitis does not respond promptly, emergent intestinal decompression with an enterostomy proximal to the transition zone is indicated.

Diagnosis

A high index of suspicion for Hirschsprung disease should be maintained for any newborn infant with abdominal distention failing to pass meconium in 24 to 48 hours. The signs of neonatal intestinal obstruction should lead to a stereotypical workup. In the presence of characteristic findings on history, examination, or radiographic studies, any infant suspected of having Hirschsprung disease should undergo rectal biopsy.

Plain Abdominal Radiographs

Plain film radiographs of the neonate with Hirschsprung disease are nonspecific and typically demonstrate distended, air-filled loops of bowel throughout the abdomen. It is often difficult to discriminate between small intestine and large intestine on plain films at this age, but the pattern is consistent with distal intestinal obstruction. Older children or adults may have a stool-filled megacolon on plain radiographs. In the presence of enterocolitis, thickened, dilated intestinal loops and pneumatosis intestinalis may be present.

Contrast Enema

When distal neonatal intestinal obstruction is suspected on plain abdominal films, a contrast enema should be performed. With an experienced pediatric radiologist, findings consistent with Hirschsprung disease can be accurately detected in most instances. The classic radiographic finding in Hirschsprung disease is a transition zone (Fig. 101.29A). A definitive transition zone may not be apparent in a neonate because proximal dilatation takes some time to develop. In addition, infants with short-segment disease or total colonic aganglionosis may not have obvious transition zones on contrast enema. In these instances, a lateral view of the rectum may show abnormal spasm (Fig. 101.29B). Contrast remaining in the rectum more than 24 hours following a study is suggestive of Hirschsprung disease.

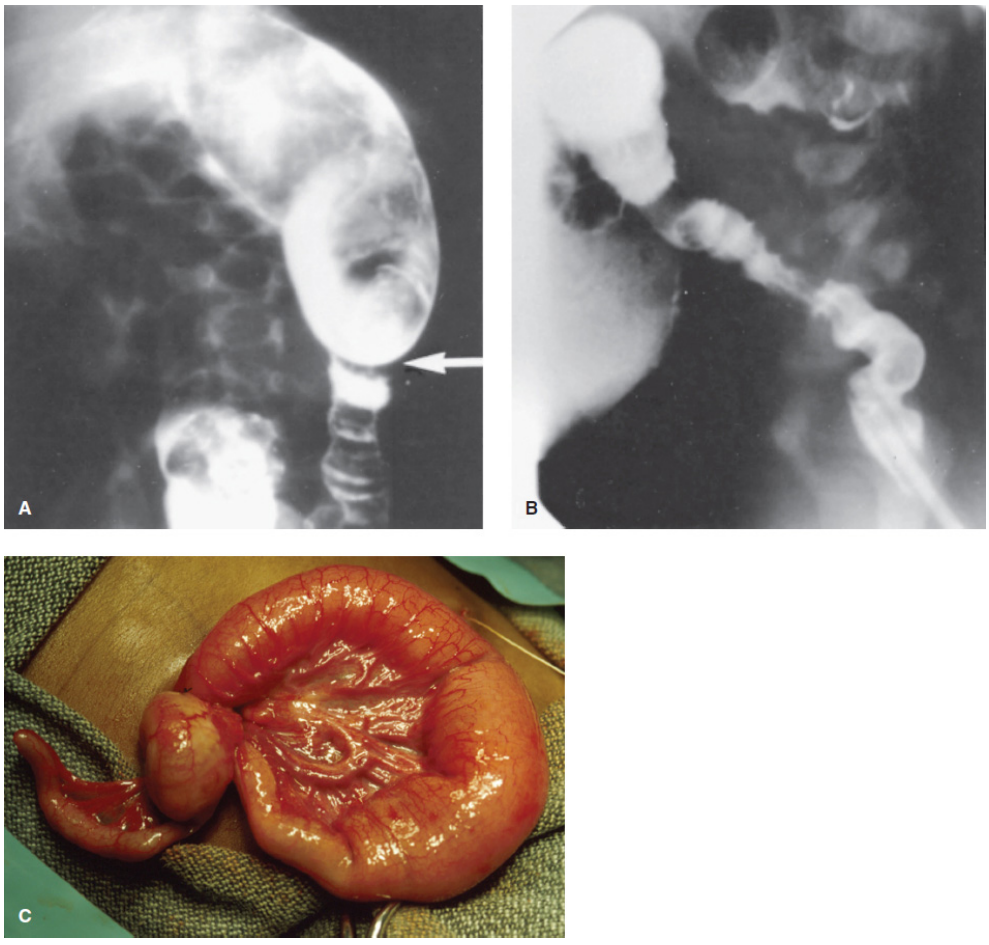


Figure 101.29 **A:** Contrast enema demonstrating a classic rectosigmoid transition zone (*arrow*) in Hirschsprung disease. **B:** Lateral view of rectum illustrates typical distal spasm of rectum. **C:** Operative photograph of rectosigmoid transition zone.

Rectal Biopsy

The diagnostic standard for aganglionosis is the rectal biopsy. Several commercially available instruments capable of performing rectal suction biopsies are in widespread use. The rectal suction biopsy can be performed at bedside or in clinic without anesthesia in all newborns and most children up to several months of age. The desire for early diagnosis and the technical simplicity of the procedure allow liberal use of this technique. When applied liberally, the vast majority (85% to 90%) of infants undergoing this procedure have normal ganglion cells on biopsy, effectively excluding Hirschsprung disease. Using the rectal suction biopsy technique, a biopsy of the mucosa and the submucosa is obtained. This is sufficient to establish the diagnosis because ganglion cells are absent from all intramural plexuses in Hirschsprung disease. The biopsy must be taken 1 to 1.5 cm proximal to the dentate line. Complications of infection, perforation, and bleeding with rectal suction biopsy are infrequent. Full-thickness rectal biopsy under general anesthesia is reserved for older children and in infants in whom suction biopsy is inadequate. An experienced pediatric pathologist must read the biopsies for maximal diagnostic accuracy. Evaluation for ganglion cells and the axons of the myenteric neurons is performed (Fig. 101.30), which may be accomplished using conventional hematoxylin-eosin staining or histochemical staining for acetylcholinesterase and calretinin. Similar histochemical staining for nitric oxide synthase can be performed. These adjunctive techniques are used routinely in some centers and can help provide additional evidence of Hirschsprung disease rather than simply demonstrating aganglionosis in the biopsy specimen. Diagnostic accuracy for Hirschsprung disease is excellent with a correctly obtained rectal suction biopsy and an experienced pediatric pathologist.[124,125]

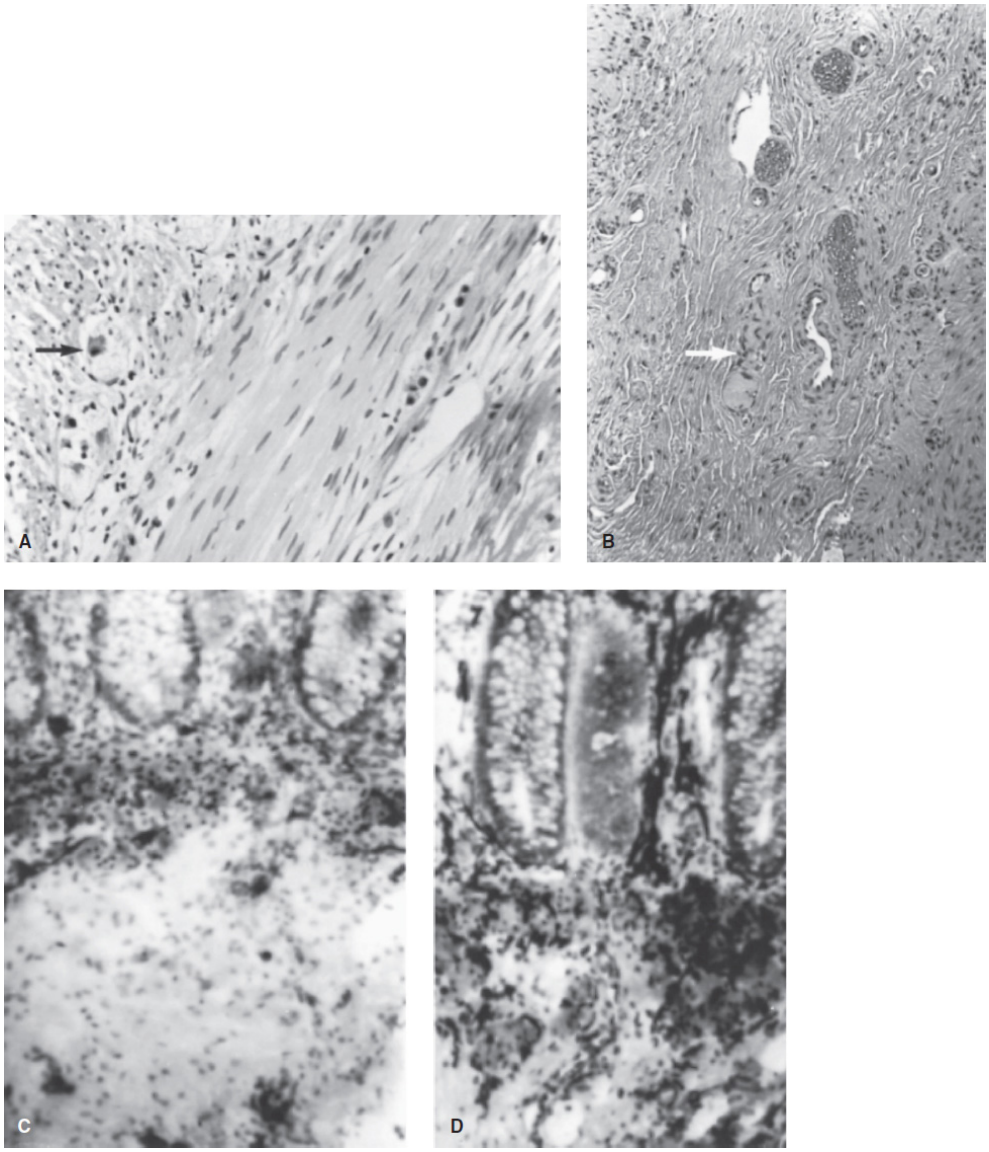


Figure 101.30 **A:** Normal rectal biopsy with ganglion cells indicated by *arrow* (hematoxylin-eosin). **B:** Rectal biopsy specimen with aganglionosis (hematoxylin-eosin). Note the characteristic thickened nerve fiber (*arrow*). **C:** Normal rectal biopsy using acetylcholinesterase histochemical staining. **D:** Similarly stained specimen from a patient with Hirschsprung disease. Many thickened submucosal nerve fibers stain densely black.

Anorectal Manometry

The absence of sphincter relaxation in response to rectal dilatation is consistent with Hirschsprung disease. Because of the relative ease and accuracy of rectal suction biopsy, anorectal manometry is not widely used in the United States for the primary diagnosis of Hirschsprung disease in infancy; however, this is used in some centers around the world and, when

applied carefully with an appropriate transduction probe, accurate manometric diagnosis is achievable in 85% to 90% of cases.

Treatment

Diverting colostomy should be considered for a newborn infant with Hirschsprung disease who has enterocolitis or multiple associated medical problems or anomalies. In the presence of enterocolitis, rectal irrigation and decompression can be an effective temporizing measure while resuscitation and broad-spectrum antibiotics are being instituted. Prompt proximal diversion will be required once the patient has stabilized. In the neonate, one approach following diagnosis is to perform proximal diversion by means of a colostomy (or enterostomy) placed in normal, ganglionated intestine. The diverting colostomy must be proximal to the histologic transition zone, and a series of biopsies examined by frozen section may be necessary to find the correct level for diversion. For classic rectosigmoid disease, a leveling colostomy is placed just proximal to the transition zone. This approach is generally done in two stages, with takedown of the stoma and definitive pull-through operation performed together weeks to months later, typically when the infant reaches 9 to 12 months of age. In older children, definitive pull-through is deferred until the colon has decompressed to relatively normal caliber.

For many infants and children without enterocolitis, a single-stage approach that eliminates the diverting colostomy has been advocated.[126,127] Despite a number of different operative techniques in performing a single-stage pull-through, results and outcomes appear nearly equivalent. Definitive repair of Hirschsprung disease with a single operation is desirable from technical and economical standpoint and essentially eliminates the complications associated with neonatal stomas. As with most aspects of pediatric surgery, an increasing experience with laparoscopically assisted, single-stage pull-through operations has been reported.[128] The contemporary, laparoscopic single-stage approach in the management of Hirschsprung disease has gained wide acceptance in the pediatric surgical community and is considered by many surgeons as the current standard of care for most infants and children.

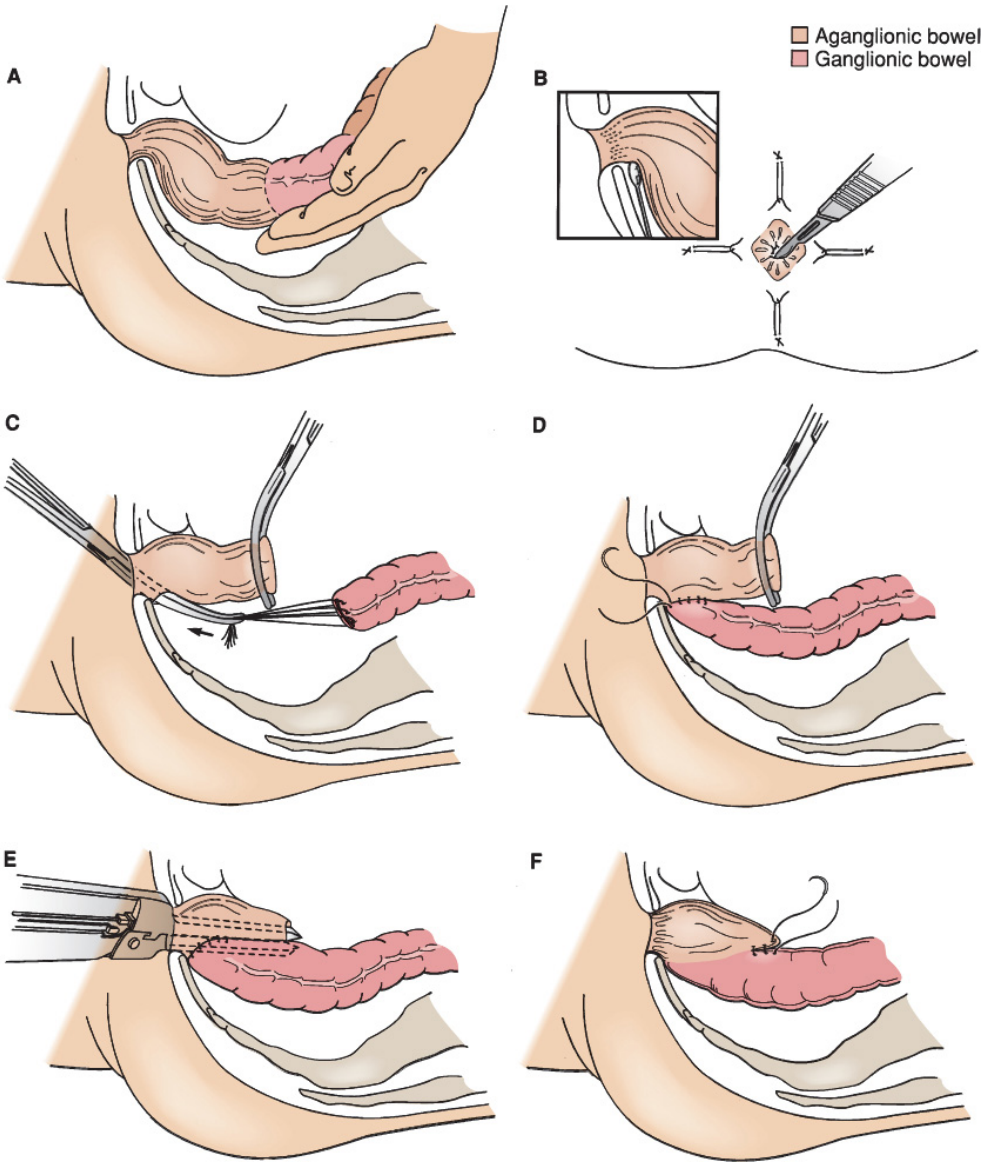


Figure 101.31 Duhamel procedure (Martin modification). **A:** Blunt retrorectal dissection. **B:** Incision in the posterior wall of the aganglionic rectum. **C:** Retrorectal pull-through after resection of the proximal aganglionic segment. **D:** End-to-side colorectal anastomosis preserving aganglionic rectum (as originally described). **E:** Stapled conversion of anastomosis into an extended side-to-side colorectal anastomosis (Martin modification). **F:** Completed procedure.

Definitive Operations for Hirschsprung Disease

The major goal of operative therapy in the treatment of Hirschsprung disease is to provide resection or bypass of the distal aganglionic rectum with the performance of a low rectal anastomosis with normally innervated proximal intestine. Numerous definitive procedures were designed to treat

Hirschsprung disease, and a brief description of the principal procedures in use follows. In general, the selection of a procedure depends on a surgeon's individual training and preference rather than compelling differences in outcome.[129,130]

Duhamel Procedure (Martin Modification)

The key elements of the Duhamel procedure are illustrated in Figure 101.31. After minimal pelvic dissection, resection of the aganglionic colon is performed. The aganglionic rectum is left in situ. Normal proximal colon is brought caudad into the retrorectal space, and a colorectal anastomosis is performed 1 cm above the dentate line. The original operation left the defunctionalized rectal pouch as shown, which proved problematic. The procedure has been modified by Martin to include a longer side-to-side colorectal anastomosis. Advantages of this procedure include its relative technical ease and limited pelvic dissection. Adoption of the stapled anastomosis has simplified this procedure significantly.

Soave Procedure

The Soave procedure is illustrated in Figure 101.32. Following resection of aganglionic colon, an endorectal dissection in the submucosal plane is performed from proximal rectum to anus. The endorectal dissection is started in the extraperitoneal rectum. This dissection is typically much easier than similar dissection for ulcerative colitis given the lack of mucosal inflammation. The dissected rectal mucosal tube is everted through the anus, excised, and normal proximal bowel is pulled through the rectal muscular cuff. The original operation did not suture the pull-through segment of proximal bowel to the rectum. A formal sutured colorectal anastomosis is now universally performed. Care must be taken to ensure that the pull-through segment is not obstructed by the muscular cuff.

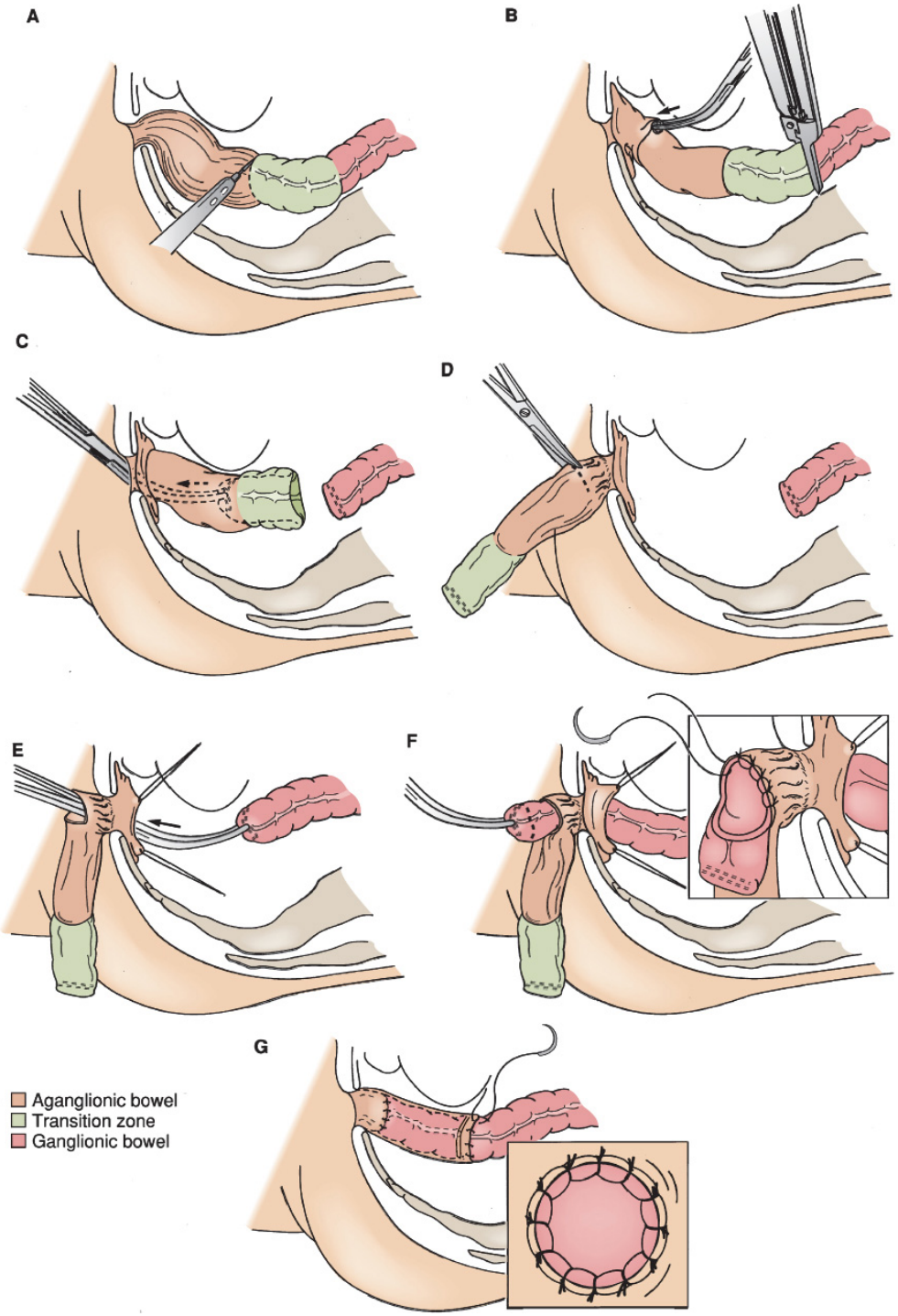


Figure 101.32 Soave endorectal procedure. **A:** Endorectal dissection initiated. **B:** Endorectal dissection complete. **C:** Eversion of the aganglionic segment and rectal mucosal tube. **D:** Incision of everted rectal tube. **E:** Endorectal pull-through. **F:** Colorectal anastomosis. **G:** Completed procedure.

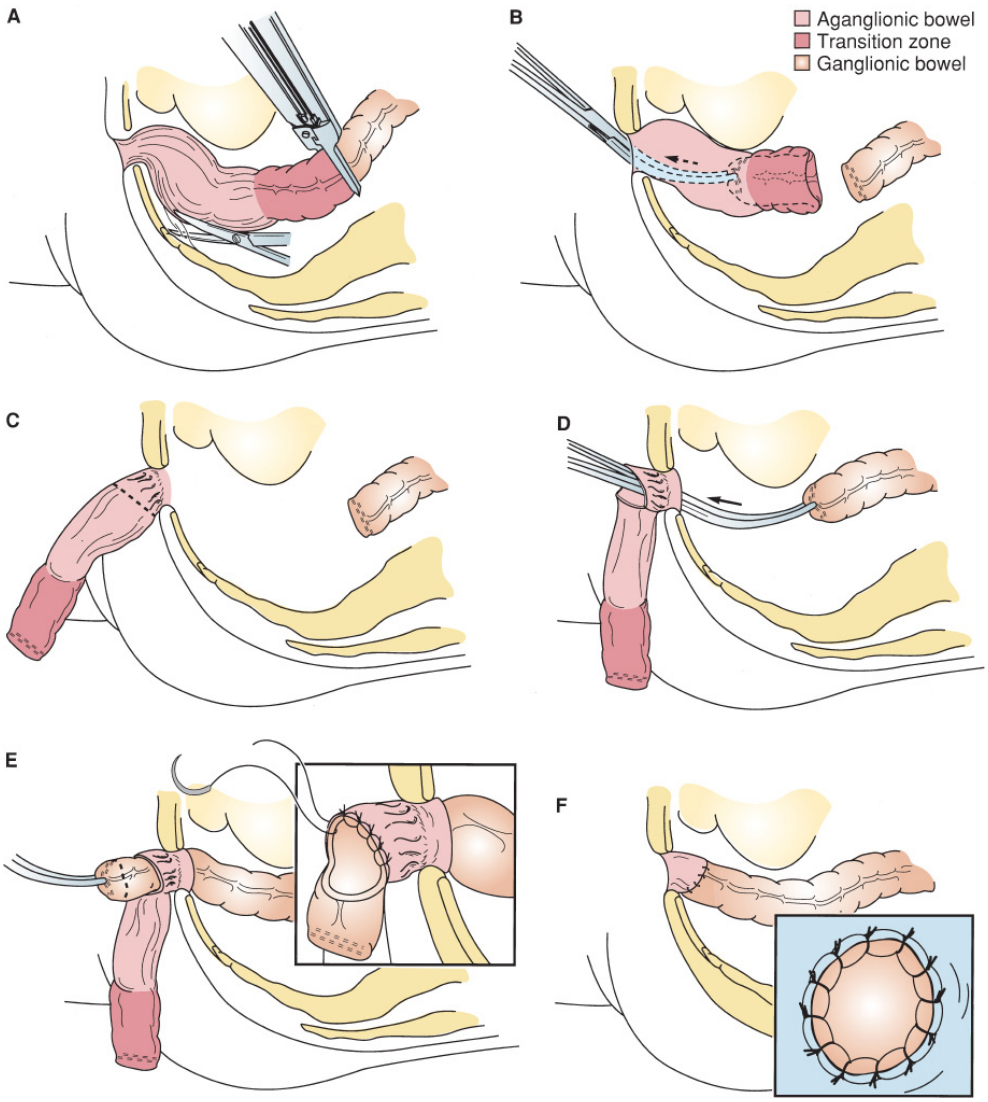


Figure 101.33 Swenson procedure. **A:** Extramural rectal dissection. **B, C:** Eversion of aganglionic segment and full-thickness rectum. **D:** Pull-through of normal, ganglionic bowel. **E:** Colorectal anastomosis. **F:** Completed procedure.

Swenson Procedure

The Swenson procedure is the original definitive procedure for the treatment of Hirschsprung disease. Long-term outcome in children who undergo a properly performed Swenson procedure is equivalent to other procedures. The basic strategy is outlined in Figure 101.33. The aganglionic segment of colon is resected and a careful, nearly complete extramural dissection of the distal rectum is performed. Care must be taken to avoid inadvertent injury to the seminal vesicles, vas deferens, ureters, and pelvic splanchnic nerves. The dissected rectum is everted through the anus onto the perineum and excised.

Normal proximal bowel is pulled through and a colorectal anastomosis is performed.

Laparoscopically Assisted Endorectal Pull-through

A multi-institutional clinical experience with a laparoscopically assisted endorectal pull-through technique for the treatment of Hirschsprung disease has been reported.[128] Potential advantages of this approach include excellent visibility of the distal rectum during dissection, early return of postoperative bowel function, and decreased length of hospital stay. The early results report outcomes similar to the other established procedures. The procedure is reviewed in Figure 101.34. Complete transanal excision of the distal aganglionic segment with primary coloanal anastomosis has also been performed for short-segment or typical rectosigmoid aganglionosis as well.

Rectal Myectomy

Resection of a longitudinal strip of the posterior rectal muscular wall has been used for definitive management of ultrashort-segment Hirschsprung disease. This procedure can be performed via transanal approach combined with submucosal dissection or by a posterior sagittal approach. Although controversial, the use of rectal myectomy as a definitive operation for Hirschsprung disease may be considered most useful in the selected older child identified with ultrashort-segment disease.[131]

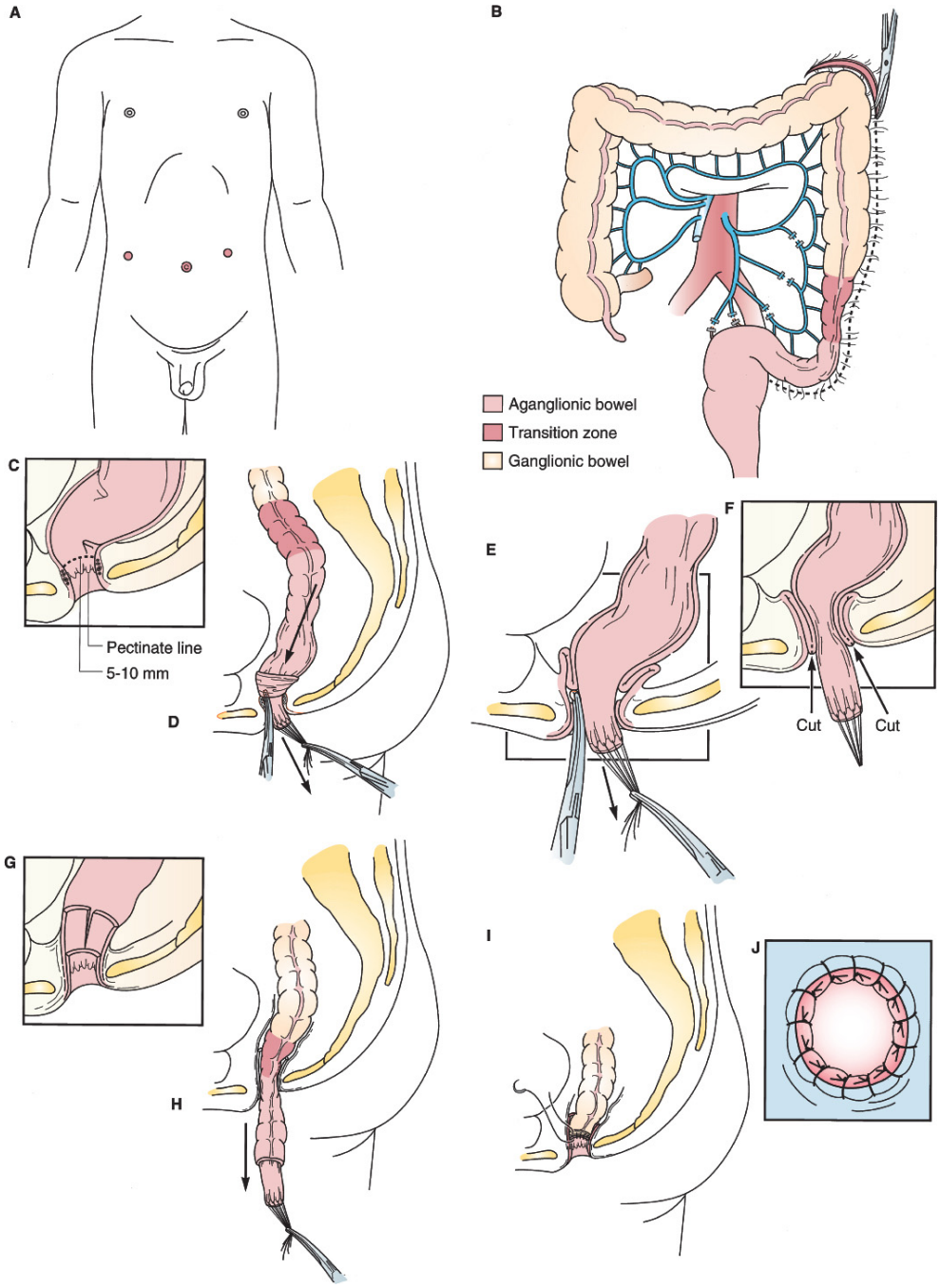


Figure 101.34 Laparoscopically assisted pull-through for Hirschsprung disease. **A:** Sites for operative trocar placement. **B:** Division of colon and rectal mesentery with mobilization of proximal colon. **C:** Circumferential incision in rectal mucosa 5- to 10-mm cephalad to the pectinate line. **D:** Mucosal traction sutures to facilitate further dissection from rectal muscular cuff. **E:** Transanal submucosal dissection is continued cephalad to meet the caudal extent of the transperitoneal rectal dissection. **F:** Circumferential incision of rectal muscular cuff. **G:** Rectal muscular cuff is split posteriorly to accommodate the pull-through segment (the pull-through segment is not shown here to clarify this maneuver). **H:** Rectum and sigmoid colon are pulled

through the rectal muscular cuff to the anastomotic site. **I:** Colon is transected at appropriate site with confirmation of ganglion cells by frozen section. **J:** Transanal, end-to-end single-layer colorectal anastomosis.

Total Colonic Aganglionosis

Total colonic aganglionosis is complex and, fortunately, relatively rare. Several different operative procedures have been described and treatment must be individualized. The endorectal pull-through with ileoanal anastomosis has been used with good success when most or all of the small bowel is normal. For extensive small bowel aganglionosis, an extended side-to-side anastomosis of normally innervated proximal small bowel to the aganglionic colon has been successfully performed. For complete intestinal aganglionosis, extended intestinal myectomy has been described.

Complications and Outcome

Complications resulting from definitive procedures for Hirschsprung disease include anastomotic leak, stricture, pelvic or rectal muscular cuff abscess, intestinal obstruction, and wound infection. These occur with a frequency of 1% to 10% with most experienced pediatric surgeons. Mortality from Hirschsprung disease is distinctly unusual unless enterocolitis is the presenting feature or associated medical problems or anomalies are present.

A unique complication following definitive repair of Hirschsprung disease is postoperative enterocolitis. The clinical presentation and pathogenesis have been discussed, and it remains an important and significant cause of morbidity. The incidence of postoperative enterocolitis ranges from 10% to 30% in most large series. Although rare, Hirschsprung enterocolitis can occur even in the presence of a diverting colostomy. Long-term outcomes appear quite good for all the procedures used, with 80% to 90% of patients maintaining good to excellent bowel function.

OTHER CHILDHOOD GASTROINTESTINAL DISORDERS

This review is limited to relatively common surgical conditions that are either congenital or unique in children. For other surgical conditions that can

affect both children and adults, the reader is referred to other chapters in this text.

Infantile Hypertrophic Pyloric Stenosis

Anatomy and Pathophysiology

The pathogenesis of infantile hypertrophic pyloric stenosis is unknown, but data suggest that local deficiency of neuronal nitric oxide synthase in the pylorus may be responsible for the clinical manifestations of the disease.[132,133] The deficiency of neuronal nitric oxide synthase leads to a lack of nitric oxide–mediated relaxation of smooth muscle and subsequent pyloric obstruction. Luminal narrowing occurs as a result of concentric hypertrophy of the pyloric smooth muscle. Clinically, this presents as progressive gastric outlet obstruction that becomes symptomatic by 2 to 4 weeks of age. The maximal narrowing and clinical symptoms of hypertrophic pyloric stenosis occurs between 4 and 8 weeks of age. The hypertrophic pyloric muscle ultimately undergoes gradual involution over a period of weeks to months.

Clinical Presentation

The reported incidence rate of hypertrophic pyloric stenosis is approximately 0.1% to 0.4% among white infants and is slightly lower in the black population. There is a distinct familial predisposition with an approximate 7% incidence rate in children of parents with a history of pyloric stenosis. The incidence rate is about four times higher in males than in females and is higher in first-born infants.[134] There is an apparent increased risk of hypertrophic pyloric stenosis in infants receiving oral erythromycin for pertussis prophylaxis.[135] Association of pyloric stenosis in infants treated for esophageal atresia and in infants with Smith–Lemli–Opitz syndrome has been reported.[136]

Infants with hypertrophic pyloric stenosis have a history of nonbilious, postprandial emesis that becomes progressively projectile. The infant otherwise appears well and will feed vigorously until late in the clinical course. The typical age at diagnosis is between ages 2 and 12 weeks of age. A history of identified feeding intolerance and formula change is common.

The definitive clinical finding on examination is a palpable, hypertrophied pylorus in the right upper quadrant to midepigastric region, often described as a firm, mobile "olive" on examination. This is a pathognomonic finding, and in the correct clinical setting, no further diagnostic imaging studies are required. An experienced clinician should be able to palpate a hypertrophied pylorus in nearly all cases. A successful physical examination requires an empty stomach, a quiet infant, and patience; repeated examinations may be necessary. Inability to palpate the pyloric mass in a quiet or anesthetized infant should place the diagnosis of hypertrophic pyloric stenosis in question. Other physical findings include visible or palpable gastric peristaltic waves, which can also be seen with any cause of gastric or duodenal obstruction.

Late findings with advanced symptoms include dehydration and a hypochloremic, hypokalemic metabolic alkalosis from gastric fluid losses. Profound metabolic alkalosis is less common in current practice but occasionally can be encountered in an extremely dehydrated infant with a long-standing history of emesis. The intravascular volume depletion and chloride-responsive alkalosis must be corrected prior to operative repair. The serum chloride should be restored to at least 90 to 95 mEq/L, and the measured CO_2 should be less than 30 mEq/L prior to induction of general anesthesia.

Diagnosis

If the examination is equivocal, either an upper gastrointestinal contrast series or a pyloric ultrasound examination can be performed. Both examinations are highly accurate and have sensitivity and specificity exceeding 95% in experienced hands. A typical contrast study demonstrating a narrowed, elongated pyloric channel is shown in Figure 101.35. Contrast studies have the advantage of evaluating other causes of symptomatic emesis, including gastroesophageal reflux disease, malrotation, and antroduodenal webs. The disadvantage of this approach is the presence of contrast in a poorly emptying stomach. Ultrasound examination of the pylorus is a preferred diagnostic test in most pediatric institutions. Ultrasound criteria for hypertrophic pyloric stenosis include a pyloric muscle thickness of 4 mm or greater and a pyloric channel length of 15 mm or greater. In general, the diagnosis of hypertrophic

pyloric stenosis is being made at an earlier age compared with several decades ago.

Figure 101.35 Ultrasound image of pyloric stenosis in coronal plane with pylorus marked by measurement bars.

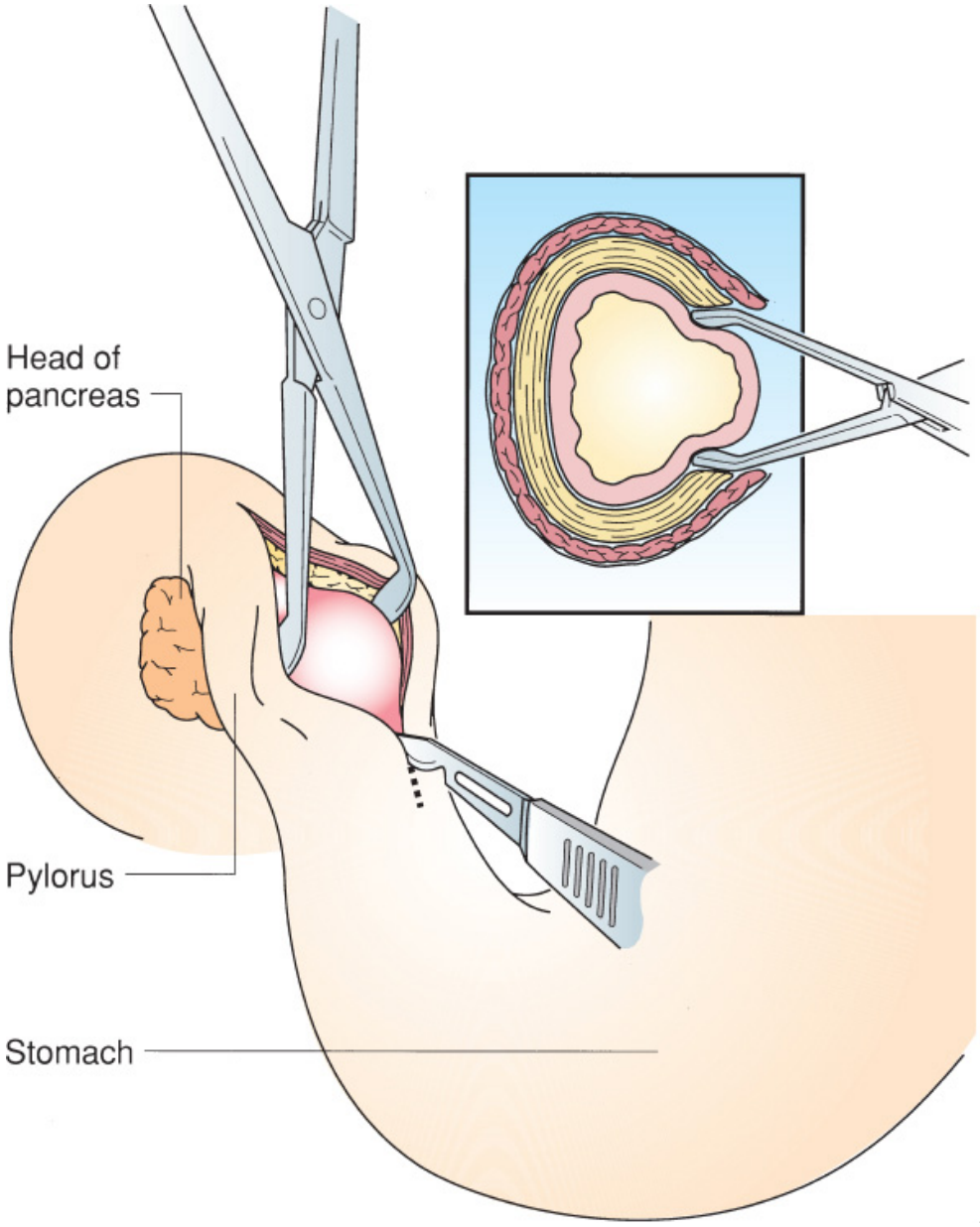


Figure 101.36 Ramstedt pyloromyotomy for infantile hypertrophic pyloric stenosis. The cross-sectional view shows herniation of the submucosa into the myotomy site, indicative of an adequate myotomy.

Treatment

Surgical pyloromyotomy has achieved universal acceptance because it offers definitive, rapid cure in virtually all infants, and morbidity rates have been negligible (Fig. 101.36). The operation is performed once the infant is rehydrated and the serum electrolytes are corrected. A single longitudinal incision is made in the hypertrophied pyloric muscle. The hypertrophied

circular pyloric muscle must be meticulously divided from the stomach to the junction of the proximal duodenum. An adequate pyloromyotomy is achieved when the submucosa bulges into the myotomy site and both edges of the divided pyloric muscle are freely mobile and can be accomplished via laparotomy or laparoscopy. Laparoscopic pyloromyotomy has been demonstrated to be efficacious and safe with similar operative times and outcome to the open repair; laparoscopic pyloromyotomy has become a standard approach at most children's hospitals.[137,138]

Postoperative feeding typically is started within 6 to 8 hours after recovery from anesthesia. Most infants are tolerant of enteral feeding and can be discharged home safely within 24 hours of operation. The surgical treatment of pyloric stenosis is straightforward, and the recovery is typically uncomplicated. A population-based study reviewing 1,777 infants with pyloric stenosis demonstrated a shorter length of stay and a lower overall complication rate in infants operated on by specialty-trained pediatric surgeons compared to general surgeons.[139] Mortality following pyloromyotomy is distinctly unusual in the absence of concomitant medical problems. Complications are rare and usually represent wound infection, technical failures related to an inadequate pyloromyotomy, or inadvertent entry into the duodenum or the stomach. Rarely, infants with inadequate pyloromyotomy may require reexploration and a second myotomy on the posterior pyloric wall. Inadvertent duodenotomy or gastrotomy must be recognized and repaired.

Intussusception

Anatomy and Physiology

6 *Intussusception* is defined as the invagination or telescoping of a proximal segment of intestine into an adjacent distal segment and is the most common cause of intestinal obstruction in infants and children aged 3 months to 3 years (Fig. 101.37). The invaginated proximal bowel is referred to as the *intussusceptum* and the recipient distal bowel is called the *intussuscipiens*. This process most commonly originates in the small intestine either at or near the ileocecal valve, with the terminal ileum passing into the cecum and colon (ileocolic intussusception). In the pediatric population, the vast majority

(95%) of cases are considered idiopathic because of a lack of an identifiable anatomic lesion causing the intussusception. Older children are more likely to have a pathologic lead point causing the intussusception. In similar fashion, infants and children with repeated episodes of intussusception have a greater probability of a pathologic lead point. Table 101.6 describes several factors that have been associated with the development of intussusception.

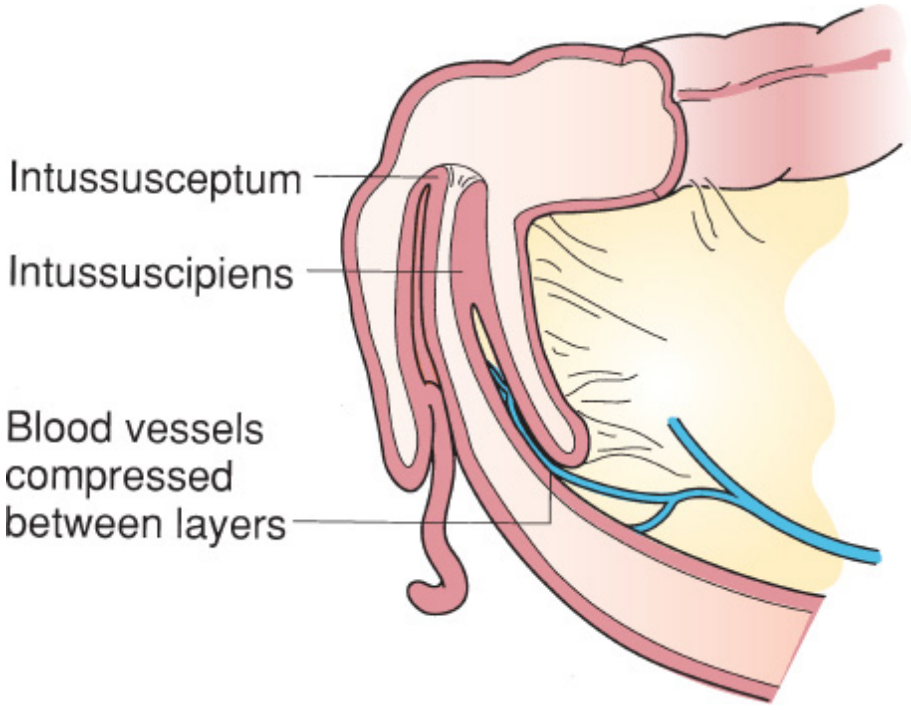


Figure 101.37 Ileocolic intussusception with the intussusceptum and intussuscipiens indicated.

Table 101.6 Predisposing Factors Leading to Intussusception
Anatomic Lead Points
Meckel diverticulum
Polyp
Lymphatic hypertrophy (Peyer patch)
Appendix
Duplication or enteric cyst
Lymphoma
Other neoplasm
Heterotopic pancreatic tissue
Associated Infections
Adenovirus
Rotavirus
Parasitic infestation
Other
Bleeding Disorders[a]
Henoch–Schönlein purpura
Hemophilia
Leukemia
Trauma
Blunt abdominal trauma
Major retroperitoneal dissections
Others
Cystic fibrosis

[a]These factors are more likely to be associated with small bowel-to-small bowel intussusception than with ileocolic intussusception.

Many cases of idiopathic intussusception in infants are probably caused by the normally prominent intramural lymph nodes (Peyer patches) in the terminal ileum acting as functional lead points. The anatomic consequence of intussusception is obstruction of the distal bowel. As bowel edema and inflammation progress, mesenteric vascular insufficiency from compression and congestion may occur. Incarceration, strangulation, and intestinal

perforation ultimately may result if this condition remains unrecognized or untreated.

Clinical Presentation

Intussusception is estimated to occur with an incidence rate of one to four cases per 1,000 children. There is a slight (3:2) male predominance; in a large retrospective series of children with intussusception, 79% were younger than 12 months, and seasonal variation in incidence was not observed.[140] An association between the development of intussusception and the administration of a previously available, tetravalent rhesus-based rotavirus vaccine (RotaShield, Wyeth Laboratories, Inc., Marietta, PA) was reported.[141] The currently available rotavirus vaccine does not appear to be associated with intussusception.[142]

Otherwise healthy infants who develop intussusception may have a characteristic clinical triad of abdominal pain, vomiting, and bloody stool. The typical infant develops the acute onset of severe, colicky abdominal pain. Intermittent episodes of irritability and crying may be associated with drawing the legs up to the abdomen. Between bouts of colic, the infant is often lethargic or sleepy. During periods of relative exhaustion, the abdominal examination may not be impressive; however, on careful physical examination, a palpable mass in the right abdomen may be appreciated in 80% to 90% of cases. Emesis is common and is often the presenting complaint. As intestinal obstruction progresses, intractable vomiting with abdominal distention and intravascular volume depletion may occur. Guaiac-positive stool is present in 90% to 95% of infants as a result of the ischemic mucosal injury to the intussusceptum. The passage of bloody stool mixed with mucus, classically described as *currant-jelly stool,* may be observed.

Diagnosis

Plain radiographs of the abdomen are generally nonspecific and may show a paucity of gas in the right lower quadrant with a mass effect in the ascending colon. Late findings demonstrate mechanical small bowel obstruction with proximal distention, air–fluid levels, and a decrease or absence of gas distally. Ultrasound examination typically reveals a mass resembling a bull's eye or target sign, corresponding to the intussusceptum within the

intussuscipiens. The target sign of intussusception also may be demonstrated by CT. Both these latter modalities do not allow for potential therapeutic reduction and may be more useful in diagnosing suspected cases of proximal jejunoileal or enteroenteral intussusception. Diagnostic enema techniques using either air or contrast approach 100% accuracy with typical ileocolic intussusception (Fig. 101.38). An approach using hydrostatic or pneumatic enema allows therapeutic reduction of intussusception as well.

Figure 101.38 Contrast enema demonstrating classic ileocolic intussusception with the intussusceptum visible in the ascending colon (*arrows*).

Treatment

Any infant with suspected intussusception in the absence of peritonitis should undergo diagnostic hydrostatic or pneumatic enema. A high index of clinical suspicion and liberal application of this approach should be maintained. The incidence of normal contrast enema examinations in this setting may exceed

75% in most pediatric centers, and this is justified by the considerable risk inherent in a missed diagnosis. An experienced pediatric radiologist and surgical evaluation are essential. Intravenous access and resuscitation should occur before attempts are made at diagnostic or therapeutic enemas.

Successful hydrostatic or pneumatic reduction of ileocolic intussusception is achieved in 60% to 90% of infants in most pediatric centers in the United States. The ability to reduce intussusception using these techniques is time dependent and diminishes substantially after the duration of symptoms exceeds 24 hours. In this setting, a contrast enema is still diagnostic and potentially therapeutic if carefully performed.[143] With most experienced pediatric radiologists, the risk of perforation or reduction of a strangulated intussusceptum is low.

The technique of retrograde reduction of intussusception is straightforward. Contrast or air is introduced into the rectum by a balloon catheter, with the height of the hydrostatic column 1 m or less. Most centers use three attempts at reduction, with each attempt no longer than 3 minutes in duration. As long as progress is being made, however, attempts can be repeated until reduction is achieved. Successful reduction of ileocolic intussusception is demonstrated by observing retrograde flow of contrast or air into the terminal ileum. Inability to demonstrate retrograde flow into the ileum suggests incomplete reduction requiring surgical exploration.

Operative Management

Infants presenting with peritonitis and small bowel obstruction with a clinical diagnosis of intussusception should undergo immediate resuscitation and exploration without attempts at retrograde enema. Surgical exploration is also required after incomplete retrograde enema reduction of intussusception or in the relatively infrequent situation of bowel perforation during diagnostic or therapeutic enema. The operative strategy is dictated by the findings. Spontaneous reduction of the intussusception is reported to occur in up to 20% to 30% of infants following induction of general anesthesia. In this situation, exploration confirming the reduction and examining the bowel for a pathologic lead point is sufficient. With persistent intussusception and viable bowel, the bowel is manually reduced, generally pushing the intussusceptum out of the distal bowel. If manual reduction cannot be performed or the intussusceptum is strangulated, then segmental resection with primary

anastomosis is performed. Attempts at reducing intussusception with clearly necrotic bowel should be avoided. Diverting enterostomy as a result of peritoneal contamination usually is not required. Appendectomy is routinely performed in all infants undergoing operative exploration for intussusception. A successful laparoscopic approach to the diagnosis and management of intussusception has been reported in approximately two-thirds of selected patients.[144–146]

Complications and Outcome

Following successful enema reduction, the infant is given intravenous fluids and observed for tolerance of oral feeding is rapid. Recovery from operative reduction or bowel resection is generally no different than from other similar gastrointestinal procedures. Most infants enjoy a complete recovery with minimal or no morbidity. Recurrent intussusception after either nonoperative or operative reduction occurs in about 5% of infants and usually can be treated with repeat enema. Mortality from intussusception is rare and is almost always the result of systemic sepsis and shock from unrecognized, strangulated intestine.

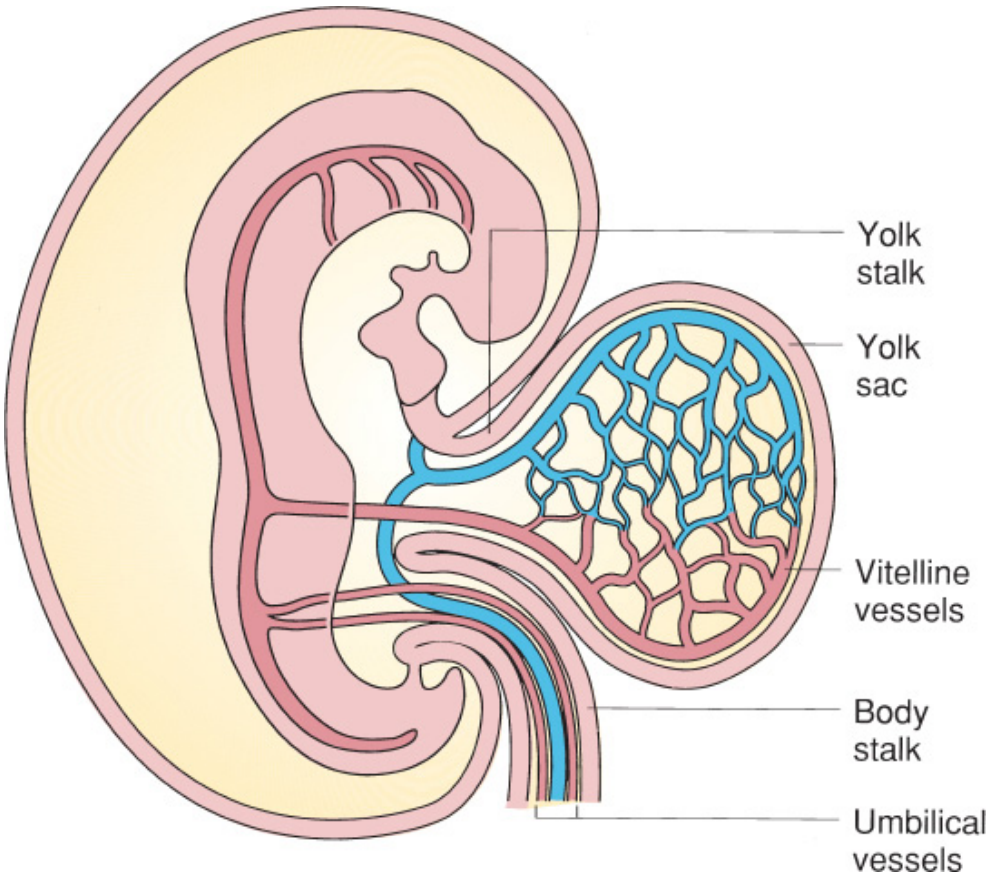


Figure 101.39 Normal embryonic relations of the yolk sac, yolk stalk, and developing gut.

Meckel Diverticulum and Related Disorders

Embryology and Anatomy

The most frequently encountered congenital anomaly of the gastrointestinal tract is Meckel diverticulum, representing one of several malformations resulting from persistence of the yolk stalk (synonymous with *vitelline duct* and *omphalomesenteric duct*) and its components. The embryonic yolk stalk connects the yolk sac and the developing midgut (Fig. 101.39). Between weeks 5 and 7 of gestation, the yolk sac involutes and the stalk fuses with the umbilical cord. Developmental failure or arrest of yolk sac involution creates a spectrum of clinical malformations as outlined in Figure 101.40, with Meckel diverticula constituting greater than 95% of these anomalies. Meckel diverticulum is a true diverticulum of variable size derived from the intestinal remnant of the yolk stalk. Typically, it is found on the antimesenteric border

of the terminal ileum approximately 40 to 50 cm from the ileocecal valve in adults. The blood supply is derived from persistent vitelline vessels supplied from the SMA. About 25% of the diverticula have a fibrous or vascular attachment to the anterior abdominal wall at the umbilicus (Fig. 101.40C). Heterotopic gastric mucosa or pancreatic tissue is found in about half of the diverticula examined at autopsy. In about 75% of patients with symptomatic diverticula, gastric mucosa is present. When symptoms occur, bleeding or perforation is generally the result of peptic ulceration of the adjacent ileal mucosa and not from the diverticulum itself.

Clinical Presentation

Symptomatic yolk stalk anomalies are usually diagnosed by history and clinical examination. Umbilical drainage from a persistent fistula or sinus tract may be noted in a newborn following separation of the umbilical cord. Intestinal prolapse or passage of stool from the umbilicus signifies a patent omphalomesenteric duct. Small bowel obstruction in an otherwise healthy infant without a history of laparotomy may be a result of volvulus around an omphalomesenteric band or intussusception from a Meckel diverticulum acting as a lead point.

The incidence rate of Meckel diverticula in the general population is about 2%, with a 2:1 male-to-female predominance. The risk of developing symptoms from the diverticulum decreases with age, and the vast majority of subjects remain asymptomatic. About half of the persons who do become symptomatic are younger than 2 years. Table 101.7 outlines several of the more common clinical presentations of symptomatic Meckel diverticulum.

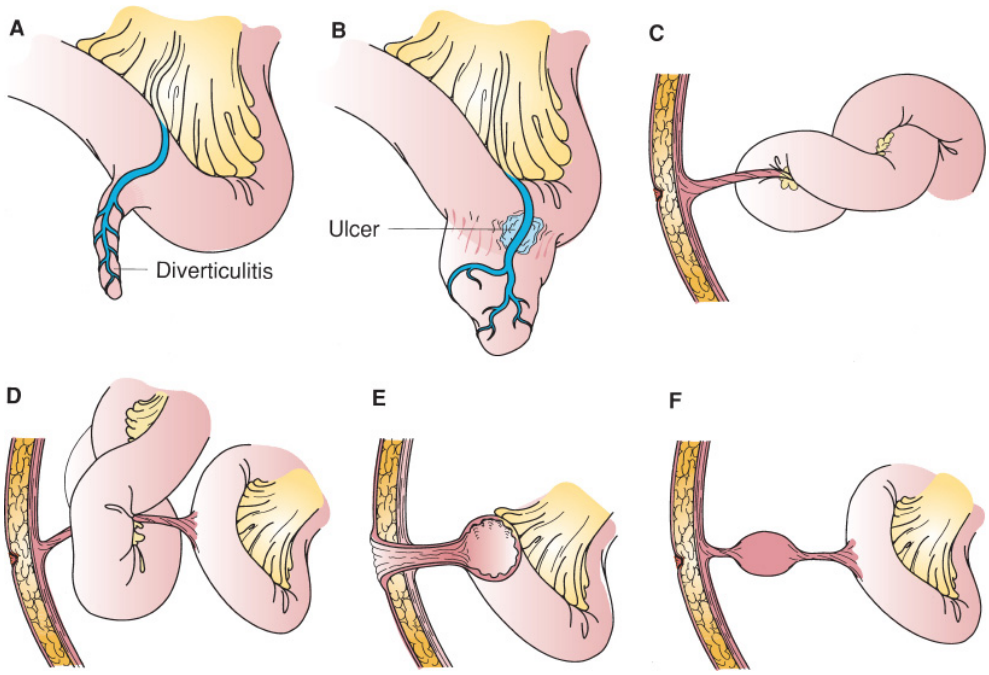


Figure 101.40 Common variants of yolk stalk malformations. **A, B:** Meckel diverticulum can manifest with inflammation (diverticulitis) or hemorrhage from acid-induced ulceration. **C, D:** Meckel diverticulum in association with abnormal band attached to the abdominal wall predisposing to volvulus and intestinal obstruction. **E:** Patent omphalomesenteric duct. **F:** Omphalomesenteric sinus and cyst formation.

Hemorrhage

Gastrointestinal bleeding related to Meckel diverticulum generally results from peptic ulceration of the adjacent ileal mucosa. Clinically, it manifests as painless, episodic hemorrhage that is typically bright red to maroon in color; melena is not characteristically seen. Bleeding from Meckel diverticulum is generally not hemodynamically significant or exsanguinating, but it can be persistent enough to require transfusion. The diagnostic test of choice is the ^{99m}Tc-pertechnetate radioisotope scan (Meckel scan) because of the high affinity of the isotope for gastric mucosa and the high probability of gastric mucosa within a symptomatic Meckel diverticulum. Diagnostic accuracy is reported to be as high as 90% for Meckel-related bleeding. Contrast studies and endoscopy have a limited role when the problem is hemorrhage from a Meckel diverticulum.

Obstruction

Intestinal obstruction associated with omphalomesenteric duct anomalies usually results from either intussusception or volvulus around an abnormal attachment between the bowel and the abdominal wall. In about 5% to 10% of persons with symptomatic Meckel diverticula, intussusception is the initial symptom. In patients with Meckel diverticula whose initial symptom is small bowel obstruction, about half have intussusception, and the remainder have volvulus, internal hernias, or other mechanical causes. Intussusception secondary to a Meckel diverticula has a decreased likelihood for successful enema reduction. Small bowel obstruction from volvulus around an omphalomesenteric band requires operative exploration and treatment.

DIAGNOSIS

Table 101.7 Signs and Symptoms of Meckel Diverticulum

Clinical Presentation	Approximate Frequency (%)
Hemorrhage	30–35
Small bowel obstruction	30–35
Diverticulitis	20–25
Umbilical fistula	10
Other	Uncommon

Diverticulitis

About one-third of patients with symptomatic Meckel diverticulum have acute diverticulitis. Similar to appendicitis, intraluminal obstruction at the base of a Meckel diverticulum can lead to distal inflammation, gangrene, and subsequent perforation. Peptic ulceration also can lead to local inflammation and perforation with the development of peritonitis. The signs and symptoms of Meckel diverticulitis are virtually indistinguishable from appendicitis, and exploration is both diagnostic and therapeutic.

Umbilical Anomalies

About 10% of patients with yolk stalk or persistent omphalomesenteric duct anomalies have umbilical problems. The usual clinical presentation is persistent drainage or intestinal mucosa found at the umbilicus. The diagnosis can be confirmed by contrast sonogram of the umbilical orifice or tract. Occasionally, ultrasound examination may be useful to demonstrate omphalomesenteric cysts. Ultimately, surgical exploration may be required for both diagnosis and treatment.

Meckel Diverticulum as an Incidental Finding

The management of an incidentally discovered Meckel diverticulum during abdominal exploration for other reasons is controversial. The risk of resecting an asymptomatic diverticulum must be weighed against the reasons for the operative exploration, patient age, and the potential for future symptoms from the diverticulum. Infants younger than 2 years are at greater probability of becoming symptomatic from Meckel diverticula. Resection is clearly indicated with demonstration of heterotopic gastric mucosa in the diverticulum to prevent peptic ulceration. This finding may occasionally be determined by direct palpation because the gastric mucosa is thicker than ileal mucosa. Abnormal omphalomesenteric bands to the abdominal wall should also be excised. If clinical judgment suggests that the diverticulum is at risk for luminal obstruction, resection is warranted.

Treatment

Infants and children with symptomatic umbilical abnormalities from yolk stalk remnants are usually well, and umbilical exploration with possible laparotomy can be undertaken electively. The yolk stalk remnant is excised, and, if present, the communication with the ileum is closed primarily with minimal morbidity and mortality. Operative exploration is required for patients with symptomatic Meckel diverticula. Typically, exploration can be accomplished through a variety of incisions. The treatment of choice is resection through either antimesenteric wedge excision or segmental bowel resection with primary closure or anastomosis. Laparoscopic diagnosis and management of Meckel diverticulum has also been described.[147] In the absence of associated medical problems, excellent functional outcome is expected with minimal morbidity and essentially no mortality unless intestinal necrosis has occurred.

Foreign Bodies

Ingestion of foreign bodies by infants and children is common. Toddlers in the age range of 9 months to 2 years are at particular risk given newly acquired mobility and the tendency for oral exploration. The type of foreign body and the location in the gastrointestinal tract on discovery dictate overall management.

Esophagus

In normal children, ingested coins and small toys can become impacted at predictably narrow portions of the esophagus, including the cricopharyngeus, the esophagus at the level of the left mainstem bronchus, and the gastroesophageal junction. Previous areas of esophageal repair or injury predispose to points of obstruction. In particular, infants and children with repaired esophageal atresia, gastroesophageal reflux, or caustic esophageal injury are at risk for impaction at these sites.

Esophageal foreign bodies produce clinical symptoms of drooling, feeding intolerance (particularly to solids), dysphagia, and pain. Unrecognized foreign bodies with unusual configuration or sharp points and edges may cause esophageal perforation and mediastinitis. The diagnosis is straightforward on plain radiographs if the object is metallic or radiopaque. If a radiolucent object is suspected, an upper gastrointestinal contrast study is usually required to confirm the diagnosis. Lateral plain films of the neck or chest may be useful to differentiate between small foreign bodies in the esophagus or the trachea.

Foreign bodies impacted in the esophagus cause partial esophageal obstruction and can cause complications including aspiration, erosion, perforation, and late stricture formation. Therefore, all esophageal foreign bodies should be removed. Extraction of foreign objects can be accomplished by using balloon catheter retrieval under fluoroscopic guidance or direct visualization using endoscopy. Performed within 24 hours of ingestion, balloon catheter retrieval of esophageal foreign bodies is relatively straightforward. This technique is limited to smooth radiopaque objects such as coins to minimize the risk of esophageal perforation. The most significant risk with balloon catheter retrieval is potential aspiration from an unprotected airway, and this must be anticipated as the foreign body traverses the pharynx.

Alternatively, for esophageal coin impaction of less than 24 hours' duration in children without a history of esophageal surgery or injury, esophageal bougienage with clearance of the coin into the stomach has been successful.[148]

Retrieval of esophageal foreign bodies under direct endoscopic vision requires general anesthesia. Either flexible or rigid endoscopy systems are widely available and used with individual and institutional preferences. Esophageal perforation, the major risk, occurs in fewer than 5% of cases in most reported series. Long-standing esophageal foreign bodies may erode into the aorta and cause life-threatening hemorrhage from aortoesophageal fistula.[149]

Distal Gastrointestinal Tract

More than 95% of foreign bodies that pass beyond the gastroesophageal junction proceed uneventfully through the gastrointestinal tract. The transit time for an asymptomatic foreign body is highly variable and can take hours to weeks. Progress of an asymptomatic radiopaque foreign body can be followed by abdominal plain films, but this is rarely useful from a clinical standpoint unless it is a battery. The stool may also be screened to confirm passage of a known foreign body.

Operative exploration or endoscopic retrieval of distal gastrointestinal foreign bodies is generally reserved for clinical symptoms related to either obstruction or intestinal injury heralded by abdominal pain, vomiting, fever, or peritonitis. In addition, persistence of an asymptomatic foreign body in the stomach for several weeks is a relative indication for upper endoscopic retrieval, particularly with foreign bodies with irregular shape, configuration, or sharpness. This is a clinical judgment that is best reserved for an experienced pediatric surgeon because remarkably complex and improbable objects may pass uneventfully through the gastrointestinal tract. For asymptomatic foreign bodies lodged distal to the stomach, a relative indication for operative removal is a fixed, persistent location in the intestine longer than 1 week in duration.

Ingested batteries, in particular alkaline disc batteries, are a potentially serious hazard to children and require a more aggressive approach. Disruption of the battery casing and spillage of the contents have been

reported to cause intestinal injury and perforation, presumably because of leakage of potassium or sodium hydroxide. Esophageal impaction of a battery warrants prompt removal when recognized because the risk of acquired esophageal injury, perforation, and development of traumatic tracheoesophageal fistula is present.[150] In the distal bowel, cathartics may be helpful to expedite passage of the battery. Operative removal may be necessary if the battery fails to progress distally over a few days or if symptoms related to the battery occur. Notably, the vast majority of batteries pass through the gastrointestinal tract uneventfully. Ingestion of multiple magnets can cause problems with small bowel obstruction or enteroenteric fistula formation.

Gastrointestinal Hemorrhage

The subject of gastrointestinal hemorrhage and general principles of management are discussed elsewhere in this book. The following section reviews some of the important and age-dependent clinical causes and unique issues of gastrointestinal bleeding in pediatric population. These causes are age dependent and are summarized in **Tables 101.8** and **101.9**.

Diagnostic workup of an infant or a child with gastrointestinal hemorrhage requires coordinated participation among pediatricians, surgeons, gastroenterologists, and radiologists. Several general principles governing the diagnostic approach to gastrointestinal bleeding in infants and children follow:

1. A clear diagnosis can be made in most situations; given the current technology available to assist with diagnosis, an aggressive approach is warranted. Diagnostic procedures such as flexible fiberoptic endoscopy, radioisotope imaging, and angiography are widely available, safe, and applicable to any age group, including the newborn. Despite these measures, in approximately 16% of cases, the cause of guaiac-positive stools in a neonate or infant remains unknown,[151] and the bleeding is self-limited.
2. The primary diagnostic investigation of choice for upper gastrointestinal bleeding is esophagogastroduodenoscopy. This procedure is optimally performed within the first 24 hours after cessation of active hemorrhage and usually requires general

anesthesia. Imaging studies for active upper gastrointestinal hemorrhage are limited in their ability to aid with diagnosis.

c. Infants and children presenting with minor lower gastrointestinal bleeding are best evaluated by a careful perineal and digital rectal examination, followed by anoscopy.

d. Massive lower gastrointestinal hemorrhage in an infant or a child outside the newborn period is most likely the result of a bleeding Meckel diverticulum.

e. If a definitive source for lower gastrointestinal hemorrhage is not found on colonoscopy, evaluation for an upper gastrointestinal source, including upper endoscopy and diagnostic laparoscopy, is warranted.

f. Pain is an uncommon symptom with pediatric gastrointestinal hemorrhage and implies a more complex problem such as volvulus, ischemic bowel, or inflammatory bowel disease. Painful gastrointestinal hemorrhage in pediatric patient requires urgent evaluation and prompt diagnostic workup.

g. In contrast to that in adults, gastrointestinal bleeding in children is rarely a symptom or sign of gastrointestinal neoplasm.

Table 101.8 Etiology and Causes of Upper Gastrointestinal Hemorrhage[a]

Patient Age Group	Common Causes	Less Common Causes
Neonatal (0–30 days)	Gastritis Esophagitis Ingested maternal blood Peptic ulcer	Iatrogenic trauma Primary coagulopathy Vascular malformation (hemangioma, telangiectasia, arteriovenous malformation) Nasal or pharyngeal bleeding Miscellaneous (leiomyoma, gastric polyp, duplication)
Infant (30 days to 1 year)	Gastritis Esophagitis Peptic ulcer	Same as less common neontal causes, plus: Drugs (steroids, nonsteroidal anti-inflammatory drugs) Foreign body, caustic ingestion Esophageal varices
Child (1–12 years)	Esophageal varices Esophagitis Peptic ulcer	Same as less common infantile causes, plus: Acquired thrombocytopenia (chemotherapy)
Older child (12 years to adult)	Esophageal varices Esophagitis Peptic ulcer	Same as less common childhood causes

[a]Order in appearance approximates clinical frequency.

Modified from Oldham KT, Lobe TE. Gastrointestinal hemorrhage in children. A pragmatic update. *Pediatr Clin North Am* 1985;32:1247–1263, with permission.

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Table 101.9 Causes of Lower Gastrointestinal Hemorrhage[a]

Patient Age Group	Common Causes	Less Common Causes
Neonatal (0–30 days)	Benign anorectal lesions (fissure) Upper gastrointestinal hemorrhage Milk allergy Necrotizing enterocolitis Midgut volvulus	Iatrogenic trauma Primary coagulopathy Vascular malformations Enterocolitis (Hirschsprung disease, other) Miscellaneous (duplication, lymphoma, lymphangiectasia)
Infant (30 days to 1 year)	Incarcerated inguinal hernia Benign anorectal lesions Idiopathic intussusception Meckel diverticulum Infectious diarrhea Upper gastrointestinal hemorrhage Milk allergy	Same as neonate, with addition of: Acquired thrombocytopenia Ingestion of colored foodstuff (pseudohematochezia)
Child (1–12 years)	Benign anorectal lesions Juvenile polyps Intussusception Meckel diverticulum Infectious diarrhea Upper gastrointestinal hemorrhage	Same as infant, with addition of: Juvenile polyposis coli/familial polyposis coli Hemolytic uremic syndrome Henöch–Schonlein purpura Systemic vasculitis (dermatomyositis, lupus) Acquired thrombocytopenia (as above plus idiopathic

		thrombocytopenic purpura)
Older child (12 years to adult)	Juvenile polyps Benign anorectal lesions Inflammatory bowel disease Upper gastrointestinal hemorrhage	Same as child, except: Henöch–Schonlein purpura and hemolytic uremic syndrome less likely Meckel diverticulum

[a]Order in appearance approximates clinical frequency.

Modified from Oldham KT, Lobe TE. Gastrointestinal hemorrhage in children. A pragmatic update. *Pediatr Clin North Am* 1985;32:1247–1263, with permission.

Neonates (0 to 30 Days of Age)

The most common cause of gastrointestinal hemorrhage in a neonate is gastritis. Endoscopic evaluation of newborns with symptomatic upper gastrointestinal hemorrhage demonstrates gastritis or esophagitis in 50% to 75% of cases. About 10% to 15% have swallowed maternal blood during birth, and 10% of newborns are found to have an underlying coagulopathy. Anatomic lesions requiring operative control are distinctly unusual in this age group. Significant and sometimes massive upper gastrointestinal hemorrhage may occur in a neonate without a definable anatomic lesion despite endoscopic evaluation. This finding is usually the result of gastritis, and treatment is directed at blood and volume replacement and correction of any underlying coagulopathy.

Significant conditions responsible for lower gastrointestinal bleeding in the newborn include NEC, malrotation with volvulus, enterocolitis, or bowel obstruction secondary to an incarcerated inguinal hernia. These clinical entities present with characteristic histories, findings on clinical examination, and surgical treatment guidelines previously discussed. Anorectal fissure is also common and easy to diagnose in neonates, and bleeding is typically self-limited.

Infants (30 Days to 1 Year)

Infants with upper gastrointestinal bleeding deserve comprehensive evaluation, including endoscopy, to identify potential lesions requiring operative intervention. The most common causes of lower gastrointestinal hemorrhage in this age group include infectious diarrhea, intussusception, food allergy, and bleeding Meckel diverticulum. Most of these lesions have distinct symptoms, signs, and diagnostic findings to facilitate diagnosis. Infectious diarrhea is usually accompanied by fever, feeding intolerance, possibly emesis, and abdominal pain. Fecal leukocytes may be present on stool examination, and enteric pathogens or their toxins can be identified by stool culture.

Children (1 to 12 Years)

An important surgical cause of upper gastrointestinal bleeding in this age group includes esophageal variceal bleeding from portal hypertension. Children with biliary atresia or extrahepatic portal venous obstruction account for most cases of variceal bleeding in this age group. In the acute setting, endoscopic sclerotherapy or banding is used as a temporizing measure for hemorrhage control; some investigators advocate maintenance sclerotherapy. Ultimately, for these children, orthotopic liver transplantation may offer definitive surgical treatment. The use of operative portosystemic shunts for acute variceal hemorrhage is not widely used in pediatric surgical practice in the United States.

Conditions causing lower gastrointestinal bleeding in this age group include juvenile polyps. These are benign, hamartomatous polyps and represent the single most common cause of lower gastrointestinal bleeding in children. About 20% to 30% of the polyps are palpable on digital rectal examination. A history of painless, bright red blood per rectum during a bowel movement is typical. The bleeding results from mucosal irritation, involution, and sloughing of a pedunculated polyp and is usually not associated with hemodynamically significant hemorrhage. Tissue may be passed or the pedunculated polyp may prolapse out the anus. A hypochromic, microcytic anemia may be present. Diagnostic workup generally involves a contrast enema to identify the polyp and evaluate the colon for synchronous lesions. Colonoscopy may require general anesthesia in this age group, and endoscopic snare polypectomy is the treatment of choice for appropriate-

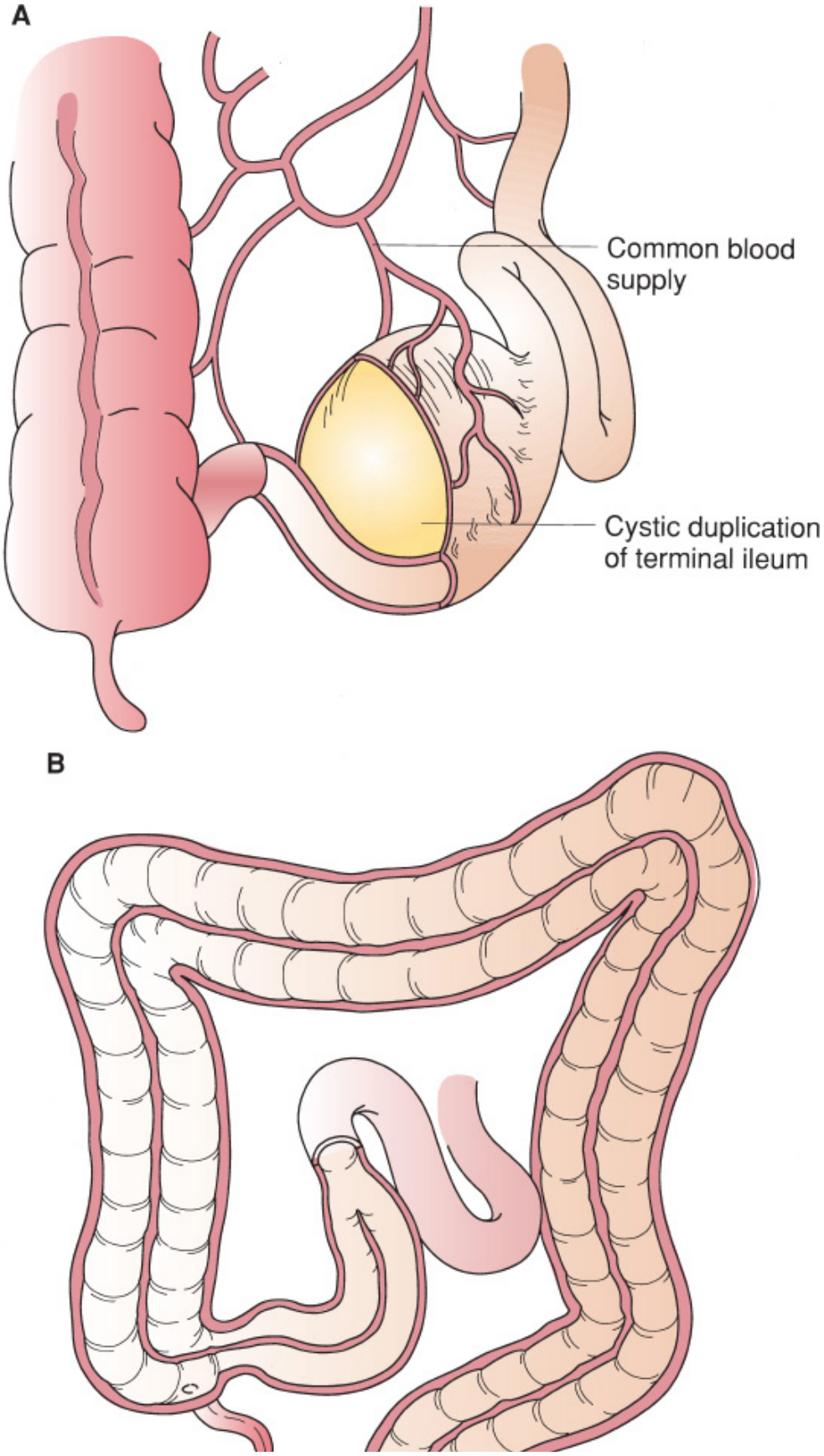
sized polyps. Infrequently, transanal excision or open resection of larger polyps is required. In the case of multiple juvenile polyps not amenable to endoscopic polypectomy, management may be expectant based on the benign natural history characterized by involution during adolescence. Histologic confirmation is necessary to differentiate these lesions from adenomatous polyps seen in familial polyposis syndromes or Gardner syndrome.

Older Children and Adolescents (Older than 12 Years)

Causes of both upper and lower gastrointestinal hemorrhage in this age group include most etiologic conditions found in adults. Importantly, inflammatory bowel disease is significant in this age group.

Intestinal Duplication

The embryologic origin of enteric duplication formation remains controversial, but duplication likely represents abnormal development of either a diverticulum or adjacent portion of the developing gut. In some cases, duplication cysts of the upper gastrointestinal tract may be associated with thoracic spinal cord or vertebral defects; this association appears to reflect abnormal sequestration and integration of developing primitive notochord elements in addition to duplication. The resulting lesions are described as either *cystic* or *tubular* based on their gross appearance (Fig. 101.41). All types of gastrointestinal-derived epithelia are found, but the clinically relevant finding is ectopic gastric mucosa. Duplications are commonly found along the mesenteric border of the native bowel. The muscular wall is typically well developed and intimately attached to the functional bowel. In addition, the blood supply is also shared with the functional intestine, an important surgical consideration.


A
Common blood supply
Cystic duplication of terminal ileum
B

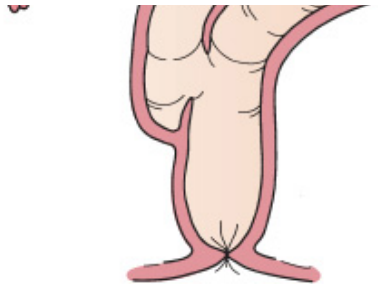


Figure 101.41 Enteric duplication. **A:** Cystic duplication of the terminal ileum. **B:** Tubular duplication of the terminal ileum and the colon.

Cystic Duplications

Cystic duplications may be found throughout the gastrointestinal tract. They are frequently located in the esophagus and the hindgut, particularly the rectum. Direct communication between a duplication cyst and the functional gut lumen is unusual. Typically, asymptomatic duplications are discovered as incidental mass lesions during diagnostic imaging studies, particularly when the location is the thoracic cavity or the rectum. Duplications also may present as symptomatic lesions from ectopic gastric mucosa leading to ulceration and bleeding. Other potential presenting symptoms of enteric duplication include obstruction, intussusception, perforation or traumatic rupture, torsion, infection, and occasional malignant degeneration. Useful examinations to define the extent of the lesion include ultrasound, CT scanning, MRI studies, and contrast studies. The identification of enteric duplication on routine prenatal ultrasound examination has been reported.

The treatment of all cystic duplications is operative. Even in asymptomatic infants and children, uncertainty regarding the nature of the mass and the potential for subsequent problems dictates surgical exploration. Esophageal and rectal duplication cysts are generally amenable to simple excision. In contrast, duplication cysts of the small intestine usually require segmental resection and primary anastomosis, given the intimate attachment and shared blood supply with the native bowel. For large cystic duplications involving longer segments of native bowel, individualized treatment strategies are required. One option is cyst marsupialization with resection of the duplication cyst wall with preservation of the common blood supply and wall between the cyst and the native bowel. This technique is combined with submucosal dissection and stripping of the remaining epithelium from the cyst wall. Another approach is internal drainage of the cyst into the adjacent

native intestine, for example, creation of a cystoduodenostomy for duodenal duplication not amenable to local resection and anastomosis; this would be distinctly unusual.

Tubular Duplications

Tubular duplications may be found anywhere along the length of the gastrointestinal tract. They are less frequent than cystic duplications and have a tendency to involve the ileum and the colon. It is believed that tubular duplication generally reflects abnormal, disordered recanalization of the gastrointestinal tract. Similar to cystic duplications, tubular lesions share a common wall and blood supply with the native bowel. Communication between the tubular duplication and native bowel lumen is common. Tubular duplications may be extensive and can involve the entire length of terminal ileum and colon. Malformations of the entire colon and rectum are associated with genitourinary anomalies, particularly duplications of the external genitalia or bladder.

Tubular duplications manifest clinically in similar fashion to cystic lesions. Symptomatic lesions most commonly present with gastrointestinal bleeding or obstruction. Treatment is operative, and an individualized strategy is required that is based on the location and nature of the duplication. Resection with primary anastomosis may require removal of an unacceptable length of normal bowel. Marsupialization with submucosal stripping of the duplication epithelium may be particularly helpful if ectopic gastric mucosa is suspected or found. Obstruction from a long, blind-ending parallel duplication that communicates with the functional gut lumen can be treated effectively with a reentry procedure such as a distal enteroenterostomy. This approach avoids a potentially complex resection of a significant length of bowel.

The outcomes of surgical management of enteric duplications are generally excellent in the absence of other associated anomalies or medical problems. Mortality attributable to the duplication itself is unusual. Postoperative morbidity is generally dependent on the nature and location of the duplication.

Mesenteric and Omental Cysts

Mesenteric and omental cysts are rare lesions thought to result from the sequestration of lymphatic tissue during development. Mesenteric cysts are

twice as common as omental cysts. Both are characterized by thin, often incomplete walls lined with endothelial cells absent of surrounding smooth muscle. They may be filled with either serous lymphatic fluid or chyle and may be unilocular or multilocular. These cysts may become extraordinarily large before producing symptoms.

Most infants and children with mesenteric or omental cysts are diagnosed prior to adolescence. Asymptomatic children are usually diagnosed incidentally during studies for other reasons. Symptomatic children present with abdominal pain, and, on examination, a soft, mobile abdominal mass is characteristic. Bleeding, rupture, obstruction, torsion, or cyst infection may be observed. Most of these lesions can be diagnosed by ultrasound or CT scan imaging. Ascites, duplication cysts, pancreatic pseudocysts, and large ovarian cysts may have a similar appearance on diagnostic imaging. Peripheral calcification and evidence of recent hemorrhage may be seen in mesenteric or omental cysts (Fig. 101.42).

The treatment for these lesions is simple excision. Total excision of mesenteric or omental cysts is generally preferable over partial excision with marsupialization. Limited resection with primary anastomosis may be required for a mesenteric cyst located adjacent to the intestinal wall, particularly if there is concern that the cyst actually may be an enteric duplication. Morbidity and mortality are generally limited to concurrent problems associated with the intestine. In particular, volvulus of a mesenteric cyst may cause vascular compromise and infarction of the adjacent intestine.

Primary Peritonitis

Bacterial peritonitis without a specific, identifiable cause is referred to as *primary peritonitis.* Spontaneous bacterial peritonitis in children with ascites or nephrosis is generally included in this group. Hematogenous seeding of ascitic fluid is probably responsible for the development of spontaneous bacterial peritonitis. The infecting bacterial organisms were classically gram-positive with a variety of staphylococcal, streptococcal, and other species accounting for most cases. In a series of infants and children with primary peritonitis, more than two-thirds of the cases were caused by gram-negative organisms such as *Escherichia coli.*[152] This trend may reflect the use of antibiotic prophylaxis directed against gram-positive organisms.

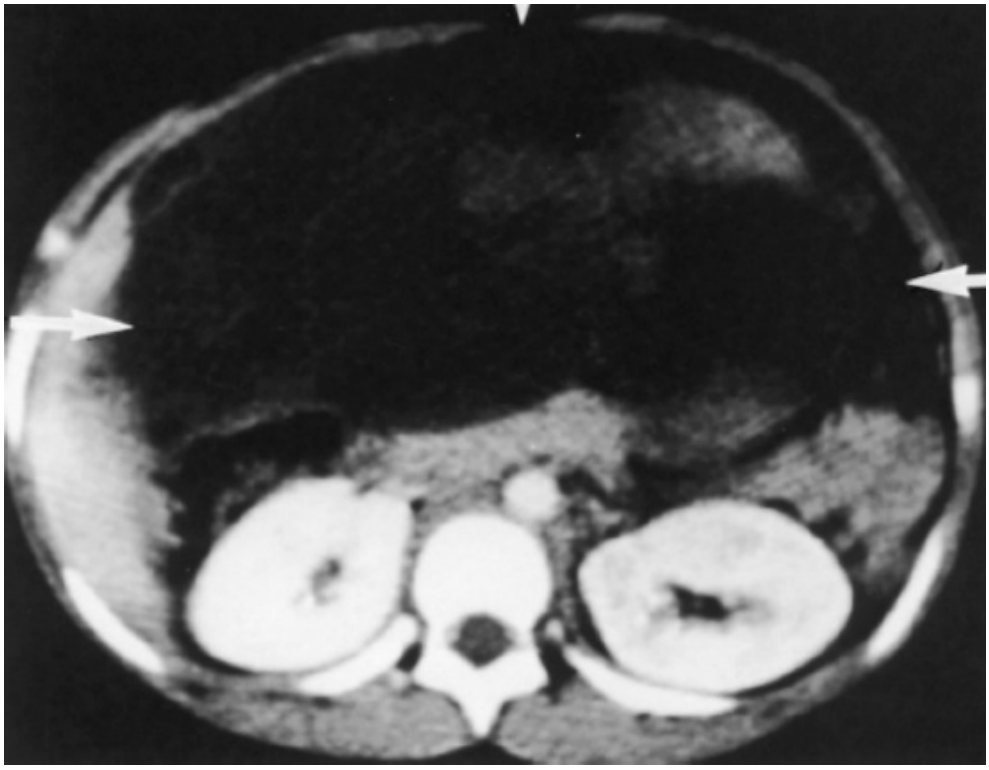


Figure 101.42 Computed tomographic scan of a child after abdominal trauma. Hemorrhage into large omental cyst is apparent (*arrows*).

The other etiologic mechanism for the development of primary peritonitis is believed to involve retrograde inoculation of the peritoneal cavity via the genitourinary tract. This etiology is characteristic of prepubertal girls 5 to 10 years of age, accounting for as many as half of the cases of primary peritonitis. The initial signs and symptoms in these children are virtually identical to those in children with perforated appendicitis: fever, emesis, abdominal pain, and tenderness on examination. Leukocytosis is characteristic, and an ileus is observed on plain abdominal films. On exploration, these children have inflammatory peritonitis without an identifiable enteric cause. Gram-negative enteric organisms are commonly cultured from the peritoneal fluid.

Infants and children with peritonitis in association with an indwelling peritoneal dialysis catheter or ventriculoperitoneal shunt may be treated successfully with intravenous broad-spectrum antibiotics. The catheter or shunt should be removed or exteriorized promptly if peritonitis does not resolve within 24 to 48 hours.[153] In association with ascites or nephrosis, diagnostic paracentesis should be performed and the peritoneal fluid

examined by Gram stain and culture. If there is any diagnostic uncertainty, laparoscopic or open operative exploration may be required to exclude intestinal perforation as a cause of peritonitis. If the appendix is normal, peritoneal cultures should be obtained and a thorough, complete abdominal exploration for other causes should be performed. Appendectomy is generally performed when the diagnosis of primary peritonitis is established by a right lower-quadrant incision. Other than perforated appendicitis, distinct causes of intestinal perforation or peritonitis in this age group include perforated Meckel diverticulum, duodenal ulcer, and acute pancreatitis. About half of the peritoneal fluid cultures are positive for a single organism. Treatment with specific antibiotics is continued until the patient is afebrile with a normal white blood cell count and normal clinical examination. Following operative exploration in primary peritonitis, the morbidity is no different than that for appendectomy, and the recovery is generally uneventful.

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Table 101.10 Common Causes of Neonatal Ascites

Maternal–fetal Rh incompatibility (rare) Structural malformations Urinary obstruction Congenital heart disease Malrotation, duplications, cyst (associated with intestinal volvulus) Biliary perforation Ovarian ascites Pulmonary abnormalities
Chylous ascites
Hematologic disorder α-Thalassemia
Infection Toxoplasmosis Cytomegalovirus
Others α_1-Antitrypsin deficiency Idiopathic

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Table 101.11 Common Causes of Childhood Ascites

Serous Ascites
Cirrhosis
Budd–Chiari syndrome
Nephrosis
Right-sided heart failure
Postoperative ascites (after renal transplantation, peritoneal dialysis, ventriculoperitoneal shunt)
α_1-Antitrypsin deficiency
Other rare metabolic disorders

Chylous Ascites
Malrotation with volvulus
Small bowel obstruction
Incarcerated hernia
Lymphangioma
Trauma (includes operative trauma)

Biliary Ascites
Neonatal bile duct perforation
Cystic fibrosis
Biliary atresia
Hepatitis
Cytomegalovirus infection

Urinary Ascites (7:1 Male Predominance)
Urinary obstruction
Posterior urethral valves
Bladder perforation
Ureterocele
Neurogenic bladder

Pancreatic Ascites
Acute pancreatitis (drugs, trauma, gallstones, infection)
Pancreatic pseudocysts

Ovarian Ascites
Cysts (torsion, rupture)
Tumors

Malignant Ascites Intra-abdominal neoplasm
Idiopathic

Ascites

The common causes of neonatal and childhood ascites are listed in **Tables 101.10** and **101.11**. The clinical presentation is that of abdominal distention with bulging flanks and demonstrable fluid on palpation and percussion. Ultrasound or CT scan imaging may be useful to confirm the clinical diagnosis. Paracentesis and routine examination of the fluid for Gram stain, cell count, cytology, protein, chemistries, and culture should be performed. Chylous ascites is characterized by a white milky appearance, high lymphocyte count, and high triglyceride content. Bile-stained fluid in the absence of demonstrable bowel perforation is characteristic of biliary ascites. High-fluid amylase content is seen in pancreatic ascites, and a low protein count (<3 g/dL) is consistent with serous ascites. Elevated urea nitrogen or creatinine in the fluid may suggest urinary ascites, particularly in a male patient. Cytology should be performed to exclude peritoneal ascites secondary to malignancy, particularly in pubertal and adolescent females.

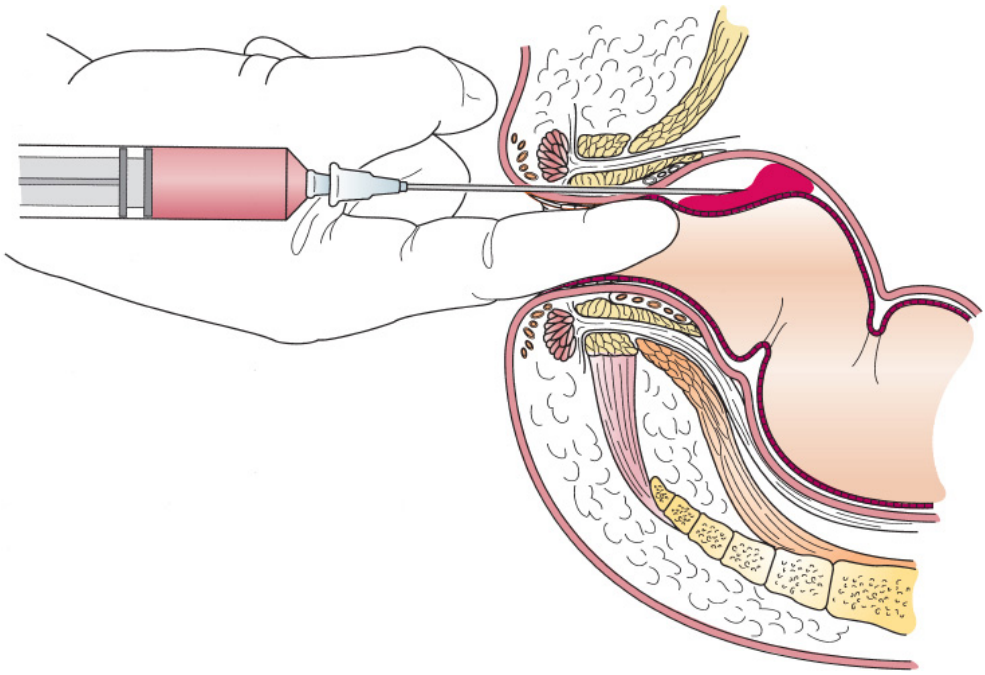

Figure 101.43 Four-quadrant injection of sclerosant into the rectal submucosa for the treatment of childhood rectal prolapse.

If the initial fluid does not provide a diagnosis in an otherwise normal-appearing child, a comprehensive diagnostic imaging evaluation is warranted. An echocardiogram should be obtained and either ultrasound or CT scan imaging performed to evaluate the genitourinary system, the hepatobiliary system, and the pancreas. A voiding cystourethrogram may also be indicated.

Treatment of neonatal or childhood ascites depends on the establishment of a specific diagnosis. In the absence of anatomic lesion or injury, spontaneous resolution of chylous ascites occurs in 50% to 75% of cases with the temporary cessation of enteral feeding and administration of parenteral nutrition. Persistence of chylous ascites for longer than 4 to 6 weeks is an indication for operative attempts to ligate the cisterna chyli. Neonatal biliary ascites may result from spontaneous bile duct perforation, in which case a diagnosis of CF must be considered. Transient bile duct obstruction typically leads to perforation at the junction of the cystic duct with the common duct. Simple external drainage is the treatment of choice, and complex hepatobiliary tract reconstruction in this setting is unnecessary and potentially hazardous. Urinary ascites in a male patient requires a workup that includes a voiding cystourethrogram to exclude posterior urethral valves. Urinary

ascites resolves with the treatment of obstructive uropathy. Pancreatic ascites is typically self-limited, and treatment by drainage procedures is generally not required or limited for relief of persistent symptoms.

Massive neonatal ascites may cause hypoventilation secondary to impairment of diaphragmatic excursion, and therapeutic paracentesis may be required. Childhood ascites generally responds to adequate treatment of the underlying problem and occasionally requires medical therapy. Placement of a peritoneovenous shunt in children for intractable ascites is rare.

Rectal Prolapse

Spontaneous rectal prolapse is relatively common in toddlers and children up to 5 years of age. A peak incidence occurs at or near the time of toilet training. There is an association between straining during bowel movement and rectal prolapse; it may be more commonly observed in children with CF, myelodysplasias with sacral neuropathy, congenital anorectal malformations, Hirschsprung disease, and colorectal polyps. However, most children presenting with rectal prolapse are normal.

A history of protrusion of mucosa or full-thickness rectum with or without bleeding is usually described. Other lesions of childhood that have a similar appearance are prolapse of an intussusceptum or passage of a polyp through the anus. The rectal examination is diagnostic. If the protruding intestine is an intussusceptum, a finger can be placed adjacent to it within the rectum; this maneuver is not possible with rectal prolapse.

Nonoperative management using manual reduction is successful in most infants and children. Sedation may be required in some instances. Therapeutic interventions include stool softeners and parental instruction on manual reduction. Spontaneous resolution over a few weeks is typical. For persistent rectal prolapse in children, operative intervention is generally governed by doing the least invasive procedure possible. Unlike adults, complex operations involving bowel resection and pelvic suspension are generally unnecessary in children with rectal prolapse. The most useful and commonly used procedure is rectal submucosal injection using a sclerosant (Fig. 101.43). With the patient under general anesthesia, injection with 5% sodium morrhuate or cow's milk[154] has been performed successfully on an outpatient basis. About 90% of children can be treated successfully with a single four-

quadrant sclerosant technique, but on occasion further sclerosis is necessary. Submucosal dissection or cauterization is also successful but may have a higher incidence of postoperative bleeding or stricture formation and usually requires a short period of hospitalization. The major objective in treating childhood rectal prolapse is to create a local extraperitoneal inflammatory process in the perirectal space. Morbidity is low and the long-term outcome is excellent.

PEDIATRIC LIVER

Tumors of the Liver

Primary hepatic tumors are rare in children and at least 60% to 70% are malignant.[155,156] Table 101.12 reviews the incidence rates and types of hepatic tumors presenting during infancy and childhood. Pediatric hepatic tumors often manifest as asymptomatic abdominal masses discovered by parents or pediatrician. Symptoms related to the tumor, such as pain, hemorrhage, hypertension, and precocious puberty, are less frequent. Initial diagnostic imaging studies include plain abdominal radiographs and ultrasound to assist in early determination as to whether the mass is cystic or solid and whether calcifications are present. CT scan imaging and MRI remain definitive in the ability to discern anatomic characteristics of the mass and its relationship to adjacent structures. Most children require operative exploration for either definitive excision or incisional biopsy in lesions deemed unresectable.

Table 101.12 Incidence of Liver Tumors in Childhood

Tumor Type	Incidence Rate (%)
Benign	
Vascular tumors	13
Hemangioma	9
Hemangioendothelioma	4
Mesenchymal hamartoma	6
Focal nodular hyperplasia	2
Adenoma	2
Teratoma	2
Other	3
Malignant	
Hepatoblastoma	43
Hepatocellular carcinoma	23
Malignant mesenchymal tumor	4
Sarcoma	2
Embryonal cell carcinoma	2
Angiosarcoma	1

Benign Tumors

Of all primary liver tumors of childhood, 30% are benign. The most common benign tumors are hemangiomas, hemangioendotheliomas, mesenchymal hamartomas, cysts, focal nodular hyperplasia, and hepatic adenoma. In most large series, hemangiomas constitute about 50% of the benign hepatic tumors observed.[157]

Vascular Tumors

Infantile hepatic hemangiomas represent a clinically diverse spectrum of vascular endothelial anomalies. They are characterized by a phase of proliferative growth over the first year of life, with subsequent involution over several years. The International Society for the Study of Vascular Anomalies classifies vascular tumors into two categories based upon the presence or absence of GLUT-1, an erythrocyte-type glucose transporter protein expressed in the endothelium of the placenta and hemangiomas.[158] Therefore, hemangiomas are GLUT-1 positive, and other, more heterogeneous vascular anomalies such as vascular malformations are GLUT-1 negative. Most asymptomatic infantile hepatic hemangiomas are detected as incidental findings on diagnostic imaging studies performed for unrelated reasons. A smaller proportion will create symptoms of enlarging abdominal mass, progressive hepatic failure, high output cardiac failure due to shunting, thrombocytopenia, or hypothyroidism from excess production of type III iodothyronine deiodinase.[159]

Most benign vascular lesions of the pediatric liver do not require operative management. Operative intervention is generally reserved for bleeding secondary to traumatic rupture symptoms not controllable with medical management. Treatment strategies remain highly individualized based upon the whether the lesions are focal, multifocal, or diffuse.[160,212] In the face of multifocal or diffuse disease associated with congestive heart failure and thrombocytopenia secondary to sequestration, medical treatment with corticosteroid therapy may be useful. More invasive procedures such as irradiation, selective hepatic arterial ligation, angiographic embolization, or hepatic transplantation remain useful in selected patients with uncontrollable symptoms. Chemotherapeutic agents, including recombinant alpha-interferon, low-dose vincristine, and cyclophosphamide, have been used for life-threatening vascular lesions. Hepatic resection is generally reserved for mass lesions of unknown diagnosis, ruptured vascular lesions with signs of active hemorrhage, or for symptomatic, locally resectable lesions.

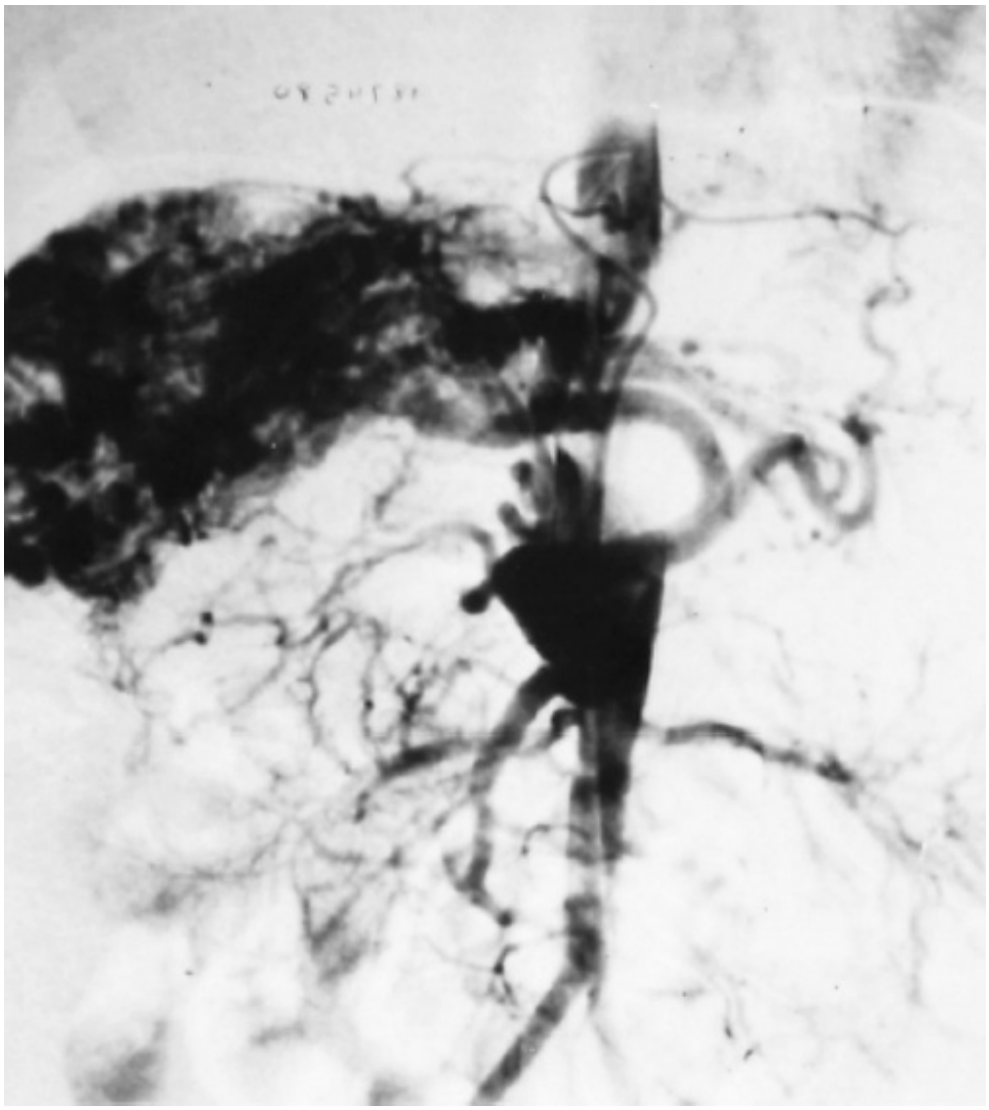

Figure 101.44 Selective visceral angiogram demonstrating large hepatic vascular malformation in a neonate with congestive heart failure. This finding is consistent with a bilobar hemangioendothelioma.

Hemangioendotheliomas are important vascular anomalies encountered in infants. The lesions vary in size from 1 cm to several centimeters in diameter and may be multiple (Fig. 101.44). Symptomatic neonates may present with an abdominal mass, hepatomegaly, and congestive heart failure. These infants may also experience spontaneous rupture and hemoperitoneum, with tachycardia, tachypnea, and hypovolemic shock. On examination, the infant may have other cutaneous hemangiomas visible on the skin. Affected infants may develop thrombocytopenia secondary to platelet sequestration in the vascular malformation (*Kasabach–Merritt syndrome*). CT scan imaging or

MRI is diagnostic. Treatment is directed at controlling symptoms using medical management principles as discussed previously; however, hemangioendotheliomas tend to be more problematic than hemangiomas because of the tendency to occur during infancy and the more extensive, symptomatic nature of the lesions.

Mesenchymal Hamartomas

Approximately one-third of benign hepatic tumors in children are mesenchymal hamartomas. A mesenchymal hamartoma is often quite large and typically presents within the first year of life as an asymptomatic, solitary abdominal mass. CT scan imaging or MRI studies are usually diagnostic and show a solid mass that may have cystic components within the liver parenchyma. Definitive diagnosis may require open tissue biopsy, and the therapy of choice is complete excision, although spontaneous involution has been described. Simple enucleation may be adequate because these tumors tend to be well circumscribed. On occasion, formal hepatic resection may be required.[161] Recurrence is low after adequate resection.

Focal Nodular Hyperplasia

This tumor occurs primarily in female children and in adults and may be associated with the use of oral contraceptives or focal hepatic injury. Focal nodular hyperplasia is usually a well-defined, solitary mass that has characteristic findings on CT scan imaging. Open or percutaneous biopsy may be required to differentiate the lesion from hepatic adenoma. This lesion results from a focal inflammatory response of normal hepatic parenchyma surrounded by areas of micronodular fibrosis and cirrhosis. Operative management is generally unnecessary unless there is a question of diagnosis or active hemorrhage from the lesion.

Hepatic Adenoma

Adenomas are rare in infants and children and constitute less than 5% of all benign hepatic lesions in the pediatric age group. There is an association between the use of oral contraceptives, exogenous anabolic steroid use, and glycogen storage disease type I (von Gierke disease). These tend to be large, solitary lesions located in the right hepatic lobe. The typical presentation is an asymptomatic abdominal mass, although symptoms are seen more commonly than with focal nodular hyperplasia. About 20% to 25% of patients

with hepatic adenoma present with hemoperitoneum from tumor rupture. On histologic examination, these lesions are composed of normal hepatocytes without evidence of dysplasia. Operative therapy is usually directed at either making definitive diagnosis or treating hemorrhage. Enucleation or local resection is adequate and recurrence rates are low.

Hepatic Cysts

Congenital cysts of the liver may be either solitary or multiple. These cysts are thought to result from failure of the intralobular or interlobular biliary ducts to fuse during development. They may be lined with cuboidal, columnar, or squamous epithelium.[162] The presence of multiple hepatic cysts is associated with polycystic kidney disease, and development of progressive hepatic and renal failure is a potential problem with this disease. The majority of children with hepatic cysts are asymptomatic. Adjunctive diagnostic imaging, including ultrasound and CT scan imaging, may be useful.

Asymptomatic congenital hepatic cysts do not require surgical therapy. Operative therapy is reserved for symptomatic cysts. Resection or drainage by marsupialization or hepaticocystenterostomy may be required. If patency to the biliary tract is present on contrast injection study of the cyst, internal drainage is necessary.

The differential diagnosis includes hydatid disease of the liver, which is suggested by calcification and loculation of the cyst wall. Hydatid disease can be diagnosed using specific serologic tests, which is an important surgical consideration prior to exploration. Patients with echinococcal cysts should be treated with mebendazole and undergo cyst injection with hypertonic saline or other scolicidal agents into the parent cyst before surgical excision. Careful control of the cyst contents is required during echinococcal cyst excision or marsupialization.

Teratomas

Teratomas of the liver are exceedingly rare and have potential for harboring immature elements capable of transforming into malignancy. Surgical resection on discovery is recommended.

Malignant Tumors

Two-thirds of childhood hepatic tumors are malignant, with hepatoblastoma constituting half of the malignancies, followed by hepatocellular carcinoma, malignant mesenchymal tumors, and sarcoma.[155] Malignant hepatic tumors are fortunately rare, and effective treatment requires a multidisciplinary approach that is best achieved in an experienced pediatric center.

Hepatoblastoma

Most hepatoblastomas are discovered in children younger than 2 years. There is a 2:1 male-to-female predominance. Hepatoblastomas usually are found as either an asymptomatic abdominal mass or symptoms of gastrointestinal obstruction from extrinsic compression by the mass. There is an association of hepatoblastoma in patients with Beckwith–Wiedemann syndrome and hemihypertrophy. On examination, a firm, palpable upper abdominal mass is notable. Obstructive jaundice is unusual. More than 90% of children with hepatoblastoma have elevated levels of alpha-fetoprotein, which is useful serum tumor marker for postoperative surveillance. In few instances, children have initial symptoms and signs of excess androgen secretion, including virilization and precocious puberty. Diagnostic imaging with CT scan imaging or MRI is essential to evaluate the extent of the tumor and evaluate for metastatic disease (Fig. 101.45).

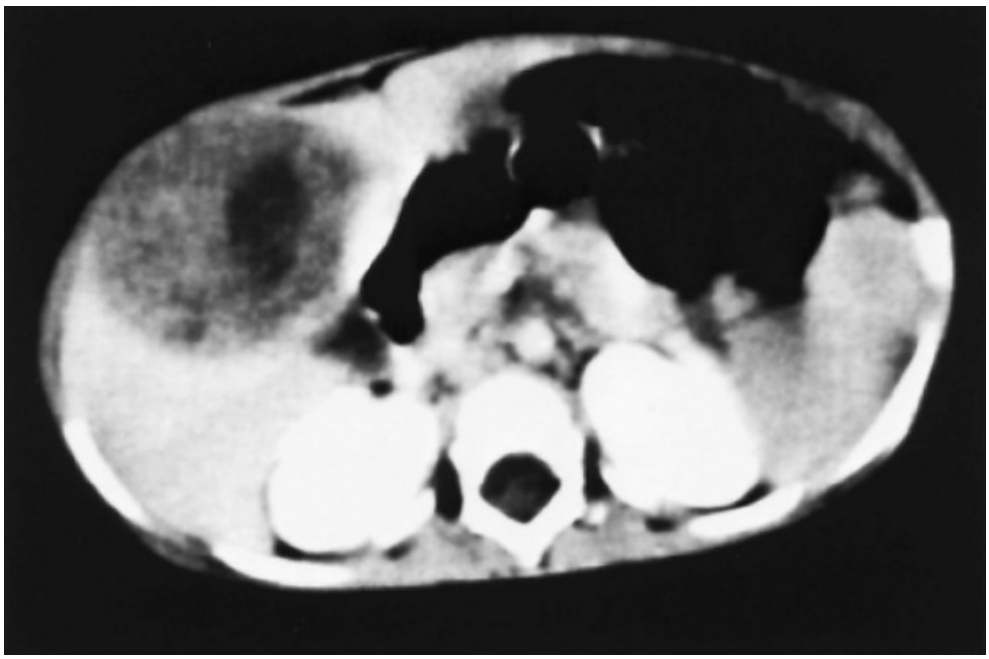

Figure 101.45 Computed tomographic scan of the abdomen demonstrating an infant with hepatoblastoma of the right hepatic lobe.

Children with hepatoblastoma require multidisciplinary management at centers familiar with their management protocols. Resectability is based on the pre-treatment extent of tumor (PRETEXT), and POSTTEXT and their approach should be standardized.[163] Most children presenting with hepatoblastoma initially have unresectable disease. However, PRETEXT 1 tumors should be amenable to primary resection whereas PRETEXT 4 tumors should be considered for liver transplant. In the absence of metastatic disease, however, an aggressive surgical approach is used. Cure and long-term survival with hepatoblastoma requires complete surgical excision of the primary lesion. Therefore, localized, resectable tumors usually are excised by formal hepatic lobectomy or extended trisegmentectomy. Children with hepatoblastomas considered initially unresectable or with metastatic disease should undergo percutaneous or incisional biopsy to confirm the histologic diagnosis, followed by multiagent chemotherapy to reduce the size of the primary tumor and control metastases.[164,165] Delayed resection is appropriate if enough functional, normal hepatic parenchyma remain after resection. More than half of the patients who initially have unresectable hepatoblastoma can be rendered disease free with the combination of chemotherapy and subsequent surgery. Cure rates for hepatoblastoma range from 60% to 80% if histologically clear margins and no metastatic disease are present. All patients with hepatoblastoma, which are not stage 1 pure fetal histology, receive chemotherapy after resection. As treatment of this disease is complex and dependent on several clinical and anatomic factors, current treatment recommendations should be referenced.[163]

Hepatocellular Carcinoma

Hepatocellular carcinoma is significantly more common in adults but is occasionally seen in older children and adolescents. There is a male predilection (2:1) and, except for the age at diagnosis, the clinical presentation is similar to that for hepatoblastoma. Children with hepatocellular carcinoma are more likely to have jaundice and abnormal liver enzymes. The high association of cirrhosis in adults (80%) is not seen in children with hepatocellular carcinoma; only 5% of children develop hepatocellular carcinoma in the background of cirrhosis. An increased risk of hepatocellular carcinoma is seen in children with Beckwith–Wiedemann syndrome, hemihypertrophy, von Gierke disease, hepatitis B, and Fanconi

syndrome. Exposure to oral contraceptives, anabolic steroids, and some chemotherapeutic agents also has been associated with hepatocellular carcinoma. This malignancy carries a poor prognosis with an overall survival rate of 10% to 20% despite aggressive surgical resection and multiagent chemotherapy. A histologic variant, fibrolamellar hepatocellular carcinoma, carries a more favorable prognosis. As with hepatoblastoma, complete surgical resection with clear histologic margins is necessary for long-term survival and cure. In the absence of metastatic disease, unresectable hepatoblastoma or hepatocellular carcinoma in children has been successfully treated by orthotopic liver transplantation. Review of data from the United Network for Organ Sharing database demonstrates good long-term survival for both hepatoblastoma (66% 10-year survival) and hepatocellular carcinoma (58% 10-year survival) treated with liver transplantation.[166]

Malignant Mesenchymal Tumors

These rare hepatic malignancies occur in children 5 to 10 years of age; initial signs are fever, pain, and an abdominal mass, which is usually quite large on diagnosis and may have both solid and cystic components. Multidisciplinary treatment, including complete surgical resection, multiagent chemotherapy, and radiation therapy, is required for cure. In general, the prognosis of primary malignant mesenchymal tumors of the liver remains poor.

Sarcomas

Children may rarely have a primary sarcoma of the liver. Embryonal rhabdomyosarcoma of the biliary tract is distinctly unusual. It may manifest with obstructive jaundice attributable to both extrinsic and intrinsic biliary tract obstruction. Undifferentiated, embryonal sarcoma of the liver has also been described. Angiosarcoma developing in the liver may be associated with exposure to toxins such as arsenic. Aggressive surgical resection may be required, but long-term survival is uncommon. Despite radical surgery, chemotherapy, and radiation therapy, the prognosis and long-term survival of children with these malignancies remain poor, and data regarding effective drug regimens are limited.[167,168]

Liver Resection

Operative principles and techniques for hepatic resection are discussed elsewhere in this book. Several unique issues in the safe performance of hepatic resection in children should be emphasized.[169] The circulating blood volume of an infant or a child is less compared to an adult, and children are sensitive to compression of the inferior vena cava causing decreased venous return to the right heart. Blood must be available for transfusion and adequate intravenous access is essential. Resection can be performed through either a subcostal incision or a right thoracoabdominal incision; in general, the ability to perform the operation safely should not be limited by the size of the incision. In children, the right and left hepatic veins are difficult to control near the inferior vena cava because of their short lengths, and intraparenchymal control from an anterior approach may be safer (Fig. 101.46).

Hepatic Infections

Hepatic infections are generally rare in the pediatric population, and their management is similar to that used in adults. An important issue is the development of hepatic abscess in an immunocompromised child and, in particular, the association of chronic granulomatous disease with pyogenic hepatic abscess formation.

Pyogenic Abscess

The most common causative factor in the development of pyogenic hepatic abscess in children with chronic granulomatous disease and other causes of immunosuppression.[170] Chronic granulomatous disease is an inherited disorder characterized by a defect in oxidative burst-mediated bacterial killing by neutrophils. These children develop skin, soft-tissue, and solid organ abscesses. A significant number of children with pyogenic liver abscesses have chronic granulomatous disease or other inherited/acquired immunodeficiency states. Liver abscesses are infrequently seen as a complication of umbilical vein catheterization, omphalitis, biliary tract disease, and hepatobiliary operations.

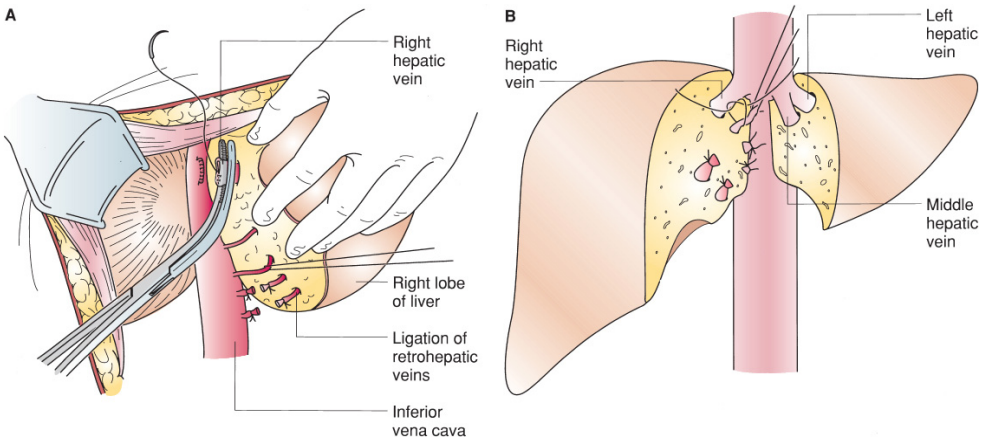

Figure 101.46 **A:** The hepatic veins in infants and children may be extremely short, making extrahepatic control impossible or dangerous. **B:** Intrahepatic control of the hepatic veins via an anterior approach may be safer in infants and children.

Patients with pyogenic liver abscess present with fever, jaundice, and leukocytosis. Hepatosplenomegaly and a tender liver may be found on physical examination. Common responsible organisms include staphylococcal species, streptococcal species, and *E. coli.* Gram-negative organisms and anaerobic bacteria are becoming increasingly prevalent. Treatment involves the use of broad-spectrum antibiotics. Large abscess cavities may require image-guided percutaneous drainage to expedite resolution of sepsis. Rarely, hepatic abscesses require open operative drainage. The outcome is dependent upon the underlying disease process. Recovery from the abscess is predictably good following adequate antibiotic therapy and drainage when necessary.

Amebic Abscess

Amebic abscess of the liver is uncommon in the United States, but it is endemic to areas of Central and South America. It is caused by infection with the parasite *Entamoeba histolytica.* Children with amebic dysentery develop hepatic infection as the parasite travels through the portal circulation. Patients have a history of chronic illness, fever, and abdominal pain. Examination typically demonstrates a tender right upper quadrant. Infection can be confirmed by a serum antibody test, and amebic abscess can be demonstrated by ultrasound or CT scan. Spontaneous rupture of amebic abscess is reported in as many as 10% of patients in some series.[171] The treatment of choice is

the antibiotic metronidazole. Surgical resection or drainage of amebic liver abscess is typically not required for resolution.

PEDIATRIC BILIARY TRACT

Embryology

The fetal liver and biliary tract develop between weeks 4 and 10 of gestation, representing the fusion of an endodermal foregut diverticulum with a mesodermal component from the septum transversum. The hepatocytes are derived from cords of endodermal cells in the hepatic diverticulum and ultimately give rise to the hepatic sinusoidal endothelium. The proximal hepatic diverticulum gives rise to the extrahepatic biliary tract, including the gallbladder, cystic duct, and common bile duct. As the intrahepatic and extrahepatic ductal systems develop, they unite to form a connected, arborizing system of cords composed of primitive ductular epithelial cells. These epithelial cells assume tubular configuration with ductal patency established between weeks 6 and 12 of gestation. Bile flow from the hepatocytes and into the biliary duct system is apparent by the beginning of the second fetal trimester.

This embryologic sequence appears to take place normally in infants who develop biliary atresia. In fact, the term *biliary atresia* does not reflect embryologic atresia resulting from failure of recanalization of the biliary tree. Rather, biliary atresia is caused by an uncontrollable inflammatory process that produces progressive obliteration of the normally developed extrahepatic biliary tract.

Biliary Atresia

Anatomy

7 The overall incidence rate of biliary atresia is about 1 in 8,000 to 12,000 live births and is the most common cause of chronic cholestasis in infants and children as well as the most frequent indication for pediatric liver transplantation.[172] Extrahepatic biliary atresia must be differentiated from biliary hypoplasia. Biliary hypoplasia describes a diminutive but patent biliary system and can result from many underlying situations such as

neonatal hepatitis and alpha$_1$-antitrypsin deficiency. Biliary hypoplasia involves both intrahepatic and extrahepatic ductal systems.

Microscopic Anatomy

Biliary atresia is characterized by replacement of the extrahepatic biliary tract with dense, fibrous inflammatory tissue. In most cases, complete obliteration of the extrahepatic biliary tract, including the gallbladder, occurs. There appears to be gradual progression of the inflammatory process with advancing age. The common hepatic duct and common bile duct are almost uniformly obliterated by the inflammatory process. Few or absent patent ductal remnants and an absence of portal inflammation may be associated with a less favorable prognosis.[173] Intraoperative evaluation for duct patency by frozen section analysis has historically been used help guide the extent of proximal resection at the porta hepatis; however, this is no longer in widespread use. The presence of bile ducts at the porta hepatis with diameter greater than 150 μm has been reported to be associated with postoperative bile flow in up to 90% to 95% of cases.[174]

Histologic features of biliary atresia reflect hepatic parenchymal injury. Neocholangiogenesis, or biliary duct proliferation of disorganized and nonpatent ducts within the liver, is considered highly suggestive but not specific for biliary atresia. Other findings include bile pigment deposition throughout the liver. Characteristic early findings in biliary atresia include evidence for acute inflammation with neutrophil predominance in the periportal regions. Older infants and children typically have chronic inflammatory changes with considerable fibrosis. Periportal bridging fibrosis is commonly seen in intermediate stages of the disease. Ultimately, progressive biliary atresia leads to intractable cirrhosis. Nearly all patients with biliary atresia have histologic evidence of liver injury. The severity and extent of liver damage may be the most important predictor of long-term outcome and survival in biliary atresia.

Pathophysiology

The mechanism causing biliary atresia remains unknown. The current concept is that the normally developed biliary tract undergoes inflammatory sclerosis and subsequent obliteration. This process appears to occur during the first few weeks to months of life. Early establishment of biliary drainage via

portoenterostomy within the first 2 to 4 months of age may be associated with reversal of liver injury and subsequent long-term survival. Conversely, infants operated on after 120 days of life typically have obliterated bile ducts. Neonatal biliary atresia shares some clinical and morphologic features of sclerosing cholangitis in adults. Data supporting an infectious etiologic agent and, in particular, reoviruses, rotaviruses, and hepatitis C, have been reported and may play a role in some cases. In addition, other noninfectious stimuli may trigger an inflammatory response directed at the neonatal extrahepatic bile duct.[175] The actual mechanism may reflect a stereotypical inflammatory response initiated by a variety of different stimuli that is ultimately directed preferentially against the neonatal bile duct.

Clinical Presentation and Diagnosis

The cardinal sign of biliary atresia is progressive neonatal jaundice during the first few weeks of life. Dark urine and acholic stools are expected findings. Progressive hyperbilirubinemia produces clinical jaundice around 2 to 4 weeks of age. The physical examination is generally unremarkable except for jaundice and possibly mild hepatomegaly. Alagille syndrome, which presents with neonatal jaundice, can usually be distinguished from biliary atresia on physical examination. Children with Alagille syndrome have biliary hypoplasia and distinctly abnormal facies, growth retardation, vertebral defects, and pulmonic stenosis.

A characteristic laboratory finding is conjugated hyperbilirubinemia consistent with obstructive jaundice. A direct fraction of bilirubin greater than 50%, or greater than 2 mg/dL, in an infant requires prompt investigation. Mild elevation of hepatic transaminases is commonly seen. The alkaline phosphatase is significantly elevated, often in the range of 500 to 1,000 IU/L. There are no specific biochemical markers for biliary atresia, as these serum profiles can be seen in other causes of neonatal cholestasis. Late findings in biliary atresia include failure to thrive, feeding intolerance, stigmata of portal hypertension, and fat-soluble vitamin deficiency.

ETIOLOGY

Table 101.13 Causes and Associations of Neonatal Cholestasis

Congenital Infectious Causes
Cytomegalovirus[a]
Rubella virus[a]
Herpes virus
Hepatitis virus B[a]
Echovirus 14, 19
Coxsackievirus B
Toxoplasmosis
Syphilis
Genetic Associations
Galactosemia
Tyrosinemia
Congenital fructose intolerance
$Alpha_1$-antitrypsin deficiency
Cystic fibrosis
Niemann–Pick disease
Trisomies 17, 18, 21
Turner syndrome
Menkes syndrome
Zellweger syndrome
Polysplenia syndrome[b]
Miscellaneous Associations
Hemolytic disease
Bacterial sepsis
Pyelonephritis
Total parenteral nutrition (prolonged)
Congestive heart failure
Hypoplastic left heart syndrome
Necrotizing enterocolitis, gastroschisis, omphalocele
Neonatal hypopituitarism
Inspissated bile syndrome (without hemolysis) neonatal shock, respiratory distress syndrome, acidosis

[a]Rarely associated with biliary atresia.

[b]Frequently associated with biliary atresia.

Table 101.13 is a partial list of the causes of neonatal cholestatic syndromes. Neonatal physiologic jaundice is commonly encountered. Because of the numerous causes of neonatal jaundice and the relative infrequency of biliary atresia, a delay in diagnosis is common. Given the age-sensitive nature of biliary atresia and the improved outcome in younger infants, the diagnostic workup should be expedient.

Radioisotope Scanning

Pertechnetate 99 m–iminodiacetic acid (^{99m}Tc-IDA) analogs are widely used for hepatobiliary imaging and provide the basis for a sensitive and specific test for biliary atresia. The sensitivity of this diagnostic examination for biliary atresia can be 100%, with a specificity of 94%.[176] To improve sensitivity, infants are administered oral phenobarbital (5 mg/kg daily) to induce hepatic microsomal enzymes and increase hepatocyte processing of ^{99m}Tc-IDA. Both hepatic uptake of radionuclide and excretion into the gastrointestinal tract are evaluated over a timed interval. Infants with primary hepatocellular disorders characteristically have impaired hepatocyte uptake of radionuclide, whereas normal infants and infants with biliary atresia have prompt uptake. Normal infants excrete the isotope rapidly into the gut through the biliary tract. In biliary atresia, there is no excretion into the gut because of the obliteration of the extrahepatic bile ducts (Fig. 101.47). The hepatobiliary scanning is a rapid test that can be performed simultaneously with other diagnostic examinations, for example, ultrasound. This test reliably identifies infants with choledochal cyst as well.

Ultrasound. A standard examination of the jaundiced infant is a comprehensive abdominal ultrasound, with particular attention given to the liver and the biliary tract. The most common ultrasonographic finding in biliary atresia is a diminutive or absent gallbladder without associated intrahepatic duct dilatation. Biliary tract obstruction from a choledochal cyst also can be reliably identified by ultrasound. Other rare causes of extrahepatic biliary duct obstruction are associated with proximal duct dilatation.

Liver Biopsy. Because the histologic findings in biliary atresia are not specific, about 20% to 25% of infants who undergo percutaneous liver

biopsy remain undiagnosed. Liver biopsy is often performed in conjunction with the workup of conjugated hyperbilirubinemia following hepatobiliary scanning and ultrasonography, but in the setting of biliary atresia, it has limited utility. The histologic examination of a percutaneous liver biopsy is probably most helpful in diagnosing nonoperative causes of neonatal jaundice, thus avoiding anesthesia and operative exploration.

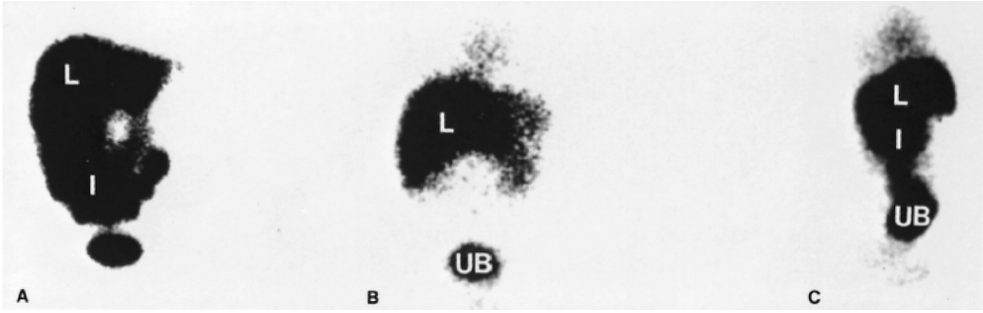

Figure 101.47 **A:** Normal scan using p-isopropyl acetanilidoiminodiacetic acid (PIPIDA) as the hepatobiliary scanning agent. At 45 minutes, isotope is clearly visible in the liver (*L*) and the intestine (*I*). **B:** Scan after phenobarbital administration in infant with biliary atresia. Even after 8 hours, isotope is apparent only in the liver and the urinary bladder (*UB*). **C:** Patient with cholestatic jaundice. At 65 minutes, isotope is visible in the liver (*L*) and the intestine (*I*). Hepatocyte uptake is variable but usually decreased or normal, whereas excretion into the gut is predictably present with cholestatic jaundice or hepatocellular disease.

Alpha$_1$-Antitrypsin Deficiency. Alpha$_1$-antitrypsin deficiency is perhaps the single most important medical condition that may be difficult or impossible to differentiate from biliary atresia. All jaundiced infants should have plasma alpha$_1$-antitrypsin levels determined before operative exploration for suspected biliary atresia. Infants with alpha$_1$-antitrypsin deficiency do not benefit from operative exploration or portoenterostomy.

Treatment

Infants with biliary atresia require surgical therapy as the initial management intervention. Medical therapy is directed to the postoperative management of the chronic liver disease. The use of sequential surgical treatment, using portoenterostomy in infancy and orthotopic liver transplantation for children with progressive hepatic failure, provides improvement in overall survival.[177,178] Limited organ availability and a higher rate of perioperative

complications limit primary liver transplantation for most infants with biliary atresia younger than 1 year. In the rare instance of unrecognized biliary atresia in an older child with established hepatic dysfunction, primary orthotopic liver transplantation may be a reasonable option.

Portoenterostomy

The recommended initial procedure for the treatment of biliary atresia is portoenterostomy. Before the development of portoenterostomy in Japan by Morio Kasai during the late 1950s, all infants with biliary atresia died of chronic liver disease and cirrhosis. Current management dictates that operative exploration and portoenterostomy be performed promptly. Early intervention by portoenterostomy to provide biliary drainage has been proposed to arrest or reverse the parenchymal liver injury, but the point at which the liver injury becomes irreversible remains unknown. From a clinical standpoint, most long-term success with portoenterostomy alone appears to be achieved in infants younger than 2 to 3 months, whereas infants older than 3 to 4 months appear to have a less favorable prognosis. Portoenterostomy for this "late" group has been reported successfully in approximately one-third of infants, however, and should be considered a potential alternative in the absence of available liver transplant donors.[179]

The initial approach to the infant with suspected biliary atresia is to perform an operative cholangiogram. If the diagnosis is confirmed, a portoenterostomy is constructed (Fig. 101.48). An open liver biopsy is routinely performed to document the state of parenchymal injury. The cholangiogram is generally attempted through the gallbladder. In the 10% to 15% instance of a patent distal biliary tree, treatment still requires portoenterostomy. A nonpatent, fibrous cord rather than a normal common bile duct is found in the hepatoduodenal ligament. This cord is dissected free proximally to the level of the porta hepatis between the portal vein bifurcation. The fibrous remnant is sharply transected at this level to preserve any patent bile ducts. A short, 15- to 25-cm retrocolic, jejunal Roux-Y limb is constructed. There has been no clear advantage with longer or modified conduits with intussusception-type antireflux valves in the prevention of cholangitis.[180,181]

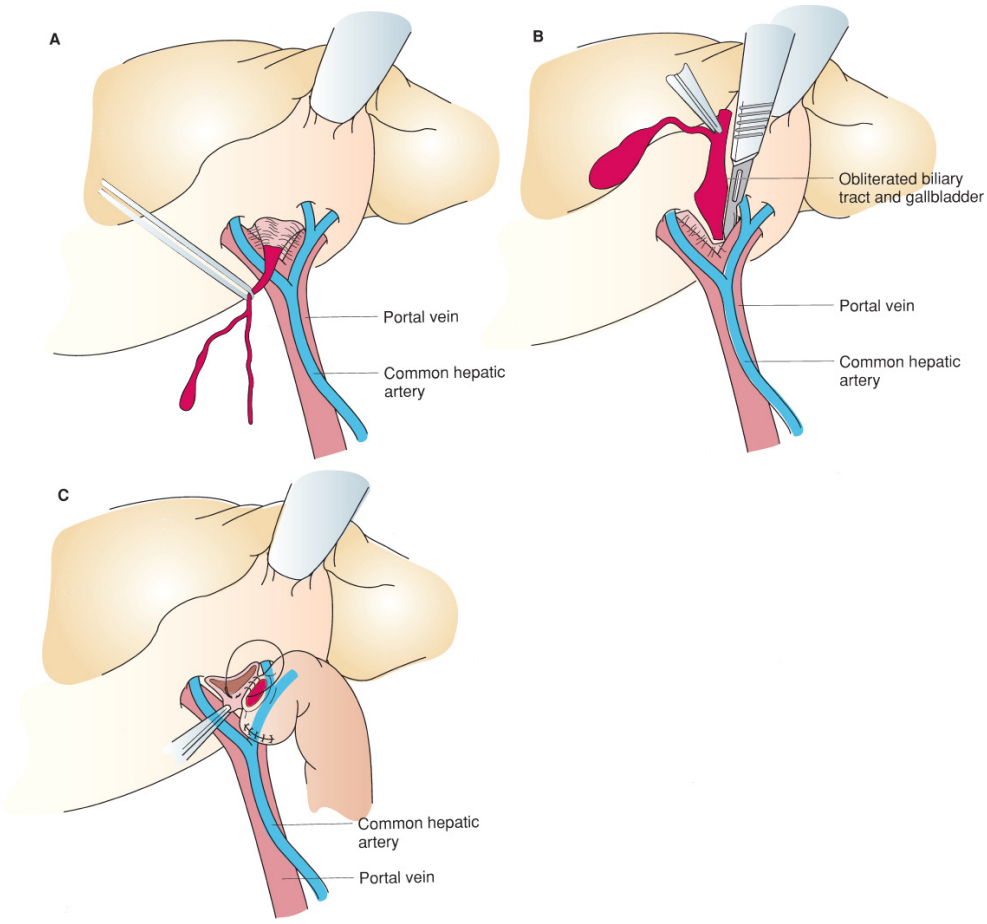

Figure 101.48 The essential features of the portoenterostomy for biliary atresia include appropriate mobilization (**A**) and transection (**B**) of the fibrous biliary tract remnant. **C:** Creation of a Roux-Y jejunal conduit with biliary enteric anastomosis completes the procedure.

Historically, some surgeons preferred to exteriorize the biliary conduit, but this practice has been abandoned due to complications and high likelihood of future liver transplantation.

Results and Complications. Following portoenterostomy, bile flow occurs in about 66% to 75% of all infants when operated on at less than 60 days of age; however, establishment of bile flow may take weeks to months. The probability of bile flow appears related to age at the time of operation.

Cholangitis is a constant concern and an important postoperative problem after portoenterostomy. The clinical signs include fever, leukocytosis, and decreased bile flow in the absence of other systemic illness. All patients are

at risk for the development of postoperative cholangitis, but reported postoperative rates of cholangitis are 40% to 50%. Cholangitis following portoenterostomy is characterized by a systemic inflammatory response and may be associated with progressive liver injury. Treatment is generally intravenous fluid resuscitation and broad-spectrum antibiotics. Occasionally, steroids or other anti-inflammatory agents may be helpful, whereas reoperation or endoscopic revision of the portoenterostomy usually is not.[182] In an effort to determine the optimal treatment of infants with biliary atresia, a group of investigators have formed the Biliary Atresia Research Consortium (BARC).[183] The primary objectives of the consortium are to establish a clinical database and tissue repository. A retrospective BARC study of 104 children with biliary atresia treated in the United States demonstrated that at 2 years of age, 58 patients were alive with their native liver and 42 had undergone liver transplantation.[184] Data from the United Kingdom demonstrated improved measurable outcomes in children with biliary atresia treated with Kasai portoenterostomy by regionalization of care to three centers in the U.K. health care system.[185]

Nearly all patients with biliary atresia have residual liver injury. Hepatic synthetic failure, portal hypertension with esophageal variceal bleeding, hypersplenism, and fat-soluble vitamin deficiencies can be problematic. Most institutions report 5-year survival rates between 30% and 50% for portoenterostomy alone. About 25% to 35% of patients undergoing a portoenterostomy survive more than 10 years without liver transplantation. The remaining two-thirds of children with biliary atresia ultimately require liver transplantation for survival. Although the failure rate for portoenterostomy is high, the possibility of long-term success is notable. In addition, the limited availability of infant donor organs and the technical limitations of liver transplantation in infants younger than 1 year make portoenterostomy an accepted initial treatment of biliary atresia in most centers.

Hepatic Transplantation

Hepatic transplantation is discussed in detail elsewhere in this text. For biliary atresia, transplantation offers a means of long-term survival in children with failed portoenterostomies. The current 5-year survival of children with biliary atresia who undergo liver transplantation ranges from

75% to 94.4%.[186,187] In addition, with the use of reduced-size cadaveric donor livers as well as living-related donor livers, the mortality rate for infants on transplant waiting lists may be decreasing. Indications for liver transplantation in biliary atresia include progressive hepatic failure despite portoenterostomy, growth retardation, and complications of portal hypertension. It is important to consider the consequences of life-long immunosuppression in these children, including the risks of infection and treatment-related malignancy.

Congenital Choledochal Cystic Disease of the Biliary Tract

Anatomy

The anatomic description and classification scheme for choledochal cystic disease initially proposed by Alonso-Lej et al. in 1959 and modified by Todani et al. are illustrated in Figure 101.49.[188,189] The most frequently encountered are type I cysts, accounting for approximately 85% to 90% of the lesions in most series. Type I cysts are characterized by fusiform dilatation of the entire common bile duct with only mild dilatation of the common hepatic duct; the intrahepatic ducts are normal. Variations are common and biliary atresia is occasionally seen in association with choledochal cystic disease.

Type I cysts are generally quite large and often cause displacement of neighboring viscera. The fusiform dilatation usually begins at the origin of the common bile duct, generally sparing the common hepatic ducts. The distal common bile duct is diminutive and typically is distorted mechanically by the large cyst, leading to the common clinical presentation of obstructive jaundice. The junction of the distal common bile duct and the pancreatic duct is not within the normal intramural duodenum but rather is extrinsic and proximal to the duodenal wall and the sphincter of Oddi (Fig. 101.50). It remains unknown whether the configuration of a long, extramural common channel allows greater pancreatic secretion reflux into the common bile duct.

Microscopic examination of the choledochal cyst wall reveals that the normal biliary epithelium is absent or replaced by abnormal and

occasionally dysplastic columnar epithelium. The cyst wall has normal smooth muscle with variable degrees of inflammation and fibrosis. The exception to this common histologic characteristic is the type III cyst, which is generally lined by normal duodenal mucosa. Choledochal cysts tend to have less inflammation in infancy and early childhood. In contrast, there is well-established inflammation involving the cyst and surrounding structures in the hepatoduodenal ligament in adolescents and adults.

Pathophysiology

The mechanism for the development of cystic lesions of the biliary tract is unclear. Choledochal cysts have been identified accurately by prenatal ultrasound, and it appears likely that these lesions represent abnormalities in the developing biliary tract. Several hypotheses for the development of choledochal cyst have been proposed. Whether the cystic dilatations result from abnormal recanalization of the primitive bile duct cords or from inflammation caused by reflux of pancreatic secretions into the common bile duct remains unknown. The pathophysiology of choledochal cyst is that of obstructive jaundice. The obstruction may be primarily the result of mechanical outflow obstruction of a diminutive distal common bile duct with a dilated choledochal cyst. Alternatively, a large inflammatory cyst can cause obstruction of the biliary tract and of neighboring viscera by extrinsic compression. When discovered during infancy, obstructive jaundice is usually the initial clinical finding. The liver injury is typically reversible, and progression to biliary cirrhosis is rare. The exception to this situation is type V disease, which is associated with a high incidence of hepatic fibrosis.

Other initial clinical situations include cholelithiasis and acute bacterial cholangitis secondary to diminished bile drainage. Children with type III cysts may have acute pancreatitis. Infrequently, extrinsic compression of the portal vein by a large choledochal cyst may produce symptoms and signs of portal hypertension. Abdominal pain and tenderness following minor injury may lead to an incidental diagnosis of choledochal cyst on imaging studies.

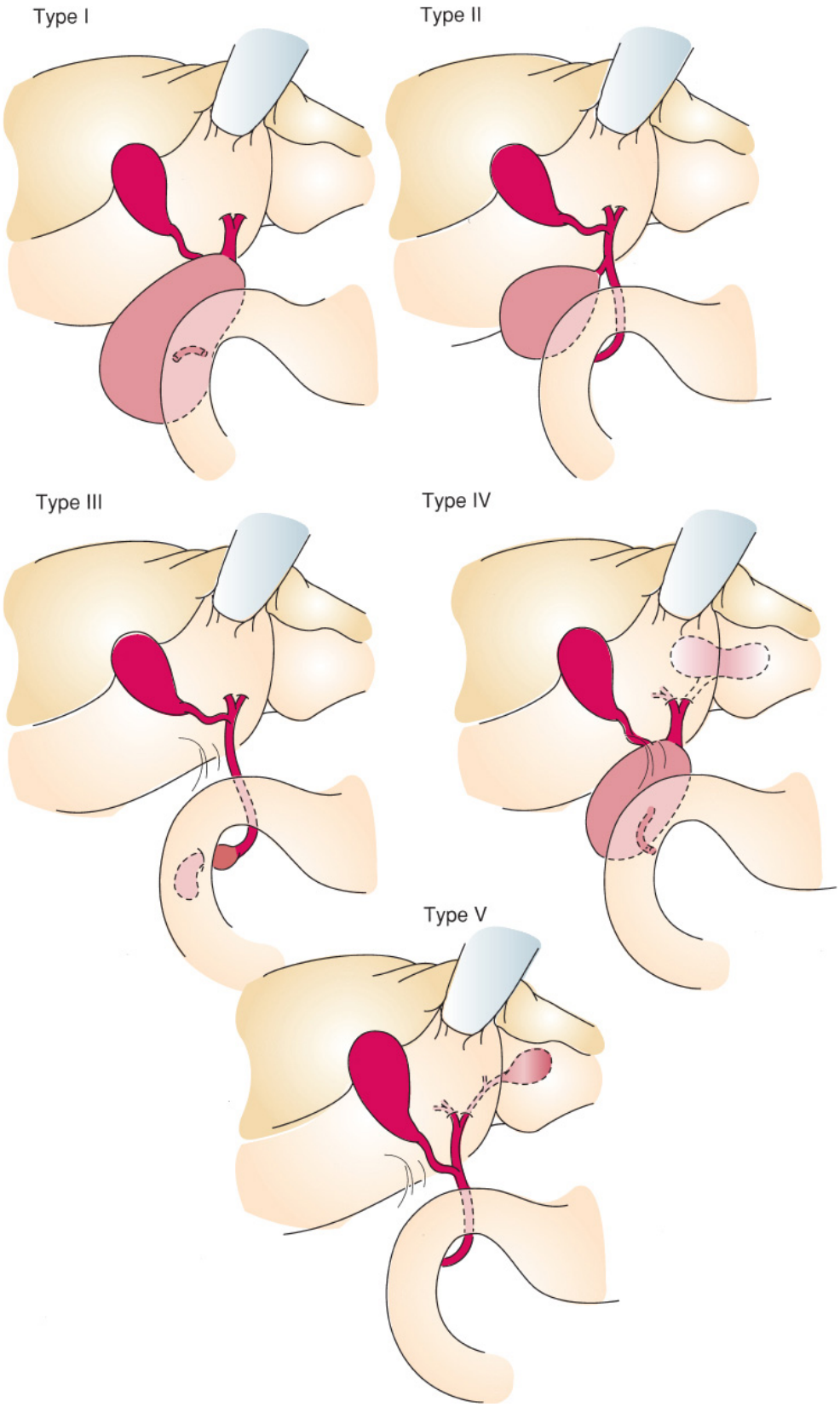

Figure 101.49 Classification of choledochal cyst.

Carcinoma of the biliary tract occurs in about 3% to 5% of patients with choledochal cyst. The number of reported cases remains small in the literature, but the incidence for biliary tract neoplasm is about 1,000 times that of the normal population.[190] Patients with choledochal cyst are at increased risk for the development of biliary tract carcinoma in adolescence or early adulthood. The dysplastic cyst epithelium may be susceptible to malignant change from chronic inflammation. Interestingly, there appears to be an increased risk of malignancy to develop anywhere in the biliary tract, gallbladder, or pancreas, and not just the choledochal cyst itself.[191] Therefore, current treatment emphasizes complete cyst excision or the cyst epithelium while providing adequate biliary drainage to prevent stasis and chronic inflammation. Infants and children treated for choledochal cyst should have long-term follow-up for complications and potential malignancy.

Clinical Presentation and Diagnosis

Choledochal cysts present most commonly in infancy and early childhood with symptoms of obstructive jaundice. In older children and adults, the classic clinical triad of episodic abdominal pain, a palpable right upper-quadrant mass, and jaundice occurs in fewer than 50% of patients. Adults occasionally present with hepatomegaly or evidence of portal hypertension. The diagnosis in infants and most children can be confirmed by ultrasound examination and ^{99m}Tc-IDA imaging studies (**Figs. 101.51** and **101.52**). In older children, both MRI cholangiography and endoscopic retrograde cholangiopancreatography (ERCP) are highly sensitive and specific in confirming diagnosis. These lesions also are diagnosed incidentally during radiologic imaging studies for other reasons. Partial duodenal obstruction may lead to an upper gastrointestinal series that shows extrinsic compression from a large type I cyst or an intraluminal filling defect from a type III cyst. CT imaging of the abdomen following blunt trauma may lead to the diagnosis of biliary tract dilatation. Liver biopsy is not specific in choledochal cyst and has little diagnostic role other than to document the extent of liver injury.

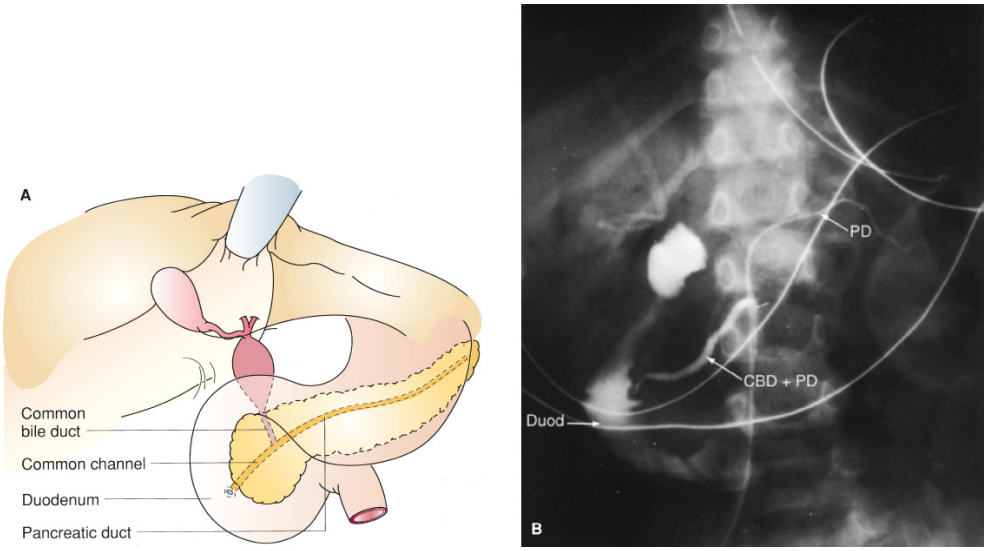

Figure 101.50 An anomalous, extramural junction between the distal common bile duct and the pancreatic duct is characteristic of type I choledochal cyst. **A:** Schematic depiction of this anatomy. **B:** Operative cholangiogram from a patient with a long extramural common channel. It has been suggested that the long common channel may allow reflux of pancreatic secretions into the common bile duct resulting in inflammation and proteinase-mediated injury to the common duct, possibly contributing to the development of the cyst itself. CBD + PD, common bile duct and pancreatic duct; Duod, duodenum; PD, pancreatic duct.

Treatment

Type I Cysts

Initial operative strategy for a type I choledochal cyst is exploration and cholangiography, usually through the gallbladder, but occasionally contrast injection must be made directly into the common bile duct. Cholecystectomy is routinely performed. Internal drainage procedures without cyst excision have been abandoned. Current consensus for the surgical management of type I choledochal cyst is performance of primary cyst excision with Roux-Y hepaticojejunostomy reconstruction (Fig. 101.53). Primary cyst excision is accomplished routinely in infants and children.[192] For adults with severe inflammation and fibrosis, dissection may present problems resulting from inflammation and adhesion of the cyst wall to the hepatoduodenal ligament. A safer approach in this situation may be intramural cyst dissection and removal of the cyst wall epithelium, leaving the posteromedial outer cyst wall adjacent to the portal vein and hepatic artery intact.

Other Types of Cysts

Type II cysts are excised completely and the choledochotomy closed primarily. Type III choledochoceles require a transduodenal approach with either marsupialization or excision of the cyst. Care must be taken to identify the ampulla, and a formal sphincteroplasty may be required to ensure adequate drainage from the biliary tract and the pancreas. Type IV and V intrahepatic cystic diseases must be approached on an individualized basis. In general, unilobar or focal cystic disease can be either resected or drained with Roux-Y jejunostomy reconstruction. Bilobar intraparenchymal disease, particularly in the setting of hepatic fibrosis, may be difficult, if not impossible, to obtain complete, adequate drainage.

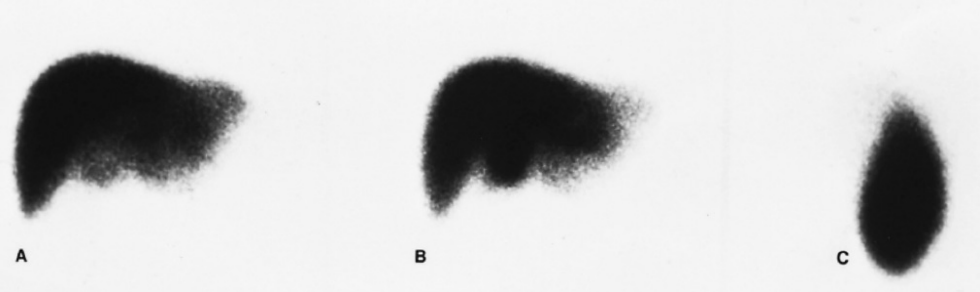

Figure 101.51 Typical ^{99m}Tc-N-substituted-2,6-dimethylphenyl carbamoylmethyl iminodiacetic acid (HIDA) scan from a child with a type I choledochal cyst. Images were made in 5 minutes (**A**), 30 minutes (**B**), and 3 hours (**C**), after isotope injection. The isotope is retained within the choledochal cyst more than 24 hours, and the pattern of hepatocyte uptake is normal.

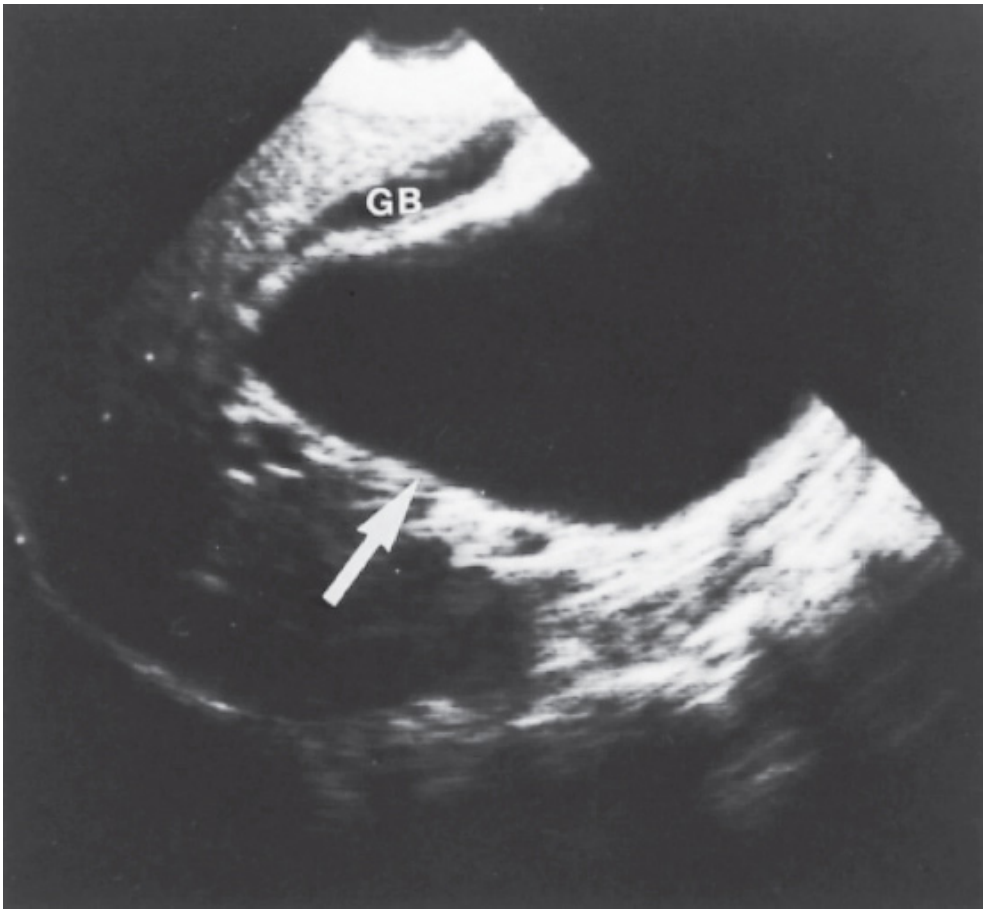

Figure 101.52 Ultrasound image of a type I choledochal cyst (*arrow;* longitudinal image). The gallbladder (GB) is also shown.

Complications and Outcome

The major complications associated with operative repair of choledochal cyst include cholangitis, stricture formation, choledocholithiasis, and development of biliary tract malignancy. A summary of the incidence of complications, mortality, and reoperation for the different procedures in 955 cases reported in the literature demonstrated a clear advantage for primary cyst excision in terms of morbidity and need for reoperation, and no significant increase in mortality occurred using this approach.[193] Currently, several series have reported excellent results with little or no mortality using total transmural excision of choledochal cysts.[194] Primary transmural excision with biliary tract reconstruction continues to be a safe and desirable operative approach for cystic lesions of the biliary tract.

PEDIATRIC PANCREAS

The embryology of the pancreas is discussed elsewhere in this chapter.

Primitive duct cells of the pancreas give rise to both the acinar cells and the islet cells of the normal pancreas. Primary islet cells become apparent at week 8 of gestation within the interlobular tissue, with acini becoming visible shortly thereafter. The primary islet cells regress after the fifth month of gestation and are usually nonexistent by term. Secondary islet cells arise from centroacinar proliferation during the third month of gestation. These intralobular cells migrate out of the acini in which they were formed and develop into islets that remain connected to the duct by a thin cellular stalk (the tubule of Bensley).

Exocrine pancreatic anomalies generally arise from defective development during embryogenesis. The most common of these conditions is annular pancreas. The circumferential distribution of pancreatic tissue around the duodenum is thought to result from interrupted migration of the ventral pancreatic anlage. Less common defects include pancreatic ductal abnormalities, pancreatic duplications, heterotopic pancreatic tissue, and congenital agenesis of portions of the pancreas.

Acute Pancreatitis

Acute pancreatitis is the most common disorder of the pancreas in both infants and children. Adult pancreatitis is often caused by either alcohol ingestion or gallstones. In contrast, 50% to 80% of cases in children, particularly adolescents, are posttraumatic or idiopathic in origin. An important clinical condition seen with moderate frequency is acute pancreatitis in the setting of immunosuppression, in particular, high-dose corticosteroids. Steroid-induced acute pancreatitis typically accounts for the third most common cause of pancreatitis in most children's hospitals. Other causes of acute pancreatitis include gallstones, CF, hyperlipidemia, juvenile diabetes mellitus, mumps, coxsackievirus infection, infectious mononucleosis, collagen vascular diseases, and anatomic lesions such as choledochal cyst. Medications significantly associated with acute pancreatitis include oral contraceptives, chlorothiazide, tetracyclines, azathioprine, and L-asparaginase. Valproic acid, an anticonvulsant useful in

some children with seizure disorders, is associated with a particularly virulent form of acute necrotizing pancreatitis that may be life-threatening.

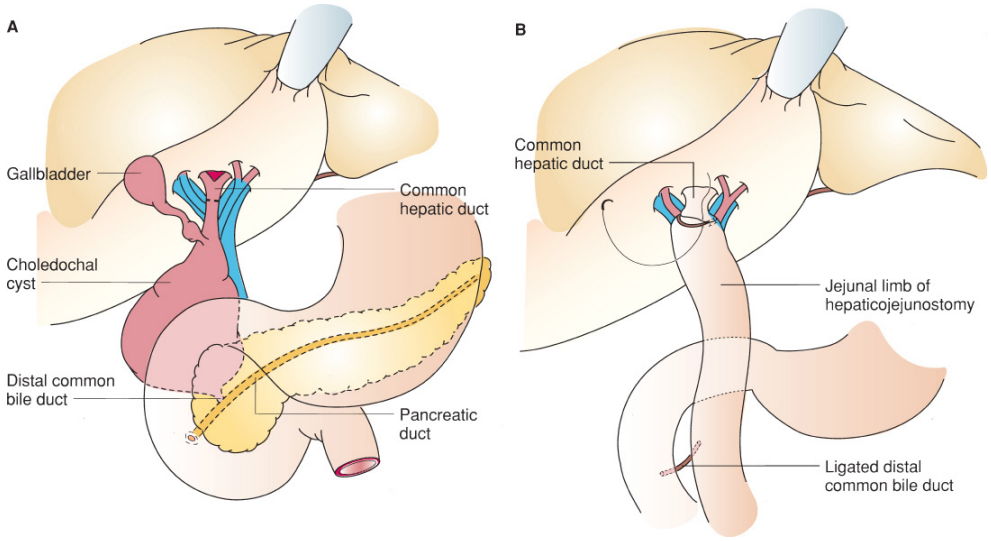

Figure 101.53 The preferred operative treatment of type I choledochal cyst consists of primary total transmural cyst excision with Roux-Y hepaticojejunostomy.

A child with acute pancreatitis presents with a history of midepigastric abdominal pain, anorexia, and emesis. On examination, the child usually has a tender abdomen with distention. Fever and leukocytosis are common. Serum amylase and lipase levels are elevated, although significant pancreatitis can occur despite a normal amylase level. Conversely, the lipase may be mildly elevated in the absence of clinical symptoms or signs of acute pancreatitis. Ultrasonography and CT imaging of the abdomen are probably the most commonly used adjunctive diagnostic tests. CT imaging is particularly useful in demonstrating edema of the gland as well as evaluating for peripancreatic fluid collections. While usually deferred during the acute phase of pancreatitis, ERCP or MRI cholangiography may be useful to evaluate the hepatobiliary tract anatomy once the inflammatory process has resolved.

Treatment principles for childhood acute pancreatitis are not different from strategies used in adults. The vast majority of children have simple edematous pancreatitis. Hemorrhagic pancreatitis and necrotizing pancreatitis are distinctly unusual in this age group but can be seen in immunosuppressed patients. Therefore, initial therapy is designed to be supportive and nonoperative in approach. Endotracheal intubation and

mechanical ventilation may be required. Intravenous fluid resuscitation, pancreatic rest by nasogastric tube decompression, analgesia, and TPN are provided. No clinical efficacy data are available to support the widespread use of anticholinergics or somatostatin analogs for acute pancreatitis in children. Operative intervention is reserved for complications of pancreatitis such as hemorrhage, infected pancreatic necrosis, or pancreatic pseudocyst.

Recurrent pancreatitis in a child usually is associated with an anatomic abnormality or specific physiologic problem. Following recovery from the acute inflammatory event, an aggressive diagnostic workup, including consideration of ERCP or MRCP to define ductal anatomy, should be performed. In particular, the presence of pancreas divisum with stenosis of the accessory papilla should be considered. Children with pancreatitis in the setting of cholelithiasis should undergo laparoscopic cholecystectomy after resolution of the pancreatitis.

Pancreas Divisum

Pancreas divisum occurs with failure of normal fusion between the dorsal and ventral pancreatic ducts. About 10% to 15% of normal persons have two separate pancreatic ducts, and up to 10% of asymptomatic persons undergoing ERCP have two complete ductal systems. The anatomic variant of pancreas divisum is not necessarily pathologic, but if the orifice of the accessory papilla is stenotic or obstructed, pancreatitis can occur.[195] Approximately 25% of affected individuals are thought to be at risk for developing pancreatitis. Because pancreas divisum is characterized by a dominant dorsal duct system dependent on secretion through the accessory papilla, stenosis of the accessory (lesser) papilla is probably necessary to produce pancreatic symptoms. Most of the experience with surgical treatment of pancreas divisum is reported in adults. Successful surgical management of children presenting with recurrent pancreatitis secondary to accessory papilla stenosis with pancreas divisum also has been reported.[196]

To diagnose pancreas divisum, ERCP is required. Endoscopic visualization of the major and accessory papillae is essential. Radiographic findings with pancreas divisum demonstrate a short or absent duct of Wirsung that does not communicate with the duct of Santorini (see Fig. 101.54).

Definitive diagnosis of pancreas divisum is made by demonstrating two separate, parallel ductal systems.

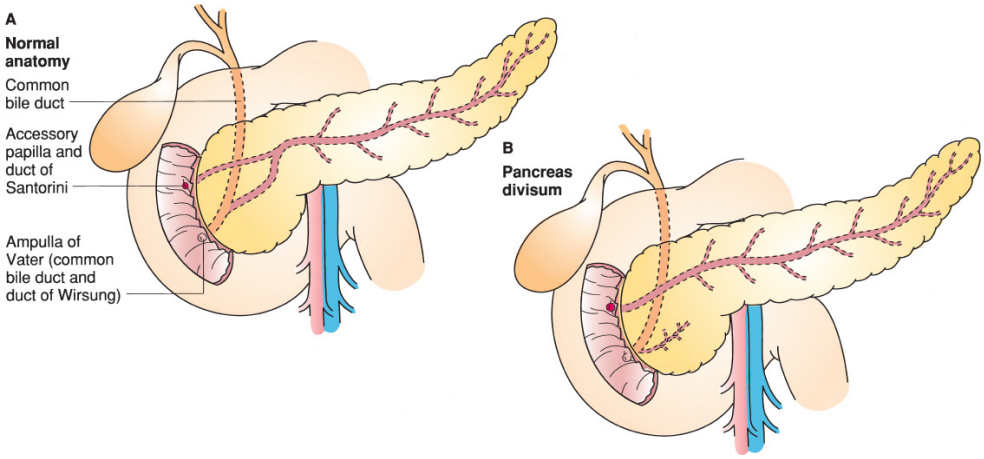

Figure 101.54 **A:** Normal pancreatic ductal anatomy. **B:** Pancreas divisum. There is no communication between the duct of Wirsung and the duct of Santorini. The duct of Wirsung is short or absent. Most of the pancreas is drained by the duct of Santorini through the accessory papilla. This anatomy is found in about 10% to 15% of normal individuals.

Few pediatric patients with pancreatitis and pancreas divisum requiring operation have been reported. Most of these children were female patients who had a history of recurrent pancreatitis. The primary operative goal is to provide adequate drainage of the duct of Santorini by performing a sphincterotomy of the accessory duct. An open dorsal duct sphincterotomy appears to be more durable than endoscopic sphincterotomy. Some surgeons advocate sphincterotomy of the main papilla as well, but dorsal duct sphincterotomy alone appears effective in preventing acute pancreatitis associated with pancreas divisum. The reported surgical outcome in the limited number of children treated for pancreatitis associated with pancreas divisum is favorable.

Pancreatic Cysts

Pancreatic pseudocysts are uncommon in the pediatric age group and are usually the result of blunt traumatic abdominal injury or acute pancreatitis. Children typically present with abdominal pain, nausea, emesis, and weight loss. There may be a palpable midepigastric mass on examination. Diagnosis

usually is made with ultrasound or CT imaging of the abdomen. The serum amylase and lipase are usually elevated.

In children, many small asymptomatic pseudocysts regress spontaneously with resolution of the pancreatic inflammation. Larger or symptomatic pseudocysts may require drainage. Symptoms and potential complications of untreated pseudocysts include hemorrhage, infection, perforation, gastrointestinal or biliary tract obstruction, or, rarely, development of pancreaticoenteric fistula. The decision to use either external or internal drainage procedures for a pseudocyst depends on the status of the pancreatic duct. In many centers, definitive external drainage of a large or symptomatic pseudocyst is performed with acceptable morbidity and mortality rates by an ultrasound- or CT-guided percutaneous approach.[197] Pseudocyst recurrence or persistent external drainage without resolution suggests significant pancreatic duct injury or complete ductal transection. Determination of whether a major pancreatic ductal injury is associated with a pseudocyst may be made by either percutaneous contrast injection of the pseudocyst or ERCP.[198] Pseudocysts associated with pancreatic duct injury may not resolve with percutaneous external drainage or endoscopic pancreatic duct stenting, so internal drainage procedures such as cystgastrostomy or cystojejunostomy with or without distal pancreatectomy may be required.[199]

Epithelial cysts of the pancreas are rare in children. Congenital cysts are lined by epithelium and acinar tissue and are seen most commonly in the body and tail of the pancreas. They may be associated with other syndromes such as von Hippel–Lindau disease, which is characterized by hereditary cerebellar cysts, retinal hemangioma, and pancreatic cysts. Congenital pancreatic cysts are typically asymptomatic unless they are large enough to cause compression or obstruction of the stomach or colon. In the absence of trauma, spontaneous rupture of a pancreatic epithelial cyst is rare. Treatment is cyst excision or internal drainage into the stomach or the jejunum.

Other rare cystic lesions of the pancreas in children include retention cysts. These cysts result from chronic ductal obstruction. They are characteristically lined by epithelium unless inflammatory obliteration has occurred. Enteric duplication cysts of the stomach or the duodenum can also be associated intimately with the pancreas and communicate with the pancreatic duct. Treatment of both retention cysts and enteric duplication cysts either within or associated with the pancreas includes excision,

occasionally internal drainage, and, if necessary, distal pancreatectomy. Not all pancreatic cysts in children can be uniformly considered benign. Suspicious lesions should be investigated thoroughly and biopsy performed. Cystadenoma, cystadenocarcinoma, and rhabdomyosarcoma associated with a pancreatic cyst have been reported. These neoplasms are treated by anatomic pancreatic resection following histologic confirmation on biopsy.

Pancreatic Neoplasms

Childhood malignant neoplasms of the pancreas are uncommon. Typically, pancreatic malignancy in childhood is found on discovery of an asymptomatic abdominal mass. Infrequently, the lesion may be found incidentally or during a diagnostic imaging workup for abdominal trauma. Jaundice may occur with a lesion in the pancreatic head causing common bile duct obstruction. The most frequently encountered lesions include islet cell carcinoma and adenocarcinoma. The treatment of choice for localized malignant neoplasms of the pancreas is surgical resection.[200] Pancreaticoduodenectomy in children can successfully control some malignancies of the pancreatic head. To promote adequate nutrient absorption and growth, children undergoing pancreaticoduodenectomy should be considered for oral pancreatic enzyme replacement and fat-soluble vitamin supplementation.[201]

Two pancreatic neoplasms seen in childhood and adolescence deserve further discussion. The *papillary cystic neoplasm* of the pancreas occurs predominantly in younger female children, is typically slow growing with low malignant potential, and is highly curable with surgical resection.[202] This tumor is thought to be a neoplasm of the ductuloacinar primordial cells of the pancreas. The other lesion is the *pancreatoblastoma,* also referred to as *juvenile adenocarcinoma of the pancreas.* Pancreatoblastoma is somewhat more common in boys than in girls and typically has slow growth with low malignant potential as well. Histologic examination demonstrates undifferentiated ductular and acinar areas with nodules of squamous epithelium, suggesting that these tumors arise from primordial pancreatic cells. Both papillary cystic neoplasm and pancreatoblastoma have more favorable prognoses than adenocarcinoma following surgical resection.

Endocrine Lesions of the Pancreas

Zollinger–Ellison Syndrome

Zollinger–Ellison syndrome is characterized by gastric hypersecretion and is discussed in detail elsewhere in this book. However, its presentation in childhood should prompt work-up for MEN syndrome. About 25% of gastrinomas occur in the setting of MEN syndrome, reviewed elsewhere in this book. At least 90% of patients with MEN type I have hyperparathyroidism secondary to hyperplasia. In addition, 30% to 80% of patients have pancreatic islet cell tumors and 15% to 50% have pituitary tumors.[203]

Hypoglycemia

There are diverse metabolic causes for hypoglycemia in infancy and childhood. These include endocrinopathies such as panhypopituitarism, hypothyroidism, adrenal insufficiency, and congenital adrenal hyperplasia (adrenogenital syndrome). Several inborn errors of metabolism interrupt normal glucose regulatory mechanisms. Systemic disease states, perinatal stress, and sepsis can predispose an otherwise normal infant to low blood glucose levels. Infants who remain unresponsive to glucose infusion typically have inappropriately high circulating insulin levels for a given blood glucose level. Hyperinsulinemia should be suspected in any infant or child younger than 1 year with persistent hypoglycemia. There are heterogeneous causes for hyperinsulinemic hypoglycemia, but the most common historical cause in infancy is nesidioblastosis, which is characterized by uncontrolled development of the pancreatic endocrine tissue that functions abnormally during infancy.[204,205] Clinically, these cells secrete inappropriately high amounts of insulin, causing clinical hypoglycemia in infants. Two distinct histologic lesions appear to be responsible for congenital hyperinsulinism. Mutations in the beta-cell K_{ATP} channel genes may lead to either focal, adenomatous hyperinsulinism or diffuse hyperinsulinism; both genotypes lead to phenotypic hypoglycemia if left untreated.

Infants with congenital hyperinsulinism usually become symptomatic from hypoglycemia within the first few hours or days of life. These infants

commonly present with neurologic symptoms such as lethargy or generalized seizures and have corresponding fasting blood glucose levels below 40 mg/dL. The diagnosis of hyperinsulinemia is supported by the clinical features of Whipple triad that includes (a) neurologic changes with fasting or activity, (b) fasting blood glucose levels below 40 to 50 mg/dL, and (c) neurologic symptoms reversed by the administration of glucose. The diagnosis is made by demonstrating inappropriately high levels of circulating insulin for a given level of blood glucose. An insulin (IU/mL) to glucose (mg/dL) ratio that is greater than 0.5 in a fasting patient is consistent with hyperinsulinemic hypoglycemia. In infants and children, an absolute insulin level greater than 5 IU/mL in the presence of a blood glucose less than 40 mg/dL is diagnostic. Ketone body production is impaired in infants with congenital hyperinsulinism.

The initial management of a hypoglycemic infant with congenital hyperinsulinism is to provide adequate glucose concentrations to prevent permanent neurologic injury. Dextrose-containing intravenous solutions are titrated to maintain blood glucose levels greater than 40 mg/dL and may require a central venous catheter. The short-term administration of somatostatin analogs to increase blood glucose levels in hyperinsulinemic states has been demonstrated to be useful.[206] Other pharmacologic agents used to reduce insulin levels and raise blood glucose concentration include diazoxide (15 mg/kg daily). The use of streptozocin to control hyperinsulinemia most often is reserved for adults with metastatic islet cell carcinoma and is not widely used in infants because of the potential side effects.

Following initial control of blood glucose and clinical confirmation of hyperinsulinemia, operative intervention should be considered a means of providing definitive control of hypoglycemia. Diagnostic imaging using CT scan imaging, MRI, or more recently, 18F-FDOPA PET scanning may be useful either to identify or to exclude a focal lesion.[207] Localization of focal lesions is important in that this approach may lead to effective glucose control with selective partial pancreatectomy and allow for preservation of normal pancreatic tissue and function.[208,209]

Operatively, the abdomen is explored thoroughly, and the entire pancreas must be visualized. Preoperative localization data guided by intraoperative ultrasound and frozen section analysis may identify focal lesions amenable to

partial resection. In the absence of a focal lesion, the infant is presumed to have diffuse islet cell hyperplasia. In this setting, the general operative strategy is total or near-total pancreatectomy.[210] Lesser procedures such as subtotal (80%) pancreatectomy do not effectively treat diffuse congenital hyperinsulinism and recurrent hypoglycemia places the infant at risk for hypoglycemic encephalopathy. Near-total pancreatectomy involves resection of the distal 95% of the gland with preservation of the spleen. The entire distal pancreas, including the uncinate process, is resected, leaving a small rim of pancreatic tissue adjacent to the duodenum (Fig. 101.55). Total pancreatectomy is usually reserved for persistent or recurrent hypoglycemia following lesser procedures. Near-total pancreatectomy controls hypoglycemia in 90% of infants with diffuse congenital hyperinsulinism. The remaining infants with persistent hypoglycemia may require further pancreatic resection. With extensive pancreatic resection, the typical postoperative course is a transient period of hyperglycemia with subsequent stabilization of blood glucose levels. Pancreatic exocrine function is ablated and oral replacement therapy is required. Despite clinical remission following resection, however, diabetes mellitus may occur as a long-term consequence in children treated either medically or surgically for diffuse congenital hyperinsulinism.[211] Therefore, these infants need long-term metabolic follow-up for both pancreatic endocrine and exocrine function.

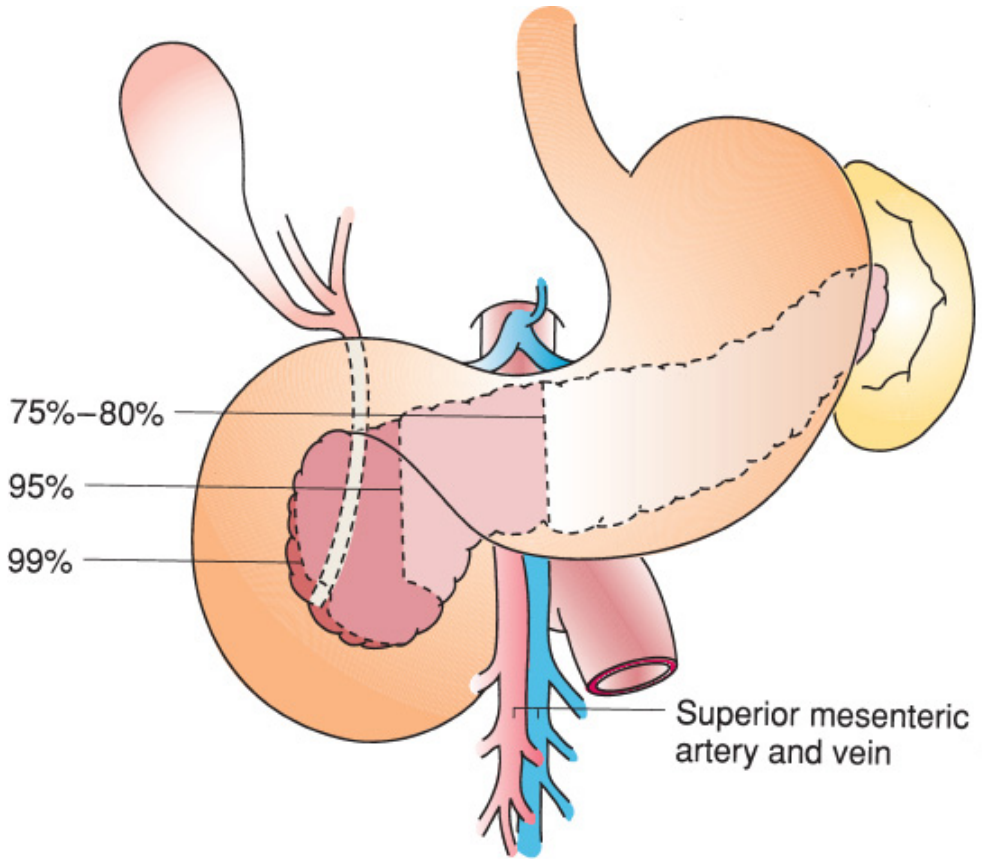

Figure 101.55 Illustration of the various degrees of pancreatic resection.

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Pediatric Genitourinary System

Natalia V. Leva and Hillary Copp

Key Points

1 Embryonic kidneys develop from the intermediate mesoderm, with the definitive kidney forming as result of inductive interaction between ureteric bud and metanephric mesenchyme. Paramesonephric (müllerian) and mesonephric (wolffian) ducts contribute reproductive structures.

2 Multicystic dysplastic kidney (MCDK) is the most common form of congenital cystic disease. It rarely causes any clinical problems and involutes over time.

3 Prenatal hydronephrosis is one of the most common anomalies detected on prenatal ultrasound, however the majority are low grade and over 80% resolve spontaneously over time. The severity of hydronephrosis correlates with the likelihood of necessary intervention.

4 Ureteral duplication is a common anomaly. Upper pole ureter can be associated with either obstructing ureterocele or ectopic ureter, whereas lower pole ureter is more likely to be associated with vesicoureteral reflux (VUR).

5 VUR is an important problem to identify and manage in children who present with urinary tract infection (UTI). VUR can lead to recurrent renal parenchymal infections, resulting in renal scarring and other lifelong problems such as hypertension and kidney disease.

6 Posterior urethral valve (PUV) is the most common congenital obstructive uropathy that leads to end-stage renal failure and renal replacement therapy. These patients are at risk for developing bladder dysfunction overtime and need lifelong follow-up with urology.

7 Hypospadias is common, occurring in 1 of 200 live births. Most cases are mild, presenting with urethral opening near the distal shaft and glans. When associated with cryptorchidism, the differential diagnostic possibilities must include disorders of sex development.

8 Undescended testes occur in 3% to 4% of full-term newborn males, and are diagnosed by physical examination. Ultrasound is not a part

of the standard workup for undescended testicle. Ninety percent of testes descend by 6 months of age, and the remainder typically descend by 9 months. The AAP recommends orchiopexy around 1 year of age.

9 Mature teratoma, which is classically benign, is the most common benign tumor in prepubertal children. Yolk sac tumors are the most common malignant testicular tumors in prepubertal boys; these are associated with elevated alpha-fetoprotein (AFP). Testicular-sparing enucleation is appropriate treatment for mature teratoma.

10 Patients with neurogenic bladder disorders (most commonly secondary to spinal dysraphisms such as spina bifida) must be evaluated with urodynamic pressure—volume study to characterize its urine storage and emptying function. Managing bladder pressure and emptying with clean intermittent catheterization (CIC) is paramount to preserve renal health and improve quality of life.

1 FETAL DEVELOPMENT OF GENITOURINARY SYSTEM

Kidneys develop as paired intermediate mesodermal structures stretching craniocaudally along the length of the abdomen. The embryonic kidneys, in order of their appearance, are pronephros, mesonephros, and metanephros. *Pronephros* is nonfunctional and transitory in mammals. By the fifth week, it is replaced by the *mesonephros*. The *mesonephros* is thought to provide a transient excretory function and also provides substrate for subsequent reproductive structures. The final step in renal development is the *metanephros,* which becomes the true functional kidney. It develops in the sacral region as a result of inductive interaction between the ureteric buds (sprouting from the distal portion of mesonephric ducts) and the condensing blastema of metanephric mesenchyme. The nephron, which consists of the glomerulus, proximal tubule, loop of Henle, and distal tubule, derives from the metanephric mesenchyme, while the collecting system, made up of collecting ducts, calyces, pelvis, and ureter, is formed from the ureteric bud.

The kidneys ascend from their initial pelvic position to their final position in the upper retroperitoneum.

At fifth week, the terminal portion of the endoderm-lined yolk sac dilates to become the cloaca. It is partitioned by the developing urorectal septum to form urogenital (UG) sinus anteriorly (future vesicourethral canal and vaginal vestibule) and anorectal canal posteriorly. During the fifth week of development, primordial germ cells migrate from the yolk sac to the posterior body wall near the mesonephros to form the genital ridges. In males, under the influence of SRY (the sex-determining region of the Y chromosome), primordial germ cells begin to differentiate into Sertoli cells, which then drive the formation of testis cords and Leydig cells (responsible for producing androgen). In females, the *paramesonephric ducts* (lying medially adjacent to the mesonephros; also known as the müllerian ducts) develop into reproductive structures, namely the uterus, and fallopian tubes. In males, mesonephric ducts (known as the wolffian ducts) develop into vas deferens and epididymis under the influence of androgen. The presence of müllerian-inhibiting substance (MIS) produced by Sertoli cells in a developing testicle causes müllerian ducts to regress in males. In females, in the absence of Sertoli and Leydig cells, mesonephric (wolffian) ducts regress and müllerian ducts continue to develop into female reproductive structures. Starting in the sixth week, under the influence of dihydrotestosterone (converted intracellularly from testosterone by the enzyme 5-alpha reductase), the genital tubercle elongates and the genital and urethral folds fuse in the midline to form the scrotum, penis, and penile urethra. Under the influence of androgens, the tubular urethra forms by canalization of the urethral plate to form a wide diamond-shaped urethral groove whose edges fuse in the midline, known as the zipper theory.[1] Both developing testicles and ovaries move to the pelvic location by the third month. In males, with androgen-influenced regression of cranial suspensory ligament and swelling/contraction of gubernaculum, the testicles undergo inguino–scrotal descent during the third trimester.

ANOMALIES OF THE KIDNEY

Renal anomalies can be categorized into several recognized variants in position, number, and shape.[2] When the kidney does not move to the normal expected position, it is termed an *ectopic kidney.* A kidney that fails to ascend and remains near the bladder becomes a *pelvic kidney,* thought to occur in 1 of 3,000. It can travel too far and rise above the ipsilateral diaphragm to become an *intrathoracic kidney.* It can cross over to the other side and end up in a contralateral position as a *crossed ectopic kidney.* Crossed renal ectopia occurs with renal parenchymal fusion in 90%. Unlike the more commonly encountered ureteral duplication, crossed ectopic kidney's ureter crosses over the midline and drains into the bladder on the contralateral side and thus the trigone appears normal on cystoscopy. In 30% to 50%, ectopic kidneys can have varying degrees of hydronephrosis and vesicoureteral reflux (VUR). Most ectopic kidneys are asymptomatic and clinically insignificant, except in cases of associated ectopic ureter. The adrenal glands develop independently from the kidney, and should be in normal position beneath the diaphragm, even if the ipsilateral kidney is ectopic. The possibility of an ectopic kidney must be entertained if a kidney is missing in the usual location during an exploratory laparotomy.

The embryonic metanephros can become fused at their caudal ends. The most common form of this anomaly is the *horseshoe kidney,* so named because the lower poles of the kidneys are linked either by a fibrous band or a section of functional tissue. It has an incidence of 0.2%. Horseshoe kidneys are notable for their low position in the body due to isthmus trapping by the inferior mesenteric artery. VUR and ureteropelvic junction obstruction (UPJO) have been found in up to 50% of patients with a horseshoe kidney.

In addition to anomalies of position and fusion, there can be an extra or *supernumerary kidney.* This very rare finding is usually discovered incidentally and occurs because there is separation of the metanephric blastema allowing a distinct kidney to develop. This should not be confused with a duplicated system where there are two collecting system draining a single kidney.

Failure of the ureteric bud to form or join the metanephric mesenchyme will result in *renal agenesis.* Bilateral renal agenesis is very rare and infants with this condition are either stillborn or perish soon after birth due to respiratory failure. The characteristic Potter face and the presence of severe oligohydramnios are pathognomonic. When unilateral renal agenesis occurs,

it is associated with a variety of other genitourinary findings; about 50% will still have a vestigial ureter, and about 30% will have VUR. Anorectal anomalies are also common. Müllerian duct anomalies—such as uterine duplication or vaginal septum—occur in 25% to 50% of females with unilateral renal agenesis, and likewise, up to one-third of females with müllerian duct anomalies will have unilateral renal agenesis. It is important to note that true agenesis is relatively rare and should not be confused with a regressed dysplastic kidney, which is often the fate of a *multicystic dysplastic kidney (MCDK)*.

2 Cystic Conditions of the Kidney

Renal cystic conditions are among the most common causes of pediatric abdominal masses, especially in infants.[3] It is important to accurately diagnose them due to their different prognoses and other associated conditions (**Table 102.1**).

MCDK is the most common form of nonheritable renal cystic condition.[4] Prior to prenatal sonographic screening, it used to be the most common cause of an infantile palpable abdominal mass and was often confused with the UPJO. MCDK is a developmental anomaly resulting in multiple noncommunicating cysts of varying sizes and is without identifiable renal parenchyma. There is typically an associated atresia of the ureter. The classic ultrasound findings are: absence of a large central lucency (i.e., no dilated, central renal pelvis); variably sized, noncommunicating cysts; and absence of renal parenchyma. MCDK is nonfunctional, and nuclear scintigraphy shows no activity. Majority of MCDK will involute and become undetectable on conventional ultrasound. For patients with a very large MCDK, they may not complete involution and a small residual clump of cysts may persist into adulthood. In these patients, there is a high incidence (15% to 25%) of contralateral VUR. Several long-term registries have shown that patients with MCDK do well, and previous concerns of hypertension, infection, malignancy, and pain are thought to be very rare. Surgery is rarely necessary unless there is confusion about the diagnosis with a cystic Wilms tumor or failure to regress with worrisome changes on serial imaging. Rarely, it will cause any symptoms.

Table 102.1 Classification of Congenital Renal Cystic Diseases
Inheritable
Autosomal recessive (infantile) polycystic kidney disease (ARPCKD)
Autosomal dominant (adult) polycystic kidney disease (ADPCKD)
Juvenile nephronophthisis Medullary cystic disease Congenital nephrosis (familial nephrotic syndrome) Familial hypoplastic glomerulocystic disease Renal cystic syndromes (tuberous sclerosis, von Hippel–Lindau disease)
Noninheritable
Multicystic dysplastic kidney (MCDK)
Benign multilocular cyst (cystic nephroma)
Simple cysts
Medullary sponge kidney Acquired renal cystic disease Calyceal diverticulum

Autosomal recessive polycystic kidney disease (ARPCKD) results from mutations in the PKHD1 gene of the chromosomal locus 6p12.2. The classic presentation is a child born with bilateral large palpable kidneys that appear very echogenic on ultrasound. The hyperechogenic appearance is due to the multiple cystic surfaces reflecting the sonographic waves. Kidney function is uniformly poor, and oligohydramnios with pulmonary hypoplasia occurs in up to 50%. Among those who survive infancy, 30% progress to end-stage renal failure. Long-term survivors can also develop portal hypertension, esophageal varices, and hypersplenism due to concomitant periportal fibrosis. There is no specific therapy other than kidney transplantation.

Autosomal dominant polycystic kidney disease (ADPCKD) affects 1 in every 400 to 1,000 people. It primarily affects the kidneys but also can have significant effects on the pancreas, liver, brain, and blood vessels. The most

common period for onset is postpubertal with most patients progressing to renal failure by the fourth to sixth decade of life, depending on the severity of penetrance. However, it can present at any age, including the newborn period. Usually, the earlier the onset, the more severe the disease.[5] Two gene mutations are associated: PKD1 (85%) and PKD2 (15%) on chromosome 16. These genes encode membrane proteins that affect cilium and calcium signaling. Cysts are present in the pancreas and liver, as well as cerebral berry aneurysms in the circle of Willis.

Acquired renal cystic disease of renal failure (ARCD) is a term that refers to the development of renal cysts in patients with end-stage renal failure. Regardless of the type of therapy (peritoneal or hemodialysis), cysts can develop in the kidneys. The longer the period of time of dialysis the more prevalent the cysts become. By 10 years of dialysis, 90% will have cysts. Transplantation and the restoration of normal renal function lead to cessation and regression of the cysts. The cysts are notable because they can bleed and develop infections. More worrisome is the development of renal cell carcinoma in about 0.2% of patients with ARCD. The condition occurs in equal frequency in adults and children.

There are other conditions that are associated with renal cysts. *Tuberous sclerosis* is an autosomal dominant condition characterized by developmental delay, epilepsy, sebaceous acne, and renal mass. The renal tumors are benign hamartomas (usually angiomyolipomas), but cysts are also common. *Von Hippel–Lindau syndrome* is an autosomal dominant condition with cerebellar hemangioblastoma, retinal angiomata, pheochromocytoma, renal cell carcinoma (30% to 40% of all VHL patients), and cysts of the pancreas and kidney.

Solitary Kidney

Patients with a solitary functional kidney in most cases can be expected to live a nearly normal life with few limitations.[6] Solitary kidney can be due to surgical removal for disease, congenital malformation, trauma, regression of an MCDK, renal donation, or in rare cases, true agenesis. In general there are no limitations on sports or other activities. Participation in contact sports (such as football, rugby, and ice hockey) is allowed with the understanding that the participant use all of the needed protective gear and that the risk of

injury leading to organ loss is very small but not zero.[7] The official position of the American Academy of Pediatrics is to allow participation in general. It is advisable that patients know their history and be able to identify the side of their functional kidney. It is also important to be aware that not every protective gear is subject to standardized testing and evaluation. Helmets used in American football, soccer shin guards, and eye protections are regulated, but most abdominal paddings are not. Therefore, although it would seem that protection should be helpful, use of such gear should not give a false sense of security.

Figure 102.1 Ultrasound demonstrating dilated renal pelvis and calyces caused by ureteropelvic junction obstruction.

3,4 ANOMALIES OF THE URETER

Ureteropelvic Junction Obstruction

UPJO is the most common form of congenital ureteral obstruction.[8] Multiple factors lead to poor transit of fluid across the obstructed UPJ. There can be an intrinsic adynamic portion of the ureter wherein the muscles lining the UPJ are aberrant. The muscle fibers are deficient and replaced with collagen. The

net effect is to alter the normal propagation of the peristaltic waves. In addition to these intrinsic issues, there can be extrinsic factors such as fibrous bands or aberrant lower pole crossing vessels trapping the ureter at the UPJ.

The classic symptoms of UPJO are flank/abdominal pain, hematuria, and infection. Inexplicable vomiting may be mistakenly termed idiopathic. Today many UPJO cases are diagnosed antenatally due to abnormal prenatal ultrasound (**Figs. 102.1** and **102.2**). Ultrasound findings of dilated renal pelvis and calyces without ureteral dilation are indicative of UPJO, but it cannot definitely establish the presence of a true surgical obstruction. Functional study, such as diuretic nuclear renography, is commonly required to assess both relative renal function and severity of obstruction. Magnetic resonance urography is a newer modality, which is increasingly utilized because it avoids ionizing radiation and yields excellent functional and anatomic details. The drawback is that it requires the patient to remain still for the duration of the study, thus general anesthesia is typically necessary. The majority of antenatally diagnosed hydronephrosis can be safely observed with spontaneous resolution in some, especially those with a preserved relative renal function.[9]

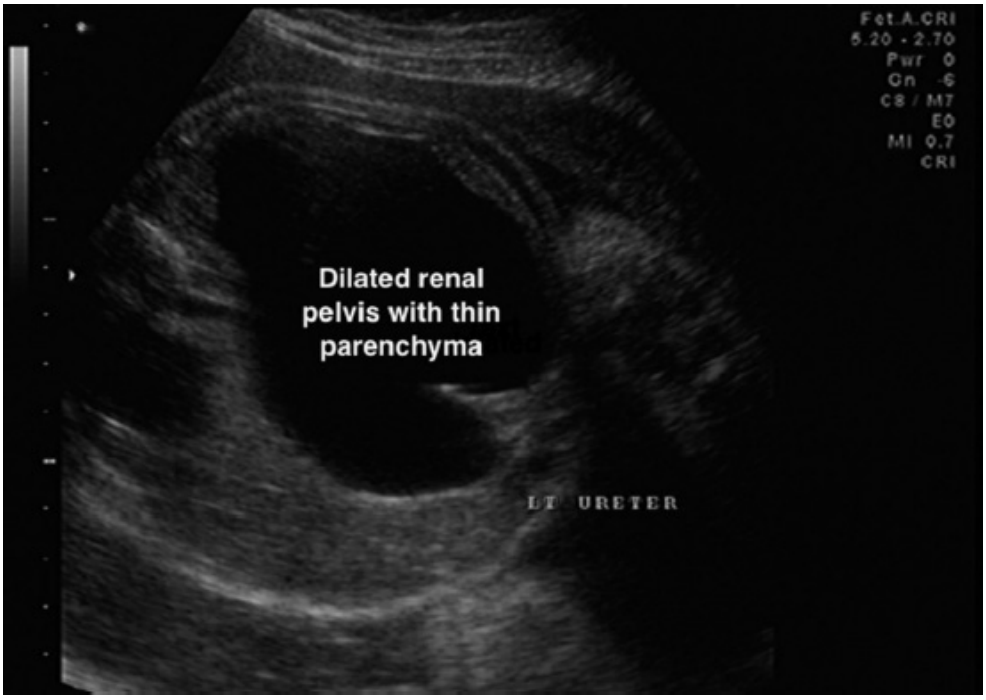

Figure 102.2 Prenatal sonography showing dilated left renal pelvis with thin parenchyma caused by ureteropelvic junction obstruction.

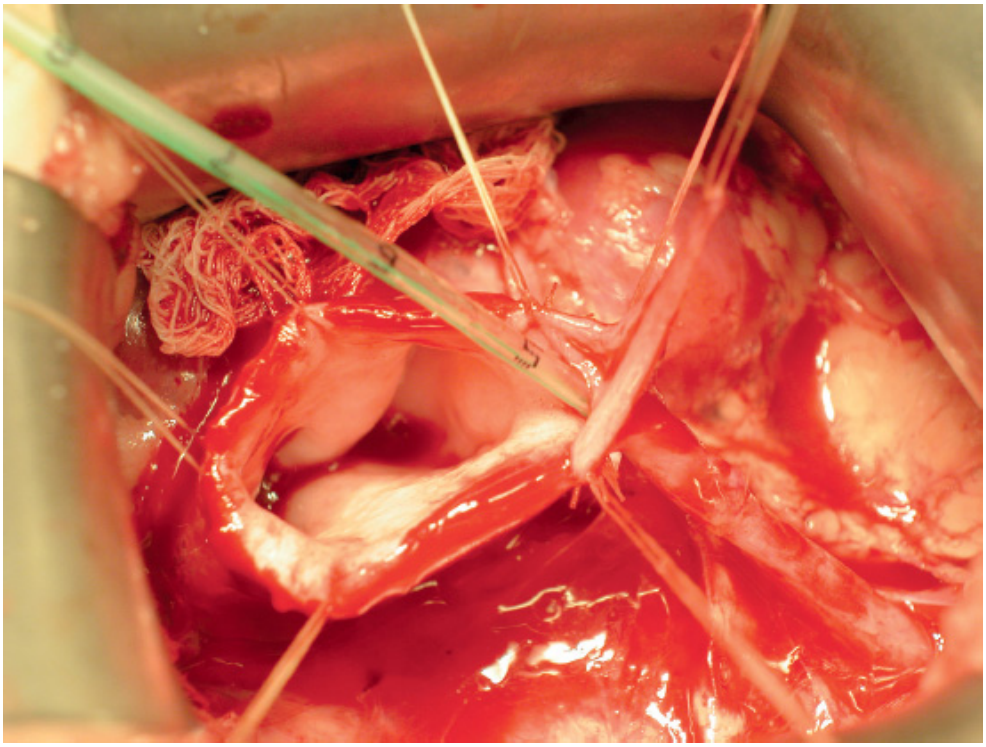

Figure 102.3 Dismembered pyeloplasty where the obstructive segment has been excised and the anastomosis is performed between the pelvic opening and spatulated ureter, creating a dependent drainage.

UPJO repair can be performed effectively using an open or laparoscopic approach, with possible aid of a surgical robot. The principle is to excise the narrowed, dysplastic portion and reconnect the ureter and renal pelvis to create a dependent drainage system (**Fig. 102.3**). This dismembered pyeloplasty can be done with a better than 95% success rate. Other approaches using renal pelvis flap are applied selectively based on the anatomy.

Ureteral Duplication

Ureteral duplication is a common anomaly of the urinary tract. The partial duplication has two ureters exiting the kidney, but they join prior to entering the bladder, so there is only one ureteral orifice in the bladder. A complete duplication has two ureters that enter the bladder separately, resulting in two orifices. These occur in about 1 in every 150 to 500 individuals. In a complete duplication, the upper pole ureter has a more inferior and medial orifice closer to the bladder neck while the lower pole ureter has a superior and lateral orifice (Weigert–Meyer rule). The more lateral position of the lower pole ureter can result in potentially shorter submucosal tunnel, making it more prone to VUR. The more medial upper pole ureter, on the other hand, can enter ectopically into the bladder neck and proximal urethra, resulting in obstruction. In females, the ectopic upper pole ureter can drain to the vestigial Gartner duct (wolffian duct remnant) and thereby open up onto the anterior lateral vaginal wall, resulting in continuous urinary incontinence. In males, the ectopic upper pole ureter can insert into reproductive structures such as vas deferens and seminal vesicle, resulting in obstruction or recurrent epididymitis. Most patients with partial or complete duplication are otherwise healthy.

Ectopic Ureter

Ectopic ureter usually drains more caudal and inferior to the normal trigone. It is commonly associated with a complete duplication as described previously. In males, they can exit into the prostatic urethra, bladder neck, and epididymis (rare). In females, they can drain into the bladder neck, urethra, and vagina. In females, an ectopic ureter that drains outside of the

bladder is the classic cause of persistent day and night wetting despite otherwise excellent toilet habits. This can be a vexing condition for many patients and families, but once properly diagnosed, it offers one of the most successful surgical solutions for incontinence (**Fig. 102.4**). Treatment is usually upper pole partial nephrectomy, upper to lower pole ureteroureterostomy, or reimplant of the upper pole ectopic ureter into the bladder.

Figure 102.4 Ectopic ureter opening outside the bladder and urethra causing continuous incontinence. Catheter is inserted into the left upper pole ectopic ureter.

Ureterocele

Ureterocele is a saccular dilation of the terminal ureter. It is classified based on location (intra versus extravesical) and number of collecting systems (single versus duplex). In duplex collecting systems, it is associated with the upper pole. The dilation varies in severity. It can be mild, contained wholly

within the bladder (**Fig. 102.5**). Or it can be massive and create a cavernous space under the trigone, extending beyond the bladder neck and into the urethra (**Fig. 102.6**). Ureteroceles are typically associated with the upper pole ureter of a complete duplication as described previously. Single-system ureteroceles do occur but are rare. Similar to UPJO, they are often found during an antenatal hydronephrosis evaluation. Other common presentations include symptomatic urinary tract infection (UTI) or prolapse. Infected ureterocele can cause severe sepsis and requires an emergent decompression of the ureterocele using an endoscopic transurethral puncture. Endoscopic puncture may ultimately be the only treatment required, however if patients have recurrent UTI or poor renal function of the obstructed kidney, other treatment approaches are available. Surgical approach depends on the function of the upper pole moiety. If the upper pole is functional, it is usually preserved, and the surgery is aimed at eliminating the distal ureteral obstruction at the level of the ureterocele. The dilated ureter is tapered and reimplanted into the bladder after excising the ureterocele, either separately or en bloc with the normal lower pole ureter in a common sheath. Alternatively, the upper pole ureter can be connected to the lower pole pelvis (ureteropyelostomy) near the kidney. If the upper pole is nonfunctional, a partial nephrectomy is preferred. Advances in minimally invasive surgery make laparoscopic and robotic techniques practical in even small children.

Figure 102.5 Intravenous urogram demonstrating ureterocele that has an appearance of "Pearl onion."

Megaureter

A persistently dilated ureter from the kidney all the way to the ureterovesical junction (UVJ) is referred to as a megaureter.[10] They are classified by description and causation; they can be refluxing, obstructing,

refluxing/obstructing, and nonobstructing/nonrefluxing. When it is due to an intrinsic abnormality of the distal ureter (such as aperistalsis or fibrosis of the UVJ), it is a called primary megaureter. When it is caused by another condition of the bladder (such as a neurogenic bladder or bladder outlet obstruction), it is called a secondary megaureter. Primary megaureters, like UPJO and ureterocele, are often diagnosed prenatally. The majority of moderate megaureters—especially those detected in utero—improve with observation. If they require treatment because of pain, UTI, or poor renal function, there are various temporizing management options including cutaneous ureterostomy. Definitive management is achieved with ureteral reimplantation with or without tapering of the wide ureter.

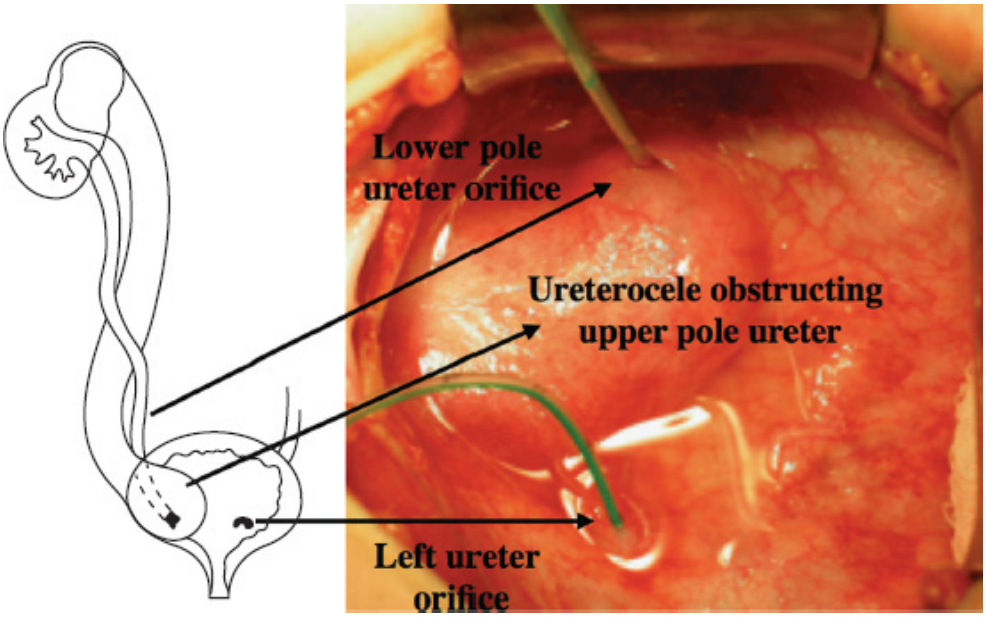

Figure 102.6 Bulging right ureterocele belonging to the upper pole. Bladder has been opened. Catheters are inserted into the right lower pole ureter and left ureter.

5 Vesicoureteral Reflux

The ureter transports urine from the renal pelvis to the bladder with active antegrade peristalsis. Once in the bladder, the urine is stored until it is emptied without sending the urine back toward the kidney. This whole process is independent of gravity. When the bladder urine moves in a retrograde manner toward the kidney, it is termed VUR (**Fig. 102.7**).[11] It is an abnormality that can occur primarily due to a congenital deficiency in the

UVJ submucosal tunnel or secondarily to high bladder pressures such as in patients with neurogenic bladder or posterior urethral valves (PUVs). The incidence of VUR in general population is estimated to be around 1%. The incidence is much higher in children who present with UTI and hydronephrosis. Among children of age 4 years or less who present with a first-time UTI, the VUR incidence can be as high as 40%. VUR is found in 25% to 30% of children with antenatal hydronephrosis. The primary form of VUR occurs because the length of the intramural tunnel is insufficient to seal the ureter during bladder filling and emptying. The secondary form usually occurs because of high storage pressure that overwhelms an otherwise normal intramuscular tunnel. Reflux is of clinical significance because it interferes with effective emptying of urine and allows bacteria to ascend to the kidneys more easily, thereby transforming cystitis into potentially damaging renal parenchymal infection (pyelonephritis). Pyelonephritis may, in turn, increase the risk of long-term kidney damage by causing parenchymal scar. Infants and children may be more prone to scarring than adults. Renal scarring and damage early in life may increase the risk of hypertension and pregnancy-related complications in females.[12,13]

Figure 102.7 Vesicoureteral reflux to the left lower pole ureter.

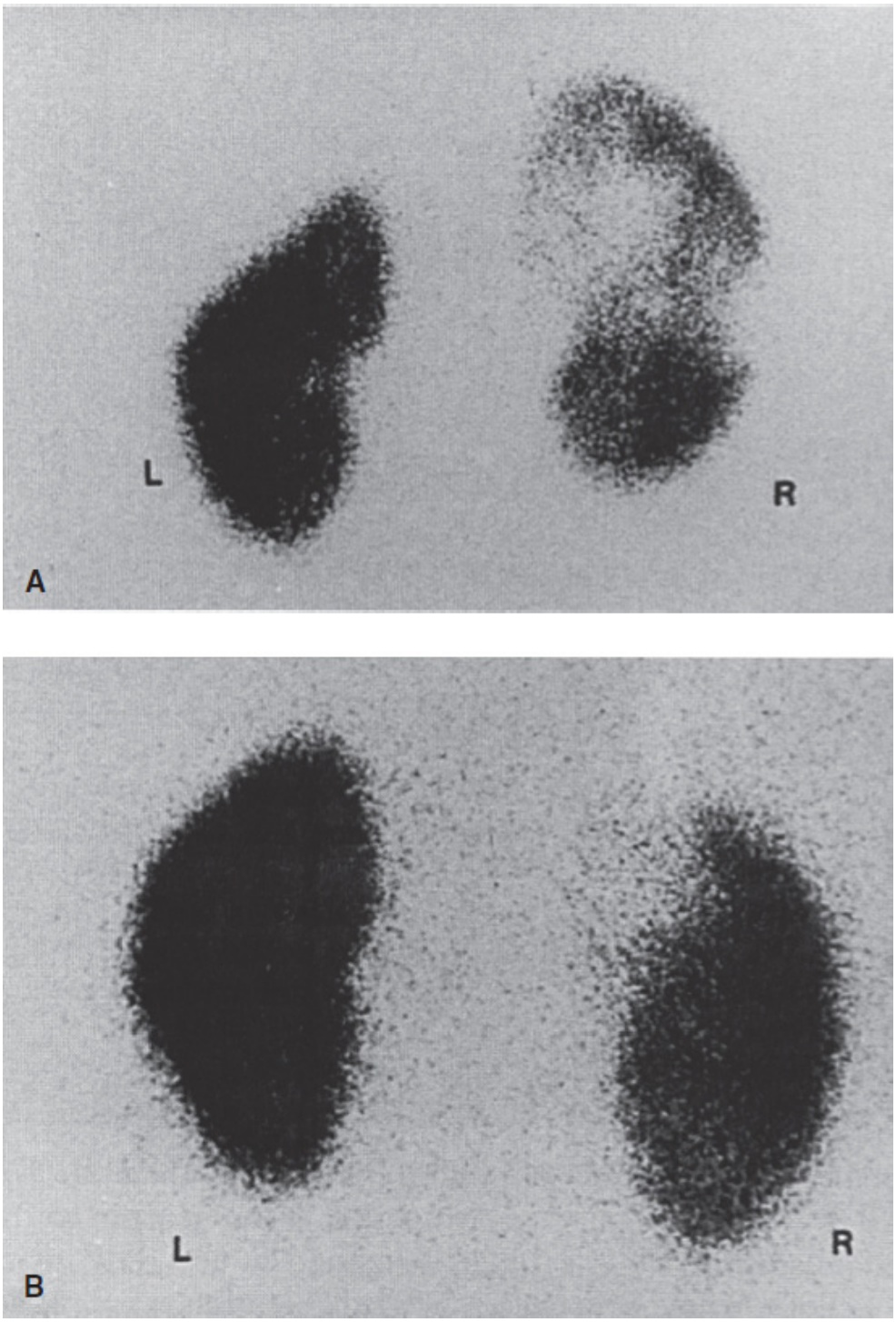

Figure 102.8 DMSA renal scintigraphy demonstrating renal parenchymal defect associated with pyelonephritis. **A:** Cortical defects seen in the right kidney during the acute phase of pyelonephritis. **B:** The same kidney 6 months later showing a persistent cortical scar involving the upper pole.

VUR severity is described using the International Reflux Study scale. Grading is important for several reasons. Most VUR patients (80%) have grades I or II with an excellent chance of spontaneous resolution (75% to 90%) over time. The higher grades (III to V) are less likely to improve with time. The diagnosis of VUR depends on the demonstration of reflux on an imaging study. Voiding cystourethrogram (VCUG) is most commonly used to diagnose reflux. It offers excellent anatomical detail of the entire lower urinary tract (bladder and urethra) and reproducible grading. In males, it provides important details regarding urethra such as possible PUVs. The presence of other anomalies such as periureteral diverticulum can affect the clinical decision making. Alternative options include nuclear cystogram (NUC) or contrast-enhanced voiding urosonography (ce-VUS) which do not require radiation. Standard ultrasound of the kidneys and bladder, while helpful in assessing renal size and appearance, cannot diagnose reflux. The detection of kidney scarring is usually confirmed with nuclear renal scintigraphy using DMSA (**Fig. 102.8**).

The management of children with VUR depends on their presentation and other clinical factors (**Fig. 102.9**). Antibiotic prophylaxis is recommended for children less than 1 year of age with febrile UTI or high-grade VUR diagnosed on prenatal ultrasound. If low-grade VUR is detected prenatally, antibiotic prophylaxis may be offered. Management of children who are older than 1 year of age takes into account bowel and bladder dysfunction in addition to grade of reflux evidence of renal scarring and parental preference.[14] The vast majority of patients have low-grade VUR and are expected to resolve spontaneously with time. The most recent multi-institution randomized clinical trial suggested that antibiotic prophylaxis is beneficial in children with dilating, high-grade reflux (grade III or higher). If they cannot remain infection free and sustain breakthrough infections, surgery may be necessary to prevent recurrent renal parenchymal infection.[15] For most patients, spontaneous resolution occurs after 4 to 5 years. However those with persistent high-grade reflux who fail conservative management may need surgery. There are two major surgical options: endoscopic antireflux surgery and ureteral reimplant. Endoscopic management consists of injection of a bulking material into the floor of the ureteral orifice. This creates a submucosal mound that turns the usual round oval ureteral orifice into an upside-down crescent. Currently, FDA-approved

dextranomer/hyaluronic acid copolymer (Deflux) is available for this approach. The efficacy of Deflux injection ranges from 70% to 80%, though current literature consists of small studies and demonstrates that rates of febrile UTI after endoscopic intervention are comparable to prophylactic antibiotics alone.[16,17] Ureteral reimplantation (ureteroneocystostomy), where the ureter is revised or repositioned to create a more effective ureterovesical flap-valve mechanism by restoring the submucosal tunnel, is the gold standard treatment for VUR. The affected ureter is detached and mobilized. A new submucosal tunnel of sufficient length (approximately three to five times the width of the ureter) is created, and the ureter is placed into it. It is critical that the muscle underneath the tunnel is firm and secure to allow the collapse of the reimplanted ureter with bladder filling and emptying. The ureter may require tapering (in megaureter or obstructed upper pole of duplication anomaly), so it can meet the needed width-to-length ratio of the tunnel. An extravesical approach is called detrusorraphy, where the muscle flaps are freed from the underlying bladder mucosa and wrapped behind the ureter at the UVJ to create a more effective flap-valve mechanism. The success rate of open surgery for VUR is very high (96% or more for grades III or less).

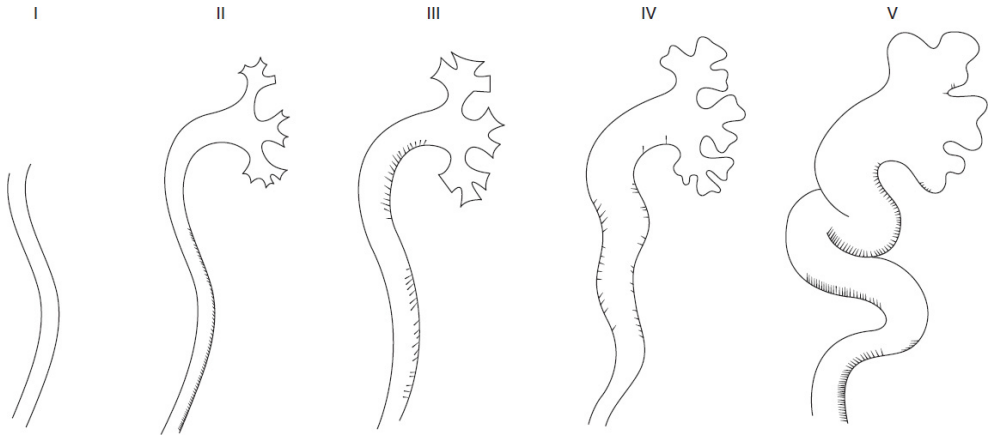

Figure 102.9 International reflux grading system. Majority of reflux are grades I or II, with high likelihood of spontaneous resolution, whereas higher grades (III to V) with dilating ureters are at a greater risk of UTI, renal injury, and nonresolution, often requiring surgery.

Traditionally, all children who present with a culture-proven UTI were recommended to undergo evaluation for VUR using ultrasound and VCUG. However, the morbidity of VUR seems to be mostly due to infections and

related complications rather than the reflux itself. It is important to stratify patients according to their risk of infection, taking into consideration grade of reflux and presence of bladder and bowel dysfunction, as not all reflux needs to be treated.[18] The goal of managing children with VUR is to prevent UTIs, renal injury and minimize the morbidity of treatment. Because most incidences of VUR are low grade and most cases of low-grade VUR resolve spontaneously, it may be reasonable to defer VCUG for only those patients who have recurrent UTIs or abnormal ultrasound. This has led to a major shift in the recommendations from the American Academy of Pediatrics (AAP) in 2011. DMSA renal imaging should be obtained to assess renal scarring and function if the renal ultrasound is abnormal. Recently a double-blind controlled randomized clinical trial looked into the benefits of antibiotic prophylaxis. The Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) study that completed in 2014 studied 600 children with proven VUR.[19] Half received antibiotic prophylaxis and half received a placebo. Prophylaxis reduced the risk of recurrent UTI by 50%, especially in those with dilating, high-grade reflux (III to V). The occurrence of new renal scarring however did not differ significantly between the two groups.

Women with a history of VUR may be at increased risk later in life for UTI during pregnancy regardless of whether the VUR was corrected or not. Renal scarring rather than the presence of active VUR itself appeared to be a key risk factor for pregnancy-related morbidity. Furthermore, there is an increased rate of VUR in offspring of parents with VUR. In general, for girls with VUR, the families should be aware that when they become adults of child-bearing age, it is important to know their medical histories, so that appropriate perinatal care and monitoring is instituted.

BLADDER ANOMALIES

Urachal Abnormality

During fetal development, urachus is the cephalad attachment of the cloaca to the allantois. As the bladder and urethral sphincter develop, it becomes atretic. It remains only as a fibrous cord from the dome of the bladder to the

umbilicus. Occasionally the urachus remains patent either completely or partially. When completely open (patent urachus), urine can be found exiting the umbilicus. In other cases, there can be a deep sinus or entrapped cyst. These can be asymptomatic and incidentally diagnosed on imaging, or they can become infected due to poor drainage and present with fever, nausea, and umbilical drainage. Detection is usually made by clinical suspicion, along with abdominal ultrasound or other imaging. Because the epithelial lining of the urachus is that of the bladder and not of the skin, rarely tumors can occur. Mucinous adenocarcinoma can arise from the urachal remnant in middle-aged or elderly patients, though the incidence is very rare. For this reason, the literature supports conservative management of asymptomatic urachal remnants.[20]

Figure 102.10 Male bladder exstrophy with associated epispadias.

Exstrophy–Epispadias Complex

During embryologic development if the cloacal membrane fails to breakdown at the appropriate time, medial migration of the mesenchyme to form the anterior abdominal wall is affected. The bladder can end up as an

exposed urothelial plate (*bladder exstrophy*) (**Fig. 102.10**).[21] The urethra may be incompletely formed dorsally (*epispadias*). The whole lower abdomen can be exposed with the hindgut or colon being unformed with the bladder split into two halves (*cloacal exstrophy*). The pelvis is also abnormally developed, and there is a diastasis of pubic symphysis.

The least severe manifestation is epispadias. In males, it is a defect with a dorsally placed urethral meatus and urethra, along with dorsal penile curvature. Visually it looks like a reverse, dorsal form of hypospadias. When the meatus is very proximal, the bladder neck and continence can be affected. In females, epispadias typically present with bifid clitoris (**Fig. 102.11**). It is more commonly associated with bladder exstrophy, but can occur as an isolated defect. Recognition and protection of the bladder plate against contact irritation is important. If possible, primary closure of the exposed bladder plate, pelvic placement, and abdominal closure should be done during infancy. Most studies have suggested that a concomitant pelvic osteotomy is beneficial for successful initial closure, especially if primary closure is delayed beyond 72 hours,[22] as well as the subsequent bladder function. Repair can be staged with closure of the bladder first, followed by subsequent bladder neck reconstruction and epispadias repair. Alternatively a complete primary repair can be accomplished with simultaneous closure of the bladder plate and reconstruction of the epispadias and genitalia. Bladder exstrophy is associated with other anomalies including inguinal hernia and VUR.

Figure 102.11 Female epispadias with its classic bifid clitoris.

The most severe form of exstrophy disease is the cloacal exstrophy. The hindgut (colon, rectum, and anus) is absent or rudimentary. The bladder plate is split into two parts on either side of the exposed cecum and hindgut remnant along with omphalocele. Initial management involves repairing the omphalocele, creating a colostomy, dissecting the bladder plates free and reconstruction to form a reservoir. In cloacal exstrophy, children are born with varying degrees of spinal dysraphism.

6 ANOMALIES OF THE URETHRA

Posterior Urethral Valves

One of the most important obstructive uropathies in males is PUVs.[23] This condition occurs when a thin membrane of tissue forms below the verumontanum and above the external sphincter, causing a blockage of antegrade flow of urine from the bladder. This results in high voiding pressures proximally leading to prostatic urethral dilation, bladder wall hypertrophy (similar to cardiac hypertrophy due to hypertension or aortic

stenosis), and VUR. Most patients today are diagnosed antenatally when they are found to have hydronephrosis. Classic prenatal sonographic findings are bilateral hydroureteronephrosis, dilated bladder, and enlarged prostatic urethra (so-called "keyhole" urethra). The poor bladder emptying throughout fetal development can result in dysplastic, poorly functioning kidneys and low urine production. Oligohydramnios (as result of low urine output) can lead to poor pulmonary development and concomitant respiratory issues. Initial postnatal treatment is to achieve immediate urethral drainage (usually with a small diameter feeding tube) and obtain VCUG when stable to establish diagnosis (**Fig. 102.12**). Most patients undergo endoscopic resection of the valves. If the patient is too small to accommodate an infant resectoscope (8.5 Fr), a temporary diverting vesicostomy may be appropriate. Supravesical diversion such as ureterostomy is rarely needed.

There are several long-term urologic concerns for boys with PUVs. PUV remains the leading urologic cause resulting in renal insufficiency and transplantation, therefore the importance of long term urologic follow-up cannot be overstated. The initial nadir creatinine with complete bladder drainage is prognostic. Patients with nadir serum creatinine values at or above 0.7 mg/dL are associated with an increased need for renal replacement therapy.[24] The early fibrosis and hypertrophy of the bladder makes valve boys more prone to develop poorly compliant bladders. These bladders have higher than normal storage pressures and over time can lead to the development of stones, incontinence, urinary retention, and worsening renal function. When recognized early, appropriate therapy using clean intermittent catheterization (CIC) along with antimuscarinic agents (such as oxybutynin) to relax the bladder muscle can help manage these so-called "valve bladders."

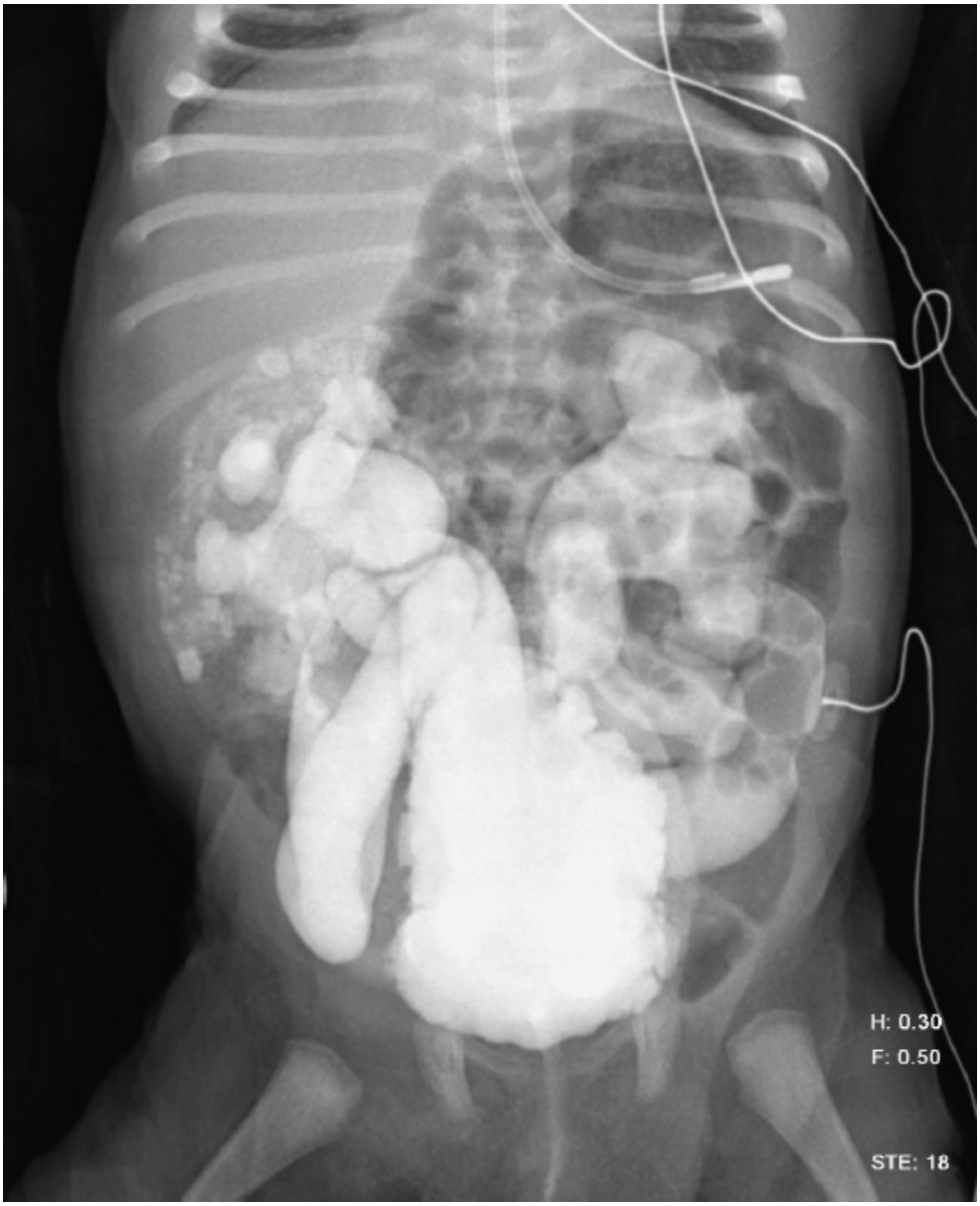

Figure 102.12 Voiding cystourethrogram of a newborn with posterior urethral valve. Bladder wall is thickened from chronic in utero obstruction. Bilateral severe vesicoureteral reflux is also shown.

7 Hypospadias

Hypospadias occurs when the ventral genital folds do not fuse completely.[25] The majority of cases do not have a known cause. There are a few important associations. When hypospadias is found concomitantly with one or more undescended or missing testicles, the probability of a disorder of sex development (DSD) is high enough to warrant a formal workup. Recently

there has been a growing interest in the role of endocrine disruptors. These are a class of agents that are not steroids but may act on steroid receptors. They include agents such as bisphenol A, polychlorinated biphenyls, phytoestrogens, and other common commercial and industrial compounds. They can fully or partially mimic natural hormones by binding with androgen receptor, thus altering the effect of endogenous sex hormones.

There are three anatomic elements in hypospadias: the urethral opening is proximal, the ventral shaft is less well developed and classically curves toward the scrotum (called ventral curvature or chordee), and the foreskin is deficient creating a dorsal hooded foreskin (**Fig. 102.13**). Most cases (80%) are distal with the meatus between the tip of the penis and the corona. Not all cases require surgery. Milder forms which do not interfere with normal voiding and whose erections are sufficient for future sexual intercourse may not need correcting, other than for cosmetic concerns. Circumcision should be delayed if a newborn is suspected to have hypospadias.

Surgical repair aims to create a functional penis that allows stand-up voiding and straight erections with good cosmesis.[26] The urethral meatus is advanced to the orthotopic position on the glans with a slit-like opening and any significant ventral curvature is corrected as well. There are a variety of techniques that can be used depending on the severity of the hypospadias. These are performed as a single stage or in multiple stages for the severe type (**Fig. 102.14**). The prepuce is an important source for free and vascular flaps. In some cases, particularly those who have undergone failed prior attempts at repair, there may not be sufficient local tissue. Grafts taken from the buccal mucosa of the inner lip or cheek can be used effectively to form a urethra. Complications of hypospadias repair include urethrocutaneous fistula, stricture, meatal stenosis, recurrent ventral curvature, and surface skin irregularities. Long-term follow-up is important for these patients because complications can occur years after the total repair.

Figure 102.13 Mild hypospadias with urethral meatus located near the neck (corona), along with dorsal hood foreskin.

Differences in Sex Development

When the genitalia do not develop in a manner that is clearly male or female in appearance, the term disorders in sexual development (DSD) is applied.[27] It replaces older terms such as hermaphroditism. This is an evolving field

and covers a spectrum of conditions, some of which can pose a significant physiologic and mental health risk. There are important concerns regarding gender assignment and genital reconstruction. For these reasons, children with DSD should receive care at a center with a multidisciplinary DSD clinic comprised of experts from urology, general surgery, gynecology, genetics, endocrinology, social work, psychology, and ethics. This multidisciplinary approach provides comprehensive and systematic evaluation and management of children with DSD.

Figure 102.14 Severe hypospadias with perineal urethral opening along with severe ventral shaft curvature (chordee).

All patients with suspected DSD require a thorough physical examination, especially of the genitalia and perineum, along with a detailed pregnancy, family, and social history. Evaluations, including electrolytes, steroid levels and precursors, gonadotropins, and karyotype, are typically assessed with further specialized tests ordered as necessary. Imaging includes renal/pelvic ultrasound and genitogram. Magnetic resonance imaging, cystoscopy, laparoscopy, and gonadal biopsies may also be necessary.

Management of DSD is complex and shared decision making with the child (when possible), family, and medical team is critical. Management options may include observation, pharmacotherapy, and/or surgery. Ultimately it is the right of the affected children's parents to make well-informed decisions on behalf of their child. However, controversy and concern exist regarding the requirement for early surgery without consent by the patient when surgery is not medically necessary. Much of what is known of the long-term outcome remains anecdotal and incomplete, lacking robust clinical outcomes data to guide management during infancy. Continued research on DSD management and outcomes is necessary to better understand how to optimally address the medical, psychological, developmental, and genetic issues for each unique individual with DSD. The primary goal of the care team is to provide parents with as much information about the condition as possible, including the wide range of management options with regard to assigning sex of rearing and the impact it may have on future gender declaration, child development, and medical and surgical management.

Anomalies of the Penis and Prepuce

Physiologic phimosis, when the foreskin cannot be retracted to expose the glans, presents in all uncircumcised infant males and resolves spontaneously as the child matures. It is inappropriate and unnecessary to retract the foreskin in most boys until they are between ages of 5 and 7 years. No special care of the uncircumcised phallus is needed. Spontaneous separation due to the accumulation of sloughing skin cells and secreted oil (forming smegma) and normal erections that occur even in small children naturally lift the prepuce away from the glans. No forceful retraction should ever be done during early childhood, since it can be very painful, traumatic, and can result in foreskin tear that will heal as a solid scar.

The indications for neonatal circumcision, arguably the single most common procedure performed worldwide, remains controversial.[28] The clear-cut medical indications are not in dispute—phimosis, paraphimosis, and balanitis. Pathologic phimosis is the inability to retract the foreskin when the child is of an age when it should have occurred naturally. Treatment with topical steroid ointment of the phimotic ring has been found to have success rates between 50% and 74%. In cases where medical therapy is not

effective, circumcision is curative. For families and patients who do not want to be circumcised a dorsal slit or partial circumcision can be performed. In paraphimosis, the foreskin is pulled back but cannot be repositioned, causing a vascular constriction in the corona. Emergent reduction is required because over time the prolonged retraction will cut off lymphatic and blood flow causing glandular necrosis. Finally for patients who have recurrent bouts of infection due to entrapment of bacteria under the foreskin (balanoposthitis), circumcision may be medically advisable. Uncircumcised males under 1 year of age are at increased for UTI and therefore circumcision may be recommended for boys with underlying genitourinary anomalies that placed them at increased risk for UTI such as PUV or VUR.

Parents may elect to circumcise their infants neonatally as part of a religious rite, social or family custom, or concerns about future hygiene. Similarly, parents may elect not to circumcise their infants as part of religion, or social or family custom. Following circumcision the glans skin changes from columnar moist epithelium to a dry tougher squamous epithelium. This change and the exposure of the glans were long theorized to help increase resistance to infection to sexually transmitted diseases (STDs) and UTI. The data from the three large-scale randomized African studies on young men who underwent circumcision to assess its effect on STD transmission (notably HIV) demonstrated a statistically significant difference. However, clinically this effect has limited utility because circumcision does not prevent or cure any infection—these studies suggest that the tougher epithelium and a dry environment may lower infection-carrier risk. Penile cancer most commonly occurs in the prepuce, thus elective early removal is theorized to help prevent later cases. However, the small benefit of reducing a relatively rare condition while subjecting many children to the risk of circumcision limits this argument. Meatal stenosis is the most common long-term complication after circumcision and occurs in 5% to 7% of circumcised boys. It classically presents with upward deflection of urinary stream but also narrow stream, straining to void. Treatment is by splitting the web of skin that has developed over the urethral meatus (meatotomy).

8 ANOMALIES OF THE TESTICLE AND SCROTUM

Undescended Testicle or Cryptorchidism

Embryologically, testicles develop just beneath the kidneys.[29] During the 12th to 18th weeks of gestation, the testicles migrate down to a pelvic position just inside the internal inguinal ring. During the third trimester, the testicle travels through the inguinal canal, exits the external inguinal ring, and enters the scrotum, driven by the swelling and contraction of the gubernaculum under the influence of androgens. Patients with undescended testicles have two times the risk of developing a germ cell malignancy, and orchiopexy more significantly reduces this risk when performed prior to puberty.[30] A scrotal position is advantageous for several reasons. Descended testicles are exposed to a lower temperature environment, which is necessary for achieving full sperm development and fertility. A scrotal position makes self-examination after puberty easier, thus facilitating an early detection. Finally, undescended testicles that are positioned near the pubic bone can be more vulnerable to injury.

Physical examination plays a key part in the diagnosis of an undescended testicle. When boys are anxious or nervous, their inguinal cremasteric muscles tense up and can draw the testicle upward into the groin. This condition is termed retractile testicles. In most cases, the retractile testicle settles in the scrotal position around the time the child goes through puberty. In some, retractile testicles can ascend to the inguinal region as the boys grow older, requiring a surgical intervention. This is referred as an ascended testicle, and may occur up to 5% to 10% of boys who are followed for retractile testicles.

About 3% to 4% of normal full-term boys may have an undescended testicle at birth. The incidence is higher in premature infants. By age 1 year corrected for prematurity, this number drops down to around 1%. This figure remains stable through puberty. For this reason, undescended testicles diagnosed within the first 6 months of life are often observed in case they descend spontaneously, but at around 1 year of life surgical orchiopexy should be performed. Furthermore, leaving a testicle in an ectopic position

beyond age 2 to 3 is thought to adversely affect future sperm cell (Ad spermatogonia) development. The location of an undescended testicle may be intra-abdominal, along the inguinal canal (canalicular), or through the external ring but not in the scrotum (superficial pouch). An undescended testicle can also be ectopic, such as perineal or femoral. Finally, it can be aberrant, dysmorphic, atrophic, or nonexistent. These are usually testicles, which suffered some form of perinatal vascular compromise that was not recognized prior to birth. The testicle seems to "vanish" over the first year of life (thus called vanishing testicle syndrome).

For palpable undescended testicles, the operative approach is usually through an inguinal incision. The testicle is mobilized by detaching the gubernaculum, cremasteric muscle, and internal spermatic sheath around the cord structures, and a tunnel is created from the inguinal incision to the scrotum. There is usually an associated patent processus (up to 80% in infants), and this is separated from the cord and ligated at the internal ring. For nonpalpable testicles, the most effective initial approach is laparoscopy. The key is to find the spermatic vessels. If spermatic vessels pass into the internal ring then the laparoscope is removed and a groin exploration is done. This may lead to a small inguinal testicle, which may have been difficult to palpate in the inguinal fat. In other cases, there is an atrophic nubbin (typically within the scrotal sac) due to a probable perinatal torsion and vascular compromise. If the testicle is seen within the abdominal cavity and well away from the internal ring, the only viable surgical option may be a Fowler–Stephens orchiopexy (done as either single or two stage), where the gonadal vessel is divided and the testicle is brought down with a vassal collateral circulation (**Figs. 102.15** and **102.16**). In a staged orchiopexy, the dominant gonadal vessel is gently clipped laparoscopically, allowing the testicle to develop a dependence on the collateral circulation. At a second procedure 6 months or later, the gonadal vessel is divided, and the testicle is carefully brought down (either open or laparoscopically) with the vasal vessels. Laparoscopy has been shown to be the most effective in determining the absence of viable testicle (vanishing testicle syndrome). The pathognomonic finding is blind ending gonadal vessels. If a blind-ending vas is seen but not the vessels, one must continue to explore for hidden testicular tissue since there is an unusual phenomenon of testicular–epididymal dysjunction, where the testicle is disconnected from the wolffian structures

(epididymis and vas). One may have to look very far to locate the vessels, even going up behind the colon and near the lower pole of the kidney. Leaving testicular tissue trapped within the abdominal cavity will increase the risk of germ cell malignancy. There are currently no reliable imaging studies that obviate the need for surgical exploration, and diagnostic laparoscopy remains the gold standard. Ultrasound is not recommended because although it is noninvasive, it has sensitivity of 45% and specificity of 78%.[31] More importantly, the surgical decision and planning are not altered by ultrasound findings. For bilateral nonpalpable testicles, biochemical markers—such as HCG stimulation test or serum MIS level—may be useful to determine the presence or absence of functional testicular tissue.

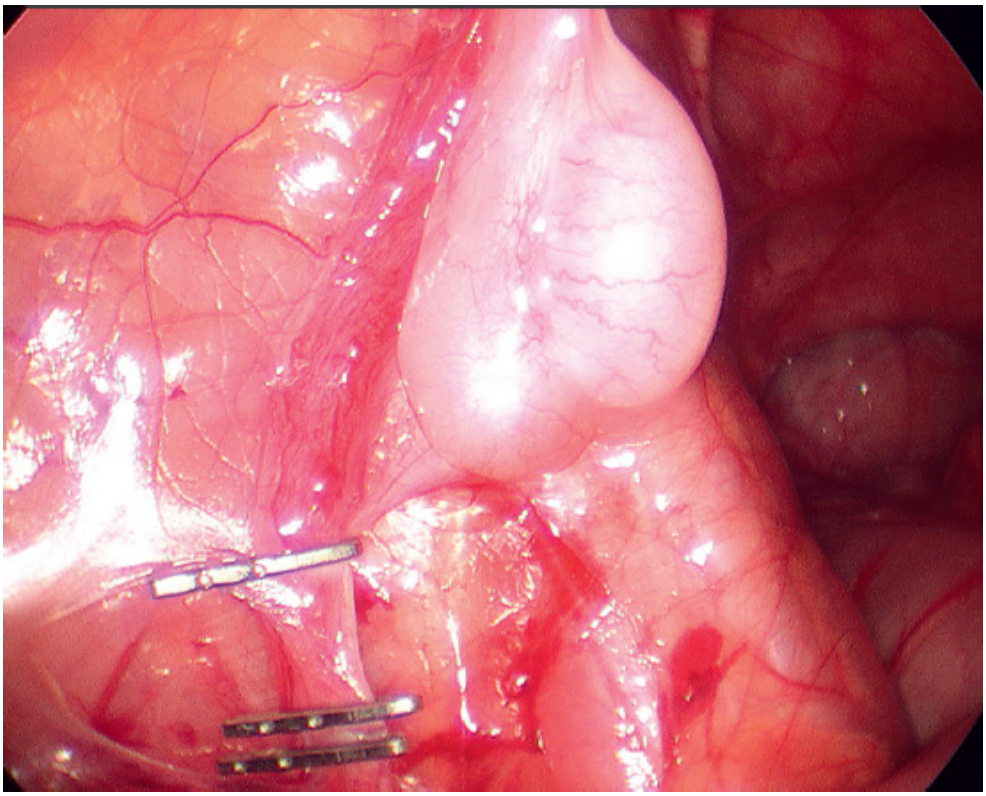

Figure 102.15 Intra-abdominal testicle is gently clipped to force its dependence on the vassal collateral circulation (first-stage Fowler–Stephens orchiopexy).

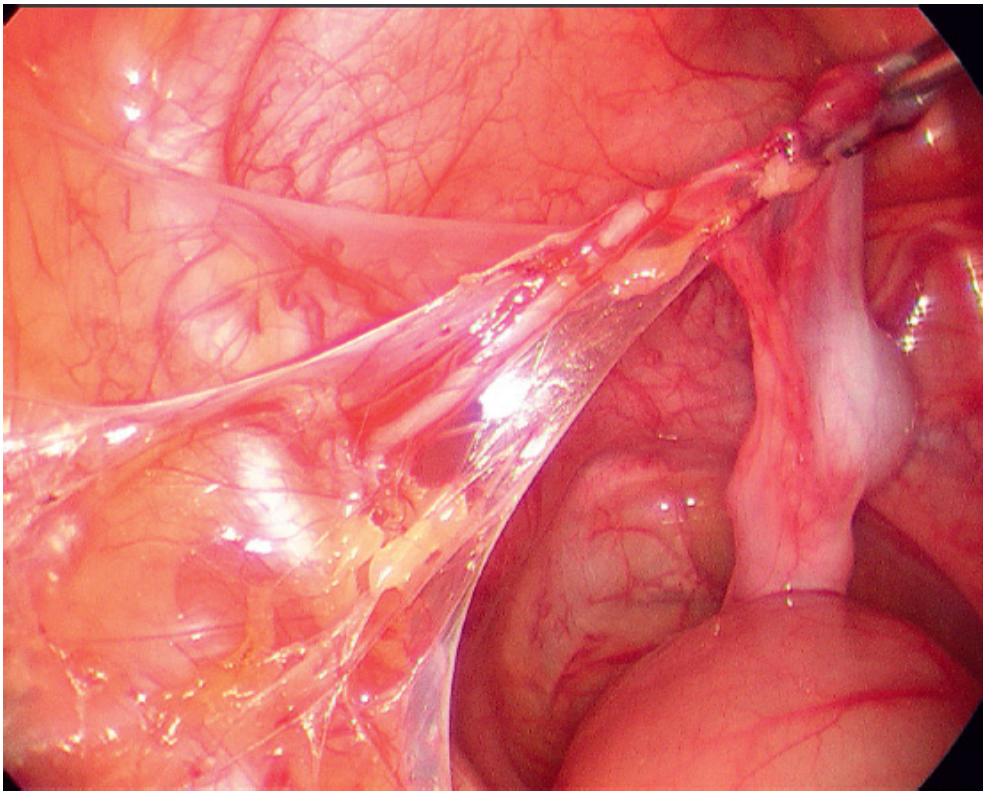

Figure 102.16 During the second-stage orchiopexy, the testicle is dissected while being attached to the vassal collateral circulation.

Torsion of Testicle and Appendages

Torsion of the testicle is the leading nontraumatic cause of loss of the testicle in boys (**Fig. 102.17**).[32] It is an emergent condition that occurs as result of the spermatic cord twisting. This results in occlusion of the lymphatic vessels, veins, and arteries leading to ischemia, necrosis, and atrophy. If there is complete occlusion of blood flow, the testicle may be salvageable up to 6 hours after onset. After 6 hours the odds of salvage diminish exponentially.[33] Most torsion occurs in older boys and adolescents—although it can occur at any age—with the torsion occurring inside the tunica vaginalis (intravaginal torsion). A horizontal lie (known as the bell-clapper deformity) caused by poor posterior fixation is believed to predispose toward torsion. Torsion can also occur among neonates, but this occurs due to poor gubernacular fixation and twisting of the cord outside the tunica vaginalis (extravaginal torsion). Neonatal torsion classically is associated with a prolonged labor. The testicle is very firm, nontender, and there can be a dark ecchymotic look

about the scrotum. Successful salvage is very rare in perinatal torsion, and exploration is controversial due to anesthesia concerns. Because of the very low salvage rate, some do not advocate an emergent exploration, while others suggest that if it is anesthetically safe, exploration is important because it establishes definitively not only the state of the suspected torsed testicle but allows fixation of the contralateral testicle. Metachronous torsion can occur and is difficult to monitor clinically. Exploration and preemptive fixation can prevent loss of the contralateral testicle.

The presentation is a sudden onset acute unilateral scrotal pain. The pain can be intense and lead to nausea and vomiting. With time, there will be increasing swelling and discoloration. The signs and symptoms will evolve over time. Initially there can be little swelling or redness. Later when the nerve endings have died, the testicle and scrotum may still be swollen and ecchymotic but less painful. Various clinical clues may help guide physical examination. These include a noticeably shortened spermatic cord, absence of a cremasteric reflex, and lack of relief of discomfort with elevation, but these are often of limited practical use when faced with an anxious patient with a tender scrotum. If one has a strong clinical suspicion based on presentation, and there are no other medical or anesthetic reasons not to go to surgery, emergent exploration—without any further imaging is appropriate. Doppler ultrasound—now readily available in most modern emergency departments—can be useful but should not delay exploration. Ultrasound can help identify other cases of acute scrotum such as torsed appendix testis, epididymitis, hernia/hydrocele, and idiopathic scrotal edema. Exploration is done through a transverse scrotal incision in each hemiscrotum or a vertical incision along the median raphe. If the testicle is necrotic, it should be removed to alleviate pain, and the contralateral testicle explored and sutured inside the scrotum in three to four quadrants to prevent future torsion. If a safe surgery is not an option, one may attempt a manual detorsion with a cord block. Untwisting as if one were opening a book (inside out) is the most commonly recommend technique, but it is by no means certain. Immediate exploration is recommended even if there is relief with manual detorsion.

Figure 102.17 Left intravaginal testicular torsion. The nontorsed contralateral testicle is also explored and secured to prevent future torsion.

When the Müllerian ducts atrophy in males, they can leave a remnant as a testicular appendage on the head of the testis. These can twist and mimic a full torsion. In pale-skinned patients, the torsed appendage during early presentation can resemble a painful small blue dot that is seen through the stretched skin. Because the appendage is vestigial and functionally useless, its torsion is managed with pain relief, anti-inflammatories, and exertion restrictions.

9 Prepubertal Testicular Tumors

There is a separate chapter that discusses common childhood tumors.[34] For this chapter, we will limit our discussion to prepubertal testicular tumors. Most testicular tumors are nonseminomatous germ cell tumors. They usually present as a distinct palpable painless mass in the scrotum. They can have a reactive hydrocele, and it is important to palpate the entire testicle before

assuming that the hydrocele is harmless. The primary imaging study is a scrotal ultrasound and biomarkers. The two most useful biomarkers are the alpha-fetoprotein (AFP) and beta-HCG. The most common types of prepubertal tumors are teratoma and yolk sac. Teratoma is benign in prepubertal age group. Histologically they contain all three germ layers (ectoderm, mesoderm, and endoderm). Due to the benign nature, testis-sparing approach is warranted. An enucleation of the mass through a tunica albuginea incision is performed if the frozen section confirms the diagnosis (**Figs. 102.18** and **102.19**). Yolk sac tumors are the most common malignant prepubertal tumor. Most present early as stage 1 (limited to the testicle and completely resected), and the AFP level will be elevated in the vast majority of cases. After radical inguinal orchiectomy, most are observed with serial imaging and tumor markers, provided that other staging workup is negative, with retroperitoneal lymph node dissection and systemic adjuvant chemotherapy being reserved for those with advanced disease (persistent retroperitoneal lymph adenopathy or increased serum markers). Seminomas and mixed germ cell tumors are extremely rare in prepubertal children, and their management should be as in adults. There are gonadal stromal tumors that can mimic a germ cell tumor. The most common are Sertoli cell tumors. They occur as painless masse and usually have no major endocrine effect. Simple orchiectomy is all that is needed. Leydig cell tumors are the second most common stromal tumor. They can be associated with precocious puberty, gynecomastia, and elevated levels of 17-hydroxy ketosteroids. They can be similar to hyperplastic adrenal nodules that are found in boys with poorly controlled congenital adrenal hyperplasia.

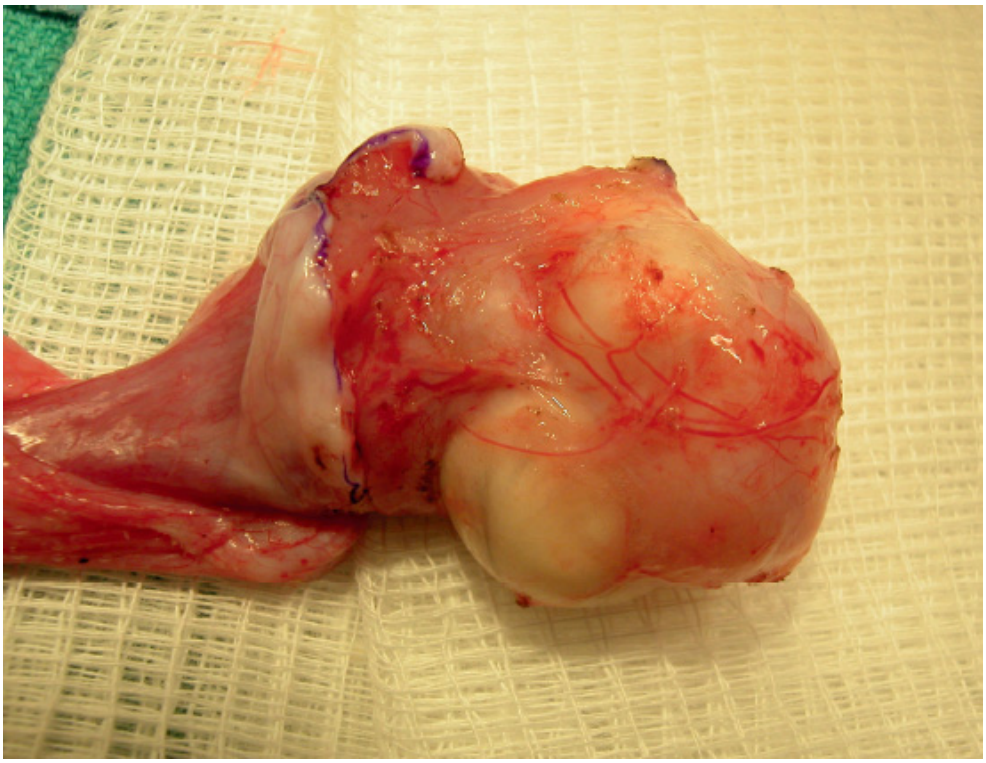

Figure 102.18 Testis-sparing enucleation of prepubertal testis tumor with cystic mass seen on the ultrasound and negative markers, likely indicating a teratoma.

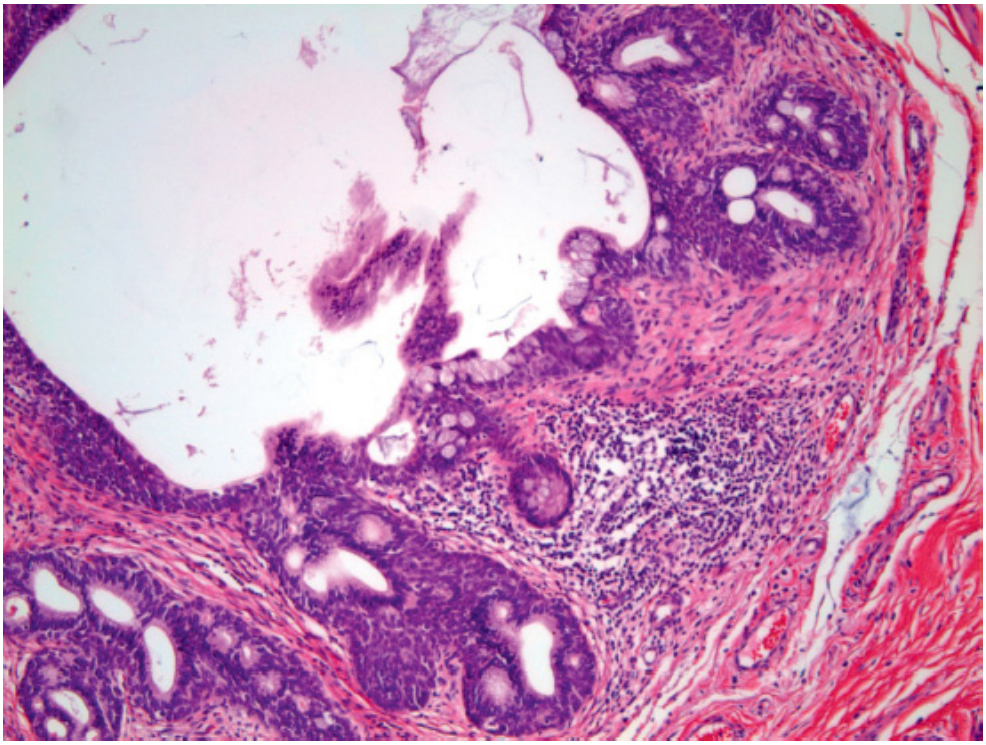

Figure 102.19 Histology of prepubertal testis tumor demonstrating mature teratomatous differentiation into ectodermal elements.

Varicocele

Varicocele is a collection of engorged varicose veins in the spermatic cord and usually is most prominent in the scrotum in the region of the pampiniform plexus. Varicoceles are graded according to their size and prominence. Grade I are varicoceles only palpable with exertion or a Valsalva maneuver. Grade II are varicoceles that can be palpated without exertion or a Valsalva maneuver and collapse when supine. Grade III varicoceles are visibly bulging and do not collapse when supine. There is also a subclinical (or grade 0) varicocele that is only detected on imaging and not on physical examination. Varicoceles are most common on the left side comprising >90% of all varicoceles. The left-sided predominance relates to the different nature of the left and right spermatic vein drainage. The right spermatic vein is shorter and inserts directly into the inferior vena cava. About 10% are bilateral. The solitary right varicocele is worrisome as it can be associated with a retroperitoneal tumor and when found warrants further evaluation with abdominal ultrasound. Varicoceles come to attention because of two major concerns. First, they can be quite sizable and uncomfortable. Second, varicoceles are associated in some cases with infertility. This is believed to be the result of two effects. The pooling of venous blood allows toxic waste products to accumulate. The pooled blood in addition may also raise the temperature of the whole scrotum. Normally, the scrotum is several degrees cooler than the deep core body temperature. At random, up to 10% to 20% of all adult males can be found to have some form of varicocele. Among men who attend infertility clinics, varicocele-associated subfertility can be as high as 40%. These observations suggest that there are many men in whom a varicocele is a trivial finding, but there are some in whom it can be an important reproductive issue. For males undergoing puberty and sexual maturation, semen analysis findings are variable and unreliable in addition to ethical concerns. For this reason, the clinical indication for intervention in boys is comparative testicular volume on ultrasound. In some, the involved testicle will have a smaller volume or lag in growth. If there is a substantial volume discrepancy (20% or greater) between the testicles, surgery is warranted. If the volumes are stable and there is no major discrepancy, observation with annual ultrasounds is recommended until the age when a semen analysis can be obtained reliably. There are several methods of

treating varicoceles; including laparoscopic, subinguinal, or inguinal incision. The vas deferens and spermatic artery are identified and may or may not be spared. The varicocele veins are then ligated and the segment between the ligatures is removed. The use of an operating microscope allows sparing of the lymphatics thereby reducing the risk of postsurgical hydrocele to well under 1%.

VAGINAL ANOMALIES

Labial Adhesions

Labial adhesions are commonly incidentally detected on well child check examinations. They occur when edges of the labia minora attach in the midline and form a thin web of skin (**Fig. 102.20**). This can obstruct the normal path of the urinary stream leading to postmicturition spotting when the girl stands up. Other symptoms include dysuria or UTI. If they are asymptomatic then there is no need for treatment and they often resolve spontaneously. Treatment in very mild cases can be successfully achieved with estrogen cream applied to the surface of the webbing over several weeks. For more severe or refractory cases, surgical incision and separation under anesthesia are needed. Minor adhesion may be left alone without clinical concerns.

Figure 102.20 Labial adhesions.

Imperforate Hymen

Occasionally the hymen will be imperforate at birth. This will present with a bulging hydrocolpos and can be confused with a prolapsing ureterocele or bladder tumor (such as sarcoma) (**Fig. 102.21**). Ultrasound or MRI can usually identify the prominent fluid-filled vagina. Puncture and drainage are

usually all that is required. In some older patients the condition may not be diagnosed until after the onset of menses. At this time, there may be cyclic discomfort due to the inability to allow the menstrual flow to pass creating a hydrometrocolpos. After a complete workup surgical drainage in the operating room is advisable to avoid introducing bacteria into the sterile collection; an infection can lead to pyocolpos or pyometrium leading to scarring and affecting future fertility.

Urogenital Sinus Anomalies

Between the fifth and seventh week of fetal development the urogenital sinus forms.[35] The caudal portion forms the lower-third of the vagina. The Müllerian ducts form the uterus as well as fallopian tubes. Anomalies can occur as part of DSD conditions resulting in either vaginal agenesis or urogenital sinus (such as that seen in masculinized females with congenital adrenal hyperplasia). Surgical reconstruction is usually required to create distinct urethral and vaginal channels. Traditional surgical approach aimed at separating the vagina from the UG sinus tract and bringing it down to the perineum, has often led to vaginal vascular compromise and stenosis. Modern techniques employ urogenital sinus mobilization en bloc, keeping the urethrovaginal confluence intact. Total mobilization has been discouraged due to concern for future urinary incontinence and pelvic prolapse. A combination of partial mobilization—leaving the anterior urethral suspensory ligaments intact—and various perineal flaps can result in an excellent outcome. The Mayer–Rokitansky–Kuster–Hauser syndrome occurs in normal genotypic females with vaginal and/or uterine dysgenesis. About one-third of these patients will have associated urologic issues—the most common being unilateral renal agenesis. The diagnosis is usually made incidentally or around the age of puberty due to amenorrhea. Treatment is vaginal dilation with estrogen cream or surgical vaginoplasty if dilation fails. There are also a variety of duplication anomalies and vaginal and/or uterine septa and consultation with gynecology is advisable on the necessity and timing of intervention. Typically the goals are to relieve any obstruction to restore normal menses and to preserve reproductive potential.

Figure 102.21 Imperforate hymen.

Prune-Belly Syndrome

The prune-belly syndrome (PBS) is a constellation of malformations also known as the triad syndrome or the Eagle–Barrett syndrome.[36] The syndrome has three key components: severe deficiency or absence of the abdominal wall musculature, bilateral hydroureteronephrosis, and bilateral undescended

intra-abdominal testicles (**Fig. 102.22**). There are also other associated genitourinary conditions including renal dysplasia, fusiform urethra, large bladder, patent urachus, hypoplastic prostate, and dilated proximal urethra. The newborn will present with a lax and wrinkled abdominal wall, along with empty scrotum. Renal dysplasia is frequent and when severe, it can lead to pulmonary hypoplasia. Stillbirths and early neonatal demise often occur because of the combination of poor renal and pulmonary function. Hydroureteronephrosis can be massive but is typically nonobstructive, and no procedure should be done simply to improve appearance. Nearly all of the patients are infertile with an anecdotal report of successful fertility using the assisted reproductive technology. For infants who survive into childhood, bilateral orchiopexy and abdominal wall reconstruction may be necessary. Evaluation for bladder function is also required since many will have a poor bladder muscle tone and high postvoid residual.

Figure 102.22 Prune-belly syndrome. Notice the wrinkled appearance of the abdominal wall due to deficiency of musculature. Scrotum is empty due to bilateral intra-abdominal testicles.

10 Neurogenic Bladder

The nervous system plays an important role in modulating the normal behavior of the lower urinary tract. There are nerve roots (emanating from the spinal cord) and peripheral pelvic nerves that carry sensory and motor signals to the bladder and urethral sphincter. Injuries or anomalies to these nerves can denervate the bladder, leading to poor emptying. The spinal cord up to the brain stem is critical to regulation of lower urinary tract function, especially the thoracolumbar sympathetic and sacral parasympathetic segments. The brain stem acts as the coordinating center. With filling, the bladder musculature—under the influence of the sympathetic input—remains relaxed thereby keeping bladder storage pressures low until emptying occurs (driven by parasympathetic input). The higher centers in the cerebral cortex allow conscious control and inhibition of reflex activity. Without this influence the bladder fills, and at a certain volume it spontaneously empties with coordination. This occurs normally in infants prior to toilet training. When the higher centers are affected (such as due to a cerebrovascular accident, tumor, traumatic brain injury, or multiple sclerosis), this control is lost or diminished and many patients will report sudden urgency and loss of urinary control. When the spinal cord is affected, the bladder will lose its inhibitory control by the brain stem and cerebral cortex and will act autonomously. The bladder will contract earlier than full capacity, and it is termed hyperreflexia. The loss of coordination between bladder muscle and sphincter, leading to poor emptying is known as detrusor–sphincter–dyssynergia.

Patients with spinal cord injury, traumatic brain injury, and acquired conditions that affect the nervous system (e.g., diabetes mellitus, multiple sclerosis, varicella zoster, brain tumors, and encephalitis) should trigger awareness about possible urinary effects.[37] Mere urine egress from the bladder is not necessarily a sign of normal voiding. It can be due to overflow incontinence or some form of dysfunctional voiding (Valsalva voiding). Likewise continence is not necessarily a sign of neurologically coordinated normal bladder function. The storage pressures can be higher than normal. When the bladder urine storage pressures are too high, it can overcome the peristaltic pressure driving urine from the kidneys down the renal pelvis and ureter. Ideally the storage pressure should be below 40 cm H_2O.[38] Above this pressure, loss of renal function will occur. A urology evaluation with

urodynamic pressure–volume assessment of the lower urinary tract should be considered if there is any condition with significant effects on the central nervous system.

Spinal dysraphism is the most common congenital cause of a neurogenic bladder in children. During development the spinal column does not form properly resulting in an exposed spinal cord, and patients are born with a neurogenic bladder and other neurologic defects. Surgical closure in utero is now being done with some evidence that volitional voiding improves.[39] The goals of effective neurogenic bladder management in the pediatric population include protecting the kidneys, achieving urinary continence and independence, and avoiding or delaying reconstructive surgery. Early evaluation of bladder storage pressures is crucial. Regular, proactive bladder pressure monitoring with urodynamics, along with ultrasound assessment of the upper tracts, has shown to reduce urologic morbidity in these patients. Children who do not empty with a safe bladder pressure require CIC. Patients with poor bladder compliance and high storage pressures may need antimuscarinic bladder muscle relaxants (such as oxybutynin). For older children, achieving social continence becomes important and a variety of surgical options may be considered in addition to CIC and antimuscarinics. Surgical bladder augmentation using intestinal segments (enterocystoplasty) is the most effective way to improve the bladder storage function (**Fig. 102.23**), but there are many well-known long-term complications, such as metabolic acidosis, mucus production, UTI, bladder stones, spontaneous perforations, and malignancy. In some patients who have difficulty with urethral CIC (such as those with severe scoliosis or girls in wheelchair), surgical creation of alternate continent catheterizable channel is an option. The Mitrofanoff procedure (the classic appendicovesicostomy where the appendix is implanted into the bladder within the submucosal tunnel for continence) can improve the quality of life significantly. If the bladder outlet is inadequate, surgical options include artificial urinary sphincter, bladder neck reconstruction with sling, and bladder neck closure. Similarly, many patients will also choose the surgical option of Malone antegrade continence enema where a catheterizable channel is created into the colon using the appendix for easy, self-administration of enema for achieving fecal continence.

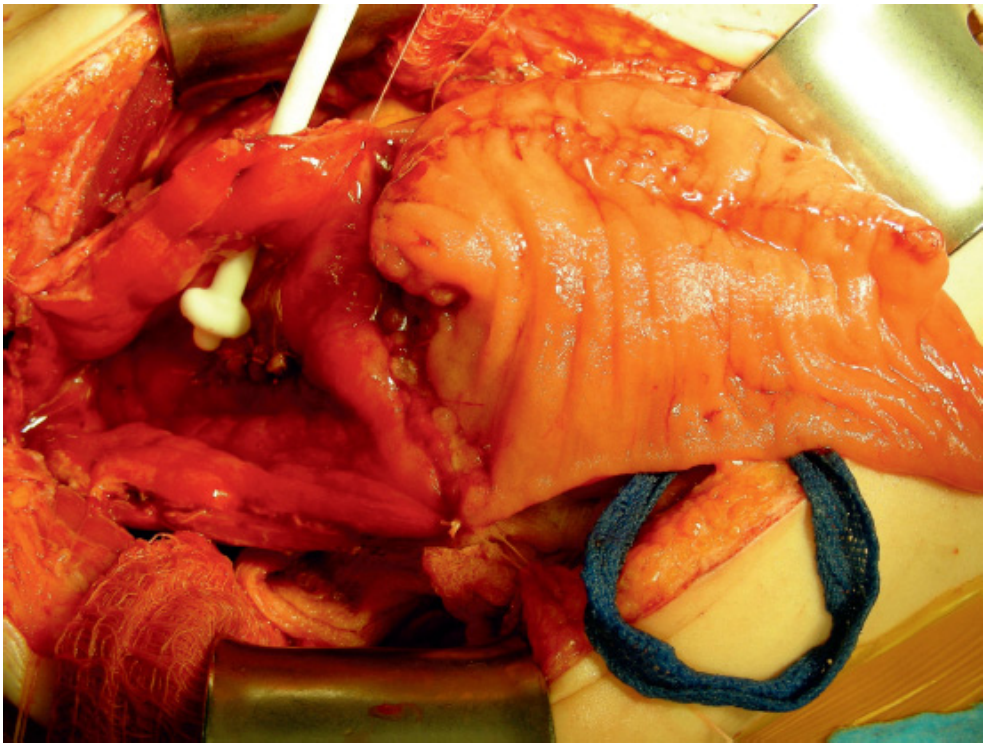

Figure 102.23 Bladder augmentation using a patch of detubularized ileum.

As children with spina bifida are living well into adulthood, consideration of long-term management of neurogenic bladder and patients with complex genitourinary reconstruction is critical. The field of transitional urology is a developing subspecialty that aims to address the needs of adolescents as the move from child-centered to adult-oriented health care.

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Childhood Tumors

Erika A. Newman

Key Points

1 Neuroblastoma occurs in the youngest of children and is the most common solid tumor in infants.

2 The landmark feature of neuroblastoma is broad clinical heterogeneity from spontaneous regression in neonates to deadly refractory metastatic disease in school-age children. This is thought to result from diverse genetic and biologic features that predict prognosis.

3 The genomic alterations that have consistently been shown to predict neuroblastoma prognosis are DNA ploidy, MYCN amplification, loss of heterozygosity (LOH) of chromosome 1p, 17q gain, loss of 14q, and loss of 11q.

4 The International Neuroblastoma Risk Group (INRG) classification system defines pretreatment cohorts based on expected survival at diagnosis. INRG classification includes INRG stage, age, histologic category, grade of tumor differentiation, MYCN status, 11q alterations, and DNA ploidy. These criteria are used to define 16 pretreatment groups that include very low-, low-, intermediate-, and high-risk categories.

5 Anaplasia is the single most important prognostic indicator in children with Wilms tumors, the second most common extracranial tumor in children.

6 In the United States, the standard of care for children with Wilms tumor starts with radical nephrectomy at the time of diagnosis for resectable primary tumors followed by chemotherapy. Radiation is administered to sites of residual and metastatic disease. Tumors with extensive intracaval and hepatic vein extension receive biopsy and neoadjuvant chemotherapy, and may require cardiopulmonary bypass for resection.

7 Treatment of rhabdomyosarcoma requires a multimodal approach that begins with complete surgical excision of resectable lesions and incisional biopsy for tumors that encroach upon contiguous

structures, blood vessels, and nerves. Modern therapies are based on prognostic factors and risk of subsequent relapse.

8 Standard surgical care for children with hepatoblastoma is complete primary resection at diagnosis for pretreatment extent of disease (PRETEXT) I and II tumors that do not involve major central venous structures. PRETEXT III and IV tumors undergo biopsy and neoadjuvant chemotherapy with early referral to a liver transplantation center for multifocal or large, central lesions.

INTRODUCTION

It is a great privilege to provide surgical oncology care for children. The surgeon is a key figure in the management of children with malignant tumors. From diagnosis through posttherapy surveillance, the surgical team has a pivotal role in ensuring the highest outcomes in the care of children with solid cancers. Surgical decisions guide clinical pathways from the mode of biopsy, central venous access for chemotherapy administration, and definitive tumor resection. Because pediatric cancers are rare with diverse presentations and histology that differ from adult cancers, the overall care of children with cancer has been improved by multidisciplinary approaches and pediatric cooperative groups set the standard in current oncologic care. The Children's Oncology Group (COG) and the International Society of Paediatric Oncology (SIOP) have made significant progress in clinical and basic science studies of pediatric malignancies and current pediatric tumor care is based upon treatment standards established through phase 1 to 3 clinical translational trials. It is a universal goal that every child diagnosed with cancer be enrolled in a cooperative group clinical trial. These trials are aimed at further understanding pediatric tumor biology and for evolving innovative treatments that have recently led to drastic rises in survival rates for various malignancies.

Compared to adults, the classification of childhood cancer is based on tumor morphology rather than emphasis on primary site in adults. The current classification scheme is the International Classification of Childhood Cancer,

Third Edition (ICCC-3) based on the third edition of ICD-0-3.[1] The ICCC-3 classifies tumors into 12 main groups that are further characterized into 47 subgroups and is used for population-based epidemiologic studies and cancer registries such as the Surveillance, Epidemiology, and End Results (SEER) program, administered by the National Cancer Institute (NCI). Utilization of a standard classification system is useful for comparing incidence and survival across regions and time periods.

INCIDENCE OF CHILDHOOD SOLID TUMORS

Each year in the United States, approximately 12,400 children and adolescents younger than 20 years of age are diagnosed with cancer. Cancer is the most common cause of disease-related mortality in children, with approximately 2,500 children dying each year. Leukemia is the most common cancer diagnosis for children 1 to 5 years of age, 5 to 9 years of age, and 10 to 14 years of age, while neuroblastoma is the most common cancer in infants. For 15 to 19 year olds, lymphomas are the most common diagnosis. Pediatric solid tumors are a spectrum of different malignancies and behind neuroblastoma, Wilms tumor is the second most common extracranial solid tumor followed by rhabdomyosarcoma. In general, there have been no large increases or decreases in pediatric cancer incidence in the last several decades when improvements in diagnostic modalities such as magnetic resonance imaging (MRI) and ultrasound are taken into consideration.

In the United States, the cancer survival rate in children has improved over time. This is largely due to multidisciplinary approaches to pediatric oncology care. There have been steady improvements in survival for childhood renal tumors, retinoblastoma, and lymphomas since the beginning of the SEER program. Although mortality rates have declined steadily for nearly all major childhood cancer categories, survival rates for high-risk tumors like neuroblastoma and rhabdomyosarcoma have not had the same survival successes.[2] Targeted immunotherapies and tumor genomic sequencing are new innovative treatment strategies that have recently provided hope for improving outcomes in resistant and refractory cases.

NEUROBLASTOMA

Epidemiology and Genetic Risk

1 In the United States, approximately 700 children are diagnosed with tumors of the sympathetic nervous system each year and of these, 650 are neuroblastoma. Neuroblastoma is the most common cancer in infancy and the most common extracranial tumor in all children. The disease accounts for 7.2% of cancers in children younger than 15 years of age. The incidence of neuroblastoma is slightly higher among males than females and is highest among Caucasians from North America, Europe, Australia, and Israel.[3] The most recent SEER data reported minimal changes in neuroblastoma incidence in the last five decades. The overall survival rate for neuroblastoma is 65% based upon SEER data from 1985 to 2000 and the disease continues to represent approximately 15% of all pediatric cancer deaths.[4,5] There is variability in 5-year survival rates based on age and stage. Survival is highest among infants and children with localized and regional disease. Black and Native American patients with neuroblastoma were found to have a higher prevalence of high-risk neuroblastoma compared with white patients, and have worse event-free survival.[6] The underlying genetic and biologic basis of this disparity is not known and warrants further study.

No causal factors for neuroblastoma have been identified. Studies examining maternal risks have been conflicting for prior miscarriage, induced abortion, repeat Cesarean birth, and vaginal infection.[7] There have been international case series reporting the use of maternal hormones for bleeding and ovulation induction. The largest study to date did not find significant association with infertility hormonal use, although results suggested an elevated risk of neuroblastoma in male offspring after maternal Clomid use.[8] These results warrant further evaluation but may serve as the focus of larger clinical studies. Parental occupation and environmental exposures have been studied.[9] They suggest that the risk of several industrial occupations, particularly power plant operators, painters, and electronic-related fields should also serve as lead points for further study. A case-control study investigating parental tobacco smoking and alcohol consumption did not find any evidence for lifestyle exposures and increased risk of neuroblastoma.[10] Associations between premature delivery (<33

weeks), very low birth weight (<1,500 g), and neuroblastoma have been observed but results are inconsistent.[7] Further investigations of parental and perinatal risk factors are required in order to draw definitive conclusions.[11]

Most cases of neuroblastoma are sporadic and data for inheritance patterns are conflicting. There are studies that link neuroblastoma occurrence with other neural crest cell anomalies such as Hirschsprung disease, neurofibromatosis, and central hypoventilation syndrome.[12] These syndromes are components of the neurocristopathies and are considered alterations in neural crest cell development that may occur with inherited loss of function mutations of PHOX2B, a regulator of autonomic nervous system development.[13,14] Despite these findings, there is not a strong pattern of inheritance of neuroblastoma and only 1% to 2% of cases are familial in an autosomal dominant manner.[15,16] Recently genome-wide sequencing studies have located heritable mutations in the anaplastic lymphoma kinase (ALK) gene as the cause of most hereditary neuroblastoma cases, the first example of a pediatric cancer arising due to a mutation in a critical oncogene.[17] Given this, genetic testing for ALK and PHOX2B should be considered in children with a family history of neuroblastoma. It is recommended that children in families found to have heritable mutations in ALK or PHOX2B undergo screening surveillance with ultrasound and urinary catecholamine metabolites.

ALK copy number mutations are also somatically acquired and highly associated with an aggressive clinical phenotype in 5% to 15% of neuroblastoma tumors.[18,19] Genome-wide association studies in sporadic cases of neuroblastoma have also recently discovered susceptibility genes that include FLJ22536, NBPF23, and BARD1 that may increase the relative risk of malignant transformation of developing neuroblastic tissue.[20–23] In general, there is a relative paucity of recurrent somatic mutations in neuroblastoma and the majority of tumors are likely driven by rare germline variants, copy number alterations, and epigenetic modifications.[23]

Pathology and Biologic Features

Neuroblastoma originates from embryonic cells of the neural crest that appear along the distribution of sympathetic nervous tissue from the neck to pelvis, most commonly in the adrenal medulla. The precise molecular

mechanisms that give rise to embryonic neural crest cells that in turn give rise to neuroblastoma are unknown. The current thinking is that defects in genes that control neural crest differentiation and proliferation underlie tumorigenesis. Peripheral neuroblastic tumors are categorized on a spectrum from malignant neuroblastoma to ganglioneuroblastoma and benign ganglioneuroma. 2 Neuroblastoma tumors have diverse clinical heterogeneity from complete spontaneous regression in neonates to resistant metastatic disease in school-age children. The origins of this disparity are unknown but may be explained by a spectrum of genetic and biologic features that are used to stratify patients for treatment.

Neuroblastoma generally occurs in the youngest of children with a median age of presentation of 19 months.[24] The age at which a child is diagnosed with neuroblastoma is an indicator of biologic features and clinical course. Neonates and infants younger than 18 months of age are more likely to have disease that either spontaneously regresses or is cured without cytotoxic therapy. In contrast, older children are more likely to have refractory metastatic disease and are at high risk for death despite multimodal cytotoxic therapies. Age contributes to prognosis in a continuous manner with the optimal age cutoff between 15 and 19 months.[24] Much of this discrepancy in outcome of neuroblastoma is thought to be associated with underlying tumor biology because there is an association between age and other biologic factors such as MYCN amplification and histopathology. Given this, accurate and complete molecular analysis of neuroblastoma tumor specimen is an important factor in treatment planning and risk stratification.

Cellular heterogeneity is a hallmark of neuroblastoma. Neuroblastic small, round blue cells with hyperchromatic nuclei characterize neuroblastoma cells with varying degrees of differentiation from immature to mature. Homer Wright pseudorosettes that palisade around blood vessels and neuritic processes are characteristic (**Fig. 103.1**). Neuroblastoma cells stain for neuron-specific enolase (NSE), synaptophysin, NB84, and tyrosine hydroxylase, a neural protein-staining pattern that differentiates neuroblastoma from other childhood tumors with similar small round blue cells.

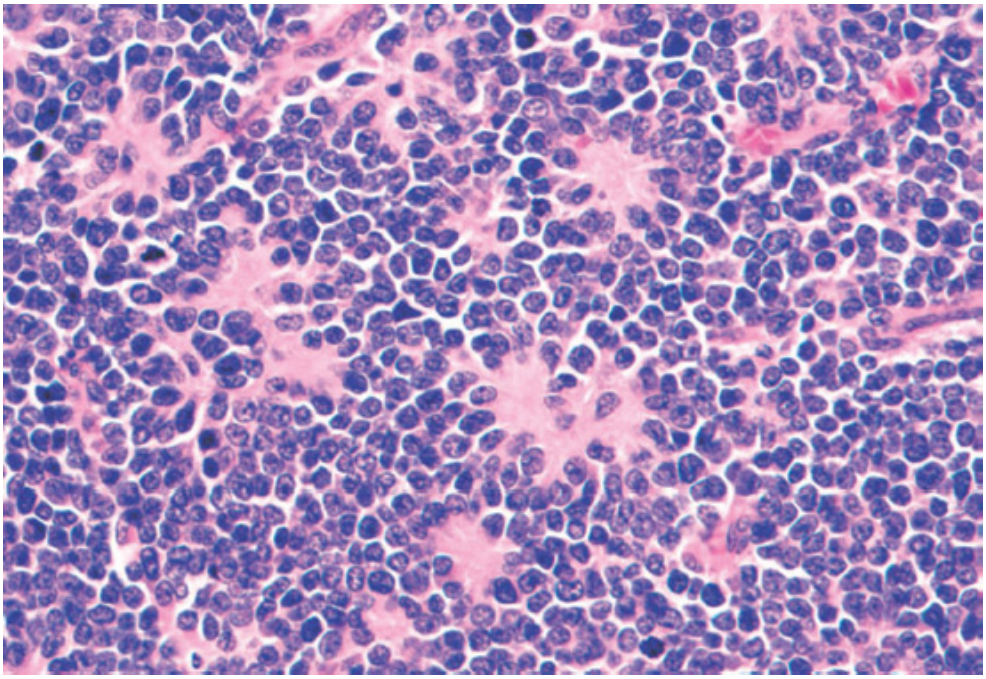

Figure 103.1 Typical neuroblastoma with small round blue cell features and Homer Wright pseudorosettes that palisade around blood vessels.

Treatment strategies for children with neuroblastoma are largely based on risk as determined by histopathologic and biologic characteristics of the tumor. The Shimada histopathologic classification system is the most widely accepted standard for microscopic evaluation of neuroblastoma tumors and distinguishes favorable and unfavorable clinical groups. The International Neuroblastoma Pathology Classification System was developed based on the original Shimada system.[25] Morphologic features of neuroblastic differentiation, schwannian stromal development, mitosis–karyorrhexis index (MKI), and patient age at diagnosis determines the important distinction between favorable and unfavorable histology (**Table 103.1**).

In addition to histopathology, combinations of prognostic features are utilized for risk assignment and treatment stratification. The DNA content (DNA index or ploidy) is the amount of DNA within the nucleus of tumor cells compared to normal cells and is an important indicator of treatment success. DNA index is determined by flow cytometry or by cytogenetic analysis. Hyperploidy or near-triploid tumors (DNA index >1) are whole chromosome gains and losses without structural genetic alterations and are associated with a better response to chemotherapy.[26] In contrast, diploid

tumors are characterized by segmental chromosomal alterations and predict poor response to therapy.

Table 103.1 Shimada Histopathologic Classification of Neuroblastoma

Favorable
Stroma rich, all ages, no nodular pattern
Stroma poor, age 1.5–5 yrs, differentiated, MKI <100
Stroma poor, age <1.5 yrs, MKI <200
Unfavorable
Stroma rich, all ages, nodular pattern
Stroma poor, age >5 yrs
Stroma poor, age 1.5–5 yrs, undifferentiated
Stroma poor, age 1.5–5 yrs, differentiated, MKI >100
Stroma poor, age >1 yr, MKI >200
MKI, mitosis–karyorrhexis index (number of mitoses and karyorrhexis per 5,000 cells)

Reprinted from Shimada H, Ambros IM, Dehner LP, et al. The International Neuroblastoma Pathology Classification (the Shimada system). *Cancer* 1999;86(2):364–372. Permission granted for previous edition.

The MYCN oncogene is a transcription factor located on chromosome 2p and also predicts survival and risk in neuroblastoma. The amplification of MYCN is the best characterized genetic abnormality, occurring in approximately one-third of neuroblastoma patients.[27,28] Significant amplification of MYCN within tumor cells (more than 10 copies detected by fluorescent in situ hybridization) reliably predicts poor survival and advanced-stage disease. Though the molecular mechanism of MYCN amplification is unknown, targeted expression in transgenic mice leads to the development of neuroblastoma tumors.[29] Enhanced expression of MYCN increases proliferation and confers growth potential both in vitro and in vivo, adding to the notion that MYCN has a critical role in neuroblastoma tumorigenesis.[30] Approximately 30% of neuroblastoma tumors have MYCN amplification, and of these, 90% are high-stage or refractory to multimodal cytotoxic therapies.[31]

Nerve growth factor (NGF) and its receptor tyrosine kinase (TRK) also correlate with disease outcome in neuroblastoma tumors. The TRK receptors are thought to have a role in regulating growth and differentiation of normal nerve cells and have been implicated in neuroblastoma pathogenesis. The expression of TRK-A, a transmembrane tyrosine kinase that is required for high-affinity binding of NGF, is strongly predictive of a favorable outcome in neuroblastoma tumors.[32,33] TRK-B, the receptor for brain-derived neurotrophic factor (BDNF) is preferentially expressed in neuroblastoma tumors with MYCN amplification while TRK-C, the primary receptor for neurotrophin-3 (NT-3) mirrors TRK-A and is expressed primarily in lower-stage tumors with favorable outcomes.[33] The absence or lack of TRK-A correlates inversely with MYCN amplification and reliably predicts poor overall survival. Differential expression of TRK-A and TRK-B indicate that NGF receptors may function in growth arrest and differentiation in neuroblastoma tumors, critical factors that may have a role in clinical course.[34]

3 Several nonrandom genomic imbalances have been identified in neuroblastoma and the presence of segmental chromosome alterations is the strongest predictor of neuroblastoma relapse.[35] The loss of heterozygocity (LOH) of chromosome 1p is a reliable prognostic factor in neuroblastoma tumors that is independent of age and stage. The loss of 1p identifies patients who are at high risk of poor survival outcomes despite otherwise favorable biologic predictors (stage 1, 2, and 4S disease).[36] LOH at 1p is most clinically valuable in predicting patients at high risk of death in the subgroup of patients without MYCN amplification, specifically those with low-stage disease.[36] Gain at 17q most commonly occurs with loss of 1p in an unbalanced translocation. Unbalanced gain of chromosome arm 17q is the most frequent segmental genetic alteration in neuroblastoma cells and is also associated with adverse outcomes.[37] The gain of 17q is strongly associated with other negative risk factors including age of more than 1 year, presence of high-stage disease, MYCN amplification, and diploidy. The most likely candidate genes involved at 17q are NM23 and BIRC5 (surviving gene).[38] Chromosome 11q loss is found in approximately 40% of neuroblastoma patients and is associated with high-risk disease features and decreased survival.[39] Similar to loss of chromosome 1p, loss of 11q is independently associated with decreased survival in the subgroup of patients with low-

stage disease and in patients without MYCN amplification. In all, the genomic alterations that have consistently been shown to predict prognosis are DNA ploidy, MYCN amplification, loss of chromosome 1p, 17q gain, loss of 14q, and loss of 11q. A systematic review of prognostic tumor markers and meta-analysis showed that of these, MYCN amplification and DNA ploidy have the strongest prognostic impact.[40]

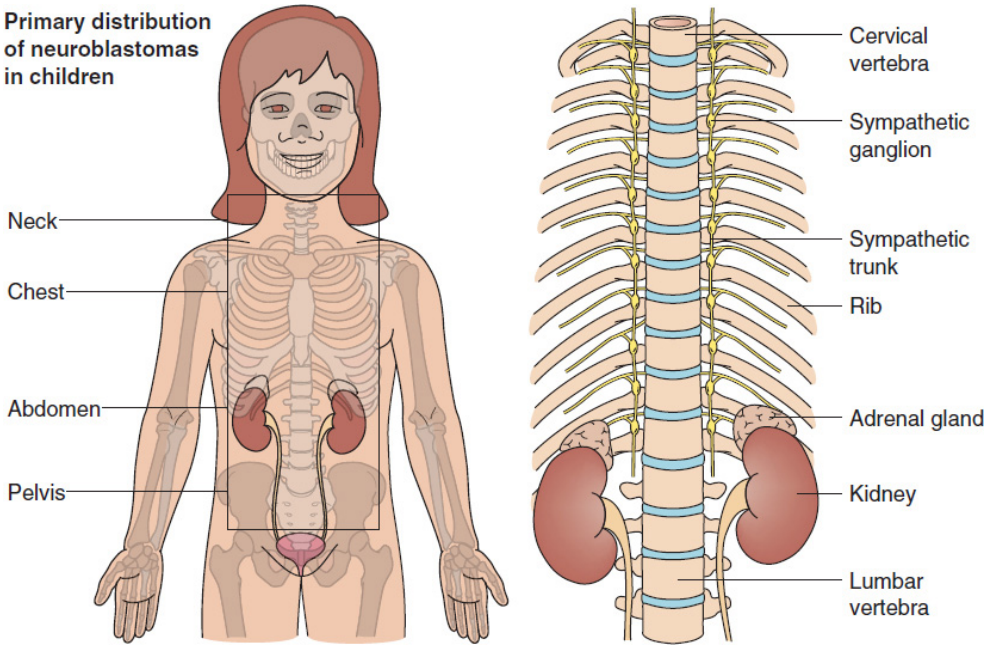

Figure 103.2 Primary distribution of neuroblastoma tumors in children.

Presentation, Diagnosis, and Staging

The majority of children with neuroblastoma are diagnosed at less than 4 years of age, with median age between 19 and 22 months. Forty percent of tumors occur in the adrenal medulla with the remaining occurring in the neck, chest, abdomen, and pelvis along the sympathetic chain. The organ of Zuckerkandl is the second most common site of neuroblastoma of abdominal origin. Compared to older children, infants are more likely to present with thoracic and cervical primary sites. Tumors at the sympathetic chain along the spinal column may expand into the intraforaminal spaces and can cause spinal cord compression (5% to 15% of patients) (**Fig. 103.2**). More than half of patients may present with regional or distant spread through lymphatic and hematogenous routes. Metastatic disease most commonly involves

regional lymph nodes, bone marrow, and cortical bone. The most common cortical bone sites are metaphyseal, skull, and the orbit. Patients with orbital bone metastases commonly present with perioribtal ecchymosis and swelling (raccoon eyes) and cortical bone metastases may result in generalized bone pain and limping. Liver metastases occur most commonly in patients with stage 4S tumors. Neonates with stage 4S neuroblastoma may present with massive hepatomegaly, respiratory compromise, and abdominal compartment syndrome requiring urgent surgical intervention. Incidental findings on prenatal ultrasound may identify fetal neuroblastoma and there may be associated maternal signs of catecholamine excess with excessive sweating, headaches, flushing, or anxiety.[41]

Most often patients with localized disease are asymptomatic with tumors diagnosed on routine physical examinations or testing for other medical conditions. In contrast, children may have a mass or abdominal distention as presenting symptoms. There are several well-documented clinical syndromes that can be present at diagnosis of neuroblastoma. Opsoclonus/myoclonus syndrome and or ataxia can occur in children with neuroblastoma and present as irregular jerking movements of the muscles. The underlying mechanism of opsoclonus is unknown but an immunologic mechanism–related antineuronal antibody is likely and patients may have late neurologic sequelae despite tumor removal.[42] The condition may be treated with adrenocorticotrophic hormone (ACTH), with plasmapheresis and intravenous gamma globulin reserved for refractory cases.[43] Most patients with opsoclonus/myoclonus syndrome tend to have localized disease and excellent survival. Up to 50% of patients with opsoclonus/myoclonus syndrome are found to have neuroblastoma tumors while only a small percentage of neuroblastoma patients present with opsoclonus. Neuroblastoma tumors that occur in the neck or upper chest may present with Horner syndrome (ptosis, miosis, anhidrosis), symptoms that may not go away with surgical excision.

Perinatal Neuroblastoma

The improvement of ultrasound and maternal imaging techniques has increased the diagnosis of neuroblastoma within the fetal and neonatal periods. Most perinatal tumors are located within the adrenal gland and are localized tumors. Upon detection, tumor growth is monitored with serial

ultrasound prior to birth and maternal care proceeds to assure optimal health of the mother. As long as there are no complications, pregnancy is carried to term. Nearly all perinatal cases have favorable biology without adverse prognostic indicators, including non-MYCN amplification. Several lines of evidence suggest that small, localized adrenal tumors detected during the perinatal period may be managed with expectant observation without surgical resection.[44–46] Given the considerable evidence of spontaneous regression in this subset of neuroblastoma tumors and the risk of adrenal surgery in infants, the COG conducted a prospective trial (ANBL00P2) of expectant observation of infants diagnosed within the first 6 months of life.[47] This study found that observation of small adrenal masses in infants younger than 6 months, without biopsy and without surgical resection was safe with excellent event-free and overall survivals. Adrenal tumors less than 3 cm (16 mL) if solid or 5 cm (65 mL) if ≥25% cystic are safely monitored with ultrasound volume measurements, computerized tomography (CT) scan, and urine catecholamine metabolite levels. If there are signs of tumor growth or dedifferentiation, the patient is referred for surgical resection without risk of upstaging of disease.

Diagnosis

The diagnosis of neuroblastoma requires an adequate biopsy specimen and a pathologist experienced with pediatric tumors. The diagnosis is established with histologic confirmation from either tissue biopsy or the presence of tumor cells within a bone marrow biopsy and increased urinary catecholamine metabolite levels. The majority of patients with neuroblastoma have elevated urinary vanillylmandelic acid (VMA) and homovanillic acid (HVA) levels and these should be evaluated during the diagnostic workup. Complete blood count and serum chemistries are evaluated as components of initial diagnostics. Levels of lactate dehydrogenase (LDH), ferritin, and neuron-specific enolase (NSE) are biologic markers that may indicate poor prognosis in patients with neuroblastoma.[48,49] Elevated ferritin (>150) and LDH (>1,000) may indicate increased risk of adverse outcomes. More than half of patients present with metastatic disease at presentation therefore initial evaluation should include cross-sectional imaging by either CT scan or MRI to define the primary

tumor size and to determine regional or distant spread (**Fig. 103.3**). Calcifications are commonly detected on imaging in patients with neuroblastoma and the mass tends to displace structures inferiorly and toward the midline. Unless the patient has neurologic symptoms, or an abnormal neurologic examination, lumbar puncture or brain imaging is not indicated. Sympathetic nervous tissue concentrates metaiodobenzylguanidine (MIBG), an analog of norepinephrine. Radioactive iodine–labeled MIBG scan is utilized in neuroblastoma staging and is used to determine treatment response.[50] MIBG scan is accurate in detecting metastatic spread, particularly cortical bone disease that may have otherwise been missed by traditional imaging techniques. Posterior iliac crest aspirates and core biopsies are required as a component of initial diagnostic testing to exclude bone marrow involvement. PET scanning or bone scans may be utilized in patients with non-MIBG avid disease.

Figure 103.3 Computerized tomography (CT) scan of a child with stage 3 neuroblastoma, crossing the midline displacing the aorta, vena cava, kidney, pancreas, and spleen.

Staging

Standard staging criteria allows physicians to tailor treatment plans based on patient risk. Until recently, the International Neuroblastoma Staging System (INSS) was the most widely accepted surgical/pathologic staging system and was established in efforts to standardize risk-group stratification by cooperative groups[51] (**Table 103.2**). INSS was largely based on the surgeon's definition of resectability and surgical approach to the primary tumor and lymph nodes. There is international variation in surgical decision making and approach to locoregional disease that may alter the prognostic value of INSS staging. This has made the performance and comparison of international clinical trials difficult. Moreover, biologic prognostic factors have become increasingly important in treatment planning and risk stratification. To address this, the European International Society of Pediatric Oncology Neuroblastoma Group proposed radiographic characteristics of the primary tumor as useful predictors of resectabil-ity and risk for developing postoperative complications (International Neuroblastoma Risk Group Staging System [INRGSS]).[52] INRGSS determines the extent of locoregional disease by the presence or absence of image-defined risk factors (IDRFs) (**Table 103.3**).[53] Stage L1 tumors are localized tumors that are confined within one body compartment and do not involve vital structures or major blood vessels, without any IDRF. L2 tumors are locoregional tumors with one or more IDRF that may involve ipsilateral continuous body compartments and have lower event-free survivals compared to L1 tumors. Stage M is distant metastatic disease and MS is limited to children less than 18 months with skin, liver, and/or bone marrow metastases (**Table 103.4**). The benefit of INRGSS is that treatment stratification is based on preoperative diagnostic imaging, rather than variable operative approaches. INRGSS now functions as one of the seven prognostic factors in the new 4 INRG pretreatment classification system.[54] The INRG classification system defines pretreatment patient cohorts based on expected 5-year event-free survival at the time of diagnosis. INRG classification includes INRG stage, age, histologic category, grade of tumor differentiation, MYCN status, 11q alterations status, and DNA ploidy. These criteria are used to define 16 clinically different pretreatment groups that include very low–, low-, intermediate-, and high-risk categories (A-R) in terms of 5-year event-free survivals of >85%, >75% to ≤85%, ≥50% to ≤75%, and <50%, respectively. These clinical categories may further assist physicians and

cooperative groups in risk-group stratification based on reliable expected event-free survival cutoffs. Importantly, INRG classification will allow comparison of international risk-based clinical trials with potential to enhance international collaborative efforts (**Table 103.5**).

Table 103.2 International Staging Criteria for Neuroblastoma

Stage	Criteria	Overall Survival (3 yrs) (%)	Event-free Survival (3 yrs) (%)
1	Localized tumor, complete gross resection with or without microscopic margin, all identified ipsilateral and contralateral lymph nodes negative	97	88
2A	Unilateral tumor, incomplete resection, negative lymph nodes	87	72
2B	Unilateral tumor, incomplete or complete resection, positive ipsilateral but negative contralateral lymph nodes	86	63
3	Infiltration of tumor across the midline with or without ipsilateral lymph node involvement; unilateral tumor with contralateral lymph node involvement, midline tumor with bilateral lymph nodes positive	62	58
4	Distant metastases to lymph nodes, bone marrow, cortical bone, liver, other organs	<40	<40
4S	Localized primary tumor with distant metastatic disease to liver, skin, bone marrow only (<10% involvement), typically neonatal presentation	75	75

Table 103.3 Image-Defined Risk Factors (IDRFs)

Ipsilateral tumor extension within two body compartments (neck/chest, chest/abdomen, abdomen/pelvis)
Neck Tumor encasing carotid, vertebrals, internal jugular vein Tumor extending to base of skull Tumor compressing trachea
Cervicothoracic junction Tumor encasing brachial plexus roots Tumor encasing subclavian vessels, carotid or vertebral artery Tumor compressing trachea
Thorax Tumor encasing the aorta or major branches Tumor compressing trachea or main bronchi Lower mediastinal tumor, infiltrating costovertebral junction between T9–T12
Thoracoabdominal Tumor encasing the aorta and/or vena cava
Abdomen/pelvis Tumor infiltrating the porta hepatis or hepatoduodenal ligament Tumor encasing branches of the SMA at the root Tumor invading one or both renal pedicles Tumor encasing the aorta and/or vena cava Tumor encasing the iliac vessels Pelvic tumor crossing the sciatic notch
Intraspinal tumor extension More than one-third of the spinal canal in the axial plane is invaded and/or the perimedullary leptomeningeal spaces are not visible, and/or the spinal cord signal is abnormal
Infiltration of adjacent organs/structures Pericardium, diaphragm, kidney, liver, duodenopancreatic block, mesentery
Conditions to be recorded but not considered IDRFs

	Multifocal primary tumors, pleural effusion with/without malignant cells, ascites with/without malignant cells

Montclair T, Broduer GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report. *J Clin Oncol* 2009;27:298–303.

Table 103.4 International Neuroblastoma Risk Group Staging System

Stage	Description
L1	Localized tumor, not involving vital structures as defined by the list of image-defined risk factors (IDRFs) and confined to one body compartment
L2	Locoregional tumor with presence of one or more IDRFs
M	Distant metastatic disease (except MS)
MS	Metastatic disease in children <18 mo with limited metastases at skin, liver, and/or bone marrow

Montclair T, Broduer GM, Ambros PF, et al. The International Neuroblastoma Risk Group (INRG) Staging System: An INRG Task Force Report. *J Clin Oncol* 2009;27:298–303.

Treatment

The treatment of neuroblastoma requires a multidisciplinary approach in order to assure the most optimal outcomes. Treatment is often multimodal with surgery, chemotherapy, radiation, bone marrow/stem cell transplantation, and immunotherapy. Risk-group assignment is essential for surgical and medical treatment decisions, as therapies are specifically tailored to risk. Patients are categorized based on INRG classification as non–high risk (very low, low, intermediate) or high risk. In general, the overall goal is to minimize surgical risks and to limit exposure to chemotherapy in patients with localized disease and favorable biologic features.

In the United States, the current treatment for children with neuroblastoma is guided by protocols established by the COG and it is recommended that

every child be enrolled on a clinical trial. ANBL00B1 is the most recently opened COG study that will determine risk stratification and treatment plans based on histology, MYCN amplification, ploidy, and serum analysis (https://clinicaltrials.gov/ct2/show/NCT00904241). This study will also further investigate other tumor biologic properties including the prevalence of segmental chromosomal alterations 1p, 11q, 14q, and 17q and analyze for independent clinical significance compared to standard prognostic indicators such as MYCN, INSS, and age.

Very Low Risk and Low Risk

For tumors that are classified as very low-risk and low-risk with favorable biologic characteristics (L1, L2, non-MYCN, no 11q alteration), survival rates are >95% with surgery alone without the need for postoperative chemotherapy.[55] Children with low-risk neuroblastoma are treated based on results of the COG Study P9641 that demonstrated excellent survival rates in asymptomatic low-risk patients with stages 1, 2a, and 2b neuroblastoma after surgery alone.[56] The study demonstrated 3-year overall survival of ≥95% with surgery alone in patients with low-risk, favorable histology disease. The goal of surgery in low-risk patients is complete surgical resection without compromising surrounding organs or blood vessels.

Surgical standards for low-risk neuroblastoma are to establish diagnosis and to resect as much tumor as safely possible without damage to contiguous structures or major blood vessels. Sampling of nonadherent regional lymph nodes and obtaining adequate tissue for biologic studies is critical. Chemotherapy in this group is reserved for patients who relapse or have treatment failure. Chemotherapy is also for patients with less than partial primary tumor resection (<50%), disease that compromises organ function or is life-threatening, and patients at risk of developing spinal cord compression. If utilized, low-dose chemotherapy is platin-based (carboplatin), cyclophosphamide, doxorubicin, and etoposide. Chemotherapy is 6 to 24 weeks depending upon patient age, weight, and extent of disease. Radiation is seldom given in this group and is reserved for patients with life-threatening symptoms.

Stage MS neuroblastoma tumors without MYCN amplification are very low–risk classification and most often spontaneously regress. Children with

MS disease require biopsy of either primary or metastatic tumor for biology studies. This subset may be spared both surgery and chemotherapy. Exceptions are patients with massive hepatomegaly causing abdominal compartment syndrome when low-dose chemotherapy and radiotherapy is given to reduce organ dysfunction. Patients with MS tumors may require decompressive laparotomy and ventilator support. In this case, attempts should be made to biopsy extra-abdominal sites and diagnosis may also be made by bone marrow biopsy. In rare and extreme life-threatening cases, treatment may be initiated based on diagnostic imaging alone.

Table 103.5 International Neuroblastoma Risk Group Classification System

INRG Stage	Age (Months)	Histologic Category	Differentiation	MYCN Aberration	11q	Ploidy	Pretreatment Risk Group
L1/L2		GN maturing, GNB intermixed					A Very low
L1		Any, except GN maturing or GNB intermixed		NA Amp			B Very low K High
L2	<18	Any, except GN maturing or GNB intermixed		NA	No Yes		D Low G Intermediate
	>18	GNB nodular; neuroblastoma	Differentiating	NA	No Yes		E Low H Intermediate
			Poorly differentiating or undifferentiated	NA Amp			H Intermediate N High
M	<18 <12 12–<18 <18 >18			NA NA NA Amp		Hyperdiploid Diploid Diploid	F Low I Intermediate J Intermediate O High P High
MS	<18			NA Amp	No Yes		C Very Low Q High R High

Cohn SL, Pearson ADJ, London WB, et al. The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report. *J Clin Oncol* 2009;27(2):289–297.

Intermediate Risk

The intermediate-risk group encompasses a broad spectrum of neuroblastoma tumors. The survival rate for patients in this group is between 75% and 90%. All patients in this subgroup receive surgery and chemotherapy. The goals of surgical resection are similar to low-risk cases, to establish the diagnosis with enough tissue for histologic and genetic testing with the most complete tumor resection, preserving organ function. If the primary tumor is resectable

without damage to surrounding organs and major blood vessels, then full resection is performed with lymph node sampling for staging upfront. Many patients in the intermediate-risk group will have locoregional disease that encroaches upon surrounding organs and major blood vessels (aorta, vena cava, mesenteric vessels, kidney, spleen). The surgeon should defer to the INRG image-defined risk factors (**Table 103.3**) during assessment for resectability. For L2 tumors with INRG image-defined risk factors and those judged to be unresectable at diagnosis, biopsy is performed with plan for neoadjuvant chemotherapy. Delayed surgical resection after 4 to 6 cycles of induction chemotherapy minimizes surgical complications and may improve resection of the primary tumor and overall survival.[57] Moderate-dose chemotherapy for intermediate-risk tumors consists of 12 to 24 weeks of cisplatin, cyclophosphamide, doxorubicin, and etoposide. The prognosis in this subgroup depends upon patient age, tumor histology, and biologic properties. Treatment protocols for children with intermediate-risk neuroblastoma are currently based on results of the COG trial A3961. This study demonstrated a high rate of survival with biologically based treatment assignment utilizing substantially reduced duration and doses of chemotherapy agents compared with previously used intensive regimens.[58] The promising results have reduced cytotoxic therapy for patients with regional disease and favorable biologic characteristics and provided framework for ANBL0531, a COG trial that further examined reduction in cytotoxic therapy as more refined risk factors emerged.[38,59]

High Risk

High-risk neuroblastoma remains one of the most challenging problems in pediatric oncology. Survival in this group remains poor despite multimodal therapy that includes aggressive surgery, intensive cytotoxic chemotherapy, and radiation. The long-term survival is between 10% and 40%. High-risk tumors are characterized by undifferentiated neuroblasts with unfavorable histology and poor prognostic indicators (MYCN amplification, 11q alterations, and diploidy). The initial surgical management of high-risk tumors begins with an adequate operative biopsy and vascular access placement. Initial biopsy can be approached by open or minimally invasive techniques including thoracoscopy, laparoscopy, and percutaneous core

biopsy. Obtaining an adequate sample size to allow for histologic and cytogenetic studies is of utmost importance and is the primary focus when determining biopsy technique. An initial biopsy should obtain tissue greater than 1 cubic centimeter of viable tumor tissue with avoidance of placement of the specimen in formalin in order to optimize cytogenetic studies. The adequacy of the biopsy specimen should be confirmed with the pediatric pathologist before leaving the operating room. Standard treatment then begins with induction chemotherapy followed by surgical local control, myeloablative consolidation therapy, and biologic agents.

Induction chemotherapy is administered to improve tumor resectability and to decrease tumor growth. Most neuroblastoma primary tumors and bone marrow are initially sensitive to chemotherapy and will have high response rates. Standard induction therapy consists of combinations of cisplatin, cyclophosphamide, vincristine, doxorubicin, and etoposide. The response rate of induction chemotherapy correlates with survival.[60] Postinduction persistent bone lesions and bone marrow involvement predict poor overall survival.[61]

Local control is achieved with the combination of aggressive surgical resection and external beam radiotherapy to the primary tumor site. Delayed resection with postinduction chemotherapy excision of as much of tumor as safely possible offers the highest treatment success. After induction chemotherapy consisting of four to five cycles, surgical exploration with the goal of gaining local control of the primary tumor is undertaken. Although the role of primary tumor resection in high-risk neuroblastoma patients has been controversial, recent studies have shown that aggressive removal of all primary tumors in high-risk neuroblastoma patients improves survival to 50% and decreases local recurrence to 10%.[62] Gross total resection of the primary tumor is defined as the removal of all visible and palpable neuroblastoma from the primary tumor site and regional lymph node tissue. The microscopic margin is nearly always positive therefore the goal is safe gross total resection with external beam radiation therapy to the surgical bed (2,000 to 2,100 cGy).

Safe tumor dissection typically requires exposure of the great vessels and spine (**Fig. 103.4**). The incision type depends on the location of the primary tumor with thoracoabdominal or transverse abdominal for large adrenal masses and midline incision for pelvic neuroblastoma. Thoracic

neuroblastoma typically has favorable biology and better survival outcomes than abdominal tumors and surgical resection is often curative. Primary thoracoscopic gross total resection is safe in neuroblastoma tumors less than 6 cm and may yield surgical and survival outcomes similar to open thoracotomy.[63,64] Cervical chain tumors may be approached by radical neck incisions and if located at the lower cervical region or apex of hemithorax, a trap-door incision often utilized in the setting of vascular trauma may be applied.[65] Every effort should be made to preserve the vagus and phrenic nerves. In general, for all neuroblastoma resections, organs and structures should be preserved, particularly the kidney. The operative complications to avoid are excessive blood loss, kidney and renal vessel injury, damage to surrounding major blood vessels or nerves, and postoperative infection and abscess. The tumor is removed by meticulous dissection in the peritumoral capsular plane. Early control of the aorta and vena cava are essential as the major blood vessels are traced. The major blood vessels often include the celiac axis, superior mesenteric artery, renal vessels, and inferior mesenteric artery. Tightly adherent tumor to blood vessels or major nerves should be left rather than risk injury though neuroblastoma typically does not invade beyond the adventitia. At times, it is beneficial to divide the tumor over major blood vessels for safe exposure when en bloc resection is not possible at encased blood vessels. Pelvic neuroblastoma typically arises from the organ of Zuckerkandl or elsewhere along the sympathetic chain and is associated with excellent long-term survival, despite residual or microscopic disease. Injuries to the lumbosacral plexus or damage to innervation to the bowel or bladder should be avoided. Selective MRI for pelvic lesions may help define neural involvement and enhance surgical planning. Nerve stimulation may be useful when approaching the pelvic sidewall. The presence of residual tumor correlates with risk of recurrence. Patients with incomplete resection may benefit from higher-dose radiation.[66]

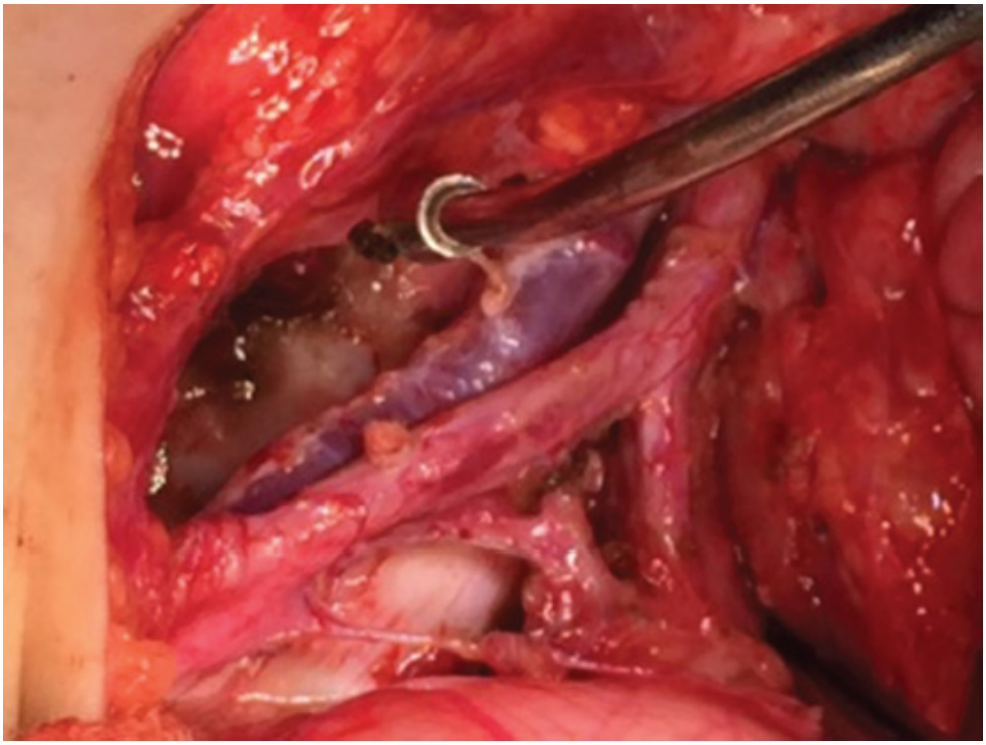

Figure 103.4 Intraoperative depiction of critical exposure during neuroblastoma resection exposing the aorta and vena cava from bifurcation distal to proximal.

Myeloablative consolidation therapy was investigated in the CCG-3891 study that demonstrated myeloablative therapy with purged bone marrow transplant improved outcome for patients with high-risk neuroblastoma.[60] The data from this trial has been confirmed with several international studies.[67] High-dose myeloablative therapy (cisplatin, etoposide, cyclophosphamide) with autologous stem cell transplantation improves outcome and progression-free survival compared to maintenance chemotherapy or observation. Over the last several decades, intensification of consolidation therapy with myeloablative doses of chemotherapy followed by autologous stem cell rescue has allowed for steady reduction in relapse rates in first remission and has now become standard of care for patients with high-risk disease.[68] The ability to harvest peripheral blood stem cells along with advances in transplant methodology has enhanced the safety of bone marrow transplantation in children.

Maintenance and biologic therapies have also improved high-risk neuroblastoma treatment. COG (ANBL0532) found that the addition of monoclonal antibody (MAB CH14.18) targeting disialoganglioside (GD2)

improved survival rates in patients with high-risk disease.[69,70] GD2 is a sialic acid–containing glycosphingolipid expressed uniformly on the surface of neuroblastoma cells. The Food and Drug Administration (FDA) approved Unituxin (dinutuximab, formerly MAB CH14.18) specifically for treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to first-line multimodality treatment (**Table 103.6**).

Future Directions

Despite advances in cytotoxic and biologic multimodality therapies, up to 60% of patients with high-risk neuroblastoma relapse and there are currently no curative salvage treatment regimens. Advances in understanding neuroblastoma tumor biology are essential for the development of novel therapies for high-risk tumors. The use of high-throughput genomic sequencing technologies will aid in patient-specific prognostic data and allow for a personalized approach to treatment. The success of anti-GD2 monoclonal antibody has launched great interest and research into improving antibody-based approaches and synergistic immunotherapies. A recent study showed promise in humanized anti-GD2 engineered to target the delivery of interleukin-2 to tumor microenvironment in patients with small tumor burden.[71] The addition of MAB CH14.18 with granulocyte/macrophage colony-stimulating factor (GMCSF), interleukin-2, and retinoic acid may prevent late relapse. Radiolabeled MIBG is also being investigated as a therapeutic agent in neuroblastoma and has a high response rate in patients with relapse and refractory disease.[50,72,73] Targeted radionucleotide has little nonhematologic toxicity though most patients experience some level of myelosuppression requiring autologous hematopoietic cell transfusion.

Table 103.6 Standard Treatment for Children with Neuroblastoma

Risk	Standard Treatment Plan
Low-risk tumors *Landmark Trials:* COG CCG P9641 trial ANBL00P2 trial	Observation Surgery alone (maximally safe resection)
Intermediate-risk tumors *Landmark Trials:* CCG A3961 ANBL0531	Chemotherapy (risk stratification, less intense, dose reduction) Surgery
High-risk tumors *Landmark Trials:* CCG 3891 ANBL0532 ANBL0032	Chemotherapy Surgery Dose intense, myeloablative chemotherapy Autologous stem cell transplant External beam radiation therapy Immunotherapy with differentiating agent

Challenges also remain in the ability to identify patients with low-risk and intermediate-risk tumors who would benefit from reduction in therapy versus those that are at risk for relapse and refractory disease. There are several large collaborative research efforts focusing on the discovery of new therapeutic targets with respect to understanding the relationship between risk and the molecular basis of neuroblastoma. One such effort is the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) program.[4] TARGET in conjunction with the Cancer Genome Atlas project conducts genomic profiling and tumor sequencing for neuroblastoma along with other pediatric solid tumors with the goal of discovering novel mechanisms that drive tumorigenesis and identifying new molecular targets for drug development.

WILMS TUMOR

Epidemiology and Genetic Risk

Various tumors arise in the kidneys in children that range from benign to malignant. Wilms tumor (nephroblastoma) is the most common renal tumor in children and is the second most common solid tumor outside of the brain in infants behind neuroblastoma. Wilms tumors occur almost exclusively in the kidney. Extremely rare extrarenal sites include the retroperitoneum, pelvis, and inguinal canal.[74] The overall incidence of Wilms tumor is 8 per million children less than 15 years of age with approximately 500 new cases per year in the United States.[4] Children most commonly present within the first 2 years of life, with nearly all diagnosed before the age of 5 years. The incidence of Wilms tumor varies by ethnicity with highest incidence in Africa and African-American children and lowest in East Asian populations.[75] The National Wilms Tumor Study (NWTS) reported the median age for Wilms tumor in boys is 36 months and 43 months for girls with unilateral tumors.[76] Bilateral Wilms tumors occur in slightly younger children with median ages of 23 months for boys and 30 months for girls. The survival of children with Wilms tumor has improved significantly over the past several decades from 30% to over 90% 5-year survival currently.[77]

Most Wilms tumors are sporadic with only 1% to 2% of cases being familial. Several genetic syndromes are uniquely associated with Wilms tumor. Sporadic aniridia, hemihypertrophy, genitourinary tract abnormalities, and Beckwith–Wiedemann syndrome are known to be associated with an increased risk of Wilms tumor in children.[78] The study of patients with sporadic aniridia and Beckwith–Wiedemann syndrome led to the discovery of WT1, a tumor suppressor gene located on chromosome 11p necessary for normal renal development.[79,80] **Table 103.7** lists known genetic syndromes associated with increased susceptibility to Wilms tumor.

Pathology and Biologic Features

Wilms tumors arise from pluripotent developmental renal precursor cells. In most cases, only one kidney is affected but may present as bilateral disease in up to 6% of children. Multicentric disease is found in 7% of patients.

Wilms tumors arise within the renal medulla and cortex and may invade renal calyces, renal vein, and inferior vena cava. The tumor is most commonly a well-circumscribed mass with a fibrous capsule. The most common sites of metastatic spread are lungs, lymph nodes, and liver. Wilms tumors are composed of a classic triphasic combination of blastemal, stromal, and epithelial cells. Characterization of histologic subtype is critical for risk stratification and for treatment planning. Blastemal predominance may indicate a high-risk category of patients with increased risk of recurrence.[81] Importantly, anaplastic cells characterize 7% of Wilms tumors and are defined by the presence of enlarged nuclei and hyperchromasia with multipolar polypoid mitotic figures (**Fig. 103.5**).[82] Compared to tumors without anaplasia, anaplastic Wilms tumors are generally found in older children and are more likely to have lymph node metastases. Differences in race are also observed with African or Latin-American children having the highest proportion of tumors with anaplasia. Tumors with diffuse anaplasia (present in more than one area of the tumor or extrarenal sites) are defined "unfavorable histology" and have higher resistance to chemotherapy compared to tumors without anaplasia.[83] 5 The single most important prognostic indicator in Wilms tumors is the presence of anaplasia.

Clear cell sarcoma and rhabdoid tumor of the kidney are also unfavorable histologic subtypes and are considered distinct entities from Wilms tumors.[77,84] Nephrogenic rests represent the persistence of developmental renal tissue in the kidney after the 36th week of gestation and 1% undergo malignant transformation to Wilms tumor. Two major categories of nephrogenic rests have been characterized, perilobar (PL) and intralobar (ILNR), distinguished by their position within the renal lobe.[80] Nephrogenic rests are considered precursor lesions of Wilms tumor and are found in nearly half of cases.[85] ILNR characterizes early developmental disturbances and occurs in aniridia and Denys–Drash syndrome, while PL develops later in nephrogenesis and occurs in patients with Beckwith–Wiedemann syndrome and hemihypertrophy. Nephroblastomatosis is the term used to describe the presence of diffuse nephrogenic rests and typically involves both kidneys. The presence of nephrogenic rests demonstrates the vast degree of heterogeneity in Wilms tumor biology as they either involute or progress to hyperplastic overgrowth or neoplastic induction.[77] Patients with nephrogenic rests are at risk for bilateral kidney involvement that decreases with age.

Several biologic factors have been identified in Wilms tumors that associate with risk. Tumor-specific LOH at chromosomes 1p and 16q are independent prognostic indicators and are associated with greater risk of relapse and mortality. The fifth National Wilms Tumor Study Group trial (NWTS-5) found that tumors with LOH at 16q had an adverse effect on prognosis with relapse rates three times higher and mortality rate 12 times higher than those without LOH at chromosome 16q.[86] Patients with LOH for chromosome 1p also had relapse and mortality rates higher than those without LOH at 1p.[87] LOH for both chromosomes 1p and 16q are found in up to 5% of Wilms tumors.

Table 103.7 Syndromes Associated with Increased Susceptibility to Wilms Tumor

Syndrome	Gene	Phenotype
WAGR (Wilms tumor, aniridia, genitourinary abnormalities, mental retardation)	11p13/WT1: deletions, PAX6	Absence of iris, genitourinary defects, mental retardation, 30% develop Wilms tumors
Denys–Drash	11p13/WT1: point mutations	Genitourinary defects, renal mesangial sclerosis and intersex disorder; 90% develop Wilms tumors
Frasier	11p13/WT1: point mutations	Genitourinary defects, focal glomerular sclerosis, and intersex disorder; rarely develop Wilms tumors
Beckwith–Wiedemann	11p15: several genes (IGF2, H19, p57, and LIT1)	Organomegaly including tongue, hemihypertrophy, hypoglycemia, umbilical hernia, increased risk of tumors (Wilms tumor, hepatoblastoma, adrenal carcinoma), 5% develop Wilms tumors
Simpson–Golabi–Behmel	Xq26/GPC3: point mutations, microdeletions	Organomegaly, renal dysplasia, excess digits, diaphragmatic and heart defects, 7.5% develop Wilms tumors
Sotos	5q35/NSD1: point mutations, microdeletions	Overgrowth, craniofacial dysmorphism, mental retardation, and increased risk of tumors (Wilms tumor, neuroblastoma, acute lymphocytic leukemia), 5%

		of patients develop Wilms tumor
Perlman	Unknown	Macrosomia, visceromegaly, cryptorchidism, excess amniotic fluid, characteristic facial features, 30% of patients develop Wilms tumors
Familial Wilms tumor 1	17q12–21	20% of patients develop Wilms tumors
Familial Wilms tumor 2	19q13,4	70% of patients develop Wilms tumors

GPC3, glypican 3; IGF2, insulin-like growth factor 2; NSD1, nuclear-receptor–binding SET-domain protein 1; PAX6, paired box gene 6; WT1, Wilms tumor protein 1.

Reprinted from Rivera MN, Haber DA. Wilms' tumour: Connecting tumorigenesis and organ development in the kidney. *Nat Rev Cancer* 2005;5(9):699–712. Permission received for previous edition.

Presentation, Diagnosis, and Staging

Children may present with a palpable asymptomatic abdominal mass identified by parents or pediatrician during well-visit examination. If present, symptoms may include intermittent abdominal pain, gross or microscopic hematuria (25% of patients), and hypertension (25% of patients). Hypertension occasionally results from either an increase in renin secretion by the tumor or by compression of the renal artery by tumor mass effect. Intraparenchymal bleeding and preoperative rupture may occur causing systemic symptoms of fever and anemia. The mass is typically nontender and nonmobile on physical examination. The child should be examined for aniridia, macroglossia, hemihypertrophy, and genitourinary abnormalities. Signs of intravascular spread may present as ascites, hepatosplenomegaly, and cardiac murmur. Standard complete blood count and serum chemistries should be assessed though renal function is usually unaffected. Red blood cells may be present on urinalysis.

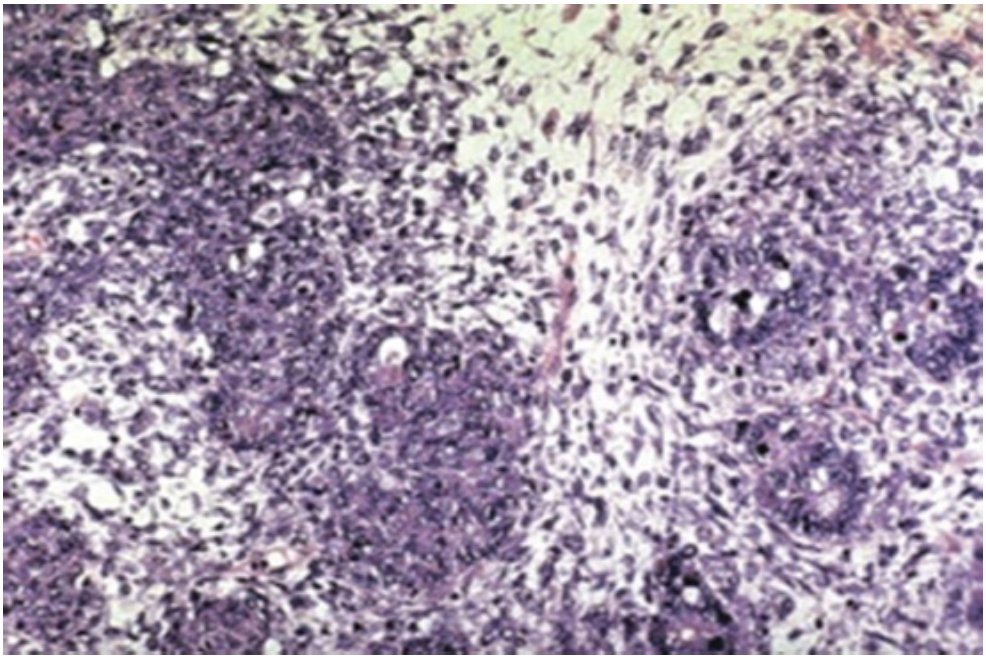

Figure 103.5 Microscopic examination of Wilms tumor showing highly cellular areas composed of undifferentiated blastemal with loose surrounding stroma with undifferentiated mesenchymal cells and immature tubules. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999, permission granted with previous edition.)

The diagnostic imaging workup is initiated with abdominal ultrasound and CT scan with oral and intravenous contrast. CT scan is the standard imaging modality that will provide information about mass location, size, extent of tumor invasion, and involvement of the contralateral kidney (**Fig. 103.6**). Critical examination of renal vasculature and intracaval extension is evaluated by Doppler ultrasonography. A good posteroanterior and lateral chest radiograph is obtained to determine the presence of lung metastases. It is critical to determine if a patient with Wilms tumor has lung metastases because these patients are assigned to higher disease stage and receive radiation to the lungs and more intensive chemotherapy. There is considerable controversy regarding the utilization of chest CT scan versus plain chest radiograph to detect lung metastases in patients with Wilms tumor because of interobserver variability in interpretation.[88] If utilized for staging workup, chest CT should be performed with standardized techniques and interpretation through a central review process. Pulmonary metastases identified on chest CT but not by plain chest radiograph may identify a subgroup of patients at increased risk of pulmonary relapse.[89] It may be

beneficial to obtain histopathologic confirmation of pulmonary metastases by surgical biopsy given the potential for upstaging and radiotherapy.[90]

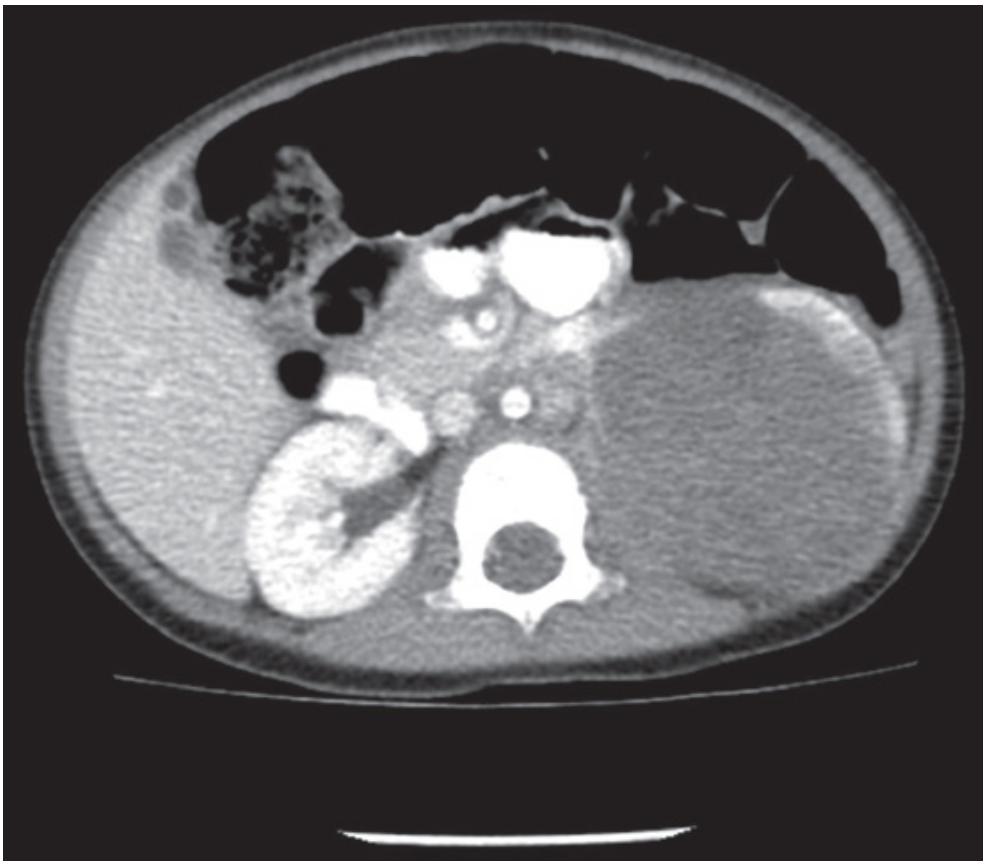

Figure 103.6 Abdominal CT scan with left Wilms tumor displacing midline organs and vessels, rim of kidney enhancing at lateral border.

In the United States, nephrectomy follows the initial diagnostic workup allowing the combination of surgical and histologic parameters to be included in staging at diagnosis. During the procedure, the surgeon must determine tumor extent, tumor rupture, and the status of regional, para-aortic and paracaval lymph nodes. Distant metastatic disease should also be determined by inspecting the peritoneal surfaces, diaphragm, and liver. The COG no longer recommends direct visualization and manual palpation of the contralateral kidney as long as the contralateral kidney is clear of tumor on cross-sectional imaging.

The staging of Wilms tumor is based on the anatomy of the tumor and lymph nodes as detailed by the National Wilms Tumor Study Group (NWTSG) staging system. The staging system incorporates clinical, surgical,

and pathologic information and allows stage-based approach to treatment to minimize exposure to cytotoxic agents (**Table 103.8**). Advanced tumor stage at diagnosis predicts an increased risk of relapse. Additionally, tumor rupture at surgery predisposes to relapse.[91] Older age is also an adverse prognostic factor and predicts disease recurrence.[92] Tumor stage and histology are the most significant prognostic factors for children with Wilms tumor.

Treatment

Most children diagnosed with Wilms tumor are cured by multimodal therapy. Much of the success in therapy is the result of collaboration and research trials conducted by three cooperative groups, the NWTSG, now a part of the COG, the United Kingdom Children's Cancer Study Group (UKCCSG), and the SIOP. In the United States and Canada, nearly all children are treated according to protocols established by the NWTSG. The primary goals of therapy are to treat based on well-defined risk groups and to achieve the highest cure rates with minimal toxicity.

Surgery is a critical component of local primary tumor control and treatment outcomes.[6] In the United States, the standard of care starts with radical nephrectomy at the time of diagnosis of resectable primary tumors followed by chemotherapy and radiation to sites of residual and metastatic disease. Preoperative chemotherapy is given to patients with inoperable tumors, bilateral disease, solitary kidney, and for tumors with intravascular extension above the hepatic veins. A significant number of patients are downstaged after preoperative chemotherapy without altering recognizable anaplasia.[93] In contrast to this treatment approach, SIOP therapy begins with chemotherapy administration for several weeks prior to nephrectomy in all patients presenting with Wilms tumors.[94] The standard chemotherapeutic drugs with activity against Wilms tumors are vincristine and actinomycin D. Doxorubicin is added to patients with stage 3 tumors and to those with unfavorable histology or adverse biologic prognostic markers such as LOH at chromosome 1p or 16q. Combinations of cyclophosphamide, ifosfamide, carboplatin, and etoposide are utilized for select stage 3 and 4 cases with unfavorable biology and for resistant or relapsed cases. In the United States, the optimal combination, duration, and mode of administration of

chemotherapy are optimized through clinical trials and studies of the NWTSG and COG.

Table 103.8 Wilms Tumor Staging Criteria

Stage	Criteria	4-Year Survival Rate (%)
1	Tumor is limited to kidney, completely excised; no evidence of rupture, intact surface	97
2	Tumor extends beyond kidney but completely excised, infiltration through renal capsule, extension into vessels outside kidney, local or open biopsy or spillage confined to flank, no residual tumor	95
3	Residual nonhematogenous tumor	91
4	Hematogenous metastases to lung, liver, cortical bone, brain, other organs	78
5	Bilateral renal involvement at diagnosis'	Same as highest unilateral stage

Survival based on outcome form patients with favorable biology in the National Wilms Tumor Study-3. Courtesy of the National Wilms Tumor Study.

The first two NWTSs, NWTS-I and NWTS-II, found that routine postoperative radiation was unnecessary in patients with tumors confined to the kidney and completely resected. Combination therapy of vincristine and actinomycin D was more effective than single-agent therapy and the addition of doxorubicin improved survival in higher-stage patients. Additionally, the duration of combination chemotherapy was successfully reduced in low-

stage patients from 15 months to 6 months without compromising survival outcomes.[95,96] These studies established criteria that identify unfavorable (anaplasia) and favorable histologic features that stratify patients into high-risk and low-risk treatment groups. High-risk patients are at a higher risk of recurrence and also include those with unresectable tumors, lymph node metastases, and diffuse tumor spill. This patient group benefits from intensified chemotherapy and abdominal radiation. These findings paved the way for NWTS-III that demonstrated successful treatment of stage 1 favorable histology Wilms tumors with lower dosing and further reduced duration of vincristine and actinomycin D. The 4-year relapse-free and survival rates with this regimen were 89% and 95%.[97] This study found that stage 2 patients with favorable histology were treated successfully with vincristine and actinomycin D without postoperative radiotherapy or doxorubicin and stage 3 patients had no differences in abdominal recurrence with reduction of abdominal radiotherapy compared to patients with high-dose radiotherapy when doxorubicin was administered (10.8 Gy compared to 20 Gy). The NWTS-III also found that patients with stage 4 favorable histology tumors were successfully treated with vincristine, actinomycin D, doxorubicin, and local radiotherapy based on local tumor stage. The addition of cyclophosphamide was without benefit. This group received lung radiation to both lungs (12 Gy) with 4-year relapse-free and overall survivals of 79% and 80.9%. The NWTS-IV trial was largely based on improving treatment results through modifying drug administration utilizing shorter and "pulse-intensive" chemotherapy regimens compared to standard divided dose regimens.[98] The results of this study revealed that shorter pulse-intensive regimens were equivalent to standard treatment regimens in terms of overall survival with total chemotherapy duration of 6 months. Since the NWTS-IV trial, survival rates for children with Wilms tumor have steadily improved with shorter chemotherapy schedules and lower treatment costs.[99] Based on results of NWTS-IV, the current overall survival rate for children with favorable histology Wilms tumor approaches 90%. Current 10-year relapse-free and overall survival for stage 1 favorable histology Wilms tumors are 91% and 96%, and for stage 2 tumors, 85% and 93%, respectively.[100] NWTS-V completed enrollment in 2003 and was designed as a nonrandomized single-arm therapeutic trial to treat patients with stage- and histology-specific treatment plans. In this study, patients were not

randomized to therapy, rather biologic properties of tumors were assessed. The aims included determining if tumor LOH for chromosomes 1p and 16q were associated with poorer prognosis in patients with favorable histology Wilms tumors and to determine if increased DNA content in tumor cells was associated with adverse outcomes.[101] LOH for 1p and 16q identified a subgroup of favorable histology patients who have a significantly increased risk of relapse and death.[87] LOH for these chromosomes is now used as an independent prognostic factor as patients with LOH for chromosome 1p and 16q have 75% relapse-free survival.

The NWTS-V also attempted to verify that surgery alone may have acceptable overall survival rates in a subgroup of children younger than 2 years of age at diagnosis with very low–risk favorable histology Wilms tumors that weigh less than 550 g.[102] The incidence of relapse was higher in this subgroup of patients receiving surgery only, but the salvage rate was surprisingly high with long-term survival being the same as patients receiving conventional postoperative chemotherapy. Given this, cooperative group trials will further study optimal management of surgery alone in this subgroup to determine if very low–risk patients may be spared adjuvant therapy.

Since 2006, the COG has opened four clinical trials for the treatment of children with Wilms tumors. For these therapeutic studies, patients are stratified into very low-, low-, standard-, and high-risk groups based on tumor histology, stage, biologic assessment, tumor weight, and age. To facilitate accurate risk assessment, it is currently recommended that all patients diagnosed with Wilms tumor be enrolled and follow protocol recommendations of AREN03B2, a biology classification-based trial. The current treatment recommendations are summarized in **Table 103.9** and are based on the most recent COG trials developed to build upon and refine results of previous NWTS.[103] The protocol guidelines recommend that stage 1 and 2 favorable histology patients undergo initial nephrectomy and lymph node sampling followed by vincristine and actinomycin D chemotherapy (Regimen EE-4A). Doxorubicin (Regimen DD-4A) is added to the treatment plan in patients with stage 1 and 2 tumors with favorable histology and LOH at chromosome 1p and 16q, as this subgroup has been shown to have an increased risk of relapse and death. Stage 1 tumors with unfavorable histology (focal or diffuse anaplasia) have lower 10-year relapse-free and

overall survivals of 69% and 82% and are treated with vincristine, actinomycin D, doxorubicin (Regimen DD-4A), and abdominal radiotherapy. Stage 3 patients with favorable histology are treated with nephrectomy, lymph node sampling, vincristine, actinomycin D, and doxorubicin (Regimen DD-4A) and abdominal radiotherapy, with 10-year relapse-free and overall survivals of 84% and 89%. Cyclophosphamide and etoposide (Regimen M) are added to the treatment regimen for stage 3 tumors with favorable histology and LOH at chromosomes 1p and 16q. The presence of diffuse anaplasia also intensifies therapy in stage 2 and 3 tumors with the addition of cyclophosphamide, carboplatin, and etoposide for 30 weeks (Regimen UH-1) and abdominal radiotherapy, with 10-year relapse-free and overall survivals of 43% and 49%. Stage 4 patients with favorable histology and pulmonary metastases are treated with nephrectomy, lymph node sampling, vincristine, actinomycin D, and doxorubicin for 24 weeks. In patients with stage 4 disease, the primary tumor is staged separately to determine the requirement for abdominal radiation. Lung radiotherapy is currently utilized if metastases remain detectable after 6 weeks of chemotherapy. For these reasons, it remains advantageous to resect the primary tumor prior to the initiation of chemotherapy even in patients with stage 4 disease. Based on results of NWTS-4, the 10-year relapse-free and overall survivals for patients with stage 4 favorable histology Wilms tumor is 75% and 81%. Stage 4 favorable histology tumors with LOH at chromosomes 1p and 16q are treated with the addition of cyclophosphamide and etoposide (Regimen M) and abdominal radiation. Stage 4 tumors with focal or diffuse anaplasia (without measurable disease) are treated with the addition of cyclophosphamide, carboplatin, and etoposide for 30 weeks (Regimen UH-1) and radiotherapy. This subgroup of patients has the worst 10-year relapse-free and overall survivals of 18%. Stage 5 Wilms tumors (bilateral tumors) with favorable histology have 10-year relapse-free and overall survivals of 65% and 78%. Patients with bilateral Wilms tumors are treated with preoperative chemotherapy (vincristine, actinomycin D, doxorubicin) and renal-sparing surgery.

Table 103.9 Recommended Therapy According to COG Protocols

Stage/Histology	Radiotherapy	Chemotherapy
Stage 1 FHWT, <2 yo, <550 g	None	None
Stage 1 FHWT, >2 yo, >550 g	None	Regimen EE-4A
Stage 2 FHWT	None	Regimen EE-4A
Stage 1, II FHWT	None	Regimen DD-4A
LOH 1p,16q		
Stage 3 FHWT	Yes	Regimen DD-4A
No LOH 1p, 17q		
Stage 1–3 focal AHWT	Yes	Regimen DD-4A
Stage 1 diffuse AHWT	Yes	Regimen DD-4A
Stage 3, 4 FHWT	Yes	Regimen M
LOH 1p,16q		
Stage 4 FHWT		
Pulmonary mets		
lesions resected at diagnosis	Yes	Regimen DD-4A
lesions resolve after 6 wks chemo	None	Regimen DD-4A
lesions persist after 6 wks chemo	Yes	Regimen M
Stage 4 FHWT nonpulmonary mets	Yes	Regimen M
Stage 2–3 diffuse AHWT	Yes	Regimen UH-1
Stage 4 diffuse AHWT	Yes	Regimen UH-1

Regimen EE-4A: Pulse-intensive AMD plus VCR (18 weeks). Regimen DD-4A: Pulse-intensive AMD, VCR, and DOX (24 weeks). Regimen M: VCR, AMD, DOX, alternating with CYCLO and ETOP (24 weeks). Regimen UH-1: CYCLO, carboplatin, ETOP alternating with VCR, DOX, CYCLO (30 weeks). Regimen I: VCR, DOX, CYCLO alternating with CYCLO, ETOP (24 weeks). Regimen UH-2: VCR, DOX, CYCLO alternating with CYCLO, carboplatin, ETOP and VCR, Irinotecan (30 weeks).

FHWT, favorable histology Wilms tumor; AHWT, anaplastic histology Wilms tumor; CCSK, clear-cell sarcoma of the kidney; MRT, malignant rhabdoid tumor of the kidney; AMD, dactinomycin; VCR, vincristine; DOX, doxorubicin; CYCLO, cyclophosphamide; ETOP, etoposide.

Ko EY, Ritchey ML. Current management of Wilms' tumor in children. *J Pediatr Urol* 2009;5(1):56–65.

Surgical Considerations

Preoperative biopsies are contraindicated unless a tumor is surgically unresectable. Unilateral radical ureteronephrectomy with abdominal exploration is accomplished through a wide transverse abdominal incision that will allow safe resection and regional lymph node sampling without rupture. A thoracoabdominal incision may be utilized as necessary for tumors reaching beyond the diaphragm. Complete abdominal and pelvic exploration is performed. The contralateral kidney does not require exploration if preoperative imaging does not suggest involvement. The lateral peritoneal reflection is incised, and the colon is reflected medially. Though a formal retroperitoneal lymph node dissection is not recommended, lack of adequate lymph node sampling along with the primary tumor resection automatically upstages treatment to stage 3 disease because of the risk of local relapse.[103] Gentle handling of the tumor is critical to avoid tumor rupture and spillage as there is a sixfold increase in local relapse and also automatic tumor upstaging to stage 3.[104] Both local and diffuse tumor rupture will increase relapse risk. It is often unsafe to attempt to ligate the renal vein prior to tumor manipulation given the size of most Wilms tumors as traditionally recommended by most authors. Later ligation of the renal vein after tumor mobilization has not been shown to adversely affect survival outcomes and early ligation should not be attempted if technically difficult. The dissection is carried out along the tumor capsule and outside of Gerota fascia identifying the renal hilum and isolating the renal artery, vein, and the ureter (**Fig. 103.7**). The renal vein and inferior vena cava are palpated for intravascular tumor extension. The ureter is divided as distal as possible to

the renal hilum though it is not necessary to remove the entire ureter. The tumor and kidney is then removed en bloc. The adrenal gland may be left in place if it is not adherent to the tumor or if the tumor arises from the lower pole of the kidney.[105] Titanium clips should be utilized to identify any gross residual tumor. The tumor and nephrectomy specimen should not be placed into fixative but delivered fresh and sterile to the pathologist to optimize histologic and cytogenetic analysis based on pediatric tumor protocols.

There have been reports of laparoscopic resection of Wilms tumor.[106] These are more likely feasible after preoperative chemotherapy with lower risk of tumor rupture, though safety has not been confirmed. Success of laparoscopy for Wilms tumor is hindered by tumor spill and by inaccurate staging.

Patient selection for preoperative chemotherapy is a critical step in surgical and treatment planning. The overall incidence of surgical complications in patients undergoing nephrectomy for Wilms tumor is 12.7%.[107] The most common surgical complications are small bowel obstruction (5.1%) and excessive hemorrhage (1.9%), followed by wound infection (1.9%) and vascular injury (1.5%) as reported by the NWTS-IV trial. Higher-stage tumors, intravascular extension, and resection of contiguous organs are risk factors associated with surgical complications. The risk of renal insufficiency after unilateral nephrectomy for Wilms tumor is low (.25%) and patients with Denys–Drash syndrome are most at risk for progressive tumor in the remaining kidney.[108] For these reasons, nephron-sparing procedures are currently reserved for children with bilateral Wilms tumor and for those at risk for developing renal failure, and not indicated for patients with standard unilateral tumors with a normal contralateral kidney.

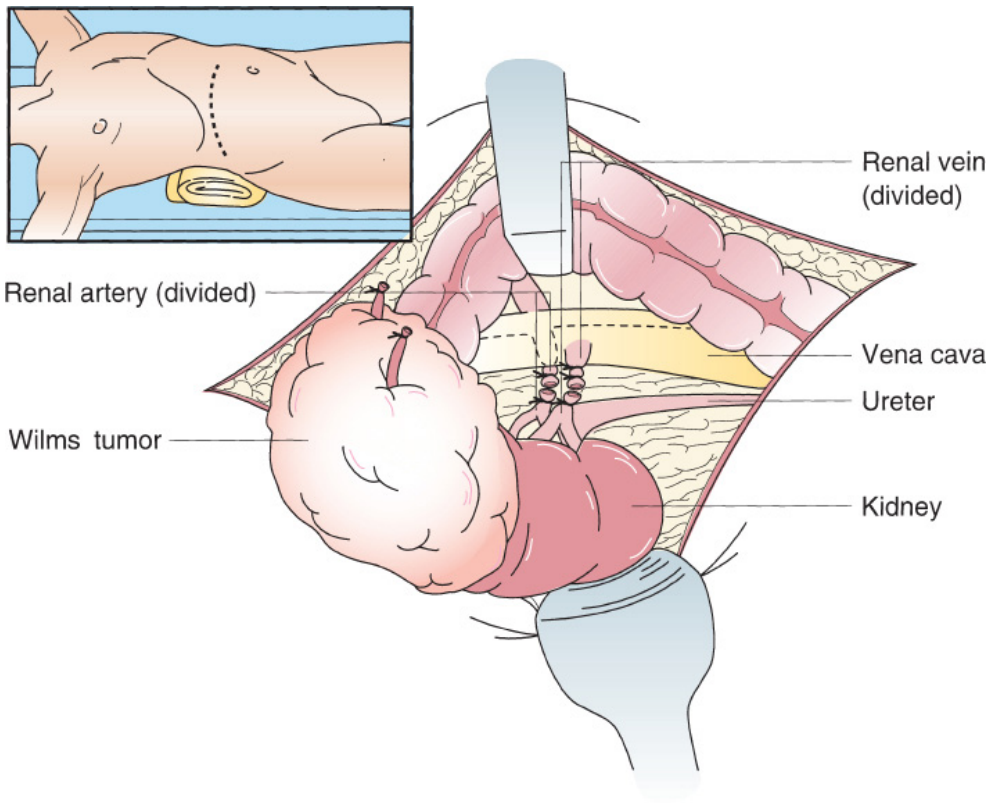

Figure 103.7 Anatomy and operative approach to resection of a Wilms tumor.

Renal Vein/Inferior Vena Cava

Four percent to 10% of patients with Wilms tumor have intravascular extension into the renal vein, inferior vena cava, and rare cases extending into the atrium. Patients may have symptoms of vascular involvement depending on the degree of venous obstruction that may include hypertension, hepatosplenomegaly, ascites, and heart failure. The preoperative ultrasonography and CT scan are accurate in detecting intravascular tumor extension, but the vessels should still be palpated prior to ligation of the renal vein during tumor excision. Studies of Wilms tumors with intravascular extension have found that preoperative chemotherapy facilitates resection by decreasing the extent of tumor thrombus. Overall frequency of complications and the 3-year relapse-free survival rates were similar between the preoperative therapy group and the upfront resection group.[109] Control of the renal vessel and vena cava below and above the tumor thrombus is essential to obtain vascular control and to minimize bleeding after venotomy. Effort should be made to avoid transecting tumor thrombus. If the patient has

intracardiac tumor extension after preoperative chemotherapy, a combined thoracoabdominal incision with cardiopulmonary bypass is the safest surgical approach for tumor thrombus excision. The overall survival of children with intravascular extension is the same as children with disease limited to the kidney of similar stage and histology.[110]

Bilateral Wilms Tumor

Five percent to 8% of patients with Wilms tumors present with bilateral disease. Bilateral Wilms tumor is found more frequently in patients with hemihypertrophy and genitourinary anomalies. Primary tumor excision at diagnosis is discouraged and patients may be enrolled on NWTS trials without an initial biopsy. If obtained because of uncertainty in diagnosis, core needle biopsies through a posterior approach are preferable to minimize contamination of the abdominal cavity and three-drug chemotherapy is initiated. All children with bilateral Wilms tumors should receive preoperative chemotherapy with the goal of renal preservation. The current COG protocol recommends reevaluation by abdominal CT scan after 6 weeks of chemotherapy to determine the feasibility of a renal-sparing procedure. If the tumor response is less than 50% shrinkage, the COG recommends bilateral open renal biopsies to assess tumor histology prior to additional chemotherapy. After 12 weeks of therapy, all patients should undergo surgical resection as continuing therapy beyond 12 weeks has not been shown to improve outcomes. The primary surgical goal is to spare as much renal parenchyma as possible while obtaining complete tumor resection. Children with synchronous bilateral Wilms tumor or tumor with contralateral nephrogenic rests that have complete radiographic response may not require surgical excision and have low risk for local relapse.[111] These children are monitored for recurrence by serial imaging. If partial nephrectomy is not safe after 12 weeks of chemotherapy then nephrectomy is recommended. In NWTS-IV, children with bilateral Wilms tumor who had partial resection with complete resection of all gross disease had local relapse rate of 8% and 4-year overall survival of 81.7%.[112]

Partial Nephrectomy

Nephron-sparing surgery is utilized in patients with bilateral Wilms tumor and in select patients at high risk for bilateral disease or renal failure. Partial nephrectomy is not indicated in patients with standard unilateral Wilms tumor given the low risk of renal failure with unilateral nephrectomy. Children with Wilms tumor predisposing syndromes such as WAGR, Beckwith–Wiedemann, and Denys–Drash syndrome are predisposed to the development of tumors in the contralateral kidney and are therefore managed with a nephron-sparing partial nephrectomy approach for unilateral tumors. Screening imaging studies in such patients at risk of developing Wilms tumors may detect lesions that are appropriate for nephron-sparing procedures. These patients may still benefit from preoperative chemotherapy to minimize the extent of renal resection. A radionucleotide renal scan (dimercaptosuccinic acid/DMSA scan) is useful to assess preoperative and postoperative renal function.

Partial nephrectomy is typically feasible only if tumor involves one pole and less than one-third of the kidney and if the collecting system and renal vein are uninvolved. For bilateral tumors, the kidney with the lowest tumor burden is addressed first to determine if partial nephrectomy is feasible. A transverse abdominal incision is utilized for abdominal exploration and partial nephrectomy utilizing the same principles of radical nephrectomy with respect to tumor spillage. Manual compression of the kidney may control blood loss and avoid vascular ischemia. Tumor resection is accomplished by opening Gerota fascia and mass excision via wedge resection with 0.5- to 1.0-cm margin of normal renal parenchyma. Enucleation may be considered for large centrally located lesions. The specimen should be examined closely for rhabdomyomatous changes and anaplasia, and nephrectomy considered in patients with positive margins or high-risk histology.[113] Renal functional outcomes after nephron-sparing surgery are assessed by serum creatinine level, glomerular filtration rate (GFR), hypertension, and proteinuria.[105] Improved surgical techniques and intraoperative ultrasound have vastly improved the safety and feasibility of nephron-sparing surgery in children at risk of postoperative renal failure.

Future Directions

Future studies will continue to focus on personalized treatment plans based on tumor biology and patient risk stratification. New COG protocols are currently in place with efforts to further improve curative outcomes while minimizing toxicity with refined stratification based on tumor-specific biologic properties. Next-generation exome sequencing has enhanced the capacity to identify disrupted molecular pathways in Wilms tumors and there is extensive research on identifying their role in Wilms tumor development and pathogenesis.[114] There are very few known genetic alterations in Wilms tumors that have been shown to drive tumorigenesis or progression. Examples of this are the discovery of new mutations in Wilms tumor genes involved in miRNA processing including SIX1 and SIX2.[115] Mutations in this pathway may underlie high-risk Wilms tumors and serve as biomarkers and new therapeutic targets. Several researchers have found significant epigenetic alterations such as changes in DNA methylation or chromatin structure in Wilms tumors. Epigenetic changes at the imprinted region at chr11p15.5 show an allele-specific pattern of methylation resulting in abnormal expression of IGF2. Targeting IGF2 is an active area of investigation in preclinical drug development.[116] Circulating epigenetically modified DNA and miRNAs have been detected in the blood of patients allowing researchers to investigate the utilization of tracking genetic mutations in the circulation as a mechanism of diagnosis, risk stratification, and tracking tumor burden in Wilms tumor.[114,117] Other areas of intense research continue in the role of myeloablative chemotherapy and the role of autologous bone marrow transplantation in patients with relapsed Wilms tumors.

NON-WILMS RENAL TUMORS

Congenital Mesoblastic Nephroma

Congenital mesoblastic nephroma (fetal renal hemartoma) is the most common renal neoplasm in neonates and infants younger than 3 months of age and is considered a separate clinical entity from Wilms tumor. In contrast to Wilms tumor, classic congenital mesoblastic nephroma is considered a benign solid tumor of infancy, occurring in a younger age group with an

excellent overall prognosis. Almost all cases are diagnosed within the first 6 months of life, representing 5% of renal neoplasms in children.[118] There may be a slightly higher incidence in boys.[119] Congenital mesoblastic nephroma has distinctive spindle cell histopathologic and clinical features that are generally considered benign and rarely metastasizes to other organs. Congenital mesoblastic nephroma is a mesenchymal tumor with three pathologic variants: classic congenital mesoblastic nephroma, a cellular subtype, and a mixed variant. Cellular congenital mesoblastic nephroma subtype is a more aggressive tumor and though rare, is capable of recurrence and metastases.[120] The cellular subtype is similar in histology to infantile fibrosarcoma and may represent a visceral form of the disease while classic histology is similar to infantile fibromatosis.[121] The cellular variant of congenital mesoblastic nephroma has been found to have a translocation (t12;15) (p13;q25) that results in ETV6-NTRK3 fusion protein, a genetic alteration also found in congenital infantile fibrosarcoma.[122] Similar to congenital infantile fibrosarcoma, trisomy 11 is also found in the cellular subtype of congenital mesoblastic nephroma.[123] These chromosomal aberrations distinguish the cellular variant of congenital mesoblastic nephroma from the classic variant.

Neonates and infants with congenital mesoblastic nephroma present with a palpable abdominal mass that is indistinguishable from other solid abdominal masses on physical examination. Hematuria is often present along with vomiting and jaundice in rare cases.[124] Hypertension or hypercalcemia is rarely present. The most common diagnostic imaging studies utilized are ultrasound and CT scan detailing the presence of a unilateral solid mass with or without cystic components, necrosis, or calcifications. The mass can be detected on prenatal ultrasound and polyhydraminos may be found in up to 70% of patients.[125] The diagnostic workup precedes in much the same manner as Wilms tumor and the lesions are often not discernible on physical examination or preoperative imaging. The standard treatment for congenital mesonephric nephroma is complete surgical resection with nephrectomy. Wide margins are recommended because these tumors can infiltrate surrounding renal parenchyma and perinephric tissues. Local recurrence, though rare, has been reported and is associated with the cellular variant.[124] Systemic chemotherapy is reserved for tumors that recur and in rare cases of metastases or unusually cellular histology.

Clear Cell Sarcoma

Clear cell sarcoma of the kidney is a rare renal neoplasm of childhood, distinct from Wilms tumor. There are approximately 20 new cases in the United States each year. The median age of diagnosis of clear cell sarcoma of the kidney is 36 months and the tumor is one of the "unfavorable histology" tumors studied by the NWTSG and the COG. There is a male predominance with male to female ratio of 2:1.[126] Clear cell sarcoma of the kidney has morphologic diversity and is composed of sarcomatous, nonepithelial cells.[127] The classic microscopic pattern of clear cell sarcoma of the kidney is cords of round or spindle-shaped cells with clear cytoplasm and frequent empty-appearing "Orphan Annie" nuclei. The cord cells are surrounded by variants of regularly spaced arborizing fibrovascular septa resulting in cord widths of between 4 and 10 cells.[127] The cellular septa are characteristic of clear cell sarcoma and aid in diagnosis. The cord cells range from ovoid to spindle-shaped and the septa range from thin "chicken-wire" capillaries to sheaths of fibroblast-like cells in a collagenous matrix.[126] Most tumors have the classic histologic pattern though almost all demonstrate a secondary variant pattern. There are eight variant patterns recognized: myxoid (50%), sclerosing (35%), cellular (26%), epithelioid (13%), palisading (11%), spindle cell (7%), storiform (4%), and anaplastic pattern (2.6%).[126] Necrosis is associated with poor prognosis and tumors without necrosis are more often stage 1 tumors with superior outcomes.

Patients with clear cell sarcoma of the kidney present with a large unilateral abdominal mass that is best visualized by abdominal ultrasound and CT scan. The tumors are typically well circumscribed and consist of a solid mass with cystic foci components. Necrosis and hemorrhage are common. There is gross extension into the renal vein in 5% of cases. The most common site of metastatic disease is ipsilateral renal hilar lymph nodes (29%) and bone metastasis is the most common mode of relapse.[126] Radiographic skeletal survey and radionucleotide bone scan is critical to determine if there are bone metastases at diagnosis. Patients may also have lung, brain, or liver metastases and therefore should have chest and central nervous system (CNS) imaging prior to initiation of chemotherapy for accurate staging. The staging system is similar to Wilms tumor. There is a high rate of metastases and relapse in early-stage tumors and intensive

chemotherapy is utilized for all cases. The current COG treatment recommendations for patients with clear cell sarcoma of the kidney include radical resection of the primary tumor and involved regional lymph nodes, followed by adjuvant chemotherapy consisting of vincristine, actinomycin D, doxorubicin, and abdominal radiotherapy (10 Gy) for all stages. Since the addition of doxorubicin to the treatment protocols of clear cell sarcoma of the kidney, patients with stage 1 disease have 6-year overall survival of 97%, stage 2 and 3 patients have 6-year survivals of 75% and 77%, respectively (compared to 30% for both stages prior to doxorubicin), stage 4 patients have 6-year survival of 50%.[126] There is active study within the COG on the benefit of the addition of cyclophosphamide and etoposide to treatment plans of patients with clear cell sarcoma of the kidney.[128] There is propensity for late relapse and patients are monitored with abdominal imaging, chest radiograph, brain MRI, and bone scans.

Rhabdoid Tumor of the Kidney

Rhabdoid tumor of the kidney is a rare and aggressive cancer in infancy, constituting 1.8% of renal neoplasms in children. The cell of origin is unknown, and the tumor was originally classified as a rhabdomyosarcomatoid subtype of Wilms but is now recognized as a distinct histologic tumor type. Histologically, rhabdoid tumors are well demarcated from the surrounding kidney and composed of solid and monotonous appearance of sheets of large cells with abundant cytoplasm, cytoplasmic inclusions, and prominent nucleoli.[129] Intense vimentin immunoreactivity is characteristic, and these tumors may also stain for cytokeratin, desmin, and neurofilament. Rhabdoid tumors may have areas of necrosis and foci of sclerosis.[129] Rhabdoid tumors may occur as separate CNS primary tumors and up to 15% of patients with rhabdoid tumor of the kidney develop CNS lesions.[130] The overall prognosis of patients with rhabdoid tumor of the kidney remains poor and age is an important prognostic factor.[131] Patients diagnosed with rhabdoid tumors at less than 1 year of age have extremely poor prognoses and are at high risk for CNS tumors, while patients older than 1 year at diagnosis have better outcomes. Low stage and female gender have also been reported as features that predict improved survival.[130] Because of the small number of patients with this disease and overall poor

outcomes, few other prognostic indicators have been identified. Rhabdoid tumors are characterized by loss-of-function mutations of the tumor suppressor gene hSNF5/INI1 located at chromosome 22q11 which encodes a chromatin-remodeling protein complex (SWI/SNF).[132] This chromosomal alteration is thought to be a characteristic genetic defect for rhabdoid tumors of all sites.[133] Both acquired and germline mutations have been observed.[134] Though the functional consequences are not yet known, mutations in INI1 have been found to result in altered transcription of genes involved in growth and differentiation.

Patients with malignant rhabdoid tumor of the kidney present with a palpable abdominal mass and often have hematuria. The diagnostic workup proceeds with an abdominal CT scan showing a large heterogeneous solid mass with areas of necrosis, hemorrhage, or calcifications. The tumor typically involves the renal hilum. A chest radiograph or chest CT scan should be obtained to evaluate for lung metastases. Lung metastasis is present in 56% of patients with rhabdoid tumor of the kidney at diagnosis and is the most common site of metastatic spread.[130] Evaluation for CNS disease should also occur at diagnosis because of the frequency of CNS primaries and metastases in patients with rhabdoid tumors. Therapy begins with radical nephrectomy and complete surgical resection including involved regional lymph nodes with paracaval and para-aortic lymph node sampling. Meticulous sampling of any potentially involved lymph nodes is critical for accurate staging. Patients are staged according to NWTS staging system and all patients receive intensified adjuvant chemotherapy and abdominal radiotherapy. Based on current COG protocols, children with stage 1 to 3 malignant rhabdoid tumor of the kidney are treated with cyclophosphamide, carboplatin, and etoposide alternating with vincristine, doxorubicin, and cyclophosphamide for 30 weeks (Regimen UH-1). Stage 4 patients receive vincristine, doxorubicin, and cyclophosphamide that are alternated with cyclophosphamide, carboplatin, etoposide, vincristine, and irinotecan for 30 weeks (Regimen UH-2). All patients receive abdominal radiotherapy. The survival rate for children with rhabdoid tumor of the kidney is dismal with overall survival rates below 25%, and very few survivors of stage 4 disease. Despite aggressive multimodal therapy, children less than 1 year of age with rhabdoid tumor of the kidney have a 4-year survival of 8.8% and children over 2 years of age have 4-year survival of 41.1%. Because previous

protocols have had minimal successes with improving relapse and survival in children with malignant rhabdoid tumors, current COG clinical trials are examining intensive chemotherapy regimens and experimental agents in this high-risk renal tumor.[131]

Renal Cell Carcinoma

Renal cell carcinoma is rare in pediatric patients and comprises approximately 5% of all renal tumors in children and adolescents.[4] The tumor is highly aggressive with frequent distant metastases. The median age of diagnosis of renal cell carcinoma in children is 9 to 10 years and children who have previously received cytotoxic chemotherapy may have predisposition to developing this cancer.[135] Pediatric renal cell carcinoma differs from adult renal cell cancer with distinct clinical and biologic differences. The microscopic pattern does not typically fit well within the standard adult subtypes. In general, histology is consistent with papillary adenocarcinoma, renal cell carcinoma not otherwise specified (NOS), and clear cell adenocarcinoma subtypes.[136] High nuclear grade and increased vimentin expression are found in higher-stage cases.[137] Patients with von Hippel–Lindau syndrome may present with bilateral renal cell carcinoma. Tuberous sclerosis, Birt–Hogg–Dube syndrome, and hereditary leiomyomatosis are other hereditary syndromes associated with renal cell carcinoma.[5] It is routine to test for translocations of the Xp11.2 and 6p21 loci, nonrandom genetic alterations that are characteristic of renal cell carcinoma.[138] Tumors with Xp11.2 translocations have papillary and clear cell features and are a separate entity in the World Health Organization classification of renal tumors.[139] This translocation may be present in up to 70% of pediatric renal cell carcinoma and involves the fusion of the TFE3 gene, a transcription factor belonging to the microphthalmia (MiTF) family.[140] The translocation involving 6p21 is the second most common translocation in pediatric renal cell carcinoma and results in the fusion of TFEB, also a member of the MiTF transcription factor family.[140]

Patients may present with a large palpable abdominal mass. Abdominal pain, hematuria, weight loss, joint pain, and anorexia may also be present. Cross-sectional abdominal and pelvic imaging (CT scan or MRI) along with chest radiograph and/or chest CT scan is critical to define the locoregional

extent of the mass and to determine metastatic spread. Distant metastatic disease is present in up to 30% of pediatric patients at diagnosis, most commonly to lung (64%), liver (57%), and bone (42%).[140] Local lymph node involvement does not necessarily predict poor outcome in renal cell carcinoma in children.[141] Imaging may show a large nonenhancing renal mass with necrosis or hemorrhage. Calcifications are more common in children with renal cell carcinoma compared to Wilms tumor.[142] Compared to adults, children with renal cell carcinoma present with higher-stage and higher-grade disease.[140] Children with renal cell carcinoma are staged based on the International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC; tumor, node, and metastases [TNM]) system although some studies utilize the modified Robson staging classification system.[138,143] The overall survival at 20 years for pediatric renal cell carcinoma is 54.9%.[144]

If the mass is resectable at diagnosis, standard treatment is radical nephrectomy with lymph node sampling followed by combination adjuvant chemotherapy, immunotherapy, and radiotherapy based on surgical pathology. The role of lymph node dissection for renal cell carcinoma has not been determined. Partial nephrectomy is reserved for patients at high risk of postoperative renal failure and multiple renal tumors, particularly patients with genetic syndrome–related disease. There are reports of successful partial nephrectomy for small, unilateral, low-stage tumors. The role of chemotherapy is unproven, as the administration of chemotherapy has not significantly improved survival outcomes. There is some evidence that immunotherapy (IL-2) may be beneficial in select cases of renal cell carcinoma.[145] The COG completed a clinical trial (2006–2014) examining outcomes of high-risk renal tumors with complete surgical resection, intensive chemotherapy regimens, and radiotherapy. The most common agents utilized are combinations of vincristine, actinomycin D, doxorubicin, cyclophosphamide, irinotecan, etoposide, and carboplatin (https://clinicaltrials.gov/show/NCT00335556). This prospective study should yield critical results on the optimal management of adjuvant therapy for this tumor.

RHABDOMYOSARCOMA

Epidemiology and Genetic Risk

Rhabdomyosarcoma is the most common soft tissue sarcoma in children with an overall incidence of approximately 350 cases per year in the United States.[146] The median age of presentation is 7 years of age and the majority of patients are diagnosed prior to 10 years of age. There is a slight male predominance and a slightly higher incidence in African-American children.[4] Rhabdomyosarcoma tumors are classified as either embryonal, alveolar, or pleomorphic histologic subtypes. Embryonal rhabdomyosarcoma (68%) is the most frequent histologic type and occurs in children younger than 4 years of age.[146] Alveolar rhabdomyosarcoma (31%) and pleomorphic subtypes (1%) occur more commonly in older children. The overall incidence of rhabdomyosarcoma has not changed much in the last 30 years although there has been an increase in incidence of the alveolar subtype and in cases presenting with distant metastases.[146] The overall survival for rhabdomyosarcoma has increased from 25% to over 80% in the last four decades. This is largely due to improvements in multimodal therapies including radical surgery, intensive combination chemotherapy and radiotherapy. Patients with embryonal subtype have the best overall survival. Patients with smaller size tumors and favorable anatomic sites also have significant survival advantage. Age relates independently to survival outcomes with infants (<1 year of age) and adolescents (>10 years of age) more likely to have poor outcome and unfavorable histologic features.[147]

Rhabdomyosarcoma is often associated with congenital malformations, most commonly the CNS and genitourinary systems, with nearly an eightfold increase in CNS anomalies in children with rhabdomyosarcoma.[148] At least 32% of children with rhabdomyosarcoma have at least one congenital anomaly and nearly half are considered major defects. The rate of genitourinary defects in rhabdomyosarcoma is similar to that seen in children with Wilms tumors. There are also several familial syndromes associated with rhabdomyosarcoma. Children in families with Li–Fraumeni syndrome are at risk of developing rhabdomyosarcoma along with cancers of the breast, bone, brain, lung, and adrenal gland.[149] Rhabdomyosarcoma has been reported at an increased incidence in patients with neurofibromatosis type 1 and in patients with Beckwith–Wiedemann syndrome.[150–152] Environmental factors have also been found to have a role in the development of

rhabdomyosarcoma. Parental use of recreational drugs has been associated with an increased risk. Several studies have suggested that cocaine and marijuana use in parents may increase the risk of rhabdomyosarcoma in offspring.[153]

Pathology and Biologic Features

Rhabdomyosarcoma is a heterogeneous group of tumors. The origin is thought to be embryonal mesenchyme that gives rise to striated skeletal muscle. Rhabdomyosarcoma can occur in any skeletal muscle group, but most commonly affected sites are head and neck, trunk, and genitourinary. The Intergroup Rhabdomyosarcoma Study Group (IRSG), now the Soft Tissue Sarcoma Committee of the COG, classifies patients with rhabdomyosarcoma into the International Classification of Rhabdomyosarcoma (ICR) that is predictive of outcome among patients with different histologic subtypes.[154] Embryonal rhabdomyosarcoma is a heterogeneous subtype with histologic features that range from primitive mesenchymal cells to highly differentiated muscle cells. The small round blue cells consist of nuclei that are generally small with a light chromatin pattern. The microscopic pattern is moderately cellular with loose myxoid stroma.[154] Embryonal rhabdomyosarcoma comprises up to 75% of rhabdomyosarcoma tumors and is considered an intermediate prognosis tumor in terms of outcomes. Alveolar rhabdomyosarcoma is associated with poor prognosis. The tumors consist of small round cells with coarse chromatin and anastomosing fibrovascular connective tissue septa forming an alveolar pattern that is similar to lung in appearance (**Fig. 103.8**).[154] Botryoid tumors have excellent prognosis and have similar histologic characteristics of embryonal tumors but grow into hollow spaces like bladder or vagina, assuming a characteristic grapelike appearance. Spindle cell rhabdomyosarcoma is another subtype of embryonal rhabdomyosarcoma that occurs most commonly at paratesticular sites and generally have excellent prognosis. Pleomorphic rhabdomyosarcomas are extremely rare in children and more common in adults. Rhabdomyosarcoma is detected on immunohistochemistry by desmin, myoglobin/Myo-D, or muscle-specific actin staining.[155] Myogenic phenotype may also be determined by electron microscopy.[156]

Recurrent chromosomal alterations have been identified in rhabdomyosarcoma, particularly in alveolar subtypes.[157] Consistent translocations between chromosome 2 and 13, t(2:13)(q35;q14) have been identified and occur in up to 55% of alveolar rhabdomyosarcoma tumors. The translocation results in fusion of the PAX3 and FKHR genes, both transcription factors that function in muscular development. The resulting gain of function fusion gene is thought to alter cellular apoptosis, growth, and oncogenesis.[158] Another PAX gene translocation, t(1;13)(p36;q14), results in fusion gene PAX7-FKHR and also occurs in alveolar tumors.[159] These recurrent chromosomal alterations rarely occur in embryonal rhabdomyosarcoma. Nearly 80% of alveolar tumors have PAX3-FKHR or PAX7-FKHR fusions detectable by polymerase chain reaction (PCR) and may aid in diagnosis.

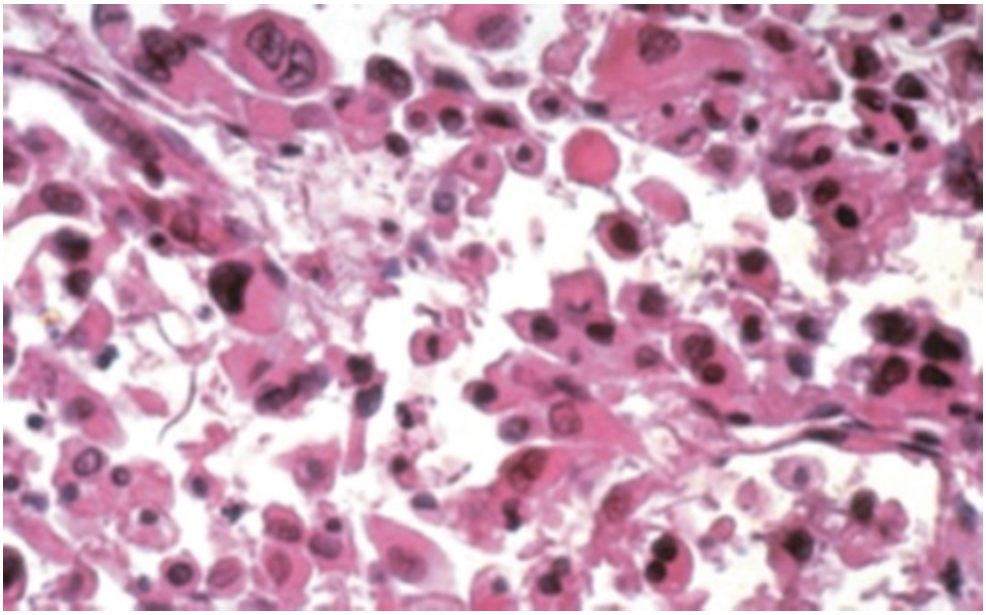

Figure 103.8 Microscopic image of typical lung-like appearance of an alveolar rhabdomyosarcoma. (From Rubin E, Farber JL. *Pathology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1997 with permission.)

Embryonic rhabdomyosarcoma is associated with allelic loss at chromosome 11p15.5, a possible tumor suppression region.[160] The mechanism of loss appears to preferentially maintain the paternal allele and lose the maternal allele, suggesting genomic imprinting.[161] Other genetic abnormalities have been identified through comparative genomic

hybridization (CGH) detecting whole chromosome gains and losses in embryonal rhabdomyosarcoma.[162] Genomic amplifications have been detected in alveolar subtypes and in embryonal rhabdomyosarcoma with anaplasia.[162]

Presentation and Diagnosis

Rhabdomyosarcoma can arise at any mesenchyme-containing site in the body. The presenting signs and symptoms depend on the site affected. Approximately 35% of all rhabdomyosarcoma tumors arise in the head and neck region and include parameningeal and nonparameningeal sites. Tumors in these areas may cause headache, facial and cervical swelling, nasal obstruction or discharge, recurrent otitis media, and cranial nerve palsies.[163] Tumors of the genitourinary track account for 25% of rhabdomyosarcoma and are most commonly located in the bladder and prostate gland. Perineal and perianal lesions may also occur. Patients may present with a palpable abdominal or pelvis mass, hematuria, dysuria, or urinary retention. Botryoid tumors are common in the vagina and cervix and may present with vaginal bleeding and inflammation. The friable grapelike mass may protrude from the vaginal orifice. Paratesticular rhabdomyosarcoma presents with a painless mass in the scrotum that is typically distinguishable from the testicle. Extremity rhabdomyosarcoma tumors may present as swelling and pain after a traumatic injury to the extremity involved. Chest wall, paraspinal, and abdominal wall rhabdomyosarcoma are considered trunk sites and often present with palpable masses or chest wall pain. Additional primary sites include retroperitoneum, abdomen, and pelvis. These lesions may present as a palpable abdominal mass or with abdominal pain. There is seldom mass effect such as rectal or bladder obstruction. Biliary rhabdomyosarcoma may cause jaundice, fever, and right upper quadrant abdominal pain.

The diagnostic workup for rhabdomyosarcoma includes a thorough history and physical examination followed by cross-sectional imaging of the involved site by CT scan or MRI. Local, regional, and distal metastatic extent of disease should be determined with assessment for abnormal-appearing lymph nodes. PET scan may aid in detection of disease for adequate staging.[164] Complete blood count, serum chemistries and liver function tests are routinely evaluated. Patients with suspected

rhabdomyosarcoma should have bone marrow biopsies and aspirates performed to determine metastatic spread to bone marrow. CT chest or chest radiograph is required to identify lung metastases. Bone scintigraphy should be obtained to search for cortical bone metastases. For most cases, brain CT scan and cerebral spinal fluid testing is reserved for patients with known CNS lesions or symptoms. An adequate biopsy is required to histologically confirm diagnosis. If the lesion is small or judged resectable on presentation, excisional biopsy with clear microscopic margins should be performed. If the tumor involves contiguous organs, major blood vessels, or nerves, then incisional biopsy is performed. It is critical that the specimen is sent fresh to the pathologist without formalin and that enough tissue is obtained for microscopic evaluation and cytogenetic analysis.

Table 103.10 TNM Pretreatment Staging System for Childhood Rhabdomyosarcoma

Stage	Site	T	Size	N	M
1	Orbit, head, and neck (excluding parameningeal), genitourinary (nonbladder/prostate)	T1 or T2	a or b	N0, N1, or N2	M0
2	Bladder/prostate, extremity, head and neck (parameningeal), other (trunk, retroperitoneum)	T1 or T2	a	N0 or Nx	M0
3	Bladder/prostate, extremity, head and neck (parameningeal), other (trunk, retroperitoneum)	T1 or T2	a b	N1 N0, N1, or Nx	M0
4	All	T1 or T2	a or b	N0 or N1	M1

Reprinted from Lawrence W Jr, Anderson JR, Gehan EA, et al. Pretreatment TNM staging of childhood rhabdomyosarcoma: A report of the Intergroup Rhabdomyosarcoma Study Group. Children's Cancer Study Group. Pediatric Oncology Group. *Cancer* 1997;80(6):1165–1170. Permission granted from previous edition.

Staging

The most widely utilized staging system for rhabdomyosarcoma is based on the (TNM) staging system. TNM staging system is applied prior to treatment and assesses disease site of origin, tumor size, nodal status, and metastases as factors in prognosis (**Table 103.10**). This system was prospectively tested in IRSG clinical trials IRS-III and IV and reflects the biology of the tumor.[165] Most tumors are greater than 5 cm in size and 20% present with distant metastases at diagnosis (stage 4). Stage 1 tumors involve the head and neck, genitourinary (nonbladder/prostate), and biliary tract sites. Regional nodes may or may not be involved with stage 1 tumors. Stage 2 tumors involve the bladder/prostate gland, extremity, cranial, parameningeal, retroperitoneal,

and trunk sites and are less than 5 cm without lymph node involvement. Stage 3 tumors are the same anatomic sites as stage 2 and are greater than 5 cm with or without lymph node involvement. Any rhabdomyosarcoma tumor with distant metastases is considered stage 4 disease.

Clinical Group Assessment and Risk Status

Both stage and group assessment is used to assign risk categories and to determine treatment plan. The IRSG developed a surgical–pathologic clinical grouping system to standardize risk assessment in the IRS I and II therapeutic clinical trials. Patients are grouped into four risk groups based on postoperative assessment of disease before initiating chemotherapy or radiation (**Table 103.11**).[166] Clinical group accurately predicts outcomes in patients with rhabdomyosarcoma.[166] Group I patients have excellent prognosis with localized tumors that are completely excised while group II patients have tumors that have microscopic residual disease or regionally invasive disease involving lymph nodes. Group III patients have gross residual disease or incisional biopsy, and Group IV patients have distant metastases at presentation. Stage, clinical group, histology, age, and anatomic site are utilized to identify low-, intermediate-, and high-risk categories, and therapy is allocated based on patient risk status. Favorable sites are orbit, head and neck (except parameningeal), genitourinary (except bladder and prostate), and biliary tract sites. Unfavorable sites are bladder/prostate, extremity, parameningeal, trunk, retroperitoneal, pelvis, and all other sites. Combinations of chemotherapy and radiotherapy are administered based on risk-group assignment. Alveolar and embryonal histology subgroups contrast in prognostic factors and in survival outcomes.

In patients with nonmetastatic rhabdomyosarcoma, tumors considered low risk are embryonic rhabdomyosarcoma tumors (stage 1 or 2) located at favorable histology sites.[167] Embryonal tumors at unfavorable sites may also be assigned as low-risk group if the tumor is grossly completely resected (group I or II). There are two subsets of low-risk patient groups. Subset A (stage 1, group I or IIa, stage 2, group1, group III orbit) is associated with worse failure-free survival (82%) in patients >10 years old, though overall survival is the same as younger patients (92%). This suggests excellent salvage therapy in this subgroup of patients. Low-risk subset B patients

(stage 1, group IIb or IIc, stage 1, group III nonorbit; stage 2, group II, stage 1, group I or II) with tumors larger than 5 cm also have worse failure-free survival (77%) but similar overall survival as patients with smaller tumors (93%).[167] Intermediate-risk embryonal rhabdomyosarcoma are patients with unfavorable anatomic sites with tumor remaining after surgical excision. This risk group has worse survival outcomes than patients with low-risk tumors. In this group, patients with unresectable extremity rhabdomyosarcoma have extremely poor failure-free (43%) and overall (46%) survival.

Table 103.11 Surgical–Histopathologic Clinical Grouping System for the Intergroup Rhabdomyosarcoma Studies I and II

Group I Localized tumor, completely resected A. Confined to organ or muscle of origin B. Infiltration outside organ or muscle of origin, regional nodes not involved
Group II Compromised or regional resection including A. Grossly resected tumors with "microscopic" residual B. Regional disease, completely resected, in which nodes may be involved and/or tumor extends into an adjacent organ C. Regional disease with involved nodes, grossly resected, evidence of microscopic residual
Group III Incomplete resection or biopsy, gross residual disease
Group IV Distant metastatic disease, present at presentation

Reprinted from Crist WM, Garnsey L, Beltangady MS, et al. Prognosis in children with rhabdomyosarcoma: A report of the Intergroup Rhabdomyosarcoma Studies I and II. Intergroup Rhabdomyosarcoma Committee. *J Clin Oncol* 1990;8(3):433–452, with permission. © American Society of Clinical Oncology.

In general, children with alveolar rhabdomyosarcoma have worse survival outcomes compared to those with embryonal histology. Patients with stage 1 or 2 disease that is grossly resected (group I or II) have 5-year failure-free survival of 80% and overall survival of 85%. Stage 1 or 2 (group III) patients have overall favorable outcomes as well. Children less than 1 year of age with alveolar histology have considerably worse survival outcomes

(43%). Patients with stage 3 tumors with nodal involvement also have poor survival outcomes (34%). Survival correlates with stage and patients with high-risk tumors with distant metastases as diagnosis continue to have the worse expected survival of 25% despite intensified cytotoxic therapy and radiotherapy.

Treatment

Much of the treatment success of rhabdomyosarcoma is credited to successful clinical trials conducted by the IRSG and the Soft Tissue Sarcoma Committee of the COG. Multimodal therapy aims to minimize the risk of relapse and optimize curative outcomes, while also minimizing treatment toxicities. The INRG has completed five major clinical trials (IRS-I, II, III, IV, V/D) that provide the foundation upon which the current treatment schema is based for all children diagnosed with rhabdomyosarcoma. IRS-V or the "D" studies further refined treatment protocols based on prognostic factors and risk stratification.[166–169]

7 The mainstay of therapy begins with surgery, either complete excision with adequate margins or incisional biopsy. The goal for surgical margins is at least 0.5 cm of normal tissue surrounding tumor. Margins should be marked and oriented to assure that pathologists can accurately identify each microscopic margin. Contiguous structures, organs, major blood vessels or nerves that would result in major disability should not be resected in the initial operation, rather an adequate biopsy should be obtained and chemotherapy given upfront. In contrast, lesions that are small and not invading surrounding structures may be completely resected prior to chemotherapy. Resection of rhabdomyosarcoma tumors with wide and completely clear microscopic margins is the most ideal initial procedure for all stages to obtain local tumor control. Pretreatment reexcision is recommended after the initial operation if there is gross residual tumor or microscopically involved margins prior to the administration of chemotherapy. This is critical for accurate staging and for optimal clinical group assignment. Debilitating or highly morbid operations are performed only after chemotherapy and radiation have been given in attempt to decrease tumor burden and minimize extent of resection.

Lymph node sampling is indicated for patients with lesions that involve the extremity (even if clinically negative) or for clinically positive lymph nodes for all other sites. Biopsy by open, core, or sentinel lymph node biopsy techniques are all acceptable based on current COG guidelines. Staging ipsilateral retroperitoneal lymph node dissection is recommended for paratesticular rhabdomyosarcoma for all males older than 10 years of age and for those less than 10 years of age with enlarged appearing lymph nodes on CT scan. In this group, staging ipsilateral retroperitoneal lymph node dissection is required for adequate staging and risk-group assessment. A nerve-sparing ipsilateral retroperitoneal lymph node dissection is recommended. The boundaries of the dissection begin at the level of the renal veins surrounding the aorta and the vena cava, extending to the deep inguinal ring. The procedure may be performed laparoscopically or through an open abdominal incision. Patients with intermediate-risk tumors may benefit from radical debulking of clinically positive lymph nodes if feasible.

The addition of chemotherapy and radiotherapy to treatment protocols for rhabdomyosarcoma has dramatically improved survival rates. Currently all children diagnosed with rhabdomyosarcoma receive adjuvant chemotherapy with or without radiotherapy. Current treatment protocols for patients with low-risk rhabdomyosarcoma (subgroups A and B) consist of vincristine, actinomycin D, cyclophosphamide, and local radiotherapy to sites of residual disease (group II and III). A recent clinical trial from the Soft Tissue Sarcoma Committee of COG (D9602) focused on eliminating cyclophosphamide, and reducing radiotherapy doses in patients with lowest-risk rhabdomyosarcoma.[170] This study found that the 5-year failure-free and overall survival were lower than similar ISR-IV patients receiving cyclophosphamide. Given these results, the COG is currently studying a more modest dose reduction of cyclophosphamide (ARST0331, closed 2012) for both low-risk subgroups with aims of maintaining the excellent outcomes of IRS-IV and further reducing toxicity.[169]

Intermediate-risk tumors are nonmetastatic and include alveolar rhabdomyosarcoma at any site (stage 1 to 3). Embryonal rhabdomyosarcoma in an unfavorable site that is incompletely excised (stage 2, 3, group III) are also considered intermediate risk. The standard chemotherapy for this group is vincristine, actinomycin D, and cyclophosphamide with radiotherapy. Improvements in survival have not progressed as much in this group

compared to low-risk tumors. IRS-IV did not show improvement in outcomes for intermediate-risk group patients by the addition of ifosfamide and ifosfamide/etoposide substituting for actinomycin D and cyclophosphamide.[171] The COG recent intermediate-risk study (D9803) compared standard vincristine, actinomycin D, cyclophosphamide to a regimen that alternated standard therapy with vincristine, topotecan, and cyclophosphamide.[172] This regimen did not significantly improve outcomes compared to standard therapy. The COG's most recent trial (ARST0531, closed 2013) randomized patients to receive standard therapy versus standard therapy alternating with vincristine and irinotecan, and earlier-onset radiotherapy.[169] The actions of vincristine and irinotecan are thought to be synergistic with enhanced cytotoxic activity based on preclinical and pilot studies. Unfortunately, this study found that despite interventions to improve local control, local failure was higher on ARST0531 than D9803 for unclear reasons that may be related to the reduced cyclophosphamide.[173]

High-risk patients have metastatic disease on presentation with dismal outcomes despite intensive cytotoxic therapy. Current therapy for high-risk tumors is based on results of the COG high-risk rhabdomyosarcoma phase II window studies (D9802) and previous IRS-I-IV trials.[174] These studies were the backbone for ARST0431 (closed 2010) which treated patients with multiple combinations of intensive chemotherapy that included vincristine, actinomycin D, doxorubicin, irinotecan, cyclophosphamide, and ifosfamide/etoposide.[175] The feasibility of concurrent early administration of radiotherapy and irinotecan is also being evaluated. Long-term follow-up on the most optimal combinations of intensified chemotherapy in high-risk rhabdomyosarcoma patients is needed. Recently, the COG study (ARST08P1) examined novel biologic agents. Cixutumumab, a monoclonal antibody against insulin-like growth factor-I receptor (IGF-IR) and temozolamide were added to intensive chemotherapy backbone regimens. Early results were promising for improved failure-free survival with cixutumumab but overall survival remains poor.[176]

Radiotherapy in the form of external beam radiation is utilized in group II to IV patients and in group I alveolar cases to enhance local control.[177] Radiotherapy is utilized as the primary means of local control in rare cases where surgical excision carries excessive risk or concern for disfigurement (orbital and vaginal). Parameningeal tumors are treated with radiotherapy

because of the high likelihood of residual disease with surgical excision. The most commonly utilized doses range from 36 Gy to 50 Gy and higher doses are administered to patients with group III or IV disease (50 Gy given in 28 fractions).[177] The IRSG studied a trial of hyperfractionated radiotherapy versus conventionally fractionated radiotherapy in patients with group III rhabdomyosarcoma and found no differences in failure rates or survival outcomes.[178]

Future Directions

Future clinical trials are focused on further tailoring therapies to reduce treatment toxicities and late adverse effects while improving curative outcomes. The current focus is incorporation of novel biologic agents to known active backbone chemotherapy regimens, particularly for patients with intermediate-risk and high-risk rhabdomyosarcoma. Human patient tumor–derived xenograft models are guiding future development of novel targeted therapies for this cancer. The NCI supports the Pediatric Preclinical Testing Consortium; a program to evaluate novel molecules for genetically characterized solid tumors, including rhabdomyosarcoma (https://ctep.cancer.gov/MajorInitiatives/Pediatric_Preclinical_Testing_Consortium.htm).

NONRHABDOMYOSARCOMA SOFT TISSUE SARCOMA

Epidemiology

Soft tissue sarcomas in children and adolescents occur in approximately 8% of all childhood solid tumors. Nonrhabdomyosarcoma soft tissue sarcoma (NRSTS) represents approximately half of these cases, occurring in 250 to 300 children per year in the United States.[179] Infants and adolescents are more commonly affected, and there is a slightly higher incidence in males and in African Americans. NRSTS comprises 27% of sarcomas in infants (<12 months), of which, 24% are fibrosarcomas, 1.7% are malignant fibrous histiocytoma (MFH), and 1.3% are peripheral nerve sheath tumors.[180] The

incidence of NRSTS has not changed in the last several decades. The overall 10-year survival has also remained steady at 73%. The tumors are distinct from rhabdomyosarcoma in terms of clinical characteristics, tumor biology, and prognosis. Most cases are sporadic although patients with Li–Fraumeni syndrome, neurofibromatosis type I (peripheral nerve sheath tumors), Gorlin syndrome (fibrosarcoma and leiomyosarcoma), and hereditary retinoblastoma have a higher risk of developing soft tissue sarcomas.[181–183] Children that are survivors of childhood cancer are at an increased risk for NRSTS, particularly those with a history of receiving radiation, high-dose anthracyclines, and alkylating agents.[184]

Pathology and Biologic Features

NRSTSs originate from developmental mesenchymal cells with heterogeneous histologic subtypes and diverse sites of origin. These tumors are classified based on histology-specific cytogenetics of the tumor. NRSTS may have segmental chromosomal alterations (balanced translocations) or widespread genomic instability (**Table 103.12**). Most of the translocations found in NRSTS generate fusion proteins from two different transcription factors that disrupt normal embryonic development and drive sarcomagenesis.[185] ETV6-NTRK3 found in infantile fibrosarcoma and ALK found in inflammatory myofibroblastic tumors are tumor cell-specific activated kinases that may have important roles in pathogenesis.[186] Dermatofibrosarcoma protuberans contain the COLIA1-PDGFB fusion gene.[187] Genetic analysis is a powerful tool for diagnosis of NRSTS and is an important component of the histopathologic assessment. Detection of tumor-specific chromosomal alterations by RT-PCR, FISH, or high-throughput sequencing analyses often aid in confirming the diagnosis and in treatment planning.

Table 103.12 Nonrhabdomyosaroma Tumor Characteristics

Tumor	Incidence[a]	Normal Counterpart[a]	Cytogenetic Abnormality[a]	Genes[a]	Common Primary Sites
Fibrosarcoma	0.6	Fibroblasts	t(12;15)	TEL (ETV6), NTRK3(TRKC)	Lower extremity, upper extremity
Desmoplastic round cell tumor[b]	Approximately 200 case reports	Lineage epithelial, neural, myogenic cells	t(11;22)	EWS, WT1	Abdomen, paratesticular, thoracic cavity
Leiomyosarcoma	0.3	Smooth muscle	Variable	Multiple gene alterations	Gastrointestinal or genitourinary, superficial dermis, retroperitoneal, lungs, uterus, vascular
Alveolar soft parts tumor	0.1	Unknown	t(x;17)	ASPL, TFE3	Thigh, buttocks, abdominal and chest wall
Neurofibrosarcoma	0.6	Schwann cell	Variable, abnormalities of chromosome 17	Multiple genetic alterations, NF1	Extremity, retroperitoneum, trunk
Liposarcoma	0.1	Adipocyte	t(12;16)	FUS, CHOP	Lower and upper extremity, retroperitoneum
Tendosynovial sarcoma	0.7	Synovial cells	t(x;18)	SYT, SSX-1, or SSX-2	Lower extremity (thigh, foot, posterior knee), upper extremity (shoulders, forearm)
Dermatofibrosarcoma protuberans	1.0	Fibroblasts	t(12;22)	COL1A,PDGF	Trunk, proximal extremities

[a]From Gurney J, Young J Jr, Roffers S, et al. In: Ries LAG, Smith MA, Gurney JG, et al., eds. *Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975–1995*. Bethesda, MD: National Cancer Institute, SEER Program; 1999.
[b]From Saab R, Khoury JD, Krasin M, et al. Desmoplastic small round cell tumor in childhood: The St. Jude Children's Research Hospital experience. *Pediatr Blood Cancer* 2007;49:274–279. (Incidence age-adjusted per million younger than 20 years old (excluding desmoplastic round cell tumor).)

Presentation, Diagnosis, and Staging

NRSTS typically present as a painless slow-growing solid mass that may invade surrounding structures. Approximately 15% of patients present with metastatic disease at presentation, most commonly lungs.[188] Survival for patients presenting with metastatic disease remains poor (35%) and disease-free progression is only 15% despite aggressive multimodality therapy. In general, diagnostic workup for NRSTS consists of cross-sectional imaging (MRI) of the primary site along with imaging (CT scan) of chest, abdomen, and pelvis for surgical planning and adequate staging. Bone scintigraphy is used only for patients with bone pain or symptoms. Bone marrow biopsy is typically not indicated. Brain imaging is reserved for patients with CNS symptoms.

An adequate tissue specimen is required to determine the histologic subtype and grade of NRSTS. Complete surgical resection of all gross disease is recommended at presentation unless a wide resection is not feasible or accompanied by high surgical morbidity. Multiple core needle biopsies may be sufficient though the quality and quantity of specimen must be adequate for histologic and cytogenetic studies. Fine-needle biopsy is not acceptable for diagnosis. The fresh specimen should be evaluated for routine histopathology, immunohistochemistry, and molecular studies including DNA and RNA cytogenetic studies, flow cytometry, and electron microscopy.[184] Array technologies are being increasingly utilized in analysis of NRSTS, allowing measurements of tumor RNA expression and gene copy number.[189] A pathologic tumor grade is assigned to NRSTS based on extent of malignancy and is an indicator of prognosis. The grading system utilized in pediatric NRSTS was developed by the Pediatric Oncology Group using concepts of adult grading systems integrating characteristics of pediatric sarcomas.[190] The Pediatric Oncology Group grading system for NRSTS assesses mitotic rate, extent of necrosis, differentiation, and histologic type and can be used as a predictor of outcome.

The size of the mass is important in initial surgical planning and determines surgical approach.[191] Tumor sizes of 5 cm is utilized by the American Joint Cancer Commission staging system of sarcoma as standard "cutoff" for resectability, though this has been difficult to translate to children with small body surface areas. This was addressed by development of an equivalency factor that is utilized to calculate prognosis of soft tissue sarcoma based on size of the mass and body surface area.[192] Although tumor size is a key prognostic factor in adult soft tissue sarcomas, the risk is not the same in patients of different body sizes and 5-cm cutoff may not pertain to infants and children.

Extent of disease, grade, size, age, and extent of resection all influence prognosis and survival outcomes in NRSTS.[193] Patients are grouped into low-, intermediate-, and high-risk (metastatic disease) categories. High-risk patients have overall survival of approximately 15% and most patients succumb to widespread metastatic disease. Intermediate-risk patients have unresectable tumors at presentation with residual disease or large (>5 cm), high-grade tumors. The survival in this risk group is approximately 50%. Low-risk tumors are completely resectable (<5 cm or equivalent) and are

low grade.[184] Low-risk patients have the best prognosis with overall survival of 90%. In general, patients with negative microscopic margins have the best outcomes and the addition of radiotherapy minimizes the risk of recurrence. A pediatric NRSTS staging system has not been validated. The IRSG surgicopathologic staging system for rhabdomyosarcoma is often utilized as well as the TNM sarcoma staging systems for adults. The COG is addressing the issue of staging for pediatric NRSTS in ongoing clinical studies.

Treatment

Complete surgical resection is critical in the management of NRSTS because of resistance to chemotherapy and radiotherapy. Primary tumors that appear grossly resectable should be excised upfront. If the surgeon anticipates that gross residual disease is likely following surgery or if complete excision is debilitating or disfiguring, tumor biopsy should be performed. This is typically seen with large (>5 cm), high-grade regionally invasive or metastatic tumors that will benefit from neoadjuvant chemotherapy and delayed tumor resection. Tumor debulking is generally not recommended. Large, potentially morbid resections like amputation and pelvic exoneration are performed only after neoadjuvant therapies. In general, incisions on the extremities should be placed longitudinally and incisions on the trunk are oriented in the axial plane. If the surgeon determines that the mass is not amendable to full excision upfront, a generous incisional biopsy is required. Primary reexcision of the primary tumor is recommended if there is gross residual resectable tumor after the initial resection with at least a 0.5-cm margin. Reexcision is also recommended if the margin status is unknown. Previous scars or needle tracts should be included en bloc with the specimen. Lymph node sampling is required for abnormal-appearing lymph nodes on clinical examination or imaging. Several histologic subtypes of NRSTS also require lymph node evaluation for risk assessment and staging purposes, even in patients without enlarged lymph nodes. These include synovial cell sarcoma, epithelioid sarcoma, and clear cell sarcoma with up to 30% risk of lymph node metastases.[191] In these groups, patients without radiologic evidence of nodal metastases may benefit from sentinel lymph

node mapping with technetium 99m and biopsy rather than traditional lymph node sampling, though results have been mixed.

The most active chemotherapeutic agents for NRSTS are doxorubicin and ifosfamide, though most NRSTSs are relatively chemoresistant. Current treatment strategies are based on protocols from the COG clinical trial ARST0332 that assigned NRSTS patients to treatment groups based on risk. Low-risk patients (grossly resected, low grade, any size) receive surgical excision alone with or without radiotherapy, depending on margin status. Intermediate-risk and high-risk (metastatic disease) patients are treated with ifosfamide and dose-intensive doxorubicin and radiotherapy either before or after surgical excision. The risk-based treatment strategy set a new standard that produced outcomes similar to or better than historical controls with radiotherapy less frequently and at lower doses.[193] Because of the limited efficacy of chemotherapy in NRSTS, novel targeted therapeutic approaches are warranted, especially for children with high-grade or relapsed tumors.[184,193]

HEPATIC TUMORS

Hepatoblastoma

Epidemiology and Genetic Risk

Hepatoblastoma is the most common malignant liver tumor in children, occurring in 0.7 to 1 per million children <15 years of age, yielding approximately 100 cases per year in the United States.[4] The incidence of hepatoblastoma has increased roughly 4% in the last three decades in the United States.[194] Hepatoblastoma occurs most commonly in infants and children between the ages of 6 months and 3 years. A slight male predominance is reported and there does not appear to be significant differences in incidence among race. The median age at diagnosis is 18 months of age. Hepatoblastoma is the third most frequent abdominal tumor after neuroblastoma and Wilms tumor. Environmental risk factors have not been confirmed. Hepatoblastoma has been found in association with prematurity and low birth weight.[195] There is a strong association with very

low–birth-weight neonates (<1,500 g) though the underlying mechanism is not yet unknown.[194]

Several inherited syndromes are associated with hepatoblastoma. Patients with Beckwith–Wiedemann syndrome are at risk for developing hepatoblastoma and require routine screening.[196] Most cases are due to defective imprinting on chromosome 11p15.[197] Hepatoblastoma may also occur in children with hemihypertrophy and trisomy 18.[198] There is an increased risk of hepatoblastoma in children of families with familial adenomatous polyposis (FAP) syndrome though no specific genetic alteration in chromosome 5 has been identified.[199] There is a nonrandom association between hepatoblastoma and children with trisomy 18.[200]

Sporadic hepatoblastoma has not been characterized by any single chromosomal abnormality and cytogenetic analyses have not revealed consistent patterns. The most common genetic abnormalities are trisomies 2, 8, and 20.[201] These genetic alterations are thought to have a role in hepatoblastoma pathogenesis, but the precise molecular mechanism is not understood. LOH of 11p15 has been detected in up to 33% of children with hepatoblastoma and it is hypothesized that a tumor suppressor gene may be located in this region.[202] Insulin-like growth factor 2 (IGF-2), a fetal mitogen is an imprinted gene on 11p15 affected by β-catenin mutations.[203] LOH at 11p is most often of maternal origin and commonly found in patients with Beckwith–Wiedemann syndrome. LOH has also been found at chromosome 1p and 1q and may have a role in tumorigenesis.[204] Translocations involving the NOTCH2 gene at chromosome 1 have been detected in hepatoblastoma tumors.[205]

Pathology and Biologic Features

Hepatoblastoma displays a combination of histologic patterns that range from epithelial and mesenchymal elements. This tumor is thought to originate from undifferentiated embryonal hepatic cells that maintain pluripotency and have potential to develop into both hepatocytes and biliary epithelial cells.[206,207] Hepatoblastoma may be classified by five different histologic subtypes that carry prognostic value: well-differentiated fetal (pure fetal), embryonal, macrotrabecular (epithelial fetal or embryonal), small cell undifferentiated, and cholangioblastic (bile ducts predominate) (**Table 103.13**).[208,209] Of

these, the most favorable outcomes are seen with well-differentiated fetal subtypes. Small cell undifferentiated tumors (anaplastic subtype) carry the worse prognosis.[210] Small cell undifferentiated tumors are often associated with low or normal serum α-fetoprotein (AFP) levels (<100) and predict adverse outcomes with poor response to chemotherapy.[211] The majority of hepatoblastoma tumors are epithelial with mixed embryonal and fetal patterns (67%), and 21% of these have mesenchymal components.[209,212] Hepatoblastoma tumors secrete interleukin 1β which induces IL-6 production, enhancing hepatocyte growth factor.[213] There is evidence that hepatocyte growth factor is secreted postoperatively and functions as a growth factor for hepatoblastoma tumor cells.[214]

Table 103.13 Relative Risk of Death for Histologic Subtypes of Hepatoblastoma

Histopathologic Subtype	Relative Risk of Death[a]
Fetal	1.07
Embryonal	1.74
Mixed	0.53
Macrotrabecular pattern	1.20
Small cell undifferentiated	3.71

[a]Adjusted for age, sex, and stage compared with other histologic subtypes.

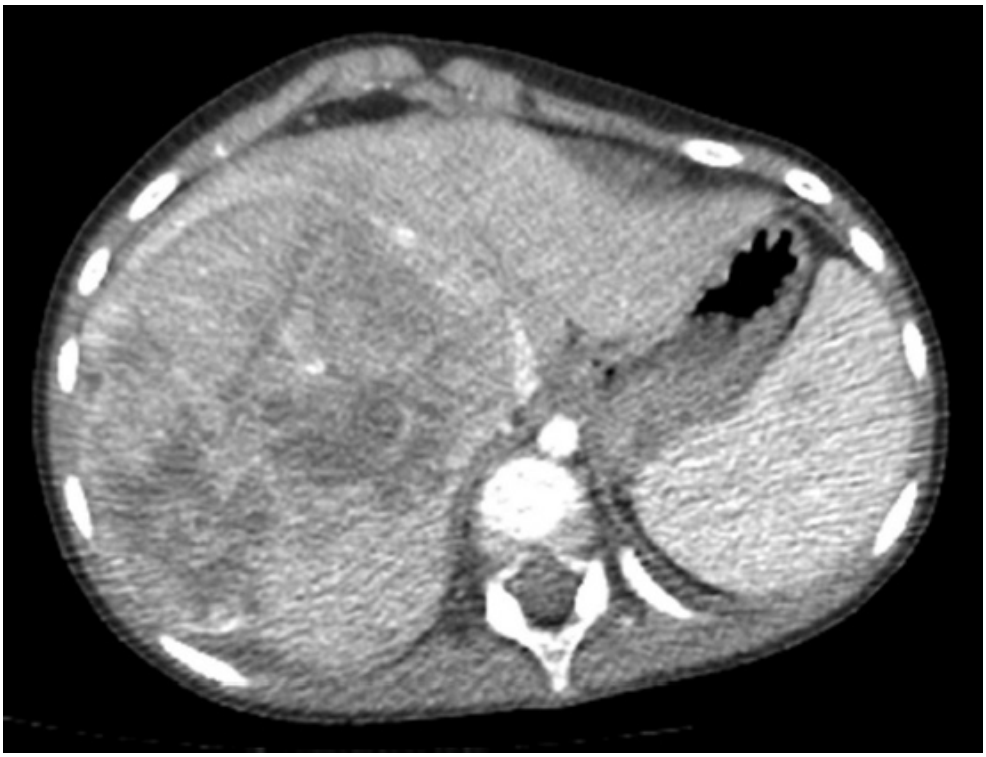

Figure 103.9 Abdominal CT scan with right hepatic lobe hepatoblastoma displacing normal hepatic vasculature and parenchyma.

Presentation, Diagnosis, and Staging

Children with hepatoblastoma present with an asymptomatic abdominal mass or abdominal swelling. Systemic symptoms like weight loss, failure to thrive, or anorexia may indicate advanced disease. Jaundice and biliary obstruction does not typically occur in patients with hepatoblastoma. Distant metastases are present in approximately 20% of patients at diagnosis and the most common site is lungs.[215] Ultrasound and cross-sectional imaging (three-phase CT scan or MRI with EOVIST) will define segmental extension of the tumor within the liver and assess for distant metastases (**Fig. 103.9**). The majority of hepatoblastoma tumors are located in the right lobe of the liver (up to 70%). The tumor appears as a solid mass with low attenuation. On MRI the lesion appears as low intensity on T1-weighted images and high intensity on T2-weighted images. There is no evidence that MRI is superior to CT scan for diagnosis or surveillance of hepatoblastoma. It is important to distinguish central venous structures and to evaluate the liver for multifocal disease. Chest CT scan is obtained to evaluate for lung metastases. Anemia and thrombocytosis are common in children with hepatoblastoma and is likely

related to cytokine secretion by tumor cells. AFP is elevated in approximately 90% of patients with hepatoblastoma and is a useful clinical marker for monitoring tumor responsiveness and recurrence. Interpretation of AFP may be difficult because the protein is expressed in the fetus and commonly remains elevated in normal neonates and infants up to 6 months of age. AFP may also be elevated in patients with hepatitis, hepatocellular carcinoma (HCC), and germ cell tumors. A high serum cholesterol level is also detected in 50% to 60% of children with hepatoblastoma.

Staging is based on the COG hepatoblastoma staging system (**Table 103.14**). This system is a postsurgical staging system that is based on outcome of the primary operation before the administration of chemotherapy.[216] Stage 1 (22%) is complete resection with clear margins. Stage 2 (0.5%) is complete gross resection with microscopic residual disease at the margins. Stage 3 (53%) is grossly positive margins, biopsy only at diagnosis, nodal involvement or tumor spill. Stage 4 disease (23%) is metastatic tumor at diagnosis.[217]

Table 103.14 Children's Oncology Group Staging for Hepatoblastoma

Stage 1	Complete resection
Favorable histology	Purely fetal histology with low mitotic index
Other histology	All other stage 1 tumors
Stage 2	Gross total resection with microscopic margins or total resection with preoperative or intraoperative rupture
Stage 3	Unresectable tumors as determined by the attending surgeon, partially resected tumors with microscopic margins, or any tumor with lymph node involvement
Stage 4	Measurable metastatic disease to lungs or other organs

Courtesy of the Children's Oncology Group Used with permission. © Children's Oncology Group.

Pretreatment extent of disease (PRETEXT) grouping is used internationally in combination with COG stage to stratify patients based the tumor's radiographic characteristics prior to treatment.[218] PRETEXT describes the anatomic involvement and Couinaud hepatic segments affected by the tumor and can be applied to patients who have not yet had operations[219] (**Fig. 103.10**). PRETEXT divides the liver into four parts termed sectors. The left lobe is divided into a lateral sector (segments 2 and 3) and a medial sector (segment 4). The right lobe is divided into an anterior sector (segments 5 and 8) and posterior sector (segments 6 and 7). PRETEXT is further annotated by V (venous involvement), P (portal vascular involvement), E (extrahepatic involvement), M (distant metastatic disease), C (caudate lobe), F (multifocal), and R (rupture prior to diagnosis) categories. Imaging is obtained after every two cycles of chemotherapy, where POSTTEXT (posttreatment of disease) is then used to reassess anatomy.

The COG utilizes stage, PRETEXT, histology, and AFP at diagnosis to determine risk for therapy assignment and for clinical trial standards. In general, excellent prognosis is expected for stage 1 tumors completely resected at diagnosis with pure fetal histology. Poor prognosis is associated with PRETEXT IV, metastatic tumors, AFP less than 100, and tumors with small cell undifferentiated histology.[212]

Treatment

Complete surgical resection is the mainstay of curative therapy for hepatoblastoma. Completely resected tumors have significantly improved survival outcomes compared with all other hepatoblastoma patients. The tumor may present as large bulky disease with mass effect on surrounding abdominal structures. The umbilical fissure is typically not involved. If the tumor appears resectable, conventional resection is performed. If the mass is judged unresectable at diagnosis, incisional biopsy is performed, and the patient is treated with chemotherapy prior to conventional resection. A complete preoperative evaluation is necessary to assess full extent of disease, PRETEXT, and to determine a safe surgical plan that will achieve the highest survival outcomes. In the United States, tumor resection at diagnosis whenever possible is the preferred standard. This is based on the

notion that a subset of patients may be spared toxicity of unnecessary neoadjuvant chemotherapy and that tumors have capacity to become resistant to prolonged chemotherapy.[216,220] The COG currently determines surgical resectability based on PRETEXT grouping.[8] Primary resection is recommended for localized PRETEXT 1 or PRETEXT 2 tumors with >1 cm radiographic margin on the middle hepatic vein, without vena cava or contralateral portal venous invasion.[216] Neoadjuvant chemotherapy is recommended for PRETEXT III or IV tumors and for multicentric tumors with central venous invasion. Patients with pulmonary metastases also receive chemotherapy upfront. Tumor volume and AFP measurements may be utilized to monitor tumor responsiveness after each cycle. Minimal benefit may be seen by prolonging induction therapy after cycle 2, therefore tailoring exposure to response may help reduce toxic effects.[221]

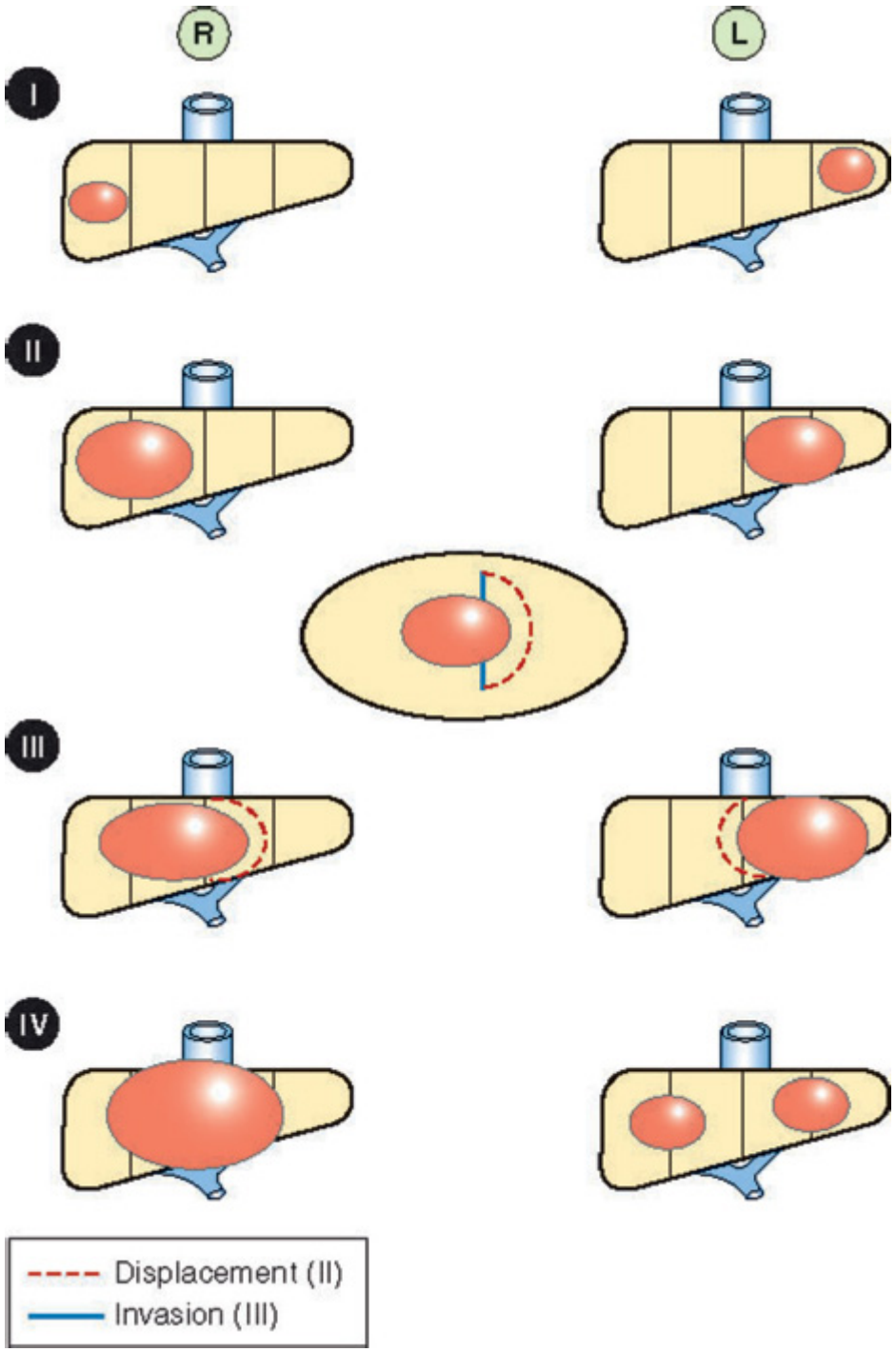

Figure 103.10 The Liver Tumor Study Group of the International Society of Pediatric Oncology (SIOP) SIOPEL-1 pretreatment extent of disease (PRETEXT) grouping system, PRETEXT Groups I–IV. R, right; L, left. (From Schnater JM, Aronson DC, Plaschkes J, et al. Surgical view of the treatment of patients with hepatoblastoma: results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group (SIOPEL-1). *Cancer* 2002;94(4):1111–1120, with permission.)

Conventional liver resection is safe and effective in children with hepatoblastoma and surgical techniques have been optimized in the last three decades.[222,223] An anatomic resection is recommended and is most often required. As much as 85% of hepatic parenchyma may be safely removed in children with full regeneration expected despite postoperative chemotherapy.[224] Mortality from liver resection in children should be low (0% to 3%) with technical advances such as the Cavitron Ultrasonic Surgical Aspirator (CUSA; Cooper Lasersonics, Santa Clara, CA) and metallic clip applicators for hemostasis while dividing liver parenchyma. The surgical principles include a generous incision with wide exposure using subcostal incisions. Dissection of the hilum with identification and isolation of the ductal and vascular structures of the segment of resection is critical. Hepatic arterial and portal venous inflow is obstructed or ligated, allowing demarcation of the resection plane. This allows the operation to proceed with minimal blood loss. Intraoperative Doppler ultrasound is often utilized to aid in locating major venous structures traversing the tumor and for assuring adequate resection margins of at least 1 cm.

Chemotherapy improves resectability of hepatoblastoma and improves prognosis in nearly all cases. Currently most patients diagnosed with hepatoblastoma receive chemotherapy either before or after resection of the primary tumor. Based on results from the Pediatric Oncology Group/Children's Cancer Study Group studies INT-0098 and P9645, patients with completely resected well-differentiated fetal histology (WDF or pure fetal histology) tumors and low mitotic activity may be treated exclusively with surgery alone.[225] Children with WDF histology tumors comprise 7% of hepatoblastoma cases and have 100% event-free survival. Most hepatoblastoma tumors are sensitive to cisplatin-based chemotherapy and overall survival increased from 30% to 70% with the addition of cisplatin.[226] The COG currently recommends cisplatin, 5-fluoruracil, and vincristine for all low-risk tumors (non–well-differentiated fetal histologic subtypes). Low-risk patients are patients with completely grossly resected tumors (stage 1 and 2, PRETEXT I or II) without any small cell undifferentiated histology elements and who do not have a low diagnostic AFP (<100). This group can expect 5-year event-free and overall survivals of 84% and 96%, respectively.[212] Intermediate-risk patients (PRETEXT II, III, or IV) are patients with gross residual disease or grossly resected

disease with small cell undifferentiated histology (without metastases) and without low diagnostic AFP (<100). High-risk tumors are any patients with metastatic disease and low diagnostic AFP level <100. Patients with intermediate-risk and high-risk tumors are currently treated with cisplatin, 5-fluorouracil, vincristine, and doxorubicin. The COG is currently determining the efficacy of the addition of doxorubicin to intermediate and high-risk patients and for patients with minimal radiographic response to standard therapy. Depending on risk group protocol, patients will receive two to six cycles of cisplatin, 5-fluorouracil, vincristine with or without doxorubicin prior to primary resection or transplantation. Outcomes for patients with hepatoblastoma after surgical resection and chemotherapy was documented in INT-0098 with 5-year event-free survivals for stage 1, 2, 3, and 4 of 91%, 100%, 64%, and 25%, respectively.[226] Overall survivals were similar. The subsets of patients with stage 3 or 4 disease that were able to have complete tumor resection and were tumor-free after induction chemotherapy had 5-year event-free survival of 83%. The role of radiotherapy in hepatoblastoma has not been defined because of the risk of hepatic toxicity and low hepatic tolerance to radiation in children. There may be a role for focal radiotherapy up to 45 Gy in patients with incomplete resection or microscopic residual disease.[227]

Liver transplantation has become a promising treatment option for children with unresectable hepatoblastoma without metastatic disease after neoadjuvant chemotherapy.[228] Liver transplantation has improved overall survival in children with large, or multifocal unresectable hepatoblastoma.[229,230] Tumors with extensive major vessel involvement or multifocal disease should be referred to centers that have pediatric liver transplant expertise.[216] Primary transplantation is also recommended for multifocal PRETEXT IV tumors despite apparent clearance after chemotherapy because of the risk of persistent microscopic disease.[231] If after four cycles of chemotherapy, the tumor remains unresectable by conventional liver resection, liver transplantation is recommended. These are typically POSTTEXT IV or POSTTEXT III with major vascular involvement that would jeopardize blood supply to the contralateral lobe.[232] A review of the United Network for Organ Sharing (UNOS) database revealed overall 1-, 5-, and 10-year graft survivals were 71%, 61%, and 58%, respectively, for patients receiving liver transplant for hepatoblastoma.

Overall 1-, 5-, and 10-year patient survivals were 79%, 69%, and 66%, respectively.[233] Other series have reported similar success.[230] The primary cause of death was metastatic and relapsed disease. For transplantation eligibility, patients with hepatoblastoma must not have any active extrahepatic or metastatic sites that have not cleared with surgery or chemotherapy. Patients with lung metastases are not excluded from transplantation if the lung disease is clear after neoadjuvant chemotherapy. It is critical to correctly identify patients who will benefit from primary liver transplant prior to attempts at conventional resection because liver transplant after incomplete tumor resection or hepatic relapse has had disappointing results, with reported survival for "rescue" transplant of only 40%.[234]

The COG and other large international cooperative groups are investigating novel therapeutic strategies. COG AHEP-0731 is a COG study that is randomizing patients with metastatic disease to receive a novel upfront window design of vincristine, irinotecan, and vincristine, irinotecan, temsirolimus prior to standard cisplatin, 5-fluorouracil, vincristine, and doxorubicin therapy.[235] Chemotherapeutic intensification by dosing and duration has had promising preliminary results and may be beneficial in patients with high-risk hepatoblastoma. The expanding role of antibodies and T lymphocytes as anticancer therapy for pediatric solid tumors may also hold promise as novel treatment agents for hepatoblastoma.[236]

Hepatocellular Carcinoma

HCC occurs more commonly in older children and is similar in histopathology to the disease in adults. HCC accounts for less than 0.5% of pediatric tumors and is the second most common malignant liver mass in children after hepatoblastoma. Risk factors and pre-existing liver diseases for HCC include cirrhosis, type 1 glycogen storage disease, autoimmune hepatitis and primary sclerosing cholangitis.[216] Areas endemic for hepatitis B have higher incidences of HCC in children. HCC is rare in infancy and there is a slight male predominance. HCC tumors are classified as either epithelial variant (75%), fibrolamellar (15%), and rarely poorly differentiated or clear cell.[237] Differences in outcome or treatment response among children with different histologic subtypes of HCC have not been confirmed. The fibrolamellar subtype is seen more often in younger children

and rarely occurs with cirrhosis. The most common presenting symptom is hepatomegaly and abdominal pain although HCC is often indistinguishable from hepatoblastoma on physical examination, imaging, and laboratory values. The diagnostic workup mirrors hepatoblastoma and diagnosis is confirmed by histopathologic examination of tumor biopsy or resection. HCC is more likely to have multifocal nodules with intrahepatic venous and lymphatic spread. More than one-third of patients have lung metastases at diagnosis. The PRETEXT grouping system is utilized for risk assessment and to determine resectability. PRETEXT III and PRETEXT IV are the most common categories at presentation in patients with HCC.

As reported by the Intergroup Pediatric Oncology Group Study 8945/CCG 8881, 17% of patients diagnosed with HCC had stage 1 disease, none had stage 2 disease, 54% had stage 3, and 28% had stage 4 disease.[217] It is not clear whether AFP levels can be used to predict outcome in HCC similarly to hepatoblastoma as study results have not been consistent.[217] The overall event-free survival for children with HCC at 5 years was 19%. Stage 1 disease had the best outcome compared to stage 3 and 4. The 5-year event-free survivals for stage 1, 3, and 4 were 88%, 8%, and 0%, respectively.[217] Overall survival was similar to event-free survival for each disease stage. Complete surgical resection or transplantation has the highest potential for cure in children with HCC. Unfortunately, fewer than 20% of patients with HCC have tumors that are resectable at diagnosis and multifocal tumors are common. In contrast to hepatoblastoma, HCC tumors are generally unresponsive to chemotherapy and outcomes for patients with stage 3 disease and higher are dismal. Transplantation is reserved for patients with localized tumor without any evidence of metastatic disease at presentation because of high risk of pulmonary metastatic relapse.[216] The guidelines for liver transplantation in HCC are largely derived from the adult experience using the Milan criteria (not more than three tumors, less than 3 cm in size, or single tumor less than 5 cm in size).[238] The COG studies on liver tumors and hepatoblastoma include children with HCC and treatment regimens have generally been the same. Treatment protocols for HCC currently consist of cisplatin, vincristine, doxorubicin, and 5-fluorouracil in multiple combinations. Compared to hepatoblastoma, these agents are not as effective in HCC and patients generally remain with poor prognosis.[226] The majority

of patients do not undergo postinduction surgery or liver transplantation because of the presence of either unresectable or metastatic disease.

Alternative approaches for local control have demonstrated some benefit in children with HCC. Hepatic arterial chemoembolization (HACE) in patients with refractory and unresectable disease requires cooperative group study, but has been shown to be well tolerated and may be effective in inducing surgical resectability in select cases of HCC.[239]

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104

The Pregnant Patient

Eugene S. Kim and Michael J. Zobel

Key Points

1. Maternal administration of antenatal corticosteroids is one of the most significant advances in the reduction of morbidity of prematurity.
2. Understanding the relative increase in the size of the gravid uterus and the displacement of intra-abdominal and pelvic structures is a critical step in surgical planning, specifically with regards to incision location, laparoscopic port placement, and patient positioning in the operating room.
3. There is no evidence that tocolytic therapy has a direct benefit on improving neonatal outcome, except for short-term prolongation of pregnancy to allow for the administration of antenatal steroids.
4. Fetal heart rate monitoring, the most commonly performed procedure during pregnancy, is associated with a substantial decrease in early neonatal morbidity, particularly in preterm fetuses.
5. Ultrasonography is considered the first-line diagnostic imaging modality of the pregnant surgical patient. Computed tomography is safest and most useful in the second and third trimester; dose-reduction protocols result in reduction in the probability of biologic effects to the fetus without sacrificing the necessary diagnostic image quality.
6. Acute appendicitis is the most common nonobstetric cause of acute surgical abdomen during pregnancy, and delays in diagnosis can have serious consequences for both mother and fetus.
7. Biliary tract disease is the most common cause of maternal hospitalization in the first year after delivery; when possible, cholecystectomy should be deferred to the second trimester to reduce the risk of pregnancy-related complications.
8. Pregnant patients with breast cancer should be managed by similar treatment strategies as nonpregnant patients, without delay of treatment, but with a few adjustments to account for potentially teratogenic interventions. Pregnancy termination does not result in improved outcomes for pregnant patients with breast cancer.

9 The most important principle of managing the pregnant patient after major trauma, the leading cause of nonobstetric maternal and fetal mortality, is that any diagnostic test or treatment should be performed if that intervention is required to save the mother's life, even if that intervention is potentially dangerous for the fetus.

10 A multidisciplinary approach is essential for safely managing these complex patients.

Nearly every general surgeon will encounter a pregnant patient with a surgical diagnosis. While many basic principles of care remain consistent, there are some critical differences that must be noted. To provide appropriate pre-, intra-, and postoperative care, the general surgeon must possess a complete understanding of the unique physiology of the pregnant patient. Moreover, any surgeon managing a gravid patient must be aware of the effects that diagnostic and therapeutic interventions might have on the fetus. To ensure the safety of the mother and the fetus, a multidisciplinary approach is essential for managing these complex patients. This chapter will review the most common surgical diseases that present during gestation and current management recommendations.

DEVELOPMENT OF THE FETUS

Human development begins immediately following fertilization of the oocyte by the sperm. Prior to 20 weeks of gestation, ultrasonography provides a better estimate of gestational age of the fetus than the estimated last menstrual period. The optimum timing of the ultrasound examination occurs during the first trimester when crown-rump length is within 5 days of the date of conception.[1–3] The earliest stages of development is referred to as the embryonic period, which extends to the end of the 8th week. By the completion of the embryonic period, organogenesis has begun with critical development of the brain and central nervous system (CNS), heart, lungs, diaphragm, intestines, and abdominal wall. Exposure to toxins, medications, or ionizing radiation during this period can have catastrophic effects on the

developing fetus. During the ensuing fetal period, which lasts from the 9th week to birth, growth and development of tissues and organs occur in preparation for birth. By the beginning of the third trimester, the fetus may survive if born prematurely, though the functional status of the respiratory system is crucial in determining viability.[4] Surfactant production, which begins by the 20th week of gestation, is necessary for both reduction of surface tension at the alveolar–air interface and proper oxygen exchange. In general, surfactant is present in only small amounts before 24 weeks, but this can be augmented by maternal administration of 1 antenatal corticosteroids, one of the most significant advances in the reduction of morbidity of prematurity.[4] Corticosteroids not only increase surfactant secretion in the fetal lung but also induce morphologic development of pulmonary epithelial cells and increase lung compliance. Corticosteroids also stimulate development of other organ systems, decreasing the incidence of necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, and death. The maximum developmental effects can be seen as early as 24 hours after maternal administration of dexamethasone or betamethasone, and administration at the first sign of premature onset of labor can improve survival, particularly before birth between 22 and 25 weeks.[5–7]

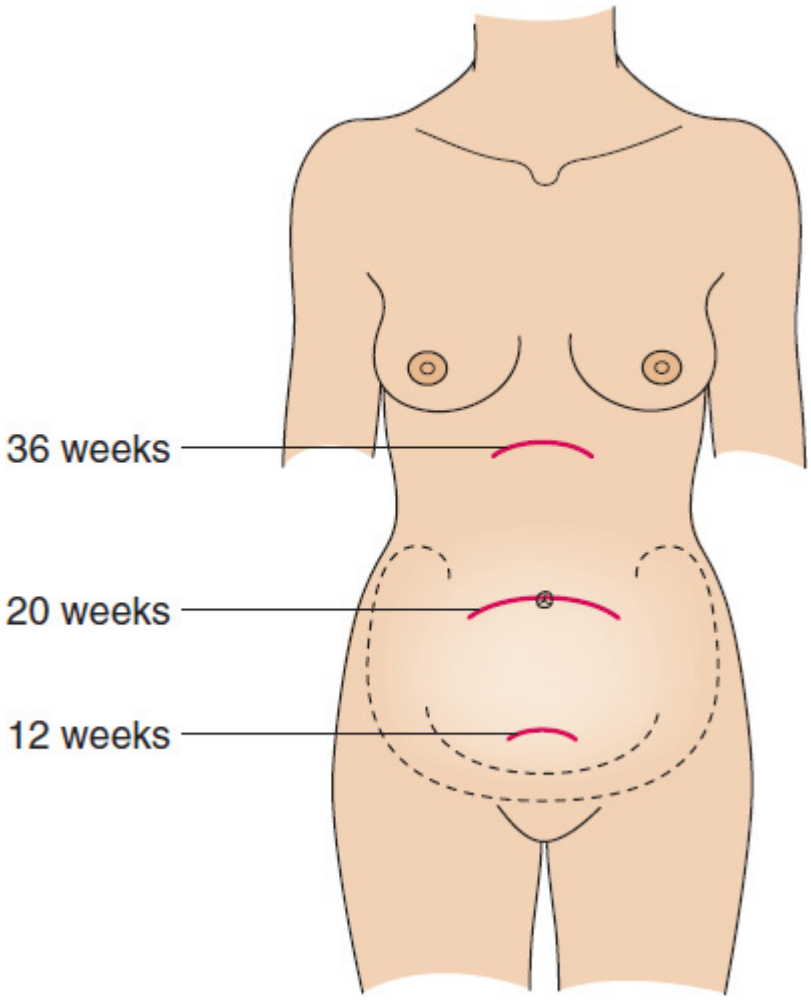

Figure 104.1 Enlarging uterus during gestation. At 12 weeks, the uterus rises out of the pelvis into the abdomen. At 20 weeks, the fundus is at the height of the umbilicus, and at 36 weeks, the uterus reaches to the upper abdomen.

ANATOMY OF THE CHANGING UTERUS

In a nonpregnant woman, the uterus resides within the pelvis, weighs approximately 70 g, and has a cavity volume of 10 mL. By the end of the first trimester, the uterus expands out of the pelvis and reaches the level of the umbilicus by 20 weeks. With progressive increase in size, the uterus contacts the anterior abdominal wall, displacing the bowel laterally and superiorly, and nearly reaching the liver by 36 weeks (**Fig. 104.1**).[8] Coupled with its ascent from the pelvis, the uterus usually rotates to the right due to the presence of the sigmoid colon on the left side of the pelvis. By the

completion of the first trimester, the size of the uterus frequently precludes entry into the abdomen below the level of the umbilicus, and thus altering port placement for laparoscopic surgery and incision location for open abdominal exploration. Furthermore, when the pregnant woman lies supine, the gravid uterus can compress the inferior vena cava, decrease cardiac preload and potentially cause hypotension. As such, patient positioning, particularly in the operating room is even more important during pregnancy to avoid aortocaval compression syndrome.

PREMATURE ONSET OF LABOR

Preterm birth is defined as birth prior to 37 weeks of gestation. Although only 12% of all live births in the United States fit this criterion, prematurity is responsible for approximately 70% of neonatal deaths, 36% of infant deaths, 25% to 50% of cases of long-term neurologic impairment in children, and a high cost to the health care system.[9–12] The etiology of preterm labor is often multifactorial, but the onset of labor from fetal and uterine stress during surgical manipulation or intra-abdominal inflammatory processes is of most concern to the surgeon. Bacterial infection of the amniotic tissues or peritoneum can also contribute to early initiation of labor, secondary to a local increase in eicosanoids, while endotoxin acts on inflammatory cells to increase production of IL-1 and IL-6, which can also amplify local prostaglandin production.[13] Uterine trauma due to surgical manipulation can affect these same mechanisms, leading to premature uterine contractions. The interrelations at various levels between the inflammatory response, uterine and maternal trauma, and the initiation of labor can represent the body's attempt to expel the fetus from a hostile uterine environment.

Tocolysis

To date, there is no evidence that tocolytic therapy has a direct benefit 3 on improving neonatal outcome, except for short-term prolongation of pregnancy to allow for the administration of antenatal steroids, transport of the patient to a tertiary care facility, and fetal neuroprotection.[14–16] In general, tocolysis is indicated between the potential period of fetal viability, beginning at 24

weeks of gestation, and 34 weeks of gestation in women with preterm contractions with cervical change. However, it is acceptable to administer tocolytics before 24 weeks of gestation following events known to cause preterm labor, such as intra-abdominal surgery and in utero fetal surgery, although evidence of efficacy for such intervention is lacking.[17,18] Prostaglandin synthesis inhibitors, magnesium sulfate, beta$_2$-adrenergic agonists, and calcium channel blockers represent the four most common pharmacologic tocolytic agents used. Studies report a 95% tocolytic success rate at 48 hours and a potential delay in delivery of 1 week in 80% of patients.[19] However, maternal and fetal side effects can be serious with tocolytic agents. Premature constriction of the fetal ductus arteriosus and necrotizing enterocolitis with the use of indomethacin has been reported and can result in neonatal pulmonary hypertension and even death.[20,21] Maternal cardiovascular side effects, including pulmonary edema, can occur in 5% of beta$_2$-agonist users and 10% of those treated with magnesium. Although this complication is rare, it can result in maternal death. The decision to use tocolytics must be made only after the diagnosis of premature onset of labor is confirmed, and the benefits of prolonging gestation outweigh the risks of tocolysis. Initiation of tocolytic therapy for potential but unconfirmed preterm labor is discouraged.[22] Maintenance therapy with any of the aforementioned tocolytic agents has not been demonstrated to prolong pregnancy or improve neonatal outcomes after an initial treated episode of threatened preterm birth and, therefore, should not be used for this purpose.[23–25]

MONITORING OF THE FETUS

Perioperative fetal monitoring, as well as the monitoring of premature uterine contractions, is based on technology developed for intrapartum fetal monitoring from the late 1950s and early 1960s. Observational studies performed at that time and in the mid-1970s convincingly established a relationship between the degree of fetal acidemia and the presence and depth of decelerations and decreased or absent fetal heart rate variability.[26,27] Established heart rate patterns and variable cardiac responses to fetal and maternal stimuli reflect an intact, well oxygenated CNS. Identification of

deviation from those patterns indicative of metabolic acidosis was hoped to decrease the incidence of hypoxic-ischemic encephalopathy and death. Research studies using the U.S. 2004-linked birth and infant death data found that the use of electronic fetal monitoring was associated with a substantial decrease in early neonatal morbidity particularly in preterm fetuses.[28] Recent data 4 indicates that of the approximately 4 million live births a year in the United States, 85% are assessed with fetal heart rate monitoring, making it the most common procedure in pregnancy.[29]

Fetal heart rate monitoring may be performed externally or internally. Most external monitor devices use the Doppler principle with computerized logic to count and interpret the Doppler signals originating from the fetal heart and maternal uterus. Internal fetal heart rate monitoring is accomplished with a spiral device attached to the fetal scalp or other presenting part. A transcervical intrauterine pressure catheter is sometimes used to monitor more accurately the strength and frequency of uterine contractions (**Fig. 104.2**). Both tracings are printed on a continuous strip of paper, with the fetal heart rate plotted at the top of the graph and uterine activity at the bottom.

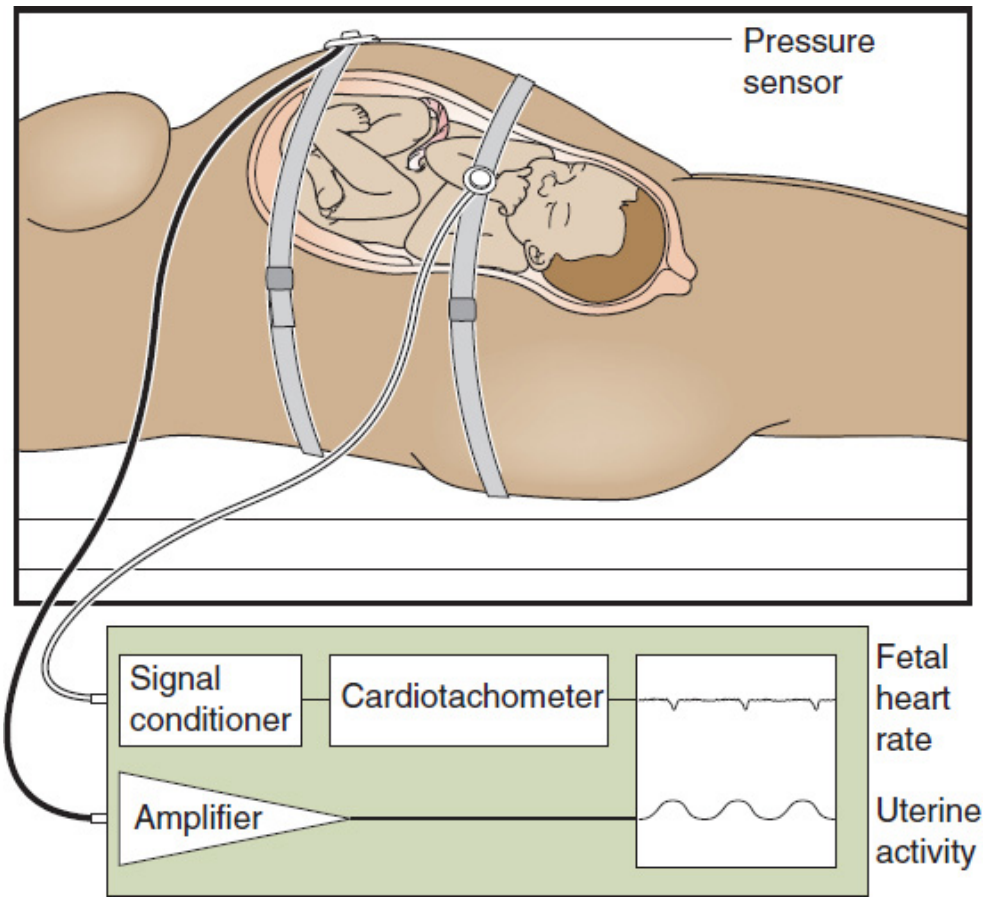

Figure 104.2 Intraoperative and postoperative fetal monitoring using noninvasive surface Doppler and pressure sensor to monitor uterine contractions. (Reproduced from Miller DA, Paul R. Antepartum–intrapartum monitoring. In: Scott JR, DiSaia PJ, Hammond CB, et al., eds. *Danforth's Obstetrics and Gynecology*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:243–255.)

Fetal Heart Rate

Normal fetal heart rate during pregnancy ranges between 110 and 160 beats/min. A prolonged baseline above 160 beats/min is considered tachycardia, whereas that below 110 beats/min is bradycardia. These terms refer to long-term patterns, and minute-to-minute variations in the heart rate away from baseline are known as accelerations or decelerations. Normal fetal heart rate tracings express continuous adjustment in the vagal tone through variability in the heart rate. The fetal heart rate response governed by a nonacidotic, well-functioning vagal conduction system manifests both long-term and short-term variability, with fluctuations of peaks and troughs ranging from 6 to 25 beats/min (**Fig. 104.3**). Decreased heart rate variability,

either long or short term, can signal diminished CNS activity. Although this can be a physiologic response of the fetal sleep–wake cycle or maternal medication and sedatives, persistently decreased reactivity can signal CNS acidosis. Fetal heart rate accelerations are normal findings in the second half of pregnancy and occur as a result of increased sympathetic stimulation and decreased parasympathetic stimulation with fetal movements. Fetal heart rate decelerations are usually encountered during uterine contractions of the intrapartum period. Evaluation of decelerations during labor and as part of intraoperative fetal monitoring can give clues to the status of the placental blood supply. Early decelerations are characterized by a symmetrical and gradual decrease and return of the fetal heart rate that mirror uterine contractions and reflect increased vagal tone from a transient increase in intracranial pressure. This pattern is considered a benign physiologic manifestation of a functioning autonomic nervous system and has no adverse outcome. Variable decelerations are distinctively recognized by their abrupt decrease in fetal heart rate of 15 beats/min or greater from the onset of the deceleration to the beginning of the fetal heart rate nadir of 30 seconds, lasting 15 seconds or greater, and less than 2 minutes in duration. When variable decelerations are associated with uterine contractions, their onset, depth, and duration vary with successive uterine contractions. Isolated variable decelerations have little clinical significance, but if persistent with inadequate recovery between contractions, fetal hypoxemia and acidosis can occur. Late decelerations present usually as a symmetric and gradual decrease and return of the fetal heart rate associated with a uterine contraction. But, late decelerations can have an ominous connotation as they can represent significant uteroplacental compromise, caused by maternal hypotension due to inferior vena cava compression, hypoxia or anemia.[30] Intraoperative fetal compromise as indicated by an ominous heart rate tracing must be treated by correcting maternal hypotension or increasing oxygen delivery with increased FiO_2, positional changes, aggressive fluid resuscitation, or blood transfusion. The inability to improve the intrauterine milieu can necessitate an emergent cesarean section to prevent fetal demise.[31]

The decision to use continuous fetal heart rate monitoring during nonobstetric surgery in pregnancy is controversial and should be based on

gestational age, type, site, duration, and extent of the procedure. For previable pregnancies (<23 weeks), documentation of fetal heart activity by Doppler before and after the procedure suffices.[32] For viable gestations, there is mixed support for fetal heart rate monitoring, but at a minimum, simultaneous electronic fetal heart rate and contraction monitoring should be performed before and after the procedure to assess fetal well-being and the absence of contractions. If the decision is to perform intraoperative electronic fetal heart monitoring, then all the necessary provisions should be made to provide optimal safety for the mother and the fetus. These include availability of obstetric care providers, anesthesiologists, neonatologists, and nurses working as a team and ready to intervene during the surgical procedure for fetal indications. Informed operative consent should thus be obtained in anticipation for a possible emergency delivery.[33]

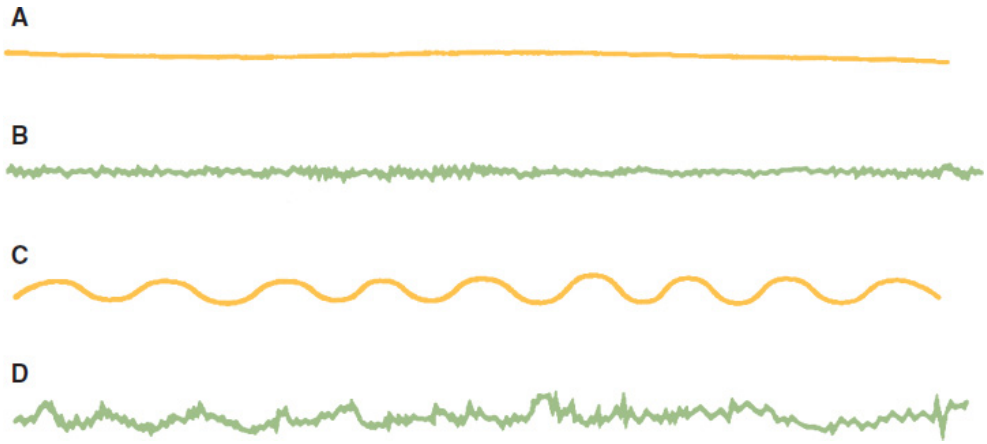

Figure 104.3 Fetal heart variability. **A:** Short-term and long-term variability both absent: abnormal. **B:** Short-term variability present, long-term variability absent: abnormal. **C:** Long-term variability present, short-term variability absent: abnormal. **D:** Both short- and long-term variability present: normal. (Reproduced from Miller DA, Paul R. Antepartum–intrapartum monitoring. In: Scott JR, DiSaia PJ, Hammond CB, et al., eds. *Danforth's Obstetrics and Gynecology*. 8th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999:243–255.)

IMAGING THE PREGNANT PATIENT

The most commonly used imaging modalities during pregnancy include plain radiography, ultrasonography, magnetic resonance imaging (MRI), and computed tomography (CT). The first and the latter are forms of ionizing

radiation. The risks of ionizing radiation can be an important source of anxiety for health care providers and patients and can alter the decision to perform the appropriate diagnostic study of choice for fear of injuring the fetus. This misconception could place both the mother and the fetus in greater danger from misdiagnosis. Although experimental data regarding the effects of ionizing radiation on the developing human fetus are impossible to obtain, animal exposure and follow-up of those inadvertently exposed to diagnostic and therapeutic radiation have provided some information. Retrospective studies of atomic bomb survivors in Hiroshima, Nagasaki, and victims of the atomic power plant disaster in Chernobyl have also allowed for evaluation of the effects of massive radiation exposure in utero.[34,35]

Ionizing Radiation

Fetal effects of ionizing radiation depend on the dose absorbed by the fetal tissue and the stage of fetal development during exposure. Exposure is defined as the amount of ionic charge created by the radiation on passing through a defined mass of air. It is a misconception to assume that the radiation dose that a pregnant woman is exposed to or absorbs is the same as that absorbed by the fetus as the latter is partially protected from radiation injury by a pregnant woman's surrounding soft tissues and uterus, both of which generally stop alpha and beta particles from penetration if they are not ingested, injected, or inhaled.[36,37] Radiographic evaluation of the abdomen and pelvis is most likely to expose the fetus to direct ionizing radiation, whereas examination of the extremities and chest leads to exposure from scatter radiation only (**Table 104.1**).[37] The potential deleterious consequences of radiation-induced ionization of vital cellular structures can be divided into four categories: (1) lethal effects, (2) teratogenic effect, (3) growth retardation, and (4) oncogenic potential. The occurrence of each effect depends upon the gestational age at the time of radiation exposure, the dose of radiation absorbed by the fetus, and fetal cellular repair mechanisms. The first three categories of adverse pregnancy outcomes have a deterministic effect whereby a threshold or No-Adverse-Effect Level exists. After exceeding the No-Adverse-Effect Level, a deterministic effect generally shows a gradient relationship with the absorbed dose—the larger the absorbed dose, the more severe the effect. On the contrary, cancer

appears to have a stochastic effect in which, the probability, but not the severity of the effect, increases with the radiation dose. Stochastic effects are monoclonal, resulting in changes to the cell genome and altered differentiation and function of the affected cells.

Table 104.1 Radiation Dosing to the Conceptus and Uterus from Selected Radiographic Examinations

Endoscopic retrograde cholangiopancreatography with no permanent films and shielding of abdomen	4 mrad
Routine chest radiograph	8–50 mrad
Routine mammography	<50 mrad
Abdomen (flat plate)	250–300 mrad
Computed tomography, chest	25–1,000 mrad (uterus shielded and not exposed)
Computed tomography, upper abdomen	670–3,000 mrad (uterus shielded and not exposed)
Computed tomography, abdomen	2,000–3,000 mrad

Data from Wagner L, Lester R, Saldana L. *Exposure of the Pregnant Patient to Diagnostic Radiation*. Madison, WI: Medical Physics Publishing; 1997; Wyte CD. Diagnostic modalities in the pregnant patient. *Emerg Med Clin North Am* 1994;12(1):9–43; and Baillie J, Cairns SR, Cotton PB. Endoscopic management of choledocholithiasis during pregnancy. *Surgery Gynecol Obstet* 1990;171(1):1–4.

Lethal Effects of Ionizing Radiation

The developing human is most sensitive to the lethal effects of ionizing radiation during the first 14 days after conception (3 to 4 weeks of gestational age). During this period, the "all or none" principle applies to the radiation-exposed embryo; it either survives undamaged or succumbs. At that gestational age, a dose of 100 to 200 mGy (10 to 20 rad) can be lethal for an embryo. Shortly thereafter, the threshold for fetal death increases to 250 to

500 mGy (25 to 50 rad). The estimated radiation dose to kill all embryos or fetuses less than 18 weeks of gestational age is 5,000 mGy (500 rad). At term, the fetal risk equals the pregnant woman's risk at 20,000 mGy (2,000 rad).[38,39]

Teratogenic Effects of Ionizing Radiation

Teratogenic effects of radiation can be seen during early organogenesis in animal studies. Exposure of rats to 100 rads at various points of development reveals a narrow window for teratogenesis. This window corresponds to weeks 2 to 4 in human development, coinciding with early organ formation. Despite these experimental data, it is difficult to link any specific human malformation with radiation exposure other than those of the CNS. Microcephaly, pigmentary changes in the retina, hydrocephalus, and optic nerve atrophy have all been reported at a significantly higher rate after exposure to radiation in pregnancy.[40] These patients were exposed to a minimum estimated dose of 100 rads, and no visceral, limb, or other malformations were found unless the child also exhibited CNS abnormalities. One explanation for this discrepancy is that the developmental period of the CNS is much longer, continuing throughout gestation and into the neonatal period, whereas other organs have a very narrow period during which morphologic alterations can be produced. Exposure to high doses of radiation during this narrow window is rare, and even if an isolated congenital abnormality were to occur, it would be difficult to separate this event from the background malformation rate. The extended period for CNS sensitivity to teratogenesis increases the prevalence of CNS malformation. CNS malformation also occurs at threshold doses; however, low levels of exposure to 10 to 20 rads of radiation do not increase the incidence of microcephaly in experimental animals over baseline.[41]

Growth Retardation from Ionizing Radiation

Growth retardation results from radiation-induced cellular depletion. Although catch-up growth can occur if exposure happens early in gestation, permanent cell depletion and growth retardation occur with exposure during later fetal stages.[42] Wood and colleagues studied growth retardation of children exposed in utero to the Japanese atomic blasts.[43] The children

within 1,500 m, when followed through age of 17 years, were 2 to 3 cm shorter and 3 kg lighter and had a head circumference 1 cm smaller than normal. Those beyond 1,500 m from the blast received less than 25 rads and had a normal head circumference, height, and weight.[44–46] Further, animal and human data support the contention that exposures of less than 5 rads should not cause either anatomic malformation or growth retardation.[41]

Oncogenic Potential of Ionizing Radiation

The correlation between childhood cancer and in utero exposure to radiation has been demonstrated. Although conclusions regarding the cause-and-effect relationship of this correlation cannot be definitively established, further studies using twins and extensive data analysis have strengthened the argument that in utero radiation can increase the rate of childhood cancer even at doses of 1 rad.[47,48] The current increase in childhood cancer is estimated at one to two cases per 3,000 children exposed to 1 rad in utero.[49] Although these risks are very small, the parent must be counseled regarding this potential danger. By reviewing the current data, it is obvious that exposure to diagnostic levels of radiation carries little chance for spontaneous abortion, teratogenesis, or growth retardation. The increased risk of future cancer, however, does exist and must be weighed against the utility of the information provided by the study.

Ultrasound

Ultrasonography uses high-frequency, acoustic radiation to create images. A surface transducer containing piezoelectric crystals converts electrical energy into sound waves. Sound waves pass through tissue layers and are reflected back to the transducer when they encounter an interface between tissues of different densities. Digital images generated at 50 to more than 100 frames per second undergo postprocessing that produces the appearance of real-time imaging. Ultrasonography is considered the first-line diagnostic imaging modality of the pregnant surgical patient because it is nonionizing, widely available, portable, and of adequate diagnostic performance. This imaging technique has been used in obstetrics for more than 50 years without reported fetal damage or harmful effects.[50,51] Ultrasonography 5 is,

however, a form of energy with effects on tissues through which the waveform penetrates. The two major mechanisms with potential effects are either direct, resulting from the alternation of positive and negative pressures (mechanical or cavitation effects) or indirect, caused by heating of tissues secondary to transformation of the acoustic energy (thermal effects). Because of these theoretical concerns, several organizations have recommended that this diagnostic procedure be performed only when there is a valid medical indication and using the lowest possible ultrasonic exposure setting.[52–54]

Computed Tomography

In the past 10 years, the use of radiologic examinations in pregnant women has increased by 107%, with the greatest increase occurring in the use of CT.[55] Computed tomography is most valuable in the second and third trimesters, when ultrasonography is of limited value, in a patient with a large body habitus, and when MRI is inconclusive or not available.[44] Because of its sensitivity for the detection of abdominal and pelvic injury as well as retroperitoneal injury in which the clinical urgency requires prompt diagnosis, CT is the test of choice for injured pregnant patients.[56–58] When CT is performed during pregnancy, using dose-reduction protocols (e.g., abdominal and internal barium shielding) results in reduction in the probability of biologic effects to the fetus without sacrificing the necessary diagnostic image quality.[59]

Magnetic Resonance Imaging

Like ultrasonography, MRI does not use ionizing radiation, instead relying on the magnetic properties of tissues to create images. Four magnetic fields interact during an MRI examination to create the image. The intrinsic magnetic field of an atomic nucleus, usually that of a hydrogen proton, is combined with a strong, uniformly applied external magnetic field and a weaker magnetic field gradient. In addition, a magnetic field is intermittently generated by pulsed radio frequency waves.[38] When the radio frequency ceases, the nuclei return to their previous orientation and emit the radio frequency they absorbed. These signals are detected, stored, and processed by a computer to create an image. Theoretical concerns include the effects of

fluctuating electromagnetic fields and high sound intensity levels with potential damage to the fetal ear. Other known dangers of MRI exposure include trauma from projection of small metal fragments into the eyes, interference with the operation of implantable electronic devices, position of metallic implants, and burns from heating of conductive materials in implants. Despite these concerns, present data have not conclusively documented any deleterious effects of MRI exposure on the developing conceptus or the pregnant woman.[45]

APPENDICITIS IN THE PREGNANT PATIENT

Acute appendicitis is the most common nonobstetric cause of acute surgical abdomen during pregnancy.[46] Disease is 6 confirmed in 65% to 75% of suspected cases for an incidence of approximately 1:1,500 births.[60] Although previous series suggested that the condition had similar incidences for nonpregnant adults, equal distribution throughout pregnancy, and a more common occurrence later in gestation, a large case-control study showed a lower incidence of appendicitis than among nonpregnant individuals, particularly in the third trimester.[61–64] The incidence decreases in the third trimester to 15% to 30% compared to rates ranging from 20% to 60% in the first and second trimesters.[65,66] A well-known fact is that the anatomic and physiologic changes of the gravid state make the diagnosis difficult. Attributing abdominal pain to other etiologies (e.g., pyelonephritis, false labor, gastroenteritis), failure to pursue further investigation, and the physicians' fear of surgically induced premature labor all contribute to delayed diagnosis and timely appendectomy in pregnancy. Appendiceal perforation rates are higher when compared with those from nonpregnant populations (55% vs. 4% to 19%).[67] This is probably explained by confounding variables leading to the delay of diagnosis and therapy. Several studies have documented a correlation between a delay in diagnosis and gestational age. In the first trimester, most diagnoses were made promptly, while a significant delay in operation with a rate of perforation of 49% was reported for patients presenting in the second trimester and a rate as high as 70% for those presenting in the third trimester.[61,68] Perforated appendicitis presents a greater infectious risk in the pregnant patient than in the population

as a whole. The large uterus interferes with proper omental migration throughout the abdominal cavity and prevents the walling off of the inflammatory process. Braxton Hicks contractions disrupt adhesion formation, and the general increase in vascularity of the abdomen with greater lymphatic drainage allows rapid dissemination of infection. The high circulatory levels of adrenocorticoids in pregnancy have also been hypothesized to diminish the tissue inflammatory response and hinder containment of infection.[69–71] All of the classic signs and symptoms of appendicitis can be masked by pregnancy (**Table 104.2**). Anorexia, nausea, and vomiting occur in 58% to 77% of pregnant patients with appendicitis.[61,68] Although anorexia, nausea, and vomiting in the first trimester are common, their occurrence during the second and third trimesters, especially if associated with abdominal pain, require a thorough investigation. In a classic 1932 study, Baer and colleagues[72] evaluated the migration of the appendix through the duration of pregnancy with barium enemas. Beginning in the first trimester, the appendix and the cecum are gradually displaced by the uterus and start a caudal migration out of the pelvis into the upper abdomen. By the third trimester, the appendiceal tip can abut the gallbladder (**Fig. 104.4**). The vague, referred epigastric pain due to early appendiceal obstruction is not changed by this anatomic consideration, but the location of the somatic pain is. In a large study of pregnant women with appendicitis, abdominal pain was present in all patients. Location of pain in the right lower quadrant, however, was common only early in gestation, and a portion of patients reported pain in the right upper quadrant. This change in symptomatology is easily understood if the anatomic changes of the appendix are taken into consideration. Both guarding and rigidity are valuable findings on physical examination but are common only in the first trimester. Elevation of the abdominal wall from the more laterally placed, upward-directed appendix and the laxity of the abdominal wall musculature caused by this distention decrease the reliability of these findings. Only 42.9% of patients in the third trimester are reported to have abdominal spasm and guarding, compared with 80% during the first trimester.[73] Psoas and obturator signs are similarly obscured as the appendix is moved from its normal location and have not been shown to have clinical significance. The results of laboratory examinations commonly used to assist in the diagnosis of appendicitis are also obscured by pregnancy. The physiologic

leukocytosis of pregnancy, ranging from 5,000 to 12,000 white blood cells (WBCs)/mL, overlaps that of appendicitis. In one collected series, the WBC count of pregnant patients with proven appendicitis was not significantly elevated over these values, and only 25% of patients had a WBC count over 15,000. Most patients (50%) had WBC counts ranging between 10,000 and 15,000, and 25% had less than 10,000 WBCs/mL.[61] Urinalysis is a useful adjunct in the workup of appendicitis but again presents a dilemma in pregnancy. Urinary tract infection is common in pregnancy as the enlarging uterus compresses the right ureter. Dilatation and stagnant flow in the right collecting system can contribute to bacterial overgrowth and infection. Pyuria without bacteria can also indicate involvement of the right ureter in the appendiceal inflammatory process. The presence of pyuria and bacteriuria does not rule out appendiceal inflammation because the two conditions may coexist in 40% of pregnant patients.[68]

Table 104.2 Variation in Signs and Symptoms of Appendicitis during Pregnancy

Signs and Symptoms	First Trimester (%)	Second Trimester (%)	Third Trimester (%)
Right lower quadrant pain	100	50	14
Right upper quadrant pain	0	17	57
Guarding (muscle spasm)	80	50	43
Nausea and vomiting	53	60	23
Tenderness on rectal examination	60	17	0
Perforation rate	20	49	70

Data from Weingold AB. Appendicitis in pregnancy. *Clin Obstet Gynecol* 1983;26(4):801–809; Tamir IL, Bongard FS, Klein SR. Acute appendicitis in the pregnant patient. *Am J Surg* 1990;160(6):571–575; and Cunningham FG, McCubbin JH. Appendicitis complicating pregnancy. *Obstet Gynecol* 1975;45:415–420.

The risk of adverse pregnancy outcomes following appendectomy has been reported by two large population-based studies. From the California Inpatient File of 3,133 pregnant women undergoing surgery for suspected appendicitis, the fetal loss rate was 23%, and it was doubled—6% versus 11%—with simple versus complicated disease.[74] In the other study, the fetal loss rate within 1 week of the procedure was 22%, particularly when the surgery was performed after 23 weeks.[60] Fortunately, these same researchers noted no additional increase in the preterm birth rate among the pregnancies that continued beyond the first postoperative week. Perforated appendicitis in pregnancy rapidly leads to diffuse peritonitis, premature labor, and fetal loss.[63,75]

Imaging Modalities

Ultrasonography is the initial nonionizing imaging modality of choice in patients with appendicitis. Findings suggesting appendicitis include visualization of a tubular structure with a diameter of more than 6.0 mm, a wall thickness of more than 3.0 mm, and lack of peristalsis (**Fig. 104.5**).[76,77] One study reviewed the value of ultrasonography in diagnosing appendicitis in pregnancy, reporting a range of sensitivity of 67% to 100% and a range of specificity of 83% to 96%, compared to diagnostic performance in the general population of 86% and 96%, respectively.[78] Ultrasonography, however, does have limitations due to body habitus, intraluminal air, and operator level of experience. The examination can also be difficult because of abdominal guarding and pain during examination. Distortion of anatomic landmarks and the displacement of the appendix by the gravid uterus complicate the diagnosis. Other structures such as an inflamed salpinx can also mimic appendicitis on ultrasonogram and a dilated uterine vein during pregnancy has been mistaken for an acutely inflamed appendix.[79,80] Chest radiography should be considered in the evaluation of patients with suspected appendicitis because right lower lobe pneumonia may manifest with lower abdominal pain. Abdominal plain films are usually avoided unless there is suspicion for visceral perforation or bowel obstruction.

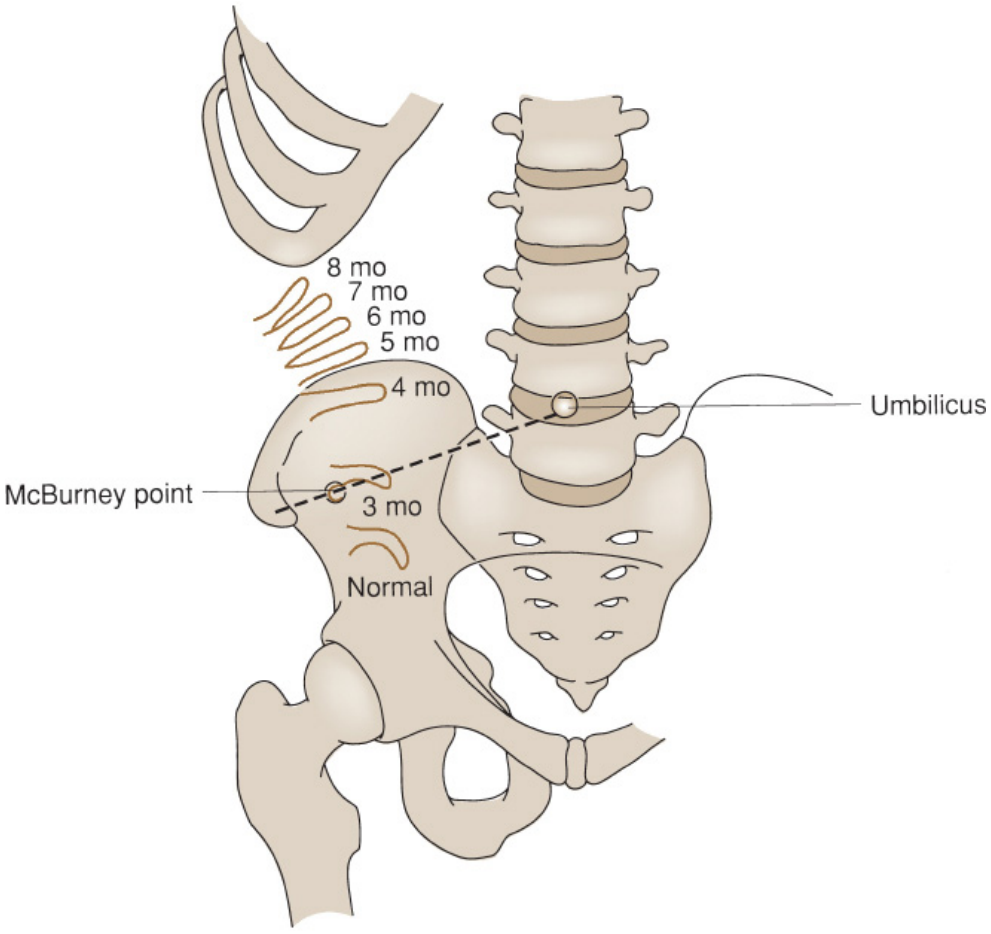

Figure 104.4 Changing location of the appendix throughout gestation.

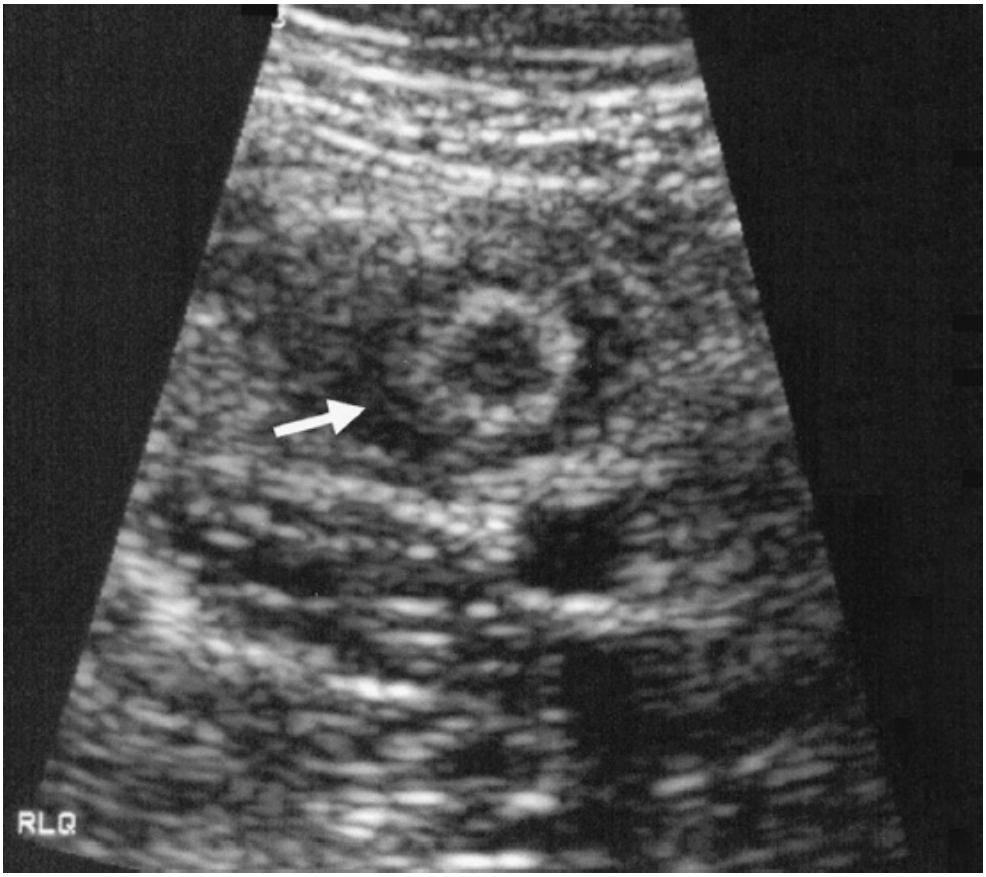

Figure 104.5 Ultrasonographic appearance of appendicitis. The appendix appears as a thick, noncompressible tubular structure with central hypoechogenicity. The walls are 5-mm thick, over the 3-mm limit for a normal appendix. (Courtesy of Dr. Beverly Coleman, Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA.)

Computed tomography (CT) has emerged as a highly reliable modality in the diagnosis of appendicitis. Appendiceal CT with rectally administered contrast can be performed within 10 to 20 minutes and does not require a waiting period for oral contrast to progress down through the cecum; it also exposes the patient to only one-third the radiation of a regular CT scan.[81] Computed tomography in the nonpregnant population is more sensitive and specific than sonography (approximately 98% each) to confirm suspected appendicitis.[82] A computed tomographic scan is considered abnormal if there is an enlarged appendix (>6 mm in maximum diameter) or if there are periappendiceal inflammatory changes such as fat stranding, phlegmon, fluid collection, and extraluminal gas. Routine use of this modality has been shown to reduce costs, expedite the diagnosis, and reduce perforation rates from

22% to 14% while decreasing the incidence of negative laparotomy from 20% to 7%.[83–85] Radiation exposure is 300 mrad with a limited helical CT scan, which is one-third of the amount of the average abdominopelvic CT scan.[86] Because even low levels of radiation in utero can increase the incidence of childhood cancer, widespread use of this modality in the pregnant patient with abdominal pain may be detrimental. Reserving the CT scan for those cases in which the clinical history, physical examination, and ultrasonography are indeterminate should still decrease the rate of perforation and negative exploration, just as it has in the nonpregnant population (**Fig. 104.6**).

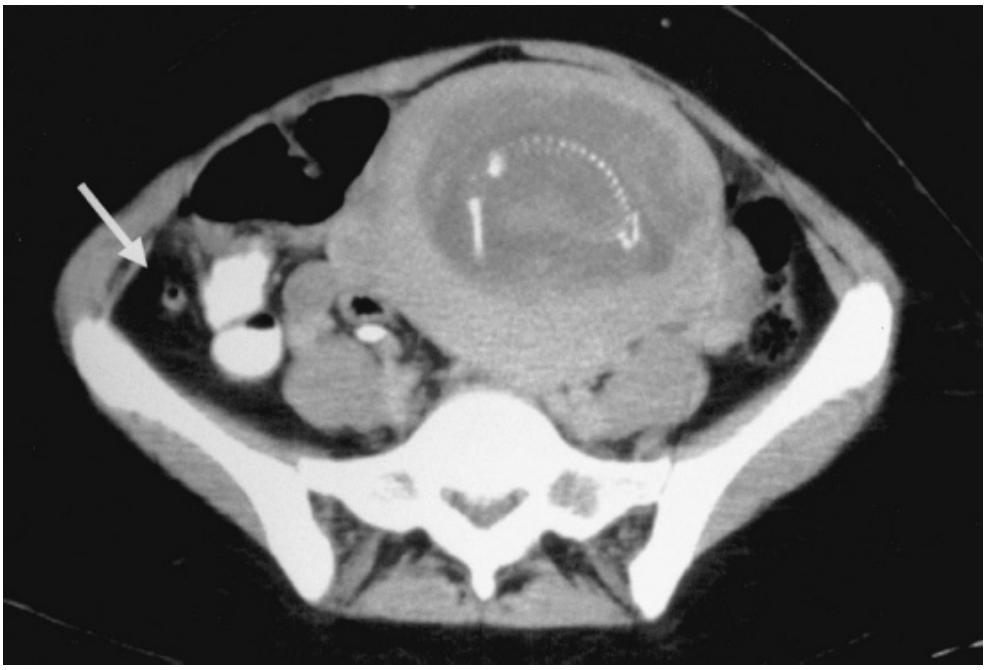

Figure 104.6 Computed tomographic (CT) scan of a woman in the 18th week of gestation presenting with a 12-hour history of right-sided abdominal pain. Abdominal examination on presentation revealed significant tenderness, and after a nondiagnostic ultrasonography, a laparotomy is considered for presumed appendicitis. A CT scan is obtained instead, revealing a normal, air-filled appendix with no sign of periappendiceal inflammation (*arrow*). The laparotomy was postponed, and 12 hours later the patient aborted a septic fetus. An unnecessary laparotomy for an atypical presentation of chorioamnionitis was avoided by the judicious use of the CT scan. (Courtesy of Dr. David Weiss, Chestnut Hill Hospital, University of Pennsylvania Health System, Philadelphia, PA.)

MRI utilizes nonionizing radiation, which has no known adverse fetal effects, and like CT, has the potential to image the whole abdomen. On MRI,

an appendix is considered abnormal when it is fluid-filled, greater than 6 or 7 mm in diameter, or demonstrates the presence of periappendiceal inflammatory changes. A study suggested that a normal appendix on MRI had a high specificity (98% to 100%) and a high negative predictive value (94% to 100%) in excluding acute appendicitis.[87] The American College of Radiology Guidance Document on MR Safe Practices in 2013 reaffirmed the use of MRI in pregnancy if considered necessary irrespective of gestational age. Intravenous gadolinium contrast has no known adverse effects in humans but its use should be based on whether the potential benefits to the patient exceed the theoretical risks to the fetus.[88]

Diagnostic Laparoscopy

Laparoscopy to evaluate the appendix is a feasible diagnostic modality during pregnancy but may be difficult during later gestation. Anatomic changes alter placement of trocars above the gravid uterus and require the use of the open Hasson technique of trocar placement under direct visualization rather than blind insufflation with a Veress needle.[89] Maneuvers to enhance operative safety of laparoscopy in pregnancy have been outlined by the Society of American Gastrointestinal Endoscopic Surgeons (**Table 104.3**).[90]

Appendectomy

Once the diagnosis of appendicitis is made, treatment is a combination of antibiotics and surgical removal, just as with nonpregnant patients. Antibiotics should be broad-spectrum, but should include Gram-negative and anaerobic coverage with care taken to avoid any teratogenic medications. A second- or third-generation cephalosporin, expanded-spectrum penicillin, or even triple agent therapy may be selected.[91] Laparoscopy is almost always used to treat suspected appendectomy during the first two trimesters, however this may vary based on surgeon preference. Recent studies have failed to demonstrate superiority of laparoscopic or open techniques, although each approach is associated with particular advantages. One recent meta-analysis of 20 studies, containing over 6,220 pregnant patients, concluded that laparoscopic appendectomy in the pregnant patient was

associated with lower overall complication rates and shorter hospital stays, while open appendectomy was associated with a reduced risk of fetal loss and later overall gestational age at the time of delivery.[92] If an open approach is selected, a muscle splitting incision is made over the *point of maximum tenderness* because the appendix customarily lies beneath that point.[46,61,68] This is opposed to the classic right lower quadrant paramedian incision, which usually necessitates medial retraction of the uterus for exposure and thus increases the risk of precipitating premature labor. In addition, by tilting the patient 30 degrees to the left, the uterus is shifted away from the operative field and off the inferior vena cava. Because of the migration of the appendix, the classic incision over McBurney point in the late second and third trimesters is not optimal. If diffuse peritonitis is present, a midline incision is usually performed. Perforated appendicitis or pus in the abdominal cavity demands thorough peritoneal cleansing along with the appendectomy. A periappendiceal abscess, just as with nonpregnant patients, can be treated with percutaneous drainage, followed by an interval appendectomy 2 to 3 months later.[93]

Table 104.3 Guidelines for Laparoscopic Surgery during Pregnancy

1. Diagnostic laparoscopy is safe and effective when used selectively in the workup and treatment of acute abdominal processes in pregnancy.
2. Laparoscopic treatment of acute abdominal disease has the same indications in pregnant and nonpregnant patients.
3. Laparoscopy can be safely performed during any trimester of pregnancy.
4. Gravid patients should be placed in the left lateral decubitus position to minimize compression of the vena cava.
5. Initial abdominal access can be safely accomplished with an open (Hasson) technique, Veress needle, or optical trocar, if the location is adjusted according to fundal height and previous incisions.
6. CO_2 insufflation of 10–15 mm Hg can be safely used for laparoscopy in the pregnant patient.
7. Intraoperative CO_2 monitoring by capnography should be done during laparoscopy in the pregnant patient.
8. Intraoperative and postoperative pneumatic compression devices in early postoperative ambulation are recommended prophylaxes for deep venous thrombosis in the gravid patient.
9. Laparoscopic cholecystectomy is the treatment of choice in the pregnant patient with gallbladder disease, regardless of trimester.
10. Cholelithiasis during pregnancy may be managed with preoperative endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy, followed by laparoscopic cholecystectomy, laparoscopic common bile duct exploration, or postoperative ERCP.
11. Laparoscopic appendectomy may be performed safely in pregnant patients with appendicitis.
12. Obstetric consultation can be obtained pre-and/or postoperatively on the basis of the severity of the patient's disease, gestational age, and availability of the consultant.
13. Tocolysis should not be used prophylactically in pregnant women undergoing surgery but should be considered perioperatively when signs of preterm labor are present.

Adapted from SAGES Committee on Standards Practice. Guidelines for laparoscopic surgery during pregnancy. *Surg Endosc* 2011;25:2479–3492.

Cesarean section at the time of appendectomy is rarely indicated. Unless there is gangrene, perforation, or a periappendiceal phlegmon, antimicrobial therapy can usually be discontinued after surgery. Although uterine contractions are common, tocolytic therapy is generally not recommended. If exploration reveals a normal appendix, an appendectomy still should be performed; removal of the normal appendix adds little to morbidity while eliminating potential confusion if symptoms should recur.[61] Laparoscopic appendectomy has been shown to demonstrate a good safety record in all trimesters with a complication rate similar to that for nonpregnant laparoscopy.[89,92,94–97] Certainly, the presence of the enlarged uterus does increase the risk of inadvertent injury with a trocar or Veress needle, which can be mitigated by the use of an open Hasson technique and direct visualization of trocar insertion after careful consideration of fundal height.[98] In addition, limiting intra-abdominal pressures to less than 12 mm Hg and reducing operative time can reduce concerns about maternal hypercarbia and subsequent fetal acidosis.

BILIARY TRACT DISEASE IN PREGNANCY

Acute cholecystitis is the second most common nonobstetrical indication 7 for surgery in pregnant women and the most common cause of maternal hospitalization in the first year after delivery.[99] Pregnancy and the postpartum period appear to predispose women to gallstone formation. This is attributed to increase in sex steroid hormone levels in pregnancy, causing biliary stasis, prolonged intestinal transit, and increased cholesterol saturation of bile. Multiparity and prepregnancy obesity are two major independent risk factors for cholelithiasis in pregnancy. One study found that gallstones occurred in 7% of nulliparous women, with the rate rising to 19% of women with two or more pregnancies. This risk of gallstones appears to increase during gestation, with sludge or stones found in 5.1% of 3,254 prospectively studied women in the first trimester, 7.9% in the second trimester, and 10.4% by 4 to 6 weeks after delivery.[100] However, among women with sludge or stone,

only 1.2% developed any symptoms attributable to the gallbladder during pregnancy.[101] Despite the predilection for stone formation in pregnancy, acute cholecystitis does not occur more frequently during pregnancy. Data suggest that cholecystitis affects only 0.1% of pregnant women.[102] Most patients with symptomatic gallstones present with complaints of typical biliary colic likely resulting from gallbladder contractions and increased pressure and luminal expansion characteristically exacerbated by a fatty meal. Less frequently, the symptoms are those of one of the complications of gallstones, acute cholecystitis, cholangitis, or pancreatitis. Signs and symptoms may include right upper quadrant pain, fever, tachycardia, leukocytosis, anorexia, and vomiting. Sepsis and jaundice may also be seen. Abdominal examination usually demonstrates voluntary and involuntary guarding and frequently a positive Murphy sign.

Laboratory studies should be normal in patients with uncomplicated cholelithiasis. However, mild elevations in serum aminotransferases and amylase may occur as a result of the passage of small stones or sludge. It is important to note that serum alkaline phosphatase levels normally increase during pregnancy because of production of an alkaline phosphatase isozyme by the placenta. Significant elevations in aminotransferases, hyperamylasemia, or increased direct bilirubin may be signs of complicated gallbladder disease. The differential diagnosis includes appendicitis, pancreatitis, peptic ulcer disease, pyelonephritis, right-sided pneumonia, acute fatty liver of pregnancy, and preeclampsia.

Abdominal ultrasound is a reliable diagnostic tool for identifying gallstones, sludge, and acute or chronic cholecystitis with a high sensitivity and specificity.[103] A diagnosis of acute cholecystitis is suspected by findings of gallbladder distention, gallbladder wall thickening, and pericholecystic fluid on ultrasonography.[104] Transabdominal ultrasonography is relatively insensitive for the detection of common bile duct stones, whereas endoscopic ultrasound is highly accurate for that purpose. Magnetic resonance cholangiopancreatography (MRCP) may be used when extrahepatic ductal stones are suspected or in complicated cases when ultrasound is nondiagnostic. Endoscopy of the biliary system by endoscopic retrograde cholangiopancreatography (ERCP), with its associated radiation exposure, can be performed safely in pregnant patients but should be limited to cases in which treatment of ductal stones is required.

The appropriate management for symptomatic cholelithiasis and acute cholecystitis during pregnancy is controversial. Suggested management for a pregnant patient with symptomatic cholelithiasis during the first trimester consists of conservative measures until elective cholecystectomy can be performed safely during the second trimester. Nonoperative management of symptomatic cholelithiasis is associated with significant recurrence bouts of symptoms, prolonged total parenteral nutrition, higher rates of preterm delivery, cesarean section, and more technically difficult cholecystectomies compared with laparoscopic cholecystectomy.[105–107] Cholecystectomy can be performed safely and effectively during pregnancy in all trimesters, though the second trimester is the optimal time to perform an elective cholecystectomy. Organogenesis is complete and the gravid uterus is not yet large enough to impinge on the operating field.[108] Removing the diseased gallbladder eliminates the potential for recurrence, and the minimal uterine retraction needed with laparoscopic access to the right upper quadrant should decrease the risk for preterm labor. Either an open or laparoscopic approach may be chosen, however laparoscopic cholecystectomy is the preferred technique for removal of the gallbladder in pregnant women.[109] Just as with nonpregnant patients, laparoscopy is associated with shorter postoperative stay and earlier diet initiation with less pain and rate of postoperative hernia.[94,110,111] After an open cholecystectomy, the reported rate of premature labor ranges from 0% to 40%, based on trimester, and a spontaneous abortion or premature birth rate of up to 22% has been reported.[112,113] The incidence of premature uterine contractions with laparoscopic cholecystectomy has been reported at 0% to 21%, but contractions are usually well-controlled by tocolytics. Most series report rates of premature birth or spontaneous abortion ranging from 0% to 7% with the laparoscopic approach.[89,114,115] Those patients presenting later in gestation can most commonly be managed symptomatically until the postpartum period, with cholecystectomy generally performed 6 weeks following delivery to allow the mother to recover and to bond with her infant.

Choledocholithiasis

Indications for evaluation of the common bile duct are no different in the pregnant patient than in the population as a whole—namely, a bilirubin elevated over 1.5 mg/dL, a dilated common bile duct, or gallstone pancreatitis.[89] ERCP can be performed in pregnancy. With proper lead shielding, judicious use of fluoroscopy time, and avoidance of permanent roentgenographic films, ERCP has been performed with no direct exposure of the fetus to radiation. Calculated scatter radiation on the order of 4 mrads during the whole examination presents the only risk from ionizing radiation.[116] Evaluation of the biliary tree, stone retrieval, and sphincterotomy can be performed under these conditions without maternal or fetal complications.[117] Other methods avoid radiation altogether and include imaging of choledocholithiasis with endoscopic ultrasonography, endoscopic papillotomy under ultrasonographic control, and MRCP for choledocholithiasis.[118–120] Success with all these modalities has been reported but may be limited by operator experience and availability.

BREAST CANCER IN THE PREGNANT PATIENT

Breast cancer diagnosed during gestation poses a complex clinical 8 situation given the need to consider the welfare of both mother and developing fetus. In general, pregnant patients should be managed by similar treatment strategies as nonpregnant patients with few adjustments to account for potentially teratogenic interventions. The most critical component of managing breast cancer in the pregnant patient is timing, as treatment should not be delayed simply due to pregnancy. That being said, pregnancy termination has also not been shown to improve outcomes for patients, so this should not be universally recommended as a means to accelerate treatment.[121] The decision to terminate a pregnancy should be made individually by each patient in conjunction with her clinician. Factors to consider include potential risks of treatment to the fetus and her anticipated ability to care for a child postpartum.

Surgical Management

The definitive treatment for localized breast cancer is surgical resection. Both mastectomy and breast-conserving surgery (BCS) are available treatment options for women with carcinoma and carcinoma in situ. Mastectomy may be chosen by women who wish to avoid radiation therapy. BCS is a safe, feasible option for the pregnant patient with no reported adverse effects with regards to locoregional recurrence or survival. Those women who elect BCS should defer radiation therapy (RT) until after delivery whenever feasible given that RT is contraindicated during pregnancy. As such, women diagnosed with breast cancer early in pregnancy might consider mastectomy given the significant delay before receiving RT. For women preferring BCS during pregnancy who do not want to defer RT, a discussion is necessary to review risks and benefits. The degree of radiation exposure to the fetus will vary based on the dose administered, as well as the gestational age and fundal height.

Axillary staging is another critical component of managing a patient with breast cancer. Most recently, the American Society of Clinical Oncology concluded there was insufficient evidence to recommend sentinel lymph node (SLN) biopsy during pregnancy.[122] The safety of SLN biopsy during pregnancy has not been fully explored but generally requires minimal radiation exposure to the abdomen.[123,124] Furthermore, Han and colleagues report that efficacy of SLN biopsy in pregnant patients is equivalent to that in nonpregnant patients, allowing for the identification of those patients who would benefit from axillary node dissection.[125] Following SLN, those patients with indication for axillary lymph node dissection should proceed just as for nonpregnant patients. Reconstruction, when indicated, should be deferred until after delivery though placement of tissue expanders at the time of mastectomy or oncoplastic closure during BCS are appropriate with little appreciable risk to the fetus with the exception of prolonged time of general anesthesia.[126]

Systemic Therapy

Chemotherapy is generally contraindicated during the first trimester due to the severe potential teratogenic effects of these therapies. During the first trimester, when organogenesis is occurring, chemotherapy has been shown to contribute to complications including congenital and chromosomal

abnormalities, as well as increased risk of spontaneous abortion or stillbirth.[127–129] After the first trimester, chemotherapy may be safely administered to pregnant patients with little if any appreciable effect on prenatal fetal development. Specifically, chemotherapy given during the second and third trimester has not been shown to increase peripartum complications or to affect cardiac, cognitive, or general development of fetuses or children in early childhood.[130,131] Importantly, chemotherapy should be stopped prior to delivery such that the mother is not experiencing chemotherapy-related toxicity at the time of delivery. Selection of chemotherapeutic agents should be made on a case-by-case basis under the guidance of an oncologist with experience treating pregnant patients. One caveat is the use of selective estrogen receptor modulators (SERMs) such as tamoxifen, which are generally avoided during pregnancy, given their association with vaginal bleeding, spontaneous abortion, and fetal death.[132] Furthermore, tamoxifen can suppress postpartum lactation, so it should be avoided in nursing mothers.

MANAGEMENT OF THE PREGNANT PATIENT WITH TRAUMA

Most cases of major maternal trauma are due to motor vehicle collisions, falls, or domestic partner violence. Approximately 7% of pregnancies are affected by trauma and as such it is the leading cause of nonobstetric maternal and fetal mortality.[133] While blunt trauma is significantly more common in pregnant patients, mortality is much higher for both mother and fetus in cases of penetrating trauma.[134] Evaluation and management of trauma in these patients are made more complex by the need to assess and care for both the mother as well as the fetus. As such, a multidisciplinary approach is preferred whenever feasible, including a trauma surgeon, an obstetrician, and a neonatologist, when appropriate. The most important principle of managing the pregnant patient after major trauma is that 9 any diagnostic test or treatment should be performed if that intervention is required to save the mother's life, even if that intervention is potentially dangerous for the fetus. The second most important element is to establish an accurate gestational age

for the fetus given that fetal intervention, including premature delivery by emergency Cesarean section, would only be indicated if the fetus has reached viability.

Primary and Secondary Survey

Evaluation of the pregnant patient should be performed systemically, in a fashion which mirrors the typical algorithm of assessing the nonpregnant patient, though with important additional considerations. Sequential assessment of the airway, breathing, circulation, and disability ("ABCD") should be completed efficiently. The pregnant patient may be more likely to experience airway edema, thus increasing the risk of a difficult airway.[135] As such, earlier intubation may be indicated. Although the cephalad growth of the uterus impinges upon the diaphragm, the thorax of the pregnant patient does increase anterior-posterior and lateral dimensions to allow for improved compensation.[136] Circulatory changes during pregnancy are frequently the most dramatic when compared to the nonpregnant patient. First, the circulating blood volume and cardiac output of the pregnant patient increases to account for the systemic vasodilation that occurs, possibly due to progesterone and estrogen. Vital signs of the pregnant patient at baseline may also more closely reflect signs of hypovolemic shock, so care should be taken in interpreting the initial heart rate and blood pressure. Second, the gravid uterus and placenta may both serve as unique sources of significant bleeding. Third, the uterus may cause compression of the inferior vena cava, particularly when the patient is in the supine position, increasing the risk of hypotension. As such, a rolled towel placed beneath the right hip or spinal board, can achieve a left lateral tilt which reduces this effect. Taken together these elements complicate assessment of the patients initial circulatory status. Neurologic assessment, including Glasgow Coma Scale, should be unaffected by pregnancy. In addition to a head-to-toe assessment of the patient for other signs of trauma, a thorough obstetric assessment of the patient should be obtained during the secondary survey. Particularly relevant areas of focus include the abdominal and vaginal exam.

Radiographic Assessment

As with assessment of potential surgical pathologies in the pregnant patient, appropriate imaging studies should not be avoided simply due to the risk of adverse effects on the fetus. The Focused Assessment with Sonography for Trauma (FAST) is an essential part of the evaluation of pregnant patients which does not confer increased risk to the fetus. FAST allows for the detection of intraperitoneal blood after blunt trauma with a reported sensitivity of 80% and specificity of nearly 100% for major abdominal injury.[137] While a small amount of physiologic free fluid is expected within the pelvis of pregnant patients, this volume is too small to be detected by FAST, so any free fluid should be assumed to be pathologic until proven otherwise.[138] FAST also allows for immediate assessment of the pregnancy, specifically rapid identification of the number of fetuses and their respective positions, estimation of gestational age, detection of cardiac activity, and placental location.[139] If CT scan is indicated for assessment of the mother in order to detect a potentially life-threatening or critical injury, this should be performed without delay. Plain films of the chest or extremities may be performed with an abdominal lead shield in place to limit fetal exposure, though this is likely not feasible for pelvic films.

Fetal Monitoring and Emergency Delivery

Continuous fetal monitoring is indicated for pregnant patients who have undergone more than minor abdominal trauma with a fetus that has reached viability. Monitoring generally consists of both an external fetal heart monitor and a tocodynamometer. The duration of monitoring is debated though most sources agree that a minimum of 4 hours is recommended in the absence of warning signs which include an abnormal abdominal or vaginal examination, abnormal fetal heart tracings, regular contractions, or the presence of coagulopathy.[140,141] All RhD-negative pregnant patients should undergo a Kleihauer–Betke test to detect fetomaternal transfusion, although any RhD-negative woman who has not been previously immunized should receive anti-D immune globulin after abdominal trauma.

Emergency cesarean section should be reserved for specific life-threatening circumstances. Generally, it is avoided in any infant who has not reached viability, as delivery would thus almost uniformly be fatal. If an infant is viable, cesarean section may be performed for an abnormal fetal

heart tracing or if maternal death is imminent. It may also be performed as a means to improve the chances of maternal survival, namely if cardiopulmonary resuscitation is ineffective or if emptying of the uterus will assist with surgical exposure for the mother.

SUMMARY

Management of the pregnant patient poses unique challenges for the general surgeon. A thorough understanding of the unique anatomic and physiologic characteristics of mother and fetus is necessary. While the first priority of surgical management of the pregnant patient is ensuring the health and safety of the mother, a surgeon must constantly be aware of the effects that interventions may have on the fetus. We have reviewed the diagnostic and therapeutic management strategies for the most common surgical pathologies encountered during pregnancy. A multidisciplinary approach to the 10 pregnant patient is ideal for ensuring the safety of the mother and the fetus.

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SECTION O: SKIN AND SOFT TISSUE

105

Cutaneous Malignancies

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Key Points

1 Cutaneous malignancies are the most commonly diagnosed cancers in the United States, with basal cell and squamous cell carcinomas, melanomas, and Merkel cell carcinomas (MCCs), in that order, the most frequently diagnosed.

2 Melanoma prognosis is inversely correlated with tumor thickness, ulceration, mitotic rate, and nodal tumor burden.

3 Excision margins for primary melanoma are based on Breslow thickness. Sentinel lymph node biopsy (SLNB) should be considered for clinically node-negative patients with melanoma between 0.8 and 1.0 mm and is recommended for lesions >1 mm Breslow thickness.

4 Treatment decisions for patients with regional or metastatic melanoma should be made in a multidisciplinary setting, reflecting the increasing role for systemic therapy (immunotherapy and molecularly targeted therapy) even for potentially resectable disease.

5 Advanced basal and squamous cell carcinomas are generally treated surgically, but radiation, immunotherapy, and molecularly targeted therapy are all useful in advanced and the rare metastatic cases.

6 MCC is an aggressive cutaneous neuroendocrine carcinoma, treated with surgery, radiation, and increasingly, immunotherapy.

7 Dermatofibrosarcoma protuberans (DFSP) is a rare soft tissue sarcoma with a propensity for local recurrence rather than systemic metastasis. It is generally treated surgically, but it is responsive to molecularly targeted therapy, which is used for advanced and the rare metastatic cases.

INTRODUCTION

1 Cutaneous malignancies are the most commonly diagnosed cancers in the United States, with several million new cases annually. One in five

Americans born today will be diagnosed with skin cancer in their lifetime. More than half of all cancers diagnosed in the United States are skin cancers.[1] The most common skin cancer types are basal cell carcinoma (BCC) and cutaneous squamous cell carcinoma (SCC). Cutaneous melanoma accounts for <2% of skin cancer diagnoses but the majority of skin cancer deaths, with an estimated 6,850 deaths due to melanoma in 2020.[1] Approximately 100,350 new cases of invasive melanoma (60,190 in men and 40,160 in women) were diagnosed in the United States in 2020, along with 95,710 cases of melanoma in situ. Invasive melanoma is the fifth most common cancer in men and the sixth most common cancer in women.[1] By 2030, it has been predicted that melanoma will be the fourth most common cancer in men and women.[2] Note that BCC and SCC are not included in these annual and future estimates of cancer frequency.[1] Merkel cell carcinoma (MCC) and dermatofibrosarcoma protuberans (DFSP) are two less common but clinically important forms of cutaneous malignancy of relevance to the surgeon.

MELANOMA

Etiology and Risk Factors

Numerous environmental and genetic risk factors have been implicated in the development of cutaneous melanoma (**Table 105.1**).[3,4] Risk factors include acute and chronic exposure to ultraviolet (UV) radiation, such as a history of blistering or peeling sunburns, outdoor recreational activities or occupations, and the use of tanning beds, and factors related to increased sensitivity to UV, such as fair complexion (blue or green eyes, blonde, or red hair). Other factors that denote an increased risk for melanoma are a personal or family history of melanoma, nonmelanoma skin cancer, atypical nevi, or multiple typical nevi (“moles”).

Table 105.1 Risk Factors for Primary Melanoma

Risk Factor	Description of High-Risk Features
Gender	Male
Age	>60 yrs
Skin phenotype	Fair skin, red hair, blue eyes, multiple typical and atypical nevi
Ultraviolet exposure history	Prior sunburns, chronic sun-induced skin damage, previous UV tanning bed use, geographic residence in areas with high UV environmental exposure
Family history	Multiple prior first-degree relatives with melanoma, pancreatic cancer, astrocytoma, uveal melanoma, mesothelioma
Other factors	Prior skin cancers or precancerous lesions, immunosuppression, rare genetic disorders (xeroderma pigmentosum, mutations in *CDKN2a, CDK4, MC1R, BRCA2, BAP1*)

Adults with more than 100 clinically normal-appearing (typical) nevi, children with more than 50 clinically normal-appearing nevi, and any patient with atypical or dysplastic nevi are at increased risk for melanoma development. An atypical nevus is not only a potential precursor lesion of melanoma but also a marker for increased risk of development of melanoma. In fact, more than 50% to 75% of melanomas develop on clinically normal skin de novo, not in pre-existing nevi. A prior history of melanoma is a marker for increased risk of developing second-primary melanomas, with 5% to 10% of individuals developing a second melanoma.

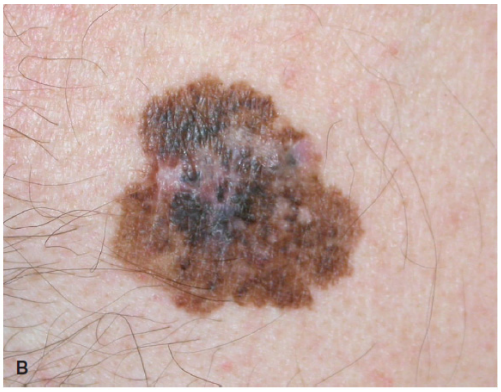
Congenital nevi are present at birth or appear within the first 6 months of infancy.[5] An estimated 1% to 6% of children are born with congenital nevi. Most congenital nevi are small, measuring less than 1.5 cm in diameter. Medium congenital nevi measure between 1.5 and 19.9 cm in diameter. Large (also termed giant) congenital nevi, measure 20 cm or greater (**Fig. 105.1A**).

The risk of melanoma development in small- and medium-sized congenital nevi is minimally increased compared to normal skin, if at all. Hence, routine removal of small and medium congenital nevi is rarely indicated in the absence of visible changes. Conversely, giant congenital nevi carry a notably increased risk for melanoma, with melanoma developing in 5% or more of these very large lesions. Of melanomas occurring within giant congenital nevi, 70% are diagnosed prior to the age of 10 years. Prophylactic removal of giant congenital nevi, often done in stages, can reduce the risk of subsequent melanoma development.[5]

Ten percent to 15% of patients with melanoma report a positive family history, but relatively few of these patients are ever found to have a specific genetic predisposition to the disease, as opposed to shared susceptibility factors like living in a geographic region with high UV exposure and engaging in similar outdoor activities as other family members. The most common inherited mutation associated with melanoma involves *CDKN2A*, also known as *p16*. This germline mutation, however, only accounts for about 0.2% of all melanoma cases. The *MC1R* gene regulates skin and hair color; inherited mutations in this gene are clearly a risk factor for cutaneous melanoma. The combination of *MC1R* mutation and red hair is associated with a very high risk of melanoma development.

Xeroderma pigmentosa is a rare autosomal recessive disorder associated with a reduced or absent ability to repair DNA damaged by UV light. Consequently, this disorder results in the development of multiple primary cutaneous malignancies, including melanoma as well as BCC and SCC. Individuals are usually diagnosed with their first cancer before the age of 10 years. Unfortunately, the development of skin cancers is relentless, with innumerable skin cancers developing unless strict sun avoidance is practiced from a very young age.

A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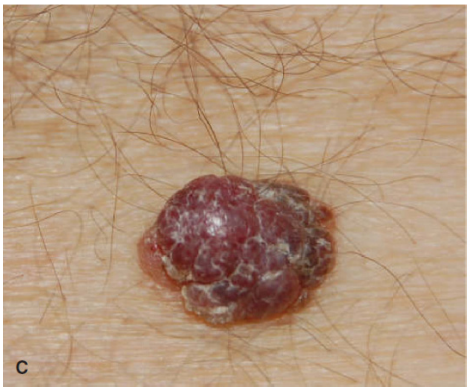
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Figure 105.1 Examples of cutaneous melanocytic lesions. **A:** Giant congenital nevus involving a large portion of the back. **B:** Superficial spreading melanoma. **C:** Nodular melanoma. **D:** Lentigo maligna (a form of melanoma in situ, also called Hutchinson melanotic freckle) on the side of the face. **E:** Lentigo maligna melanoma (melanoma arising in a lentigo maligna) on the cheek. **F:** Acral lentiginous melanoma on the instep of the foot. **G:** Subungual melanoma of the thumb. **H:** Amelanotic desmoplastic melanoma (note overlying telangiectasias and dark-colored punch biopsy site) on the heavily sun-exposed scalp.

Clinical Diagnosis and Classification

Melanoma typically has a characteristic appearance, but this is not always the case. The ABCDE rule was developed to help clinicians distinguish skin lesions concerning for melanoma from benign moles (**Table 105.2**). However, many benign skin lesions exhibit some or even most of the features associated with the ABCDE rule and, conversely, some primary melanomas present with few or none of these features. An alternative and complementary diagnostic aid is the "ugly duckling sign," where any skin lesion that is substantially different from all the others should be approached with a relatively high index of suspicion. The risk factors for melanoma should also be accounted when determining the clinical suspicion for melanoma.

Cutaneous melanomas have been classified into four major histologic subtypes (**Table 105.3**): superficial spreading (**Fig. 105.1B**), nodular (**Fig. 105.1C**), lentigo maligna melanoma (**Fig. 105.1D,E**), and acral lentiginous melanoma (**Fig. 105.1F**), which includes subungual melanoma (**Fig. 105.1G**). In general, the prognoses associated with all these subtypes are based on the same factors, such as the Breslow thickness, the presence or absence of ulceration, and regional/distant disease. Thus, the subtype classification of a melanoma generally does not constitute an independent prognostic factor.

Table 105.2 The ABCDE Diagnostic Aid for Primary Melanoma[a]

Asymmetry	A portion of the pigmented lesion does not match the remainder
Border Irregularity	Edges are blurred, jagged, or notched
Color Variation	Lesion has variable areas of color with shades of brown, black, white, red, and/or blue
Diameter	Greater than 6 mm
Evolution/Elevation	Change over time or lesion raised above skin level

[a]Adapted from American Academy of Dermatology Ad Hoc Task Force for the ABCDEs of Melanoma, Tsao H, Olazagasti JM, et al. Early detection of melanoma: reviewing the ABCDEs. J Am Acad Dermatol 2015;72(4):717–723.

Table 105.3 Common Subtypes of Cutaneous Melanomas

Name	Approximate Frequency (%)	Features
Superficial spreading melanoma	60	Common in melanomas arising from a pre-existing nevus Typically exhibits the classic clinical features of melanoma (see **Table 105.2**)
Nodular melanoma	20	Frequently lacks classic ABCDE features of melanoma Often diagnosed late
Lentigo maligna melanoma	18	Typically occurs on sun-exposed areas of head and neck or hands, often in older individuals Lesions are flat, broad, and asymmetric Extensive subclinical extension relatively more
Acral lentiginous melanoma	2	Occurs on hands and feet ("acral skin") Represents up to 60% of all melanomas occurring in people of color Often diagnosed late due unusual location and appearance Subungual melanoma commonly mistaken for hematoma

Other rare but notable melanoma subtypes include mucosal, ocular, desmoplastic (**Fig. 105.1H**), nevoid, amelanotic, and pediatric melanomas.[7] Mucosal melanomas occur in the nasal, oral, esophageal, anal, and vulvovaginal regions. Ocular melanomas can be either uveal or conjunctival.

Uveal melanomas occur in the iris, ciliary body, or choroid of the eye and have a predilection to metastasize to the liver. Mucosal and uveal melanomas are associated with relatively poor prognoses, related in part to advanced disease at presentation due to delayed detection. When patients present with metastatic melanoma of unknown primary origin, these subtypes should be considered as possibly overlooked sites of primary origin. Desmoplastic melanomas are named for their characteristic microscopic appearance, and can be pure or mixed (the latter with more than 10% of the lesion having nondesmoplastic features). Desmoplastic melanomas tend to be amelanotic and thicker at presentation (**Fig. 105.1H**), and are associated with a higher rate of neurotropism, a lower rate of lymph node metastasis, and a higher risk of local recurrence than other forms of cutaneous melanoma. Desmoplastic melanomas tend to have a higher mutational burden compared to nondesmoplastic melanomas, which can have implications for treatment and response to immunotherapy.[8] Nevoid melanomas and amelanotic melanomas often lack classic clinical features of melanoma, and histologically may share features with benign nevi. As such, they are often misdiagnosed or diagnosed late. Pediatric melanomas are those arising in children before age 18. Some represent typical adult melanomas detected earlier in life and hence share all the epidemiologic factors and presenting features associated with melanoma in adulthood. Most melanomas occurring in the first few years of life arise from giant congenital nevi, while many melanomas in children and adolescents have histologic features similar to benign Spitz nevi—and are called Spitzoid melanomas—and have a distinct epidemiology, presentation, and likely outcome compared to typical adult melanoma.[7]

Staging and Prognostic Factors

2 A great deal of information is available regarding various factors that correlate with the clinical outcome for patients with melanoma.

Microstaging

Microscopic characteristics of the primary tumor provide prognostic features of cutaneous melanoma—the so-called "microstaging." The microstaging method that is used routinely was originally described by Breslow. This

method classifies the primary tumor according to its thickness in millimeters, as measured with a micrometer inside the microscope eyepiece, from the top of the granular layer of the skin to the base of the tumor. Many investigators have documented an inverse correlation between tumor thickness and survival.[9,10] The series of >46,000 patients reported by Gershenwald et al. is summarized in Table 105.4.[11] The ulceration status and mitotic count are also independent prognostic factors, but currently only ulceration is used to determine microstaging of the primary lesion. Prior to the use of the Breslow method, melanomas were microstaged according to the level of invasion into the histologic layer of skin. This is known as the Clark level of invasion. Several studies have confirmed that Breslow thickness conveys more accurate prognostic information than Clark level. Furthermore, patients frequently misinterpret the Clark level as representing the overall tumor stage —leading to confusion and undue concern. For these reasons, use of Clark level has diminished.

Table 105.4 Melanoma TNM and Staging Categories with Survival Rates

Pathologic Stage	TNM[a]	5-Yr Survival (%)	10-Yr Survival (%)
IA	T1aN0M0 T1bN0M0	99	98
IB	T2aN0M0	97	94
IIA	T2bN0M0 T3aN0M0	94	88
IIB	T3bN0M0 T4aN0M0	87	82
IIC	T4bN0M0	82	75
IIIA	T1a/b-T2aN1aM0 T1a/b-T2aN2aM0	93	88
IIIB	T0N1b/cM0 T1a/b-T2aN1b/c-N2bM0 T2b-T3aN1a-N2bM0	83	77
IIIC	T0N2b-T3cM0 T1a-T3aN2c-3cM0 T3b-T4aN1a-N3cM0 T4bN1a-N2cM0	69	60
IIID	T4bN3a-N3cM0	32	24
IV	AnyT, AnyN, M1	25[b]	

[a]AJCC 8th Edition Staging System, see **Table 105.5** and Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer Eighth Edition cancer staging manual. CA Cancer J Clin 2017;67(6):472–492.

[b]Stage IV 5-year survival outcome data from Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70(1):7–30.

The presence of regional lymph node metastases is associated with a worsened prognosis. The tumor burden (clinically occult vs. clinically detected) of involved lymph nodes has a significant correlation with long-term survival.[9–11] In contemporary data, the 10-year survival rate for patients with involved lymph nodes ranges from as high as 88% (Stage IIIA) to as low as 24% (Stage IIID), based primarily on tumor burden (size and number of nodal metastases) and thickness and ulceration status of the primary lesion.[11] The use of sentinel lymph node biopsy (SLNB) has identified a subgroup of patients with clinically occult nodal disease who have a favorable prognosis compared with patients with clinically detected nodal involvement.

Clinical and Pathologic Staging

The American Joint Committee on Cancer (AJCC) developed a staging system that classifies melanomas according to tumor thickness (T), nodal status (N), and absence or presence of metastatic disease (M). The current AJCC 8th edition system took effect in 2018 and is summarized in **Tables 105.4 and 105.5**: stage 0 (in situ melanoma), stage I (localized disease, thin primary), stage II (localized disease, thicker primary), stage III (regional nodal, in transit, or satellite metastases), and stage IV (distant metastases).[11]

Other Prognostic Factors

The major prognostic factors that predict survival in melanoma patients have been accounted for in the AJCC staging system—namely, tumor microstaging, nodal status, and absence or presence of distant metastases. The presence of ulceration in a melanoma is associated with a poorer prognosis. Men have a higher proportion of ulcerated lesions than women (27% vs. 19%, respectively).[10] Although ulceration appears to correlate with thickness of the melanoma, the presence of ulceration is an independent prognostic factor and has been included in the staging system.[9,11] In addition, a mitotic count of 1 per mm^2 or greater is an independent prognostic factor.[12] The presence of grossly visible or microscopic satellites, by definition located within 2 cm of the primary melanoma, or in-transit metastases (located more than 2 cm from the primary and between the primary and the regional nodal basin) are also

poor prognostic signs and are considered evidence of intralymphatic metastasis in the AJCC staging system.[11,13]

Treatment of Primary Melanoma

Biopsy

For localized melanoma, the tumor thickness is the single most impactful variable that determines therapy and prognosis. The ulceration status and mitotic count also represent independent prognostic variables. The ideal biopsy allows the pathologist to characterize the entire lesion. If the melanoma is transected with a partial-thickness biopsy, the ability to obtain an accurate measurement of tumor thickness may be lost. Therefore, a superficial shave biopsy is never recommended for a pigmented lesion suspected of representing melanoma. Saucerization, also called a deep shave biopsy, down to the subcutaneous fat is a better approach.

Excisional biopsy with 1 to 2 mm margins is the preferred method for biopsy of suspicious pigmented skin lesions, as it provides the pathologist with the total specimen for histologic interpretation and accurate microstaging. Formalin-fixed, paraffin-embedded permanent sections should be used for biopsy diagnosis of primary cutaneous melanoma to accurately determine tumor thickness and other histopathologic prognostic variables. Frozen sections have essentially no role in the diagnosis or microstaging of primary melanoma. If the lesion proves to be a melanoma, the biopsy represents the first stage of a two-stage procedure. The second stage is radical wide excision, with margins ranging from 0.5 to 2.0 cm depending on the tumor thickness, with or without SLNB. Performing a wide excision with 1 or 2 cm margins as the first diagnostic step is not recommended, as several benign and malignant lesions can mimic melanoma and doing so may compromise the ability to accurately perform SLNB if the diagnosis of melanoma is confirmed. For a suspected melanoma on the extremities, the excisional biopsy should optimally be oriented along the long axis of the extremity, parallel to the lymphatics. Performing a biopsy oriented transversely on the extremity may compromise the accuracy of lymphatic mapping and could also obligate the patient to a skin graft to close the subsequent wide excision defect.

For suspicious lesions that are too large for excisional biopsy, an incisional biopsy may be performed, typically using a punch biopsy. Incisional biopsies for melanoma do not increase the risk of local recurrence and distant metastasis or affect patient survival. They should generally be performed on the most raised area of the lesion to maximize the obtainable diagnostic and prognostic information. The most raised area usually corresponds to the maximal thickness of the lesion, but not always. Several incisional biopsies can be obtained from different areas for large lesions to provide the best possible information for making treatment decisions.

Staging Workup

Current consensus guidelines have attempted to standardize staging workup for melanoma.[14,15] The staging workup starts with a history (concentrating on constitutional, respiratory, neurologic, hepatic, musculoskeletal, gastrointestinal, skin, and lymphatic systems) and physical examination (including a total body skin examination and palpation of lymph nodes). Routine imaging (chest x-ray, computed tomography [CT] scans, positron emission tomography [PET] scans), and blood studies (complete blood cell count, comprehensive metabolic profile, liver function tests, serum lactate dehydrogenase [LDH] levels) in asymptomatic, clinically node-negative patients are low in both sensitivity and specificity and are not routinely performed. False-positive and indeterminate staging tests are common and lead to more evaluation and patient distress. For appropriate patients, SLNB represents the best baseline staging test, with both relatively high sensitivity and specificity in patients at significant risk for metastasis. The likelihood of detecting stage IV disease with imaging studies is very small if the SLNB is negative. Both ultrasound and PET scanning have been examined as methods of identifying nodal metastases prior to surgery. While they detect disease in a minority of patients, most metastases to the regional nodes are smaller than the threshold ultrasound and PET can detect, so their routine use is not a cost-effective strategy.[16,17] If a thorough history and physical and detailed review of systems reveal no signs or symptoms suspicious for regional or distant disease, then no further staging is necessary prior to surgery. However, a high index of suspicion should be maintained, and a thorough

symptom-directed workup should be initiated for any worrisome finding on the history and physical.

Table 105.5 American Joint Commission on Cancer Melanoma Staging System, TNM Definitions

Primary Tumor	
TX	Primary tumor thickness cannot be assessed
T0	No evidence of primary tumor (unknown primary or completely regressed primary)
Tis	Melanoma in situ
T1	≤1.0 mm Breslow thickness[a] a. <0.8 mm without ulceration b. With ulceration or ≥0.8 mm
T2	1.1–2.0 mm a. Without ulceration b. With ulceration
T3	2.1–4.0 mm a. Without ulceration b. With ulceration
T4	>4.0 mm a. Without ulceration b. With ulceration
Regional Lymphatic Metastasis	
NX	Nodal status cannot be assessed and no in-transit or satellite metastasis
N0	No regional lymphatic metastasis
N1	Metastasis in one regional node or only in-transit or satellite metastases without nodal metastases a. One clinically occult nodal metastasis (diagnosed by SLNB) b. One clinically detected nodal metastasis (palpable or found on imaging studies) c. In-transit or satellite metastasis without documented nodal metastasis
N2	Metastasis in two to three regional nodes or one regional

	node plus in-transit or satellite metastases a. Two to three clinically occult nodal metastases (all diagnosed by SLNB) b. Two to three clinically detected nodal metastasis (at least one palpable or found on imaging studies) c. One clinically occult or clinically detected nodal metastasis plus in-transit or satellite metastases
N3	Metastasis in ≥four regional nodes, matted nodes, or in-transit or satellite metastasis with metastasis in at least two regional nodes a. ≥4 clinically occult nodal metastases (all diagnosed by SLNB) b. ≥4 clinically detected nodal metastasis (at least one palpable or found on imaging studies) or any matted nodes c. ≥2 clinically occult or clinically detected nodal metastases, or any matted nodes, plus in-transit or satellite metastases
Distant Metastasis	
M0	No evidence of distant metastasis
M1a	Distant skin, subcutaneous, muscle, or nonregional lymph node metastasis (0). With normal serum LDH level (1). With elevated serum LDH level
M1b	Lung metastasis without or with M1a sites of disease (0). With normal serum LDH level (1). With elevated serum LDH level normal LDH
M1c	Non-CNS visceral metastases without or with M1a and/or M1b sites of disease (0). With normal serum LDH level (1). With elevated serum LDH level
M1d	CNS metastases without or with M1a, M1b, and/or M1c

sites of disease
(0). With normal serum LDH level
(1). With elevated serum LDH level

[a]Breslow thickness should be reported rounded to the nearest 0.1 mm.

CNS, central nervous system; LDH, lactate dehydrogenase; SLNB, sentinel lymph node biopsy.

Adapted from Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer Eighth Edition cancer staging manual. *CA Cancer J Clin* 2017;67(6):472–492 and Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al. (eds.) *AJCC Cancer Staging Manual*. 8th ed. New York: Springer International Publishing; 2017:563–585.

Table 105.6 Randomized Controlled Trials: Narrow versus Wide Excision Margins

Trial[a]	Subjects (No.)	Narrow Resection Margin (cm)	Wide Resection Margin (cm)	Tumor Thickness (mm)	Tumor Site	Median Length Follow-up (years)
French 2003	326	2	5	<2.1	T, E, H&N	10.0
Intergroup 1996	470	2	4	1.0–4.0	T, E	7.6
Swedish 2000	989	2	5	0.8–2.0	T, E	11.0
WHO 1991	612	1	3	<2.0	T, E	7.5
UK 2004	900	1	3	>2.0	T, E	5.0

[a]There was no difference in any outcomes in the first four trials. UK 2004 showed increased locoregional recurrence but no difference in local or in-transit recurrence.
E, extremity; H&N, head and neck; T, trunk; UK, United Kingdom; WHO, World Health Organization.

Approximately 5% to 10% of newly diagnosed melanoma patients present with clinically involved lymph nodes. Any clinically suspicious node should be confirmed to represent melanoma, preferably by fine-needle aspiration (FNA) biopsy, as enlarged lymph nodes may be reactive (particularly after a skin biopsy). Ultrasound-guided FNA biopsy can be useful in cases where the suspicious node is difficult to localize and/or immobilize. To facilitate subsequent management, excision of the enlarged node(s) as a diagnostic maneuver should be limited to cases where a needle biopsy was unable to establish a diagnosis. Patients documented to have macroscopic regional disease should undergo formal staging prior to definitive treatment, as a significant percentage may have more advanced regional or distant disease that may alter the therapeutic approach. Staging for clinical stage III melanoma should include a serum LDH level; brain MRI and either CT scan of the chest, abdomen, and pelvis (as well as neck for primary sites draining

to the cervical nodes such as head, neck and upper chest/back primary sites) or whole-body PET/CT scan.

Excision of Primary Melanoma

3 The goal of surgical excision of primary melanomas is to reduce the risk of local recurrence. For melanoma in situ, excision margins of 0.5 to 1.0 cm are accepted as the standard of care; however, this practice is not based on a prospective clinical trial. For invasive melanomas, the accepted standard of care is radical wide excision with margins ranging from 1 to 2 cm—to a depth down to, but not necessarily including, the underlying investing muscular fascia. The recommended excision margin is dependent upon the Breslow thickness as based upon results of several randomized controlled trials listed in **Table 105.6**.[18] Current consensus guidelines recommend margins of 1 cm for melanomas 1.0 mm or less in thickness, 2 cm for melanomas greater than 2.0 mm thick, and 1 to 2 cm for melanomas 1.1 to 2.0 mm thick (**Table 105.7**). For this last group, the width of the margins should be based on the anatomic location of the melanoma and the morbidity of excising 2 cm versus 1 cm, including the need for an advancement flap or skin graft. For several locations, such as melanomas on the head/neck or mucosal surfaces, the maximum attainable margins are dictated by anatomic constraints. Most subungual invasive melanomas (**Fig. 105.1G**) are best managed by partial amputation of the digit, although conservative excisions with skin grafting can be considered for thin and noninvasive subungual melanomas.

For melanomas with ill-defined borders—especially lentigo maligna melanoma on the head and neck—subclinical extension well beyond the clinically evident tumor is commonplace and staged contoured marginal excision may be useful. The first stage involves removal of narrow (~2 mm wide) peripheral strips of normal-appearing skin at the locations of the anticipated margin edge (i.e., the strips are taken circumferentially using a 1 to 2 cm margin from the tumor periphery/biopsy edge as appropriate for the thickness). If any of the peripheral strips are positive, additional strip(s) constituting the new, anticipated margin are excised (**Fig. 105.2**). The second stage of central tumor excision (inside of the previous peripheral strips) with definitive reconstruction may proceed once the peripheral strips are

confirmed negative on final pathologic analysis.[19] For lesions thick enough to require SLNB, this can be performed in conjunction with the initial marginal excision.

Sentinel Lymph Node Biopsy

For clinically node-negative patients with melanoma ≥1.0 mm thick, SLNB is recommended for tumor staging. SLNB should not be routinely performed for all patients with thin melanoma, but should be considered for patients with a melanoma Breslow thickness of 0.8 to 1.0 mm, particularly if they have other risk factors for regional metastases, including a mitotic count of 1 mitosis/mm^2 or greater, ulceration, angiolymphatic invasion, younger age, or a broadly transected deep margin on shave biopsy.[15,20] Reasons to avoid SLNB include significant medical comorbidities and if the patient does not desire SLNB after an informed discussion.

Two tracers are typically used for identifying sentinel nodes: a radiolabeled colloid and a blue dye—either 1% isosulfan blue (Lymphazurin) or methylene blue. Isosulfan blue carries a risk of allergic reaction in a very small number of patients, which can be life-threatening.[21] Methylene blue dye has an extremely low risk of allergic reaction, but if not diluted or completely resected can cause skin necrosis. One to 4 hours before surgery, or in some cases the afternoon before surgery, the radiolabeled colloid solution is injected intradermally around the primary tumor or excisional biopsy site. Lymphoscintigraphy imaging is then performed to identify SLN both in and outside the expected nodal basin. Most commonly, planar lymphoscintigraphy images are obtained, but SPECT-CT provides enhanced anatomical localization and is particularly useful for head and neck melanomas and for lymph nodes in unusual sites (**Fig. 105.3**). The blue dye is injected intradermally in the operating room immediately prior to the procedure. Using a combination of a hand-held gamma probe and visualization of blue-stained lymphatics or nodes can help identify nodes. The combination of the blue dye and radiolabeled colloid enables the detection of sentinel nodes in >97% of cases.[22] Sentinel nodes are serially sectioned by the pathologist for hematoxylin and eosin staining and immunohistochemical staining for melanoma markers such as S-100, Melan-A, and HMB-45. This is done to examine for micrometastases that can be

missed by the traditional process of bisecting nodes.[23] If metastases are found in the sentinel node, BRAF immunohistochemistry can be performed to assess for the presence of a BRAF V600E mutation (**Fig. 105.4**).

Table 105.7 Recommended Surgical Margins for Melanoma Excision

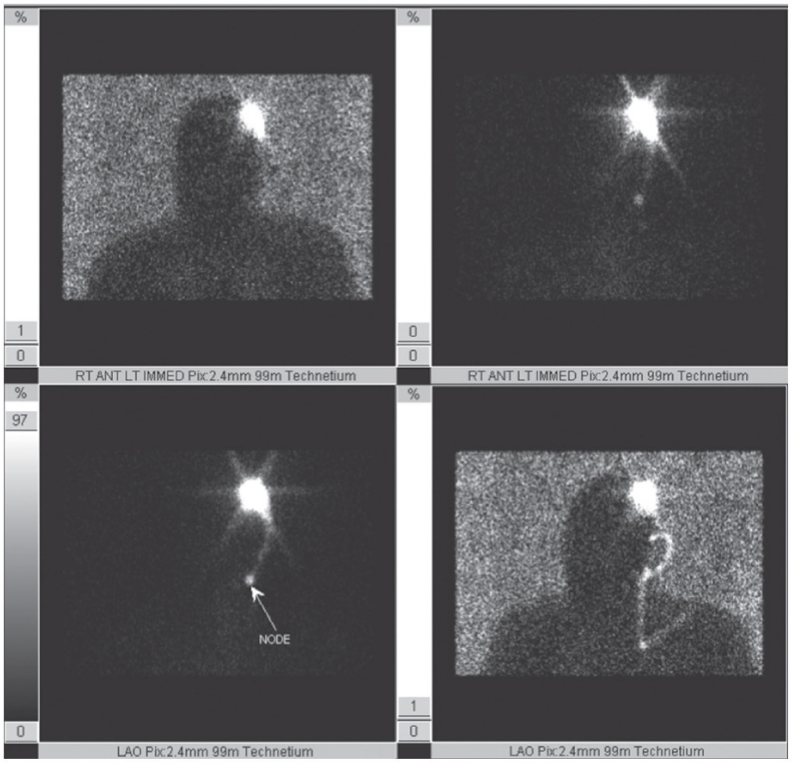
Melanoma Thickness (mm)	Recommended Excision Margin (cm)
In situ	0.5–1.0
≤1.0	1.0
1.1–2.0	1.0–2.0
>2.0	2.0

Margins may need to be modified on the basis of anatomic considerations but still should obtain histologically confirmed tumor-free margins.

Data from Thompson JF, Henderson MA, Williams G, Ross MI. Treatment of primary melanoma. In: Balch CM, Atkins MB, Garbe C, Gershenwald JE, Halpern AC, Kikwood JM, McArthur GA, Thompson JF, Sober AJ, eds. *Cutaneous Melanoma*. 6th ed. Switzerland: Springer Nature; 2020:573–594.

Figure 105.2 Contoured marginal excision for lentigo maligna of the face. **A:** Extensive, poorly defined lentigo maligna (melanoma in situ) of the left cheek. The *inner line* represents the clinical extent of the lesion, while the *outer two lines* represent the proposed marginal excision strips, each a minimum of 5 mm from the clinical edge of the lesion. **B:** Two to 3 mm wide strips have been excised at each of the contoured margins. **C:** Each strip is oriented for the pathologist and submitted for permanent section pathologic analysis. The resultant defects are closed with a running suture. If any strip contains tumor, indicating an inadequate margin has been obtained, then an additional margin is obtained and analyzed in the same fashion. **D:** The final result after excision of the entire central specimen and immediate reconstruction with a split-thickness skin graft. (Images courtesy of C. Wayne Cruse, MD, Moffitt Cancer Center.)

A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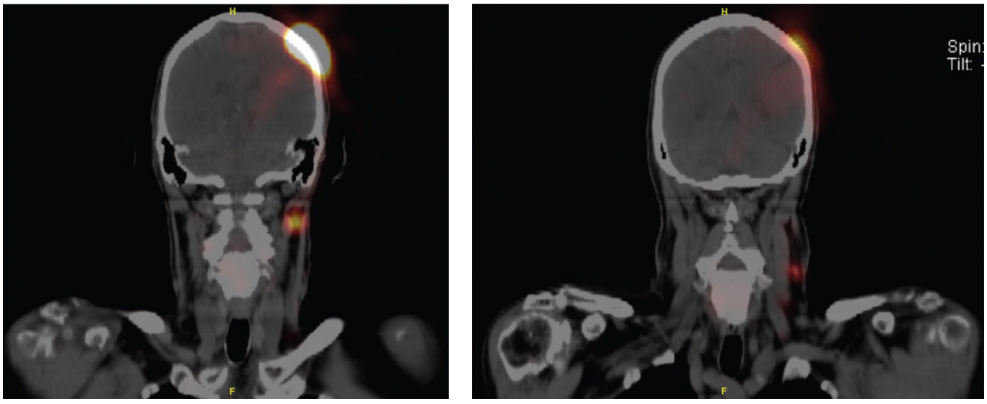
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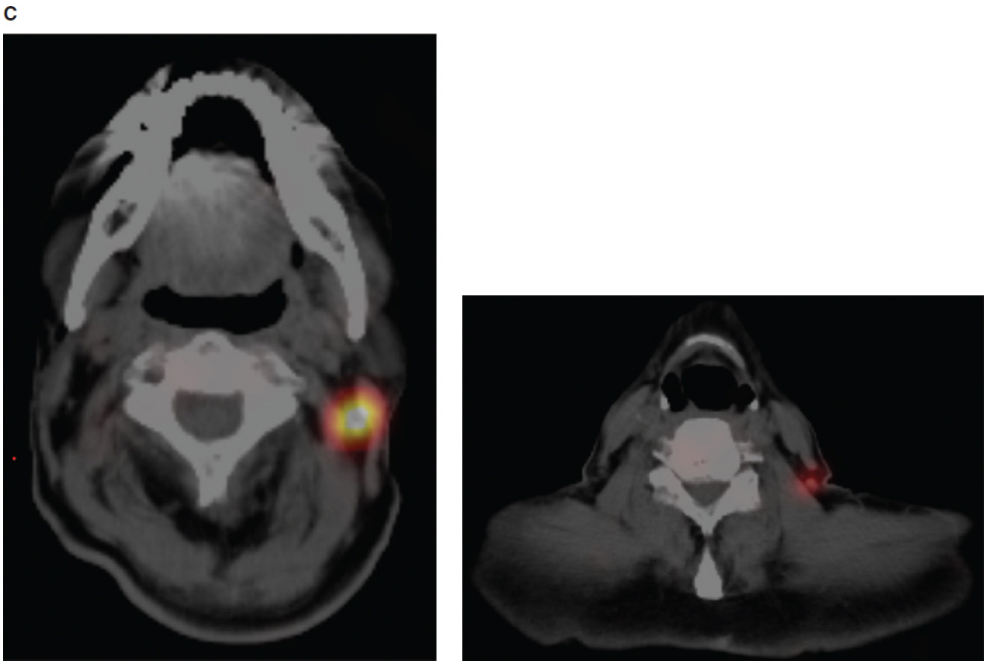

Figure 105.3 **A:** Planar lymphoscintigraphy for sentinel lymph node localization in patient with an intermediate-thickness melanoma of the left frontal scalp. One cervical node is identified (**lower left panel**). In the **lower right panel**, the nuclear medicine technologist has used a radioactive marker to outline the left ear, sternocleidomastoid muscle, and clavicle. **B:** Coronal SPECT-CT lymphoscintigraphy in the same patient shows the primary site on the scalp, and upper cervical (**left panel**) as well as lower cervical (**right panel**) sentinel nodes. **C:** Axial views show the upper cervical lymph nodes to be directly subjacent to the center of the left sternocleidomastoid muscle (**left panel**), while the lower cervical nodes are just posterior to the posterior edge of the muscle (**right panel**).

The Multicenter Selective Lymphadenectomy Trial I (MSLT-I) randomized patients to radical wide excision alone or in combination with SLNB.[24] Those with isolated nodal progression on the nodal observation arm underwent a therapeutic lymph node dissection while those with a positive SLNB underwent completion lymph node dissection (CLND). The final results indicated a superior disease-free survival rate in the SLNB group, for patients with both intermediate-thickness melanoma (71.3 ± 1.8% vs. 64.7 ± 2.3%; hazard ratio [HR] 0.76, $P = 0.01$) and thick melanoma (50.7 ± 4.0% vs. 40.5 ± 4.7%; HR 0.70, $P = 0.03$). Although MSLT-I showed no overall survival benefit with SLNB, subset analysis showed that SLNB-positive patients had a 10-year melanoma-specific survival of 62.1 ± 4.8% compared with 41.5 ± 5.6% for patients who recurred during observation. Even after

accounting for false-negative SLNB, the results remained significant (HR 0.67, 95% confidence interval [CI] 0.46 to 0.97, $P = 0.04$).

Treatment of Regional Metastatic Melanoma

4 Until recently, all patients with sentinel node micrometastases were recommended to undergo CLND of the positive lymph node basin(s). However, the clinical utility of this practice has been questioned, as approximately 80% of CLND specimens do not have residual nodal disease and the morbidity of CLND can be substantial—including chronic lymphedema in about 20% to 25% of patients.[25] Attempts to retrospectively identify clinicopathologic factors that predict disease within the non-SLNs did not identify reliable ways to identify those who could potentially benefit from CLND. In addition, retrospective studies questioned the clinical utility of CLND for SLN-positive patients.[26]

The practice of performing CLND following a positive SLNB has largely been abandoned after MSLT-II demonstrated CLND does not improve overall survival. This trial randomized 1,934 patients with a positive sentinel lymph node to CLND or nodal basin surveillance with serial ultrasonography. MSLT-II demonstrated no overall survival benefit for patients undergoing CLND (86 ± 1.3% vs. 86 ± 1.2%, $P = 0.42$) at a median follow-up of 43 months. Non-SLN metastases, identified in 11.5% of the patients in the CLND group, were a strong, independent prognostic factor for recurrence (HR 1.78, $P = 0.005$). Lymphedema was observed in 24.1% of the patients in the CLND group and in 6.3% of those in the nodal observation group.[27] These results were confirmed in another randomized trial, the German DeCOG-SLT study.[28] Given these results, most patients with a positive SLNB are preferably managed by active nodal surveillance, with therapeutic node dissection performed in the event of subsequent isolated nodal metastasis. Active nodal surveillance typically involves evaluation of the nodal basin by clinical examination and ultrasound every 3 to 4 months for the first 2 years, every 6 months for years 3 to 5, and annually until year 10.

Therapeutic Lymphadenectomy

For melanoma patient presenting with clinically detected tumor-involved nodes (AJCC 8th edition stage IIIB–D), including those who recur in the nodal basin after a positive or false-negative SLNB, therapeutic lymphadenectomy (radical node dissection) remains the standard of care, typically in combination with postoperative (adjuvant) or even preoperative (neoadjuvant) systemic therapy. A small percentage of stage III melanoma patients (about 10% of all clinical stage III cases) present with clinically evident nodal disease in the absence of a known primary cutaneous melanoma.[29] Almost all of these cases represent nodal metastases from primary cutaneous melanomas that either regressed spontaneously or were removed in the past but not recognized as malignant.[7] When patients present with isolated nodal disease from an unknown primary site, the outcomes of lymphadenectomy are generally as good or better than those for patients with known primary tumors.[29]

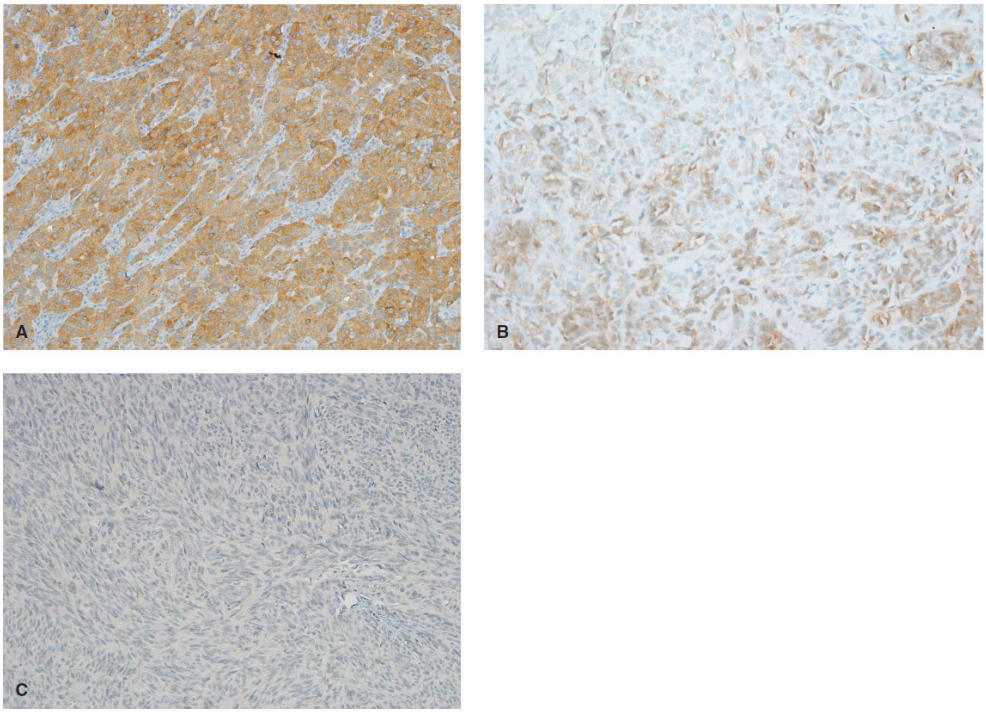

Figure 105.4 Sentinel lymph node micrometastases from melanoma stained with a BRAF V600E antibody: **A:** The result is strongly positive, with nearly 100% of tumor cells showing strong staining. **B:** The result meets minimum criteria for a positive result, with over 50% of tumor cells showing staining above background. **C:** A negative result, with virtually no staining of tumor cells, in a patient whose tumor proved to have a BRAF V600D mutation on molecular pyrosequencing. (Images courtesy of Jane L. Messina, MD, Moffitt Cancer Center.)

Adjuvant Therapy

Although the prognosis for patients with early-stage cutaneous melanoma is quite good, a lesser percentage of patients with thick primaries (>4 mm) or regional node involvement are cured by surgery alone. The development of effective adjuvant therapy capable of increasing survival in high-risk groups of patients has been a long-standing goal. Until recently, numerous randomized trials evaluating systemic chemotherapeutic agents (most notably dacarbazine), nonspecific immunotherapy (such as Bacille Calmette–Guérin [BCG]), tumor-specific vaccines, biochemotherapy, and interferons in the adjuvant setting either failed to demonstrate any impact on survival or were associated with prohibitive toxicity that limited their clinical value.[30,31] The success of new immunotherapy and molecularly targeted agents in the treatment of unresectable metastatic melanoma, however, spawned a series of randomized clinical trials that revolutionized the adjuvant therapy of high-risk resected melanoma.

Immune checkpoint inhibitors are intravenously-administered antibodies which block key regulatory molecules on the surface of T cells, enhancing an antitumor immune response. Ipilimumab, an anti-CTLA4 antibody which blocks the negative regulatory CTLA4 molecule, was the first immunotherapy proven to increase survival for metastatic melanoma and was the first new adjuvant therapy agent to be approved for stage III melanoma.[30,31] Compared to a placebo, adjuvant therapy with ipilimumab significantly improved relapse-free and overall survival in patients with stage III melanoma after lymphadenectomy. The 5-year overall survival was 65.4% in the ipilimumab arm compared with 54.4% in the placebo arm (HR 0.72, $P = 0.001$). Severe or life-threatening immune-related adverse events occurred in 41.6% of the ipilimumab arm patients, and 1.1% of patients died due to the toxicity of treatment.[32]

Anti-PD1 antibodies have improved antitumor efficacy with less toxicity than anti-CTLA4 antibodies in metastatic melanoma,[31] and randomized trials have compared adjuvant immunotherapy with an anti-PD1 antibody to either placebo or ipilimumab. Adjuvant therapy with the anti-PD1 antibody pembrolizumab significantly prolonged relapse-free survival compared to a placebo, with a lower incidence of severe or life-threatening adverse events (14.7%, with one treatment-related death) than was seen in the ipilimumab

trial.[31] Another randomized adjuvant therapy trial directly compared ipilimumab to the anti-PD1 antibody nivolumab. This trial confirmed that adjuvant anti-PD1 therapy was less toxic than adjuvant ipilimumab, with severe or life-threatening adverse events seen in 14.4% of the patients (and no treatment-related deaths) in the nivolumab arm versus 45.9% of those in the ipilimumab arm (and two treatment-related deaths). Importantly, adjuvant nivolumab resulted in significantly longer relapse-free survival than adjuvant ipilimumab.[34] Although adjuvant anti-PD1 immunotherapy is clearly less toxic than adjuvant ipilimumab, a small percentage of patients experience long-term, life-altering immune-related endocrine and cardiac toxicities. Somewhat surprisingly, overall survival was not significantly different between those treated with nivolumab and ipilimumab adjuvant therapy (4-year overall survival 77.9% versus 76.6% [HR 0.87, $P = 0.31$], respectively).[35] It remains possible that further analyses will demonstrate at least some survival advantage for anti-PD1 adjuvant therapy compared to ipilimumab or interferon, as some adjuvant therapy trials still await analysis. It is also possible that the immune-related adverse events seen with adjuvant immunotherapy represent a robust immune response that is associated with better outcomes,[36] although this remains to be definitively established.

Patients with metastatic melanoma whose tumor harbors a BRAF V600 mutation (about 45% of all cases) have another treatment option besides immunotherapy: BRAF/MEK molecularly targeted therapy has been shown to improve survival in these unresectable stage IV patients. The combination of dabrafenib (an oral BRAF inhibitor) and trametinib (an oral MEK inhibitor), administered for 1 year after lymphadenectomy for stage III melanoma, was compared to placebo in a randomized trial. Although there was concern that the inhibitory impact of the drugs would fade shortly after the year of therapy ended, long-term results of the trial suggest that is not the case. At a median follow-up of 59 months, 5-year relapse-free rates were 52% in the dabrafenib plus trametinib arm versus 36% in the placebo arm (HR 0.51). Distant metastasis-free survival also favored dabrafenib plus trametinib (HR 0.55).[37] Notably, an interim analysis of the overall survival impact of adjuvant dabrafenib plus trametinib, conducted using very strict statistical criteria, indicated that the combination was showing a survival advantage that was trending toward but has not yet reached statistical significance.[38] Although about a quarter of treated patients had to discontinue their adjuvant

therapy due to side effects, these adverse effects almost always resolved quickly after the drugs were stopped. As yet, adjuvant dabrafenib plus trametinib has not been compared head-to-head with adjuvant anti-PD1 immunotherapy in BRAF-mutant stage III melanoma.

In addition to defining the optimum adjuvant therapy for BRAF-mutant stage III melanoma, other questions remain about adjuvant therapy for melanoma. The possible added value of combining ipilimumab with nivolumab is being evaluated in adjuvant clinical trials, with one smaller randomized trial suggesting this more toxic combination might be superior for patients with resected stage IV melanoma.[39] All of the adjuvant clinical trials reported in stage III melanoma to date required CLND for patients with a positive SLNB, and most required a minimum tumor burden in the sentinel node of 1 mm for the size of the largest nodal metastasis. Therefore, significant questions remain about adjuvant therapy for SLNB-positive patients who are managed with active nodal surveillance, including how to manage resectable recurrence during adjuvant therapy, and for patients with lesser nodal tumor burdens.

Neoadjuvant Therapy

Neoadjuvant therapy is defined as systemic therapy delivered for a prespecified time to patients with resectable disease prior to proceeding with definitive surgery. For stage III melanoma, neoadjuvant therapy can involve single-agent or combination immunotherapy, or for patients whose tumors harbor a BRAF V600 mutation, combination BRAF plus MEK inhibition. In contrast, "upfront systemic therapy" can be defined as administration of systemic therapy prior to surgery with no specific plan to carry out resection at a defined point in time if at all. Sometimes upfront systemic therapy is carried out with the hope of converting unresectable stage III disease to a resectable state, but it can also be used in patients with resectable disease. Preoperative systemic therapy has several key advantages over giving the same drugs in the postoperative adjuvant setting,[31] the most important of which may be the ability to assess the response of the tumor to treatment clinically (by physical examination and/or cross-sectional imaging), metabolically (by ^{18}F-FDG PET scanning), and pathologically. Patients who obtain a complete or near-complete pathologic

response to preoperative treatment appear to have a particularly good outcome and may ultimately need less radical surgery and no postoperative systemic therapy (**Fig. 105.5**). Many clinical trials of neoadjuvant therapy are now underway, including some trials comparing preoperative treatment to the same drugs given entirely postoperatively.

Adjuvant Radiation Therapy

Although cutaneous melanoma is often thought of as radioresistant, there are clearly situations when adjuvant postoperative radiation can be useful. Desmoplastic melanoma is a rare subtype of cutaneous melanoma that appears to be particularly likely to recur locally, especially when there is evidence of perineural extension of the disease, yet particularly sensitive to radiation. Available evidence suggests that postoperative radiation can substantially decrease the risk of local recurrence of desmoplastic melanoma, especially when the primary tumor is thick, situated on the head or neck, or in the presence of perineural extension.[40] Postoperative radiation to the tumor-involved nodal basin after therapeutic lymphadenectomy has been studied in a randomized trial. Adjuvant postoperative radiation can decrease the in-basin regional recurrence risk, at the expense of an increase in the risk for lymphedema and other toxicities, but it does not impact overall survival.[41] Adjuvant nodal radiation should be considered in patients with multiple involved nodes, especially in the presence of extranodal extension.

Treatment of In-Transit Disease

In-transit metastatic melanoma is defined as any recurrence between the primary melanoma site and the regional lymph nodes and is thought to be due to intralymphatic metastasis. In-transit metastatic melanoma without distant metastasis is classified as stage III disease and can be challenging to treat. Treatment involves either excision, regional chemotherapy, intralesional therapy, or systemic therapy. Prior to proceeding with treatment, a complete staging workup for metastatic disease is recommended. Surgical excision should be considered when the number of lesions is relatively small, and particularly when the time from previous treatment to the development of the recurrence is relatively long.

When the in-transit disease is unresectable but limited to an extremity, regional administration of high-dose hyperthermic chemotherapy can be effective. Isolated limb perfusion (ILP) uses an extracorporeal membrane oxygenator (as used in cardiac surgery) to deliver chemotherapy doses 15 to 25 times higher than can be obtained with systemic delivery. The surgeon isolates the vessels and uses a tourniquet at the proximal aspect of the extremity to prevent systemic uptake of the chemotherapy. Using the bypass machine, the limb is oxygenated and perfused with hyperthermic (38° to 40°C) chemotherapy, most commonly melphalan alone or combined with other drugs. After 60 to 90 minutes of treatment, the drug is flushed from the circulation and systemic circulation is restored. Response rates between 80% and 90% are reported, with complete response rates between 40% and 65% that can be durable.[42,43] Toxicities can range from mild erythema and edema to epidermolysis, functional impairment, compartment syndrome, and extremely rarely, a need for amputation.

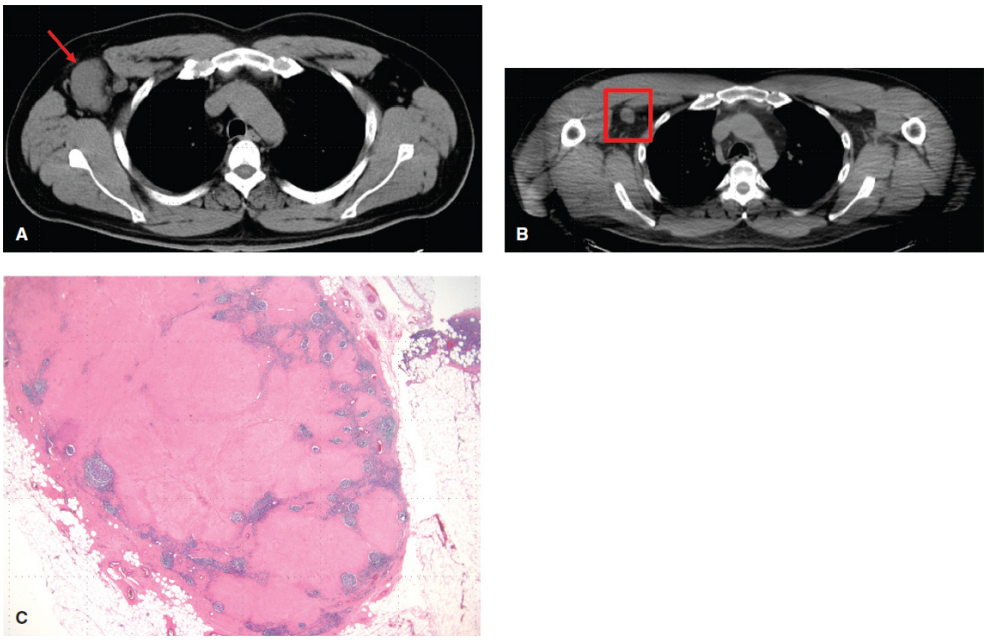

Figure 105.5 Neoadjuvant therapy for stage III melanoma. **A:** Pretreatment CT scan showing a large right axillary lymph node (*arrow*) that developed 2 years after radical wide excision of a thin (T1a) melanoma of the ipsilateral arm. **B:** Scans after 6 months of BRAF/MEK inhibition, showing a partial response to therapy (*box*). **C:** Histologic specimen from the lymphadenectomy, showing posttreatment changes but no viable tumor (pathologic complete response). The patient received no further therapy and remains disease-free more than 4 years later. (Images courtesy of Jane L. Messina, MD, Moffitt Cancer Center.)

Isolated limb infusion (ILI) is a minimally invasive alternative to ILP. Rather than surgical isolation of the vessels, percutaneous catheters are placed with fluoroscopic guidance into the artery and vein and connected to an extracorporeal circuit incorporating a heating coil but not using a cardiac bypass oxygenator. A tourniquet is placed on the proximal extremity, and slightly lower doses of chemotherapeutic agents are used. Some studies have reported response rates equivalent to ILP, although others report slightly lower response rates.[44,45] However, the greater convenience and lower toxicity of ILI, lack of evidence of a survival difference compared to ILP, and the ability to repeat the procedure if necessary has made ILI the regional chemotherapy approach of choice in most melanoma centers worldwide.

When resection or ILP/ILI is not feasible, a number of intralesional therapies have been utilized in the past, particularly BCG, interleukin (IL)-2, and granulocyte-macrophage colony–stimulating factor (GM-CSF). A relatively new intralesional therapy agent, talimogene laherparepvec (TVEC), is an oncolytic immunotherapy derived from the herpes simplex virus type-1. In a randomized phase III trial, TVEC demonstrated an improved response rate lasting at least 6 months compared to a control arm of subcutaneous GM-CSF (19.0% vs. 1.4%; $P < 0.0001$) and a trend toward improved overall survival.[46] A subsequent retrospective, nonrandomized study reported a 57% response rate with TVEC for patients with generally less advanced disease compared to the randomized trial (**Fig. 105.6**), highlighting the importance of patient selection.[47] Other intralesional or topical agents under investigation currently include PV10 (Rose Bengal), plasmid IL12 electroporation, and topical diphencyprone. A recent retrospective review of patients with in-transit metastatic melanoma treated with systemic immunotherapy (PD1 antibody blockade, CTLA4 blockade, or combination therapy) reported a 54% response rate.[48] The combination of intralesional therapy and systemic immunotherapy is an area of active clinical investigation.[49]

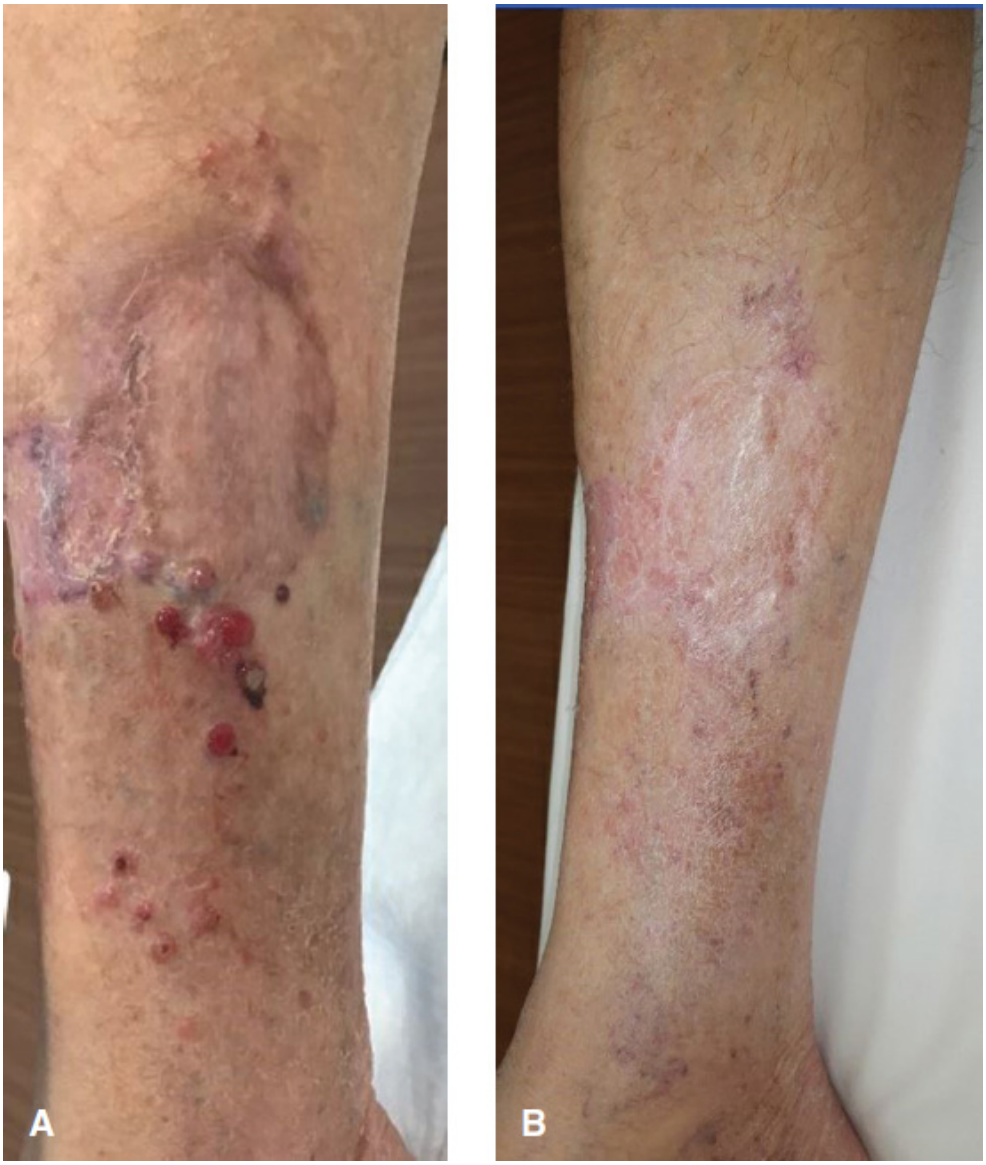

Figure 105.6 Example of response to intralesional talimogene laherparepvec (TVEC). **A:** Multifocal satellite (within 2 cm of the primary site) and in transit (>2 cm from the primary site but proximal to the draining nodal basin) metastases from a thick, ulcerated (T4b) primary melanoma of the leg previously treated with radical wide excision and split-thickness skin graft reconstruction. **B:** After eight injections of TVEC, there is no palpable or visible tumor remaining.

Treatment of Disseminated Melanoma

Evaluation for Metastatic Disease and Clinical Course

The follow-up evaluation for patients with AJCC stage I, II, or III melanoma who are rendered disease-free by surgery should include regular histories and physical examinations. The use of extensive and frequent radiographic studies and blood work in asymptomatic, clinically disease-free patients is rarely productive.[50] For AJCC stage IA to IIA, the consensus guidelines recommend that clinically disease-free patients should undergo a history and physical examination with emphasis on skin and nodal examinations every 6 to 12 months as clinically indicated. For AJCC stage IIB to IV, clinically disease-free patients should undergo a history and physical examination every 3 to 6 months for 2 years, then every 3 to 12 months for 3 years, and then annually as clinically indicated. Imaging studies (CXR, CT, or PET/CT) can be considered every 3 to 12 months for the first 3 to 5 years.[15]

Melanoma can disseminate to any organ. The most common sites of recurrence are skin, subcutaneous tissues, and distant lymph nodes, followed by visceral sites. Common visceral sites of metastasis are the lungs, liver, brain, bone, gastrointestinal tract, and adrenal glands. Most patients who die with disseminated disease have multiple organ involvement. Over the past 10 years, there have been tremendous advances in the systemic therapy of melanoma. There are now multiple molecularly targeted therapies and immune checkpoint inhibitors that have been approved for the treatment of advanced melanoma, with several new therapies and combinations in clinical trial.[31] How to proceed in the management of advanced melanoma should be based on several factors, including the patient's medical condition and comorbidities, the potential for cure or palliation, and the impact of treatment on quality of life.

Surgery

For most cancers, surgery is rarely considered as a curative option in stage IV disease. Historically, melanoma has been an exception to this, with documented long-term survival among patients who undergo resection of one or a few metastatic lesions. Several retrospective studies, as well as prospective studies, have suggested that metastasectomy may result in prolonged disease-free survival in select patients.[51,52] The rationale for surgical extirpation of metastatic disease was in part driven by the lack of effective systemic therapies in melanoma. The role of surgery for stage IV

disease is rapidly evolving as new, highly effective therapies have emerged. Despite the excitement surrounding these new agents, there may be potential advantages to metastasectomy. Careful patient selection is key, as is a true multidisciplinary approach. Patients being considered for metastasectomy should undergo a thorough search for additional sites of disease, including a detailed history and physical, serum LDH, CT or PET scan, and MRI of the brain. Factors to consider when formulating a treatment plan include the age and health of the patient, the number and locations of the metastases as well as the ability to achieve negative margins, the morbidity of the operation, the disease-free interval between the original diagnosis and the development of distant disease, the need for palliation of active symptoms or the prevention of impending problems (e.g., bowel obstruction from a small intestinal metastasis), and the available systemic options. For select patients, surgery may be considered as a first-line therapy, potentially delaying the need for systemic therapies, or be used in conjunction with systemic therapies, either after neoadjuvant therapy or for resection of lesions that fail to respond. The successful incorporation of surgery in the management of stage IV disease is dependent upon true multidisciplinary collaboration between surgical, medical, and radiation oncologists.

Chemotherapy

Melanoma is responsive to few chemotherapeutic drugs. The most widely used single chemotherapeutic agents have been dacarbazine and its oral analog temozolomide, with objective response rates of 5% to 12%.[53] Most responses are transient; only 1% to 2% of patients achieve a durable long-term response. Attempts to improve upon these results using combination chemotherapy, or biochemotherapy (where chemotherapy is combined with interferon and IL-2), failed to dramatically improve upon single-agent therapy alone, although biochemotherapy and combination chemotherapy with carboplatin and paclitaxel have slightly higher response rates than single-agent dacarbazine or temozolomide.[54]

High-Dose Interleukin-2

IL-2 is a cytokine secreted by antigen-activated helper T cells, initially discovered to be a T cell growth factor but subsequently found to have many other immunologic effects, including an important role in the enhancement of immune responses. High-dose IL-2 (600,000 IU/kg every 8 hours for up to 14 doses) is associated with an objective response rate of 15% to 20%, with a small percentage of patients (around 5%) experiencing long-term, durable complete responses.[31] However, IL-2 treatment requires inpatient care, as toxicity is often severe and can include hypotension, pulmonary edema, decreased renal function, respiratory insufficiency, and neurotoxicity. Currently, the main role for IL-2 treatment is in conjunction with adoptive cellular therapy using tumor-infiltrating lymphocytes (TILs), an area of active clinical investigation in patients with metastatic melanoma refractory to currently available treatments.[55] This treatment capitalizes on the phenomenon that melanoma-specific T cells naturally infiltrate tumors, but it is rare for the endogenous immune response to eradicate metastatic melanoma by itself. However, if a small piece of tumor can be safely surgically harvested and delivered under sterile conditions to a licensed Good Manufacturing Practices facility, the resident TIL can be selectively expanded to large numbers and then used as a cellular treatment product. TIL treatment as currently administered requires a preparative, nonmyeloablative chemotherapy regimen that is followed by adoptive transfer of TIL and IL-2. TIL treatment in patients with metastatic melanoma has been associated with responses of up to 56%.[56] A multicenter clinical trial has reported a 36% response rate in patients whose disease is refractory to anti-PD1 antibody therapy (**Fig. 105.7**).[57] The surgeon plays an important role in this treatment modality, as selection of nonnecrotic, sterile tumor for harvest via a procedure with an acceptable projected duration for recovery is of critical importance for the treatment to be successful.[58]

Immune Checkpoint Inhibitors

For many years, immunotherapy research centered on the generation of an antitumor immune response through the use of nonspecific immunostimulants, vaccines, and assorted adjuvants. However, immune checkpoint inhibition, which essentially takes the brakes off the patient's inherent antitumor immune

response, has rapidly emerged as an effective form of immunotherapy in melanoma.[31]

Ipilimumab is a monoclonal antibody that binds to the cytotoxic T lymphocyte–associated antigen-4 receptor. This receptor is found on regulatory T cells and cytotoxic T cells after they have been activated, with its primary function to inhibit T cell responses. Blocking the binding between CTLA-4 and its ligand B7 suppresses this inhibitory function (essentially removing the brakes) and promotes continued T cell activation. In an analysis of pooled data from several clinical trials, the 3-year overall survival rate for patients with unresectable metastatic was 22%, with many of them being durable as the rate of additional deaths between 3 and 10 years was relatively low.[59] Ipilimumab is associated with immune-related toxicities, specifically enterocolitis, hepatitis, endocrinopathies, and dermatitis. While these can be severe, most are reversible if recognized and treated early, although endocrine toxicities in particular can be long-lasting.

Figure 105.7 Example of response to adoptive cellular therapy with tumor-infiltrating lymphocytes (TILs). **A:** Extensive recurrent melanoma of the distal foot and toes after prior margin-positive excision, progressive after multiple lines of systemic immunotherapy and chemotherapy. The tumor was BRAF wild type, and the patient also had widespread metastatic disease. The patient was enrolled onto a clinical trial testing adoptive cellular therapy with TILs. After harvest of tumor from a metastasis in the groin, TIL were grown ex vivo and reinfused into the patient after preparative lymphodepleting chemotherapy. High-dose interleukin-2 was administered for several days, and the patient tolerated therapy well and received no further treatment. **B:** Three months after therapy, there is clear evidence of tumor shrinkage at the primary site (shown) and all metastases. **C:** Six months after therapy, the tumor has almost completely regressed. The patient received no further therapy and remains well 2 years later.

Activated CD4 and CD8 T cells also express the programmed death 1 (PD1) receptor which, once bound to its ligand PD-L1, triggers a decrease in T cell proliferation, IL-2 release, and T cell survival. Malignant cells often express PD-L1 that binds to the receptors and blocks T cell killing. Pembrolizumab and nivolumab are monoclonal antibodies against PD1 that prevent binding to PD-L1. Both have shown response rates in as many as 45% of treated patients, with frequent responses even in those patients who have already progressed on or after treatment with ipilimumab. They were both approved by the FDA. As with anti-CTLA4, anti-PD1 can be associated with immune-mediated toxicities, including colitis, endocrinopathies, and pneumonitis. In phase III randomized trials comparing either nivolumab or pembrolizumab with ipilimumab, in previously untreated patients, the anti-PD1 antibodies were associated with improved response rates, progression-free survival, and overall survival with lower toxicity,[31] leading to a shift

toward anti-PD1 therapy as the first-line therapy in advanced melanoma. In addition, studies of combination therapy with anti-PD1 and anti-CTLA4 antibodies have demonstrated improved response rates and progression-free survival with increased but manageable toxicity, but it remains to be seen if the survival is better for the combination than for anti-PD1 alone.[60]

BRAF and MEK Inhibitors

The mitogen-activated protein kinase (MAPK) pathway is a key pathway in melanoma pathogenesis, with nearly half of melanomas having constitutive activation due to mutations in the *BRAF* gene.[61] Activation of the pathway leads to unregulated cell proliferation. Vemurafenib, dabrafenib, and encorafenib are orally administered targeted therapies that block the constitutively active mutant BRAF. Common adverse effects include arthralgia, rash, fatigue, alopecia, and the development of cutaneous keratoacanthomas and SCCs, and even second-primary BRAF wild-type melanomas. Patients treated with BRAF inhibition have dramatic responses, but unfortunately the survival benefit is limited because of the eventual development of resistance in most patients. Combining a BRAF inhibitor with an inhibitor of MEK1/2, a downstream regulator of BRAF, was associated with an improvement in response rates, progression-free survival, and overall survival compared with the BRAF inhibitor alone.[62–64] In addition, combination BRAF/MEK inhibitor therapy is also associated with fewer secondary cutaneous malignancies than with a BRAF inhibitor alone. The FDA has now approved three BRAF/MEK inhibitor combinations, vemurafenib plus cobimetinib, dabrafenib plus trametinib, and encorafenib plus binimetinib, for the treatment of patients with advanced melanoma with BRAF V600 E/K mutations.

The Impact of Treatment on Unresectable Metastatic Melanoma

Metastatic melanoma was once one of the most treatment-refractory types of cancer, but the availability of the new drugs described above has changed that picture dramatically. Five-year survival rates for patients with

unresectable metastatic melanoma now reach levels previously thought impossible. In a large randomized trial comparing ipilimumab to nivolumab or the combination of nivolumab plus ipilimumab, 5-year survival was 52% in the nivolumab plus ipilimumab arm and 44% in the nivolumab alone arm, compared with 26% in the ipilimumab arm. Among the subset of patients whose melanoma had a BRAF mutation, their 5-year survivals were an astonishing 60% in the nivolumab plus ipilimumab arm and 46% in the nivolumab alone arm, reflecting the potential for salvage treatment with BRAF/MEK inhibitors.[60] The use of these powerful therapies earlier in the course of the disease, as adjuvant and/or neoadjuvant therapy, can potentially improve outcomes even more. This emphasizes the critical importance of multidisciplinary, multimodality treatment for patients with melanoma—even if it is readily resectable—in order to direct the right treatment to the right patient and maximize the benefits of both surgical and nonsurgical treatments.

NONMELANOMA SKIN CANCERS

5 BCC and cutaneous SCC account for over 95% of all skin cancers and are also referred to as keratinocyte carcinomas due to their cell of origin.[65] Based on 2012 data, 5.4 million keratinocyte carcinomas were diagnosed in the United States annually, and that figure has doubtless increased since. The public health burden on the U.S. population from these lesions is highly significant.[66] Patients with clinically localized keratinocyte cancers have an excellent prognosis, with the vast majority curable with appropriate local treatment and fewer than 1% resulting in death. Mortality is primarily associated with SCC rather than BCC, with immunosuppressed patients being at dramatically higher risk of metastatic disease and death.

Etiology

Both BCC and SCC are most commonly induced by significant exposure to UV light from the sun and/or tanning beds. These cancers are predominantly located on the head, neck, trunk, lower legs, and hands, where sun exposure is common. Skin cancer is a significant occupational hazard for people who work outdoors. The phenotype at increased risk is one with fair skin who

sunburns and freckles easily, has blue or green eyes, and has red or blonde hair. Melanin pigment in the skin appears to be a protective factor, and the incidence of keratinocyte cancers is substantially lower in dark-skinned individuals. Immunosuppression is a major risk factor for keratinocyte cancers.[65]

A number of genetic syndromes are associated with an increased risk of developing keratinocyte cancers, including Gorlin syndrome, xeroderma pigmentosa, and albinism. Gorlin syndrome is an autosomal dominant disorder associated with multiple BCCs, palmoplantar pits, jaw cysts, frontal bossing, and hypertelorism. The mutated gene in Gorlin syndrome is *PTCH1*, a gene in the Hedgehog pathway, which is the pathway that is overactivated in virtually all BCCs. Xeroderma pigmentosa is associated with markedly defective repair of DNA damage due to UV light. Albinism is a disorder characterized by a partial or complete deficiency in melanin production and, thus, loss of protective pigment.

Another factor associated with keratinocyte cancers, primarily SCC, is chronic exposure of the skin to chemicals such as arsenic and hydrocarbons (found in coal tars, soot, and asphalt). Cigarette smoking has been associated with SCC of the lip and mouth. Human papillomavirus has been associated with cutaneous SCC in the genital and acral/periungual areas and also in SCC arising in immunosuppressed patients. Radiation has been associated with increased risk of both SCC and BCC.[65]

Basal Cell Carcinoma

BCC is the most common form of skin cancer. BCCs rarely metastasize but are characterized by slow growth that can be relentless and highly destructive without treatment. The most common subtype of BCC is the well-circumscribed nodular variety. These tumors often present as pearly papules or nodules with telangiectasias. They may be pruritic and bleed occasionally. With time, the center ulcerates to create rolled borders; such ulcerating BCCs may be referred to as "rodent ulcers" (**Fig. 105.8A**). Occasionally, the lesions are pigmented and can be confused with melanoma. This variant has been called pigmented BCC (see **Fig. 105.1I**). In some cases, BCC has histologic features of squamous or eccrine differentiation. Superficial BCCs are another common entity and are frequently multifocal. Clinically, these are

flat, scaly pink to red lesions (**Fig. 105.8B**) but if neglected they can ulcerate (**Fig. 105.8C**). They can be confused with psoriasis or other eczematous, scaly dermatoses.

The most locally aggressive type of BCC is characterized by a histopathologic infiltrating, aggressive growth pattern, referred to as morpheaform, sclerosing, or fibrosing BCC (**Fig. 105.8D**). Clinically, these tumors may appear to be scar-like, and they frequently have microscopic finger-like fronds of tumor cells that invade the surrounding structures well beyond the clinical margins of the lesion. These small, finger-like islands may be missed with standard histologic margin analysis and are associated with an increased risk of local recurrence. Although most BCC tumors are relatively localized, extensive subclinical involvement is common even without a morpheaform histology. Numerous risk factors are associated with possible extensive subclinical invasion and increased rates of local recurrence for BCC after standard treatment (**Table 105.8**).

Figure 105.8 Examples of basal cell carcinoma. **A:** Nodular basal cell carcinoma on the nasal ala, illustrating the classic "rodent ulcer" central depression. **B:** Superficial basal cell carcinoma on the thigh. **C:** Ulcerated basal cell carcinoma on the ankle. **D:** Morpheaform basal cell carcinoma on the cheek (*arrow*).

Cutaneous Squamous Cell Carcinoma

SCC is the second most common form of skin cancer. SCC most often arises in chronically sun damaged skin or within an actinic keratosis but may also develop in burn scars or chronic inflammatory wounds, known eponymously as a Marjolin ulcer. SCC has a greater propensity for regional and distant metastasis than BCC, but metastatic disease is less frequent when compared to melanoma or MCC. Nonetheless, the high incidence rate of SCC means that metastatic SCC occurs frequently enough to be seen in any busy practice devoted to cutaneous surgical or medical oncology. Metastasis to regional lymph nodes accounts for approximately 80% to 90% of these cases of metastatic SCC. Involvement of distant sites, such as the lung, liver, brain, bone, and skin, account for the other 10% to 20%. In immunosuppressed

individuals, SCC occurs much more frequently and with a more clinically aggressive behavior than in the general population.[65]

Table 105.8 Basal Cell and Squamous Cell Carcinoma: Higher-Risk Factors for Subclinical Invasion and Recurrence

▪ Recurrent tumor
▪ Anatomic location *High risk:* Central face, eyelid, eyebrow, periorbital, nose, lip, chin, mandible, temple, ear, in front or behind the ear, genitalia, hand, and foot *Medium risk:* Cheeks, forehead, pretibia, scalp, and neck *Low risk:* Trunk, extremity (excluding hand/foot and pretibia)
▪ Size Lesions ≥6 mm on high risk area Lesions ≥10 mm on medium risk area Lesions ≥20 mm on low risk area
▪ Histology *Basal cell:* Aggressive growth pattern (morpheaform, fibrosing, sclerosing, infiltrating, micronodular) *Squamous cell:* Poorly differentiated, acantholytic, desmoplastic, adenosquamous, or carcinosarcomatous subtypes
▪ Depth of invasion Clark level IV (lesion that involves the reticular dermis), V (lesion that invades into subcutaneous fat), or ≥4 mm
▪ Perineural invasion
▪ Rapid growth and/or ill-defined borders
▪ Etiology Scar, chronic ulcer or inflammatory process, sinus tract, sites of prior radiation therapy
▪ Immunosuppression

Adapted from Claveau J, Archambault J, Ernst DS, et al. Multidisciplinary management of locally advanced and metastatic cutaneous squamous cell carcinoma. *Curr Oncol* 2020;24(4):e399–e407 and

from Peris K, Fargnoli MC, Garbe C, et al. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. *Eur J Cancer* 2019;118:10–34.

Figure 105.9 Examples of squamous cell carcinoma. **A:** Squamous cell carcinoma presenting as a non-healing sore with ill-defined pink borders. **B:** Ulcerated squamous cell carcinoma. **C:** Keratoacanthoma type squamous cell carcinoma.

SCC often presents as a nonhealing sore with ulceration and inflammatory pink borders, or as an erythematous nodule with overlying keratotic crust or ulceration (**Fig. 105.9A,B**). One noteworthy variant, keratoacanthoma type SCC, is characterized by a typical cratered appearance (**Fig. 105.9C**) and rapid local growth but little or no propensity to metastasize. The lesions may develop in patients taking BRAF inhibitors, especially when used as single agents without a concurrent MEK inhibitor.[67] Several risk assessment tools

are available to stratify the risk of recurrence and metastasis in SCC.[68,69] Factors that may determine a higher risk for local recurrence, extensive subclinical invasion, and metastasis are noted in Table 105.8.

Surgical Treatment of the Common Nonmelanoma Skin Cancers

Most keratinocyte cancers are small, low-risk lesions with 90% to 95% cure rates after standard treatment techniques, including electrodesiccation and curettage (ED&C), cryosurgery, radiation therapy, or surgical excision. Most BCCs and SCCs can be removed with conservative excisions using narrower peripheral and deep margins of excision than are used for melanoma or MCC. Excision margins for most localized BCC and SCC lesions should be in the range of 0.4 to 0.5 cm, but larger resectable tumors should be treated surgically in a manner similar to melanoma using 1 cm margins of excision taken down to fascia. Mohs surgery should be considered for BCCs and SCCs that exhibit the higher-risk factors in **Table 105.8**, particularly if they are situated in an anatomical area (e.g., face or ears) where skin conservation is of critical importance. While SLNB may be considered for carefully selected SCC at high risk of regional metastasis, criteria that reliably identify cases with at least a 5% to 10% risk of nodal metastasis have not been prospectively validated.[70,71]

Mohs Surgery

Mohs micrographic surgery is useful for the treatment of selected high-risk keratinocyte cancers (**Table 105.8**) as a tissue-sparing technique that achieves high cure rates. Mohs surgery is usually performed with local anesthesia in an outpatient surgical unit. After removal of all gross tumor, the surgeon excises a further thin 2 to 3 mm layer of tissue that includes all peripheral and deep margins of the excision. This layer of tissue is mapped, color coded for orientation, and sent to the Mohs technician for frozen section processing. In this way, both the deep and peripheral margins are examined in one horizontal plane by frozen section analysis, theoretically allowing total margin analysis. After histologic interpretation of the frozen

section specimens by the Mohs surgeon, the precise anatomic location of any residual tumor can be identified and that area reexcised and reanalyzed by frozen section until all margins are tumor free (**Fig. 105.10**). If appropriate, rapid immunohistochemical staining can be used to augment the evaluation of the margins. Closure or relatively straightforward soft tissue reconstruction can be performed on the same day (**Fig. 105.11**) or subsequently for more complex defects. A multidisciplinary approach involving Mohs, plastic, head and neck, and oculoplastic surgeons and radiation oncologists may be needed for extensive tumors.

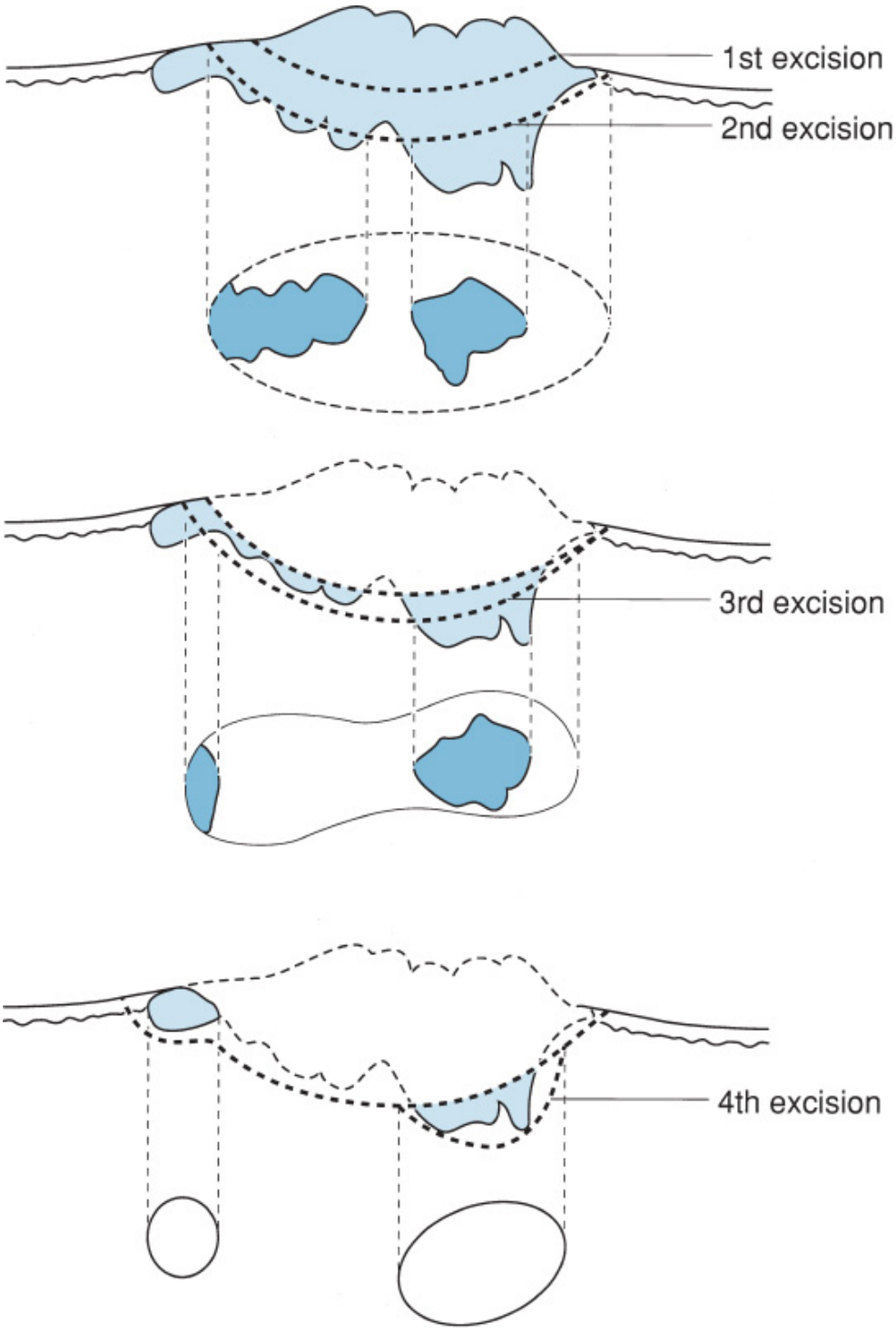

Figure 105.10 Mohs micrographic surgical technique. In this case, after the first excision to debulk the visible tumor, the second layer demonstrated relatively diffuse multifocal involvement of the margin by tumor. Accordingly, a third layer across most of the prior margin was obtained, which still showed two isolated foci of tumor at the excision margin. A fourth and final stage taking additional tissue only at those two sites resulted in complete, margin-negative excision of the tumor.

A randomized trial compared Mohs surgery to standard surgical excision for high-risk primary and recurrent basal cell cancer of the face.[72] A total of 408 patients with primary BCC were randomized; the 10-year recurrence rate was superior after Mohs (4.4% vs. 12.2%) but this did not reach statistical significance (P = 0.10). For 204 patients with recurrent BCC, however, the 10-year recurrence rate was significantly lower for Mohs than standard excision (3.9% vs. 13.5%, respectively; P = 0.02). Many recurrences occurred more than 5 years after surgery: 56% of the recurrences for primary and 14% of the recurrences for recurrent BCC.[72] In general, Mohs surgery should be considered for keratinocyte carcinomas that are associated with a relatively high risk of recurrence after standard treatment, especially recurrent tumors, and for primary sites where conservation of normal tissue is important.[73]

Adjuvant and Primary Radiation Therapy

Radiation therapy can be considered in the primary treatment of low-risk and even selected high-risk keratinocyte carcinomas and provides an alternative to surgery in cosmetically sensitive areas. For cutaneous SCC at high risk of local recurrence, such as those with perineural spread,[74] adjuvant radiation therapy to the primary site may decrease the risks of local recurrence after margin-negative resection as noted in consensus guidelines. Adjuvant radiation therapy may also be considered for selected aggressive, deeply invasive BCCs, particularly for recurrent tumors or those with extensive perineural spread or persistently positive margins after surgery as noted in consensus guidelines.

Locally Advanced and Metastatic BCC

The definition of locally advanced skin cancer is not universally accepted. Large, deeply invasive but resectable tumors can reasonably considered locally advanced, but some definitions restrict the term to encompass nonmetastatic keratinocyte cancers not amenable to either surgery or radiotherapy with reasonable expectation for cure due to multiple recurrences, infiltration through the fascia into underlying muscle or along major nerves, bony invasion, as well as tumors in which curative resection

would result in unacceptable complications, morbidity, or deformity.[76] BCC grows slowly, so locally advanced tumors usually represent long-neglected lesions. Uncontrolled Hedgehog pathway signaling is central to the pathogenesis of both hereditary and sporadic BCC and represents an opportunity for molecularly targeted therapy. Inactivating mutations of the tumor-suppressor *PTCH1* (patched) gene or less frequently activating mutations in the proto-oncogene smoothened (*SMO*) result in the unregulated activation of the Hedgehog pathway; aberrations in one gene or the other are found in virtually all BCCs, so routine mutational analysis is not required prior to initiating targeted therapy. Vismodegib and sonidegib are Hedgehog pathway inhibitors approved by the FDA for the treatment of locally advanced and (for vismodegib) metastatic BCC. Objective response rates approach 30% for metastatic BCC and exceed 40% for locally advanced BCC. Unfortunately, tumors frequently develop resistance to therapy. Adverse events occur in more than 30% of patients, and include muscle spasms, taste disturbances, alopecia, weight loss, and fatigue. In locally advanced BCC, preoperative use of one of these Hedgehog inhibitors can result in sufficient shrinkage to permit definitive treatment with surgery and/or radiation.[75] New treatment options are clearly needed for locally advanced and metastatic BCC that is refractory to Hedgehog inhibitors. Anti-PD1 immunotherapy has been shown to induce objective responses in some of these patients.[77]

Locally Advanced and Metastatic SCC

Locally advanced SCC represents another challenging clinical scenario. Feasibility of resection for locally advanced SCC should take both anticipated functional and cosmetic outcomes into account. Imaging to assess resectability and to rule out distant disease is typically warranted. Surgical excision of locally advanced SCC followed by adjuvant radiation therapy is the appropriate treatment for cases that are amenable to resection with acceptable cosmetic and functional outcomes. For unresectable cases, options include definitive radiation therapy up to 70 Gray with or without systemic chemotherapy (typically cisplatin or carboplatin)[69,70] and systemic immunotherapy with an anti-PD1 antibody such as cemiplimab or pembrolizumab.[77,78] These approaches can also be used to shrink locally

advanced tumors sufficiently to permit resection. Anti-PD1 immunotherapy has been associated with response rates for locally advanced and metastatic SCC that exceed the historical response rates and duration of response associated with chemotherapy or epidermal growth factor receptor (EGFR) inhibitor therapy.[79,80]

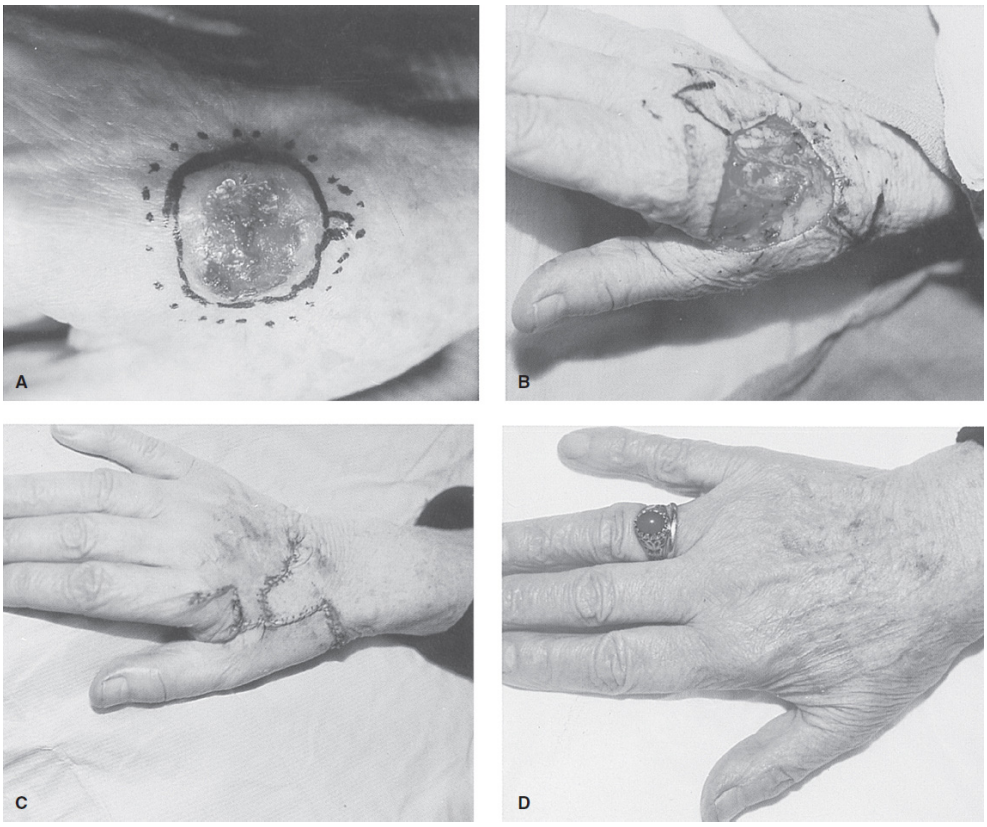

Figure 105.11 **A:** Patient with a 3 × 3 cm basal cell carcinoma on the right dorsal hand with mixed nodular and aggressive growth histologic pattern. **B:** Complete excision of the tumor required two Mohs stages involving 10 frozen sections. The final Mohs surgery defect measured 4.0 × 4.8 cm with preservation of underlying tendons. **C:** The defect was reconstructed immediately following the final Mohs stage under local anesthesia in the Mohs surgery unit using birhombic flap soft tissue reconstruction. **D:** Result 3 months after surgery.

Metastatic SCC may manifest as either regional nodal disease, in-transit disease, or distant disease. For resectable nodal metastatic SCC, radical lymphadenectomy followed by adjuvant radiation therapy is appropriate;[69] clinical trials of postoperative adjuvant anti-PD1 immunotherapy are underway. Distant metastatic disease is typically treated with systemic immunotherapy but this approach must be used with great caution in patients

with immunosuppression due to organ transplantation.[81] While systemic treatment options for distant metastatic SCC have traditionally included chemotherapy or EGFR inhibitors such as cetuximab,[69,70] anti-PD1 immunotherapy is now considered the first-line treatment of choice in patients who do not have a contraindication to this therapy.

Other Cutaneous Malignancies of Interest

Other cutaneous malignancies that may be encountered by the surgeon for further management include MCC, sweat gland carcinomas, and DFSP. Many other types of cutaneous malignancies exist, and their description is beyond the scope of this chapter.

6 MCC, also termed cutaneous neuroendocrine carcinoma, is an aggressive skin cancer with a higher per case mortality than melanoma.[82] The incidence of MCC is low compared to other cutaneous malignancies (approximately 1,500 annually in the United States), but the number of cases has at least tripled over the last two decades. MCC most commonly occurs in older individuals, with less than 5% of cases diagnosed before age 50. The majority of tumors (90%) are located on sun-exposed skin, equally distributed between the head and neck and extremities. The remaining 10% are located on the trunk and buttocks. Chronic UV exposure is an important pathogenetic factor in many cases, but the observation that MCC incidence is markedly increased in immunosuppressed patients ultimately led to the discovery of a virus (Merkel cell polyomavirus) as a contributing factor in the pathogenesis of MCC even in the absence of extensive UV exposure.[83,84] Primary MCC typically presents as a new-onset, growing, red or purple, dome-shaped or subcutaneous nodule, frequently mistaken for a sebaceous cyst (**Fig. 105.12A**). The most common location of metastasis is the draining lymph node basin. Histologically, MCC is a small blue round-cell tumor with positive immunohistochemical staining for cytokeratin-20 (CK-20) in a characteristic paranuclear dot-like pattern (**Fig. 105.12B**). Small cell lung cancer, another neuroendocrine carcinoma histologically indistinguishable from MCC and occasionally CK-20 positive, expresses thyroid transcription factor-1 (TTF-1), which is consistently absent in MCC.[85] AJCC staging for MCC distinguishes stage I (primary tumor <2 cm without nodal disease), stage II (primary tumor ≥2 cm without nodal disease), stage III (microscopic

or clinically apparent regional lymph node metastases), and stage IV disease (distant metastasis).[86] Presentation of MCC in the regional lymph nodes without an identified cutaneous primary is not uncommon.[87] Five-year survival rates for stages I, II, and III in the AJCC database were 81%, 67%, and 52%, respectively, while stage IV disease carried a dismal 11% 2-year survival rate. More recent results, however, suggest that these survival figures may be overly pessimistic.[88] The majority (70%) of patients with MCC present with clinically localized disease (stage I or II), 25% have palpable lymphadenopathy (stage IIIB), and 5% present with distant metastases (stage IV). Multidisciplinary management of MCC is clearly appropriate. Surgical treatment consists of radical wide excision with 1 to 2 cm margins, as performed for melanoma. MCC is much more sensitive to radiation than melanoma, however, so wide margins of excision are discouraged.[89] Postoperative radiation therapy to the primary tumor bed should be considered but whether all primary MCC cases should receive it and the impact of postoperative radiation on overall survival remains unclear.[90,91] SLNB with immunohistochemical staining using CK-20 is routinely recommended for primary MCC to stage the nodal basin and guide regional nodal therapy. Sentinel node–detected regional lymph node metastases can be treated by regional therapeutic lymphadenectomy and/or radiation therapy.[92] Adjuvant radiation therapy to the regional nodal basin should be considered for clinically detected nodal metastases. For nonsurgical candidates, primary treatment of MCC with radiation therapy may also be considered.

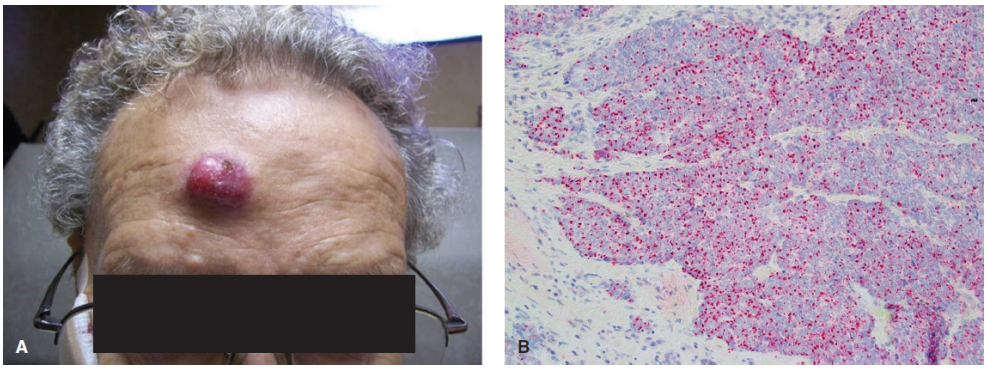

Figure 105.12 **A:** Primary Merkel cell carcinoma on the forehead. **B:** Characteristic immunohistochemical pattern showing dot-like positivity of cytokeratin 20 (CK20) staining in Merkel cell carcinoma. (Photomicrograph courtesy of Jane L. Messina, MD, Moffitt Cancer Center.)

The management of locally advanced and metastatic MCC dramatically changed with the recognition that MCC is very sensitive to immunotherapy with anti-PD1 or anti-PDL1 immunotherapy.[93,94] Interestingly, whether the MCC is associated with UV exposure or viral etiology does not markedly impact the response rates to immunotherapy. Adjuvant immunotherapy for MCC is currently under active investigation, and a trial of neoadjuvant anti-PD1 immunotherapy suggested that this is a very promising approach.[95,96] Chemotherapy has failed to demonstrate a survival benefit in an adjuvant setting in the treatment of localized or regional MCC and should be reserved for refractory unresectable or metastatic disease or patients with contraindications to immunotherapy.

Sweat gland carcinomas represent a broad scope of cutaneous adnexal malignancies with variable risk for local, regional, or distant metastasis, most commonly of eccrine or apocrine origin. These are rare tumors (0.005% of skin malignancies) that have a diverse and confusing nomenclature.[97] The aggressive types of sweat gland carcinomas have a propensity for both local recurrence and regional or systemic metastasis. Clinically, these tumors appear as indurated plaques, papules, or nodules commonly on the head and neck or extremities and are red, blue, pink, or skin colored (**Fig. 105.13**). Histologic subtypes that are particularly associated with a risk of regional lymph node or systemic metastasis include hidradenocarcinoma and porocarcinoma.[97] Recommended treatments have included wide excision of the primary tumor with consideration of SLNB for high-risk lesions based on larger tumor size, high histologic grade of atypia, or increased mitotic rate. Postoperative radiation therapy may also be considered as adjuvant treatment in selected cases.

Figure 105.13 Sebaceous carcinoma on the nose.

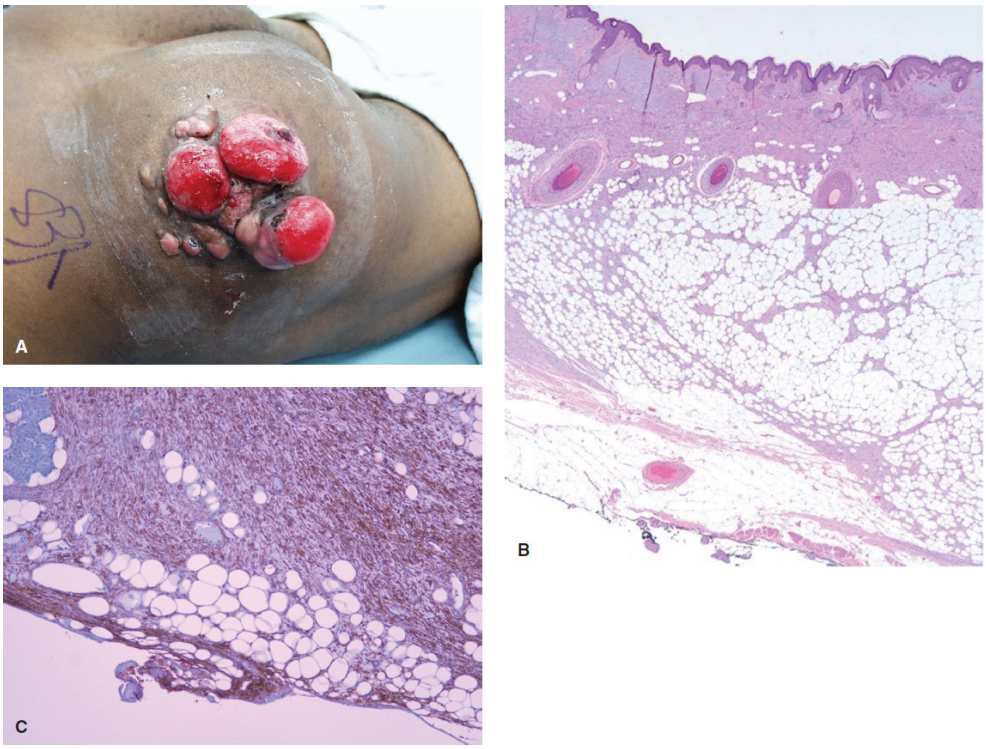

Figure 105.14 **A:** Dermatofibrosarcoma protuberans (DFSP) in an African-American patient. **B:** Low-power (20×) hematoxylin and eosin-stained microscopic appearance of DFSP showing a spindle cell neoplasm with infiltration through full thickness of dermis into subcutaneous fat, approaching the inked deep margin. **C:** High-power (200×) view with CD34 immunohistochemistry staining cells of DFSP extending through subcutaneous fat and present at the deep tissue margin. (Images courtesy of Jane L. Messina, MD, Moffitt Cancer Center.)

7 DFSP is a rare low-grade soft tissue sarcoma (accounting for approximately 1% of all soft tissue sarcomas) with a propensity for local recurrence rather than systemic metastasis.[98] It is a spindle cell tumor that typically demonstrates immunoreactivity to CD34 and has a characteristic gene translocation leading to activation of the platelet-derived growth factor receptor (PDGFR). These tumors appear as slow-growing, firm, flesh-colored to dull red plaques (**Fig. 105.14A**) that may be mistaken for keloids or hypertrophic scars. Although DFSPs may appear well circumscribed, they characteristically demonstrate extensive subclinical involvement, manifest histologically as finger-like projections of tumor cells (**Fig. 105.14B**). DFSP can undergo transformation into a high-grade soft tissue sarcoma, usually fibrosarcoma. For nontransformed DFSP, complete excision with negative margins is almost always curative, but a thorough assessment of the

peripheral and deep margins is critical to ensure that the entire tumor has been resected. Treatment commonly consists of radical wide excision with 1 to 2 cm margins and comprehensive pathologic margin assessment[99] or Mohs surgery,[100] particularly for lesions on cosmetically sensitive areas like the face. Reconstruction involving extensive undermining, skin grafts, or flaps should be delayed until negative histologic margins are confirmed.[98] Radiation therapy is indicated in those rare cases when negative margins cannot be obtained or for transformed lesions. Imatinib, a PDGFR inhibitor, has shown significant antitumor activity in the treatment of unresectable or metastatic DFSP, and can be used for neoadjuvant therapy of locally advanced lesions.[101]

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Sarcomas of Soft Tissue and Bone

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Key Points

1. Sarcomas are a rare and heterogeneous group of cancers that most commonly arise from mesoderm-derived elements such as muscle, fat, cartilage, blood vessels, bone, and other connective tissue but also from ectoderm-derived tissue such as nerve/nerve sheath. They are histologically distinct from cancers of epithelial origin.
2. Clinical behavior and prognosis are largely defined by anatomic location, histologic subtype, tumor grade, size, and ability to achieve complete resection.
3. For extremity sarcomas, radiotherapy is indicated for high-risk tumors to decrease disease relapse. Limb-sparing, function-preserving procedures are favored in order to maximize functional outcomes.
4. Increasing use of multimodality therapies, variably combining surgery, chemotherapy, and radiotherapy, have dramatically improved outcomes for sarcomas such as osteosarcoma and Ewing sarcoma.
5. Surgery is the cornerstone of treatment for intra-abdominal and retroperitoneal sarcomas. Complete resection for primary retroperitoneal sarcomas may require en bloc resection of adjacent or involved organs, most commonly the kidney and colon. The benefit of radiation therapy is less certain for retroperitoneal sarcomas, as it does not consistently reduce locoregional recurrence rates.
6. The use of imatinib mesylate, a selective tyrosine kinase inhibitor, in the management of gastrointestinal stromal tumors (GISTs), is a paradigm for the successful use of targeted molecular therapies.

INTRODUCTION

1 Sarcomas are a heterogeneous group of cancers that arise from mesenchymal cells, or mesoderm-derived elements, including muscle, fat,

cartilage, blood vessels, bone, and other connective tissue and ectoderm-derived tissue, such as nerve/nerve sheath. Though mesoderm-derived elements comprise nearly two-thirds of the body's mass, sarcomas are relatively rare. In 2020, just over an estimated 13,000 new cases of soft tissue and bone sarcoma were expected to be diagnosed in the United States,[1] which accounts for less than 1% of all new cancers. Sarcomas also represent an extremely heterogeneous group of cancers, but taken together, 5-year overall survival is about 50%[2] to 60%.[2,3] Anatomic location, tumor size, grade, and histopathology are important determinants of clinical presentation, treatment, and prognosis.

Sarcoma originates from the Greek word "sarkoma," meaning "fleshy excrescence." As early as AD 130–200, these fleshy tumors were regarded as cancerous by Galen.[4] With the evolution of light microscopy and cellular pathology, there was increasing recognition of soft tissue sarcomas as distinct pathologic entities. Sarcomas, then called "soft cancers," were differentiated from carcinomas by neuroanatomist Charles Bell as early as 1816. Rudolf Virchow refined the definition of sarcoma as "new formations of connective tissue," and developed classifications according to microscopic features which separated sarcomas from carcinomas of epithelial origin. Modern foundations for the classification and histogenic descriptions of sarcoma are attributed to the work of James Ewing, who over the course of his career as a pathologist refined the classification of sarcomas, including the importance of grade in disease outcome.[5]

Multimodality therapies, including surgery, radiation, and systemic/targeted therapy, have been combined to improve local and systemic tumor control. Over the past few decades, evolution of the multidisciplinary approach has enabled successful treatment options to evolve from radical amputation to limb-sparing procedures for extremity sarcoma. As refinements in pathologic classification continue, so does progress in the use of treatment modalities. Modern molecular diagnostics are increasingly being translated to clinical practice, and tailored treatment options are being developed as the histologic diversity of soft tissue sarcomas is continually elucidated and better understood. As with many rare tumors, referral to high-volume centers with multidisciplinary clinical expertise is indicated when feasible.

EPIDEMIOLOGY

Soft tissue sarcoma can occur in all age groups and are equally distributed between genders. While the median age at diagnosis varies by histopathologic subtype, sarcomas are relatively rare in the adult population. However, sarcomas are among the most common cancers seen in children and young adults, representing approximately 15% of pediatric malignancies and often occurring in children under 5 years of age.[6] There are over 75 distinct histopathologic subtypes. Further, sarcomas can occur at any anatomic site, and accordingly, anatomic site influences treatment and outcomes.

While the vast majority of sarcomas arise spontaneously, there are some predisposing conditions to consider. Sarcomas are not thought to be the result of malignant degeneration of a long-standing benign lesion such as a lipoma. An injury or other traumatic incident may lead to the initial recognition of a mass, but there are no data to support the notion that antecedent trauma leads to the development of either soft tissue or bony sarcomas. Clinical evaluation and subsequent workup, including biopsy, should be able to distinguish malignant growths from a variety of benign posttraumatic lesions, such as myositis ossificans, which must be differentiated from, for example, an extraosseous osteogenic sarcoma.

Toxic exposures have been related to the development of sarcoma. Largely of historic interest, the industrial use of thorium dioxide (Thorotrast), arsenic, and vinyl chloride led to accumulation of toxins in the liver and were associated with the development of hepatic angiosarcomas. Several other predisposing conditions are known to be associated with the development of sarcoma. The classic Stewart–Treves syndrome was originally described in patients with lymphedema following radical mastectomy and radiation for breast cancer who then developed lymphangiosarcoma of the affected arm. Since then, long-standing extremity edema from other causes has also been linked to the development of lymphangiosarcomas. Kaposi sarcoma was previously an uncommon cutaneous vascular tumor thought limited to elderly men of Mediterranean origin. In the early 1980s it became one of the first described opportunistic diseases associated with HIV infection. Though the incidence of HIV-associated Kaposi sarcoma has markedly declined with effective

antiretroviral therapy, it remains an important cause of morbidity among HIV-infected patients and other immunosuppressed patients such as renal allograft recipients.[7–9]

Various types of radiation have been implicated in the delayed development of sarcomas. For example, incidental ingestion of luminous paint containing ^{226}radium by factory workers led to the development of osteosarcomas. With the increasing use of external-beam radiation in cancer treatment, there has been a noted increase in the modern incidence of secondary sarcoma in patients previously treated with radiation for a variety of malignancies. Following median latent periods of approximately 8 years (range 6 to 20 years), radiation-associated sarcomas are being increasingly diagnosed in previously radiated areas. Common radiation-associated sarcoma subtypes are angiosarcomas, undifferentiated pleomorphic sarcoma, fibrosarcoma, osteosarcoma, and leiomyosarcoma, and they are commonly, but not uniformly, high grade.[10,11] Notably, with the advent of breast conservation therapy for breast cancer (consisting of partial mastectomy/lumpectomy and adjuvant radiation therapy), there should be an appropriate index of suspicion for breast angiosarcomas with findings of skin changes on the breast (**Fig. 106.1**).

Figure 106.1 Radiation-associated angiosarcoma. This 79-year-old woman developed skin changes on her breast 7 years after breast conservation therapy (lumpectomy and radiation therapy) for a 2-cm invasive ductal adenocarcinoma. Radical surgery including removal of all of the irradiated anatomic breast skin in addition to a mastectomy was performed.

GENETIC CANCER SYNDROMES

While the vast majority of sarcomas are sporadic, numerous genetic alterations are associated with both bone and soft tissue sarcomas.[12,12a] There are well-described genetic predispositions to sarcoma. Patients with neurofibromatosis type 1 (NF-1, or von Recklinghausen disease) have mutations in the neurofibromin 1 or 2 gene (*NF1* or *NF2*, respectively) which are associated with the development of malignant peripheral nerve sheath tumors (MPNST) in an estimated 5% of patients over a lifetime.[13] A genetic predisposition to desmoid tumors or desmoid fibromatosis is associated with familial adenomatous polyposis (FAP), or Gardner syndrome which is the result of germline mutations in the adenomatous polyposis coli (*APC*) gene.[14,15] Intra-abdominal and extremity desmoids are a common extracolonic manifestation of FAP and can be a source of increased

morbidity in these patients following proctocolectomy for the prevention or treatment of colon cancer.[16]

While somatic activation of c-KIT and overexpression of KIT protein are well described in the pathogenesis of gastrointestinal stromal tumors (GISTs), there are described germline mutations as well. Familial GISTs have been ascribed to germline mutation in *c-KIT* as well as in the *SDHB, SDHC*, and *SDHD* succinate dehydrogenase (SDH) subunits, in association with Carney triad (GIST, pulmonary chondromas, extra-adrenal paragangliomas) or Carney–Stratakis syndrome (GIST, paraganglioma).

One well-documented mechanism of sarcoma development is the inactivation of tumor suppressor genes. Retinoblastoma was known to be associated with a mutation in the retinoblastoma gene (*RB1*), a 13q chromosomal deletion. Investigation of the link between familial retinoblastoma and osteosarcoma led to the discovery that a genetic defect in *RB1* also plays a role in the pathogenesis of sarcomas.[17,18]

Another inherited defect of a tumor suppressor gene associated with soft tissue sarcomas is the Li–Fraumeni syndrome, caused by an inherited mutation in the *p53* gene, a key growth-regulatory gene.[19] Germline mutations in affected patients are associated with high incidences of childhood rhabdomyosarcomas, breast cancer, brain tumors, lung cancer, and leukemias.[20] *p53* abnormalities may be seen in as many as 60% of osteosarcomas and malignant fibrous histiocytomas, as well as approximately 33% of other sarcomas.[21] Several oncogenes that can induce malignant transformation and drive proliferation have also been associated with sarcoma development, including amplifications of *N-myc*, *c-erbB2* and members of the *ras* family.[22]

Cytogenetic aberrations have been recognized in a number of soft tissue sarcomas.[12] Several histologic subtypes of sarcomas have each been found to have specific genetic alterations—usually simple karyotypes including fusion genes due to reciprocal translocations or specific point mutations (**Table 106.1**). These chromosomal translocations serve as powerful diagnostic markers and may be important in determining tumor biology and subsequent tumor behavior. For example, identification of the translocation of t(X;18)(p11;q11) can confirm the diagnosis of synovial sarcoma if there is any doubt of its histopathology. There are data to suggest that the SYT-SSX1 fusion

transcript carries a worse prognosis than the SYT-SSX2 fusion transcript, with median survivals of 6.1 years and 13.7 years, respectively.[23,24]

A better understanding of the molecular biology of sarcomas has revolutionized diagnosis of specific histopathologic subtypes and has elucidated potential pathways for targeted molecular therapy.

SOFT TISSUE SARCOMAS

Clinical Presentation

The most common presentation of a soft tissue sarcoma is that of an asymptomatic mass. Most sarcomas tend to grow in a centrifugal fashion, usually pushing surrounding structures away rather than directly invading them and generally remaining within their compartment/fascial plane of origin. Encasement of structures can occur, but again, this largely occurs in the absence of direct invasion. Compression generally does not produce pain, swelling, or obstructive symptoms until the tumors become quite large or directly impinge on a nerve. Because of surrounding anatomic structures, some tumors of the extremities tend to be detected at a relatively smaller size, whereas tumors of the retroperitoneum are rarely smaller than 10 cm at the time of diagnosis.[5] Even very large abdominal or retroperitoneal sarcomas present with nonspecific abdominal symptoms such as fullness, early satiety, or minor abdominal discomfort (**Fig. 106.2**). While most sarcoma histologic subtypes displace surrounding structures, some do invade across fascial planes, including myxofibrosarcoma and fibromyxosarcoma. The differential diagnosis for a soft tissue sarcoma includes benign lesions (e.g., lipomas, leiomyomas, neuromas) and other malignant lesions (e.g., primary carcinoma, lymphoma, metastatic disease from melanoma or testes cancer).

Table 106.1 Cytogenetic Abnormalities in Soft Tissue Sarcoma Subtypes

Histologic Subtype	Cytogenetic Alteration	Molecular Alteration
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	*PAX3-FOXO1* fusion
	t(1;13)(p36;q14) double minutes	*PAX7-FOXO1* fusion
	t(2;2)(q35;p23)	*PAX3-NCOA1* fusion
	t(X;2)(q35;q13)	*PAX3-AFX* fusion
Alveolar soft part sarcoma	t(X;17)(p11.2;q25)	*TFE3-ASPSCR1* fusion
BCOR-rearranged sarcoma	Inv(X)(p11p11)	*BCOR-CCNB3* fusion
	t(X;4)(p11;q31)	*BCOR-MAML3* fusion
	t(X;22)(p11;q13)	*ZC3H7B-BCOR*- fusion
CIC-rearranged sarcoma	t(4;19)(q35;q13) or t(10;19)(q26:q13)	*CIC-DUX4* fusion
	t(X;19)(q13;q13.3)	*CIC-FOXO4* fusion
Clear cell sarcoma	t(12;22)(q13;q12)	*EWS-ATF1* fusion
	t(2;22)(q32.3;q12)	*CREB1-ESWR1* fusion
Dedifferentiated liposarcoma	Ring and giant marker chromosomes	Amplification of 12q13-15: *MDM2, CDK4, HMGA2*
Desmoplastic small round cell tumor	t(11;22)(p13;q12)	*EWS-WT1* fusion
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13); ring forms of chromosomes 17 and 22	*COL1A1-PDGFB* fusion
Endometrial stromal	t(7;17)(p15;q21)	*JAZF1-SUZ12* fusion

sarcoma, low grade		
	t(6;7)(p21;p15)	*PHF1-JAXF1* fusion
	t(6;10)(p21;p11)	*EPC1-PHF1* fusion
	t(1;6)(p34;p21)	*MEAF6-PHF1* fusion
	t(X;17)(p11;q21)	*MBTD1-CXorf67* fusion
Endometrial stromal sarcoma, high grade	t(10;17)(q22;p13)	*YWHAE-NUTM2* fusion
	t(X;22)(p11;q13)	*ZC3H7B-BCOR* fusion
Epithelioid hemangioendothelioma	t(1;2)(p36;q25)	*WWTR1-CAMTA1* fusion
	t(X;11)(p11;q22)	*YAP1-TFE3* fusion
Epithelioid sarcoma	Deletion 22q	*SMARCB1* inactivation
	t(8;22)(q22;q11)	
	t(10;22)	
Ewing sarcoma	t(11;22)(q24;q12)	*EWS-FLI1* fusion
	t(21;22)(q12;q12)	*EWS-ERG* fusion
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q11)	*EWSR1-NR4A3* fusion
	t(9;17)(q22;q11)	*TAF2N-NR4A3* fusion
	t(9;15)(q22;q21)	*TCF12-NR4A3* fusion
	t(3;9)(q11;q22)	*TGF-NR4A3* fusion
	t(9;17)(q22;q11)	*RBP56-NR4A3* fusion
Fibrosarcoma	t(12;15)(p13;q26)	*ETV6-NTRK3* fusion
Gastrointestinal stromal tumor	Deletion 14q, 22q, 1p, 15q	*KIT* or *PDGFRA* mutation (85% of cases); *NF1, SDHX, BRAF* mutation, *SDHC*

		hypermethylation, other
Inflammatory myofibroblastic tumor	t(1;2)(q22;p23)	*TPM3-ALK* fusion
	t(2;19)(p23;p13)	*TPM4-ALK* fusion
	t(2;17)(p23;q23)	*CLTC-ALK* fusion
	t(2;2)(p23;q13)	*RANBP2-ALK* fusion
	t(2;2)(p23;q35)	*ATIC-ALK* fusion
	t(2;11)(p23;p15)	*CARS-ALK* fusion
	t(2;4)(p23;q21)	*SEC31L1-ALK* fusion
	t(2;12)(p23;p12)	*PPFIBP1-ALK* fusion
	t(2;20)(p23;p12)	*RRBP1-ALK* fusion
	t(3;6)(q12;q22)	*TFG-ROS1* fusion
	t(6;17)(q22;p13)	*YWHAE-ROS1* fusion
Fibromyxoid sarcoma, low grade	t(7;16)(q33;p11)	*FUS-CREB3L2* fusion
	t(11;16)(p11;p11)	*FUS-CREB3L1* fusion
Mesenchymal chondrosarcoma	t(8;8)(q13;q21)	*HEY1-NCOA2* fusion
Malignant peripheral nerve sheath tumor	Various	*SUZ12* or *EED* mutation (80% of cases), *NF1* inactivation
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	*FUS-DDIT3* fusion
	t(12;22)(q13;q12)	*EWSR1-DDIT3* fusion
Pseudomyogenic hemangioendothelioma	t(7;19)(q22;q13)	*SERPINE1-FOSB* fusion
Sclerosing epitheliod fibrosarcoma	t(11;22)(p11;q12)	*EWSR1-CREB3L1* fusion

	t(7;16)(q33;p11)	*FUS- CREB3L2* fusion
Solitary fibrous tumor	Inv(12)(q13q13)	*NAB2-STAT6* fusion
Synovial sarcoma	t(X;18)(p11;q11)	SS18-SSX1 orSS18-SSX2 fusion

Adapted from Schaefer IM, Cote GM, Hornick JL. Contemporary sarcoma diagnosis, genetics, and genomics. *J Clin Oncol* 2018;36(2):101–110.

In general, the vast majority of soft tissue masses tend to be benign, but concerning features which should prompt a higher index of suspicion for malignancy include large size (>5 cm), deep location (subfascial, intramuscular, intra-abdominal), variations in texture on examination, immobile nature or noted fixation to underlying structures, or changes to an existing lesion (increasing size or worsening compressive symptoms). There are no reliable tumor markers for sarcomas, so serum bloodwork is generally not useful in the evaluation of soft tissue masses. However, advances in the understanding and detection of circulating tumor DNA could lead to future serum tests for diagnosis of primary and recurrent sarcoma and measurement of response to therapy.

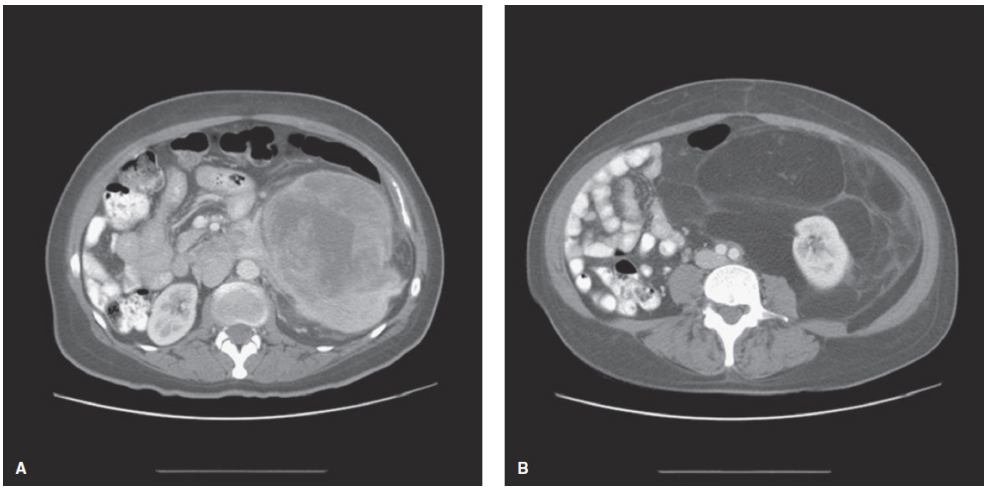

Figure 106.2 Dedifferentiated liposarcoma of the retroperitoneum. This 51-year-old woman presented with only vague symptoms of abdominal fullness from a very large retroperitoneal mass. The CT scan demonstrates a heterogeneous soft tissue mass in the upper abdomen (**A**) which blends into a more fatty component (**B**) which encases the left kidney and displaces abdominal contents. She underwent radical resection en bloc left nephrectomy, distal pancreatectomy, splenectomy, left colectomy, and segmental resection of inferior vena cava.

Diagnosis

Diagnostic Imaging

Accurate radiologic imaging is critical in the diagnostic workup of sarcoma to provide information about the precise location and extent of the primary tumor. Computed tomography (CT) scans and magnetic resonance imaging (MRI) are the most important imaging modalities for evaluating the resectability of soft tissue sarcomas, providing definition of the primary tumor in relation to bone, muscle, neurovascular structures, and adjacent organs. Plain radiographs of bones and radionuclide bone scans rarely provide useful information regarding invasion of bone by the tumor, though the former can be quite useful for primary bone tumors. Both CT and MRI can provide critical information for treatment planning. While MRI may be preferred for extremity sarcomas, CT is the modality of choice for abdominal, pelvic, and retroperitoneal tumors. However, there appears to be no difference between high-quality CT and MRI in terms of ability to determine involvement of nearby structures, bone, or neurovascular structures.[25–27]

Imaging is also important as part of the extent of disease workup. Because extremity sarcomas are known to predominantly metastasize to the lungs, directed chest imaging should be performed at the time of diagnosis. While chest radiography (CXR) may be used, CT scans are increasingly utilized as the primary screening examination of choice for higher-risk patients, such as those with high-grade lesions or tumors larger than 5 cm.[28] Any abnormal CXR must be followed by a chest CT scan per protocol, usually involving thinner sections without IV contrast, for more detailed evaluation of potential pulmonary metastases (**Fig. 106.3**). CT of the chest, abdomen, and pelvis should be considered in any patient with a myxoid liposarcoma of an extremity because this subtype often metastasizes to the abdomen or other "fat pads" such as the axilla. Paraspinal imaging with MRI may be indicated for myxoid liposarcoma as well, as bone and soft tissue metastases in this region may develop.

Figure 106.3 Pulmonary metastasis. A noncontrasted CT scan of the thorax demonstrates a 1.1-cm noncalcified nodule consistent with pulmonary metastasis in the upper lobe of the right lung.

MRI is the most commonly used imaging modality for the primary site of extremity sarcomas.[25,29] Sequencing routinely involves axial T2-weighted and precontrast/postcontrast T1-weighted images. Contrast enhancement with gadolinium is crucial for detecting and characterizing lesions with coronal, sagittal, and other reconstructions. This imaging modality can accurately delineate between muscle groups and distinguish tumor and neurovascular structures (**Fig. 106.4**). Magnetic resonance angiography (MRA) may be useful if more accurate delineation of vascular structures is required for surgical planning.

Positron emission tomography (PET) scanning using fluoro-13-deoxyglucose also offers the potential for noninvasive analysis of tumor

metabolism and has been shown to correlate with both tumor grade and response to treatment for many types of cancers.[30–33] PET may be helpful in distinguishing between benign and malignant lesions concerning for sarcoma and in assessing response to treatment.[34] However, its accuracy and potential for false-negative results are still incompletely defined, so its use is not routine, either for staging or for surveillance. Even with a PET scan, formal imaging with contrasted CT or MRI is necessary so costs and extent of imaging should be considered.

Diagnostic Biopsy

Properly performed biopsies are critical in directing a multimodality treatment approach. Image-guided techniques are commonly applied so that open biopsy is rarely required. Fine needle aspiration (FNA) is frequently used for the evaluation of enlarged lymph nodes, thyroid nodules, or breast masses. However, FNA often does not provide sufficient material for definitive histopathologic diagnosis (including subtype classification), especially for an index presentation of sarcoma. In select cases, FNA may be useful to demonstrate recurrent disease. Core-needle biopsy (CNB) is considered the initial procedure of choice for diagnosis of soft tissue sarcomas.[35] CNB, usually with multiple passes, retrieves sufficient material for immunohistochemical staining, and when necessary, for cytogenetic analysis or flow cytometry. Image-guided CNB, either using CT or ultrasound, allows for the biopsy of deep masses that may not be easily palpable and can help target suspicious areas in a heterogeneous field for better diagnostic value. An adequate sample from a viable area of sarcoma is required for definitive diagnosis and accurate grading. CNB is associated with low complication rates (<1%), including bleeding. Concerns about recurrence along the tract are obviated with judicious planning of the biopsy tract, the use of a sheathed needle device, and/or excision of the biopsy tract at the time of definitive resection when possible.

Open surgical biopsy, or incisional biopsy, is rarely needed given the success of CNB. However, open biopsy should be considered when core-needle specimens yield nondiagnostic findings *and* if preoperative diagnosis is definitely required for treatment planning. Several important technical factors must be considered when performing an incisional biopsy. Incisions

must be oriented along the long axis of extremities to facilitate subsequent complete resection with definitive surgical management. A transverse incision in the extremity often commits the patient to more more extensive procedures than would be otherwise necessary, potentially compromising the ability to obtain clear margins with definitive limb-sparing procedures. Attempts to enucleate the sarcoma within its "pseudocapsule" and without a proper margin is strongly discouraged, though excisional biopsy can be considered as the primary approach for small, superficial lesions by experienced surgical oncologists.[5] Extensive dissection during a biopsy, including undermining surrounding subcutaneous layers, should be consciously avoided in order to contain the extent of disease and best manage subsequent procedures. Attention to meticulous hemostasis also prevents extensive "seeding" of the area.

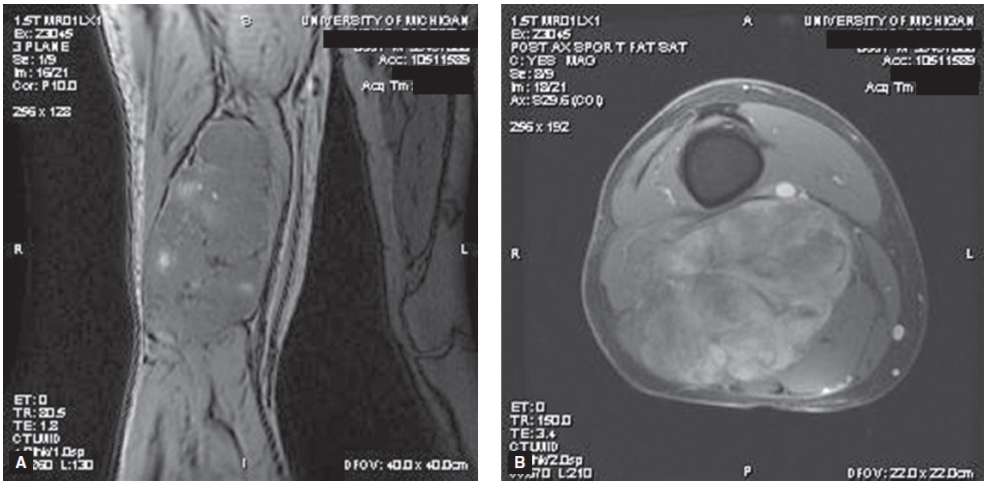

Figure 106.4 Extremity sarcoma. MRI demonstrates a 20-cm low-grade myxoid liposarcoma. **A:** Coronal reconstruction demonstrates location in the distal right thigh. **B:** Axial images show displacement of the popliteal vessels and vastus medialis anteriorly; the common tibioperoneal nerve and biceps femoris laterally; and, the semimembranosis and semitendinosus muscles medially.

PATHOLOGIC CLASSIFICATION

Histopathologic designation of soft tissue sarcomas reflect an extremely heterogeneous group of tumors. Sarcomas are generally classified according to the tissues they mimic rather than the type of tissue from which the tumor arises. Some sarcomas have no recognizable normal tissue counterpart and

are characterized by other distinguishing histologic features.[5,36,36a] The various types of benign and malignant soft tissue tumors are noted in Table 106.2. Bone tumors are listed in Table 106.3 for completeness, but discussion about their management is beyond the scope of this chapter. The development of specialized markers for identifying individual types of sarcoma has led to greater precision in their classification. In a small proportion of tumors (approximately 10% in most series), the tumor cells are so poorly differentiated that no specific histogenesis can be determined, and these may be designated as spindle cell sarcomas or undifferentiated pleomorphic sarcomas.

One of the most critical pieces of pathologic information for clinicians treating sarcoma patients is histologic grade. Histologic grade according to the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) grading system is assessed based on the expert assessment of degree of tumor differentiation, the frequency of mitotic figures, and the presence or absence of spontaneous tumor necrosis (**Table 106.4**).[36b] While grading criteria have undergone numerous revisions over the years, in general, low-grade tumors have relatively little cellular atypia, few mitoses, and no tumor necrosis. High-grade tumors show a significant degree of necrosis in addition to atypia and frequent mitotic figures. Tumor differentiation scores, a component of the FNCLCC grading system, is assigned consistently for specific histologic subtypes, as detailed in Table 106.5 and representatively depicted in Figure 106.5. A consistently applied grading system discriminates between tumors with good prognosis (low grade) and those with relatively poorer prognosis (high grade). In the past, various grading systems have been used including a two-tiered systems (low and high), a three-tiered system (low, intermediate, and high), and a five-tiered system. The current American Joint Committee on Cancer (AJCC) staging system recognizes a classification system ranging from Grade 1 (G1) to Grade 3 (G3) tumors, taking into account histology, tumor differentiation, mitotic count, and tumor necrosis.[37–39] There can be disagreement about grading schemas and expert pathology opinion can vary from center to center.[40,41] As such, it is important to take note of tumor classification when interpreting results from clinical trials or retrospective reports.[42] The metastatic potential for low-grade lesions is approximately 5% to 10% compared to up to 50% to 60% for high-grade tumors.[2] For

sarcomas with intratumoral variability, the highest grade encountered is used to categorize the tumor.

Staging

Because of the prognostic importance of staging, stage classification of the primary tumor is based on both clinical and histologic information. The usual TNM classification used by the AJCC[39] for other solid tumors is modified to a TNMG system for most soft tissue sarcomas, including trunk and extremity sarcomas (**Tables 106.6A** and **106.6B**).

The most recent version of the AJCC staging system for sarcomas includes a number of changes. There is increased emphasis on individual histologies. There are new staging systems for retroperitoneal sarcoma (nodal disease is IIIB rather than IV), head and neck sarcoma (revised T stage size cut-offs, Table 106.6**C**), and visceral sarcoma (revised T stage, Table 106.6**D**), separate from the one for trunk and extremity sarcomas.[43–46] The principal difference between retroperitoneal and trunk/extremity sarcoma staging is that nodal disease is considered stage IIIB for the former and IV for the latter (**Tables 106.7A** and **106.7B**).[45,46] Uterine sarcomas and GIST[47] (**Tables 106.8A** to **106.8C**) continue to have separate staging systems, as do bone sarcomas. There is a new size category reflecting the increased risk of metastasis as tumor size increases. The previous distinction between superficial and deep has proven to be less useful, and has been eliminated.

Table 106.2 WHO Histologic Classification of Soft Tissue Tumors

Classification	Benign	Intermediate (locally aggressive)	Intermediate (rarely metastasizes)	Malignant
Adipocyte tumors	Lipoma Lipomatosis Lipomatosis of nerve Lipoblastoma/ lipoblastomatosis Angiolipoma Myolipoma Chondroid lipoma Extrarenal angiomyolipoma Extra-adrenal myelolipoma Spindle cell/ pleomorphic lipoma Hibernoma	Atypical lipomatous tumor/well-differentiated liposarcoma		Dedifferentiated liposarcoma Myxoid liposarcoma Pleomorphic liposarcoma Liposarcoma, not otherwise specified
Fibroblastic/ Myofibroblastic tumors	Nodular fasciitis Proliferative fasciitis Proliferative myositis Myositis ossificans Fibro-osseous pseudotumor of digits Ischemic fasciitis Elastrofibroma Fibrous hamartoma of infancy Fibromatosis coli Juvenile hyaline fibromatosis Inclusion body fibromatosis Fibroma of tendon sheath Desmoplastic fibroblastoma Mammary-type myofibroblastoma Calcifying aponeurotic fibroma Angiomyofibroblastoma Cellular angiofibroma Nuchal-type fibroma Gardner fibroma Calcifying fibrous tumor	Palmar/plantar fibromatosis Desmoid-type fibromatosis Lipofibromatosis Giant cell fibroblastoma	Dermatofibrosarcoma protuberans (DFSP) (fibrosarcomatous DFSP, pigmented DFSP) Solitary fibrous tumor Inflammatory myofibroblastic tumor Low-grade myofibroblastic sarcoma Myxoinflammatory fibroblastic sarcoma/atypical myxoinflammatory fibroblastic tumor Infantile fibrosarcoma	Adult fibrosarcoma myxofibrosarcoma Low-grade fibromyxoid sarcoma Sclerosing epithelioid fibrosarcoma Malignant solitary fibrous tumor
So-called fibrohistiocytic tumors	Tenosynovial giant cell tumor (localized type, diffuse type, malignant) Deep benign fibrous histiocytoma		Plexiform fibrohistiocytic tumor Giant cell tumor of soft tissue	
Smooth muscle tumors	Deep leiomyoma			Leiomyosarcoma (excluding skin)
Pericytic (perivascular) tumors	Glomus tumor (glomangiomatosis) Myopericytoma (myofibroma, myofibromatosis) Angioleiomyoma			Malignant glomus tumor

Skeletal muscle tumors	Rhabdomyoma (adult, fetal, and genital types)			Embryonal rhabdomyosarcoma (botryoid, anaplastic) Alveolar rhabdomyosarcoma (solid, anaplastic) Pleomorphic rhabdomyosarcoma Spindle cell/sclerosing rhabdomyosarcoma
Vascular tumors of soft tissue	Hemangioma (synovial, venous, arteriovenous hemangioma/ malformation, intramuscular) Epithelioid hemangioma Angiomatosis Lymphangioma	Kaposiform hemangio-endothelioma	Retiform hemangioendothelioma Papillary intralymphatic angioendothelioma Composite hemangioendothelioma Pseudomyogenic hemangioendothelioma Kaposi sarcoma	Angiosarcoma Epithelioid hemangio-endothelioma
Chondro-osseous tumors	Soft tissue chondroma			Extraskeletal chondrosarcoma Extraskeletal osteosarcoma
Gastrointestinal stromal tumors (GIST)	GIST, benign			GIST, malignant
Nerve sheath tumors	Schwannoma Melanotic schwannoma Neurofibroma (plexi-forma neurofibroma) Perineurioma Granular cell tumor Dermal nerve sheath myxoma Solitary circumscribed neuroma Ectopic meningioma Nasal glial heterotopia Benign Triton tumor Hybrid nerve sheath tumors			Malignant peripheral nerve sheath tumor (MPNST) Epithelioid MPNST Malignant Triton tumor Malignant granular cell tumor Ectomesenchymoma Malignant perineurioma
Tumors of uncertain differentiation	Acral fibromyxoma Intramuscular myxoma Juxta-articular myxoma Deep ("aggressive") angiomyxoma Pleomorphic hyalinizing angiectatic tumor Ectopic hamartomatous thymoma	Hemosiderotic fibrolipomatous tumor	Atypical fibroxanthoma Angiomatoid fibrous histiocytoma Ossifying fibromyxoid tumor Mixed tumor, not otherwise specified Myoepithelioma Myoepithelial carcinoma Phosphaturic mesenchymal tumor	Synovial sarcoma (including biphasic) Epithelioid sarcoma Alveolar soft-part sarcoma Clear cell sarcoma of soft tissue Extraskeletal myxoid chondrosarcoma Extraskeletal Ewing sarcoma Desmoplastic small round cell tumor Perivascular epithelioid cell tumor (PEComa) Intimal sarcoma
Undifferentiated/ Unclassified sarcomas				Undifferentiated spindle cell sarcoma Undifferentiated pleomorphic sarcoma Undifferentiated round cell sarcoma Undifferentiated epithelioid sarcoma Undifferentiated sarcoma NOS

Adapted from Fletcher CD, Bridge JA, Hogendoorn PC, et al. *WHO Classification of Tumors of Soft Tissue and Bone*. 2013.

Table 106.3 WHO Histologic Classification of Bone Tumors

Classification	Benign	Intermediate (locally aggressive)	Intermediate (rarely metastasizes)	Malignant
Chondrogenic tumors	Osteochondroma Chondroma (enchondroma, periosteal chondroma) Osteochondromyxoma Subungual exostosis Bizarre parosteal osteochondormatous proliferation Synovial chondromatosis	Chondromyxoid fibroma Atypica cartilaginous tumor/chondrosarcoma grade 1	Chondroblastoma	Chondrosarcoma grades 2 and 3 Dedifferentiated chondrosarcoma Mesenchymal chondrosarcoma Clear cell chondrosarcoma
Osteogenic tumors	Osteoma Osteoid osteoma	Osteoblastoma		Low-grade central osteosarcoma Conventional osteosarcoma (chondroblastic, fibroblastic, osteoblastic) Telangiectatic osteosarcoma Small cell osteosarcoma Secondary osteosarcoma Parosteal osteosarcoma Periosteal osteosarcoma High-grade surface osteosarcoma
Fibrogenic tumors		Desmoplastic fibroma of bone		Fibrosarcoma of bone
Fibrohistiocytic tumors	Benign fibrous histiocytoma/ nonossifying fibroma			
Hematopoietic neoplasms				Plasma cell myeloma Solitary plasmacytoma of bone Primary non-Hodgkin lymphoma of bone
Osteoclastic giant cell–rich tumors	Giant cell lesion of the small bones	Giant cell tumor of bone		Malignant giant cell tumor of bone
Notochordal tumors	Benign notochordal tumor			Chordoma
Vascular tumors	Hemangioma	Epithelioid hemangioma		Epithelioid hemangioendothelioma Angiosarcoma
Myogenic tumors	Leiomyoma of bone			Leiomyosarcoma of bone
Lipogenic tumors	Lipoma of bone			Liposarcoma of bone
Tumors of undefined neoplastic nature	Simple bone cyst Fibrous dysplasia Osteofibrous dysplasia Chondromesenchymal hamartoma Rosai–Dorfman disease	Aneurysmal bone cyst Langerhans cell histiocytosis (monostatic, polystatic) Erdheim–Chester disease		
Miscellaneous tumors				Ewing sarcoma Adamantinoma Undifferentiated high-grade pleomorphic sarcoma of bone

Adapted from Fletcher CD, Bridge JA, Hogendoorn PC, et al. *WHO Classification of Tumors of Soft Tissue and Bone*. 2013.

Table 106.4 Histologic Parameters in the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC) Grading System

Histologic Parameter	Score	Definition
Tumor differentiation	1	Closely resembling normal adult mesenchymal tissue, potentially difficult to distinguish from benign counterparts (e.g., well differentiated liposarcoma)
	2	Histologic typing is certain (e.g., myxofibrosarcoma)
	3	Undifferentiated or embryonal sarcomas, synovial sarcoma
Mitotic count	1	0–9 mitoses per 10 HPF
	2	10–19 mitoses per 10 HPF
	3	>19 mitoses per 10 HPF
Tumor necrosis	0	No necrosis
	1	<50% tumor necrosis
	2	≥50% tumor necrosis
Histologic grade	Grade 1	Total score 2–3
	Grade 2	Total score 4–5
	Grade 3	Total Score 6–8

Adapted from Coindre JM. Grading of soft tissue sarcomas: review and update. *Arch Pathol Lab Med* 2006;130(10):1448–1453.

Table 106.5 Tumor Differentiation Score According to Histologic Subtype in the Federation Nationale des Centres de Lutte Contre le Cancer (FNCLCC)

Differentiation Score	Histologic Subtype
1	Well-differentiated liposarcoma Well-differentiated leiomyosarcoma Malignant neurofibroma Well-differentiated fibrosarcoma
2	Myxoid liposarcoma Conventional leiomyosarcoma Conventional malignant peripheral nerve sheath tumor (MPNST) Conventional fibrosarcoma Myxofibrosarcoma Myxoid chondrosarcoma Conventional angiosarcoma
3	High-grade myxoid (round cell) liposarcoma Pleomorphic liposarcoma Dedifferentiated liposarcoma Rhabdomyosarcoma Poorly differentiated/pleomorphic leiomyosarcoma Poorly differentiated/epithelioid angiosarcoma Poorly differentiated malignant peripheral nerve sheath tumor (MPNST) Malignant Triton tumor Synovial sarcoma Extraskeletal osteosarcoma Extraskeletal Ewing sarcoma Mesenchymal chondrosarcoma Clear cell sarcoma Epithelioid sarcoma Alveolar soft part sarcoma Malignant rhabdoid tumor Undifferentiated (spindle cell and pleomorphic sarcoma)

Adapted from Coindre JM. Grading of soft tissue sarcomas: review and update. *Arch Pathol Lab Med* 2006;130(10):1448–1453.

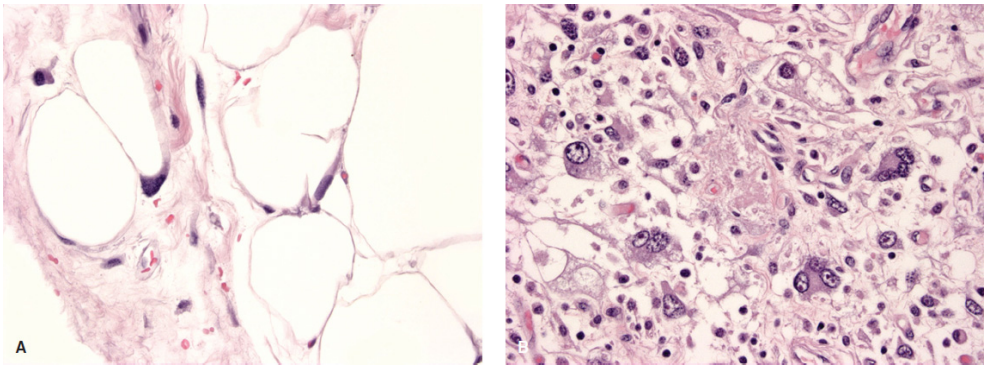

Figure 106.5 Histologic grading of sarcomas. Photomicrographs demonstrate the appearance of different grades within the same histologic subtype. **A:** Well-differentiated liposarcoma (lipoma-like) of the retroperitoneum with noted few atypical lipoblasts. **B:** High-grade, dedifferentiated liposarcoma of the retroperitoneum with highly atypical lipoblasts. (Courtesy of David R. Lucas, MD, University of Michigan, Ann Arbor, MI.)

Table 106.6A American Joint Committee on Cancer (AJCC): TNM Classification of Soft Tissue Sarcomas of the Trunk and Extremity

Classification	Description
Tumor Grade	
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3
Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
T1	Tumor ≤5 cm in greatest diameter
T2	Tumor >5 cm and ≤10 cm in greatest diameter
T3	Tumor >10 cm and ≤15 cm in greatest diameter
T4	Tumor >15 cm
Lymph Node Involvement	
N0	No regional metastases to lymph nodes or unknown lymph node status
N1	Regional lymph node metastases
Distant Metastasis	
M0	No known distant metastasis
M1	Known distant metastasis

Not including Gastrointestinal stromal tumors.

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Table 106.6B Stage Grouping of Soft Tissue Sarcomas of the Trunk and Extremity

T	N	M	G	Stage Group
1	0	0	1, X	IA
2, 3, 4	0	0	1, X	IB
1	0	0	2, 3	II
2	0	0	2, 3	IIIA
3, 4	0	0	2, 3	IIIB
Any T	1	0	Any G	IV
Any T	Any N	1	Any G	IV

Used with permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.

Table 106.6C American Joint Committee on Cancer (AJCC): T Classification of Soft Tissue Sarcomas of the Head and Neck

Classification	Description
Primary Tumor	
TX	Primary tumor cannot be assessed
T1	Tumor ≤2 cm in greatest diameter
T2	Tumor >2 cm and ≤4 cm in greatest diameter
T3	Tumor >4 cm
T4	Tumor with invasion of adjoining structures

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One of the challenges with AJCC staging of sarcomas is that a critical factor, histologic subtype, is not included. Prognostic nomograms based on histologic subtype or site of origin have been developed.[48–52] These include prognostic factors as continuous rather than categorical variables. Some are now available for download on a smart phone app (www.sarculator.com).[48,49,51,52]

Additionally, some sarcomas are difficult to classify in the staging system, and descriptive clinical features are described for them instead. Sarcomas that fall into that category include alveolar soft-part sarcoma, angiosarcoma, desmoplastic small round cell tumor, epithelioid hemangioendothelioma, extraskeletal myxoid chondrosarcoma, inflammatory myofibroblastic tumor, Kaposi sarcoma, osteosarcoma of soft tissue, phyllodes tumor, rhabdomyosarcoma, and solitary fibrous tumor.[53] Finally some tumors are locally aggressive but have little to no risk of metastatic disease and are thus excluded from the AJCC staging system, including desmoid tumor.[53]

By far the most common site of metastasis is the lungs though metastases to other sites do occur. Metastases to the liver should be considered for GIST and pelvic or abdominal visceral sarcomas.

TREATMENT

Principles of Surgery

3 Complete resection remains the cornerstone of treatment for soft tissue sarcomas. Performing a wide excision of the tumor with negative margins is the goal of resection with curative intent. Simple enucleation, if even possible, usually results in an inadequate resection and should be avoided. Technical aspects of resection which must be taken into consideration include anatomic location and extent of disease. Often, soft tissue sarcomas are surrounded by a zone of compressed reactive tissue that forms a pseudocapsule. Care should be taken to avoid entry into the tumor and pseudocapsule during course of dissection. Enucleation commonly results in microscopically positive margins and re-resection should be considered though anatomic location may preclude effective clearance of margins even with a second operation.

Table 106.6D American Joint Committee on Cancer (AJCC): T Classification of Soft Tissue Sarcomas of the Abdominal and Thoracic Viscera

Classification	Description
Primary Tumor	
TX	Primary tumor cannot be assessed
T1	Organ confined
T2	Tumor extension into tissue beyond organ
T2a	Invades serosa or visceral peritoneum
T2b	Extension beyond serosa (mesentery)
T3	Invades another organ
T4	Multifocal involvement
T4a	Multifocal (2 sites)
T4b	Multifocal (3–5 sites)
T4c	Multifocal (>5 sites)

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Table 106.7A American Joint Committee on Cancer (AJCC): TNM Classification of Retroperitoneal Sarcomas

Classification	Description
Tumor Grade	
GX	Grade cannot be assessed
G1	Grade 1
G2	Grade 2
G3	Grade 3
Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
T1	Tumor ≤5 cm in greatest diameter
T2	Tumor >5 cm and ≤10 cm in greatest diameter
T3	Tumor >10 cm and ≤15 cm in greatest diameter
T4	Tumor >15 cm
Lymph Node Involvement	
N0	No regional metastases to lymph nodes or unknown lymph node status
N1	Regional lymph node metastases
Distant Metastasis	
M0	No known distant metastasis
M1	Known distant metastasis

Not including Gastrointestinal stromal tumors.

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Table 106.7B Stage Grouping of Retroperitoneal Sarcomas

T	N	M	G	Stage Group
1	0	0	1, X	IA
2, 3, 4	0	0	1, X	IB
1	0	0	2, 3	II
2	0	0	2, 3	IIIA
3, 4	0	0	2, 3	IIIB
Any T	1	0	Any G	IIIB
Any T	Any N	1	Any G	IV

Used with permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.

Table 106.8A American Joint Committee on Cancer (AJCC): Tumor and Mitotic Rate Classification of Gastrointestinal Stromal Tumor

Classification	Description
Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of a primary tumor
T1	Tumor ≤2 cm
T2	Tumor >2 cm and ≤5 cm
T3	Tumor >5 cm and ≤10 cm
T4	Tumor >10 cm
Mitotic Rate	
Low	≤5 mitoses per 5 mm^2, or per 50 HPF
High	>5 mitoses per 5 mm^2, or per 50 HPF

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Metallic clips placed in the tumor bed following resection can help define the limits of resection and aid in surveillance as well as planning of future treatment. Closed suction drainage catheters may be used to obviate postoperative seroma formation following resection of extremity or truncal sarcomas. However, in the era of Enhanced Recovery After Surgery pathways, the true need and benefit for such drains should be re-evaluated. Drains should be placed reasonably close to the incision so that the site can be included in a postoperative radiation field and, for extremity sites, should be brought out distally rather than through a site proximal to the incision to minimize the extent of proximal involvement if amputation ever becomes necessary. A unique characteristic of sarcoma is the general lack of metastasis to regional lymph nodes. If regional lymphadenopathy is discovered in conjunction with a diagnosis of sarcoma, therapeutic lymphadenectomy can be considered since clearance of disease may be

associated with improved outcomes.[54,55] For selected histopathologic subtypes (e.g., epithelioid sarcoma, clear cell sarcoma), in patients with clinically negative node examination, there may be a role for sentinel lymph node biopsy to identify occult micrometastatic disease.[56]

Table 106.8B Stage Grouping of Gastrointestinal Stromal Tumor, Gastric and Omental

T	N	M	Mitotic Rate	Stage Group
1, 2	0	0	Low	IA
3	0	0	Low	IB
4	0	0	Low	II
1, 2	0	0	High	II
3	0	0	High	IIIA
4	0	0	High	IIIB
Any T	1	0	Any rate	IV
Any T	Any N	1	Any rate	IV

Used with permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.

Table 106.8C Stage Grouping of Gastrointestinal Stromal Tumor, Small Intestinal, Esophageal, Colorectal, Mesenteric, and Peritoneal

T	N	M	Mitotic Rate	Stage Group
1, 2	0	0	Low	I
3	0	0	Low	II
4	0	0	Low	IIIA
1	0	0	High	IIIA
2, 3, 4	0	0	High	IIIB
Any T	1	0	Any rate	IV
Any T	Any N	1	Any rate	IV

Used with permission of the American College of Surgeons. Amin MB, Edge SB, Greene FL, et al., eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017.

Taken together, sarcomas of the upper and lower extremities and trunk make up the majority of soft tissue sarcomas. Large truncal tumors may require reconstruction with a myocutaneous flap or prosthetic materials if resultant defects cannot be closed primarily (**Fig. 106.6**). Largely of historical interest now, radical amputations were once the mainstay of treatment for extremity sarcoma, but modern surgical approaches involve limb-sparing procedures (**Fig. 106.7**), which maximize functional outcomes. As recently as the 1970s, more than 50% of all soft tissue sarcomas of the extremity were treated with radical amputations. The accepted standard of care changed after the group at the National Cancer Institute, led by Rosenberg,[57] published the results of a randomized trial of limb-sparing resection plus adjuvant radiation therapy compared to amputation, finding no differences in disease-free survival rates (71% vs. 78%, respectively) and the overall survival rates (83% vs. 88%, respectively) at 5 years. This trial demonstrated that amputation was not mandatory and in 1985, a National

Institute of Health consensus statement recommended limb-sparing procedures for most patients with high-grade extremity sarcomas.[58] Radical amputations, such as hemipelvectomy, hip disarticulation or forequarter amputation, are now reserved for patients who are not suitable candidates for limb-sparing approaches, usually because of extent of disease, bony or joint invasion, or for otherwise unsalvagable recurrence after previous limb-sparing surgery (**Fig. 106.8**).[59] There is no improvement in survival with this approach under these circumstances and serious morbidity must be taken into account.[60]

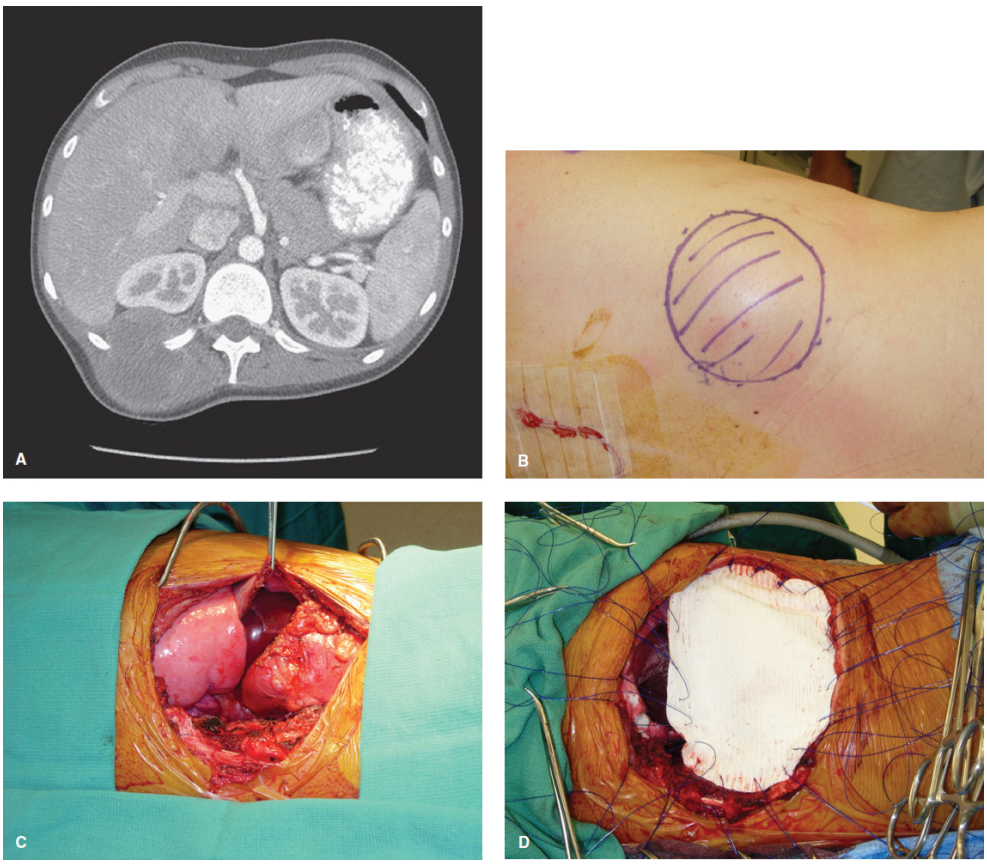

Figure 106.6 Chest wall sarcoma. A 20-year-old man with a 7.5-cm right posterior chest wall epithelioid sarcoma involves the 11th and 12th ribs as seen on CT scan (**A**) and on physical examination (**B**). Chest wall resection was performed, including a portion of diaphragm. Resulting chest wall defect (**C**) was repaired using prosthetic mesh (**D**).

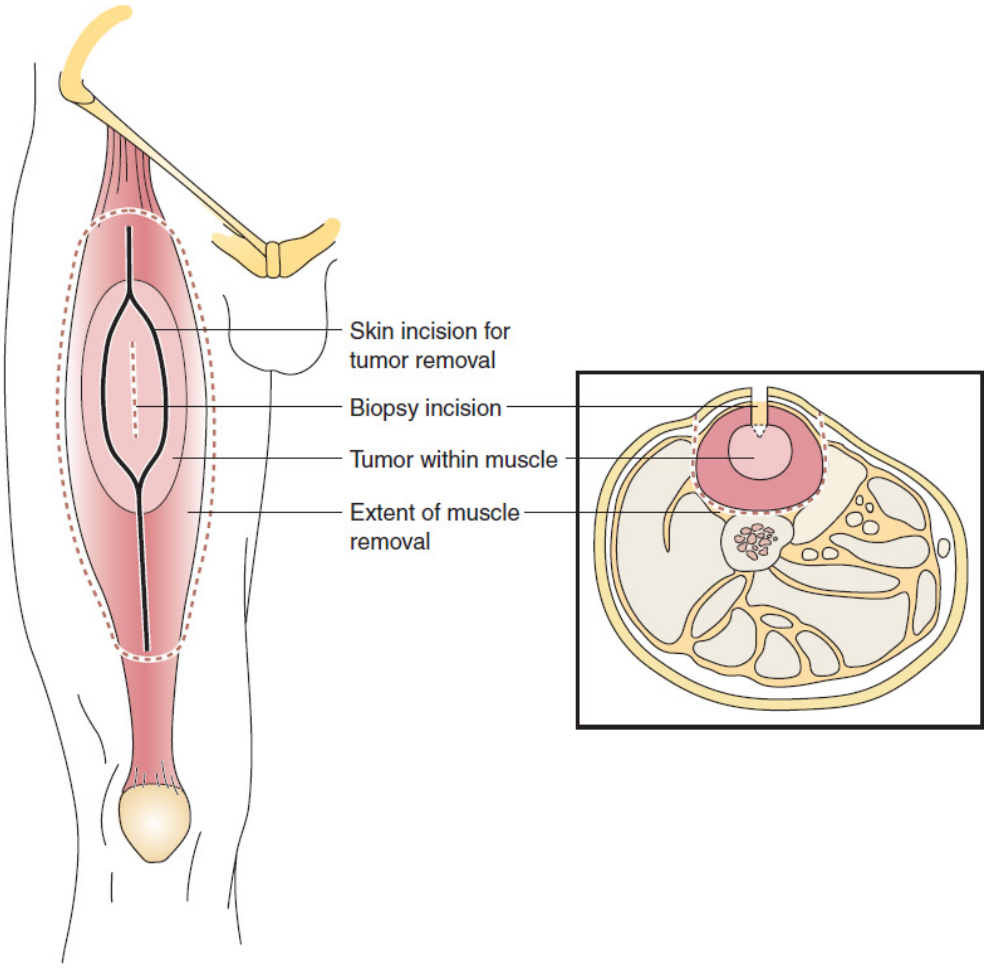

Figure 106.7 Wide excision involves removal of the tumor with a margin of normal tissue. If necessary, major vascular structures or nerves may be resected.

Acceptance of multimodality therapy has led to the ability to perform wide excisions while preserving function when treating extremity or truncal soft tissue sarcomas.[5,61,62] Radiation can be employed in the neoadjuvant or adjuvant setting, and evidence from randomized trials as well as retrospective studies support similar local control and progression-free survival rates with both strategies. A Phase III trial in which patients were randomized to preoperative or postoperative radiation showed similar primary outcomes, but found that preoperative radiation was associated with much higher wound complications (35% vs. 17%, respectively), and this was especially true for lower extremity tumors. The interesting tradeoff was a higher rate of late treatment effects in the postoperative radiation group, attributed to relatively higher treatment doses and volumes. Based on the data from this trial, either neoadjuvant or adjuvant radiation therapy may be

offered around resection of trunk or extremity sarcomas. Patients should be made aware of the tradeoffs—higher risk of wound healing complications with neoadjuvant radiation therapy versus higher risk of long-term joint stiffness and fibrosis with adjuvant radiation therapy.

Judicious use of radiation has allowed for the sparing of major neurovascular structures, though if necessary, arteries and/or veins can be resected en bloc with the tumor and subsequent reconstruction can be done with autologous or prosthetic graft materials. In cases of neurologic compromise, customized adjuncts from experienced physical medicine departments can help restore reasonable function. For instance, resultant foot drop from peroneal neuropathy can be managed with an ankle–foot orthotic and gait training. In appropriate cases, resection should be planned in conjunction with a plastic surgeon to provide complex soft tissue reconstruction with microvascular free flaps particularly if the size of defect following resection prohibits primary closure or if there is concern about a high risk of wound complications based on preoperative radiation.

Adjuvant and Neoadjuvant Therapy

4 The role of external-beam radiotherapy (EBRT) is best defined by a trial comparing limb-sparing surgery alone with limb-sparing surgery and adjuvant radiation, showing improved 10-year local recurrence rates with radiation. In high-grade sarcomas, the recurrence rate was 0% versus 22%, respectively though no significant effect on overall survival was appreciated.[63] Certainly, in the setting of involved surgical margins which could not otherwise be resected, adjuvant radiation therapy is associated with improved local control.[3,64]

Typically, the entire surgical bed and drain sites are included in the field, along with wide margins around the sarcoma, when postoperative radiation is given. Hemaclips marking the site of resection can be placed at the time of resection to help with radiation planning. It is important that an individualized approach be taken with each patient since radiation can result in severe complications when used inappropriately. For example, the entire circumference of the extremity should not be irradiated as this may cause massive lymphedema and could cause long-term neurovascular compromise. Severe fibrosis, necrosis, fractures, and contractures can also occur with

focused treatment and result in impaired function. Wound healing may be compromised in patients undergoing adjuvant radiation and in selected cases, use of rotational flaps for coverage can prevent or minimize chronic wound healing problems.[65] Similarly, radiation must be used judiciously in sensitive areas such as the abdomen and retroperitoneum since nearby visceral structures are exquisitely sensitive to higher doses of radiation. Dose-limiting toxicity must be considered when recommending such therapies.

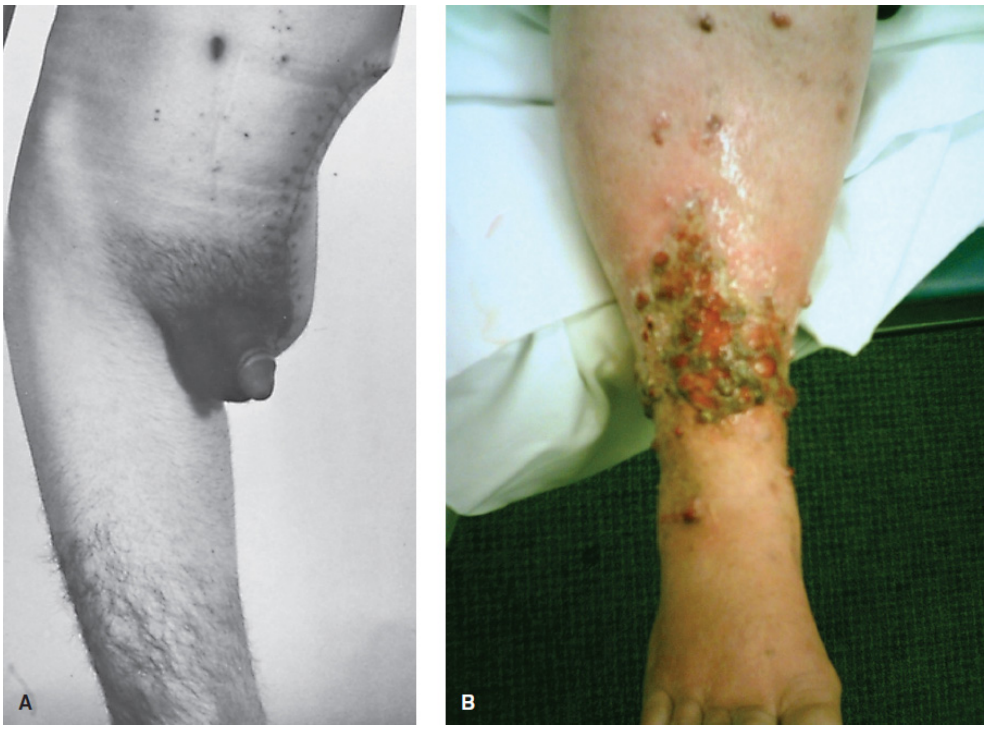

Figure 106.8 **A:** Radical amputations for extremity sarcomas include one joint above the most proximal extent of tumor. Now largely of historic interest, tumors of the proximal thigh or buttock were previously routinely treated with hemipelvectomy. **B:** While limb-sparing procedures are now done whenever possible, amputation may be necessary for certain cases. This 60-year-old woman had high-grade angiosarcoma of the right leg with extensive satellite metastases extending above her knee. She required above-knee amputation.

An alternate approach to adjuvant radiation is brachytherapy, which involves the placement of multiple catheters or seeds in the tumor resection bed to administer iridium-192. Unlike the several week course needed to complete external-beam radiation, a course of brachytherapy can be completed in a few days time. In theory, brachytherapy produces less radiation scatter in critical areas, decreasing toxicity while obtaining

equivalent functional outcome.[66] However, brachytherapy requires special equipment and can involve technically complex treatment planning by an experienced radiation oncologist. From a therapeutic standpoint, brachytherapy and external-beam radiation appear to be equivalent when properly administered. In recent years, stereotactic body radiation therapy (SBRT) has begun to replace some of the indications for brachytherapy. Nonetheless, brachytherapy can be particularly useful if the patient is no longer a candidate for EBRT due to prior radiation to that site. Some centers offer intraoperative radiation therapy (IORT), though its effectiveness is unproven. If IORT is employed, it is currently done in conjunction with a planned external-beam boost dose.[67]

Patients with high-risk (large [>10 cm], high-grade) extremity sarcomas may be considered for preoperative treatment with chemotherapy or with chemoradiation since overall local control rates are disappointing with postoperative radiation alone.[61] Local control rates were considerably higher when large tumors were treated before surgery and in some cases, tumors initially considered unresectable without amputation shrank sufficiently to permit limb-sparing resection. There are several benefits of preoperative radiation. With the tumor in situ, there tends to be a smaller overall treatment volume and the theoretical advantages of more effective radiation because it is being delivered to an undisturbed tumor bed. There is also the potential benefit of decreased seeding during the course of resection and improved margin status because the radiation may shrink the tumor's pseudocapsule and render it relatively acellular. However, there is one major disadvantage to preoperative radiation and that is its detrimental effect on wound healing. Some groups have used an intraoperative or postoperative boost dose of radiation to the resection bed if there are concerns that margins are involved.

Increasing data support the use of resection alone for selected patients; those who have small (<5 cm), low-grade tumors seem to have acceptable local control and excellent long-term survival without radiation if wide margins are obtained at the time of resection.[68,69] Most patients undergoing resection may be candidates for additional radiation therapy because of high risk for recurrence, though its role in lower- or intermediate-risk patients is somewhat undefined, and the so-called therapeutic ratio of risk and benefits to radiation treatment must be carefully considered. Validated prognostic

tools may be helpful for individual patients weighing the benefits of available treatment options. Kattan et al. developed a nomogram to help better predict individual risk for 12-year disease-specific mortality in sarcoma patients using multiple prognostic factors simultaneously.[50] More recently, Callegaro and colleagues developed a multi-institutional, externally validated nomogram which is now available as part of the smart phone app (www.sarculator.com).[48]

For extremity sarcomas, the importance of pathologically negative margins must be emphasized. While differing widths of margins have been called "optimal," it is generally agreed that 1 to 2 cm are adequate, but that microscopically clear margins may be sufficient. Involved margins, along with age, recurrent presentation, and fibrosarcoma or MPNST subtypes, significantly increases the risk of local recurrence.[3,70] Patients presenting with involved margins following the index operation should be offered re-resection in order to obtain surgical clearance of margins. Several studies have shown no compromise in survival if complete resection is achieved with a second operation.[71] Interestingly, it is unclear if local recurrence predisposes to subsequent distant metastasis or if margin status is merely a proxy for aggressive disease.[70,72] Some histologies, such as myxofibrosarcoma, tend to track microscopically along neurovascular structures and fascial planes well beyond the visible extent of disease, and wider surgical margins should be considered.

Since the main cause of death in patients with soft tissue sarcoma is distant metastatic disease, continued efforts have been made to develop effective systemic therapies.[5,73] Postoperative adjuvant chemotherapy has been controversial because risk of adverse toxic effects may not be outweighed by the relatively low response rates and lack of durable results. The histologic subtypes of sarcoma vary in their responsiveness to chemotherapy. For example, osteogenic sarcoma, rhabdomyosarcoma, and Ewing sarcoma (the "pediatric" sarcomas) have had high rates of success with multimodality treatments including adjuvant chemotherapy.[61] Unfortunately, most randomized trials are underpowered to detect modest differences in survival and promising response rates reported in smaller nonrandomized clinical trials are not duplicated in subsequent larger randomized trials. In general, adjuvant chemotherapy is never indicated for patients with low-grade sarcomas and patients with small sarcomas of higher grades. Initial interest

in adjuvant chemotherapy for extremity soft tissue sarcoma was piqued by a randomized trial reported by Rosenberg et al. which demonstrated an improvement in disease-free and overall survival with adjuvant doxorubicin, cyclophosphamide, and high-dose methotrexate.[74] After a longer follow-up period (median follow-up 7.1 years), however, both disease-free and overall survival were not statistically significant.[75]

Over the years, single agents as well as combination chemotherapy regimens have been used in the adjuvant treatment of soft tissue sarcomas. Two of the more active agents include doxorubicin and ifosfamide. However, multiple randomized trials of postoperative chemotherapy have not demonstrated an improvement in disease-free or overall survival with intermediate- or long-term follow-up though there was a trend toward improved outcomes with chemotherapy in many studies.[61,76–78] The Sarcoma Meta-Analysis Collaboration evaluated the effect of adjuvant doxorubicin-based chemotherapy in 1,568 patients from 14 trials.[79] Although the time to local and distant recurrences, as well as recurrence-free survival, were significantly better in the treatment group, an overall survival advantage was not seen (HR 0.89, $p = 0.12$). Because of the rarity of disease and heterogeneity of tumor characteristics, most studies are too small to provide adequate power for testing responses in specific histologic subtypes. In general, many regimens have combined two of the most active agents, doxorubicin (or other anthracycline) and ifosfamide, and results from a randomized trial did show improved disease-free survival and overall survival; distant relapse rates were not different however.[80] A phase III trial randomizing patients with high-risk extremity soft tissue sarcomas (ESTS) to 5 cycles of epirubicine/ifosfamide or no chemotherapy following surgery (with or without radiation) failed to show a significant difference in disease-specific survival with long-term follow-up.[80,81] Outside of clinical trials, adriamycin and ifosfamide combination therapy is commonly used for high risk, primary extremity, and truncal sarcomas in the adjuvant setting. Newer regimens with promising results include the combination of gemcitabine and docetaxel which was initially discovered to be active in heavily pretreated uterine leiomyosarcomas and is currently being considered for use in that subtype as well as in high-grade undifferentiated pleomorphic sarcomas and other high-risk subtypes.[82–84] A phase II study comparing adriamycin and ifosfamide to the combination of gemcitabine and docetaxel found that the

latter regimen had a slightly lower hospitalization rate and trends toward longer disease-free survival rates.

Even with advances in systemic chemotherapy and targeted agents, data supporting greatly improved overall survival rates are sparse, especially in the adjuvant setting. For advanced tumors, treatments with single agents or combination regimens such as dacarbazine, doxorubicin, epirubicin, ifosfamide, gemcitabine, docetaxel, temozolomide, trabectedin, and eribulin have been trialed extensively. Newer targeted therapies have shown some promise in certain histologic subtypes. For example, tyrosine kinase inhibitor (TKI) agents such as pazopanib, imatinib, sorafenib, and sunitinib have shown efficacy in multiple subtypes after initial success with GISTs. The class of mTOR inhibitors (sirolimus, temsirolimus, everolimus) have demonstrated promise for perivascular epithelioid cell tumors (PEComas), lymphangioleiomyomatosis, and angiomyolipomas.

One potential advantage of upfront systemic chemotherapy is the ability to assess tumor response in situ. By seeing whether the tumor responds to the chemotherapy, both radiologically and pathologically, it may be possible to spare patients prolonged therapy if they have not shown a response, or to continue therapy postoperatively if there is response. Interdigitated neoadjuvant chemotherapy (doxorubicin, ifosfamide, and dacarabazine) and radiation therapy improved survival in a single-institution series, but when generalized to a multi-institutional study, the toxicities were prohibitively high.[85–87] However, data from a trial of preoperative doxorubicin- and ifosfamide-based chemotherapy conducted by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada did not demonstrate any survival benefit compared to surgery alone.[88]

A series of recent European trials have also explored the utility of neoadjuvant chemotherapy for extremity soft tissue sarcomas. These studies established that three cycles of neoadjuvant therapy are not inferior to five cycles.[89] One particularly innovative trial randomized patients with high-risk extremity sarcoma to three cycles of neoadjuvant epirubicin/ifosfamide or three cycles of a histotype-tailored regimen (trabectedin for myxoid liposarcoma, gemcitabine/dacarbazine for leiomyosarcoma, gemcitabine/docetaxel for unclassified pleomorphic sarcoma, high-dose ifosfamide for synovial sarcoma, and ifosfamide/etoposide for malignant

peripheral nerve sheath tumor).[90] The hypothesis was that a tailored, histotype-specific regimen would be superior, but that proved not to be the case.

Some agents such as gemcitabine may have chemosensitizing properties,[91] making preoperative chemoradiation strategies attractive. Based on current evidence, neoadjuvant chemoradiation, either concurrent or sequential, should only be offered to selected high-risk patients on clinical protocol.[92] It is important to follow patients on neoadjuvant therapy closely since tumor progression is expected to be seen in approximately 30% of patients.[93,94]

Commonly used measures of radiologic response to treatment may not be good surrogate endpoints for treatment response.[34] The pathologic correlations of treatment-induced necrosis or histologic response to therapy with clinical outcomes have also not been well defined in soft tissue sarcoma.[95] Some patients who have a clinical or pathologic response to chemotherapy may have improved local control and decreased distant disease-free survival, but no overall survival advantage.[96] In other cases, lack of measurable response did not seem to predict significant differences in event-free endpoints.[93] These issues must be carefully considered in the design of future trials.

Alternative approaches to standard systemic therapy have been attempted with limited success. For example, preoperative radiation therapy in combination with intra-arterial doxorubicin chemotherapy initially showed good local control, but results could not be duplicated in subsequent randomized trials and treatments were associated with high morbidity.[97,98] Regional chemotherapy administered via hyperthermic isolated limb perfusion has been attempted for advanced extremity sarcomas. Extracorporeal circulation allows the delivery of drug concentrations 10 to 20 times higher than with systemic delivery and a European study showed a limb-salvage rate of 71% for unresectable extremity sarcomas using melphalan and tumor necrosis factor-α.[99,100] However, this technique is uncommonly used in the United States and usually reserved for highly selected patient populations.

Retroperitoneal and Intra-Abdominal Sarcomas

5 Management of intra-abdominal (visceral) and retroperitoneal sarcomas deserves special consideration since specific anatomic location may dictate work-up and subsequent management. The grouping of visceral sarcomas generally includes tumors of the gastrointestinal tract and gynecologic organs, and less commonly, genitourinary organs. Location often precludes early diagnosis, unless the mass is found incidentally. Though some patients have noted increased abdominal girth, an abdominal mass can be appreciated with focused physical examination, but it is uncommonly the presenting complaint. Typically, vague symptoms of mass effect intra-abdominally triggers medical evaluation. Neurovascular symptoms related to compression or invasion can occur and manifest as paresthesia, dysesthesia, weakness, and swelling or varicosities in the lower extremities.

Complete history and physical examination should exclude signs and symptoms of lymphoma (e.g., B-symptoms such as fevers and night sweats) and presence of scrotal masses concerning for testes cancer. Serum laboratory testing can be helpful if lymphoma (e.g., elevated lactate dehydrogenase [LDH]), germ-cell tumors (e.g., elevated beta-human chorionic gonadotropin [β-HCG] or alpha-fetoprotein [AFP]), or adrenal tumors (e.g., cortisol levels or adrenocorticotropic hormone [ACTH]) are in the differential diagnosis. High-quality cross-sectional imaging with CT or MRI is critical for diagnosis and treatment planning. Use of oral and intravenous contrast defines extent of primary disease and the relationship of the tumor to nearby structures. Chest imaging should be obtained to assess for presence of pulmonary metastases. Hepatic involvement is the second most common site of distant spread in intra-abdominal and retroperitoneal sarcomas, so a CT scan that includes the proper contrast phasing for examination of the liver should be done.

For large tumors, preoperative image-guided CNB can almost always be performed by experienced interventional radiologists with minimal risk of needle track seeding (**Fig. 106.9**).[101–103] Complete resection is the treatment of choice for intra-abdominal (visceral) and retroperitoneal sarcomas whenever possible. Only complete resection is associated with long-term survival benefit, with retroperitoneal liposarcomas being a possible exception.[104,105] For retroperitoneal sarcomas, median survival for those with an incomplete resection is similar to those who were observed (unresectable)[106] (**Fig. 106.10**). In general, incomplete resection should only

be considered for palliation of intractable symptoms. While successful palliation may be achieved in carefully selected patients, aggressive tumor biology limits the ability to maintain sustained relief of symptoms.[107]

In order to completely remove the sarcoma, en bloc resection of nearby structures should be considered when necessary. Resectability is more a function of location than of size, grade, or histologic subtype. Common reasons for unresectability include distant metastasis, peritoneal metastasis, extensive multifocality, and prohibitive vascular involvement. Though sarcomas do not uniformly invade other structures, involvement of vascular structures or mesentery (mesocolon) may lead to resection of solid organs or bowel that may not be directly involved. Furthermore, detailed pathologic analysis does show that adjacent structures, such as ureters, can be invaded even when no invasion is suspected.[108–110] When nephrectomy may be necessary, it is important to assess bilateral renal function with preoperative contrast scanning. Concomitant nephrectomy, when necessary, is associated with comparable outcomes for retroperitoneal sarcomas overall.[111] Commonly resected organs include the following: kidney, colon, adrenal gland, pancreas, and spleen.[112] For tumors located in the pelvis, it may be necessary to perform en bloc resection of the colon/rectum, bladder, and uterus. When vascular structures limit complete resection of tumor, resection with ligation or reconstruction of vessels must be considered if technically feasible (**Fig. 106.11**).

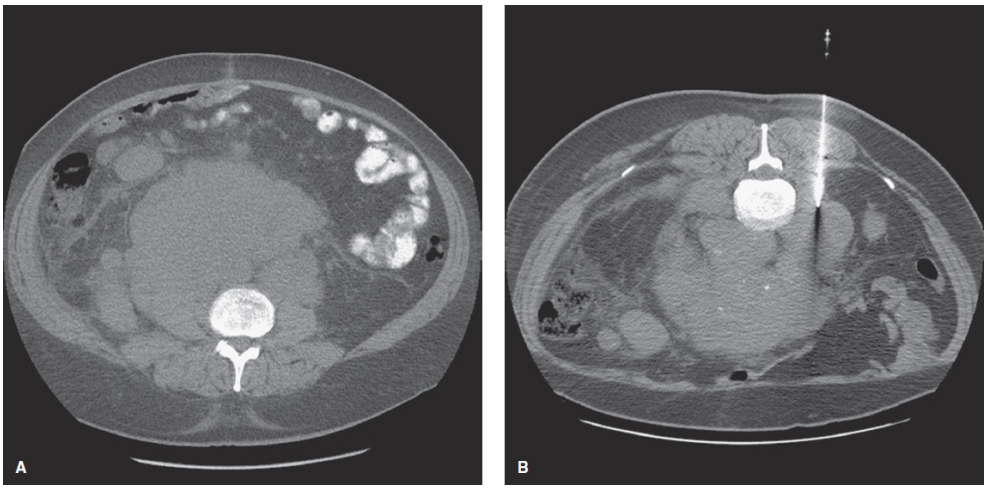

Figure 106.9 Biopsy can be helpful in the workup of retroperitoneal masses. **A:** CT scan shows a retroperitoneal mass encasing the IVC and aorta. **B:** Image-guided biopsy is demonstrated here. Pathology confirmed a diagnosis of large B-cell lymphoma.

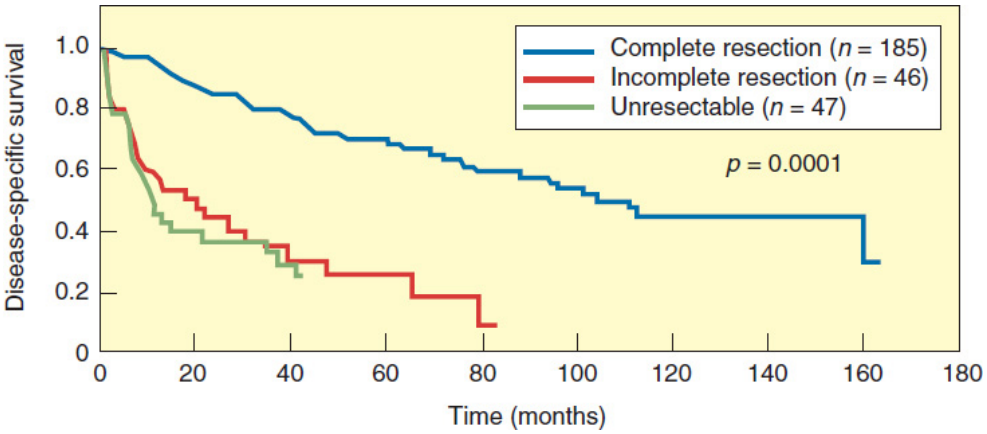

Figure 106.10 Kaplan–Meier plot of disease-specific survival for patients with retroperitoneal sarcomas treated at Memorial Sloan Kettering Cancer Center. Disease-specific survival is 103 months in patients who underwent complete resection of retroperitoneal sarcomas, compared to 18 months in those who had an incomplete resection or just observation. (From Lewis JJ, Leung D, Woodruff JM, et al. Retroperitoneal soft-tissue sarcoma: analysis of 500 patients treated and followed at a single institution. *Ann Surg* 1998;228(3):355–365.)

Even when resection is possible and complete gross resection is achieved, margin status is often compromised by constraints of visceral anatomy. A transperitoneal approach allows for excellent exposure and facilitates en bloc resection of with early control of the vascular supply to the tumor. Analyses of relatively aggressive approaches to resection include complete compartmental resections and liberal use of en bloc visceral resection show

better local control, but high-grade tumors tend to recur systemically.[113–115] Proper patient selection for the so-called "aggressive resection" needs to be weighed against the natural history of sarcoma. It is generally agreed that the best chance for curative intent resection is at the time of first operation. Complex multivisceral operations should be referred to higher-volume centers with experienced sarcoma surgeons when possible. Unfortunately, large national database studies suggest that only approximately 10% of patients undergoing surgery for primary retroperitoneal sarcoma are treated at high-volume centers.[116]

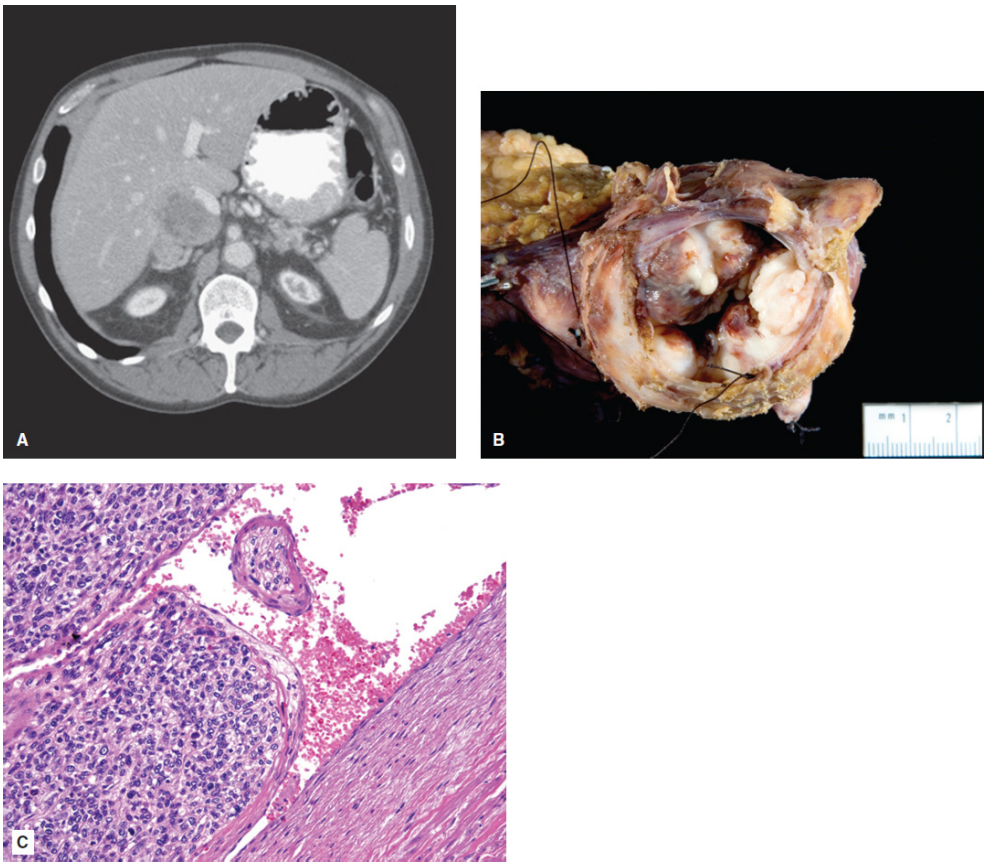

Figure 106.11 Inferior vena cava (IVC) leiomyosarcoma. **A:** CT scan demonstrates a 9.2 × 6.4 × 4.4 cm mass within the lumen of the retrohepatic IVC. **B:** Photograph of the gross specimen. Cross-sectional view from the superior aspect of the specimen demonstrates the extensive filling of the lumen with multilobulated tumor. **C:** Photomicrograph demonstrating intraluminal high-grade leiomyosarcoma with nuclear atypia and pleomorphism. Uninvolved smooth muscle of the IVC is shown (right lower quadrant). (Courtesy of Jason Carvalho, MD and David R. Lucas, MD, University of Michigan, Ann Arbor, MI.)

Even with aggressive surgical management, local recurrence rates range from 40% to 70% for high-grade tumors.[12,113,117] Unlike extremity sarcomas, local progression is associated with decreased survival. Difficulty obtaining negative margins and high recurrence rates support a role for carefully selected multimodality treatments. The major advantage of preoperative radiation is the displacement of small bowel and other structures by the in situ tumor. However, the benefits of radiation for extremity sarcomas have not been similarly appreciated for retroperitoneal sarcomas and no improvement in disease-free intervals has been noted.[118,119] In fact, the only randomized trial to examine the benefit of radiation plus surgery versus surgery alone found no improvement in the rate of abdominal recurrence-free survival, though there may be a potential use in selected patients with well-differentiated liposarcoma.[119] Large field sizes and the dose-limiting toxicity of abdominal viscera limit the utility of postoperative radiation. The role of chemotherapy, either in the pre- or postoperative setting, is unproven for intra-abdominal and retroperitoneal sarcomas.[120,121] Several trials of postoperative adjuvant chemotherapy do not show any benefit for patients with retroperitoneal sarcoma, and in one series, treated patients fared worse than those not receiving chemotherapy.[122] In one trial of an aggressive multimodality approach, there was an improvement in locoregional control but no overall survival advantage and significant toxicity from the chemotherapy and radiation therapy.[123] Though some histologic subtypes, such as leiomyosarcoma, pleomorphic sarcoma, or myxoid/round cell liposarcoma, may be relatively more responsive to systemic treatments, a paucity of data exist to guide appropriate use of therapy. Randomized controlled trials have been notoriously difficult to accrue patients to. Of note, different histologic subtypes arising in the retroperitoneum have different patterns of recurrence.[113] In particular, high-grade dedifferentiated liposarcoma and leiomyosarcoma can spread commonly to the lungs, and a phase 3 trial testing histotype-specific neoadjuvant chemotherapy is anticipated to start accrual in 2020.[113]

Special consideration is also given to complete resection with functional preservation in head and neck sarcomas and genitourinary sarcomas. As is true of sarcomas in other anatomic locations, histologic grade and size adversely affect prognosis for head and neck sarcomas.[124] Resections with negative margins may not require adjuvant radiotherapy treatments.

Similarly, grade, size, location, and histologic subtype similarly predict disease-specific survival for genitourinary sarcomas.[125] Regional relapse is influenced by margin status so radical resections are necessary. Unfortunately, recurrences are not uncommon and may be difficult to control due to anatomic location.

Recurrent or Metastatic Disease

About two-thirds of soft tissue sarcoma recurrences occur in the first 2 years after diagnosis and treatment, though recurrences may be seen at any time.[126] Recurrences may be classified as locoregional or distant. Though no standardized follow-up regimens exist, routine history and physical examination (clinical follow-up) and interval chest imaging are recommended for the first 2 to 3 years. Site-specific imaging guidelines are less clear. Directed cross-sectional imaging studies are helpful if location of tumor precludes early detection of recurrence on clinical evaluation alone. Of course, the choice of imaging study depends on availability, cost, and anatomic site being examined. MRI of the extremity or trunk can help detect locoregional recurrences when they are relatively small. CT scans may be useful for demonstration of intra-abdominal or retroperitoneal recurrences which would otherwise be clinically undetectable. However, there is no evidence that earlier detection improves survival for retroperitoneal sarcomas,[106] so a less aggressive imaging schedule may be appropriate. A randomized trial in India failed to find any survival benefit in using CT scans of the chest over CXR for surveillance for extremity sarcomas.[127] There are some retrospective data suggesting that lower-risk extremity sarcomas may simply need distant site surveillance, since risk of local recurrence is low and when it occurs, is often detectable on clinical examination alone.[128]

If chest radiography is used, abnormal findings should be followed with a CT scan of the chest. Low-grade lesions infrequently metastasize in the absence of local recurrence, though can recur locally up to 20 years after original resection. For high-grade lesions, surveillance should be directed toward detecting local recurrence and metastatic disease. Patients with locally recurrent or even metastatic sarcomas can be considered for subsequent resection if tumor biology supports potential cure or effective palliation with removal of known disease. A nomogram to predict the

outcomes after resection of recurrent retroperitoneal sarcoma has been reported, though these are subject to selection bias.[52] Recurrent disease, especially within the abdomen or retroperitoneum, becomes more difficult to treat with each recurrence.[117]

If a recurrence is suspected, a biopsy should be performed to confirm diagnosis and review histologic subtype as well as tumor grade, with comparison to the original tumor if possible. In the absence of distant disease, an aggressive surgical approach is warranted with the goal being the same as with a primary sarcoma: control of the tumor and preservation of as much function as possible. For patients who were initially treated with surgery alone and who recur locally, multimodality treatment with repeat resection, radiation, and sometimes chemotherapy is associated with survival rates close to those of previously untreated patients.[129–131] Independent predictors of survival in patients with locally recurrent extremity soft tissue sarcomas include histologic grade, size of recurrent disease, and recurrence-free interval.[132]

The most common site of distant metastatic disease is the lung, and its presence is not detectable by symptoms. Again, CT is the preferred imaging modality, though its very high sensitivity for detecting pulmonary nodules as small as 2 mm decreases its specificity.[133,134] Occasional patients have liver, bone, or central nervous system metastases, though these sites of disease are relatively uncommon. Once diagnosed, metastatic disease is best approached with systemic chemotherapy, either as a single agent or with combination treatments. Pulmonary metastases are the most common form of distant disease, and metastasectomy in carefully selected patients seems to improve outcomes. Taking patient selection into account, resection of pulmonary metastases in combination with radiation and/or chemotherapy, may improve outcomes compared to resection alone[135,136] (**Fig. 106.12**). However, there are no randomized trial data to determine if there is truly any benefit to resecting lung metastases. Patients considered for resection generally have better outcomes if they have a limited number of metastases, longer disease-free intervals, and leiomyosarcoma or osteosarcoma histologies.

Gastrointestinal Stromal Tumors

6 Another subtype of sarcoma which deserves separate consideration is GIST. Prior to modern molecular diagnostic techniques, these tumors were likely to have been considered leiomyosarcomas based on histologic features.[12] It is now known that GISTs are differentiated from GI leiomyosarcoma based on lack of well-differentiated smooth muscle cells. GISTs are composed of more primitive mesenchmyal cells and originate from the interstitial cell of Cajal, which functions within the GI autonomic nervous system. Immunohistologic diagnosis is primarily made via expression of KIT (CD 117) cellular markers (**Fig. 106.13**). KIT overexpression is usually related to mutations in the *KIT* gene, although *PDGFR*-α mutations can also result in KIT overexpression in approximately 3% to 5% of GIST. KIT-negative GISTs have been reported, though tumor genotyping should be done to either *KIT* or *PDGFR*-α mutations even with negative immunohistochemistry for KIT.[137] Mutations in *NF1* and *BRAF* have been reported in GIST, and deficiency in *SDH* can cause GIST as well.

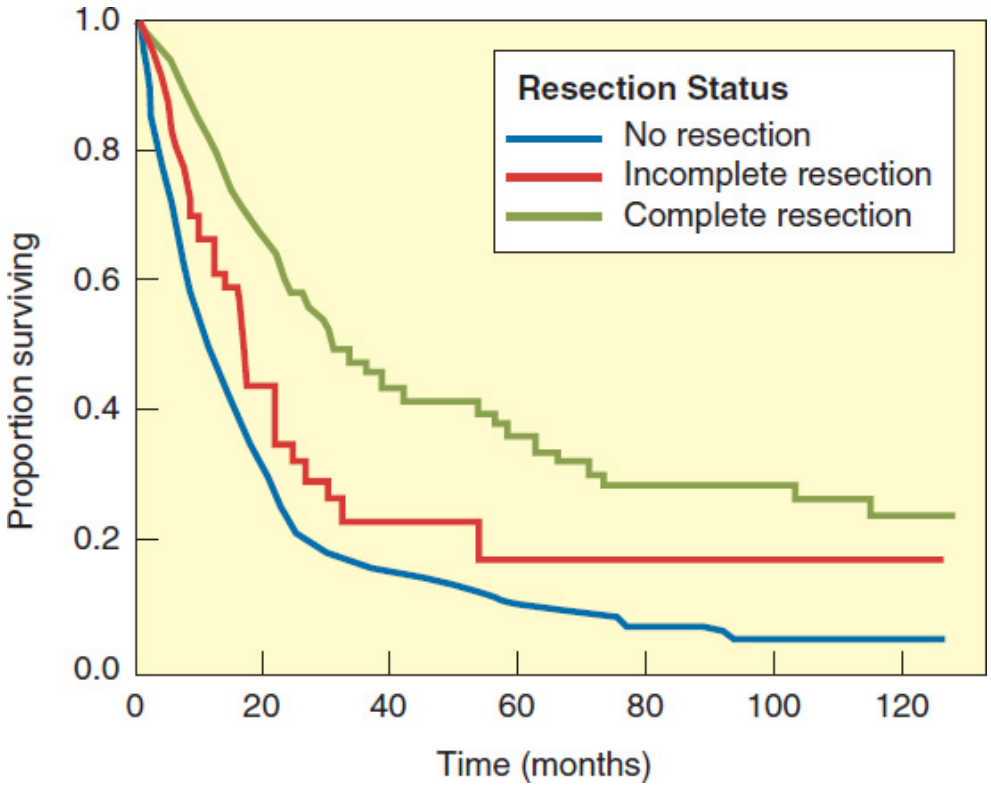

Figure 106.12 Kaplan–Meier plot of disease-specific survival for patients with pulmonary metastases treated at Memorial Sloan Kettering Cancer Center. Patients treated with complete resection had a median survival of 33 months. Patients who underwent incomplete resection or who did not undergo resection had median survival of 16 months and 11 months, respectively. (From Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. *Ann Surg* 1999;229(5):602–610.)

The *KIT* proto-oncogene encodes for KIT protein, a transmembrane glycoprotein receptor with an intracellular tyrosine kinase domain. Binding of the KIT ligand induces dimerization and autophosphorylation of KIT, activating a cascade of intracellular signaling which results in cell proliferation and tumorigenesis. A gain of function mutation in KIT occurs in up to 90% of GIST[138] and results in ligand-independent (constitutive) activation of tyrosine kinase function.[139] KIT mutation is found in 90% of GISTs and the most frequent sites of mutation are found in exon 11 (70%) or exon 9 (10%), whereas rare mutations are found in exon 13 or exon 17.[140] Mutation status may affect prognosis, and testing has become more routine in the evaluation of GIST.

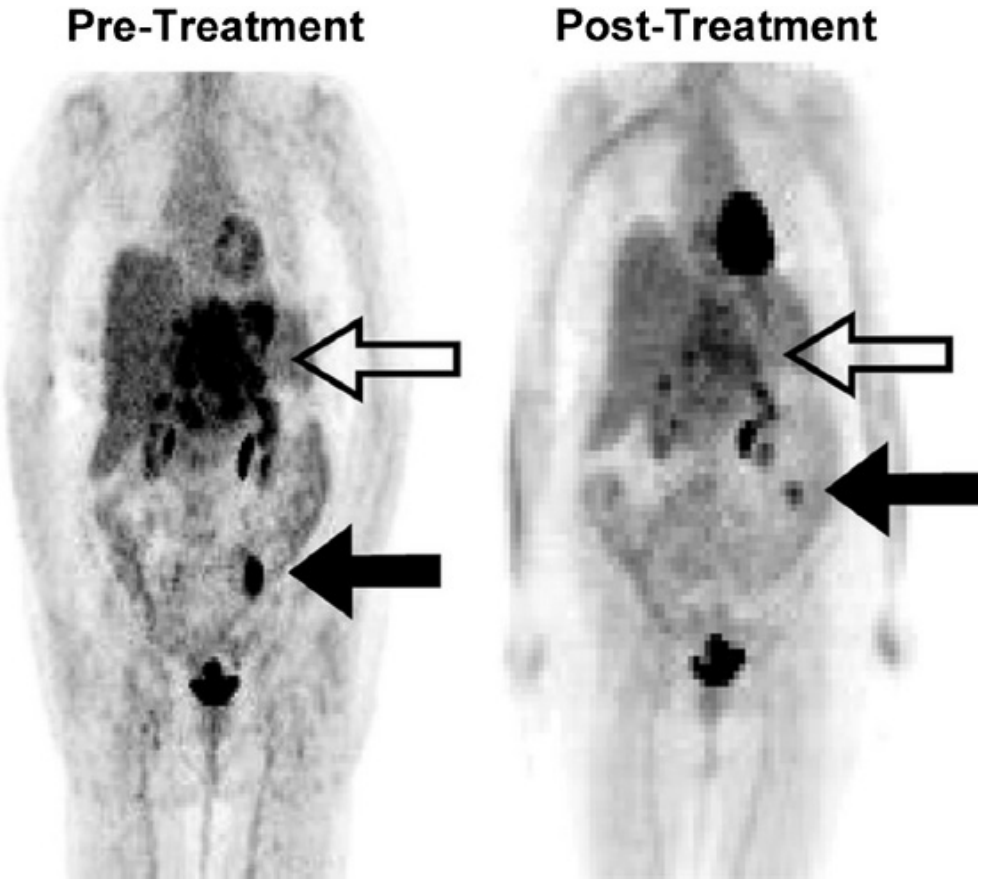

Figure 106.13 18FDG-PET scan showing response of metastatic GIST to imatinib mesylate. This patient presented with primary disease in the small bowel and synchronous metastatic disease in the liver. The scan at presentation (**left**) compared to the one obtained after 3 weeks of therapy (**right**) shows decrease in size of tumors and decrease 18FDG uptake in both the small bowel and liver tumors consistent with a good response to imatinib. The patient eventually went on to complete surgical resection. (From Gold JS, DeMatteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. *Ann Surg* 2006;244(2):176–184.)

Swedish epidemiologic data estimate 14.5 cases per million, which translate to an annual U.S. incidence of 4,000 to 5,000 new cases of GISTs per year.[141] GISTs are largely sporadic, but they have been seen in association with hereditary syndromes such as Von Recklinghausen disease and Carney triad, and familial germline mutations have been identified. Clinical presentation can be indolent: most patients have nonspecific symptoms such as nausea, emesis, or abdominal discomfort. Infrequently, GISTs can rupture or bleed, leading to a more emergent presentation. GISTs are most commonly found in the stomach (50% to 60%), with 30% to 40% of

tumors in the small bowel, 5% in the colon or rectum, and 5% in the esophagus. Rarely, GISTs develop within the mesentery, omentum, or retroperitoneum. Most GISTs are found in adults over the age of 40, with a median age of 60 years. Tumors found in children or young adults are considered a separate entity since pediatric GISTs have a more epitheliod histology and wild-type KIT or PDGFR-α genotype, often harboring mutations in one of the subunits of SDH.[142]

Complete resection is the treatment of choice for primary GIST, but recurrences are common and 5-year survival following resection of a localized tumor is approximately 50%.[143] Recurrences are common and thought to occur at 18 to 24 months from the time of the index operation. Lymph node dissection is not warranted because GISTs very rarely metastasize to regional nodes. Treatment of GIST was revolutionized with the development of imatinib mesylate (Gleevec), a selective tyrosine kinase inhibitor, representative of the emerging paradigm of molecularly targeted therapies. The proof of concept for this treatment paradigm was demonstrated in 2000 when a patient with diffuse metastatic disease achieved a near complete metabolic response[144] on PET and with 75% reduction in tumor size at 8 months and histologic evidence of myxoid degeneration and lack of mitotic activity. Contemporary use of imatinib in patients with metastatic GIST is considered an appropriate first-line treatment of metastatic disease (**Fig. 106.13**).

For patients who present with localized tumors, resection remains the mainstay of treatment. Interestingly, emerging evidence suggests that incidentally discovered, very small GISTs (<2 cm) may be successfully managed expectantly.

The use of imatinib in the adjuvant setting has been informed by a number of clinical trials. Mutation status is predictive of treatment success: *KIT* exon 11 mutations are associated with better response rates and survival endpoints than exon 9 mutations and wild-type GISTs. Because of high rates (>50%) of recurrence or metastasis following resection, at least 3 years of imatinib is recommended for high-risk tumors, including tumors which are greater than 5 to 10 cm in size or contain more than 5 mitoses per 50 HPFs, based on phase III trials.[145,146] Safety and efficacy for up to 5 years of adjuvant imatinib have been confirmed in a single-arm phase II study, and a randomized trial comparing 3 to 5 years of adjuvant imatinib is underway.[147] Risk

stratification must be approached with care; other factors which need to be considered include location of tumor and mutation status. It is reasonable to consider the use of imatinib for large or borderline resectable lesions prior to surgical resection. Most of these cases require continued treatment after resection given high risk of recurrence or metastasis. Second and third (and beyond) line therapies are available for drug-resistant disease, but as expected, responses following failure of first-line therapy are highly variable.

Desmoid Tumors/Desmoid Fibromatosis

Desmoid tumors warrant separate notation in the discussion of soft tissue sarcomas because of their distinct biologic behavior.[14,148] Desmoid tumors, or aggressive deep-seated fibromatosis, are part of a rare group of fibrous tissue proliferations which have no propensity for metastasis but tend to be locally aggressive. The natural history of desmoid tumors is not well defined and poorly understood. Clinical behavior and therefore, recommended treatments, are often dictated by anatomic site. Location of tumors can limit therapeutic options and result in significant morbidity with or without surgical resection.

Desmoid tumors are uncommon with an estimated incidence rate of two to four cases per million per year. The median age of diagnosis is 35, range 16 to 79 years. Desmoids are slightly more common in women than men. Desmoid tumors are classically described as an abdominal wall tumor, seen in young women during the postpartum period.[149] However, desmoids can occur at any site in the body and three main anatomic groupings are described: (1) trunk or extremity, (2) abdominal wall, and (3) intra-abdominal (bowel and mesentery). Fibromatosis is usually seen sporadically, but can be associated with FAP.

Desmoids are characterized by a monoclonal fibroblastic proliferation arising from muscular or aponeurotic structures. On gross examination, the tumors appear firm and smooth, with a surrounding pseudocapsule. However, microscopically, the tumor characteristically extends beyond this pseudocapsule, with fibrous septae of tumor extending radially. Desmoid tumors had previously been classified as an unchecked reactive process rather than a neoplastic process, but uniform patterns of X-chromosome

inactivation seems to confirm tumors of clonal composition.[150] There appears to be an increased estrogen receptor-β, but not estrogen receptor-α, expression in 80% of desmoid specimens.[151] These findings lend some support for the treatment of tumors with adjuvant agents such as tamoxifen.

Tumors tend to be located in deep in the muscles or along fascial planes, such as at a point of muscular insertion. Patients will usually present with a greater than 5 cm, localized, firm mass with an indolent pattern of growth, which can minimally painful. Intra-abdominal presentations can be associated with mass effect, intestinal obstruction, or mucosal ischemia. Desmoid tumors are notoriously infiltrative, and microscopically involved margins are seen in a significant number of patients following resection.

Surgery is no longer considered the standard of care or first-line treatment.[152,153] Many patients can undergo watchful waiting as a front-line approach, as many will never need resection. If tumors do grow under observation, systemic therapy or targeted therapy should be considered. Resection is only rarely needed and should not be offered without considering alternative options first. However, women with desmoids considering a pregnancy may be considered for resection as desmoids may grow during pregnancy.[154]

CONCLUSIONS

As understanding of sarcomas continues to evolve, it has become increasingly clear that therapy must be individualized to each unique presentation, taking into account histologic subtype, primary tumor site, tumor grade, patient comorbidities, and the full spectrum of multidisciplinary treatment options. Patient referral to a specialized sarcoma center is recommended.

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107

Plastic and Reconstructive Surgery

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Key Points

1. The process to obtain a closed wound will take a number of steps, the first of which will be excision of necrotic and grossly infected tissue. Antibiotics alone will not heal a problem wound.
2. The incidence of problem wounds is growing exponentially. Surgeons are seeing more patients with chronic medical problems that lead to nonhealing wounds. The management of these wounds requires a comprehensive evaluation of the patient factors that are adding to the problematic nature of the wounds.
3. The use of negative pressure devices has changed the approach to chronic wound management.
4. The ability to move vascularized soft and hard tissue from either local, regional, or distant sites allows surgeons to reconstruct congenital, traumatic, and oncologic defects and move patients forward and return them to a functional condition.
5. Pediatric congenital anomalies should be addressed with a comprehensive team of experienced specialists. Cleft lip and palate can be complete or incomplete, unilateral or bilateral. The problem affects speech, eating, swallowing, breathing, facial growth, hearing, and dental development.
6. Successful outcome for patients with complex hand problems requires meticulous surgical technique and careful attention to postop hand therapy.
7. Reconstructive and aesthetic procedures of the breast have become very common in our society. Oncologic reconstruction can be achieved with implant-based techniques or autologous tissue. Both offer women a safe and reliable return to appearance optimization and self-confidence.
8. The use of autologous tissue, for the most part, utilizes excess soft tissue of the lower abdominal wall. The tissue can be mobilized on and perfused by the rectus abdominis muscle or transferred as a microvascular free tissue transfer. The choice of techniques is based on patient factors and surgeon experience.

9 The request for aesthetic surgery procedures in our society is growing exponentially.

10 Aesthetic surgery is at its core elective surgery, performed on patients who are trying to achieve a change in something about their appearance. Whether that desired change is obvious to others is less important. Thus, there is very little room for error in evaluation, both physical and psychological. The surgery itself must be carried out by experienced surgeons who understand anatomic basis of the surgery.

11 The advent of nonsurgical aesthetic techniques, most of which utilize injectable medications, has opened up the field of aesthetic surgery to a much wider patient population.

The specialty of plastic surgery was initially approved as a subsidiary of the American Board of Surgery in 1938 and given the status of a major specialty board in 1941. The field of plastic surgery saw major growth during the two world wars. The urgent need for surgeons to treat burns, craniomaxillofacial trauma, hand and upper extremity injuries, and the associated ongoing reconstruction that many of these patients required, spurred a rapid development of new techniques and surgeons interested in limiting their practice to this field. The field of microsurgery, craniomaxillofacial surgery, reconstruction of peripheral nerves, oncologic reconstruction, and gender-affirming surgery are all fields that have been developed or expanded by plastic surgery. It is often forgotten that the first successful human renal transplant was performed by a plastic surgeon.[1] The scope of plastic surgery may be the broadest of any surgical specialty (**Table 107.1**). For this chapter we will limit our discussions to those areas that will be of the greatest interest and benefit to the reader.

MANAGEMENT OF THE PROBLEM WOUND

Plastic surgeons are often called upon by surgical and medical colleagues to assist in the management of recalcitrant wounds. When attempting to design a

treatment plan it is important to first do a thorough patient and wound analysis. The specific patient factors that are affecting the wound-healing process need to be identified. Maximizing the patient's nutritional status, controlling serum glucose, and physical therapy to improve patient conditioning to increase mobility will all help in management. A pressure wound can be improved by instituting algorithms such as pressure-reducing mattresses and other devices, eliminating soiling and moisture control and scheduled repositioning. Thus, we see that elimination of controllable factors can influence our success in closing a problem wound. The local wound [1] conditions can be improved with debridement of necrotic tissue and moisture control in an effort to maximize our eventual efforts at closure. While there are many different causes of nonhealing, problem wounds, the factors mentioned above will aid in in the management of all of them. Due to the varied types and locations of wounds there is no one reconstructive option to close a given defect. The use of an algorithmic approach needs to be followed and a number of options need to be considered for the given problem. You always need to have a fallback option.

Wound Evaluation

Problem wounds are often associated with a multiplicity of causes. These can be both local and systemic. It is critical to evaluate all of these factors if you want to achieve success. The causative etiology of the wound is the first factor to consider. A venous stasis ulcer is very different that an open tibial fracture. While both are lower extremity wounds the management of them is markedly different. The duration of the wound, previous surgical and nonsurgical treatment attempts and history of wound infections are important factors in decision making. Associated complicating factors such as previous malignancy, [2] irradiation, or chronic trauma are all associated with nonhealing wounds. Patient systemic factors that are associated with impaired wound healing such as immune deficiency, immune suppression, chemotherapy, and chronic medical conditions such as diabetes, problems requiring chronic steroid use, nicotine addiction, dietary deficiency, and the natural immune compromised state associated with old age must all be taken into consideration when addressing a nonhealing wound (**Fig. 107.1**, lower extremity wound in elderly diabetic female).

Table 107.1 The Spectrum of Plastic Surgery
Aesthetic surgery
Burns: acute and reconstructive surgery
Craniofacial surgery
Cutaneous and soft tissue oncology
Hand and upper extremity surgery
Head and neck oncology
Microvascular surgery
Maxillofacial and orthognathic surgery
Peripheral nerve surgery
"General" reconstructive surgery Face (ear, lip, nose, and eyelid) Breast Trunk Lower extremity

The careful examination of the wound requires recording the size and depth of the wound. All progress will be compared to these early measurements. The presence of compromised or exposed structures such as bone or vascular structures must be recognized early on and a plan to address them must be formulated. Traumatic wounds may contain foreign bodies. These wounds can be evaluated with plain films to evaluate for the presence any foreign material. The recognition and elimination of necrotic tissue is a necessity prior to any reconstructive effort. Chronic wounds may actually represent a malignant process either local or emanating from deeper tissues. All debrided tissue must go to pathology for evaluation. All chronic open wounds must be understood to be colonized. However, this is quite different than an "infected" wound. The classic signs and symptoms of infection that all surgeons recognize; pain, erythema, fetid drainage, swelling, fluctuance, and decreased function are all easily identified. The presence of a positive

bacterial culture from a surface swab does not indicate a clinically significant infection.[2] The soft tissue surrounding the wound must be evaluated. Will it tolerate the mobilization, and undermining needed to create a flap or other techniques used to move tissue in an effort to close a wound? Tissue that has been irradiated or has had previous surgical attempts at elevation and closure may not tolerate further surgical insult and actually lead to a larger wound. (See **Table 107.2** for factors associated with impaired wound healing.)

Figure 107.1 Problem lower extremity wound in elderly diabetic woman on chronic steroid therapy. The wound is secondary to minor shear injury.

Table 107.2 Local and Systemic Factors that Affect Wound Management

Local Factors	Systemic Factors
Infection	Immune deficiencies
Local malignancy	Distant malignancy
Foreign bodies	Diabetes mellitus
Local toxins	Cigarette smoking
Radiation	Chemotherapeutic agents
Ischemia	Hereditary healing disorders
Venous insufficiency	Nutritional deficiency
Lymphatic insufficiency	Old age
Repetitive trauma	Uremia
Reduced sensation	Glucocorticoid therapy, immunosuppressive agents

Obesity and diabetes are ubiquitous in our society and are recognized risk factors for compromised wound healing. These two factors may also make local flaps and tissue rearrangement fraught with problems.

Directed laboratory studies such as serum glucose, HA1c, prealbumin, hemoglobin and hematocrit, and renal and liver function tests may be useful adjuncts to treatment planning. Tissue biopsy rather than surface swabs may be useful in evaluating the need for antibiotic therapy.[3] Bacterial counts greater than 10^5 per gram of tissue represent a bacterial load that may not support wound closure with skin graft or tissue rearrangement. The use of wound biopsy information has been used in the management of burn wounds.[4] The presence of bacteria in the deep dermis closely correlates with burn wound sepsis. It is also very important to determine if osteomyelitis is a contributing factor in recalcitrant wounds. Open wounds that extend to bone can be evaluated with standard radiographs, CT, or MRI, however the only way to definitively prove or disprove osteomyelitis is with a well-directed bone biopsy. MRI can be used to delineate the extent of boney involvement. The imaging studies can reveal fractures, osteolytic areas and loss of cortical integrity, and suspicion of bone involvement with infection but not conclusively diagnose osteomyelitis. If osteomyelitis is diagnosed it will

require extensive resection/debridement and delay the reconstruction until you can be sure the infection is cleared. Antibiotics alone will not cure osteomyelitis. The necrotic bone is devascularized and antibiotics will not penetrate to the involved bone. The combination of bone debridement and antibiotics directed by the identification of the pathogens as cultured from the bone biopsy will allow for definitive elimination of bone infection and predictable wound closure.

The Treatment Paradigm for Wound Management

Following thorough evaluation of wound and patient factors you should address those factors discussed above that can be modified to optimize the outcome of wound closure. The goals are to have a closed wound and restore the patient's level of function. In our evaluation we recognize that some problems in wound healing should be anticipated and prevented prior to definitive surgery. The worst-case scenario is that the patient has a surgical procedure for wound closure and then goes on to develop another wound or the surgical site breaks down. As mentioned earlier, glucose control, control of fluids, and drainage and pressure off loading must be planned prior to surgery. The bedridden or paralyzed patient must have close nursing care for repositioning and the family must be educated as to the necessary preventive measures. Aggressive physical therapy will ensure maintenance of joint motion, decrease extremity edema, and optimize the patients conditioning for the postop period. These plans should be made and discussed with the care team, patient, and family prior to definitive surgery.

There will be, by necessity, some period of time prior to definite surgery when the wound will need to be optimized. We discussed the need for debridement of necrotic tissue, control of infection, and moisture/drainage control. Dressings and nonsurgical adjuncts can be very useful in preparing the site for surgery. Moist to dry dressings are the most commonly used dressing to debride a dirty wound. The operative word is moist not wet. If the dressings are too wet they will not dry out between dressing changes and will macerate the tissue causing more problems. These types of dressing have been used for over 100 years and are still recognized as being quite

effective for debriding wounds. Saline, calcium hypochlorite 3% to 4% or weak acetic acid solution can all be used as the moistening agent. The dressing actually debrides the wound by drying out and having the necrotic material stick to the dressing. The dressing is removed and the debris is removed with it. The dressing must be changed two to three times per day. Wounds with significant drainage will need to have the more frequent dressing changes.

Moist wound environments heal faster than dry wounds.[4,5] The best option for moist wound healing is keeping the native scab in place. Since there should not be a need for debridement with a clean wound, a nonadhering occlusive dressing can be applied. Hydrogels which are very effective in maintaining a moist wound healing environment are a good option for relatively clean wounds. A well-prepared wound cleared of necrotic debris can go on to heal by secondary intention with local wound care and dressing changes.

For the most part, the application of topical antibiotics is not indicated in the management of noninfected wounds. As discussed, all open wounds will be colonized and there is no real benefit to attempt to sterilize them. However, the judicious use of topical antibiotics can be helpful in certain situations. Significant burn wounds are often dressed with silver sulfadiazine. Silver sulfadiazine is bactericidal for many gram-negative and gram-positive bacteria as well as yeast. Mafenide acetate, also a sulfa-based drug, is also used for burns and other deep partial-thickness and full-thickness wounds. It is rapidly absorbed through open wounds and can be used on ear wounds due to its ability to penetrate cartilage. Mafenide is a potent carbonic anhydrase inhibitor and can cause hyperchloremic metabolic acidosis with chronic use. This drug can cause considerable pain on application, limiting its use. This drug also has antibacterial activity against most gram-positive and many gram-negative species commonly found in wounds. These topical drugs are not effective against methicillin-resistant *Staphylococcus aureus* (MRSA)–colonized wounds. Mupirocin topical ointment can be used in this situation with good effect. There has been an explosion in the use of nanocrystalline silver in dressings, both barrier and alginates. The silver dressings have low toxicity and excellent antibiotic properties. They can add significant cost to the dressing regimen.

Over the last number of years there have been a number of advances in the nonsurgical management of wounds, particularly problematic chronic wounds. These advances include the use of biologic and nonbiologic agents such as the application of growth factors to wounds, cellular therapies, and other physical modalities.[6] Recombinant platelet derived growth factors (PDGFs) may be useful in the management of chronic pressure wounds and diabetic foot ulcers[7,8]; there is no clear evidence that topical growth factors have a significant role in the management of acute wounds. Wound repair is a complex process and is influenced by numerous secreted factors, including cytokines, chemokines, and growth factors. In theory, application of stem cells to wounds is advantageous over administration of a single agent because stem cells have a unique feature of interacting with wound environment and modulate their activity to release multiple factors, which may facilitate wound healing process. However, the use of stem cell therapy to treat difficult wounds must be considered to be unproven and at this time investigational.[9]

The use of "off the shelf" skin substitutes such as bilaminate bovine collagen/silicone sheet have shown to have application in complex burn, oncologic, and trauma wounds.[10] It acts as a dermal substitute and renders a more stable construct and skin graft bed. Human and xenograft acellular dermal substitutes have been widely used in the management of all types of wounds. The thicker versions of these materials can be used to add structural support to complex abdominal wall and breast reconstruction.

Perhaps the most impactful innovation on the management 3 of chronic and problem wounds has been the development and application of negative pressure wound therapy. There are many options now available but all have the same basic elements of a sponge which is placed in the wound. It is then covered with an impervious plastic adhesive sheet and a suction device is place on a hole cut into the plastic sheet. There have been a number of innovations to the basic setup. The sponge can come with various pore sizes and can be impregnated with silver for infected wounds. Sponge and plastic sheeting systems have been modified for the management of complicated abdominal wounds with exposed viscera. These systems have changed the approach to complex open abdominal wounds. The use of the negative pressure device has been shown to control wound fluid, decrease wound edema, promote tissue perfusion, and stimulate granulation tissue in the

wound bed. There have been numerous clinical and experimental papers that attest to the efficacy of the negative pressure wound devices.[11] The systems are relatively easy to use, decrease the need for frequent dressing changes, help to control wound fluid, and decrease edema. The negative pressure wound devices should not be used in infected wounds. As pointed out throughout this discussion a positive culture from a surface swab indicates a colonized wound not an infected wound. The cost of the system needs to be balanced against all of the other positive factors including a shorter time to wound closure.

Surgery for Problem Wounds

Surgery for problem and chronic wounds falls into two categories; wound bed preparation and then wound closure. The use of aggressive surgical debridement can turn a chronic wound with hyperkeratotic margins, necrotic slough, and arrested progression to wound contraction into a wound that is ready for closure (**Fig. 107.2**, sacral pressure wound in elderly diabetic patient). Most chronic wounds will require at least one surgical debridement to put it in the optimum condition for reconstruction. Those wounds that involve bone will not respond to long-term antibiotics alone. This will just prolong the treatment course or lead to failed reconstruction Osteomyelitis will need to be totally excised to have any chance of successful closure.

Figure 107.2 Chronic sacral pressure wound in elderly diabetic man. Note the rolled hyperkeratotic margins and slough at base.

The Reconstructive Ladder

Plastic surgeons make a mental treatment plan when they see a chronic or problem wound. Of course, imaging and other adjuvant studies can cause a change in the plan but the basic process follows the very well-established "reconstructive ladder." The "ladder" (**Table 107.3** reconstructive ladder) helps to develop a treatment paradigm beginning on the first rung of the ladder, which presents the simplest approach to wound closure, [4] which would be allowing the wound to heal by secondary intention. The highest rung on the ladder would require a distant flap that may require a microvascular technique. It is not necessary to stop on every rung of the ladder and an experienced surgeon may understand that the return to normal function needs to take first priority. A single operation is the preferred method when possible, it is always preferred to use autologous tissue, and the long-term durability of the reconstruction must be considered. The use of autologous tissue will in most cases create a secondary wound. The harvest of split-thickness skin graft may effectively double the total wound burden. The harvest of a distant muscle or fasciocutaneous flap may have a

deleterious effect on the patient's function and again, create another wound. So clearly there is no "free lunch." The job of the reconstructive surgeon is to weigh the possible risk–benefit ratio and produce a reasonable outcome. Independent of the option chosen for wound closure, there are a few principles that are shared by all. First and foremost, careful surgical technique is required if we want to avoid complete or partial failure. The surgeon should incorporate these points into all they do. Make sure the bed is prepared for a graft or flap. Flaps, local or distant, do not do well when placed under tension. Pulling or forcing the tissue into the defect will cause microvascular compromise leading to macrovascular compromise and eventual partial or complete failure. Be sure there is good perfusion and venous drainage. If the flap appears to be ischemic or venous outflow appears to be compromised remove some of the insetting sutures and allow the flap to recover. In some cases, you may not be able to inset the flap at this juncture but rather will need to allow it to adjust to this new relative hypovascular situation. This is called the delay phenomenon. It is also referred to as vascular delay or ischemic preconditioning (**Fig. 107.3**, example of surgical delay). It describes the observation that a tissue rendered partially ischemic will undergo neovascularization and enhance its vascularity. The field of reconstructive surgery uses this phenomenon to facilitate the survival of flaps. Careful attention to hemostasis is a must in reconstructive efforts. Skin grafts, **whether of split-thickness or full-thickness type**, depend on being in intimate contact with the prepared recipient bed. The presence of even a minimal amount of blood or fluid will result in loss of some or all of the graft due to loss of that intimate contact. The distinction to be made here is the difference between a graft and a flap. A graft, which could be skin, tendon, nerve, fat, cartilage, or bone, is transferred without a blood supply and requires vascular ingrowth from the surrounding bed. Each tissue, and in fact, the volume of the transferred tissue has a particular physiologic requirement for vascularization and survival. So a split-thickness skin graft may survive where a full-thickness graft will not. A flap, on the other hand, is transferred with its vascularity intact. Thus, the flap is much less dependent on the local vascular milieu. The flap can be transferred with its vascular "leash" which may give it a limited arc of rotation. The option is to transfer the flap as a free tissue transfer. In this case the tissue is transferred with the vascular pedicle identified and dissected out

and divided just prior to transfer. The pedicle is then immediately anastomosed to an identified artery and vein at the recipient site. Obviously this technique will allow the movement of large amounts of tissue from distant sites to a defect and obtain a closed wound with one operation. This technique requires a great deal of expertise and sophisticated equipment but has changed the entire field of reconstructive surgery.

Table 107.3 The Reconstructive Ladder
Vascularized free tissue transfer
Local pedicled flap (fasciocutaneous or muscle)
Local cutaneous or fasciocutaneous advancement or rotation flaps
Skin grafts
Delayed primary closure
Primary closure
Healing by secondary intention

Healing by Secondary Intention

Allowing the wound to heal by secondary intention is a very acceptable course of action for smaller wounds. Some of the closure is due to wound contraction and then eventually epithelial migration to cover the surface. The process has a few problems that need to be recognized. The wound contraction can lead to a wound *contracture* which can distort adjacent soft tissue landmarks such as the labial commissure or the eyelid. Secondary healing across a joint may lead to limited range of motion of the affected joint. The time to closure may take months and may require debridement on a few occasions as the margins become hyperkeratotic and progress stagnates. After a period of no progression the decision may need to be made to move up the reconstructive ladder.

Primary Wound Closure

The next step on the ladder is closure of the wound with primary intention. This is the common approach for a laceration or acute soft tissue defect

following an excision of a small benign or malignant lesion. The principles outlined above apply here as well. Careful tissue handling, meticulous hemostasis, and closure without tension are required for a durable repair. A layered repair typically refers to the use of absorbable sutures to bring together the dermis and underlying subcutaneous tissue, which both closes dead space and relieves tension on the epidermis. Closing the deep and superficial fascia and the dermis in layers will almost effectively render a closed wound without any epithelial sutures. The skin sutures should be done with a monofilament nonabsorbable material, nylon or polypropylene would be preferred. When closed without tension and with the edges slightly everted there is less likelihood to develop obvious scar and wound dehiscence. The placement of a closed suction drain of appropriate size will help to decrease the chance of fluid buildup and keep the tissue in contact with the bed. Inability to close the wound without tension would dictate the use of another technique, moving to another rung on the ladder.

Figure 107.3 Example of surgical delay. Because of associated medical problems, the patient was not a candidate for microvascular tissue transfer. **A:** Lower-third tibial defect secondary to an open ankle fracture. Note exposed bone, which precludes use of a skin graft. **B:** In the first stage, a bipedicle flap was created anterior to the defect. The deep perforators to the skin of the flap were divided by full undermining. The flap is perfused only from the proximal and distal ends. **C:** The incisions were repaired, and the wound was dressed. **D:** After 5 days, the bipedicle flap was again elevated and part of the distal pedicle was divided (*arrow*). The incisions were again closed, and the wound was dressed. This procedure was repeated 10 days after the initial operation to leave only a small skin bridge at the distal end of the flap. **E:** Fourteen days after the initial procedure, the remaining distal skin bridge was divided and the flap transferred. The donor site was skin grafted. This photograph depicts full survival of the flap and complete take of the skin graft.

Skin Grafts

Skin grafts have changed the approach to the closure of open wounds. Their use was initially proposed in the 1880s but the technique fell out of favor due to failure to recognize the need for recipient bed preparation and careful

harvest techniques. The real understanding of skin grafting techniques did not develop until World War II. There was a tremendous need for improved management of burn injuries. Basic science and clinical research finally made the use of skin grafting a predictable and relatively easy way to close burn wounds and saved many lives.

Skin grafts are of two basic types: full thickness and split thickness. The difference is based on the amount of dermis harvested with the epidermis. The entire dermis is harvested with the full-thickness graft and the split-thickness graft can have a variable amount of dermis depending on the requirements of the wound. The full-thickness graft will contract less and heal with less of a noticeable depression because of the thickness of the graft. The full-thickness graft is often used for defects of the head and neck because it can be harvested locally from the face or neck and will maintain a good color match (**Fig. 107.4**, full-thickness skin graft to orbit). The full-thickness graft may have lower survival because of the thickness of the dermis representing an impediment to diffusion of serum into the graft. The take, or survival of the graft is dependent on the bed preparation and the ability to successfully revascularize the graft within 48 to 72 hours. The graft needs to be stabilized with some combination of sutures and dressings to keep the graft in intimate contact with the bed to encourage the revascularization of the graft. The presence of shear force on the graft will doom all or part of the graft. The early survival of the graft is dependent on plasmatic imbibition whereby serum from the bed needs to diffuse into the grafted tissue. Inosculation is the process by which blood vessels in skin graft grow to meet the vessels (inosculate = kiss) of the recipient bed. Within hours microvasculature from the wound bed grow into the graft and form connections with microvasculature of the graft. Thus, it is very clear that wound preparation is paramount for successful grafting. The graft will not take on bone that does not have adequate periosteum or tendon without paratenon. Skin grafts will not take on cartilage. If the bed cannot be prepared to support the process of imbibition and inosculation then the decision has to be made to move up the reconstructive ladder. The donor site for the full-thickness graft must be closed primarily. The use of the full-thickness graft is limited by the size of the defect and the ability to close the donor site primarily. With split-thickness skin grafts, the donor site wound heals by reepithelialization. Epithelial cells migrate from remnants of skin

adnexal organs, hair follicles, and sweat glands, in the underlying dermis and eventually grow across the wound bed. The donor site can be dressed with an occlusive dressing to maintain a moist environment or a petrolatum impregnated sheet of gauze which is allowed to dry onto the wound to create a pseudo scab. It will take 10 days to 2 weeks to heal the donor site.

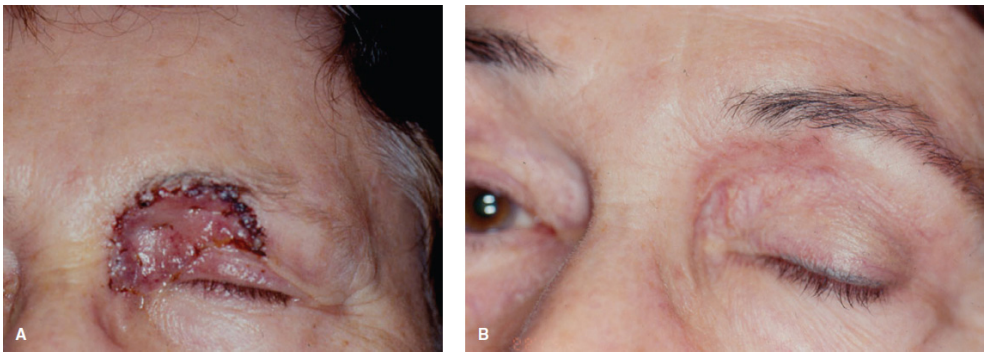

Figure 107.4 **A** and **B**: Full-thickness skin graft to the orbit (**A**) early post op, (**B**) 4 months post op. (Images courtesy of Jane L. Messina, MD, Moffitt Cancer Center.)

Random Flaps

The use of local tissue rearrangement that is adjacent to the wound is a very common method for closing wounds. It can be simple undermining to separate the tissue from deeper fascia or complex designed flaps based on the principles of "Z" or "W" plasties with back cuts and elevation of tissue. The advantage of these reconstructive techniques is the fact that we are using adjacent tissue. The color match and tissue thickness and properties will mimic the tissue that was present in the wound. This is especially useful in closure of wounds on the head and neck. It must be remembered that these are random pattern flaps perfused by the dermal plexus of vessels. Care must be taken when designing the flap so that there are not scars crossing the flap indicating a disruption of the dermal plexus. Longitudinal scars running in the long axis are also associated with disrupted dermal vessels. The basic movements of these flaps are rotation, advancement, and transposition depending on how the tissue needs to be moved into the defect. The defect size and location, the nature of adjacent tissue, presence of scars, and previous surgery may dictate if these local flaps can be used to close the defect. While the length width ratio must be taken into consideration there are certain procedures that can improve the vascularity of the flap.[12,13] The use

of the delay phenomenon has been shown to improve random flap survival. Delay is defined as the partial interruption of blood flow to the designed flap. This preconditions the flap to relative ischemia prior to division of the tissue. The technique of random flaps can be augmented by expanding the flap using subcutaneous tissue expanders. The expander is placed in a subcutaneous pocket and is gradually filled with fluid in an effort to create new skin. The expansion of the tissue is actually functioning as a delay technique and preconditioning the expanded tissue to relative ischemia.

Axial Pattern Flaps

The identification of larger caliber vessels longitudinally traveling along a defined skin region has changed the way plastic surgeons can reconstruct wounds. This has moved the entire field forward. Random pattern flaps are limited by the dermal plexus supplying the tissue. The arc of rotation will be a limited and the flap will need to be in close proximity to the wound. With axial blood supply any piece of tissue can be transferred on its vascular pedicle; in essence the tissue is transferred with its own blood supply. Using the principles of Taylor and Palmer[14] and the angiosome concept they developed, we are able to design flaps based on our knowledge of vascular anatomy. An angiosome is defined as a region of tissue supplied by an artery and its venae comitantes. The choke vessels crossing the boundaries of a given angiosome are able to enlarge thus allowing us to incorporate an adjacent angiosome into the flap. This facilitates the use of larger flaps to fill the given defect.

Fasciocutaneous flaps are a category of axial pattern flaps. The application of these very widely used flaps developed out of the understanding that the inflow to the dermal plexus is derived from vertically oriented vessels arising at the level of the deep fascia. This fasciocutaneous system consists of vessels which reach the skin by passing along the fascial septa between adjacent muscle bellies and then fan out at the level of the deep fascia to form a plexus from which blood reaches the skin. Fasciocutaneous flaps depend on less immediately obvious anatomy and the concept is one of potential underlying skin vascular territories rather than the well-circumscribed anatomical territories of the axial-pattern cutaneous flaps. The vessels form a subfascial plexus based on a horizontal orientation at the deep fascial level. This horizontal orientation is relative to the skin

surface. Several workhorse fasciocutaneous flaps have been developed on the subfascial plexus of vessels. The radial forearm flap is a thin pliable fasciocutaneous flap that is very adaptable for head and neck reconstruction where the inherent bulk of other flaps would be an impediment. The radial forearm flap is also well suited for hand and foot reconstruction where again a thin pliable flap would be needed. The anterolateral thigh flap (ALT) is very well suited to larger defects. These flaps are based on septal and or muscular perforators based on the descending branch of the lateral femoral circumflex artery. A cuff of muscle can be taken with the fasciocutaneous portion to fill deep complex wounds. Perhaps the most elegant use of a fasciocutaneous flap is the fibula free flap. This flap is actually an osteoseptocutaneous flap which has the advantage of providing vascularized bone for structural integrity and thin pliable tissue for a soft tissue defect. This flap is most commonly used in composite reconstruction of the head and neck particularly defects of the mandible and adjacent soft tissue.

Muscle and Musculocutaneous Flaps (Table 107.4 Workhorse Muscle, Myocutaneous and Perforator Flaps)

These flaps based on the classification system described by Mathes and Nahai[15] came into wide use in the early 1980s. The understanding that tissue can be transferred on an axial blood supply had been widely accepted. Adapted from this principle is the fact that whole muscles and if needed, the overlying skin and subcutaneous tissue can be transferred on its dominant pedicle or the pedicle can be divided and the tissue transferred as a free tissue transfer with a microvascular anastomosis. Multiple expendable muscles have been transferred with excellent results (**Fig. 107.5**, Rectus femoris flap). The rectus abdominis, latissimus dorsi, and gracilis are used successfully for wounds of all sizes. Functional muscle transfers are possible if the motor nerve to the muscle is preserved or the motor nerve is coapted to another motor nerve at the transfer site. In our discussion of fasciocutaneous flaps we described perforators emanating vertically from the muscle surface or intermuscular septum to supply the skin. The use of this construct has revolutionized autologous breast reconstruction. The transverse rectus abdominis myocutaneous (TRAM) flap is a hardy myocutaneous flap with a large skin and subcutaneous paddle based on periumbilical perforators. The muscle carries the blood supply to the soft tissue to create the breast mound.

The TRAM flap has evolved into the perforator flap. The careful dissection of the perforators to the skin allows the muscle to be preserved and avoid the morbidity of the loss of a large motor muscle. The use of perforator flaps are now often preferred over muscular flaps. These flaps are most often transferred as free flaps requiring a microvascular anastomosis.

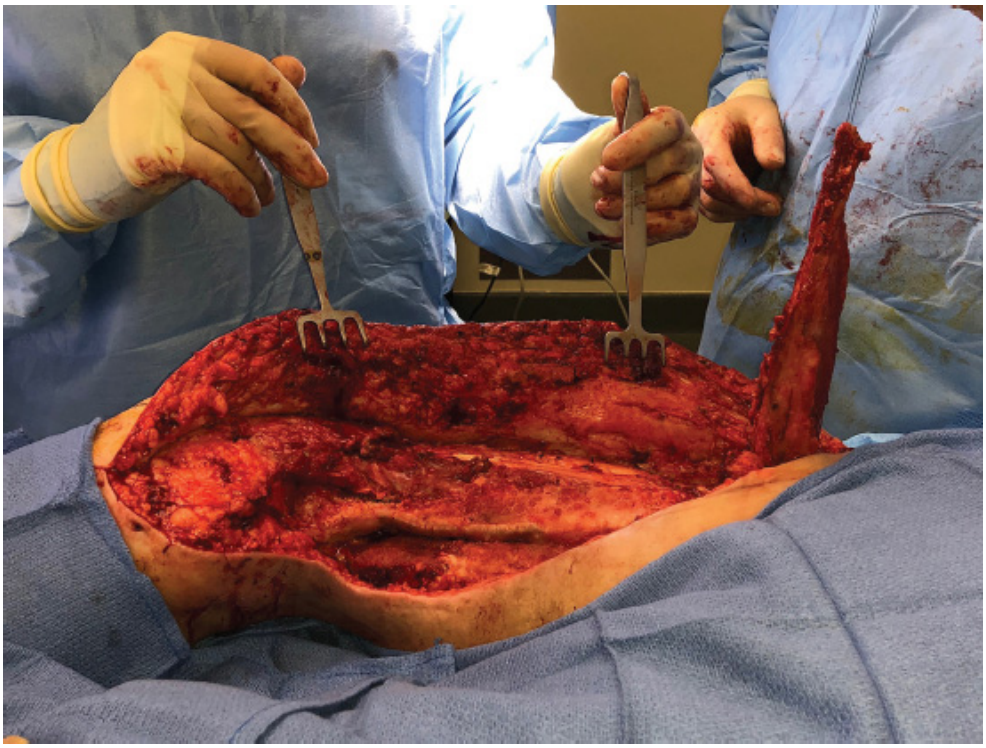

Figure 107.5 Pedicled rectus femoris flap to cover exposed vascular structure.

Table 107.4 Workhorse Muscle, Myocutaneous, and Perforator Flaps

Flap	Myocutaneous	Perforator	Common Uses
Temporalis	No	No	Orbital and intraoral reconstruction, facial reanimation (pedicled flap)
Pectoralis major	Yes	No	Intraoral and neck reconstruction; reconstruction of sternal defects (muscle only)
Latissimus dorsi	Yes	Yes	Breast reconstruction, neck reconstruction, free flap for very large defects
Rectus abdominis	Yes, including TRAM	Yes, including DIEP	Breast reconstruction, sternal reconstruction, reconstruction of groin defects, free flap for medium-sized defects
Gluteus maximus	Yes	Yes, including SGAP	Ischial pressure sores, sacral pressure sores, SGAP used for breast reconstruction
Biceps femoris	Yes	No	Ischial pressure sores
Tensor fascia lata	Yes	No	Trochanteric pressure sores, abdominal wall reconstruction
Gracilis	Yes	Yes	Perineal reconstruction,

			vaginal reconstruction, facial reanimation (muscle free flap), free flap for small defects
Rectus femoris	Yes	No	Infected hip wounds, abdominal wall reconstruction
Medial gastrocnemius	Rarely	No	Knee defects, proximal third tibial defects
Soleus	No	No	Middle third tibial defects

DIEP, deep inferior epigastric perforator; SGAP, superior gluteal artery perforator; TRAM, transverse rectus abdominis myocutaneous.

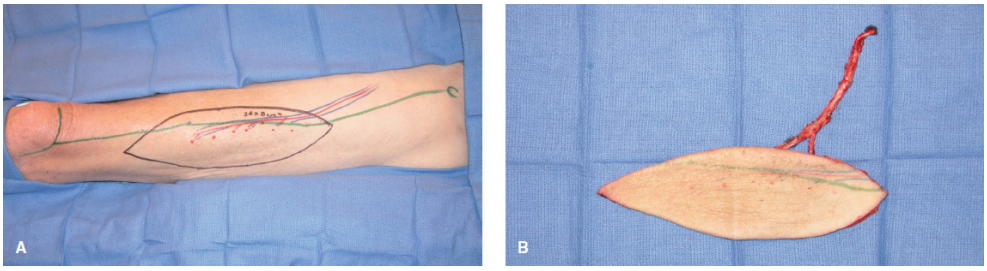

Figure 107.6 **A:** Anterolateral thigh flap designed on the leg and (**B**) free flap dissected out and ready for transfer.

Microvascular Free Tissue Transfers

Perhaps the most important innovation in reconstructive surgery is the development of microvascular surgery. The use of pedicled flaps limits the distance to which the flap can be moved. Historically there were a number of procedures developed to facilitate the movement of tissue to a site distant from the donor site. All of them require multiple operations and are not very efficient. An example of this is the so-called "walking flap" where a soft tissue flap is elevated and sutured into the form of a tube. It is left in situ for a few weeks to allow local vessel conditioning to ischemia. It is then

divided at one base and then "walked" to the next site where it is again sutured to a new site to allow vascular ingrowth. This process is repeated until the flap arrives at the site of the initial wound defect. With the wide use of microsurgery all of these adjunctive procedures are now of historical significance only. It is now felt that any tissue with an axial blood supply and a pedicle vessel of 1 mm or greater can be used for a reconstructive procedure. Now there is a trend to supermicrosurgery, a technique of dissection and anastomosis of small vessels ranging from 0.3 to 0.8 mm. This technique that has been developed over the last 20 years has revolutionized the fields of lymphedema treatment and soft tissue reconstruction.

The basic principle of microsurgery is that circulation can be established in the harvested tissue using microvascular anastomoses between the axial vessels, artery and venae comitantes in the flap and local vessels at the site of the wound. The vascular anastomosis, performed with 8-0 or 9-0 suture, is often done under the microscope or some surgeons prefer loupe magnification. Loupe magnification may move things along faster since there is less time expended in the setup of the operating scope. Obviously these procedures require a very high level of expertise and specialized equipment. However, the survival rate for free tissue transfers is greater than 95%. The ability to move large pieces of tissue, including composite tissues of skin, subcutaneous tissue, muscle, bone, and even sensory and motor nerves is really only possible using microvascular techniques. The movement of these tissues from distant sites means that the surgeon does not need to rely on local tissues for reconstruction and can move out of the zone of injury. Radiation, scar from previous surgery or damage from high-energy trauma are no longer a problem because the transfer of tissue is from a site outside of these problems (**Fig. 107.6**, ALT free flap). It cannot be stressed too strongly that microvascular surgery has changed reconstruction of head and neck oncologic defects with the ability to transfer composite grafts and bowel. Lower extremity limb salvage is much more predictable using microvascular free flaps. As stated earlier fasciocutaneous perforator free flaps have largely replaced musculocutaneous and muscle flaps. The most commonly used flaps are the anterolateral thigh flap (ALT), deep inferior epigastric artery perforator (DIEP), and the smaller radial forearm free flap.

The ALT is now a common first choice for head and neck reconstruction that does not require bone. The DIEP has totally changed the approach to

breast reconstruction often supplanting the TRAM flap.

The ubiquitous application of microsurgery has led to the evolution of new techniques that could not be imagined before. The ability to create prelaminated composite tissue flaps, whereby bone and other tissues can be embedded in a tissue flap and allowed to mature and become vascularized at the distant site and then be transferred with its own vascular supply represents a new approach to complex wound reconstruction. The incorporation of biologic and nonbiologic materials, even 3D printed constructs, to act as a scaffold for the application of stem cells and the eventual development of new tissues, is the exciting future of reconstructive surgery. The principles of microvascular reconstruction and immunomodulation for solid organ transplantation have opened up the field of vascularized composite allotransplantation (VCA). The use of these techniques for upper extremity and face transplantation are two areas of application. The inherent problems associated with the antirejection medications and the problem of chronic rejection are still limiting factors in the wide application of these new and exciting options on the frontier of reconstructive surgery.

PEDIATRIC PLASTIC SURGERY

Concern about interference with normal growth makes correction of pediatric deformities a four-dimensional challenge. Microsurgical precision as well as familiarity with brain development, developmental milestones, and acquisition of language are necessary to manage the spectrum of congenital, neoplastic, or traumatic deformities encountered in the 5 pediatric population. Additionally, familiarity with dysmorphology, genetics, dental organogenesis, otolaryngology, and the distinct growth trajectories of commonly affected structures define the scientific boundaries of this subspecialty. Surrounding oneself with a multidisciplinary team of specialists in those fields is common practice and the concentration of skills in the plastic surgeon places them in a central role.[16,17]

Congenital Anomalies

Cleft Lip and Palate

With an incidence of 1 in 650 live births approximately (7,000 new cases per year),[18] clefts of the lip and/or palate are the most common congenital anomaly in the United States. The clefting anomaly is along the midline of the posterior soft and hard palate, and branches laterally anterior to the incisor foramen, involving one or both anterior palate, alveolus, lateral incisor, lip vermilion and phitral column, nostril floor, and lateral pyriform aperture. Viewed from below, they map to a Y-shape (**Fig. 107.7**), with various involvements of each limb. They are thought to result from failure of fusion along the maxillary prominences and the lateral and medial nasal prominences within the first branchial arch and frontonasal process between the 6th and 12th week of gestation.[19,20] Correction of this anomaly is often staged, with ongoing debate about timing and techniques (**Table 107.5**). Tightness across a repair, extent of denuded bone surfaces, and early surgery adversely affect future growth. Conversely, early repair of the soft palate musculature may improve speech outcomes. Surgical tenets of avoiding straight line repair over the lip and soft palate, avoiding or minimizing lateral "relaxing" incisions over the hard palate, and meticulous technique under optical magnification are widely adopted (**Fig. 107.8**).

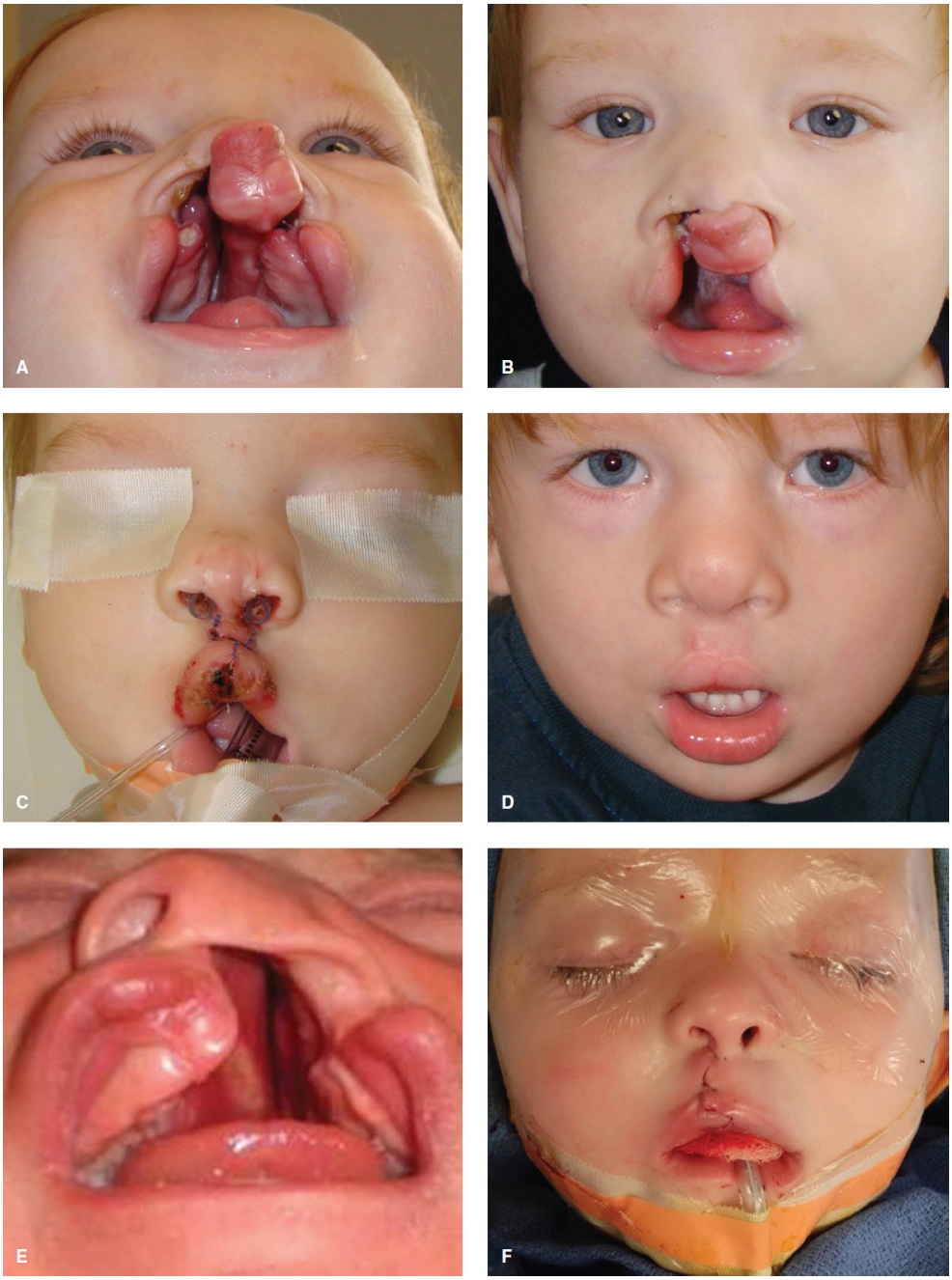

Figure 107.7 **A, B:** Bilateral cleft lip and palate, the complete expression of the anomaly. The maxillary palatal shelves are separate from each other and from the vomer in the midline. The oral and nasal cavities are communicating. The orbicularis oris muscle is discontinuous and inserts abnormally over the lateral pyriform. The nose is severely deformed and the anterior part of the maxillary arch is outside of the oral cavity (premaxillary escape). **C:** Intraoperative view of the completed repair, overcorrecting certain structures and undercorrecting others to account for differential future growth "Repair in the fourth dimension."[21,22] **D:** Results at 4 years post operatively. **E:** Unilateral cleft lip and palate, a misnomer since the unaffected side is secondarily deformed. **F:** The abnormally inserted

orbicularis oris musculature is reoriented and interdigitated, the lip skin, mucosa, and nose are reconstructed using anthropometric landmarks as a guide, placing scars along anatomical lines (philtral column) and avoiding linear scars.

Table 107.5 Stages of Repair for Complete Cleft Lip and Palate

0–3 mo	Presurgical orthodontics[a]
3–6 mo	Cleft lip repair
9–12 mo	Cleft palate repair
3–6 yrs	Pharyngoplasty or palatal lengthening[a]
7–9 yrs	Alveolar bone graft
10–12 yrs	Rhinoplasty and lip revision[a]
16–18 yrs	Orthognathic surgery[a]

[a]Optional or as indicated.

While the major surgeries are mostly completed in the first year of life, the child is followed by a multidisciplinary team until skeletal maturity in late teens (**Table 107.6**). The clefting anomaly affects major components of human communication systems, including hearing mechanism, speech musculature, and nonverbal communication using the facial musculature. Secondary revision surgery and esthetic procedures in this population challenge the surgical armamentarium of the Plastic Surgeon. In craniofacial surgery, “nothing short of perfection is acceptable.”

Table 107.6 Members of a Cleft Team
Plastic surgery
Otolaryngology
Orthodontics
Speech and language therapy
Genetics
Pediatrics
Behavioral/developmental pediatrics
Audiology
Oral surgery
Social worker

Craniosynostosis

The incidence of craniosynostosis is estimated around 1 in 2,500 live births. The condition arises due to premature fusion of the calvarial intramembranous sutures and/or the base of skull enchondrosis. The former condition is usually isolated, while the latter often syndromic. When multiple sutures are involved, elevated intracranial pressure is a concern, while base of skull suture involvement results in proptosis with risk of corneal exposure, nasopharyngeal airway restriction, and severe facial deformity (**Fig. 107.9**).[24]

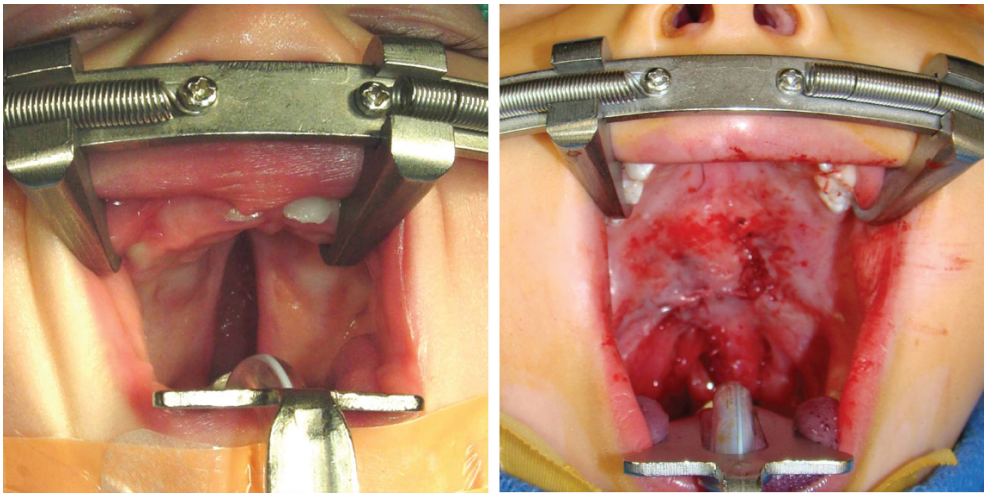

Figure 107.8 Cleft palate repair using a double-opposing Z-plasty technique.[23] The levator levi palatini muscle is abnormally inserted over the posterior palate shelf, and needs to be disinserted and rearranged into a sphincter configuration. The mucosal surfaces are lengthened using Z-plasty principles to prevent or minimize linear contracture. "Relaxing incisions" along the gingival edge of the palate facilitate repair but lead to severe secondary growth deformities and can be avoided in most cases. Cleft palate repair is a unique technical challenge due to anatomical space constraints and microsurgical precision needed. The vast majority of patients can expect a normal deglutition and speech mechanism using current techniques. **Left:** before, **right:** after palatoplasty.

Figure 107.9 Syndromic craniosynostosis: Crouzon syndrome. Calvarial sutures and base of skull enchondrosis fuse prematurely, resulting in restricted growth of intracranial volume and oropharyngeal spaces. Elevated intracranial pressure, proptosis with poor globe protection, and obstructive apnea can be corrected surgically by combined frontal, facial, and mandibular (FFM) advancement using distraction osteogenesis. **Above**, before, and **below**, after combined FFM with cranial vault expansion.

Restriction perpendicular to a suture results in overgrowth parallel to its axis generating seven distinct patterns of deformity (**Fig. 107.10**) distinguishable from the more common pattern of deformational plagiocephaly.

Intracranial volume doubles in the first year of life, and adds another volume between 12 and 42 months, reaching about 85% adult size, at which time growth rate slows down markedly. Afterward, growth of the intracranial compartment by resorption of the inner cortex and apposition of new bone on the external cortex is thought to be sufficient to compensate for absence of growth across suture lines. Based on these observations, surgical correction of synostosis is often performed between 6 and 12 months. Earlier surgery is

technically easier but may result in insufficient overcompensation, thus increasing the risk of secondary surgery. Surgical correction can be done by remodeling of large portions of the calvarial vault (**Fig. 107.11**). Alternatively, a more limited release of the affected suture can be done, followed by remodeling using external molding orthosis ("helmeting") or implanted expansion springs.

Microtia

Microtia is defined as partial or near-total absence of the external ear, often accompanied by atresia of the external auditory canal. The middle ear is variably affected, but the inner ear is often intact. The most important functional aspect of reconstruction is early restitution of hearing using band-held bone conduction hearing aids. This can be switched to a bone-anchored device after reconstruction of the external ear to avoid interference with local flap options. Drilling and relining of the external auditory canal is sometimes complicated by the position of the facial nerve in the middle ear, and has yet to produce consistent audiologic results.

Reconstruction of the absent pinna has significant psychosocial benefits to the affected child. Children seem to have poor compliance with bone-anchored external ear prostheses, while acceptance is much higher in adults. Options to replace the missing ear fibrocartilage framework include prosthetics (porous polyethylene, silicone) or autogenous rib hyaline cartilage. Coverage options include the temporoparietal fascial flap covered by skin grafts, or a retroauricular pocket of glabrous skin. A commonly practiced technique involves a custom-carved autogenous rib cartilage framework buried in a retroauricular pocket of glabrous skin and elevated secondarily to create a retroauricular sulcus. This technique has been used since the 1950s and is in constant refinement.[21] Although the pinna is 85% adult size by age 4 to 5 years, reconstruction often is deferred until 7 to 10 years of age to allow for development of rib cartilages. A template of the unaffected ear is made, reversed, and transposed to the affected side to an anthropometrically correct position. The anterior, cartilaginous portion of ribs 5 to 8 is harvested preserving as much perichondrium as possible. These are carved into a two- or three-layer cartilage framework emulating the external ear anatomy, with some modifications to accentuate contour, notably

in the scapha. The earlobe is often present and is transposed into correct position, while the cartilage framework is implanted into a subcutaneous pocket in the existing glabrous skin. Suction drainage and external pressure dressings are critical to emergence of the desired anatomy (**Fig. 107.12**). The retroauricular sulcus is secondarily created by elevation of the framework, placement of a retroauricular wedge of cartilage, and coverage with a fascial flap and skin grafting.

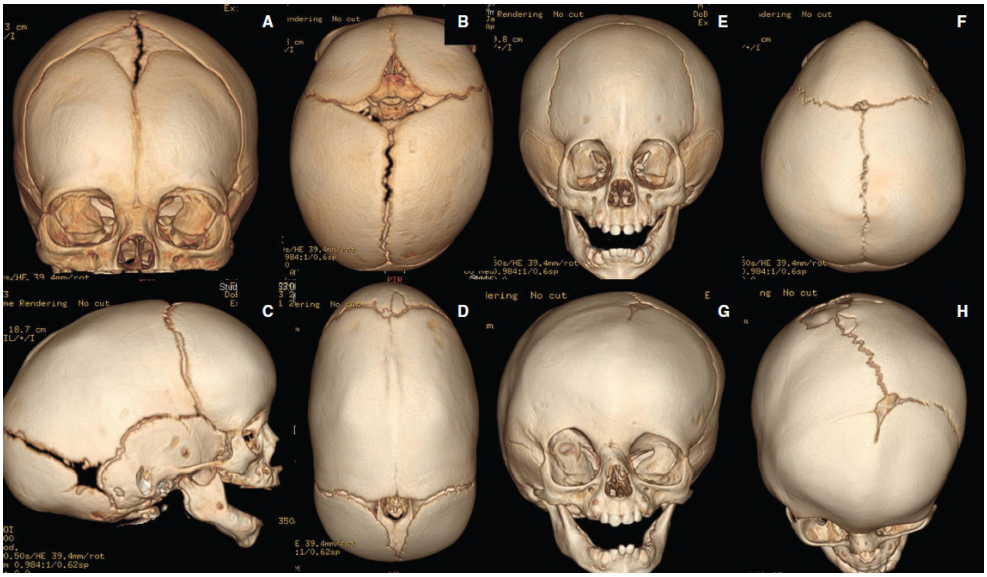

Figure 107.10 Isolated craniosynostoses: (**A**) frontal and (**B**) vertex view of normal suture configuration in an infant. The occipital skull flattening is due to positional deformation (deformational plagiocephaly). **C**: Lateral and (**D**) vertex view of the most common isolated premature synostosis of the sagittal suture, resulting in an elongated skull (dolichocephaly). **E**: Frontal and (**F**) vertex view of premature fusion, likely intrauterine, of the metopic midforehead suture resulting in a triangular head shape (trigonocephaly). **G**: Frontal and (**H**) vertex view of unilateral fusion of the right coronal suture resulting in asymmetry of the forehead and right orbit, and secondary bulging of the left parietal and right midface (right unicoronal synostosis).

Figure 107.11 Multiple suture synostosis in an infant, before and after total cranial vault remodeling. The risk of elevated intracranial pressure increases exponentially with the number of sutures involved. **Left,** before and **right:** after cranial vault remodeling.

Figure 107.12 Lobular-type microtia with near total absence of the pinna and external auditory canal. The lobule is often present, but maloriented. A vestigial cartilaginous remnant is present and needs to be carefully excised preserving overlying skin. Facial nerve, facial soft tissues, temporomandibular joint, ocular tumors, squamosal synostosis, and vertebral and other anomalies are sometimes present. Reconstruction involves harvesting an often large amount of autogenous rib cartilage that is carved into an ear framework based on a template of the contralateral ear. The framework is implanted under existing skin, and elevated secondarily.

Childhood Tumors

While pediatric malignancies are often encountered and may require extensive craniofacial approaches (**Fig. 107.13**), common tumors are usually benign and include hemangiomas, dermoid cysts, pilomatricomas, and melanocytic nevi.

Hemangiomas typically involute spontaneously but should be distinguished from the similar-looking vascular malformations. Hemangiomas respond to propranolol in spectacular fashion and this has changed their management markedly in recent years. Symptomatic hemangiomas that fail to respond to propranolol, or if they involve an orifice, block vision or breathing, or distort a cartilaginous structure such as nasal cartilages or tarsal plates

require surgical treatment (**Fig. 107.14**). Vascular malformations are treated according to their nature by surgical debulking, sclerotherapy, or pulse dye laser. Complete extirpation is usually not feasible due to extent of the anomaly (**Fig. 107.15**).

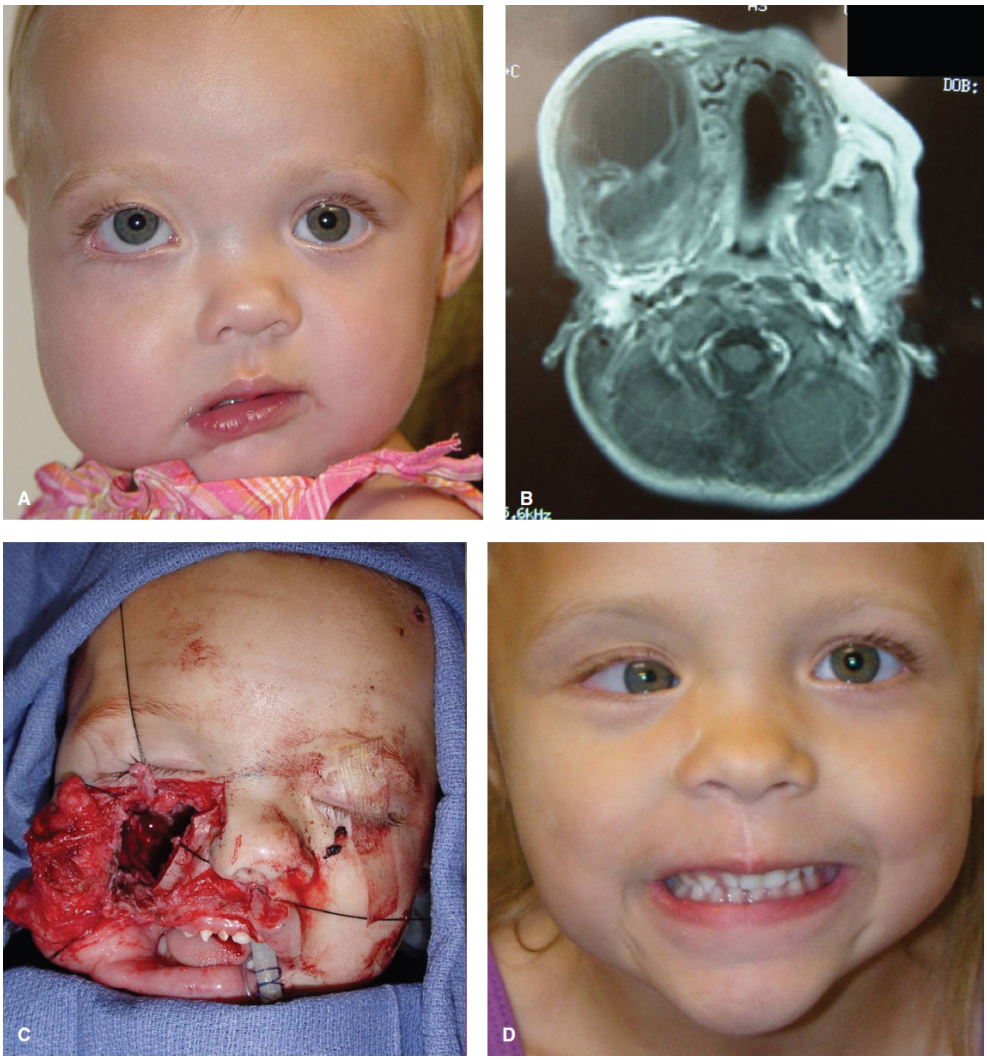

Figure 107.13 Childhood tumors sometimes require complex craniofacial approaches. This child with a large ganglioglioma of the pterygomaxillary space and medial orbit (**A**, **B**) was approached with a (**C**) Weber–Ferguson approach. Secondary deformities are carefully minimized with choice of approach and use of autogenous tissue for reconstruction (**D**). Multimodality treatments result in their own secondary growth restrictions.

Congenital melanocytic nevi are often a psychosocial concern but only large ones are thought to carry a risk of malignant degeneration. Management options include direct excisional biopsy, serial excision, or tissue expansion

(**Fig. 107.16**).[25] Excision and skin grafting often results in significant deformity, but may be needed for its expediency in cases of associated malignancy or severe atypia. Depigmenting lasers or chemical peels can improve cosmesis in cases where excision is prohibitive but may impede detection of an underlying malignancy.

Traumatic Deformities

Simple lacerations are appropriately managed in the emergency setting; however, compound injuries often require specialized care.

While most simple childhood fractures are treated by closed reduction, complex and compound fractures are a particular challenge. They require meticulous anatomical reduction of the involved segments, accounting for the hidden greenstick deformity, and the competing impetus of limiting soft tissue and growth center disruption while providing anatomical reduction and sufficient fixation. Long-term growth sequelae are a concern (**Fig. 107.17**).[26]

Figure 107.14 **A:** Bleeding nasal hemangioma resulting in 1.2 total blood volume transfusion prior to arrival. **B:** Hemostasis obtained using multiple large tacking sutures. A forehead flap is marked on the forehead. **C:** At the completion of excision, the nasal cartilages are splayed and will require repositioning. **D:** After transfer of the forehead flap.

Dog bites and lawnmower injuries produce devastating soft tissue defects that require the full spectrum of plastic surgery techniques. Facial soft tissue loss is particularly hard to replace in a child due to the lack of regional redundancy.

HAND AND UPPER EXTREMITY SURGERY

Hand surgery is a discipline shared by General Surgery, Plastic Surgery, and Orthopedic Surgery. Regardless of background, the trained hand surgeon should have a thorough understanding of 6 bony and soft tissue physiology and be able to diagnose and treat traumatic and nontraumatic conditions of the hand utilizing the advancements in imaging, microsurgery, and wound management. Successful outcome of complex hand reconstruction also depends on frequent postoperative vigilance and on competent postoperative hand therapy. The following section will show examples of common hand conditions due to trauma, congenital, or acquired causes. It is by no means a comprehensive review.

Nomenclature

Nonambiguous nomenclature is important for clarity. Avoid numerical identifiers. Some refer to the thumb as the first finger and the index finger as the second finger, while others refer to it as the first finger and the small finger as the fourth finger. Use instead: thumb, index, middle (long), ring, and small (little). For the phalanges, identify them by name: proximal, middle, or distal phalanges and NOT by numbers: P1, P2, or P3. The numbering of phalanges is confusing, as it is not obvious which bone P1 or P3 refers to: Is P1 the distal or the proximal phalanx? It is more confusing for the thumb, as there is no middle phalanx. So is it unclear which bone P2 refers to. For the metacarpals, the numerical system can be used, though the author recommends name descriptors to avoid confusion: thumb, index, ring, or small metacarpal bone. For laterality, use “radial” to identify the side of the hand or finger closer to the radius, rather than lateral. Use “ulnar” for the side closer to the ulna, rather than medial. This avoids confusion, particularly if the hand is rotated during the examination and not in anatomic position. Using “palmar” is more easily understood than “volar.” “Dorsal” is used for the back of the hand.

Figure 107.15 **A:** Lymphatic malformation of the right cheek, nasolabial fold, and upper lip. Overgrowth of the affected area is a common finding. **B:** After debulking using multiple subcutaneous and transmucosal approaches. Often, long-term improvement in form and function can be achieved with such methods. **C:** Large lymphaticovenous malformation of the left lower extremity, in the setting of Klippel–Trenaunay syndrome. **D:** Post debulking, improved contour is noted. This was done prior to orthopedic correction of overgrowth of the upper tibial metaphysis for improved postoperative fit of external splints and orthoses.

Anatomy and Examination

The hand at rest has a natural flexion cascade with each adjacent ulnar-sided finger slightly more flexed (**Fig. 107.18**). Any alteration to this can suggest a flexor or the extensor tendon rupture or laceration. At the wrist, the flexor carpi radialis and the palmaris longus tendon should also be visible. The thenar and hypothenar eminences should be full, and if either is flat, this can suggest nerve or musculoskeletal pathology. The fingers should be sensate, warm, and well vascularized. Evaluate the hand for disturbances in posture, skin, color, contour, and function.

Figure 107.16 **A:** Giant congenital melanocytic nevus of a large portion of the occipital scalp (40% total scalp area). **B:** During active tissue expansion of the unaffected scalp. **C:** After first-stage excision and flap advancement. Secondary expansion will be needed for complete excision.

Infection

Common hand infections include cellulitis, paronychia, deep space abscesses, and suppurative flexor tenosynovitis.

Cellulitis

It is an infection involving the dermis usually due to an abrasion, puncture, or a systemic infection (**Fig. 107.19**). Symptoms include increased warmth, erythema, and lymphadenopathy. For early and mild cases, it can be treated with warm compresses, elevation, removal of foreign body if present, and antibiotics. *S. aureus* and group A beta-hemolytic Streptococcus are the common organisms found. Cellulitis associated with an abscess requires incision and drainage, antibiotics, and wound care until resolution.

Paronychia

It is an infection of the lateral fingernail fold (paronychium). An eponychia is an infection of the dorsal nail fold (eponychium). If both the lateral and dorsal nail folds are involved, it is called a runabout infection. Paronychia occurs due to a break in the nail fold from trauma, hangnail, manicure, or nail biting. The most common organisms are *S. aureus* or oral anaerobes. Symptoms include swelling, erythema, and pain. With progression, there is fluctuance and purulence, and drainage from the nail fold. If severe, a paronychia can progress to a cellulitis ascending into the finger, hand, or forearm. Initial treatment for early paronychia consists of warm soaks, oral antibiotics, and splinting. Surgery is necessary if pain increases or worsening of fluctuance and purulence. Under digital block and a digital tourniquet, incise through the nail fold at the fluctuance. Send the fluid for culture and irrigate the wound with saline. Place a wick into the incision and dress with dry gauze and splint × 1 day. The patient should remove the dressing the following day and begin washing the finger and the wound twice a day with soap and warm water followed by a light gauze until the infection has resolved. We recommend oral anti-staphylococcal antibiotics for about 5 days.

Figure 107.17 **A:** Orbital dystopia secondary to untreated fracture of the left zygomaticomalar complex and orbital roof 2 years prior to presentation. Although most pediatric fractures can be treated with closed reduction, orbital roof fractures sometimes result in secondary deformities due to the pressure of the growing brain. Note the reflex head tipping to maintain binocular vision and harmonize visual and vestibular somatosensory orientation signals. **B:** Post–orbital wall reconstruction and translocation of the malar complex. Secondary strabismus surgery is typically deferred for a few months.

Figure 107.18 In its resting repose position, notice that the middle finger is more flexed than the index, and the ring more flexed than the middle, and the small finger more flexed than the ring. This is referred to as the "natural cascade."

Figure 107.19 Cellulitis of right hand. Note the erythema and swelling on the dorsal right hand, the index, and middle fingers. The *blue line* on the dorsal mid forearm represents the extent of the erythema upon presentation 1 day earlier, prior to intravenous antibiotics.

Figure 107.20 Deep space infection of the Thenar space.

Deep Space Infections

They occur in approximately 5% to 15% of all hand infections. There are six potential deep spaces defined by fascial separations: four in the palmar hand (thenar space, midpalmar, hypothenar space, and interdigital web space), one in the dorsal hand (the dorsal subaponeurotic space), and one in the volar forearm (Parona space). The most common organisms are *S. aureus* and Streptococcus species. Penetrating trauma is the most common cause. Other possibilities include contiguous spread from an adjacent deep space infection, subcutaneous abscess, or pyogenic flexor tenosynovitis. The hand is swollen and tender (**Fig. 107.20**). Active and passive finger motion results in severe pain. The swelling and purulence may be more noticeable dorsally because the dorsal skin has higher compliance. Should a deep space infection be suspected, CT scan is helpful to confirm and delineate the location and extent of the infection. Surgical drainage should be done by a hand surgeon in the operating room.

Suppurative Flexor Tenosynovitis

It is an infection within the potential space of the flexor tendon synovial sheath between the proximal borders of the A1 annular pulley at the distal metacarpal neck to the insertion of the flexor digitorum profunda (FDP) distal to the A5 pulley. The small finger sheath is continuous with the ulnar bursa, and the thumb flexor sheath is continuous with the radial bursa. Penetrating trauma is the most common cause followed by hematogenous dissemination from an adjacent infection (**Fig. 107.21**). The most common organisms are *S. aureus* and Group A Streptococcus. Mixed organisms and gram-negative bacteria are possible pathogens in intravenous drug users, diabetics, or in immunocompromised patients. The infection within the synovial sheath destroys the almost frictionless gliding surfaces causing scarring and tendon adhesions, thus early diagnosis and aggressive treatment is important. Kanavel first described the symptoms in 1925.[27,28]

Today his descriptions are known as the cardinal signs of Kanavel used to diagnose the infection. They are: (1) exquisite tenderness over the path of the flexor sheath; (2) marked symmetrical swelling of the finger described as "sausage shape"; (3) flexed posturing of the affected fingers; (4) pain on passive extension of the involved finger(s).

Treatment of early infection (24 to 48 hours) remains nonoperative with immobilization, elevation, and high-dose empiric intravenous antibiotics for *S. aureus* and Group A Streptococcus. Failure to improve, infection greater than 48 hours' duration, and gross purulence are indications for surgical intervention. Surgery is aimed at removing the purulence within the synovial sheath by open incision and irrigation. This should be done under general anesthesia and by a hand surgeon in the operating room.

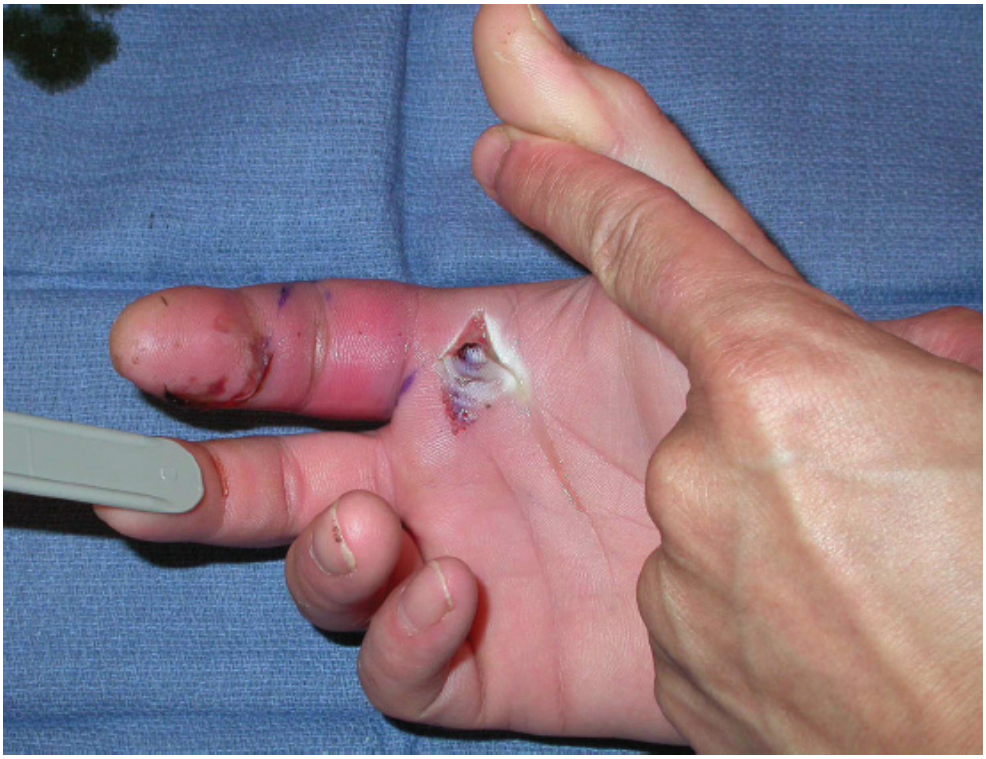

Figure 107.21 Note the fusiform swelling in the index finger with a flexed posture.

Other Infections

They include septic arthritis and human and animal bites (**Fig. 107.22**). Septic arthritis should be the diagnosis of exclusion, as many medical conditions such as gout and pseudogout may mimic an infection with joint pain, warmth, and erythema. Joint aspiration with Gram stain, white count, and culture of the fluid is done for definitive diagnosis. Human and animal bites are treated similarly with aggressive irrigation and debridement and directed antibiotics.[29]

Trauma

Trauma is the most common reason why patients come to the Emergency Department to be evaluated for hand concerns. Be sure to get three-view radiographs of the hand (PA, oblique, lateral). If the radiographs are equivocal and clinical suspicion is high for a fracture or abscess, get a CT scan.

Soft Tissue Injuries

Fingertip Injuries

These are common injuries resulting from recreational or 'industrial activities. If no bone or tendon is exposed, the wound can be treated with secondary intention, skin grafts, or be repaired with avulsed skin, if available, as a composite graft. If bone is exposed, the bone can be shortened slightly or it can be repaired with a local flap such as a V-Y flap (**Fig. 107.23**).

Figure 107.22 Marked erythema on the dorsal wrist due to a cat bite.

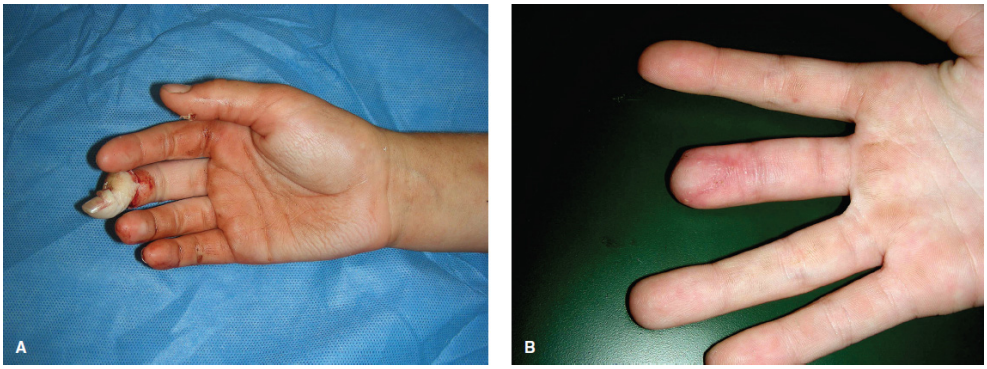

Figure 107.23 The distal right middle finger (**A**) was avulsed and was not suitable for replantation. The exposed DIP joint was closed with a V-Y flap (**B**) shown at 1 month postoperatively.

Nail Bed Injuries

The hallmark of a nail bed injury is a subungual hematoma that can be associated with an underlying distal phalangeal fracture. The pressure within the confined space caused by bleeding results in severe pain. The hematoma evacuation is done for pain relief. Previous teaching was that if the hematoma was 25% of the nail bed surface or larger, that the nail should be removed and the nail bed repaired. Recent studies showed no noticeable difference in the outcome between hematoma evacuation versus nail removal and nail bed repair, though there was an increase in cost by four times in the nail bed repair group.[30]

Nail bed repair could be done using medical adhesives (cyanoacrylates) instead of fine sutures. It has been shown that there is no difference in outcome between suture repair and medical adhesive for nail bed injuries.[31]

For hematoma evacuation, most recommendations have been to use an ophthalmic cautery for trephination. The author's preferred method is to decompress the hematoma using a freer elevator to detach the nail plate from the underlying nail bed at the area of hematoma using gentle sweeping motion starting at the edge of the nail and advancing forward until the hematoma drains. The nail is trimmed shorter. This method allows for improved passive drainage with gravity, rather than expecting the hematoma to drain dorsally against gravity through the trephinated nail. This method also avoids the possibility of iatrogenic nail bed injury, which can occur with the cautery or the biopsy punch.

Tendon Laceration

Causes of tendon ruptures are usually due to penetrating trauma by knife or ballistic injury. High-energy blunt trauma can cause closed tendon ruptures.

Flexor Tendons Lacerations

Generally, when the laceration is deep on the palmar surface, both the tendon(s) and the neurovascular structures are damaged in the fingers. On examination, there would be a visible laceration with loss of the natural cascade with decreased sensation to the finger distal to the laceration (**Fig. 107.24**). If one artery is lacerated, the other digital artery maintains perfusion. If both are lacerated, there is generally sufficient dorsal collateral circulation to keep the finger viable, unless there is vascular compromise from vascular injury, gross wound contamination or an associated open fracture. Tendon repairs can be done electively within 1 week of the injury.

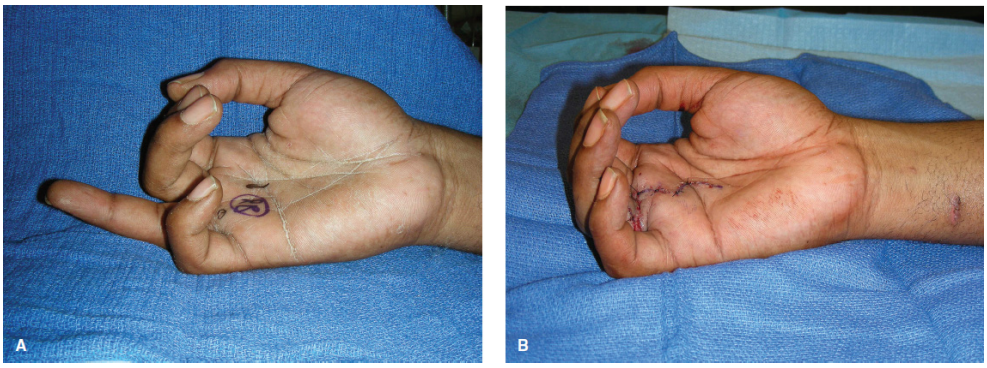

Figure 107.24 **A:** Zone II FDP and flexor digitorum superficialis (FDS) and digital nerve lacerations. Note the loss of the natural cascade at rest with the ring finger completely extended. **B:** Normal cascade reestablished after flexor tendon repair.

Figure 107.25 Mallet fracture with the extensor tendon still attached to the dorsal proximal distal phalanx. If there is more than 25% of the articular surface involved, most would recommend operative treatment.

If the penetrating trauma occurs in the forearm, the injury can appear deceptively benign and these require operative exploration as multiple tendons, ulnar or radial nerves, and arteries can be damaged. Postoperatively, protect the hand and the forearm with a dorsal splint with ongoing hand therapy starting 1 week postoperatively.

Extensor Tendon Laceration

Unlike flexor tendon lacerations, the lacerated ends of extensor tendons generally do not retract away from each other due to their attachments to adjacent structures. Most injuries are due to penetrating trauma, though closed injuries can result in: (1) mallet finger which the extensor tendon ruptures from the distal phalanx without a fracture or with a fracture consisting of a small dorsal piece of the distal phalanx (**Fig. 107.25**). The inciting cause is an axial load to the distal finger with forced flexion at the distal interphalangeal joint (DIP) or (2) a boutonniere deformity due to rupture of the central slip from the dorsal proximal phalanx. Most of the time, both the mallet and the boutonniere are treated with splints for 4 to 6 weeks. Open injures with extensor tendon lacerations are repaired in the operating

room. Postoperative splinting and hand therapy are critical in successful outcomes.

Fractures

There are 27 bones in the hand and 2 bones in the distal forearm that are subject to fractures. Most of the hand and finger fractures, including some Salter–Harris fractures, can be treated nonoperatively if nondisplaced. Surgery with reduction and internal fixation (with plate/screws or K-wires) (**Fig. 107.26**) is required for fractures that are unstable, displaced, or in bones known to have poor outcomes without surgery (e.g., Seymour fracture in the pediatric population and scaphoid proximal pole fracture). Fractures associated with a communicating wound require operative irrigation and stabilization. The benefit of hardware stabilization is the ability for early mobilization to decrease joint stiffness that can result in poor hand function.

Replantation

The first successful finger replantation was reported in 1968 by Komatsu and Tamai.[32]

Since then, guidelines have been established with the indications for replantation being: (a) thumb amputation, (b) multiple finger amputations, (c) pediatric population amputations, and (d) mid hand, wrist, or distal forearm amputations. Contraindications for replantation are (a) associated life-threatening injuries, (b) multiple-level injuries in the amputated part, causing injuries along the vessels and preventing blood flow into the replanted part, and (c) severe contamination of the part, which carries a high probably of systemic infection if replanted. Replantation of a single digit due to the tight fibro-osseous tunnel in flexor zone 2 is generally not recommended due to tendon adhesions that results in poor postoperative function. Single finger amputation in zone 1 is not contraindicated as stiffness in the DIP joint is well tolerated and nerve regeneration to the replanted part is rapid due to the short distance from the injury to the distal nerve receptors, and the appearance of the replanted finger is superior to that of an amputation.

Figure 107.26 Intraoperative fluoroscopy of intramedullary K-wire fixation of displaced index and middle metacarpal shaft fractures.

Complex Hand and Forearm Reconstruction

There are times when multiple tissue components (bone, skin, nerve, tendons, artery) are injured and require reconstruction. A systemic approach is required for the reconstruction to restore form and function. If secondary to trauma, initial treatment should address critical life or limb-threatening issues such as limb ischemia or compartment syndrome, followed by debridement if needed of any nonvascularized or infected tissue; then once

the soft tissue is free of contaminant, formal reconstruction of bone, tendon, nerves, and soft tissue deficits should begin (**Fig. 107.27**). For soft tissue reconstruction of wounds after tumor resection functional reconstruction, which includes tendon and nerve reconstruction, may be needed as well as soft tissue coverage.

Congenital Anomalies

Limb development can be interrupted by environmental or genetic factors during critical first trimester of embryo development.

Syndactyly

The term syndactyly is derived from the Greek prefix *syn-* ("with, together") and the Greek noun *daktylos* ("finger, digit"). Syndactyly has an incidence of 1 in 2,000 to 3,000 live births and is the most common of the congenital hand anomalies.[18,33] It is a failure of differentiation in which the fingers fail to separate into individual appendages, which usually occurs between the sixth and eighth weeks of in utero development.

Figure 107.27 Self-inflicted right distal forearm wound with lacerated FCR, radial artery, median nerve, and complete transaction of the FDS and FDP. He arrived to the hospital several days after his injury and was taken to surgery. His wounds became infected (**A**) requiring several operative debridements (**B**) and with allograft placement (**C**), eventual pedicled right groin flap and divided 3 weeks after placement.

Syndactyly can be an isolated occurrence or it can be associated with other abnormalities, for example, polydactyly, cleft hands, ring constrictions, and craniofacial syndromes such as Apert syndrome (**Fig. 107.28**). It is a shared feature of more than 28 syndromes, including Poland, Apert, and Holt–Oram syndromes.[34] Syndactyly is classified as simple when only the skin is involved and complete if it extends to the finger tips (**Fig. 107.29**) and incomplete if it is short of the tips. If there is bone and nail plate involvement it is classified as a complex syndactyly.

Figure 107.28 Complex syndactyly associated with Apert syndrome.

Untreated, syndactyly can impair finger and hand function, particularly if it is complete or involves the border digits (e.g., small and ring or thumb and index) as there is differential finger growth rates, which can result in finger deviation or joint contractures.

If it is complex or border digits are involved, surgical release can be done as early as 6 months of age and at about 1 year of age or later if only the central rays (middle or ring fingers) are involved in a simple complete or incomplete syndactyly. Bilateral operations can be done with reasonable patient tolerance up to about 12 to 18 months of age as both upper extremities need to be immobilized for about 2 weeks. Only one side of each digit is released should both sides of a finger be involved in the syndactyly, with the other side released at a later time—generally 6 months later. This is to avoid devascularizing the digit. Well-vascularized skin flaps are designed in a zigzag fashion on the dorsal and palmar surfaces with a trapezoidal-shaped dorsal skin flap to resurface the sides of the fingers and the web space. Full-thickness skin grafts from the groin are used to resurface the areas not covered by the flaps.[18]

Polydactyly

Polydactyly or extra fingers can occur on the ulnar side of the hand (postaxial), the radial side (preaxial), or the central rays (central).

Postaxial polydactyly has variable presentation. It can be mild and presents as a nubbin on the ulnar side of the little finger usually at the level of the proximal phalanx or as a rudimentary finger attached by a small neurovascular pedicle**.** Sometimes the accessory finger is partially or fully developed. The incidence is 1 in 143 live births in Africans and African Americans and has a strong hereditary component (often autosomal dominant) without other associated syndrome. In the Caucasians at about 1 in 1,339 live births and the patient should be evaluated for other syndromes.[35] Treatment may be as simple as observation if it is a nubbin or may require either bedside ligation with surgical clips or formal surgery for reconstruction for the more fully formed digit.

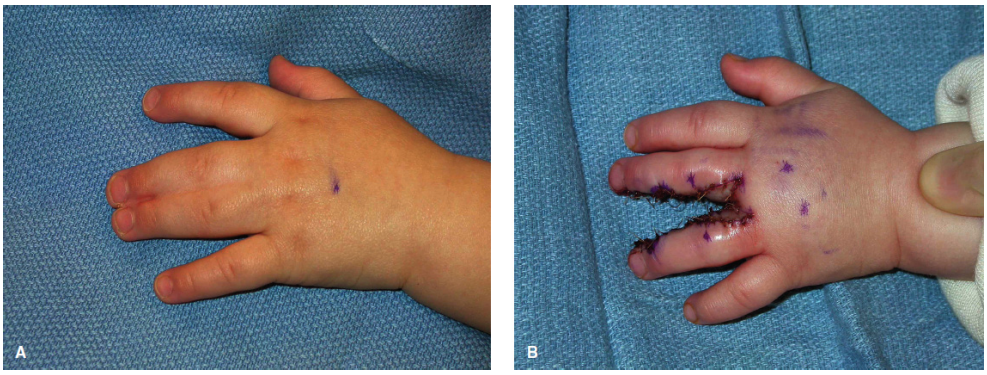

Figure 107.29 A 12-month-old child with a complete simple syndactyly between the middle and ring finger in the left hand (**A**) before and (**B**) after syndactyly release.

Preaxial polydactyly involves the radial side of the hand and usually the thumb. It occurs in 1 of every 3,000 live births and may be associated with several syndromes (Holt–Oram syndrome, Fanconi anemia).[36]

Central Polydactyly

It is rare and can present as incomplete to fully formed index, middle, or ring fingers. Central polydactyly can be associated with syndactyly, cleft hand, and other syndromes.[37,38]

Surgery is geared to removing the duplication and reconstructing the hand to make it appear and function as normal as possible.

Thumb Hypoplasia and Agenesis

Thumb hypoplasia occurs 1 in 100,000 live births with 50% being bilateral and in unilateral presentation the right is more commonly involved. It has a spectrum of presentation from mild diminution to complete absence. In 60%, it is associated with longitudinal deficiencies of the radius. In the embryo, the thumb develops between the fifth and eighth weeks at the same time as the cardiovascular system. Insults at this time can alter thumb development and 86% of hypoplastic thumb have associated abnormalities of the cardiovascular, neurologic, and hematopoietic systems. Thumb hypoplasia is associated with at least 30 syndromes (Holt–Oram syndrome, VACTERL association, and thrombocytopenia absent radius [TAR] syndrome).[39,40]

Thumb hypoplasia categorization has five types. Originally described by Muller in 1937, it has been improved by Blauth, Buck-Gramcko in 1967 and Manske in 1995.[41]

- Type I: Normal components are present but small with underdevelopment the abductor pollicis brevis and opponens pollicis. Type 1 does not require surgical intervention.[42,43]
- Type II: There is a contracted web space between the thumb and index finger with more severe hypoplastic thenar muscles. There is laxity of the metacarpophalangeal joint (MP) ulnar collateral ligament with joint instability. Surgery is aimed at restoring thumb stability and intrinsic function with opponensplasty and deepening of the web space usually with a four-flap Z-plasty.
- Type IIIA and type IIIB: The metacarpal bone is less developed and the thenar musculature is nearly absent. The thumb has poor function. Type IIIA has a stable carpometacarpal (CMC) joint, type IIIB does not. Treatment for type III is based on the presence of a stable CMC joint. Type IIIB requires reconstruction and type IIIB requires amputation and index finger pollicization.
- Type IV: The thumb is floating and also called pouce flottant. Similar to the appearance of a postaxial polydactyly, the thumb is incompletely formed and is attached to the adjacent finger by a neurovascular bridge.

There are no thenar muscles and no extrinsic tendons. Type IV in the Western countries is usually reconstructed with index finger pollicization.

- Type V: There is no thumb and requires pollicization.

Acquired Conditions

Osteoarthritis

There is gradual loss of cartilage in the joint with age. The DIP joints and the thumb CMC joints are more prone to be affected. Treatment is geared toward pain relief while maintaining function. This can be achieved by oral anti-inflammatory medication, gentle range of motion while avoiding strenuous activities, and splinting as needed. Should this not work, intra-articular steroid injection can provide temporary relief. Surgical treatment is reserved as the last option. For the DIP joint as there are no effective joint replacement, arthrodesis remains the only surgical option. For the proximal interphalangeal (PIP), MP, and the CMC joints, both arthroplasty and arthrodesis can be done. In general, for the thumb, arthroplasty with autologous tissue (generally the flexor carpi radialis) remains the preferred method for reconstruction (**Fig. 107.30**).

Tendinitis

Inflammation of tendons, from increased physical activities, can cause inflammatory synovitis around the tendon, decreases tendon glide and increases resistance, causing pain and decreased range of motion. When this occurs in the hand involving the flexor tendons at the A1 pulley, this results in trigger finger. Recommendations are for decreasing aggressive activities, rest/splinting, oral anti-inflammatory medications, steroid injections, and A1 pulley release if nonsurgical intervention is unsuccessful. Injections typically offers 30% efficacy.[44]

Figure 107.30 A 59-year-old with left thumb pain. Preoperative radiographs show advanced left thumb CMC joint arthritis.

When the tendinitis occurs in the first dorsal extensor compartment, this is known as De Quervain tenosynovitis. Treatment is similar to trigger finger.

Peripheral Nerve Compression

In the upper extremity, all three major nerves (radial, ulnar, and median) can be compressed at anatomic narrowings along their paths. The median nerve can be compressed at the carpal tunnel, resulting in numbness in the palmar thumb, index, middle, and radial side of the ring finger. With progression and severity there is weakness in thumb opposition and thenar atrophy. Less often the median nerve can be compressed by the pronator teres. The ulnar nerve is usually compressed at the cubital tunnel at the elbow more than at Guyon canal at the ulnar wrist. The radial nerve can be compressed in the dorsal proximal forearm, known as radial tunnel syndrome if the compression is more proximal and involves the extensor carpi radialis longus (ECRL) tendon nerve branch and the dorsal radial sensory nerve or posterior interosseous nerve (PIN) syndrome, if it involves only the PIN. Like tendinitis, treatment is nonsurgical. Evaluation with electrical studies (EMG/NCV) is recommended to confirm and to establish degree of compression and if there is progressive decline in sensory or motor function, surgery is then recommended. Less-invasive release with endoscopic assistance is alternative to the traditional open techniques.[45]

Dupuytren

Dupuytren contracture is a condition where the localized nodules develop in the palmar fascia. These nodules can progress to longitudinal pretendinous cords spanning the base of the palm to usually the PIP joint restricting finger extension and can later cause fixed contractures at the PIP and MP joints. Though found in all racial groups, it is found more frequently in the Northern European population. There is usually a familial history and slight male to female predominance (ratio: 1.7:1).[46] Surgical excision of the cord used to be the mainstay for treatment until 2010 when the FDA-approved collagenase injections to alter the mechanical properties of the cord.[47]

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an autoimmune condition mediated by inflammatory cells that attack the synovial tissues in the body. Persistent synovitis in the joints results in articular damage and degradation of the soft tissue support at the joint and rupture of the overlying tendon.

Prior to the advent of effective biologic agent (immunosuppressant or cytokine modulators, e.g., Humira and Enbrel [these are trade names]), surgery was a main stay in the treatment of RA. The goals of surgery were for pain control and improved and restoration of function. It did that in three different ways: preventative, corrective, and salvage.[48] Preventative surgery included synovectomy may be used to avoid the sequel of synovitis such as pain, joint destruction, and tendon rupture. Corrective surgery included tendon transfer for tendon ruptures.

With progressive attenuation of the supporting joint structures at the wrist, there is radial deviation of the metacarpal and with destruction of the metacarpophalangeal MP joints; there is subluxation and ulnar deviation of the fingers at the MP joints. This results in pain and difficulty with finger flexion and extension MP joints and irreversible joint damage. Salvage procedure entails joint arthroplasty at the MP joints with silicone joints and wrist fusion (**Fig. 107.31**).

PLASTIC SURGERY OF THE BREAST

The breast is an anatomic feature that signifies empowerment, 7 helps define self-image, and contributes to sexuality as well as serving a functional role for lactation during pregnancy in females.[49] As such, patients frequently request both aesthetic and reconstructive procedures of the breast. These will be subdivided in the following sections: reduction mammoplasty, mastopexy, augmentation mammoplasty, gynecomastia reduction of the male breast, breast reconstruction, and transgender surgery. Breast dimensions and anatomical characteristics are important considerations for all surgical procedures and will be addressed first. Special consideration should be given to the current scientific climate related to breast implants and this will be addressed separately as it pertains to both aesthetic and reconstructive patients.

Breast Characteristics

Results of plastic surgery of the breast are impacted by several anatomical considerations. Breast size, shape, composition, vector, footprint, and

nipple-areola complex (NAC) orientation are important factors. Breast shape can be impacted by whether the meridians of the breasts are more parallel or divergent. Poor-quality skin (e.g., with striae) and a breast with relatively more adiposity than gland can lead to a softer, less full, "saggier" appearance. The superior border of the breast is variable in different patients leading to significant differences in breast appearance. Size can be relative to overall body habitus. Some breasts have more lateral fullness than others. The intermammary space differs between patients.[50,51] NAC orientation greatly impacts breast appearance. Ptosis (**Fig. 107.32**) is defined in **Table 107.7**.[52]

Reduction Mammoplasty

The main goal of a breast reduction is to decrease the volume, and therefore weight, of the breast to decrease associated aggravating symptoms while maintaining or improving breast appearance. Preoperative considerations relate to patient expectations for appearance and financial coverage of the procedure. Surgical considerations include incision, and subsequent final scar, position, pedicle orientation to supply blood to the NAC and preserve parenchyma, and management of the NAC. Postoperative considerations include wound care and imaging changes.

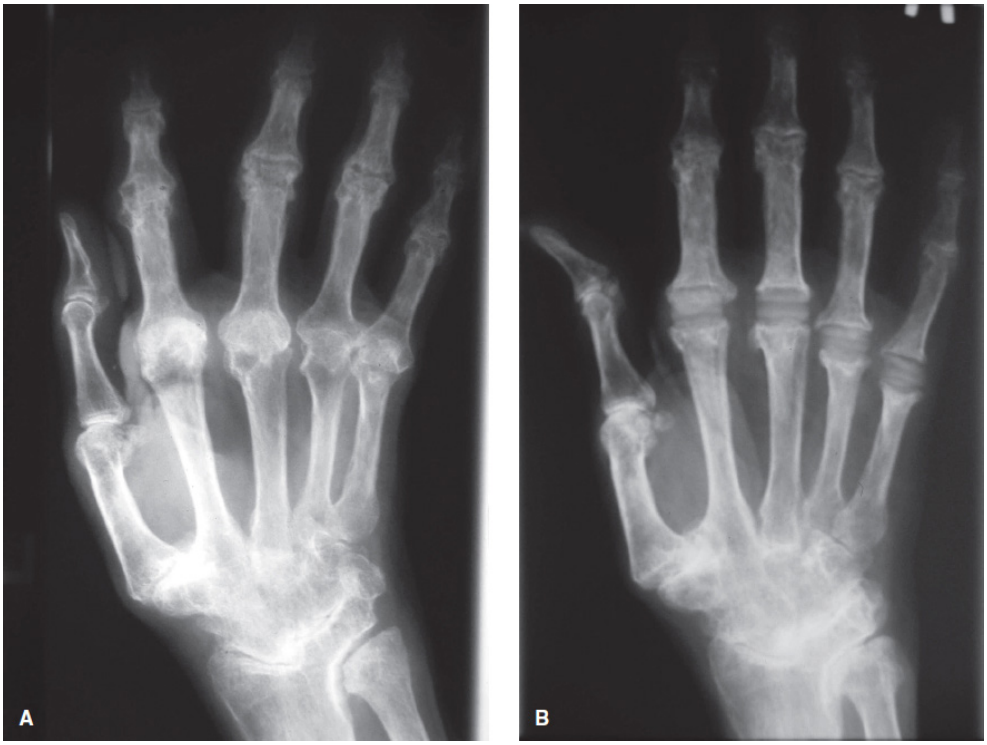

Figure 107.31 Preoperative (**A**) and postoperative (**B**) view of the right hand. Note the restoration of normal finger alignment.

Preoperative Evaluation

Patients seeking reduction mammoplasty often complain of neck and back pain, difficulty with the fit of clothes, management of breast mobility during exercise, grooving of the shoulders from brassiere (bra) straps, and recalcitrant rashes in the intertriginous folds. Most patients seek not just a smaller breast mound, but also a mound that is lifted with a footprint higher on the chest wall (rather than upper abdominal wall) and a NAC with less ptosis and reduced size (to match the overall smaller size of the breast mound).[53,54] A careful conversation must ensue regarding postoperative size preferences and inability to guarantee an exact size. Often the conversation will relate to bra cup size and should include counseling regarding the inexact nature of this methodology since bra cups are not standardized between companies and change with chest width (bra band size number). Many patients seek this procedure as a covered benefit through health insurance, and the surgeon should be familiar with various insurance criteria. A commonly used insurance coverage criterion relates to body surface area

calculated from height and weight, converted to a suggested weight of tissue to be resected through the Schnur table, though it is commonly believed that this table does not accurately convey a relationship between resected weight and symptom reduction.[55] A specific consideration in the preoperative workup is baseline imaging, and recommendations for baseline mammography relate to patient age and breast cancer risk factors.[56]

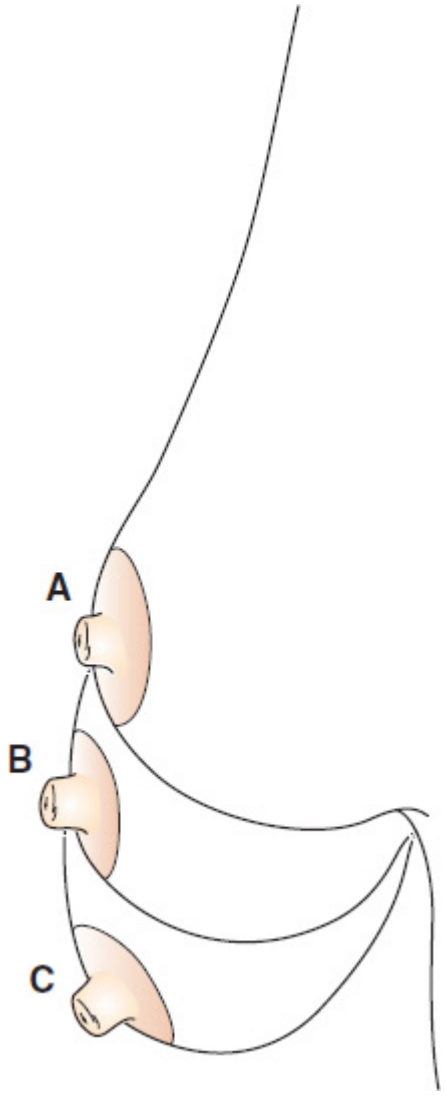

Figure 107.32 Breast ptosis. **A:** Mild. **B:** Moderate. **C:** Severe.

Surgical Approaches

Reduction mammoplasties can be done via a number of different approaches but the most commonly used are dermal parenchymal pedicles either

centrally or inferiorly based. The pedicle is designed to maintain blood supply and sensory function to the NAC. The widely used inferior pedicle technique (**Fig. 107.33**) produces an inverted "T"-shaped scar with the transverse portion in the inframammary fold. Many patients did not like this large scar. This led to the development of the vertical scar mammoplasty (**Fig. 107.34**). **Table 107.8** elucidates the typical components of breast reduction surgery.[53,54] Postoperative drain placement remains controversial. Several studies demonstrate no evidence of improvement in outcomes with drains, but common practice demonstrates high prevalence of ongoing drain usage in practice.[57] Most often this procedure is performed in an outpatient setting.

Table 107.7 Breast Ptosis Definitions[52]

Grade 1	Nipple at the level of the inframammary fold (IMF)
Grade 2	Nipple between the level of the inframammary fold and the lowest border of the breast
Grade 3	Nipple at the lowest border of the breast
Pseudoptosis	Breast gland hanging well below the IMF

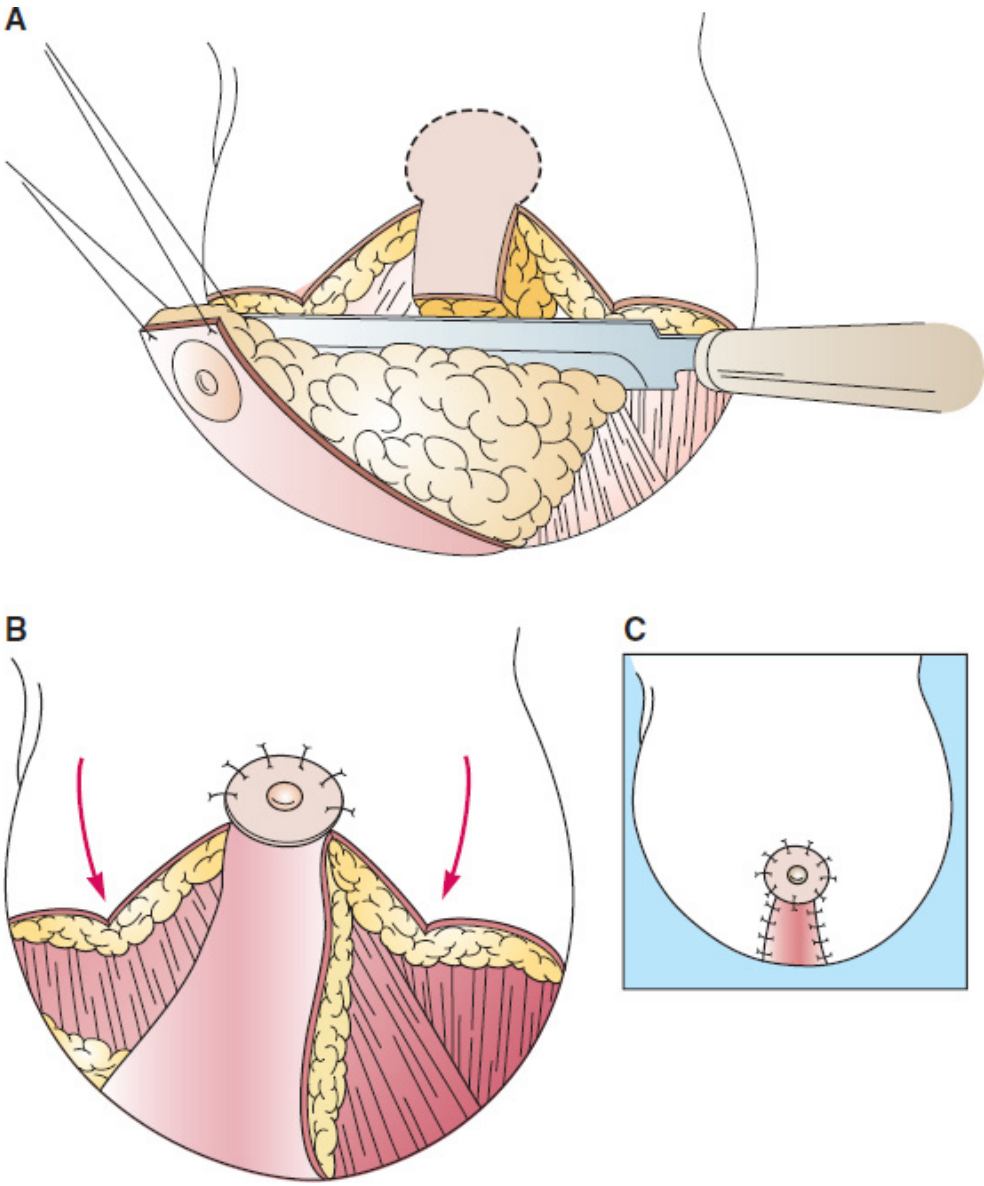

Figure 107.33 Inferior pedicle technique for reduction mammoplasty.

Postoperative Follow-Up

Patients overall demonstrate high rates of satisfaction and relief of symptoms following breast reduction surgery. However, complication rates, particularly wound-healing complications are relatively high and may require frequent clinic visits.[51,54] Imaging changes in mammography can include planar parenchymal scar, fibrosis, and fat necrosis, among other things (**Fig. 107.35**).[58]

Mastopexy

Mastopexy, or breast lift, is often considered by patients who have noted either ptosis of the NAC or pseudoptosis of the breast gland as defined earlier in this chapter. Preoperative discussions should clearly address the limitations of this technique, as the patient's baseline breast dimensions are not likely to change significantly. Namely, the patient is unlikely to achieve breasts that are separated more narrowly or widely. Neither is the patient likely to achieve significant upper pole fullness (often considered cleavage), since the upper border of the breast will be minimally changed and will likely still demonstrate a more natural "ski-slope" contour. Surgery *will* decrease ptosis and pseudoptosis and can remove some striae (stretch marks) resulting from weight or volume changes related to conditions like pregnancy, breastfeeding, or change in body habitus. However, skin quality that has predisposed to striae may predispose to further stretching of the breast skin envelope over time and decrease the longevity of the postsurgical results. Surgical approaches are similar to those discussed above for breast reduction, and the more minimal scar approaches are chosen more frequently for this surgery. NAC transposition is routinely expected, though risk of NAC loss or dysfunction is still present and should be discussed preoperatively.[59] Insurance coverage for this procedure is quite variable. Imaging considerations are similar to those for breast reduction, both pre- and postoperatively (**Fig. 107.36**).[56,58]

Augmentation Mammoplasty

Breast augmentation is designed to increase breast size and potentially influence breast shape and nipple position. Preoperative counseling is essential as decision for this surgery is most often driven by patient desire rather than strictly abnormal symptomatology or danger to health. Preoperative considerations relate to patient expectations and should include financial planning for likely future medical intervention related to the initial surgery. Intraoperative choices relate to material used for augmentation, incision (and, therefore, scar location), and manipulation of the pectoralis major muscle. Postoperative considerations relate to activities, garments, and future treatment.

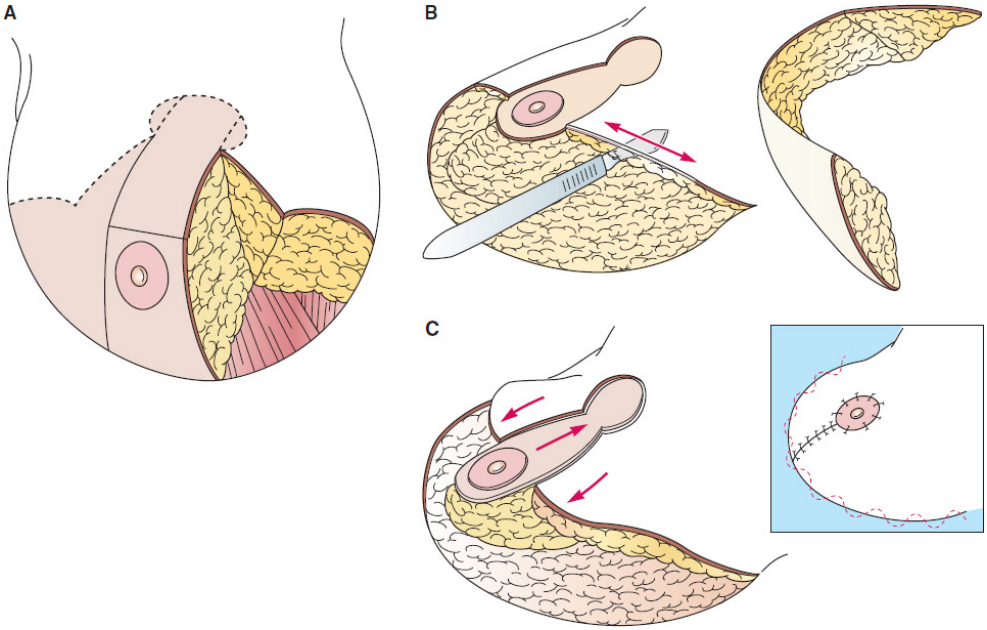

Figure 107.34 Central pedicle technique for reduction mammoplasty.

Table 107.8 Surgical Approaches for Reduction Mammoplasty[53,54]

Surgical Approach	Options	Considerations
Incision/scar	Periareolar (Scar only around the areola)	Scar only at junction of different types of skin so may be less visible, often used for smaller reductions because it allows for skin reduction in fewer dimensions, may distort areola or periareolar scar over time due to differential forces, areola may widen over time without permanent "blocking" suture
	Vertical ("Lollipop" scar: circle around the areola and vertical "stick")	Has risk of excess tissue or standing cone deformity at inferior most aspect of incision
	Inverted T ("Wise-pattern" or anchor-shaped scar adding scar along inframammary fold to vertical scar)	Used most commonly for largest reductions, healing concerns at "triple point" where vertical and inframammary scars meet
Pedicle	Inferior	Common choice, concern over pseudoptosis (bottoming out) of breast mound over time
	Superior	Often used with vertical skin incisions
	Superomedial	Often used in gigantomastia, considered to decrease risk of need for free nipple grafting
	Other	Lateral, superolateral, etc. could be

		used when technique is performed with lumpectomy for breast cancer in oncoplastic setting if common pedicles not feasible
Nipple-areolar complex (NAC)	Transposition	Most likely to maintain sensation, reactivity, functionality, and "normal" appearance of NAC
	Skin graft	More common in larger reductions with greater proposed nipple transposition distance, can be patchy in coloration, flat, nonreactive, and poor (if any) sensation
	3D tattoo	Considered a salvage technique if a NAC fails to survive

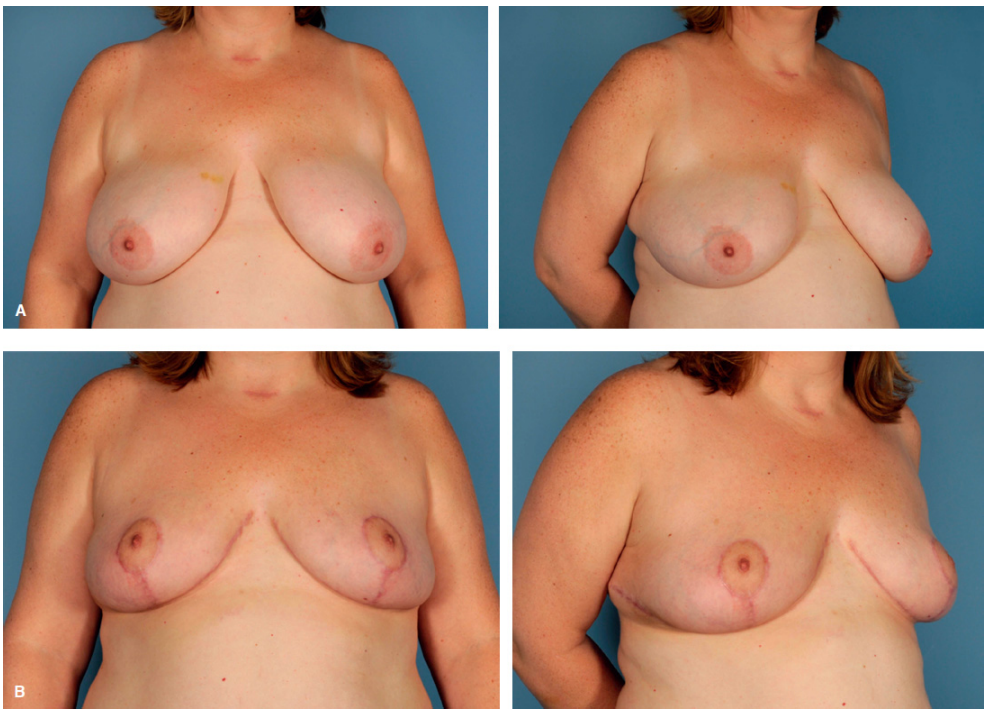

Figure 107.35 Wise-pattern bilateral breast reduction. **A:** Preoperative. **B:** Postoperative.

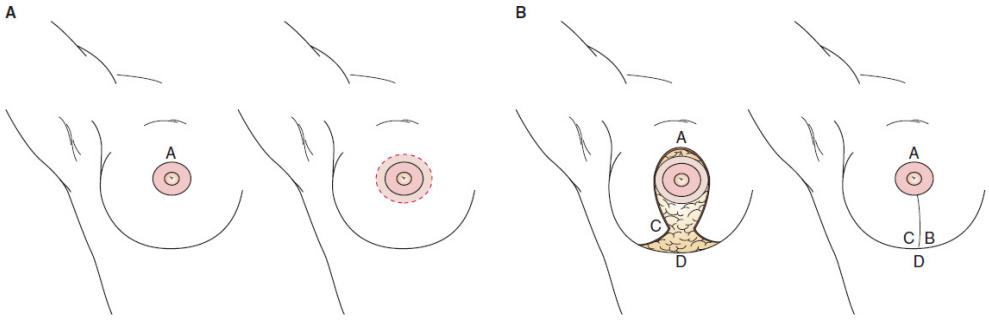

Figure 107.36 Mastopexy incisions. **A:** Circumareolar. **B:** Vertical.

Preoperative Evaluation

Patients should be assessed for the etiology of their interest in augmentation mammoplasty and their expectations for the impact surgery will have on their life situations. Goals related to overall size, lateral breast profile (e.g., the "hour glass" look), upper pole appearance (also known as "cleavage"), and noticeability of the result should be discussed. If prosthetic implants are planned, counseling should include the components discussed in a subsequent section on breast implants. Existing soft tissue quality assessed through a pinch test is important for surgical approach planning.[60] A specific consideration in the preoperative workup is baseline imaging, and recommendations for baseline mammography relate to patient age and breast cancer risk factors.[56] Patients planning to fund the augmentation without insurance intervention will need to understand that treatment of complications or subsequent likely maintenance surgery may not be covered by insurance policies either.

Surgical Approaches

Table 107.9 addresses the main choices related to surgical approaches for breast augmentation.[60,61]

Postoperative Follow-Up

As patients undergoing this surgery are concerned with appearance, surgeons must convey careful consideration of return to exercise and use of postoperative garments. Massage techniques and timing and scar therapies

may be important components of the postoperative period. Follow-up will likely be needed for prosthetic implants as they are not expected to last forever.[60] Important imaging considerations related specifically to breast implants are addressed in a subsequent section, and there may be changes to baseline breast imaging following breast implant placement (**Fig. 107.37**).[62]

Gynecomastia Reduction

Gynecomastia, or male breast enlargement, may have a variety of etiologies, including pubertal changes, hormonal abnormalities, medications, and more sinister causes such as testicular cancer. Assessing if and when to perform surgery is a critical component in the preoperative period. Surgical approaches differ significantly from those used for reduction of the female breast. Postoperative care remains important.

Table 107.9 Surgical Approaches for Augmentation Mammoplasty[60,61]

Surgical Approach	Options	Considerations
Incision/scar	Periareolar	Scar at junction of different types of skin considered minimally visible unless abnormal scarring occurs, requires dissection through breast gland
	Inframammary	Scar in fairly hidden location in most patient positions but through normally unmarked skin, IMF position may change with procedure
	Axillary	Somewhat remote, may make manipulation of surgical field more difficult
	Transumbilical	Remote from site, may make manipulation of surgical field more difficult
Implant placement	Subglandular	May help address a small amount of preoperative ptosis, may impact capsular contracture, increased visibility/palpability of implant if very thin soft tissue
	Partially submuscular	Multiple definitions, including "dual plane," considered to preserve surveillance imaging of gland more than subglandular approach
Augmentation material	Silicone implant	See "Breast Implants" section
	Saline implant	See "Breast Implants" section
	Autologous fat grafting	Use of liposuction to harvest slurry of tumescent solution, fat, oils, and other debris, followed by various

	fat separation techniques and injection of fat in small droplets throughout parenchyma of breast, imaging considerations as postoperative appearance is different than alternate augmentations

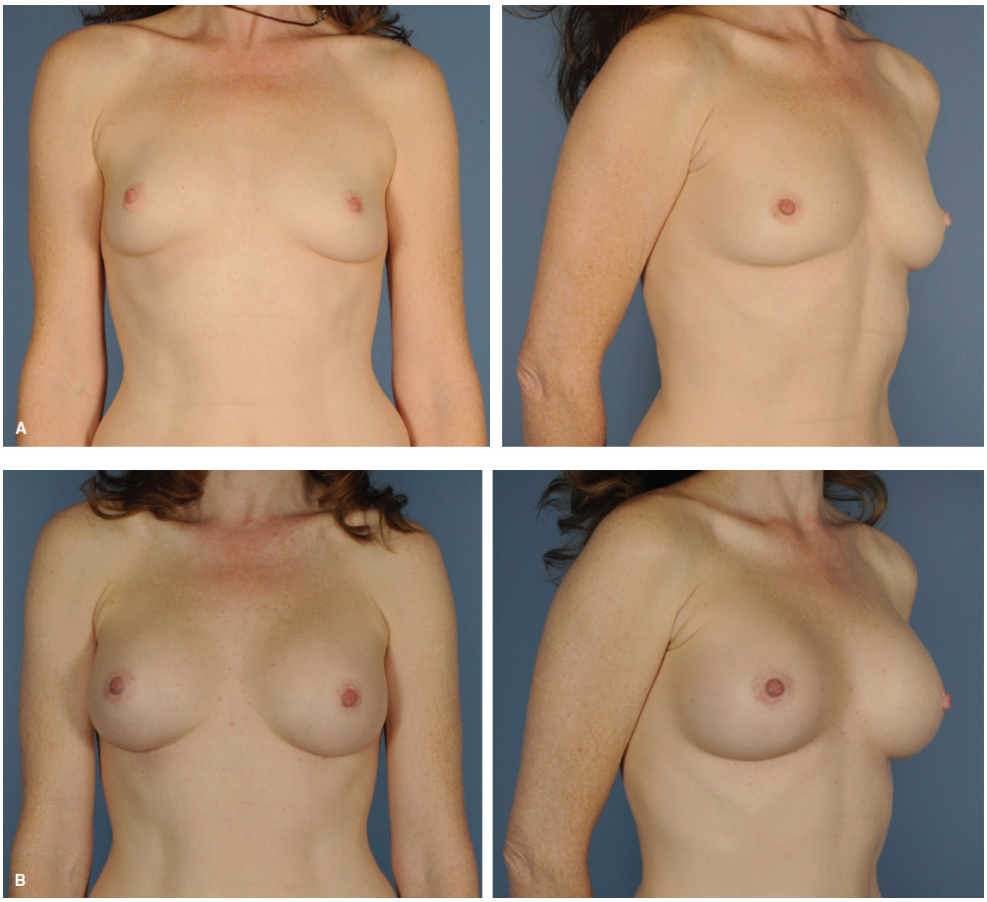

Figure 107.37 Breast augmentation via inferior mammary fold (IMF) incisions. **A:** Preoperative. **B:** Postoperative.

Preoperative Evaluation

Patients presenting for gynecomastia reduction are quite diverse. Some may be very young men, suffering from excess breast volume induced by pubertal changes in the recent past. Other patients have waited years to see spontaneous resolution of the peripubertal onset of disease without

improvement. Others may be of varying ages, complaining of breast tissue excess related to obesity, medications, or other medical conditions, including sinister causes such as testicular cancer. Given the complex etiologies, spontaneous resolution in some cases, and potential for nonsurgical interventions at times, careful coordination with other medical providers may be considered essential. Full medical history and physical examination and formal endocrinology workup should be considered preoperatively. Imaging may be necessary specifically related to the breast, particularly if asymmetry, irregularity, or mass increases the suspicion of male breast cancer.[63]

Surgical Approaches

Surgical approaches account for the increased visibility of the male chest (making scars less acceptable than in female breast reduction), the dense, fibrous, gritty nature of male glandular enlargement, and the expected male NAC position and size (drastically different than on the female breast). Many of the approaches have significant limitations. The more common approaches and their considerations are listed in **Table 107.10**.[64]

Postoperative Follow-Up

Routine postoperative care to follow healing is recommended. The diversity of surgical approaches necessitates a diversity of postoperative regimens. Scar therapy may be important given the visibility of the surgical site.

Breast Reconstruction

Breast reconstruction most commonly follows oncologic resection, but similar techniques may be applied after trauma or developmental irregularities. Preoperative considerations are many, and most importantly, must recognize the necessity of multi-disciplinary approaches for optimal outcomes. Surgical approaches are also multitudinous, regarding both technique and timing. Postoperative care largely focuses on complication minimization, recognizing the frequent need for adjuvant oncologic treatments.

Table 107.10 Surgical Approaches for Male Gynecomastia Reduction[64,65]

Approach	Consideration
Liposuction alone	Minimal scars, best used for gynecomastia with large adipose component and minimal skin excess
Marginal liposuction and direct periareolar excision of gland	Usually through partial periareolar scar, direct excision of gritty firm tissue under and around NAC with liposuction for feathering at margins, best if minimal skin excess
Amputation and nipple-areolar complex (NAC) skin grafting	Best for large amount of skin excess and NAC ptosis, scar for skin resection (transverse orientation) planned for subpectoralis muscle location often better tolerated than inframammary fold (IMF) since defined IMF in males is abnormal, direct excision of large amount of tissue in mastectomy-type approach, NAC position and size planned to match more "normal" male appearance, best if enough preoperative ptosis that NAC excision site is removed in resection of excess skin
Pedicled nipple transposition approaches	Variety of approaches, often uniquely designed for each patient to address moderate amounts of skin excess, tissue excess, and NAC ptosis, must take care not to apply female reduction techniques designed to "cone" the breast into a female shape

Preoperative Evaluation

Patients approach breast reconstruction with many different goals, including appearance optimization with and without clothes, sensation normalization,

scar minimization, and restoration of the feel of the breast to palpation.[66] Neoadjuvant and adjuvant cancer treatments including radiation therapy, chemotherapy, and previous surgery may alter surgical reconstruction options available. The surgical approaches span a diverse spectrum of complexity and technique, making medical comorbidities important considerations. Patients must understand that reconstruction most often requires staging with revisions to optimize the outcomes. Planning for repeated periods of decreased activities of daily living may be necessary. Various surgical techniques impact length of postoperative follow-up and potential for future necessary surgical interventions.[67–69] The delivery of this information occurs during a time in which the patient has other medical decisions to make which can impact survival and quality of life. Surgical planning must recognize the difficulty experienced by patients when confronted by the large amount of information and multiple decisions to be made and include future alternatives should complications arise or patients' preferences change.

Surgical Approaches

Table 107.11 addresses basic approaches to postmastectomy reconstruction technique.[67–72]

Table 107.11 Postmastectomy Breast Reconstruction Techniques[67–73]

Surgical Approach	Options	Considerations
Autologous tissue	Pedicled flaps (i.e., latissimus dorsi, thoracodorsal artery perforator [TDAP], rectus abdominus)	Requires donor site, often requires muscle sacrifice
	Free tissue transfer (i.e., rectus abdominus, deep inferior epigastric perforator [DIEP], superficial inferior epigastric perforator [SIEP], superior/inferior gluteal artery perforator [SGAP/IGAP], transverse/diagonal upper gracilis [TUG/DUG])	Requires donor site, perforator flaps designed to preserve muscle and minimize morbidity, longer surgeries with more inpatient requirements, more similar to natural breast tissue, maintenance surgeries not usually required after reconstruction complete
	Fat grafting	Minimal scarring at donor site, often requires multiple stages to achieve volume other methods accomplish in one surgery, often used as a revision technique
Implants	Tissue expander	Used as staging, temporary changeable volume implant with port for repeated transcutaneous access, can be prepectoral or subpectoral, recently the

		prepectoral location has been rapidly gaining popularity
	Implant (i.e., silicone vs. saline, round vs. anatomic, textured vs. smooth)	Likely requires maintenance surgery, requires adequate skin envelope, foreign body, shorter surgeries with fewer inpatient admissions, also can be prepectoral or subpectoral (see above), see "Breast Implant" section for further details
Biologics	Acellular dermal matrices	Used as an adjunct for tissue reinforcement, often used to reinforce the breast pocket, particularly with implant-based reconstruction or to reinforce the fascia at an autologous donor site (usually abdomen)

Timing is also an essential consideration in breast reconstruction. Ideally, all patients would have access to breast reconstruction counseling at the time of breast cancer diagnosis and initial treatment, but many patients present in delayed fashion after lumpectomy and radiation or mastectomy. Patients who have already undergone mastectomy who then desire reconstruction may consider tissue expansion followed by implant or autologous reconstruction or autologous reconstruction without expansion. Patients who present prior to mastectomy may consider immediate autologous reconstruction, immediate implant-based reconstruction, staging with a tissue expander, or planning for a delayed reconstruction.[67–69]

The application of free tissue transfer techniques has changed the approach to autologous breast reconstruction. The 8 use of pedicled rectus abdominis-based reconstruction, the TRAM flap, has given way to the widespread use of perforator flaps. The most widely used are based on the deep inferior epigastric perforators (DIEP). These flaps for the most part, spare the rectus abdominis muscle and create a breast mound from excess lower abdominal wall adipose tissue. The free flaps have proven to be quite hardy and tolerate radiation and chemotherapy well or can be staged as mentioned above.

Other cancer treatments may impact reconstruction choices. Radiation therapy increases wound healing complications, infections, and overall failures in implant-based reconstruction. Autologous reconstruction is most commonly planned, when possible, for after radiation, to deliver healthy soft tissue into a damaged area. Chemotherapy may alter the body's resistance to infections and may alter timing of reconstructive surgeries. Nipple-sparing procedures preserve the skin envelope and more of the natural breast architecture, but they allow for little manipulation of the skin envelope when irradiated and abnormal.[67,68]

Reconstruction after lumpectomy and radiation therapy is another consideration. If planned prior to lumpectomy, oncoplastic breast rearrangement techniques can be considered. These include reductions, lifts, and complex tissue rearrangements through various scar patterns. The contralateral breast may also be addressed for symmetry. Operating to reduce deformity after lumpectomy and radiotherapy has increased risks of complications related to issues such as wound healing and infections but may include techniques such as autologous fat grafting, implant placement, autologous flap reconstruction, or mastectomy and YYYreconstruction.[67,74]

Postoperative Follow-Up

Postoperative follow-up is usually frequent and occurs over time given the frequently staged nature of reconstruction. Postsurgical drains are often used. Complications like compromised skin, wound healing problems, infections, and seromas are encountered and can impact overall reconstructive success (**Figs. 107.38** and **107.39**).[67,69]

Transgender Surgery

Transgender surgery is increasing in frequency over time and will be more completely addressed elsewhere. A multidisciplinary approach to breast surgery in the setting of more global considerations of transgender health is considered important. Hormonal interventions are also important to include in the complete approach. Future cancer risk must also be addressed. Insurance coverage has greatly increased over time, expanding the reach of these techniques. Surgical approaches converting a female-appearing chest to a male-appearing chest are similar to those considered for gynecomastia surgery, particularly regarding scar location and NAC position and size. Converting a male-appearing chest to a female-appearing chest includes consideration of augmentation with special emphases on differences in baseline anatomy, breast gland amount and composition, pectoralis muscle differences, and potential staging due to stretch of tissue over time. Postoperative care remains important as discussed above.[75,76]

Breast Implants

Patient should be made aware of several factors including: predicted lifespan of implants, likelihood of leakage of contents over time, expectation of imaging and further surgery, and somewhat decreased ability to image as much of the breast tissue with mammography following implant placement. Anaplastic large cell lymphoma has been linked to breast implants and is under current active study. Breast implant–associated systemic symptoms (malaise, arthralgias, and many others) are also being reinvestigated, and at the current time seem to impact only small numbers of patients receiving implants. Patients will require counseling regarding smooth versus textured implants, silicone versus saline implants, and anatomic versus round implants. Current imaging recommendations for silicone implants should be discussed.[77–79]

AESTHETIC SURGERY

Plastic surgery at its core is a function of restoring structure and function. A principle such as "replace like with like" seems basic at face value; however, it is challenging on many levels as one can note from other sections of this chapter. A myriad of unique clinical issues must be addressed from scalp to toe and requires a full understanding of anatomy. In addition to the restoration of function in reconstructive plastic surgery, the discipline of plastic surgery encompasses aesthetic plastic surgery, colloquially termed "cosmetic surgery." The 9 quest to surpass normalcy and achieve "perfection" requires an artistic approach to medicine and is paramount in guiding patients who are seeking to enhance their own self-esteem and body image. In the process of undergoing these procedures, a functional benefit also may often result. After undergoing an abdominoplasty, repair of the rectus abdominis muscle diastasis has been noted to help patients improve posture, increase core strength, and decrease stress urinary incontinence—all sequelae of term pregnancy. A rhinoplasty improves the overall outward appearance of a patient's face, but also may improve nasal airway breathing.

No surgical discipline requires greater attention to the 10 patient's underlying psychological conditions/stability than aesthetic surgery. Carefully selected patients with realistic goals who have an appropriately executed procedure are likely to be satisfied in all facets. However, a patient poorly selected with unrealistic goals or elements of psychological instability may undergo a perfectly successful operation with an aesthetically pleasing outcome to an outsider but could be viewed as a colossal failure in the eyes of the patient leading to devastating consequences. Aesthetic surgery requires the surgeon to: pay meticulous attention to detail, carefully select patients, rigorously plan procedures, and precisely execute technically challenging procedures. Identifying the motivations of patients for undergoing the procedures is also important and through applying of sound surgical principles and technical expertise, the aesthetic plastic surgeon will experience lifelong career and personal satisfaction.

Cosmetic Procedures for the Head and Neck

Brow Lift

A natural sequela of facial aging is often brow ptosis. The dynamic nature of the frontalis muscle results in patients often contracting the muscle to elevate the brow to decrease the appearance of patient's ptosis. When left untreated, brow ptosis results in patients appearing fatigued, angry and/or aged. In severe cases, brow ptosis may cause visual field obstruction on upward gaze; correction of this deformity can produce dramatic aesthetic and functional improvements. Patients are often not aware of their brow ptosis and may present to the plastic surgeon's office complaining of "heavy eyelids." In many cases, the etiology of their complaint is brow ptosis rather than upper eyelid ptosis or dermatochalasis. These patients will require a brow life alone, or in conjunction with a blepharoplasty, to correct their aesthetic and functional concerns.

Figure 107.38 Staged bilateral implant-based breast reconstruction. **A, B:** Preoperative appearance. **C, D:** After tissue expansion. **E, F:** Final postoperative results after expander exchange for implant and nipple-areola complex tattooing.

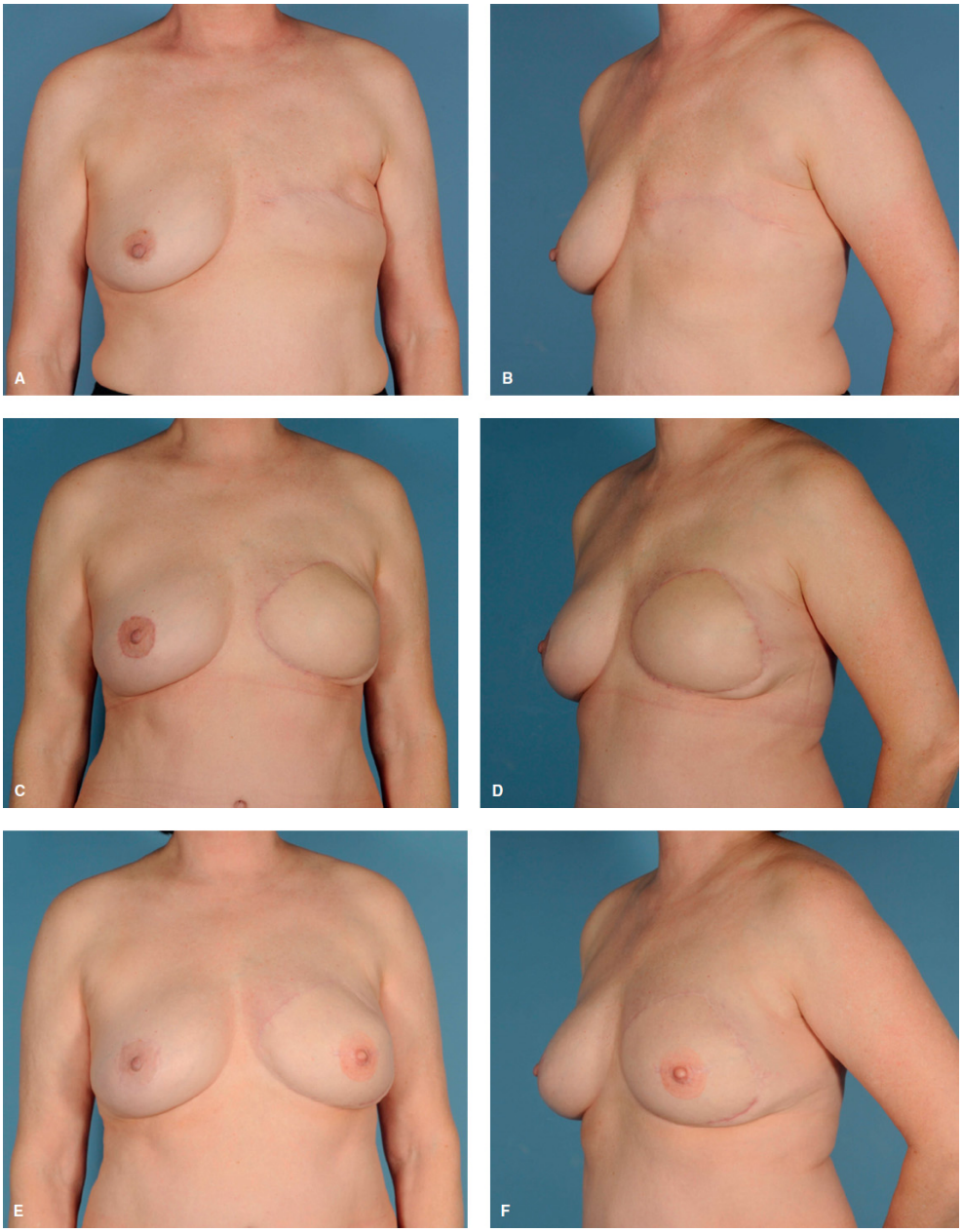

Figure 107.39 Delayed DIEP breast reconstruction. **A, B:** Appearance after mastectomy. **C, D:** Appearance after left DIEP flap reconstruction. **E, F:** Final result after tattooing of nipple-areola complex.[5]

Correction of brow ptosis can be achieved with either an open or endoscopic approach. The traditional open approach requires a bicoronal incision with resection of excess scalp or forehead. Unfortunately, this approach results in a lengthy scar, possible scar alopecia, and paraesthesia of the scalp and forehead due to transection of branches of the supraorbital and supratrochlear nerves. In addition, an open coronal brow lift in male

patients with a receding hairline or female patient with an elongated forehead requires resection of hair-bearing scalp moving non–hair-bearing forehead skin further posteriorly accentuated baldness. This tradeoff is not worth the aesthetic deformity of increasing the appearance of hairline recession. Techniques have evolved to decrease scar burden by performing temporal incision-only brow lifts. The limitations of this approach include minimal correction of central brow ptosis and medial eyebrow depression. To counteract the accentuation of a receding hairline from the bicoronal approach, an anterior hairline brow lift incision evolved which involves placing the incision at the junction of the hairline and forehead skin. Most male patients are not a candidate for this procedure as many men will experience elements of hairline thinning anteriorly. Female patients with elongated foreheads do well with this approach, however, are reluctant to wear their hair in a ponytail as they will likely expose a visible scar. Male patients can opt for a direct brow lift approach, which involves the surgeon selecting a deep horizontal forehead rhytid and resecting skin above or below landing the scar in the original rhytid. After 6 to 12 months of wound healing, the incision is often camouflaged within the natural crease. Finally, to reduce many of the complications associated with open approaches, the endoscopic brow lift was developed and has become the primary approach for repair of brow ptosis.[80] The endoscopic brow lift requires only three to five 1-cm incisions behind the hairline to gain access to the forehead and glabellar rhytids, producing less of an aesthetic deformity and limiting the amount of scarring. There is also evidence to suggest that the endoscopic approach produces a more lasting result than the traditional approach.[81] Finally, it has been reported that anesthesia of the forehead and scalp is significantly reduced when an endoscopic approach is utilized for correction of brow ptosis, as compared to an open coronal approach.

Endoscopic and open brow lifts may be performed under local or general anesthesia. Patients are marked preoperatively in the upright position. The desired brow position is at the level of the orbital rim in male patients and 1 cm above the orbital rim in female patients. The position of the brow in relation to the supraorbital rim changes from medial to lateral; the lateral brow should be more elevated than the medial brow. During an open brow lift, a coronal incision is made and the entire forehead it mobilized in a subgaleal or subperiosteal plane down to the orbital rim. The supraorbital

and supratrochlear nerves are dissected free of surrounding tissues and observed. The supraorbital muscle is resected if prominent glabellar rhytids are present. Excessive resection of the corrugator muscles will result in widening of the eyebrows in the midline. The periosteum is released at the level of supraorbital rim when a subperiosteal plane is utilized for mobilization of the forehead; the dissection is carried down to the level of the supraorbital rim when a subgaleal plane is used for forehead mobilization. The forehead is then elevated and redraped posteriorly, the redundant scalp is resected, and the wound is closed. In an endoscopic brow lift, incisions are made within the hair-bearing scalp at the midpupillary line and over the temporal fossa. The entire forehead flap is elevated under endoscopic guidance, the procerus and corrugator muscles are resected as necessary, and the forehead is retracted posteriorly. The forehead is then secured into its new position. Various methods of forehead fixation have been described including absorbable and nonabsorbable plates, screws, multipronged anchors, or cortical tunnels.[82]

Postoperatively, patients are instructed to avoid vigorous physical exercise for at least 6 weeks. Bruising and swelling are anticipated for the first 2 to 3 weeks following the procedure. The final result is not expected for at least 6 to 8 weeks following the procedure. Patients are instructed that the final scar appearance will mature between 9 and 12 months post surgery.

Rhytidectomy

Few areas of the body betray the age of an individual as greatly as the face. The negative impacts of aging process, gravity presence, solar exposure, and smoking are particularly manifested on the face. The loss of skin elasticity which lead to fine facial wrinkling and skin laxity can be attributed to ultraviolet radiation and tobacco. Aging and gravity result in gradual relaxation of the facial retaining ligaments producing midfacial ptosis, deepened and nasolabial folds, “jowling” along the mandibular border, and redundancy of cervical skin.[83] Many patients become aware of these aging features while reminiscing on old family photographs, as their youthful appearance consisting of high cheekbones, a sharp mandibular border, and smooth skin is more apparent. As the aging process continues and a patient reflects on his/her former features, he/she may lose self-confidence while

interacting in professional and social settings. This drop in self-esteem often leads one to consult with the plastic surgeon who will execute a facial rejuvenation plan in order to restore his/her youthful facial features. After this process is carefully completed, both the patient and surgeon will see gratifying results.

During the original consultation, the patient first outlines their surgical expectations and motivations, which are then evaluated by the surgeon. It is important that the concerns of the patient are reasonable and not out of proportion to their physical deformity. If this does occur, even a perfectly executed operation may still have an undesirable outcome in the eyes of the patient.

Many surgeons will refuse to perform a cervicofacial rhytidectomy in any patient who is actively smoking or utilizing any products containing nicotine. This is due to these patients having a significantly increased risk for developing postoperative complications, including skin flap necrosis, infection, or wound dehiscence. Patients are consequently instructed to quit prior to undergoing elective aesthetic surgery, and whether a patient has been utilizing nicotine in any form can be determined through urine cotinine levels. Additionally, patients with coexisting medical illnesses require preoperative medical clearance and are referred to a general practitioner for medical optimization. If the patient is deemed a moderate or high risk for general anesthesia because of medical comorbidities, then the operation may be postponed until those medical conditions are optimized. The surgery will ultimately be cancelled if the risk of anesthesia is too high for a patient.

Patients between the ages of 40 and 50 years with good skin quality, mild midfacial ptosis, and early “jowling” may benefit from a minimally invasive facelift. This operation is typically combined with an endoscopic brow lift to provide upper and lower facial rejuvenation with minimal scarring and is performed under local or general anesthesia. First, bilateral temporal and superior buccal sulcus incisions are made. The temporal force dissection is then carried down to the level of the superficial layer of the deep temporal fascia. Under endoscopic guidance, the superficial layer of the deep temporal fascia is then incised to expose the temporal fat pad. The dissection then proceeds caudally until the zygomatic arch is identified. A subperiosteal plane of the dissection provides access to the midface while preserving the integrity of the frontal branch of the facial nerve. The subperiosteal plane of

dissection is continued into the midface with care taken to avoid the infraorbital nerves. The masseter is mobilized from its lateral attachments. The superior buccal sulcus incisions are made, and a midface subperiosteal dissection is performed under both direct visualization and endoscopic guidance. Once the dissection is completed, the entire midface is suspended in the desired position with sutures or specialized anchors spanning from the superficial layer of the deep temporal fascia to the midface periosteum. Symmetry of the suspension is then confirmed, and the wounds are closed by layers. Mild midface ptosis, mild jowling, and early nasolabial fold prominence can all be corrected through this procedure, however deformities from significant skin laxity will not be corrected under this technique. In order to fix the latter, a traditional cervicofacial rhytidectomy will be required.[82,84]

A traditional rhytidectomy can be performed under local or general anesthesia in patients who require resection of excess skin. The skin incision is made over the temporal fossa 4 to 5 cm cephalad to the root of the helix and extended caudally toward the apex of the ear. The incision is then extended anterior to the ear, behind the tragus, around the base of the earlobe into the retroauricular sulcus, across the mastoid, and caudally along the anterior hairline of the neck. The skin flap is then elevated just superficial to the superficial musculoaponeurotic system (SMAS) and platysma. This plane of dissection maintains a thin layer of subcutaneous fat on the skin flap to preserve viability, while avoiding injury to the facial nerve branches, greater auricular nerve, parotid gland, and jugular vein. The flaps are elevated medially to the nasolabial fold in the face and to the midline in the neck. In some operations, a platysmal diastasis may exist which creates platysmal banding, an obtuse cervicomental angle, and a prominent neck. If this occurs, a platysmal plication may be performed through a 2- to 3-cm submental incision to correct the diastasis and improve the appearance of the neck. At this point, the remainder of the cervicofacial rhytidectomy can be performed in various ways, all with the goal of repositioning the tissues that have migrated into dependent positions, leading to facial aging changes. The surgeon may simply choose to not perform any additional dissection at this point and simply reposition the skin, resect the excess skin, and close the incisions. The surgeon may also choose to do one of the following: SMAS plication, standard SMAS dissection, extended SMAS dissection, or deep-

plane dissection. All of these operations are designed to improve control of facial and cervical tightening, while reducing the tension on the skin closure. Once the dissection of the facial tissues is completed and all planes are mobilized optimally, the SMAS and platysma are placed under tension and secured to create the desired facial appearance. The skin flaps are then redraped posteriorly, the patient is examined for symmetry, and a skin resection is performed. Hemostasis is obtained through judicious use of bipolar electrocautery. The wounds are closed in layers and a pressure dressing is applied. Drains are typically used in both the face and neck.[7,85–88]

Figure 107.40 A 63-year-old female presented to the office concerned with facial aging. The patient was displeased with the overall appearance of fatigue and looking sad, despite feeling well and energetic (**A**, **B**). She requested facial rejuvenation of the eyes, cheeks, neck, and overall skin texture. The patient underwent a facelift, neck lift, periorbital rejuvenation, and facial laser resurfacing. She is pictured here 1 week prior to surgery (**A**, **B**) and 1 year after her procedure (**C**, **D**).

Postoperatively, the patient is immediately evaluated for any evidence of a hematoma or facial nerve injury. Identifying a hematoma early is crucial in order to avoid overlying skin necrosis, and facial nerve injuries only occur in 2% to 3% of cases. On the first postoperative day, the pressure dressings and drains are removed, and the patient is further examined for evidence of a late hematoma, unrecognized facial nerve injury, or compromised skin flap. Patients should expect to have significant swelling and bruising for at least 2 weeks following the procedure. The final postoperative desired outcome is not realized until approximately 6 months following the procedure (**Fig. 107.40**).

Blepharoplasty

Eyelid surgery is one of the most frequently performed cosmetic surgery procedures. Blepharoplasty is often employed to correct both functional and/or aesthetic deformities. Visual field obstruction, or an angry, aged, or tired look in the patient may occur due to excessive skin and fat of the eyelids. In older patients, excess skin and wrinkling may occur, whereas in younger patients, persistent bags under their eyes or fine wrinkling ("crow's feet") at the lateral canthus is most common. Each clinical entity requires a unique approach based on the diagnosis and presentation, and meticulous attention to details is critical for the successful outcome of a blepharoplasty.[89] Preoperatively, all patients considering blepharoplasty should undergo a complete ophthalmologic examination to evaluate visual acuity, upper lid ptosis, exophthalmos, lower eyelid laxity, and symptoms of "dry" eye. Should lower lid laxity be present, and a standard blepharoplasty is performed, the patient may develop a lower lid malposition with ectropion postoperatively. Blepharoplasty may also significantly exacerbate symptoms of dry eye. Because of this, it is critically important to perform a comprehensive evaluation of the health of the eye prior to performing any eyelid surgery.

Once the optimal health of the eye is confirmed, an operative plan can be formulated and executed to correct the concerns of the patient. The operation can be performed under local or general anesthesia. The blepharoplasty incisions are first designed preoperatively with the patient in the upright position. Older patients frequently require skin excisions or removal or repositioning of orbital fat prior to the operation. To begin, local anesthesia with epinephrine is infiltrated for pain control and hemostasis.

The upper eyelid blepharoplasty begins with an elliptical excision of upper eyelid skin and orbicularis oculi muscle. This skin excision is designed based on the amount and location of the dermatochalasis. Very rarely will a patient require removal of fat from the upper eyelids, as these excessive fat resections will produce a "hollowed-out" appearance. Under some circumstances however, there may be a substantial amount of excess orbital fat in the upper eyelids and conservative fat resection may be helpful to achieve the desired postoperative outcome. If a fat resection occurs, small openings are made in the orbital septum to gain access to the two compartments of periorbital fat. A conservative fat resection is then performed to avoid a potential postoperative hollowed-out appearance. The

skin is then redraped and the wounds are closed in a single layer. If an upper lid blepharoplasty and brow lift are being performed within the same operation, the brow lift should be performed first, so that the amount of excess upper eyelid skin can be determined after the brow has been elevated.

The traditional lower eyelid blepharoplasty begins with a subciliary incision. A 4- to 5-mm rim of orbicularis oculi is then preserved along the lower eyelid margin. The dissection is then carried deep to the orbicularis oculi muscle until identification of the orbital septum. The orbital septum is then divided to gain access to the three compartments of periorbital fat in the lower lid. Fat may be resected in cases of prominent herniation, but it is necessary to avoid over resection. A trend in blepharoplasty surgery has emphasized repositioning the herniated periorbital fat over the inferior orbital rim rather than resecting fat in order to dramatically improve the appearance of the lower eyelids. This approach of repositioning the orbital septum medially has proven to be very helpful in eliminating tear trough deformities. Once the periorbital fat has been resected or repositioned, the skin/muscle flap is redraped superiorly and the redundant tissue is excised. The lower eyelid wounds are closed with interrupted sutures of 6-0 silk. Ancillary procedures, including a medical canthoplasty, a lateral canthoplasty, lateral canthopexy, or horizontal lid shortening may also be necessary to improve the position of the lower eyelid. If a lower lid blepharoplasty is being performed in conjunction with a rhytidectomy, the rhytidectomy should be performed first, so that the amount of excess lower eyelid skin can be determined after the facial soft tissues have been elevated.

The tired appearance of the lower eyelids is commonly a result of excessive or herniated periorbital fat in younger patients. A lower lid blepharoplasty through a transconjunctival approach allows for the removal or repositioning of the periorbital fat without creating an external scar. First, the conjunctiva is divided transversely 1 mm above the sulcus to gain access to the orbital septum. The septum is then divided, and the periorbital fat is removed or repositioned from all three compartments. Preserving the periorbital fat and simply repositioning the orbital septum into a more optimal location, obviates the need for fat resections. The transconjunctival incision is allowed to heal by secondary intention, allowing rejuvenation of the lower lids without an external incision. Recently, a multiplanar approach for the rejuvenation of the lower eyelids has been employed to reduce the

incidence of lower eyelid ectropion postoperatively. These approaches combine both subciliary incisions for removal of excess skin and transconjunctival incision for repositioning or resection of the periorbital fat. Experienced plastic surgeons have demonstrated outstanding outcomes with this approach as apparent through clinical case review. In conjunction with the non–external incision lower blepharoplasty, the surgeon can treat the lower eyelid skin with a resurfacing laser. The use of ablation and coagulation during full field ablative lasers induces a calculated "burn" of the skin leading to contraction and skin quality improvement. This technique often precludes the need for actual skin resection leading to no visible scar.

Postoperatively, patients are immediately evaluated for corneal abrasions, changes in visual acuity, or hematomas, which may require emergent intervention. Artificial tears are used to maintain appropriate lubrication and sutures are removed 5 to 7 days following the operation. Patients are instructed to not partake in any vigorous physical exercise during the early postoperative period. It is expected that patients will be bruised and swollen for approximately 2 weeks following the blepharoplasty and that it will be approximately 6 to 8 weeks before the desired outcome is noticed.

Rhinoplasty

No aesthetic surgical procedure may be a "game of millimeters" more than rhinoplasty. Cosmetic surgery of the nose requires meticulous planning and execution often involving alteration of both the external appearance and internal anatomy of the nose. The nose may be aesthetically unappealing or functionally impaired as a result of trauma, surgery, or a congenital deformity. Different familial and ethnic traits give rise to a plethora of nasal appearances. Because of this, it is necessary that any expectations the patient has regarding the procedure are realistic and achievable and align with the goals of both the patient and the surgeon. The patient must be prepared physical and mentally for the operation.

Preoperatively, a complete nasal history is obtained with particular attention paid to nasal airway obstruction, allergies, trauma, and previous surgery. A photographic analysis is performed to evaluate facial and nasal dimensions. The surgeon examines the photographs, discusses the plan with the patient, and the potential structural and functional outcomes are reviewed.

Rhinoplasty may be performed under local or general anesthesia. The patient is prepared for surgery by intranasal injections of vasoconstrictors containing lidocaine and epinephrine. Topical vasoconstrictors are applied to the nasal lining and septum. The operation can be performed in an "open" or "closed" fashion. The open technique requires a transcolumellar incision extended intranasally to allow exposure of the cartilage and bones of the nose. Direct visualization of the nose structure allows for greater precision in cartilaginous sculpting, grafting, and nasal bone repositioning. The paired lower lateral cartilages create the shape and provide the support for the nasal tip. Any deformity involving the nasal tip requires manipulations of this cartilage, including resections for a bulbous or over projecting tip, suturing to reposition an asymmetric nasal tip, or cartilage grafting to increase tip projection. The paired upper lateral cartilages and nasal bones define the shape of the nasal dorsum and control nasal airflow. A prominent dorsal hump may require resections of both the upper lateral cartilages and nasal bones. Osteotomies of the nasal bones may be required to narrow nasal width by disconnecting the base of the nasal bones from the maxilla. In contrast, "saddle nose" deformities may require cartilage or bone grafting to provide dorsal augmentation. Alloplastic materials have been described for use as dorsal graft, tip grafts, or columellar struts to increase nasal projection. Many surgeons discourage use of such alloplastic grafts due to problems with infection, extrusion, and migration producing a suboptimal result acutely or chronically. Autogenous cartilage grafts from the nasal septum, ear, or rib may also be used to improve nasal appearance or airflow. These grafts can be harvested and sculpted to create the desired cosmetic appearance of the nasal dorsum and tip. "Spreader grafts" can also be placed between the nasal septum and the upper lateral cartilage to increase the size of the internal nasal valve area, improving nasal airflow. The "closed" rhinoplasty technique allows access to the nasal cartilage and bones through intranasal incisions. This is the preferred method of experienced rhinoplasty surgeons because it is less invasive, however it is difficult to perform many of the complicated cartilage grafting and suturing techniques with limited exposure.

Following the rhinoplasty, an external splint is used to maintain the position of the nasal bones and cartilage for 10 to 14 days. Patients are instructed to keep their head elevated and apply ice packs, and should expect

nasal swelling, pain, and bruising for 2 to 3 weeks. If osteotomies are performed, the patient may also experience periorbital ecchymosis. A full year is required for complete resolution of nasal tip swelling, especially if an open-tip rhinoplasty has been performed. Approximately 10% of primary rhinoplasty patients will require an operative revision due to dissatisfaction with the cosmetic or functional outcome. This revision should not occur for at least 1 year following the original surgery in order to ensure all postoperative swelling and tissue remodeling has stabilized.

Genioplasty

Often performed in conjunction with rhinoplasty, facial harmony is achieved by simultaneously performing a genioplasty. This frequently executed plastic surgical operation improves facial appearance by manipulating the position of the central mandible aka "chin." The vertical height and anterior projection of the chin is able to be adjusted due to the design of the mandibular symphysis osteotomy.[90] An advancement genioplasty may be performed in patients with a "weak" chin to enhance chin projection and improve the cervicomental angle. Chin augmentation may also be accomplished with an alloplastic implant, eliminating the need for an osteotomy. A reduction genioplasty may be performed in patients with a very prominent chin, where the vertical height and anterior projection can be reduced. The lip position and neck appearance may be altered from these procedures; however, the dental occlusion is not affected.

After the initial consultation, a complete physical examination, photographic analysis, and radiographic evaluation are performed to evaluate facial harmony and determine the extent of the advancement or reduction. Dental occlusion is also carefully examined to ensure that orthognathic surgery is not required to correct chin position.

These operations are typically performed under general anesthesia but can also be performed under local anesthesia if desired. Local anesthesia containing epinephrine is first injected intraorally for hemostasis and postoperative pain control. An inferior buccal sulcus incision allows access to the mandibular symphysis. The osteotomy is then measured and marked based on the preoperative photographs and lateral radiographs, while avoiding the mental foramen. The bony segment is mobilized and secured in

its new position with plates and screws. If an alloplastic chin augmentation is to be performed, incisions can be performed in the submental region or intraorally to allow placement of the implant. Postoperatively, the swelling and pain is expected for approximately 4 to 6 weeks. During this time, the patient is instructed to perform meticulous oral hygiene and avoid foods that may traumatize the inferior buccal sulcus incision.

Cosmetic Procedures of the Trunk and Extremities (Body Sculpting)

Abdominoplasty

In recent years, there has been tremendous emphasis on body contouring. The explosion of technology-based nonsurgical modalities has led to increased interest in improving the appearance of the trunk. Abdominoplasty surgery addresses abdominal deformities such as excess abdominal skin, fatty tissue, and abdominal wall laxity through various surgical procedures. Abnormalities in any of these tissue planes may create a very aesthetically unappealing abdomen and create the need for the patient to seek surgical treatment. These procedures, which include dermatolipectomy, liposuction, and abdominal wall plication are able to correct the underlying pathology and are often combined and tailored to fit the surgical needs and desires of the patient. It is critical to define the physical anomaly responsible for the abdominal deformity so that the appropriate operative procedure or combination of procedures can be planned and executed.[91,92]

A standard abdominoplasty combines a dermatolipectomy, liposuction, and abdominal wall plication to correct deformity in each of the three previously mentioned abdominal wall layers. The operation is performed under general anesthesia and starts with a bikini-line incision extending from the cephalad margin of the pubic escutcheon to the iliac crests bilaterally. Once the skin incisions are made the abdominal flap is elevated off the underlying abdominal wall fascia. A circumferential incision is made around the umbilicus to allow complete elevation of the abdominal flap up to the costal margin. The patient is then placed in a flexed position, the abdominal flap is redraped caudally, and the redundant skin is resected. If any

abdominal wall laxity is identified along with the skin redundancy, then a vertical, midline abdominal wall plication is also performed. Occasionally, suction-assisted lipectomy (SAL) is performed at the time of abdominoplasty to help recontour the abdomen and flanks. Aggressive SAL of the abdomen flap, however, may critically compromise flap vascularity and contribute to flap necrosis. It is helpful to perform SAL along the lateral and posterior iliac crests bilaterally to reduce the prominence which may have developed following the anterior dermatolipectomy and caudal repositioning of the skin flap. A small incision is then made in the midline of the abdomen at the level of the iliac crests for delivery of the umbilicus into its new position. Closed-suction drains are placed prior to wound closure, but not necessary. In this instance, employing a series of progressive tension sutures is paramount to close the dead space. Typically, a series of 15 to 20 sutures are used to approximate the Scarpa fascia to the anterior rectus sheath.

A "mini-abdominoplasty" can be performed to treat mild abdominal skin redundancy and abdominal wall laxity. The previously described approach regarding a standard abdominoplasty is executed, except the skin incision is limited to the central portion of the abdomen. A limited skin resection can be performed through this approach along with an abdominal wall plication. If necessary, SAL can be used in combination with this procedure.

Endoscopic abdominoplasty can be used to treat abdominal wall laxity (i.e., postpartum rectus diastasis) and localized collections of fatty tissue. Patients who undergo this procedure must have good skin quality and only mild to moderate lipodystrophy. The endoscopic abdominoplasty is performed through two incisions, a 3- to 5-cm transverse incision within the pubic hair and a circumferential incision around the umbilicus. These incisions function as the two access ports through which the endoscopic instruments are passed. The entire abdominal wall is then elevated off of the abdominal wall fascia under endoscopic visualization with electrocautery, the midline of the abdominal wall is plicated from pubis to xiphoid, and the abdominal wall is then recontoured with SAL, which is also performed through the two incisions (**Fig. 107.41**).

Liposuction

Liposuction is world's most frequently performed cosmetic surgery procedure. Sculpting the body through this well-described technique is designed to eradicate deposits of fat from isolated anatomic regions by utilizing various diameter cannulas with a myriad of port sizes and configuration. It is not considered a form of weight loss and is therefore not performed in obese patients. Rather, patients who are within 20% to 30% of their ideal body weight and have localized collections of fat that are refractory to diet and exercise will see the greatest benefits. A complete evaluation of skin elasticity is necessary in patients who are considering liposuction because once fat is surgically removed, the skin must be able to contract down to the contour of the remaining subcutaneous tissue. If the skin quality is poor, then wrinkling, dimpling, or skin ptosis may severely compromise the desired aesthetic outcome.[91]

Over the past several years, various energy sources have been used in conjunction with SAL to liquefy fat and induce skin tightening by reaching a critical thermal threshold. Ultrasonic-assisted liposuction (UAL), laser-assisted liposuction (LAL), power-assisted liposuction (PAL), and helium plasma–assisted liposuction are the major types of energy and/or mechanical adjuvants to liposuction currently used. SAL can be used in all areas of the body, however its efficacy may be augmented by employing energy and/or mechanical power in more fibrous anatomic regions such as the flank, upper abdomen, or male breast.[91,93] A number of technologic advances have led to new techniques for performance of liposuction or liposculpting. None of these new techniques have yet to prove clinically superior in rigorous clinical trials, and standard SAL continues to be the most effective.

Figure 107.41 A 32-year-old female presented to the plastic surgery clinic with concerns related to the appearance of her abdomen. The patient was displeased with the "stomach" region after having three children. She had no further plans of having any children. Her primary complaints were extra skin and stretch marks above and below her umbilicus, fullness in the pubic region, and extra fat in her waist/love handles. The patient underwent a drain-less abdominoplasty with liposuction in the waist/love handles. She is pictured here 1 week prior to surgery (**A**–**C**) and 9 months after (**D**–**F**) her procedure.

As with all aesthetic procedures, it is necessary that patients undergo a complete evaluation preoperatively to ensure that their goals can be achieved through liposuction. Preoperative photographic documentation is performed on all patients. Markings are then made with the patient in the upright position. Access ports (6 to 8 mm), through which liposuction is performed, are marked in concealable areas. Patients can undergo these procedures under local or general anesthesia. Tumescent fluid (1,000 mL of LR, 50 mL

of 1% lidocaine, and 1 mg of epinephrine) is then infiltrated for pain control and hemostasis.

SAL is performed with metal cannulas connected to an aspirating device that generates a negative pressure of 1 atmosphere. Various cannula configurations are used to perform the resection. Fatty tissue is aspirated into the holes of the cannula and then resected by movement of the cannula tip. The operation is performed through multiple access ports, starting with large (6- to 8-mm diameter) cannulas and progressing to smaller (3- to 4-mm diameter) cannulas with fewer holes to allow more precise body contouring. Overlapping patterns of resection are used to avoid contour irregularities.

UAL and LAL are surgical techniques that allow body contouring through the liquefaction and aspiration of fatty tissue. Whether used alone or in combination with traditional SAL, UAL and LAL are effective for treating lipodystrophy in fibrous anatomic regions such as the flank, upper abdomen, and male breast. The UAL probe tip produces sound waves at an ultrasonic frequency of 20 to 30 kHz. The sound waves cause cavitation which disrupts lipocytes. LAL probe tip uses various nanometers of laser to heat and liquefy fat. Lower power suction is then employed to remove the resultant fluid. If UAL or LAL is used incorrectly, patients may experience severe complications, including full-thickness skin loss from incision and increased risk of seroma formation.

Postoperatively, all patients are placed in a compressive garment for 2 weeks, 24 hours per day. This early postoperative compression significantly reduces the chances of hematomas forming. Prolonged compression reduces swelling and the potential for skin wrinkling. All patients experience some degree of ecchymosis, swelling, and decreased sensibility. The final aesthetic result will not be realized for approximately 9 to 12 months following the procedure (**Fig. 107.42**).

Figure 107.42 A 47-year-old male presented to the plastic surgery clinic with concerns of abdominal contour. Despite aggressive diet and exercise, he was not able to achieve the definition he wanted (**A**, **B**). The patient underwent power-assisted liposuction with further abdominal etching to the abdomen and bilateral love handles. He is pictured here before and 12 months after the procedure (**C**, **D**), respectively.

NONSURGICAL AESTHETIC PROCEDURES

Minimally Invasive Procedures

11 Though not surgical in nature, the authors would be remiss to not mention the advent of minimally invasive procedures, primarily injectables, in the aesthetic plastic surgeon's armamentarium. Entire textbooks are devoted to these treatments, however, for the sake of completeness and cursory

overview, they are mentioned here. The 2002 FDA approval of Botox for moderate to severe frown lines resulted in a consequential sky rocket of the aesthetics industry.[94] In 2018 alone, 15.9 million minimally invasive cosmetic procedures were performed, a 228% increase since the year 2000.[94] Among the most popular of these treatments are three classes of injectables: neuromodulators, dermal fillers, and adipocytolytic agents.

Neuromodulators alter the interaction of a neuron with a neurotransmitter, and botulinum toxin type A specifically blocks the release of acetylcholine, the principal neurotransmitter at the neuromuscular junction.[95] When injected into the face, this causes temporary paralysis of the muscle, resulting in loss of function. Aesthetically, this is used to decrease the appearance of fine lines and creases. Botulinum Toxin Type A was first approved by the FDA in 1989 and is now the world's most frequently performed aesthetic procedure. In 2018, over 7.4 million injections were performed with botulinum toxin. The brand names include Botox, Dysport, Xeomin, and Jeuveau, and are most commonly injected to the forehead, glabellar, and crow's feet regions of the face. This muscle paralysis can last anywhere between 3 and 4 months, dependent on the metabolism of the patient.

Figure 107.43 A 66-year-old female presented to the clinic interested in improving the excess fat and loose skin in her neck, but without any surgical intervention. Patient is pictured before (**A**) and 8 weeks after (**B**) her FIRST treatment with deoxycholic acid (Kybella). She also underwent dermal fillers along the jawline to improve the contour.

Dermal fillers are a gel-like substance that when injected subcutaneously, intradermal and supraperiosteal restore volume, smooth lines and creases, and enhance the overall facial contour. This rejuvenation can be achieved through products consisting of either hyaluronic acid (HA), calcium hydroxylapatite (CaHA), and poly-L-lactic acid. Products compromised of HA, such as the Juvederm, Restylane, and Revanesse can keep the skin plump and hydrated anywhere from 6 to 12 months. CaHA products, such as Radiesse· last longer and assist in stimulating natural collagen production. However, unlike HA fillers, there is no reversal agent for calcium-based dermal fillers. Poly-L-lactic acid products, such as Sculptra, can last up to 2 years and also stimulates natural collagen production.

Adipocytolic agents are the third class of injectables, with Kybella being the only FDA-approved product currently on the market. Kybella contains deoxycholic acid which is a naturally occurring molecule in the body that aids in the breakdown and absorption of dietary fat. When injected, the fat cells lyse, prompting the inflammatory cascade to begin the skin tightening component. Kybella was approved by the FDA to treat submental fat in 2015, and in 2018 alone 63,993 patients were injected with the product.[94] Patients typically need two to three treatments spaced 6 weeks apart in order to achieve the ultimate satisfactory outcome and will experience swelling of up to 7 days (**Figs. 107.43** and **107.44**).

Figure 107.44 A 45-year-old male presented to the clinic with a desire to get rid of his "double chin." **A–C**: He was not interested in having a surgical procedure and wanted a "cleaner neck line." He is pictured here right before deoxycholic acid (Kybella) injection and 3 months after his second treatment (**D–F**).

SUMMARY

The surgical specialty of Plastic and Reconstructive Surgery is perhaps the most far reaching surgical field. The scope of practice is not limited by patient age, sex, anatomic body part, or mechanism of disease. Hospitals cannot function as state-of-the-art medical centers of the 21st century without a robust group of plastic and reconstructive surgeons. Congenital anomalies, trauma victims, oncology patients, and many others all have improved quality of life, return to normal function, and improved self-esteem because of the advances made by modern plastic and reconstructive surgery. This dynamic field will continue to develop new approaches to issues such as wound healing, composite tissue allotransplantation, gender reaffirmation, autologous tissue transfers for complex reconstructive questions and peripheral nerve reconstruction and healing as well as many other complex questions that need innovative answers.

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